Critical Care for Potential Liver Transplant Candidates

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Foreword

Since its introduction to clinical practice in 1963, liver transplantation has become *the* treatment for both acute and chronic end-stage liver failure as well as for liver-dependent metabolic diseases. By any measure, the improvements seen in this therapeutic option have been spectacular. Even its founding father, Thomas E. Starzl, could not have foreseen how commonplace this procedure would become such that as of today more than 400,000 liver transplantations have been performed worldwide. In the Western world, most transplantations are performed using grafts from deceased donors. However, in the Eastern world, the procedure, instead, relies almost entirely on grafts from live donors.

According to a statement from the 1983 NIH Consensus Conference, transplantation may be a promising alternative to current therapy in the management of a variety of serious liver diseases in their late phase. This would be true for both children and adults. In addition, the conference report not only defined ten absolute and five relative contraindications to transplantation but also outlined the characteristics of the ideal recipient. However, if we were to follow these recommendations today, not a single patient would receive a transplant. Improvements in surgical techniques in both donor and recipient as well as in anaesthesia and peri-operative care have nearly eliminated all but one (active, non-hepatic-related sepsis) of these contraindications. Early survival rates (in the 20% range) pale in comparison to today's rates, which approach 90%. Long-term outcomes, however, have remained almost unchanged. This is due to the fact that many patients with functioning grafts die from cardiovascular, renal, and infectious diseases and also as a result of de novo tumor formation. Most of these complications are either directly or indirectly linked to life-long immunosuppression. This will be the focus, no doubt, of intense research in the next few years.

The spectacular progress made in recent years has, however, caused a serious problem. Liver transplantation, in some ways, has become a victim of its own success. The increasing number of referrals to transplant centers around the world has resulted in an ever-widening gap between the number of potential recipients and the number of available grafts. This gap is steadily increasing, resulting in an increase in mortality while patients wait for a life-saving transplant (up to 30%). This is

because, with increasing experience, transplant teams are selecting more and more patients with severe comorbidities. Unfortunately, many of these patients succumb to their comorbidities while on the wait-list. Care of these potential recipients is very labor-intensive and care of these newly transplanted patients is carried out in a context of high risk. This situation is complicated further by the development of surgical variants of the procedure (e.g., split and living donor liver transplantation) and the frequent use of *extended criteria* grafts in order to offer transplantation to as many patients as possible. As a result of these developments, experienced transplant physicians may have the impression that we have returned to the high morbidity and mortality experienced in the adolescent phase of transplantation (1964–1990). The dedicated professionals in transplant centers continue to pave the way for a new generation of transplant caregivers. This new generation of transplant teams has expanded their interest, expertise, and influence in areas specifically related to managing hepatic encephalopathy, infectious diseases, cardiovascular, renal, and mechanical ventilatory support, as well as in the growing fields of combined transplantation and transplant oncology. The transplant team most familiar with each individual patient must be intimately involved in all decisions regarding patient care, including listing and, even more importantly, delisting.

This book, *Critical Care for Potential Liver Transplant Candidates*, is a timely addition to the literature. An international group of highly respected transplant clinicians outline the diagnosis and management of a wide variety of cardiopulmonary, renal, coagulation, infectious, and electrolyte disturbances seen in liver transplant recipients. Current knowledge and areas of uncertainty in need of research specific to these patients are discussed.

The editors of this book, Dmitri Bezinover from Penn State University, Penn State School of Medicine, USA, and Fuat Saner from Essen University Hospital, Germany, should be congratulated for bringing together a group of world experts to prepare this book. It should be on the desk of all clinicians involved in the care of liver transplant patients.

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Christopher Wray and James Y. Findlay

Introduction

Liver transplantation constitutes a significant cardiovascular challenge. It involves undertaking a major surgical procedure on a patient with an already altered cardiovascular status during which there is the potential for large and rapid volume shifts, changes in cardiac loading and vascular compliance, and alterations in electrolytes. Pre-existing cardiac conditions may increase the risk of perioperative morbidity and mortality. Additionally, cardiac conditions can influence post-transplant long-term survival. The pretransplant cardiac evaluation is thus a critical part of the evaluation process, with the goal of identifying conditions that can affect the transplant outcome in both the immediate perioperative period and the longer term. Identification of conditions allows pretransplant interventions, as indicated, to be undertaken, perioperative management to be optimized, and postoperative follow-up to be planned. An increased risk of both perioperative and long-term mortality associated with cardiac conditions can also play a significant part in the determination of transplant candidacy.

