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CAD-LT score effectively predicts risk of significant coronary artery disease in liver transplant candidates

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Background & Aims: Patients with cirrhosis and significant coronary artery disease (CAD) are at risk of peri-liver transplantation (LT) cardiac events. The coronary artery disease in liver transplantation (CAD-LT) score and algorithm aim to predict the risk of significant CAD in LT candidates and guide pre-LT cardiac evaluation.

Methods: Patients who underwent pre-LT evaluation at Indiana University (2010-2019) were studied retrospectively. Stress echocardiography (SE) and cardiac catheterization (CATH) reports were reviewed. CATH was performed for predefined CAD risk factors, irrespective of normal SE. Significant CAD was defined as CAD requiring percutaneous or surgical intervention. A multivariate regression model was constructed to assess risk factors. Receiver-operating curve analysis was used to compute a point-based risk score and a stratified testing algorithm.

Results: A total of 1,771 pre-LT patients underwent cardiac evaluation, including results from 1,634 SE and 1,266 CATH assessments. Risk-adjusted predictors of significant CAD at CATH were older age (adjusted odds ratio 1.05; 95% CI 1.03–1.08), male sex (1.69; 1.16–2.50), diabetes (1.57; 1.12–2.22), hypertension (1.61; 1.14–2.28), tobacco use (pack years) (1.01; 1.00–1.02), family history of CAD (1.63; 1.16–2.28), and personal history of CAD (6.55; 4.33–9.90). The CAD-LT score stratified significant CAD risk as low (≤2%), intermediate (3% to 9%), and high (≥10%). Among patients who underwent CATH, a risk-based testing algorithm (low: no testing; intermediate: non-invasive testing *vs.* CATH; high: CATH) would have identified 97% of all significant CAD and potentially avoided unnecessary testing (669 SE [57%] and 561 CATH [44%]).

Conclusions: The CAD-LT score and algorithm (available at www.cad-lt.com) effectively stratify pre-LT risk for significant CAD. This may guide more targeted testing of candidates with fewer tests and faster time to waitlist.

Lay summary: The coronary artery disease in liver transplantation (CAD-LT) score and algorithm effectively stratify patients based on their risk of significant coronary artery disease. The CAD-LT algorithm can be used to guide a more targeted cardiac evaluation prior to liver transplantation.

Introduction

Preoperative cardiac evaluation in liver transplantation (LT) is conducted to risk-stratify LT candidates and to exclude those deemed to be at high risk of postsurgical complications.[1,2] Patients who have significant coronary artery disease (CAD) are more likely to experience post-LT cardiac events.[3,4] Currently, there are no concrete guidelines for preoperative cardiac evaluation in LT candidates, and clinical practice is mostly dictated by center-specific protocols.[5–8]

Previous studies from Indiana University demonstrated that the sensitivity of stress echocardiography (SE) as a non-invasive modality for detecting significant CAD was low (37%), and that using risk factor-based cardiac catheterization (CATH) regardless of SE results was associated with a lower rate of post-LT myocardial infarction and mortality.[9,10] Moreover, similar overall mortality was observed between patients with revascularized CAD and those with non-obstructive CAD, indicating that revascularized patients had a non-prohibitive risk for surgery.[9]

There is currently no risk assessment tool to estimate the probability of significant CAD in LT candidates. The present study was designed to develop an algorithm for pre-LT cardiac evaluation. Available data included clinical, stress testing, and angiographic characteristics for all patients undergoing LT evaluation at a high-volume center. These data were then analyzed to derive independent predictors of abnormal SE results and the presence

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of significant CAD on CATH. Lastly, the identified predictors were employed in a model to develop the coronary artery disease in liver transplantation (CAD-LT) score, a clinical tool to guide the pre-LT evaluation process, on which the algorithm is based.

Patients and methods

The study population consisted of all patients who underwent LT preoperative evaluation by a single cardiologist at Indiana University from 2010 through 2019. Patients referred for multiorgan transplant and liver re-transplantation were excluded. Data were collected retrospectively with a detailed individual chart review. Extracted data included patient clinical demographics, etiology of cirrhosis, cardiac risk factors, model for end-stage liver disease (MELD) score, SE results, and CATH results. A certain percentage of patients did not proceed to LT during the study period (non-LT group). The status of these patients was documented and is presented in the results.

The risk factor-based protocol for use of CATH at this center has been described previously.[9,10] Briefly, CATH was performed at the discretion of a single interventional cardiologist and was based on the presence of a combination of predefined CAD risk factors (age >60 years, tobacco use >10 pack years, diabetes, hypertension requiring medications, personal history of CAD, family history of CAD, and obesity [body mass index >30 kg/m^2]). Personal history of CAD was defined as previous percutaneous coronary intervention, coronary artery bypass grafting, or myocardial infarction. Similarly, a family history of CAD was defined as the occurrence of the aforementioned CAD in any first-degree family member.

