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Significance of Coronary Artery Calcium Found on Non−Electrocardiogram-Gated Computed Tomography During Preoperative Evaluation for Liver Transplant

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Guidelines to evaluate patients for coronary artery disease (CAD) during preoperative evaluation for orthotopic liver transplantation (OLT) are conflicting. Cardiac catheterization is not without risk in patients with end-stage liver disease. No study to date has looked at the utility of non−electrocardiogram-gated chest computed tomography (CT) in the preliver transplant population. Our hypothesis was that coronary artery calcium scores (CACSs) from chest CT scans ordered during the liver transplant workup can identify patients who would benefit from invasive angiography. Nine hundred and fifty-three patients who underwent coronary angiography as part of their OLT workup were considered. Charts were randomly selected and reviewed for the presence of a chest CT performed before coronary angiography during the OLT workup. Agatston and Weston scores were calculated. CACS results were compared with coronary angiography findings. Nine of 54 patients were found to have obstructive CAD by angiography. Receiver-operating characteristic analysis demonstrated that an Agatston score of 251 and a Weston score of 6 maximized sensitivity and specificity for detection of obstructive coronary disease. An Agatston score <4 or Weston score <2 excluded the presence of obstructive CAD; using these thresholds, 13 patients (24%) or 15 patients (28%), respectively, could have theoretically avoided catheterization without missing significant CAD. In conclusion, our data identify the strength of CACS in ruling out coronary disease in patients being evaluated for OLT. Calcium scoring from non−electrocardiogram-gated CT studies may be integrated into preoperative algorithms to rule out obstructive CAD and help avoid invasive angiography in this high-risk population. **(Am J Cardiol 2019;124:278−284)**

Coronary artery disease (CAD) is an important consideration in the preoperative evaluation of patients for orthotopic liver transplantation (OLT).[1−3] However, guidelines to evaluate patients for underlying CAD during preoperative evaluation for OLT are conflicting.[4−6] Cardiac catheterization is not without risk in end-stage liver disease (ESLD) patients, who are often thrombocytopenic and coagulopathic.[7,8] It is for these reasons that liver transplant teams rely on noninvasive stress testing before OLT.[2,9,10] These tests are burdened by inaccuracies.[2,9] The coronary artery calcium score (CACS) has been established as a predictor of CAD, cardiovascular events, and all-cause mortality,[11−13] and has been incorporated into the American College of Cardiology Foundation and American Heart Association guidelines for evaluating low-to-intermediate-risk individuals.[14,15] However, only limited data are available regarding the utility of CACS in liver transplant patients. Studies have shown an association between traditional CAD risk factors and CACS in liver transplant recipients.[16,17] CACSs have also been predictive of cardiovascular complications within 1 month of liver transplant.[18] Two studies have demonstrated an association between Agatston scores from electrocardiogram (ECG)-gated computed tomography (CT) scans and cardiac catheterization findings in liver transplant candidates.[19,20] No study to date has looked at the utility of non−ECG-gated CT scans in the preliver transplant population, which are routinely performed to exclude pulmonary pathology or metastatic disease. Little is known about the prognostic significance of CACS from nongated CT,

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although limited data have suggested it correlates well with ECG-gated studies.[21–23] The aim of this study was to determine the predictive value of incidental coronary artery calcium discovered on non−ECG-gated chest CT in the preliver transplant population. Our hypothesis was that by retrospectively evaluating CT scans ordered during the liver transplant workup, it may be possible to more accurately identify patients who would benefit from invasive angiography.