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Coronary Artery Disease

Interest in underlying cardiovascular disease in liver transplant (LT) patients has increased in the past two decades. Recognition of the impact of cardiovascular disease on post-transplant outcomes has driven research and the publication of consensus documents regarding preoperative cardiac evaluation in LT candidates [1, 2]. Although postoperative survival has continued to improve during this time, major demographic shifts in LT candidates have occurred. Reflecting the general population, LT candidates are aging. More than 20% of LT candidates in the United States are now aged 65 years or older [3]. Cardiovascular disease is highly associated with aging, as are many conditions that impact cardiac risk. End-stage liver disease (ESLD) patterns are changing in LT candidates as well. New antiviral treatment regimens for hepatitis C virus (HCV) infection and the emergence of non-alcoholic fatty liver disease (NAFLD) as a major cause of cirrhosis are likely to play a role in determining future LT candidate populations. Older patients with comorbidities including cardiovascular disease may be excluded from LT candidacy. Likewise, in intensive care unit (ICU) LT patients with a severe manifestation of ESLD, underlying cardiovascular disease may impart additional perioperative risk. Although a number of cardiovascular conditions are of concern in adult LT candidates, coronary artery disease (CAD) is the primary focus of pretransplant cardiac assessment.

Importance

The negative impact of CAD on post-LT survival was initially reported in patients in the 1990s and early 2000s. These series demonstrated inferior outcomes in single-center cohorts with CAD [4–6]. Recent studies have shown that cardiovascular morbidity and mortality are common in the post-transplant period, although direct causation from underlying CAD is difficult to determine in retrospective analyses. Cardiac events were one of the most common etiologies of early postoperative mortality in a large OPTN database analysis of LT patients in the United States over a 10-year period [7]. In another large database series from the United Kingdom over a 13-year period, cardiac disease was the fourth most common cause of postoperative mortality after 1 year, responsible for 8.7% of deaths [8]. Postoperative immunosuppression contributes to the development of hypertension, hyperlipidemia, diabetes, and renal dysfunction, which may enhance the progression of underlying CAD. The cure for ESLD is also associated with significant metabolic changes that can lead to CAD. In a single-center series, 30% of LT recipients with a diagnosis of post-transplant metabolic syndrome suffered cardiovascular complications compared to 6% of patients without that diagnosis [9]. In the last 15 years, significant attention has focused on the detection and management of CAD in LT patients. The expansion of upper age limits for LT candidacy and the aging of the general population have further driven this interest. Compared to the corresponding period for most non-cardiac surgical procedures, the perioperative period in LT is associated with

prolonged hemodynamic and metabolic instability and the potential for a hypercoagulable state. Underlying obstructive CAD in this setting may increase the likelihood for plaque rupture and/or a mismatch between coronary supply and demand.

There is wide variance in the prevalence of CAD reported in LT candidates [10]. Differences in patient populations, diagnostic methods, and categorizations of CAD severity contribute to this variability. Most studies have been conducted with a single-center cohort and a relatively small sample size. Overall, recent studies suggest that the prevalence of CAD in LT candidates is at least equal to that of the general population (the reported rate of CAD in the general US population aged 45–64 years in 2015 was 6.1%) [1, 11]. In older LT candidates and in those with traditional CAD risk factors, CAD prevalence may be much higher [12]. Patients with a diagnosis of NAFLD have a higher likelihood of CAD compared to the general population, with prevalence rates reported as ranging from 7.4 to 21.6% [13, 14]. The prevalence of CAD is likely to increase in LT candidates as the population ages and the rates of CAD risk factors increase. The emergence of NAFLD is likely to have a major impact on the cardiovascular risk of LT candidates as well. According to 2016 UNOS data, HCV infection is no longer the leading indication for LT in the United States, which is likely to represent an increased number of LTs for the diagnosis of NAFLD [15].

Screening

Screening for asymptomatic CAD has become an essential part of the preoperative selection process for adult LT candidates. However, preoperative cardiac evaluation of LT patients is challenging. Currently, there is no standard for the preoperative CAD evaluation of LT candidates, and randomized prospective studies investigating preoperative paradigms are lacking for this population. Even though the majority of LT programs use the guidelines of the American Association for the Study of Liver Diseases (AASLD), there are wide variations in practice between centers. Candidates may remain listed for long periods of time prior to an organ offer, and CAD may progress during the interim. Progression of cirrhosis resulting in severe manifestations of ESLD may necessitate an urgent cardiac reevaluation prior to transplant. The urgency of surgery, the continued mismatch between organ supply and demand, and the need for programs to maintain acceptable outcomes distinguish LT from other non-cardiac surgeries.