The primary outcomes for this study were i) abnormal SE, ii) any CAD, and iii) clinically significant CAD. A clinically significant (positive) SE was defined as the presence of chest pain, S-T segment depression (horizontal or downsloping, ≥1 mm at least 60–80 ms after J point), or presence of new or worsening regional wall motion abnormality during SE. All patients were instructed to stop beta-blockers before stress testing. SE was considered diagnostic only if the patient achieved at least 85% of age-predicted maximal heart rate. “Any CAD” on preoperative CATH was defined as having luminal irregularities, non-obstructive CAD, and obstructive (*i.e.* significant) CAD. Significant CAD was defined as 50% or higher stenosis in a major vessel or 70% or higher stenosis in at least a moderate-sized branch vessel warranting percutaneous or surgical intervention.

Statistical analysis

Overall patient demographics and clinical characteristics were assessed and reported, as well as results of invasive and non-invasive testing. Bivariate comparison of these characteristics and results was then conducted to better understand the patients in this cohort that did or did not undergo LT. Though this comparison was not a primary endpoint for the study, this subgroup analysis provides clinical context for those patients that did not progress to LT, and allows the reader to review factors that potentially impeded progression to transplant.

The median (interquartile range) for continuous variables and frequency and percentages for categorical variables were used to describe the patient cohort. The chi-square test was used for categorical variables, with Fisher's exact test being used for those categorical variables with expected cell count less than five. Shapiro-Wilk normality test was used to examine the normality assumption of continuous variables and the Wilcoxon rank-sum test was used for the analysis of continuous variables that deviated from normality. Three subsequent multivariable logistic regression models were constructed to estimate the adjusted odds ratio (aOR, 95% CI) of an abnormal SE result, any CAD, and significant CAD. The variables used in the multivariable model were selected based on published literature regarding risk factors of significant CAD, clinical experience, and a p value <0.10 from bivariate analysis of significant CAD and potential factors. Multicollinearity of the factors used in the multivariable models was evaluated using variance inflation factor. The predictive ability of each multivariable model was evaluated using receiver-operating characteristics analysis. The area under the curve was computed to quantify the model performance demonstrating optimal sensitivity and specificity for predicting the outcome variables. A 10-fold internal cross-validation was performed for each model to examine the cross-validated area under the curve after predictive modeling. The dataset was randomly divided into 10 subsets, with each subset serving as the testing set for the remaining 9 subsets pooled together (training set).[11–13] A point-based risk stratification approach was used to quantify the impact of the risk factors in the multivariable model by generating the CAD-LT risk score in order to estimate the risk of significant CAD in LT candidates.[14] Multivariate analyses to identify objective risk factors of significant CAD were only performed in patients who underwent CATH. In this method, (1) we first estimated the parameters (β_i) for each variable (i) in the multivariable model; (2) then we organized the risk factors in the model to determine the reference values (W_{ij}) for each category (j) of the variable; (3) then we indicated a referent risk factor profile (W_{iREF}) as the base category that receives a point of 0 (least risk category); (4) then we computed the distance of each remaining category from the base category in terms of regression units $A = (\beta_i * (W_{ij} - W_{iREF}))$; (5) then we set a constant such that it reflects an increase in risk associated with 5-year increase in age by using $B = 5 * \beta_{age}$; (6) finally, points for each category of the risk factor were computed using A/B and rounding-up to 0 decimal places.[14] Based on empirical evidence and clinical experience, groups were then defined by a probability of 0.10 or higher (high-risk group, 10% risk or greater) and 0.02 or lower (low-risk group, 2% risk or less), while those patients between these values were considered intermediate-risk. Finally, a pre-LT cardiac testing algorithm was constructed, as informed by risk stratification using the CAD-LT score.

Data for this study were collected and maintained using strict data security protocols to protect patient health information. Retrospective use of previously collected clinical data from transplant patients has been approved by the Indiana University institutional review board and informed consent was waived due to the retrospective nature of the study. Data analysis was performed using Stata/MP 16.1 (StataCorp LLC, College Station, TX, USA). Patients and donors in this study were strictly managed in accordance with the Declaration of Istanbul.

