Received: 22 January 2024 | Revised: 19 March 2024 | Accepted: 24 March 2024

DOI: 10.1111/liv.15926

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

CACS, CCTA and mCAD-LT score in the pre-transplant assessment of coronary artery disease and the prediction of post-transplant cardiovascular events

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Funding information
Asociación Española para el Estudio del Hígado; Instituto de Salud Carlos III;

Abstract

Background: The optimal cardiovascular assessment of liver transplant (LT) candidates is unclear. We aimed to evaluate the performance of CT-based coronary tests (coronary artery calcium score [CACS] and coronary CT angiography [CCTA]) and a modification of the CAD-LT score (mCAD-LT, excluding family history of CAD) to

Abbreviations: ACLF, acute-on-chronic liver failure; ACS, acute coronary syndrome; AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CA, coronary angiography; CACS, coronary artery calcium score; CAD, coronary artery disease; CAD-RADS, coronary artery disease-reporting and data system; CCTA, coronary computed tomography angiography; CT, computed tomography; CVD, cardiovascular disease; CVE, cardiovascular events; CVR, cardiovascular risk; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; DSE, dobutamine stress echocardiography; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; HCV, hepatitis C virus; HTN, arterial hypertension; ICA, invasive coronary angiography; IQR, interquartile range; LT, liver transplant; MASLD, metabolic-associated steatotic liver disease; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; NPV, negative predictive value; PCI, percutaneous coronary intervention; PPV, positive predictive value; SPECT, single-photon emission computed tomography; WL, waiting list.

Jordi Colmenero and Gonzalo Crespo share senior authorship.

Agència de Gestió d'Ajuts Universitaris i de Recerca

Handling Editor: Luca Valenti.

diagnose significant coronary artery disease (CAD) before LT and predict the incidence of post-LT cardiovascular events (CVE).

Methods: We retrospectively analysed a single-centre cohort of LT candidates who underwent non-invasive tests; invasive coronary angiography (ICA) was performed depending on the results of non-invasive tests. mCAD-LT was calculated in all patients.

Results: Six-hundred-and-thirty-four LT candidates were assessed and 351 of them underwent LT. CACS, CCTA and ICA were performed in 245, 123 and 120 LT candidates, respectively. Significant CAD was found in 30% of patients undergoing ICA. The AUROCs of mCAD-LT (.722) and CCTA (.654) were significantly higher than that of CACS (.502) to predict the presence of significant CAD. Specificity of the tests ranged between 31% for CCTA and 53% for CACS. Among patients who underwent LT, CACS ≥ 400 and mCAD-LT were independently associated with the incidence of CVE; in patients who underwent CCTA before LT, significant CAD at CCTA also predicted post-LT CVE.

Conclusion: In this cohort, mCAD-LT score and CT-based tests detect the presence of significant CAD in LT candidates, although they tend to overestimate it. Both mCAD-LT score and CT-based tests classify LT recipients according to their risk of post-LT CVE and can be used to improve post-LT risk mitigation.

KEYWORDS
CACS, CAD-LT score, coronary angiography, coronary artery disease, liver transplantation

1 | INTRODUCTION

Cardiovascular disease (CVD) is one of the main problems faced by liver transplant (LT) recipients.[1] Indeed, cardiovascular events (CVE) are the most important cause of early death after LT and they are also among the most frequent causes of death and disability in the long term.[2,3] Concurrently, the profile of LT candidates now includes older patients with an increasing prevalence of steatotic liver disease as LT indication, as well as cardiovascular-related comorbidities,[4] thus the incidence of CVE is likely to continue increasing.

The optimal preoperative cardiovascular evaluation strategy for patients undergoing LT evaluation is unknown. American and European Hepatology societies guidelines[5,6] recommend stress testing in LT candidates with cardiovascular risk (CVR) factors to evaluate the presence of asymptomatic coronary artery disease (CAD) but, importantly, they are around 10 years old. It is now well known that the blunted chronotropic response and chronic vasodilation characteristic of advanced cirrhosis decreases the performance of stress tests in these patients.[7–9] Furthermore, it is uncertain what combination of CVR factors should trigger invasive investigations in LT candidates.[10] In this regard, a risk factor-based score, the coronary artery disease in liver transplantation (CAD-LT) score, was recently proposed to stratify LT candidates according to their risk of significant CAD in invasive coronary angiography (ICA).[11] To the best of our knowledge, no study has tested this score (or modifications thereof) in the assessment of the presence of CAD in LT candidates in other cohorts.