History, Risk Factors, Cardiac Symptoms, and Functional Capacity

Current ACC/AHA guidelines recommend a stepwise process for the preoperative cardiac evaluation of non-cardiac surgical patients that relies on determining functional status and analyzing key risk factors. An indication for noninvasive ischemia testing is based on this approach in most clinical situations [16].

A known history of previous CAD in an LT candidate requires an updated cardiology evaluation prior to listing. However, the frequency of reevaluation over an extended listing period has yet to be precisely defined. As the ESLD population ages, more patients are likely to have traditional CAD risk factors. CAD risk factor analysis is important for LT candidates, as having more than one pretransplant risk factor has been shown to correlate with the risk of significant CAD [17].

Diagnosis of occult CAD on the basis of a history of cardiac symptoms is problematic in LT candidates. A variety of cardiovascular conditions that may produce cardiac symptomatology are prevalent in this population. The presence of cardiac dysfunction due to cirrhosis, a syndrome termed cirrhotic cardiomyopathy (CCM), may be responsible for many cardiac symptoms. In critically ill transplant candidates, underlying renal failure due to hepatorenal syndrome (HRS) may contribute to volume overload and symptoms of diastolic heart failure. Etiologies of systolic failure such as alcoholic cardiomyopathy may produce symptoms of congestive heart failure. Deconditioned ESLD patients are usually unable to exercise to the point of producing ischemic symptoms. Finally, asymptomatic myocardial ischemia and silent myocardial infarction (MI) are common in candidates with longstanding diabetes.

Determining the functional capacity of LT candidates is also challenging. ESLD contributes to deconditioning, malnutrition, sarcopenia, renal failure, and pulmonary complications. These factors collectively impact exercise tolerance and mobility. Critically ill ICU LT candidates may have a prolonged history of immobility that prevents an accurate assessment of their functional status.

Noninvasive Ischemia Testing

Based on the known prevalence of underlying CAD and the difficulty of applying current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for noninvasive ischemia testing to LT candidates, most centers perform comprehensive noninvasive testing on a large proportion of adult LT candidates. There is a significant body of research focused on evaluating a variety of noninvasive methods in LT candidates. In general, most studies have been performed with small, single-center cohorts, and results vary across studies due to differences in study methods, patient characteristics, and outcome measurements. In particular, a comparison of noninvasive results with coronary angiography, the current standard for determining a diagnosis of CAD, was not performed in many of the studies. Although comprehensive noninvasive testing is common in most centers, there are concerns regarding efficacy, cost, and logistics [1]. Nevertheless, important information on the utility of noninvasive methods for the detection of asymptomatic CAD in LT candidates has emerged.

Resting Electrocardiogram (EKG)

A preoperative resting 12-lead EKG is necessary prior to listing adult LT candidates. Although occult obstructive CAD may be present despite a normal resting EKG, the presence of Q waves, left bundle branch block, frequent premature ventricular contractions (PVCs), and repolarization abnormalities associated with silent myocardial ischemia provide valuable diagnostic information that can direct further CAD evaluation. In addition, EKG manifestations of CCM such as prolongation of the QT interval, bradycardia due to chronotropic dysfunction, and arrhythmias such as atrial fibrillation (AF) are especially important to consider in documenting the condition of critically ill patients with advanced ESLD [18].

Stress Echocardiography

Pharmacologic stress echocardiography with dobutamine (DSE) has been extensively evaluated in LT candidates. The use of exercise echocardiography is limited by poor functional capacity in many patients with cirrhosis and has rarely been studied. Although an early single-center study demonstrated a strong positive predictive value (PPV) for the detection of obstructive CAD, further studies have shown significant variability in both the sensitivity and specificity of DSE for the prediction of underlying obstructive CAD compared to coronary angiography [19–22]. Incomplete and non-diagnostic studies are common with DSE in LT candidates due to failure to reach the target heart rate, and beta blockade for portal hypertension and chronotropic dysfunction from CCM may be implicated [22]. In LT candidates with an underlying vasodilatory state, tests may be terminated early due to cardiac symptoms, dysrhythmia, or hypotension. Despite the inaccuracy of DSE for predicting underlying obstructive CAD, the test appears to have value for identifying patients at low risk for postoperative cardiac events. In an analysis of seven studies in which DSE was employed for the preoperative screening of LT candidates, the reported specificities and negative predictive values for perioperative and long-term postoperative cardiac events were very good [23]. These findings suggest that a normal DSE predicts a low likelihood of perioperative cardiac events, especially in candidates with few CAD risk factors. Many centers use DSE as the initial CAD screening test in pretransplant paradigms. However, as the sensitivity of DSE for detecting obstructive CAD in LT candidates is poor compared to the general population, candidates at high risk for underlying CAD may be referred for coronary angiography regardless of DSE results.