Results

Clinical characteristics of the study population

A total of 1,771 patients underwent pre-LT cardiac evaluation during the study period (2010–2019). Of these, 924 proceeded to LT (52%) while 847 did not (48%). Patients' demographic and clinical characteristics are summarized in Table 1. The mean age was 56 ± 10 years, the median (interquartile range) body mass index was 28.4 (24.6–32.9) kg/m^2, 64% were men and 89% were

Table 1. Univariate and bivariate analysis of 1,771 liver transplant candidates, with a comparison of patients who did or did not undergo liver transplantation.

Clinical characteristics	Overall (%)	Liver transplantation	No liver transplantation	*p* value[Δ]
Number	1,771 (100%)	924 (52%)	847 (48%)	
Age (years)	56 (9.9)	55.1(10.3)	57.1 (9.4)	0.0004**
Less than 30	49 (3%)	36 (4%)	13 (2%)	<0.001
30 to 39	80 (4%)	50 (5%)	30 (3%)	
40 to 49	249 (14%)	136 (15%)	113 (13%)	
50 to 59	762 (43%)	407 (44%)	355 (42%)	
60 and older	631 (36%)	295 (32%)	336 (40%)	
Gender				<0.001
Male	1,128 (64%)	625 (68%)	503 (60%)	
Female	643 (36%)	299 (32%)	344 (40%)	
Race				0.02
White	1,576 (89%)	829 (90%)	747 (88%)	
Black	139 (8%)	58 (6%)	80 (9%)	
Other	56 (3%)	37 (4%)	20 (3%)	
Body mass index*	28.4 (24.6-32.9)	28.4 (24.8-32.5)	28.5 (24.5-33.6)	0.370**
Less than 25.0	480 (28%)	249 (27%)	231 (29%)	<0.001
25.0 to 29.9	541 (32%)	296 (33%)	245 (30%)	
30.0 to 34.9	414 (24%)	245 (27%)	169 (21%)	
35.0 and higher	280 (16%)	115 (13%)	165 (20%)	
Etiology of liver disease***				
Hepatitis C	653 (37%)	317 (34%)	336 (40%)	0.02
Alcoholic liver disease	501 (28%)	227 (25%)	274 (32%)	<0.001
Non-alcoholic fatty liver disease	405 (23%)	203 (22%)	202 (24%)	0.35
Primary sclerosing cholangitis	132 (7%)	90 (10%)	42 (5%)	<0.001
Autoimmune	59 (3%)	39 (4%)	20 (2%)	0.03
Primary biliary cirrhosis	57 (3%)	37 (4%)	20 (2%)	0.05
Cryptogenic	50 (3%)	24 (3%)	26 (3%)	0.55
Other	130 (7%)	81 (9%)	49 (6%)	0.02
MELD score*	14 (10-19)	14 (10-18)	14 (11-19)	>0.999
Cardiac risk factors				
Diabetes mellitus				0.004
No	1,179 (67%)	644 (70%)	535 (63%)	
Yes	592 (33%)	280 (30%)	312 (37%)	
Hypertension				0.77
No	1,104 (62%)	573 (62%)	531 (63%)	
Yes	667 (38%)	351 (38%)	316 (37%)	
Tobacco				<0.001
Never	775 (44%)	466 (50%)	309 (36%)	
Current (at evaluation)	426 (24%)	146 (16%)	280 (33%)	
Former	570 (32%)	312 (34%)	258 (30%)	
Tobacco pack years				<0.001
0 to 20	1,262 (71%)	720 (78%)	542 (64%)	
21 to 40	311 (18%)	144 (16%)	167 (20%)	
>40	198 (11%)	60 (6%)	138 (16%)	
Patient history of coronary artery disease				
No	1,616 (91%)	870 (94%)	746 (88%)	
Yes	155 (9%)	54 (6%)	101 (12%)	
Family history of coronary artery disease				
None	1,108 (63%)	588 (64%)	520 (61%)	
Immediate family (any)	663 (37%)	336 (36%)	327 (39%)	

MELD, model for end-stage liver disease.
[Δ]Calculated using chi-square and Fisher's exact tests for categorical variables and Shapiro-Wilk normality and Wilcoxon rank-sum tests for continuous variables.
*Median (interquartile range).
**Wilcoxon rank-sum tests/test of difference between Medians.
***Many patients had more than one disease process simultaneously.

identified as white. Regarding cardiac risk factors, 33% were diabetic, 38% were hypertensive, 56% were current or former smokers, 9% had a personal history of CAD and 37% had an immediate family history of CAD. The most common etiologies for cirrhosis were hepatitis C (37%), followed by alcohol-related liver disease (28%) and non-alcoholic liver disease (23%). The median (interquartile range) MELD score was 14 (10-19).