Key points

- Computed tomography-based tests that quantify calcification of coronary arteries and non-invasively depict coronary anatomy and a slight modification of a simple clinical score that was recently developed are able to detect liver transplant (LT) recipients that have higher risk of post-LT cardiovascular events.
- All these tests can help detect the presence of significant coronary artery disease before LT, but they all tend to overestimate it in the setting of screening of asymptomatic candidates in whom exclusion of significant coronary artery disease is paramount.
- These results can be useful to design coronary artery disease screening protocols in LT candidates and to establish post-transplant risk mitigation strategies.
- Future research is needed to evaluate new technical advances and combinations of tests to improve the detection of significant coronary artery disease in LT candidates.

Computed tomography (CT)-related techniques, both coronary artery calcium score (CACS) and coronary CT angiography (CCTA), are being increasingly used in the general population to assess the presence and severity of CAD, and they may be a reliable screening option for preoperative non-invasive evaluation of CAD in LT candidates.[12–16] Recent expert reviews[10,17] and, more importantly, an AHA scientific statement endorsed by the AST[18] recommend these techniques to evaluate the presence of CAD before LT, and at the same time highlight the need to collect more information regarding their diagnostic and prognostic yield in large, well-characterized cohorts.

Considering all this, we performed this study with two main aims: (1) to evaluate and compare the performance of CT-based tests and a modification of the CAD-LT score (mCAD-LT) in the assessment of significant CAD before LT; and (2) to investigate the ability of these tests to predict post-LT CVE.

2 | METHODS

2.1 | Study design and patient population

We retrospectively reviewed the data of all patients evaluated for a LT in our hospital between July 2015 and September 2020. We recorded the aetiology of the liver disease, indication of LT, liver function, smoking status, body mass index (BMI) and laboratory variables (serum creatinine and estimated glomerular filtration rate [eGFR]). The presence of pre-LT CVR factors was assessed according to the International Classification of Diseases–11 codes (World Health Organization Classification of Diseases). We recorded the presence of cardiovascular disease before LT, defined as previous episodes of myocardial infarction, acute coronary syndrome (ACS), stable angina, ischaemic or haemorrhagic stroke or transient ischaemic attack, heart failure, diagnosis of peripheral artery disease and arrhythmia. A modified CAD-LT score[11] (mCAD-LT score) was calculated excluding the variable 'family history of CAD' due to >70% missing data. To calculate this mCAD-LT score, we maintained the same points of the original publication for the rest of the variables of the score (age, sex, diabetes [DM], hypertension [HTN], tobacco pack-years and personal history of CAD). Consequently, the results of the score rank from −2 to 23.

2.2 | Pre-transplant evaluation and management of silent coronary artery disease

Since 2015, the CAD assessment before LT in our centre is a tiered protocol (Figure 1) that can include, depending on pre-specified clinical risk, (a) no screening test further than electrocardiogram (ECG) and transthoracic echocardiography; (b) CACS, assessed with the Agatston method[19] and categorized in 0 (absence of coronary atherosclerosis), 1–399 (mild–moderate) and ≥400 (severe),[20–22] followed by CCTA in the same procedure depending on CACS results[23]; or (c) stress tests. ICA is performed depending on the results of non-invasive tests.

In patients who underwent ICA, significant disease was defined as stenosis ≥50% in a main vessel, and percutaneous revascularization was indicated in cases of stenosis ≥70% amenable to percutaneous coronary intervention (PCI). Patients with ≥70% stenosis in the three vessels were reviewed in multidisciplinary discussion to decide revascularization. In case of coronary stenosis 50%–70%, measurement of the fractional flow reserve (FFR) was performed and percutaneous revascularization was indicated if positive (<.8). Revascularized patients received 1 month of dual antiplatelet therapy (DAPT) before being activated in the waiting list, followed by at least 1 year of aspirin alone. Bare metal or second-generation drug-eluting stents were used for PCI depending on the time period and availability.