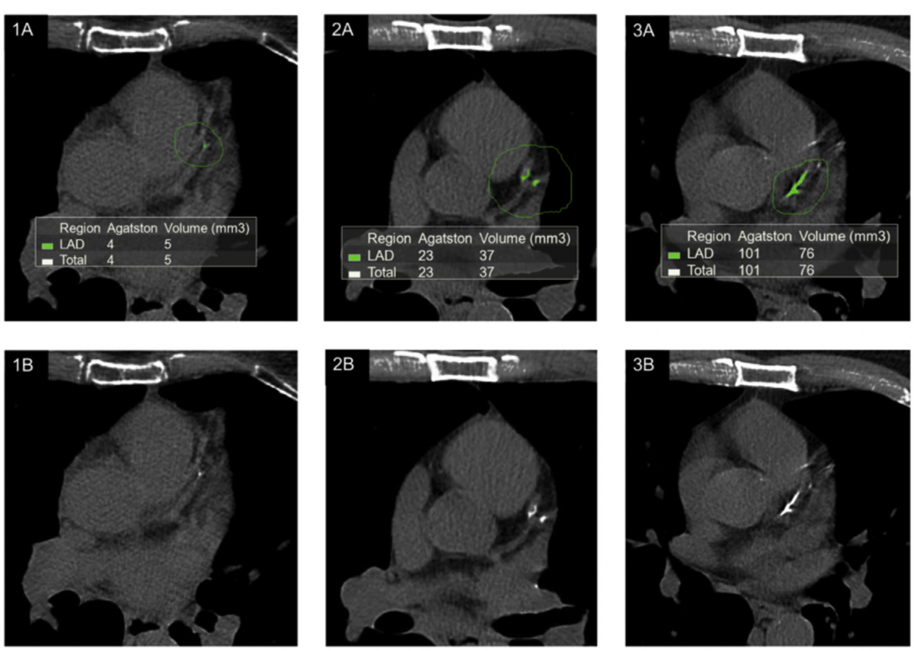
Methods

Patients who underwent coronary angiography as part of their liver transplant workup from 2006 to 2015 at a single academic medical center were retrospectively considered. At the time of OLT evaluation, the decision to proceed with angiography was based on a previously published protocol.[9] Charts were reviewed for coronary interventions performed, including balloon angioplasty, bare-metal stent placement, and drug-eluting stent placement. Additionally, charts were reviewed for periprocedural complications, including access site and bleeding events, myocardial infarction, and stroke. Patients were included if information on both interventions and complications were available. Patients with a history of CAD and revascularization before liver transplant workup were excluded.

Based on a starting point selected by a random number generator, charts were reviewed for the presence of a non−ECG-gated chest CT performed before coronary angiography during the liver transplant workup. Based on the data from ECG-gated CT scans in the ESLD population,[20] it was determined that a sample size of 44 patients would be required to provide 80% power to detect a difference between those with and without obstructive CAD at an α of 0.05. To account for potential dropout from incomplete medical records and/or irretrievable CT images, the minimum target sample size was set at 50 patients.

Using VitreaAdvanced (Vital Images Inc., Minnetonka, Minnesota), CACSs were derived from these non−ECG-gated CT scans (Figure 1). Agatston scores were calculated for the left main, left anterior descending, left circumflex, and right coronary arteries; these scores were subsequently totaled.[11] Absolute scores were then further categorized based on standard cutoffs that have been proved predictive of coronary disease.[24] Agatston scores were also adjusted for age and gender, and patients were classified into percentiles using standard protocols based on data generated from a cohort of over 35,000 patients.[25] Additionally, a Weston score was calculated for each vessel and summed for each patient (Figure 1).[23] Weston scores have been validated against Agatston scores[22] and also account for artifact,[23] which is common in non−ECG-gated studies. CACS results were compared with coronary angiography findings, with significant stenosis considered ≥50% diameter stenosis of at least 1 major coronary artery (Figure 2).

Patients without obstructive coronary disease were compared with those who had obstructive coronary disease on



Mild calcium by Agatston score (1A) and corresponding punctate focus representing a Weston score of 1 (1B); Moderate calcium by Agatston score (2A) and corresponding scattered plaque representing a Weston score of 2 (2B); Severe calcium by Agatston score (3A) and corresponding blooming plaque representing a Weston score of 3 (3B).

Figure 1. Agatston and Weston calcium scores of left anterior descending (LAD) lesions seen on non−ECG-gated chest CT.