When compared to the non-LT group, LT patients were slightly younger (55 *vs.* 57 years, p <0.001), more likely to be men (68% *vs.* 60%, p <0.001), less likely to be diabetic (30% *vs.* 37%, p = 0.002), or to have any history of smoking (50% *vs.* 63%, p <0.001) or personal history of CAD (6% *vs.* 12%, p <0.001). There was a larger proportion of patients with body mass index ≥35 kg/m^2 in the non-LT group (13% *vs.* 20%, p <0.001). Non-LT patients were also more likely to have alcohol-related liver disease (25% *vs.* 32%, p <0.001). There was no significant difference in the MELD score or in the prevalence of hypertension or family history of CAD between both groups.

A summary of patients who did not progress to transplant (non-LT group) during the study period is presented in Table S1. A total of 189 patients (22%) died during the evaluation period prior to receiving LT, and 182 (21%) were lost to follow-up. There were 117 patients (14%) who were either on the waitlist for LT or were still undergoing LT evaluation during the study period. The most common reasons for which patients were not listed for LT were low MELD score (13%), cardiopulmonary comorbidities (6%), ongoing substance abuse (5%), and hepatocellular carcinoma not meeting Milan criteria (4%).

SE and CATH results

SE and CATH results are summarized in Table 2. A total of 1,634 patients (92%) underwent stress testing, with SE being the non-invasive modality of choice. There was no difference in the proportion of LT and non-LT patients who had SE (93% *vs.* 91%, $p = 0.13$). Of these 1,634 patients, 74% had a normal SE, 10% had non-diagnostic SE and 8% had a positive SE. Non-invasive stress testing results were significantly associated with LT status ($p = 0.003$). In a *post hoc* comparison, non-LT patients were more likely to have abnormal SE results compared to LT patients (9% *vs.* 7%, $p = 0.11$). Compared to LT, the non-LT patients also had a higher proportion of non-diagnostic SE (12% *vs.* 8%) and the *post hoc* comparison showed that there was a significant difference in normal *vs.* non-diagnostic or equivocal SE result between LT and non-LT groups ($p = 0.004$).

A total of 1,266 patients (71%) underwent CATH. A significantly larger proportion of patients in the non-LT group underwent CATH (74% *vs.* 69%, $p = 0.02$). Of these 1,266 patients, 56% were found to have no disease, 28% had non-obstructive CAD, and 16% had significant CAD. CATH results were significantly associated with LT status ($p < 0.001$). More specifically, in a *post hoc* comparison, patients who underwent LT were more likely to have normal results on CATH (59% *vs.* 53%, $p = 0.23$), while those who did not undergo LT were significantly more likely to have significant CAD (9% *vs.* 19%, $p < 0.001$). Characteristics of LT and non-LT patients stratified based on the presence of significant and non-significant CAD are shown in Table S2.

As previously mentioned, the decision to proceed with CATH was at the discretion of a single interventional cardiologist and was based on the presence of a combination of risk factors upon evaluation. The retrospective analysis of data effectively showed that the major risk factors were age >60, personal history of CAD and diabetes, while the minor risk factors were body mass index >30 kg/m^2, family history of CAD, hypertension, and tobacco use >10 pack years. This was based on the percent of patients who had CATH with presence of a sole risk factor as follows: personal history of CAD (100%), age >60 (86%), diabetes (83%), tobacco use >10 pack years (33%), hypertension (27%), body mass index >30 kg/m^2 (20%), and family history of CAD (18%). Overall, patients who underwent CATH had an average of 2.8 risk factors while those who did not had an average of 1.4 risk factors.

The sensitivity and specificity of SE in detecting significant CAD were similar in both the overall and the intermediate-risk populations (29% and 89%, respectively). These results show a similar specificity (89%) to that previously reported in a cohort consisting solely of patients who underwent LT.[9] The sensitivity, on the other hand, was lower in the current total cohort than in the LT cohort from the previous study (29% *vs.* 37%).

Predictors of abnormal SE and CATH results

The predictors of abnormal SE results, any CAD on CATH, and significant CAD on CATH on multivariable analysis are presented in Tables 3, 4, and 5. Only patients with diabetes ($p < 0.01$) and those with a personal history of CAD ($p < 0.001$) had higher odds of an abnormal SE (Table 3). Significant predictors for both any CAD and significant CAD were similar and included older age, male sex, diabetes, hypertension, tobacco use (pack years), family history of CAD, and personal history of CAD (Tables 4 and 5). More specifically, for each 1-year increase in patient age, the odds of having any CAD or odds of having significant CAD increases by 1.07 or 1.06 times, respectively. However, to put this into perspective, if age is increased by 10 years, for example, the odds of having any CAD, or of having significant CAD, doubles ($p < 0.001$). Females in this cohort had lower odds of any CAD or of significant CAD compared to males.