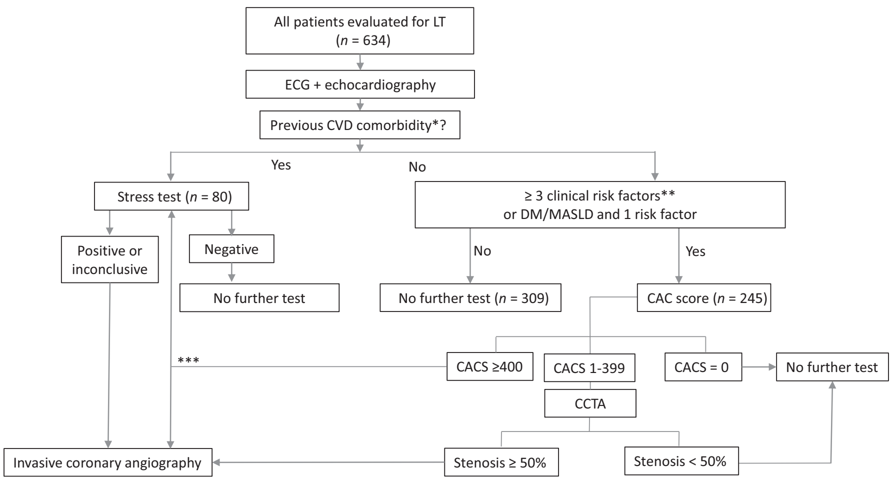

FIGURE 1 Coronary artery disease (CAD) screening protocol. CACS, coronary artery calcification score; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiogram; MASLD, metabolic dysfunction-associated steatotic liver disease. *coronary heart disease, heart failure, cerebrovascular disease, peripheral artery disease, chronic kidney disease. **age (male ≥45 years, female ≥50 years), arterial hypertension, dyslipidemia, diabetes mellitus, smoking history, MASLD. *** in patients with CACS ≥400, next step was either stress test or invasive coronary angiography at physician discretion.

2.3 | Post-transplant cardiovascular management

The post-LT cardiovascular management of LT recipients at our institution has been previously reported.[24] In brief, in 2018 we implemented a multidisciplinary protocol that included a detailed evaluation of cardiovascular risk, as well as management of immunosuppression, and pre-established treatment strategies and referral of patients with HTN, DM or dyslipidaemia.

2.4 | Post-transplant cardiovascular events

Patients who underwent LT during the study period were followed until 30 September 2022. The date and type of post-LT events were compiled by two investigators (GP and GC). In patients with more than one episode of CVE, only the first was included in the analysis. The CVE considered were ACS (including myocardial infarction with or without ST elevation or unstable angina), ischaemic or haemorrhagic stroke, arrhythmia (ventricular tachycardia, atrial flutter or fibrillation), peripheral artery disease and heart failure. We also performed a subanalysis including only atherosclerotic cardiovascular disease (ASCVD)-related events (ACS, stroke and peripheral artery disease).

2.5 | Statistical analysis

Categorical variables are shown in absolute number and percentage and quantitative variables in median and interquartile range (IQR). Comparisons were performed using Fisher test for categorical variables, and Mann–Whitney or Kruskall–Wallis tests for continuous variables. We calculated the area under the receiver-operating characteristic curve (AUROC) to evaluate the diagnostic capacity of Agatston score, CCTA and the mCAD-LT score to diagnose significant CAD in patients undergoing ICA. Kaplan–Meier curves and the log-rank test were used to investigate the incidence of post-LT CVE. Pre-transplant variables associated with the incidence of post-LT CVE were assessed by univariate and multivariate Cox regression analysis. mCAD-LT score was included in the multivariate analysis instead of the individual variables comprised in the score that resulted statistically significant in univariate analysis (age, diabetes and previous CVE). In this analysis, we evaluated the first-line pre-LT CAD screening test performed (no extra test, CACS or stress test) categorizing CACS in the three groups previously described (0, 1–399 and ≥400), in order to include the whole cohort that underwent LT in the analysis. A subanalysis including only ASCVD was also performed. A p-value $< .05$ was considered statistically significant. All statistical analyses were done using the SPSS package Version 28 (IBM Corporation).

