Low Yield of Routine Pre-Operative Coronary CT Angiography in Patients Evaluated for Liver Transplantation

Running title: Di Carli et al.; Coronary CTA for peri-operative CAD screening

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Journal Subject Codes: Atherosclerosis:[150] Imaging, Diagnostic testing:[29] Coronary imaging: angiography/ultrasound/Doppler/CC

Key words: liver transplantation, Editorial, cardiac computed tomography, coronary atherosclerosis
Although coronary revascularization prior to non-cardiac surgery has not been shown to reduce the risk of cardiac events, pre-operative noninvasive screening for obstructive coronary artery disease (CAD) is commonly performed. Such testing is even more likely to be performed among patients who are candidates for organ transplantation. The rationale for such testing in candidates for organ transplantation include the need to determine (1) the peri-operative risk, and (2) if the patient’s cardiovascular risk is high enough that organ transplantation would be futile and an inappropriate use of a scarce organ.1 While screening for obstructive CAD in patients with end stage renal disease evaluated for kidney transplantation seems reasonable given the high prevalence of atherosclerosis and cardiovascular risk in these patients, there is intense debate of whether such approach should also be considered among patients with end stage liver disease (ESLD) in whom there is a generally much lower frequency of CAD, at least based on relatively small retrospective reports.2-6

In this issue of Circulation, An et al provide new data regarding the prevalence of obstructive CAD among a large number of asymptomatic patients evaluated for liver transplantation who were referred for coronary computed tomography angiography (CCTA).7 This retrospective study included 1,045 consecutive patients with liver cirrhosis without any history of chest pain or CAD undergoing CTCA as part of the pre-liver transplant workup. In this cohort with low-intermediate likelihood of CAD, CCTA revealed no CAD in 62%, non-obstructive CAD in 30%, and angiographically obstructive CAD (≥50% stenosis) in 7.9% of patients (N=83). There were only 39 (3.7%) patients who had a significant stenosis (>70%), most being single vessel CAD. Using propensity scores, the study cohort was matched with 6,283 controls with healthy livers undergoing CTCA as part of a health evaluation program. The matched comparison revealed that the frequency of obstructive CAD was similar in the cirrhotic
and healthy cohorts (7.9% vs. 7.2%, respectively). However, non-obstructive CAD seemed slightly more prevalent among the patients with liver cirrhosis than in the matched controls (31% vs. 23%, respectively). Interestingly, in the pooled cohort of liver cirrhosis and control subjects (N= 7,328), a diagnosis of liver cirrhosis did not associate with obstructive CAD in multivariable modeling.

Importantly, 24 of the 83 cirrhotic patients with obstructive CAD by CCTA were referred for cardiac catheterization, and only 6 (0.6% of the entire cohort) with multivessel CAD ultimately underwent revascularization. Liver transplantation was subsequently performed in 57 of 83 patients with obstructive CAD by CTCA. Post-operatively, one patient had a NSTEMI and two patients developed arrhythmia (atrial fibrillation and ventricular tachycardia). There were no deaths. During a median 2.3-year follow-up there were only two late revascularizations.

The study by An and colleagues provides important data regarding the yield of noninvasive testing in a large cohort of patients with liver cirrhosis as well as the implications of such testing, and contributes to the ongoing debate concerning pre-transplant risk assessment in liver disease patients.

Is cardiac testing required in every asymptomatic patient being considered for liver transplantation?

This is a legitimate question especially given the low yield of testing identified in this large series. A recent AHA/ACC scientific statement suggests that non-invasive testing may be considered in liver transplantation candidates with multiple CAD risk factors (i.e., diabetes, prior cardiovascular disease, left ventricular hypertrophy, age >60 years, smoking, hypertension, dyslipidemia) regardless of functional status (Class IIb recommendation; Level of Evidence C). The study by An and colleagues supports these recommendations, as independent risk factors for
obstructive CAD in this series included advanced age, male gender, hypertension, diabetes, and alcohol-related cirrhosis. However, the specific number or combination of risk factors to warrant testing is less clear. Based on the current report and other prior studies, the recommendation for pre-operative testing of liver transplant candidates with a history of cardiovascular disease and/or diabetes, especially those older than 60 years, seems reasonable as these patients probably have a higher likelihood of prognostically significant CAD. Indeed, nearly 50% of patients with obstructive CAD in the current study were older diabetics. Another intriguing finding in the current study was the association between alcoholic, but not viral cirrhosis, and obstructive CAD, which was independent of other coronary risk factors. Because this was a relatively small proportion of the patients in this report, this requires further studies to more firmly define the role of alcoholic cirrhosis as risk factor for atherosclerosis in this population. However, the cost-effectiveness of routine noninvasive testing in younger candidates for liver transplant without symptoms, evidence of cardiovascular disease, or diabetes, appears more controversial. In order to augment the low yield of testing, thereby enhancing the clinical- and cost-effectiveness of diagnostic evaluations, it would probably be useful to enrich the prevalence of disease in the latter group before the use of noninvasive testing. One potential approach may be the use of an aggregate score incorporating and weighting multiple risk factors present.\textsuperscript{8,9} Indeed, previous studies have shown that incorporating a clinical score into a testing strategy in patients without liver cirrhosis can enhance the yield of cardiac imaging and improve its cost-effectiveness.\textsuperscript{10-12}