The CAD-LT score

The CAD-LT score is presented in Table 6. The odds for each predictor from the regression model were equated to a number of points. The points for each factor were then added (or subtracted) to achieve an overall CAD-LT score. The scored risk

Table 2. Summary of pre-liver transplant cardiac testing, with a comparison of patients who did or did not undergo liver transplantation.

Pre-liver transplant cardiac testing	Number (%)	Liver transplantation	No Liver transplantation	*p* value[Δ]
Number (%)	1,771 (100%)	924 (52%)	847 (48%)	
Stress echocardiography	1634/1,771 (92%)	861/924 (93%)	773/847 (91%)	0.13
Normal	1,315 (74%)	717 (83%)	598 (77%)	0.003
Wall motion abnormalities	98 (5%)	39 (4%)	59 (8%)	
EKG changes without wall motion abnormalities	49 (3%)	31 (4%)	18 (2%)	
Non-diagnostic or equivocal	172 (10%)	74 (9%)	98 (13%)	
Cardiac catheterization	1,266/1,771 (71%)	639/924 (69%)	627/847 (74%)	0.023
No CAD (normal coronary arteries)	708 (56%)	377 (59%)	331 (53%)	<0.001
Non-obstructive CAD	355 (28%)	205 (32%)	150 (24%)	
Obstructive CAD requiring intervention	176 (14%)	57 (9%)	119 (19%)	
Significant CAD not amenable for revascularization	19 (1%)	0 (0%)	19 (3%)	
Significant CAD not revascularized due to loss to follow-up for staged intervention or per interventionalist's discretion	8 (1%)	0 (0%)	8 (1%)	

CAD, coronary artery disease.
[Δ]Calculated using chi-square and Fisher's exact tests.

Table 3. Multivariable analysis to estimate the odds of abnormal stress echocardiography result.

Variables	Odds ratio [95% CI]	*p* value[Δ]
Age (per year)	1.01 [0.99–1.02]	0.400
Male	1.11 [0.85–1.44]	0.454
Diabetes	1.42 [1.09–1.86]	0.010
Hypertension	1.05 [0.80–1.37]	0.698
Tobacco use (pack years)	0.99 [0.98–1.00]	0.122
Family history of coronary artery disease	1.04 [0.81–1.35]	0.572
Personal history of coronary artery disease	2.65 [1.79–3.93]	<0.001

[Δ]Calculated using multivariable logistic regression.

categories were divided into low (-2 to 3), intermediate (4-8), and high (9-25). The low-risk group had a 2% or less chance of having significant CAD, the intermediate-risk group had a risk between 3% and 9%, while the high-risk group had 10% or greater risk of significant CAD. The low-risk group was purposely placed at a very low threshold (2%) to minimize the risk of a missed diagnosis of significant CAD in a patient going for LT. The mean cross-validation area under the curve was 0.76 (95% CI 0.72–0.80]. Using the final model obtained, the computed optimal sensitivity and specificity for predicting the outcome variables were 21% and 96%, respectively. A web-based calculator for the CAD-LT score is available (www.cad-lt.com).

Algorithm for the use of the CAD-LT score

An algorithm for the use of the CAD-LT score in clinical practice is presented in Fig. 1. In this algorithm, all patients with liver disease presenting for cardiac evaluation will undergo a medical review to calculate their CAD-LT score. Patients with a score ≥9 (high-risk category) proceed directly to CATH. Using the cut-off of ≥9 indicated that 90% of patients with significant CAD are stratified into the high-risk group. Patients with a score ≤3 (low-risk category) need no further CAD evaluation prior to listing for LT (no individuals in this group were found to have significant CAD). Patients in the intermediate-risk category (score 4 to 8) undergo non-invasive testing. If the test for the intermediate-risk patient shows high probability for significant CAD, they proceed to CATH for definitive diagnosis. Intermediate-risk patients with a low probability of significant CAD on non-invasive testing are further stratified into low-intermediate (4-6) and high-intermediate-risk (7-8). Those in the low-intermediate-risk group require no additional work-up for CAD (miss rate for significant CAD of <1%). On the other hand, in patients with high-intermediate-risk, further work-up (*i.e.* alternative non-invasive testing modality *vs.* CATH) can be considered depending on the evaluating physician's clinical discretion and risk tolerance (miss rate for significant CAD of 4%). Applying this testing algorithm retrospectively to patients who underwent CATH (n = 1,266) would have detected 97% of patients with significant CAD and would have potentially decreased the number of CATH by 561 (44%; non-high-risk patients who would not be recommended for CATH as an initial test) and the number of SE in this subset (n = 1,174) by 669 (57%; 665 in the high-risk group and 13 in the low-risk group). This result translates into marked cost savings.