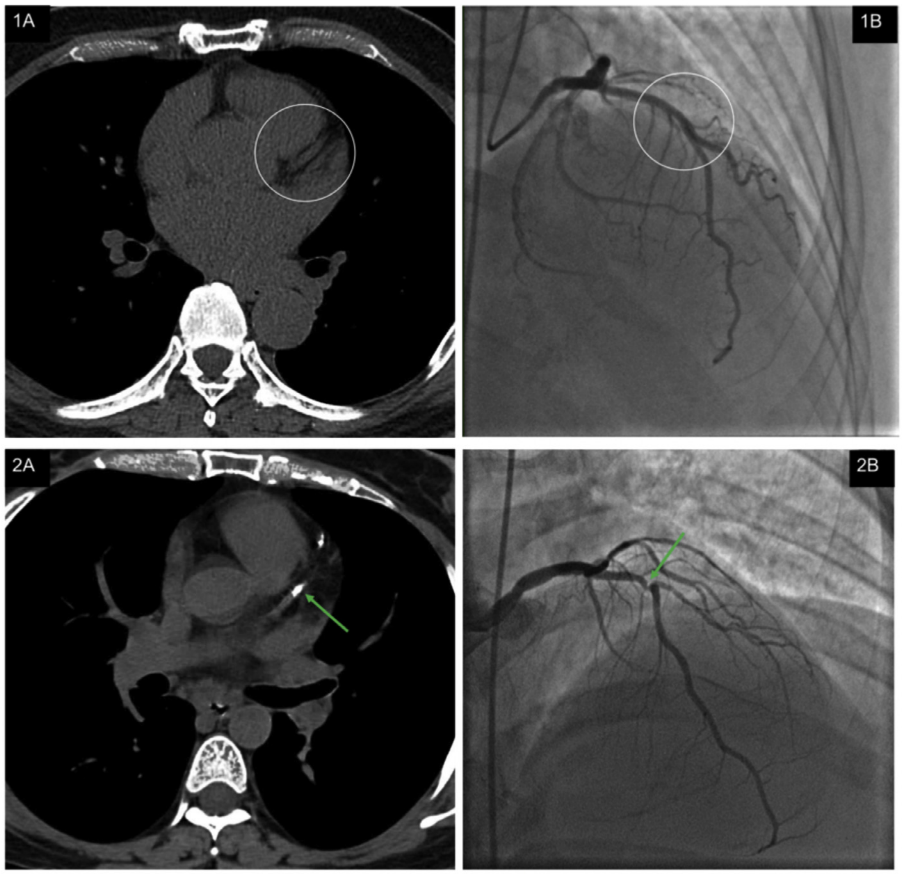


Figure 2. Non−ECG-gated CT coronary calcium versus angiography.

baseline characteristics as well as absolute Agatston scores, Agatston score categories, age-, and gender-adjusted Agatston scores, and Weston scores. The Wilcoxon rank sum test was used for continuous variables and Fisher's exact test was used for categorical variables. Absolute Agatston scores were log transformed due to skewness.

Based on Agatston scores, a receiver-operating characteristic (ROC) curve was derived and sensitivity, specificity, positive predictive value, and negative predictive value were calculated. ROC analysis was also repeated using Weston scores. The area under the curve (AUC) was compared between the Agatston and Weston scores using DeLong et al's test.[26] The Pearson correlation coefficient between Agatston scores and Weston scores was calculated.

Agatston scores were determined by 1 reader (BW) for all patients. Additionally, a randomly selected subset of 20 patients also had Agatston scores independently determined by a second reader (BB), to assess inter-reader reliability. An intraclass correlation coefficient was calculated for these scores. Additionally, a Bland-Altman plot was created to compare readers for these 20 patients and a Tukey mean difference analysis was performed to assess the degree to which the mean differences between measurements differ from zero.

Results

Nine hundred and fifty-three patients who underwent coronary angiography as part of their liver transplant workup from 2006 to 2015 at a single academic medical center were retrospectively considered. Of these 953 patients, 741 (78%) had intervention and complication data available. Seventy of 741 patients (9.4%) had at least 1 coronary intervention performed during their liver transplant workup and 39 of 741 patients (5.3%) had at least 1 complication as a result of catheterization. The majority of these complications were bleeding events, which were seen in 23 patients. Twelve patients had periprocedural myocardial infarctions and 2 patients had periprocedural strokes. Seventeen of the 39 patients who had complications also had interventions performed.