*What is the best imaging approach to screening for CAD in candidates for liver transplantation?*

The 2012 ACC/AHA Scientific Statement on “Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates” concluded “prospective studies on optimal screening strategies for the presence of CAD are lacking and much needed.” To that
end, the study by An et al provides useful data regarding the feasibility and potential utility of coronary CTA. There are several potential advantages for the use of coronary CTA for CAD screening in patients with advanced liver disease. It has a very high sensitivity (~90%) and negative predictive value (~96%) for excluding significant CAD.\textsuperscript{13} Given its high negative predictive value, a normal scan result (expected in approximately two thirds of patients with ESLD based on the current report) effectively excludes obstructive CAD and abolishes the need for further investigation. Stress myocardial perfusion scintigraphy and echocardiography have been used in these patients with mixed results,\textsuperscript{1} likely related to the variable sensitivity of these approaches. A related advantage of coronary CTA over stress imaging is that it does not require exercise or pharmacologic (vasodilator) stress testing. This is clinically relevant in these patients because transplant candidates in general are often too debilitated to complete maximal exercise testing. In addition, the efficacy of vasodilator stress testing in patients with ESLD has been questioned due to the enhanced systemic vasodilation observed in these patients.\textsuperscript{6} Finally, the use of coronary CTA may serve as a more effective gatekeeper to cardiac catheterization, thereby avoiding the somewhat higher risk of bleeding complications in patients with ESLD.

*What are the implications of identifying angiographic CAD?*

It is well recognized that the presence of obstructive CAD (≥50% stenosis) is a poor predictor of myocardial ischemia. Thus, a testing strategy using coronary CTA for CAD screening should include follow-up stress testing to determine the need for invasive angiography and coronary revascularization in patients with abnormal CTA results, as was the case in the current study. As many as two thirds of these angiographic lesions are not flow-limiting and do not require coronary revascularization.\textsuperscript{14,15} The safety of avoiding coronary revascularization in most patients with solely angiographic findings is also supported by the fact that in the study by An et
al, liver transplantation was successful performed in 57 patients with obstructive CAD; of whom only 6 underwent coronary revascularization, with only 1 subsequent myocardial infarction, 2 late coronary revascularizations and no deaths.

In the study by An et al, approximately one third of patients had non-obstructive plaque (with 90% involving 4 or fewer coronary segments) and it is therefore intriguing to consider the value of identifying such lesions. Among non-transplant candidates referred for clinical CTA, there is evidence to suggest that the presence of extensive non-obstructive plaque (i.e. >4 segments) is associated with an increased rate of myocardial infarction and cardiovascular death. In addition, the presence of such disease by coronary CTA is associated with initiation or intensification of lipid lowering therapies and aspirin. However, among patients evaluated for organ transplantation, there is no data to indicate whether the identification of such plaque could lead to improved patient outcomes. Since peri-operative cardiac events are thought to occur from both demand-mediated ischemia and plaque rupture, it is likely that a small proportion of non-obstructive plaque may represent high risk (“vulnerable”) plaques. However, in the current era of coronary CTA (or invasive angiography), the positive predictive value of identifying high-risk plaque characteristics is extremely low, and beyond the use of statin therapy, there are no compelling therapies that would be initiated for such lesions. Given that post-transplant immunosuppressive medications may contribute to the progression of atherosclerosis, it is conceivable that information regarding the presence of non-obstructive plaque could be used to identify higher risk populations beyond the post-operative period, but this will require longitudinal studies with longer follow-up.

In summary, the study by An identifies a low risk of obstructive CAD among patients with liver disease and therefore supports the fact that routine testing of all patients prior to liver
transplantation may not be warranted. Consequently, better algorithms are needed in order to identify which patients require screening for CAD prior to liver transplantation. Finally, additional studies are required to compare how different non-invasive approaches compare as well as whether pharmacological or interventional therapies can be used to effectively mitigate the low risk of events in these patients.

**Conflict of Interest Disclosures:** None.

**References:**