Discussion

The present paper presents a landmark study for the thousands of LT candidates who undergo cardiac testing annually. Clinicians, guided by the CAD-LT algorithm generated from this study, will provide a more precise assessment of cardiac risk while potentially saving the health system the costs and risks of unnecessary stress testing and CATH.

The principal findings of this study are:

1) Predictors of significant CAD in LT candidates included older age, male sex, diabetes, hypertension, tobacco use (pack years), family history of CAD, and personal history of CAD.
2) The CAD-LT score is an easy-to-use clinical tool that may be employed in an office-based setting to predict the risk of significant CAD in LT candidates based on easily defined clinical risk factors.
3) The CAD-LT algorithm based on the CAD-LT score guides cardiac evaluation, and detects significant CAD with high sensitivity (97%), thus markedly decreasing unnecessary stress testing and CATH.

The CAD-LT algorithm provides a cost-effective approach to preoperative cardiac evaluation for LT, while retaining a high sensitivity for the detection of significant CAD. The use of the CAD-LT algorithm is predicted to markedly decrease the number of stress tests and CATH required for this population, while improving patient care. End-stage liver disease is a terminal condition, with the only definitive treatment being LT. This algorithm streamlines the cardiac evaluation, enabling these critically ill patients to proceed more quickly to the transplant list. Exclusion of unnecessary tests provides not only systemic cost savings but also minimizes the individual risk of complications and of false-positive and false-negative test results. With a significant percentage of these liver failure patients no longer

Table 4. Multivariable analysis to estimate the odds of any coronary artery disease.

Variables	Odds ratio [95% CI]	*p* value[Δ]
Age (per year)	1.07 [1.05–1.09]	<0.001
Male	1.79 [1.39–2.38]	<0.001
Diabetes	1.48 [1.14–1.91]	0.002
Hypertension	1.40 [1.08–1.81]	0.009
Tobacco use (pack years)	1.01 [1.00–1.02]	0.028
Family history of coronary artery disease	1.56 [1.21–2.00]	0.001
Personal history of coronary artery disease	8.56 [5.12–14.30]	<0.001

[Δ]Calculated using multivariable logistic regression.

Table 5. Multivariable analysis to estimate the odds of significant coronary artery disease.

Variables	Odds ratio [95% CI]	*p* value[Δ]
Age (per year)	1.05 [1.03–1.08]	<0.001
Male	1.69 [1.16–2.50]	<0.001
Diabetes	1.57 [1.12–2.22]	0.009
Hypertension	1.61 [1.14–2.28]	0.007
Tobacco use (pack years)	1.01 [1.00–1.02]	0.012
Family history of coronary artery disease	1.63 [1.16–2.28]	0.001
Personal history of coronary artery disease	6.55 [4.33–9.90]	<0.001

[Δ]Calculated using multivariable logistic regression.

requiring stress testing and CATH, the wait time to obtain these procedures will be lessened for all. The 2 groups benefiting the most from the CAD-LT algorithm are those in the high- and low-risk groups. The high-risk patients now proceed directly to CATH. This shortens the time needed to obtain a test that will ultimately be required prior to listing for transplant. Similarly, low-risk patients can move directly to LT listing without any further testing, also saving time and money. Patients in the intermediate-risk group would require non-invasive testing *vs.* CATH to further stratify their risk according to the proposed algorithm. In our experience, SE as the non-invasive modality of choice had low sensitivity and high specificity for detecting significant CAD. In the present study, the sensitivity and specificity of SE in detecting significant CAD were 29% and 89%, respectively. A previous study of LT recipients from our center has reported the sensitivity of SE to be 37% with a specificity of 89%.[9] Hence, a positive SE would lead to CATH, but a negative test would not necessarily exclude significant CAD in this LT population and further work-up with another non-invasive modality *vs.* CATH might still be needed. Similarly, the assessment of single photon emission computed tomography to detect myocardial ischemia had poor sensitivity, while coronary computed tomography angiography had poor specificity and positive predictive value for the detection of CAD.[15–17] However, coronary computed tomography angiography and calcium scoring have very high sensitivity and negative predictive values that can be potentially useful in low-intermediate risk patients to rule out CAD. These tests also require certain patient physical and clinical characteristics to obtain interpretable images. Since SE was the non-invasive diagnostic modality of choice used in our center during the study period, we were unable to provide data on other testing modalities. However, we acknowledge the role that other non-invasive modalities can have in evaluating intermediate-risk patients, particularly if care is individualized. Therefore, depending on the risk tolerance for missing significant CAD, the availability, and the center's experience with a particular non-invasive testing modality, the choice of the diagnostic test for intermediate-risk patients is left to the clinician's discretion, if a non-invasive strategy is chosen.