Review of 308 charts yielded 56 patients who had a non−ECG-gated chest CT performed before coronary angiography. Two of the 56 patients had CT images that could not be retrieved and were excluded. Statistical power was

Table 1
Comparison of patients who underwent liver transplant workup

Variable	Obstructive coronary disease		Significance p value
	No (n = 45)	Yes (n = 9)	
Age (years)	64 [59.0, 67.5]	67 [53.5, 72.0]	0.59
Female	21 (47%)	3 (33%)	0.72
Hypertension	32 (71%)	6 (67%)	1.00
Hyperlipidemia	8 (18%)	4 (44%)	0.08
Diabetes mellitus	24 (53%)	5 (56%)	1.00
Smoker	15 (33%)	4 (44%)	0.70
Prior coronary artery disease*	2 (5%)	1 (11%)	0.44
Liver disease etiology:			
Alcohol	7 (16%)	2 (22%)	
Viral hepatitis	26 (58%)	4 (44%)	0.51
Non-alcoholic steatohepatitis	5 (11%)	0 (0%)	
Other	7 (16%)	3 (33%)	
MELD score†	22.4 [9.73, 32.4]	14.1 [7.9, 29.5]	0.35
Creatinine†	1.35 [1.0, 3.1]	1.1 [1.0, 2.5]	0.68
International normalized ratio†	1.55 [1.2, 2.2]	1.4 [1.0, 2.2]	0.53
Platelet count†	50.5 [30.5, 94.5]	84 [46.5, 187]	0.06

Continuous variables were compared with the Wilcoxon rank sum test, median [interquartile range]. Categorical variables were compared with Fisher's exact test, n (%).
* Based on data for n = 52 patients only.
† Based on data for n = 51 patients only.

Table 2
Calcium scores by coronary disease

	Obstructive coronary disease		Significance p value
	No (n = 45)	Yes (n = 9)	
Agatston score	28 [0, 144.5]	311 [144, 1178.5]	0.003
Agatston score positive*	5 (11%)	4 (44%)	0.03
Adjusted Agatston score positive†	10 (22%)	7 (78%)	0.003
Weston score	2 [0, 5.5]	8 [6, 10]	0.0005

Continuous variables were compared with the Wilcoxon rank sum test, median [interquartile range]. Categorical variables were compared with Fisher's exact test, n (%).
* Positive >400.
† Positive ≥75th percentile for age and gender.

Table 3
Agatston score category by coronary disease

Agatston Score category	Obstructive coronary disease		Significance p value
	No (n = 45)	Yes (n = 9)	
0	12	0	0.006*
1-100	18	2	
101-400	10	3	
>400	5	4	

* Comparison through the Wilcoxon rank sum test.

achieved with 54 patients included in the final analysis. The median time between the non−ECG-gated chest CT and coronary angiography was 26.5 days (interquartile range 7 to 58 days). Nine of these 54 patients with non−ECG-gated chest CT studies were found to have obstructive CAD; the other 45 patients did not have obstructive coronary disease.

There were no significant differences in baseline clinical characteristics between patients with and without obstructive coronary disease (Table 1). Specifically, these groups did not differ in regard to age, gender, or cardiovascular risk factors. Three patients had a history of CAD without previous revascularization. There were no significant differences in groups with regard to etiology of liver disease or model for ESLD score. Additionally, there were no significant differences between groups in baseline INR or platelet counts.

Absolute Agatston scores were significantly higher in the group with obstructive coronary disease compared with those without obstructive disease, 311 (144, 1178.5) versus 28 (0, 144.5); p = 0.003 (Table 2). Using a standard cutoff of 400,[24] patients with obstructive coronary disease were more likely to test positive compared with those without obstructive disease (44% vs 11%; p = 0.03; Table 2). Similar results were found for adjusted Agatston scores using a standard cutoff of ≥75th percentile (Table 2).[27] Weston scores were also significantly higher in the group with obstructive coronary disease compared with those without obstructive disease, 8 (6, 10) versus 2 (0, 5.5; Table 2). Based on standardized categories, Agatston scores were significantly higher in patients with obstructive coronary disease compared with those without obstructive disease, p = 0.006 (Table 3).