Nuclear Myocardial Perfusion Imaging

Stress myocardial perfusion scintigraphy or single photon emission contrast tomography (SPECT) has been studied in LT cohorts as well. A number of studies have shown wide variability in both sensitivity and specificity for the detection of obstructive CAD with SPECT in LT candidates [24–26]. The results of one study showed that SPECT had the same accuracy as risk factor analysis for the detection of severe CAD in a cohort of LT candidates [26]. The vasodilatory state associated with ESLD may have an impact on the efficacy of SPECT in LT candidates.

Cardiac Contrast Tomography/Coronary CT Angiography

Cardiac contrast tomography (CT) scanning for quantifying the calcium burden present in coronary arteries has been described as a viable screening method for CAD in a cohort of low-risk LT candidates [27]. Cardiac CT has advantages in LT candidates, as diagnostic accuracy is not affected by exercise capacity, vasodilatory state, or heart rate. Likewise, coronary CT angiography, an alternative to invasive coronary angiography, provides detailed imaging of coronary anatomy, and has been described as a viable screening test in a cohort of low- and medium-risk LT candidates [28].

Cardiopulmonary Fitness Evaluation

Functional cardiovascular testing including the assessment of metabolic equivalents (METs) that patients are able to attain may be employed in the preoperative testing paradigm for non-cardiac surgery. Functional testing for the preoperative assessment of LT candidates has been studied. Both the 6-min walk distance test and the cardiopulmonary exercise test (CPET) have been assessed in LT candidates, and a limited cardiopulmonary reserve has been shown to correlate with worse post-transplant survival using either method [10]. It should be noted that in many LT candidates, especially in those with critical illness, functional cardiac testing is not likely to be applicable.

Coronary Angiography

Coronary angiography allows for the definitive diagnosis of the severity and distribution of CAD, regardless of its functional impact. Angiography is invasive and associated with risks that may be increased in LT candidates. Studies have

demonstrated the safety of angiography in patients with cirrhosis, although with only small samples [29, 30]. Vascular injuries and transfusion are more common with angiography in ESLD patients compared to patients without cirrhosis [30]. Upper extremity arterial access for coronary angiography has become standard at many centers and has been shown to be safe and effective in a cohort of ESLD patients [31].

Recommendations

Two recently published documents provide recommendations for the preoperative evaluation of CAD in LT candidates, although these two documents differ in terms of some specific details [1, 2]. According to a consensus document from the American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF), noninvasive stress testing should be considered regardless of functional status based on the presence of three or more CAD risk factors. These risk factors include an age of greater than 60 years, a history of tobacco use, hypertension, hyperlipidemia, left-ventricular hypertrophy, diabetes, and a history of known cardiovascular disease. This document also includes the recommendation that each center identify a cardiology consultant for the preoperative evaluation of LT candidates [1]. In an AASLD and American Society of Transplantation (AST) practice guideline included in the document, both an assessment of cardiac risk factors and stress echocardiography as an initial CAD screening test are recommended. Also recommended are the use of coronary angiography as indicated by the clinical situation and consideration for cardiac revascularization in LT candidates with significant CAD [2].

Many centers use screening paradigms that include compulsory noninvasive testing, aggressive coronary angiography for positive or non-diagnostic stress test results, and direct coronary angiography for high-risk candidates regardless of stress test results. Although angiography allows for standardized grading of CAD lesions, the severity of CAD that may be of significance during the perioperative period of LT has not been defined. Fractional flow reserve (FFR), a method for determining the functional significance of a flow-limiting coronary lesion, has become the standard for assessing the need for revascularization in intermediate coronary lesions [32]. FFR is likely to have a significant role in determining the need for preoperative revascularization of discrete coronary lesions in LT candidates.

Management of CAD in LT Candidates

There is no consensus regarding management strategies for LT candidates with significant CAD. Furthermore, the extent of CAD that excludes candidates from LT has not been defined. Current ACC/AHA guidelines do not recommend