Cardiac evaluation before liver transplantation: A step forward?

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Editorial

“Akin to running a marathon” is a common way to describe the stress imposed on the cardiovascular system by a liver transplantation (LT). In fact, liver transplant recipients (LTRs) often have to tolerate profound, sudden and prolonged haemodynamic modifications during surgery and in the early post-operative period. However, unlike healthy marathon runners, LTRs might have underlying heart diseases that impact short- and long-term survival.¹ Among the very few absolute contraindications to LT are “severe cardiac diseases” (including critical coronary artery disease [CAD]), while major adverse cardiac events (myocardial infarction, heart failure and acute coronary syndrome) are among the most common post-operative complications.²–⁴

Cardiovascular diseases account for up to 50% of all hospitalizations in the first 90 days after LT and cardiac deaths are responsible for nearly 40% of all deaths in the first 30 days after LT.¹ Pre-operative cardiac risk stratification of the LT candidate involves the assessment of the following factors: (i) age and gender; (ii) assessment of the cardiovascular system (particularly to exclude significant systolic or diastolic left ventricular dysfunction, pulmonary hypertension and CAD); (iii) evaluation of comorbidities (diabetes mellitus and renal dysfunction are among the most relevant). The main goal is to plan appropriate pre- and post-surgical management and to exclude candidates who are too fragile, in order to allocate a limited resource (the graft) to an increasing number of patients with end-stage liver disease (ESLD) in the most appropriate way.

Supported by excellent 1- and 5-year survival rates, LT indications are rapidly expanding, and candidate demographics have consistently changed, with older, more fragile patients now increasingly considered (and accepted) for active LT listing.⁵–⁷ Therefore, relevant cardiovascular risk factors (age >60 years, hypercholesterolemia, arterial hypertension, diabetes mellitus, tobacco use, prior cardiovascular disease, and ventricular hypertrophy) are highly prevalent among LT candidates.²–⁴ Not surprisingly, an increased prevalence of CAD is now being reported among LTRs, ranging from <5% in Italy to 7–25% in the rest of Europe and the USA.⁵–⁸ Non-alcoholic steatohepatitis (NASH), secondary to the metabolic syndrome and frequently associated with CAD, is now the second leading indication for LT in the USA.⁷ Moreover, ESLD can be complicated by the so-called “cirrhotic cardiomyopathy” (CCM), characterized by impaired systolic response to physical stress and diastolic dysfunction. The presence of CCM increases the rate of post-LT complications (including acute coronary syndromes).⁹ According to animal models, vascular inflammation may link CCM to the risk of developing CAD.⁹

Therefore, it is pivotal to exclude significant CAD in the pre-operative cardiac risk assessment.⁵–⁶ Patients with critical CAD, particularly if silent or unrecognised, are more prone to develop intra- and post-operative cardiac complications, making the timely identification of CAD crucial for an appropriate pre-operative management including coronary revascularisation (if indicated), to mitigate the cardiac risk and to improve short- and long-term outcomes.⁶ A number of risk stratification tools or algorithms have been proposed in recent years to evaluate LT candidates for CAD.¹⁰–¹³ Unfortunately, many suffer from a lack of uniformity and disagreement on the indications for non-invasive stress testing, computed tomography coronary angiography (CTCA) or invasive coronary artery imaging (CATH). Other problems include the absence of standardisation on the use of biomarkers and clinical risk factors, small sample sizes, and single centre adoption.¹⁴–¹⁶

In this issue of the Journal of Hepatology, Rachwan et al. from the Indiana University Medical School propose the use of the “CAD-LT score” and the derived algorithm with the aim to predict the risk of significant CAD in LT candidates, with potential benefits in terms of safety, efficacy and cost savings.¹⁷ This retrospective study assessed clinical characteristics, aetiology of ESLD, MELD (model for end-stage liver disease) score, cardiac risk factors, stress echocardiography (SE) and coronary arteriography (CATH) findings in 1,771 LT candidates over a 10-year period. The CAD-LT score included risk factors (age, male gender, diabetes, hypertension, tobacco use, family history of CAD and personal history of CAD) that independently predicted significant CAD on CATH, defined as stenosis ≥50 in a major vessel or ≥70% in a moderate-sized branch vessel, on multivariate regression analysis. The main study finding was that a pre-operative cardiac screening algorithm based on CAD-LT score would have identified the majority (89%) of patients with an underlying significant CAD reducing unnecessary testing (57% of SE and 44% of CATH). The authors should be commended for providing an easy-to-use risk stratification tool to estimate the probability of significant CAD in LT candidates. If validated in

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other prospective cohorts of patients, it should reduce the number of unnecessary SE and CATH procedures and may become standard of care in the future. However, some potential limitations should be highlighted.

First, according to clinical practice in their centre, Rachwan et al.15 set a very low threshold to prescribe SE and CATH. Indeed, 92% of LT candidates underwent SE and 71% CATH. Although the proportion of negative results (77%) raises the question of whether such a high rate of invasive CATH is justified, a possible explanation for this practice might reside in the insufficient predictive value of SE. In fact, similar to previous investigations,16,17 SE demonstrated a very low sensitivity (29%) for significant CAD among LT candidates, leading to a high number of false negative results. A possible explanation for this finding is that cardiac modifications typical of ESLD such as high cardiac output and vasodilation impair the response to drugs (dobutamine or dipyridamole) used to elicit myocardial ischaemia.17 According to this perspective, the role of non-invasive SE in the assessment of LT candidates would be very limited and a strategy of direct CATH prescription based on the presence of risk factors would be justified. On the other hand, it is well known that the correlation between anatomically defined significant CAD and inducible myocardial ischaemia is poor.18 It is the ability of a coronary artery lesion to cause myocardial ischaemia rather than the degree of stenosis, as assessed visually by CATH, that really influences peri- and post-operative adverse events. The CAD-LT score proposed by Rachwan et al.15 aims to estimate the probability of anatomically defined significant CAD – whether implementation of such an algorithm impacts on peri-LT outcomes remains to be established. It is noteworthy that a previous study from the Indiana University Medical School reported on the outcome of a smaller group of LTRs who underwent pre-operative CATH or not according to the presence of coronary risk factors. Patients with significant CAD received systematic coronary revascularisation before LT. Although the overall incidence of adverse cardiac events after LT was very low (<1%), mortality in patients with significant CAD remained higher than in those without despite pre-LT coronary revascularisation.19 Most patients in this cohort also underwent SE, but no data were provided about the predictive value of stress testing for cardiac events and mortality.

Second, management of “intermediate risk patients” according to the CAD-LT score remains challenging. According to the proposed algorithm, these patients should undergo SE to decide whether CATH is needed. This indication, however, seems counterintuitive, given the postulated low sensitivity of SE. To come out from this long-standing limbo, a step forward might be the use of coronary calcium score (CAC) or CTCA to replace the “non-invasive stress testing”. There is emerging evidence that both CAC and CTCA could predict cardiac outcomes after LT.10,20 The new generation high temporal resolution computed tomography scanners should speed up the study, overcoming the clinical and logistic problems posed by the most problematic cirrhotic LT candidates. Fractional flow reserve computation from CTCA datasets has recently emerged as a promising non-invasive test to assess the haemodynamic severity of CAD and could provide, if confirmed, information about the haemodynamic significance of coronary lesions and guide decision making.21 Fine tuning the non-invasive anatomic imaging could be the step forward.

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