ROC analysis demonstrated that an Agatston score of 251 maximized sensitivity and specificity for detection of obstructive coronary disease (Figure 3); using this threshold, sensitivity and specificity were 78% and 87%, respectively. The positive predictive value and negative predictive value were 54% and 95%, respectively. Only 2 patients (3.7%) with a negative test based on Agatston score

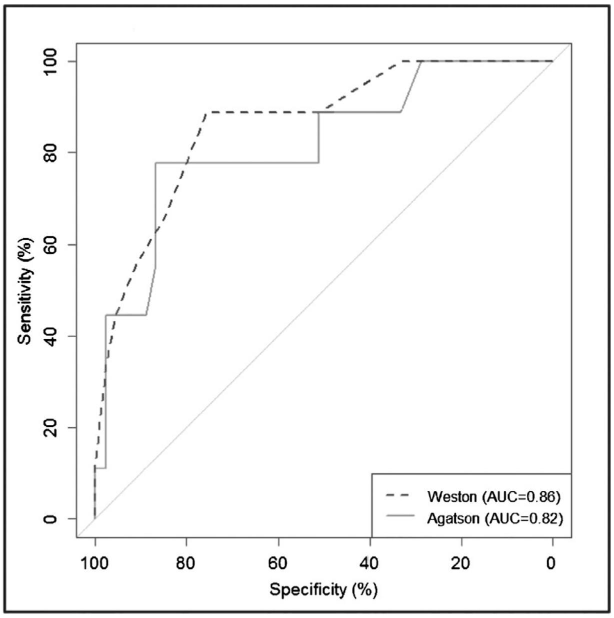


Figure 3. ROC analysis for obstructive coronary disease.

<251 had obstructive coronary disease. Additional ROC analysis demonstrated that an Agatston score of 4 provided 100% sensitivity and a 100% negative predictive value; using this threshold, 13 patients (24%) could have avoided catheterization without missing any obstructive coronary disease.

ROC analysis demonstrated that a Weston score of 6 maximized sensitivity and specificity for detection of obstructive coronary disease (Figure 3); using this threshold, sensitivity and specificity were 89% and 76%, respectively. The positive predictive value and negative predictive value were 42% and 97%, respectively. Only 1 patient (1.9%) with a negative test based on Weston score <6 had obstructive coronary disease. Additional ROC analysis demonstrated that a Weston score of 2 provided 100% sensitivity and a 100% negative predictive value; using this threshold, 15 patients (28%) could have avoided catheterization without missing any obstructive coronary disease.

ROC analysis showed the AUC for the Agatston score was 0.82 (95% confidence interval 0.66 to 0.98) and the AUC for the Weston score was 0.86 (95% confidence interval 0.74 to 0.99; Figure 3); this difference was not statistically significant (p = 0.256). It should be noted that the Weston score did have a slightly higher AUC compared with the Agatston score, suggesting a trend toward better performance in identifying obstructive coronary disease in this population.

There was a strong, positive correlation between Agatston scores and Weston scores for all patients (r = 0.93; Figure 4). There was a positive correlation for Agatston scores between both readers (intraclass correlation coefficient = 0.98). Additionally, by Bland-Altman analysis, there was no significant difference between readers in terms of Agatston scores (p = 0.38).

Discussion

This study demonstrated the predictive value of incidental coronary artery calcium discovered on non−ECG-gated CT in patients who underwent preoperative evaluation for liver transplant. It also demonstrated that Agatston scores can be applied to non−ECG-gated studies in this population. Additionally, this study showed that Weston scores approximated Agatston scores in predicting obstructive coronary disease. Our results suggest that coronary calcium scoring may be an important addition to the risk stratification of liver transplant candidates.