2.6 | Ethical issues

The study was performed in accordance with the Declaration of Helsinki. All study data were pseudoanonymized with access restricted to only those personnel authorized to participate in the study. The study was approved by the Clinical Research Ethical Committee of Hospital Clinic, Barcelona, Spain (HCB/2022/0310).

3 | RESULTS

3.1 | Patient population

A flow chart of the study is shown in Figure 2. Six-hundred-and-thirty-four patients underwent LT candidacy assessment, and 351 of them eventually underwent LT during the study period. Baseline characteristics of the 634 LT candidates, categorized according to their first-line CAD screening test (Figure 1), are shown in Table 1.

3.2 | Performance of CACS and CCTA as CAD primary screening test

Among the 245 candidates that underwent CACS as initial CAD assessment test, median Agatston score was 84 (IQR 2–404). Fifty-three (21.6%) patients had Agatston = 0, 129 (52.7%) had Agatston 1–399 and 63 (25.7%) had Agatston ≥400. Agatston score was associated with older age, male sex, alcohol-related liver disease, HTN, smoking history, past CVE and mCAD-LT score (Table 2).

3.2.1 | Patients with CACS 1–399

CCTA was performed in 123 of the 129 patients with Agatston score 1–399 (95.3%). Forty-six patients (37.4%) had significant coronary lesions (≥50%), and 12 (9.8%) had lesions at the limit of significance or that could not be reliably assessed with CCTA. Finally, 53 patients underwent ICA and 14 (26.4%) had significant lesions in ICA, all within patients with significant lesions at CCTA (34.1%).

3.2.2 | Patients with CACS≥400

Out of the 63 candidates with CACS≥400, 46 eventually underwent ICA, while 14 underwent stress tests without further tests. In the other 3 patients, LT was contraindicated in 2 cases due to non-cardiovascular reasons, and in the remaining patient, who had acute-on-chronic liver failure (ACLF), consensus was achieved to undergo LT without ICA. Among the 46 patients with CACS ≥400 that underwent ICA, significant lesions were found in 14 (30.4%).

3.3 | Invasive coronary angiography

From the whole population of 634 LT candidates, 120 (18.9%) eventually underwent ICA. Thirty-six patients (30%) showed

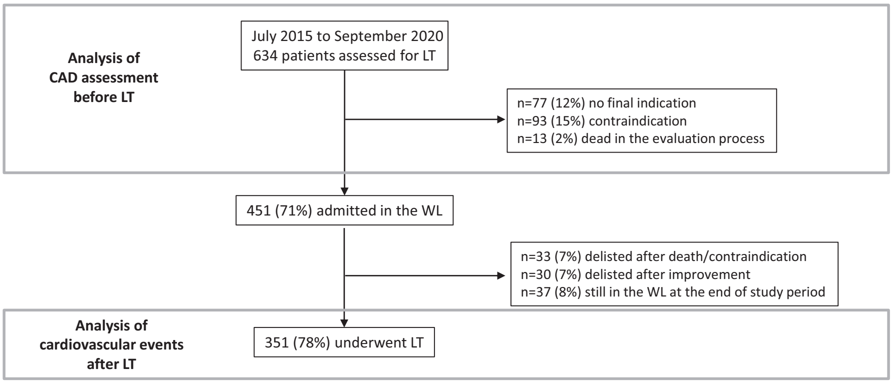

FIGURE 2 Flowchart of the study. CAD, coronary artery disease; LT, liver transplantation; WL, waiting list.

TABLE 1 Baseline characteristics of LT candidates included in the study, categorized according to the first-line CAD screening test.