Table 6. The CAD-LT risk score to predict significant coronary artery disease in liver transplant candidates.

Points associated with each category of the predictors		Risk score associated with points total		
Factors	Points	Points total	Estimate of risk	Risk category
Age		-2	0.006	Low-Risk
<30	0	-1	0.007	
30-39	2	0	0.010	
40-49	4	1	0.013	
50-59	6	2	0.016	
60-70	8	3	0.021	
>70	10	4	0.028	Intermediate-Risk
Sex		5	0.036	
Male	0	6	0.046	
Female	-2	7	0.060	
Diabetes		8	0.077	High-Risk
Yes	2	9	0.098	
No	0	10	0.124	
Hypertension		11	0.156	
Yes	2	12	0.195	
No	0	13	0.240	
Tobacco pack years		14	0.292	
0-20	0	15	0.350	
21-40	1	16	0.413	
>40	2	17	0.479	
Family history of CAD[†]		18	0.546	
Yes	2	19	0.611	
No	0	20	0.672	
Personal history of CAD[‡]		21	0.728	
Yes	7	22	0.778	
No	0	23	0.820	
		24	0.856	
		25	0.886	

CAD-LT, coronary artery disease in liver transplantation.
[†]Defined as history of CAD in a first-degree family member.
[‡]Defined as history of percutaneous coronary intervention, coronary artery bypass grafting and/or myocardial infarction.

The prevalence of significant CAD in LT candidates is variable and its diagnosis is dependent on the modality used for its detection, as well as on the population studied.[6,7] The prevalence of significant CAD in this large cohort of LT candidates who underwent CATH according to a risk factor-based protocol was 16%. The routine incorporation of CATH as part of pre-LT work-up is controversial, with an appropriate-use score of 5 out of 9 per the American College of Cardiology guidelines.[18] However, CATH is commonly obtained as part of the pre-transplant evaluation of patients with end-stage liver disease at many transplant centers in order to definitively rule-in/out significant CAD prior to undertaking a high-risk and costly LT.[9,10,19] If the treating physician has a high clinical suspicion for CAD, it certainly remains in their prerogative to order any test that they deem necessary and appropriate, while keeping in mind possible complications. While a previous study conducted at this center in a similar cohort of exclusively transplanted patients showed a low rate of acute kidney injury (4%), and low rate of major and minor bleed (0% and 3%, respectively) following CATH, patients with end-stage liver disease are still at a theoretically higher risk of complications such as kidney dysfunction and coagulopathy.[9,10,19,20]

The CAD-LT algorithm limits the use of non-invasive testing to the intermediate CAD-LT risk category. As previously mentioned, our experience with SE as the non-invasive modality is that it has high specificity and low sensitivity in the LT population. Current guidelines from American College of Cardiology/American Heart Association recommend obtaining non-invasive stress testing in patients with 3 or more cardiac risk factors, while those from the American Association for the Study of Liver Disease recommend SE for all LT candidates.[21–23] In another study, where 25% of patients had significant CAD (defined as luminal stenosis >70%) on angiography, only 14% had positive SE.[24] While a higher specificity (98%) for SE in detecting significant CAD has previously been reported in a study of 389 LT patients, only 278 (70%) were able to reach the target heart rate.[25] This sheds light on the