The most recent recommendations from the American Heart Association and the American College of Cardiology Foundation suggest noninvasive stress testing based on cardiovascular risk factor assessment for patients without active cardiac disease.[4] However, guidelines from the American Association for the Study of Liver Diseases and the American Society of Transplantation recommend noninvasive cardiac testing for all adults who underwent liver transplant workup.[5] Alternatively, many cardiologists advocate for invasive angiography in patients with more than 2 cardiac risk factors before listing for OLT.[6]

Data on cardiac catheterization in ESLD patients raise concerns about safety. Studies have demonstrated higher

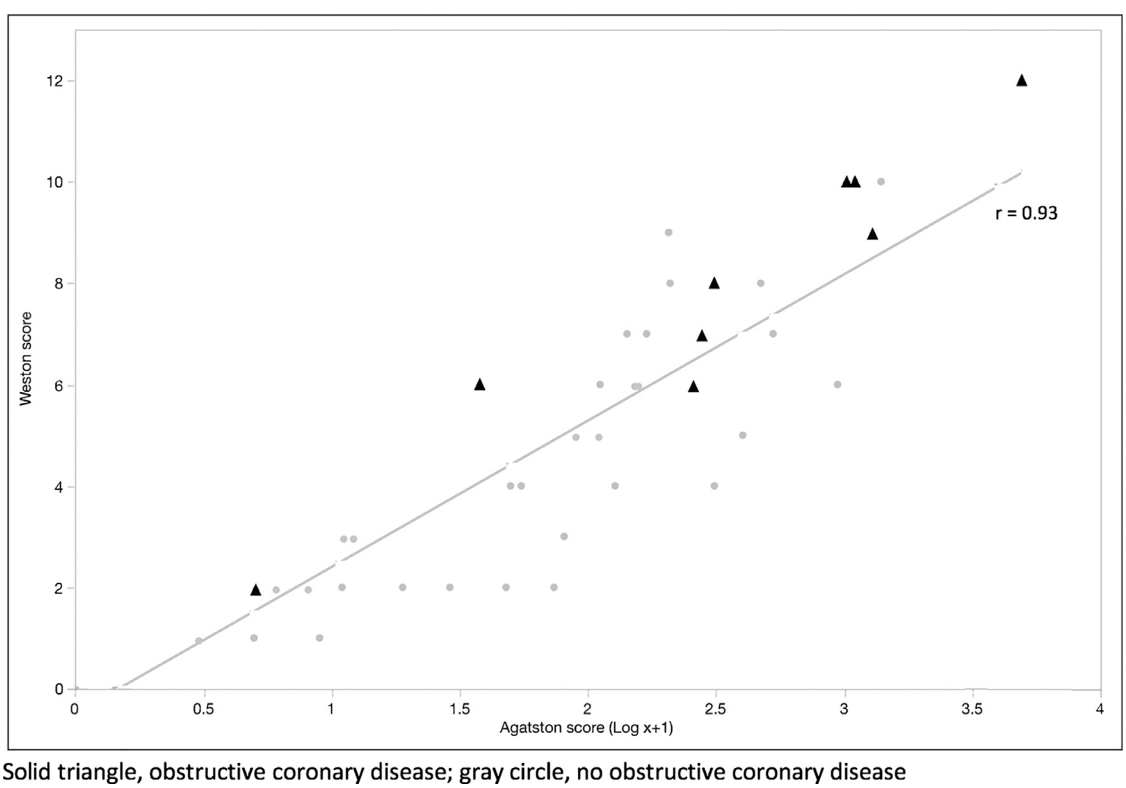


Figure 4. Agatston score versus Weston score.

rates of complications, such as major bleeding and pseudoaneurysm formation, in patients with liver failure compared with control patients who underwent left heart catheterization.[8] Additionally, the interventional cardiology community recommends the use of special considerations in these patients, such as prophylactic platelet and/or fresh frozen plasma transfusions as well as smaller vascular sheaths.[7]

In our subgroup of 741 patients with catheterization outcomes data, 22 of 671 (3.3%) who underwent diagnostic angiography and 17 of 70 (24.3%) who had interventions performed experienced complications. These figures are higher than average for all patients who undergo diagnostic and interventional cardiac catheterization, respectively.[28,29] Although the majority of the complications seen in our population were bleeding events (59% of patient complications), which may be regarded as relatively benign, treatment can be complex in liver transplant candidates due to underlying thrombocytopenia and coagulopathy.