Variable	All ($n=634$)	No extra test ($n=309$)	CACS ($n=245$)	Stress test ($n=80$)	p-Value
Sex (male)	451 (71)	190 (61)	195 (80)	67 (84)	<.001
Age, years	58 (51–63)	54 (48–60)	61 (57–65)	61 (55–65)	<.001
Aetiology (non mutually exclusive)					
HCV	159 (25)	72 (23)	56 (23)	31 (39)	.03
Alcohol	257 (41)	102 (33)	124 (51)	32 (40)	.007
MASLD	125 (19)	21 (7)	87 (35)	17 (21)	<.001
Indication					.003
Decompensated cirrhosis	335 (53)	147 (48)	151 (62)	30 (37)	<.001
Hepatocellular carcinoma	179 (28)	62 (20)	73 (30)	38 (47)	<.001
BMI, kg/m^2	26 (23–30)	25 (22–28)	29 (25–31)	26 (24–30)	<.001
Diabetes	180 (28)	30 (10)	113 (46)	37 (46)	<.001
Arterial hypertension	177 (28)	57 (18)	96 (39)	27 (34)	<.001
Dyslipidaemia	98 (16)	25 (8)	55 (22)	18 (23)	<.001
Active/previous smoking	342 (54)	134 (44)	164 (68)	51 (64)	<.001
Previous CVE	62 (10)	11 (4)	27 (11)	26 (32)	<.001
mCAD-LT score	8 (6–10)	6 (4–8)	9 (8–11)	9 (6–12)	<.001

Abbreviations: BMI, body mass index; CACS, coronary artery calcium score; CVE, cardiovascular events; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; mCAD-LT score, modified coronary artery disease in liver transplantation score.

significant stenoses, and a coronary stent was placed in 9 of them (25%). In 7 (19.4%) patients, the lesions were deemed non-treatable and LT was contraindicated, and in the remaining 20 (55.6%) the decision was to proceed to LT without stenting after multidisciplinary discussion. No patient underwent pre-LT surgical revascularization. Among the 120 patients that underwent ICA, complications were noted in 6 (5%), and included haemorrhagic complications ($n=2$), allergic reactions to contrast or infused platelets ($n=2$), acute kidney injury (AKI) ($n=1$) and post-procedure fever ($n=1$). All complications resolved without sequelae.

The variables associated with significant lesions among patients that underwent ICA are shown in Table 3. The AUROC of mCAD-LT score to predict the presence of significant CAD in ICA was .722 (.625–.820), $p<.001$. In contrast, the AUROC of the Agatston score was .512 (.381–.642), $p=.858$; and the AUROC of CCTA was .654 (.504–.804, $p=.09$). The differences between the AUROCs of CACS and mCAD-LT, and between the AUROCs of CACS and CCTA were statistically significant ($p=.018$ and $p=.042$, respectively), while there were no differences between the AUROCs of CCTA and mCAD-LT. Best cut-off point of mCAD-LT was 10, which yielded a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of, respectively, 86%, 50%, 42% and 89% and correctly classified 73 out of 120 (61%) patients. When the cohort was divided in the mCAD-LT score terciles, patients in the highest tercile (mCAD-LT≥11, $n=33$) had 48% prevalence of significant stenoses, as compared with 29% of patients in the intermediate tercile (mCAD-LT 9–10, $n=41$) and

TABLE 2 Baseline characteristics of patients that underwent coronary artery calcium score (CACS) as first-line coronary artery disease assessment.

Variable	CACS (*n* = 245)	CACS = 0 (*n* = 53)	CACS 1–399 (*n* = 129)	CACS ≥ 400 (*n* = 63)	*p*-Value
Sex (male)	195 (80)	31 (58)	110 (85)	54 (86)	<.001
Age, years	61 (57–65)	58 (52–62)	62 (57–66)	62 (58–66)	.003
Aetiology (non mutually exclusive)					
HCV	56 (23)	15 (27)	34 (27)	7 (11)	.016
Alcohol	123 (50)	16 (30)	62 (48)	46 (73)	<.001
MASLD	87 (36)	18 (33)	45 (35)	24 (38)	.555
Indication					
Decompensated cirrhosis	155 (63)	34 (62)	75 (59)	46 (73)	.110
Hepatocellular carcinoma	75 (31)	11 (20)	50 (39)	14 (22)	.545
BMI, kg/m^2	28 (25–31)	27 (24–31)	29 (25–31)	28 (25–32)	.917
Diabetes	113 (46)	23 (42)	60 (47)	30 (48)	.615
Arterial hypertension	96 (39)	13 (24)	52 (40)	31 (49)	.017
Dyslipidaemia	54 (22)	11 (20)	24 (19)	19 (30)	.109
Active/previous smoking	157 (65)	27 (52)	88 (69)	49 (78)	.012
Previous CVE	27 (11)	2 (4)	10 (8)	15 (24)	<.001
mCAD-LT score	9 (8–11)	7.5 (6–10)	9 (8–11)	10 (8–12)	<.001

Abbreviations: BMI, body mass index; CVE, cardiovascular events; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; mCAD-LT score, modified coronary artery disease in liver transplantation score.