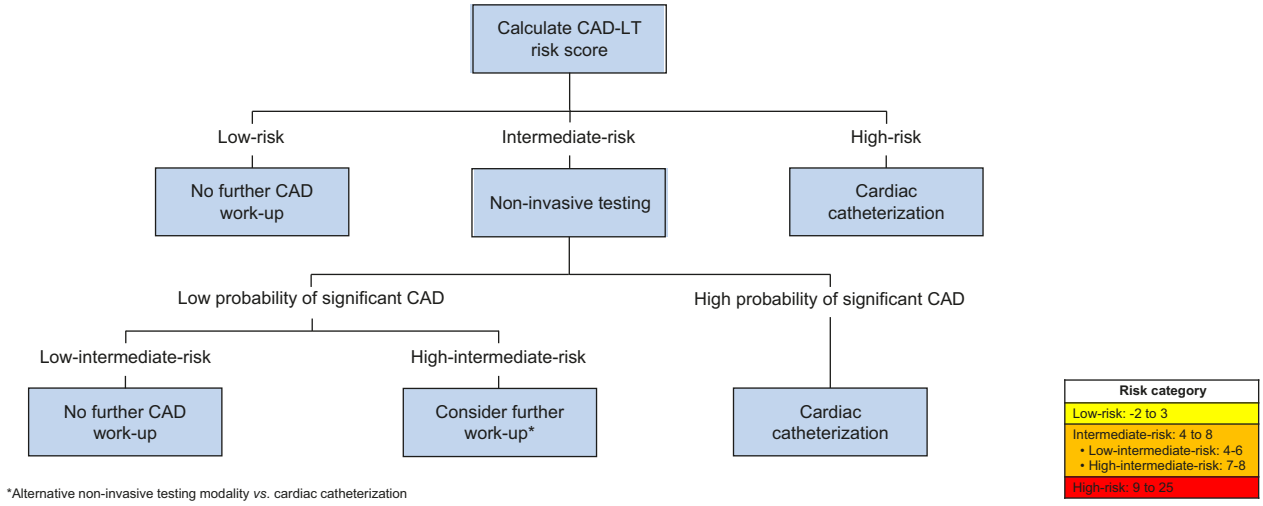

Fig. 1. Algorithm for the use of the CAD-LT risk score. CAD-LT, coronary artery disease in liver transplantation.

barriers to using SE in the LT population due to the concurrent use of beta-blockers, and the presence of peripheral vasodilation and chronotropic incompetence in the LT population.[6,26]

The CAD-LT score and algorithm are dedicated to the LT population, while commonly used risk stratification tools for non-cardiac surgeries such as Revised Cardiac Risk Index exclude transplant patients.[27] A major goal of preoperative transplant evaluation is to reduce cardiac morbidity and mortality.[1] Previous studies have demonstrated that aggressive risk factor-based CATH screening is associated with a low rate of myocardial infarction and cardiac mortality.[9,10] The CAD-LT algorithm directs high-risk patients to CATH, while at the same time limits its use in low- and intermediate-risk patients with an overall sensitivity of 97% in detecting significant CAD in LT candidates.

Approximately half (48%) of the patients evaluated for transplant in this study did not progress to transplant with the most common reasons being low MELD score, cardiopulmonary comorbidities, and substance use (Table S1). These findings were similar to a study of 337 patients evaluated for LT where almost half (49%) were deemed ineligible for LT. Of these individuals, 49% had a low MELD score, 26% had medical comorbidities and/or needed medical optimization, and 17% were ineligible because of substance use.[28] It is imperative to start the evaluation process for the aforementioned medical and psychosocial comorbidities early on to enhance the opportunity for LT eligibility as soon as it is clinically appropriate. However, given this large number of patients referred for LT who ultimately do not proceed to transplant, it is incumbent on the field to minimize unnecessary cardiac testing to lessen the burden on the system.

The study has several important limitations that should be considered before adopting the CAD-LT algorithm. First, the study is retrospective and is subject to the limitations of the study design and population. Second, we acknowledge that there was over-testing in this cohort. The aim of the protocol that was used for pre-LT evaluation in our center was to improve transplant outcomes. Having now studied the cohort retrospectively, we share the experience of our center in order to construct a robust algorithm that balances good transplant outcomes, while limiting the number of tests and maintaining cost-effectiveness. The value of this manuscript is in the large percentage of patients who underwent both SE and CATH as this helps establish the true incidence of significant CAD in this patient population. Lastly, the risk score was validated using an internal cross-validation cohort from a single academic center. Therefore, a second cohort in another center or a prospective cohort is required for external validation.

The CAD-LT score (available at www.cad-lt.com) is an easy-to-use, cost-effective, and sensitive clinical tool that predicts the risk of significant CAD in LT candidates. The use of the CAD-LT score with the associated cardiac evaluation algorithm may result in improved outcomes, while reducing the overall number of non-invasive or invasive procedures performed during the evaluation process.

Abbreviations

aOR, adjusted odds ratio; CAD, coronary artery disease; CAD-LT, coronary artery disease in liver transplantation; CATH, cardiac catheterization; LT, liver transplantation; MELD, model for end-stage liver disease; SE , stress echocardiography.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

R.R., I.K. and R.M. contributed to study design, data acquisition and interpretation, and writing and editing of the manuscript. L.T. contributed to the statistical analysis. R.B.C, E.E.A, M.S., S.M., and M.R. contributed to data acquisition, and critical revision of the manuscript. M.L., C.K., J.F., M.G., P.B. and R.M. contributed to the critical revision of the manuscript. All authors reviewed and approved the final manuscript. R.R., I.K. and R.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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Supplementary data

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