To avoid potential complications, liver transplant teams have turned to pharmacologic stress testing in OLT candidates. In 1 study of 389 patients who underwent preoperative evaluation before OLT, dobutamine stress echocardiogram (DSE), and single photon emission computed tomography (SPECT) had sensitivities of 9% and 57%, respectively, for perioperative cardiac events.[2] Similar results were seen in a larger (n = 473) study, which focused on the use of SPECT imaging in the preliver transplant evaluation: we demonstrated a sensitivity of only 62% for adenosine and 35% for regadenoson SPECT, in diagnosing severe CAD and concluded that SPECT was a poor screening test in the pre-OLT population.[9]

Two studies have demonstrated relations between ECG-gated CT scans and cardiac catheterization findings in OLT candidates.[19,20] These studies used only Agatston scores to evaluate patients and were limited in terms of sample size. Data from coronary CT angiography have shown a prognostic value similar to DSE and carry the additional risk of contrast dye.[10] In addition, CT angiography needs to be gated and can be difficult to obtain in ESLD patients who are often tachycardic. The ability to use non−ECG-gated CT exams would facilitate obtaining important noninvasive information about CAD in the ESLD population.

Our data confirm the strength of calcium scoring in ruling out coronary disease in patients being evaluated for OLT. By lowering the threshold for considering a patient to be positive to an Agatston score of 4 or a Weston score of 2, we predicted nonobstructive coronary disease with 100% certainty in our population. This would have prevented 13 (24%) or 15 (28%) catheterizations, based on Agatston or Weston scores, respectively. Using this calcium screen threshold could thereby prevent complications from invasive angiography.

Many liver transplant candidates undergo nongated, noncontrast chest CT during their workup. We found that 56 of the 308 patients (18.1%) randomly reviewed for this study had a nongated chest CT ordered within 6 months of angiography. The most common reason for this was staging for hepatocellular carcinoma (HCC). However, other reasons included history of obstructive or parenchymal pulmonary disease, screening for lung cancer, concern for pulmonary infection, evaluation for pulmonary hypertension, or arteriovenous shunt, and to follow up abnormalities on chest x-ray or pulmonary function testing. A limitation of this study includes the potential bias regarding CAD risk introduced by the subgroup of transplant candidates who underwent chest CT. Limited data suggest similar rates of mild-to-moderate CAD and preoperative revascularization in liver transplant candidates with HCC versus those without HCC.[30]

Other limitations of this study include its retrospective nature and the biases inherent in this design. The associations we found are only hypothesis generating and suggest a need for randomized, prospective studies in the future. Additionally, this study was relatively limited in terms of sample size analyzed due to the retrospective nature of the design and frequency with which nongated CT was performed during the precatheterization time interval. Fortunately, the sample size obtained did fulfill our power requirement and demonstrated a significant difference in coronary calcium between ESLD patients with and without obstructive CAD.

Another specific limitation involves the interpretation of nongated CT using criteria designed for gated studies. The chest imaging obtained in this study was for noncardiac purposes and not part of a protocol for cardiac risk stratification, and thus it is difficult to estimate the true prevalence of coronary calcification in OLT candidates. Moreover, many of the images did contain motion artifact, which can falsely elevate the Agatston score. A strength of this study was also including the semiquantitative Weston score, which is less subject to motion artifact; this may be 1 of the reasons that the Weston score outperformed the Agatston score in our study. Additional data are needed comparing these scores in non−ECG-gated studies.

Future studies should evaluate whether the addition of a calcium score impacts the preoperative evaluation of liver transplant candidates. The Agatston and Weston score cutoffs established in this study can be used to prospectively risk stratify patients for angiography. Ultimately, calcium scoring may be integrated into preoperative algorithms to rule out obstructive disease and help to avoid invasive angiography in this high-risk population.

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