TABLE 3 Variables associates with the presence of significant lesions in patients who underwent invasive coronary angiography (ICA).

Variable	All ICA *n* = 120	Stenosis ≥ 50% *n* = 36	No stenosis or stenosis < 50% *n* = 84	*p*-Value
Sex (male)	107 (89)	33 (92)	74 (88)	.75
Age	62 (58–66)	62 (59–66)	62 (57–66)	.65
Diabetes	68 (57)	25 (69)	43 (51)	.066
Arterial hypertension	59 (49)	22 (61)	37 (44)	.086
Active/previous smoking	92 (77)	31 (86)	61 (73)	.111
Tobacco pack-year	23 (4–44)	33 (10–45)	20 (0–37)	.055
Previous CVE	27 (22)	9 (25)	18 (21)	.669
Previous ischaemic cardiac disease	9 (7)	6 (17)	3 (4)	.013
Agaston score (*n* = 97)	377 (97–760)	472 (96–866)	370 (84–684)	.866
Agaston ≥ 400 (*n* = 97)	27 (28)	14 (30)	13 (26)	.821
mCAD-LT score	10 (8–12)	12 (10–14)	9 (8–12)	<.001

Abbreviations: CACS, coronary artery calcium score; CCTA, coronary computed tomography angiography; CVE, cardiovascular events; mCAD-LT score, modified coronary artery disease in liver transplantation score.

6% of patients in the lowest tercile (mCAD-LT <9, $n = 46$), $p < .001$. Sensitivity, specificity, PPV and NPV of CACS≥400 were 52%, 53%, 30% and 74%, correctly classifying 51 out of 99 (52%) patients. Sensitivity, specificity, PPV and NPV of CCTA were 100%, 31%, 34% and 100% and it correctly classified 26 out of 53 (49%) patients. As stated above, very few patients without significant lesions at CCTA underwent ICA. Importantly, ICA discarded significant lesions in all these patients.

3.4 | Prediction of post-transplant cardiovascular events

From the whole cohort of 634 candidates, 351 underwent LT during the study period (Figure 2). The characteristics of LT recipients are shown in Table 4. After a median follow-up of 38 (24–54) months, 54 (15.4%) patients presented a CVE. Most CVE were new-onset arrhythmia ($n = 20$, 37%), followed by ACS ($n = 11$, 20.4%) and heart failure ($n=8$, 14.8%). Seven patients (12.9%) were diagnosed with cerebrovascular disease, 6 (11.1%) with peripheral arteriopathy and 2 (3.7%) had sudden death.

The uni- and multivariate analysis of variables associated with the incidence of CVE after LT are shown in Table 5. In multivariate analysis, both mCAD-LT score and CACS≥400 were independent predictors of post-LT CVE, as was undergoing stress test as first-line CAD screening test. The cumulative incidence of 2-year post-LT CVE according to first-line CAD screening test with categorized CACS, and to mCAD-LT tertiles is shown in Figure 3.

In the subgroup of LT recipients with underwent CCTA ($n=75$), stenosis ≥50% (coronary artery disease-reporting and data system [CAD-RADS] ≥ 3) was associated at univariate analysis with CVE ($p=.038$, HR 4.455, 95% CI 1.087–19.054) (Figure S1). Similarly, in the 60 LT recipients with pre-LT ICA, significant stenosis ($n=14$) was at the limit of significance ($p=.07$, HR 2.410, 95% CI .932–6.232). However, among these, receiving stent ($n=4$) was not associated with a different risk of post-LT CVE ($p=.733$, HR .683, 95% CI .076–6.125).

TABLE 4 Characteristics of the 351 patients who underwent liver transplant (LT).

Variable	$n=351$
Sex (male)	241 (67)
Age, years	59 (52–63)
Aetiology (no exclusive)	
HCV	94 (27)
Alcohol	117 (33)
MASLD	59 (17)
Indication	
Decompensated cirrhosis	160 (46)
Hepatocellular carcinoma	112 (32)
MELD score at LT	18 (10–22)
Creatinine (mg/dl) at LT	.99 (.77–1.31)
eGFR (mL/min/1.73 m^2) at LT	80 (58–90)
BMI, kg/m^2	26 (23–30)
Diabetes	98 (28)
Arterial hypertension	88 (25)
Dyslipidaemia	52 (15)
Active/previous smoking	168 (48)
Previous CVE	24 (7)
mCAD-LT score	7 (5–10)
First-line CAD screening group	
No extra test	182 (52)
CACS	117 (33)
Stress test	52 (15)

Abbreviations: BMI, body mass index; CACS, coronary artery calcium score; CVE, cardiovascular events; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; MASLD, metabolic-associated steatotic liver disease; mCAD-LT score, modified coronary artery disease in liver transplantation score; MELD, model for end-stage liver disease.

For the prediction of post-LT CVE, the sensitivity, specificity, PPV and NPV of mCAD-LT≥10 were 48%, 79%, 30% and 89%, while the same characteristics were 52%, 84% 44% and 88% for CACS≥400 and 62%, 75%, 23% and 94% for CCTA.

The univariate Cox regression analysis of variables associated with the incidence of post-LT ASCVD-related CVE are shown in Table S1. On adjusted analyses, CACS ≥400 and undergoing stress test as first-line CAD screening test remained predictors of post-LT ASCVD-CVE, while mCAD-LT was not ($p=.102$). Table S2 shows the characteristics of the 11 patient that had ACS after LT.

4 | DISCUSSION

The potential role of CACS/CCTA in the detection of CAD in LT candidates has been suggested by several studies[25,26] that also raised concerns regarding their accuracy in this population. In our cohort, the largest proportion of patients had coronary calcifications (CACS>0). Among these, however, the prevalence of significant stenoses in ICA was low, and it was not predicted by the Agatston score, that showed an AUROC of .512. Even in patients with suspected significant lesions in CCTA, the presence of significant lesions in ICA was 34%. The low specificity is a well-known limitation of CCTA that is not unique to LT candidates and that, importantly, depends on the pre-test probability of CAD. In the general population with stable angina (higher expected probability of CAD), 78% specificity and 97% sensitivity of CCTA have been reported.[27,28] Differently, ours is an asymptomatic population with 30% pre-test probability of CAD and in whom screening aims at identifying patients at risk to select those to undergo ICA. In this setting, assuming a low specificity (thus performing ICA in patients without significant CAD) is probably more clinically acceptable than a low sensitivity (discarding ICA in patients that eventually have significant CAD). In the general population, a negative CCTA of sufficient quality virtually rules out obstructive CAD and significantly reduces unnecessary invasive procedures. Indeed, in our cohort, among patients who underwent CCTA and ICA, sensitivity and NPV were 100%. It needs to be highlighted, however, that ours is a clinical practice protocol in which patients without significant CAD at CCTA were not supposed to undergo ICA, and those patients that underwent ICA without significant CAD at CCTA had inconclusive lesions or at the limit of significance, thus a full picture of the diagnostic capacity of CCTA cannot be given. Finally, we set the threshold of significant CAD at CCTA at 50% precisely in order to increase sensitivity and not miss patients with significant disease at ICA. Increasing the cut-off at 70% may have increased specificity, as shown in other populations,[29] but at the potential cost of missing patients with significant disease. In addition, future prospective studies are needed to address whether the combination of CT-based risks and clinical scores, or the addition of technical improvements such as the non-invasive measurement of FFR in CCTA,[30] result in improved stratification of patients. Similarly, it must be stressed that CACS and CCTA also provide other advantages over clinical scores, including depicting coronary anatomy for

TABLE 5 Uni- and multivariate Cox regression analysis of pre-transplant variables associated with the cumulative incidence of cardiovascular events among liver transplant (LT) recipients.

Variable	HR (95% CI) univariate	*p* (uni)	HR (95% CI) multivariate	*p* (multi)
Age, per year	1.074 (1.027–1.122)	.002	–	–
Sex (ref = female)	1.705 (.814–3.573)	.157	–	–
MASLD	.962 (.426–2.169)	.925	–	–
Alcohol	2.404 (1.301–4.441)	.005	1.069 (.590–1.939)	.825
HCV	.978 (.490–1.952)	.950	–	–
MELD	1.012 (.975–1.051)	.532	–	–
Creatinine levels, per mg/dl	.993 (.918–1.073)	.854	–	–
eGFR, per mL/min/1.73 m^2	.991 (.980–1.003)	.132	–	–
BMI, per kg/m^2	1.106 (1.031–1.186)	.005	1.037 (.967–1.111)	.308
Diabetes	2.314 (1.252–4.275)	.007	–	–
Arterial hypertension	1.594 (.836–3.039)	.157	–	–
Dyslipidaemia	1.155 (.512–2.606)	.728	–	–
Smoking habit (ref = never smoker)	–	.011	–	.417
Former smoker	2.033 (.887–4.654)	.094	1.405 (.734–2.693)	.305
Current smoker	.870 (.368–2.058)	.751	.878 (.356–2.167)	.778
Cumulative tobacco (pack-year)	1.009 (.997–1.021)	.135	–	–
Previous CVE	2.809 (1.245–6.337)	.013	–	–
mCAD-LT score	1.173 (1.093–1.259)	<.001	1.089 (1.004–1.187)	.045
Time era (ref = 2015–2017)	.640 (.375–1.093)	.102	–	–
First-line CAD screening group with categorized CACS (ref = no extra test)	–	<.001	–	.005
CACS 0	1.507 (.433–5.244)	.519	1.197 (.334–4.288)	.782
CACS 1–399	1.572 (.660–3.748)	.307	.903 (.346–2.353)	.834
Stress test	4.522 (2.228–9.175)	.001	2.546 (1.178–5.500)	.017
CACS ≥ 400	6.652 (3.075–14.392)	<.001	3.853 (1.583–9. 377)	.003

Note: Age, diabetes and previous CVE (that include CAD) were not included in multivariate analysis as they are incorporated in mCAD-LT score.
Abbreviations: BMI, body mass index; CACS, coronary artery calcification score; CAD, coronary artery disease; CVE, cardiovascular events; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; mCAD-LT score, modified coronary artery disease in liver transplantation score; MELD, model for end-stage liver disease.

ICA and showing the burden of high-risk plaque that tend to be non-calcified. Finally, as shown above, the ability of CCTA to discard significant CAD is a meaningful asset and permits to avoid a number of unnecessary ICA.

The CAD-LT score is a clinical risk score that was significantly associated in the original publication, comprising a large cohort of LT candidates that underwent ICA, with the presence of significant CAD.[11] In our population, a modification of the CAD-LT score correctly classified 61% of patients according to the presence or absence of significant CAD. Although our study is the first that tests a CAD-LT derived score in assessing the presence of significant CAD in LT candidates, we acknowledge that we did not perform a formal validation of the CAD-LT score. First, we did not include family history of CAD, as this feature was not properly registered in our cohort. Indeed, it is not infrequent that family history of CAD is poorly recorded in electronic medical records.[31] Second, the path along which patients arrived to ICA was different in our cohort with respect to the original study: while our patients were selected according to non-invasive techniques (thus the prevalence of significant CAD was 30%), Rachwan, Kutkut et al performed a nearly 'all-comers' approach with a prevalence of 16% of significant CAD. However, we believe these results help to indirectly validate the CAD-LT score as a useful tool in the assessment of LT candidates. Indeed, this is supported by its capacity to predict post-LT CVE, also shown by a recent study.[32] Our findings can be clinically relevant, particularly in settings where CT-based techniques are not widely available, or when assessing patients, such as those with acute-on-chronic liver failure (ACLF), in whom an expedite and rapid evaluation is necessary and performing ICA after a non-invasive technique may result in significant delay.

Previous studies in LT candidates suggest that either CCTA findings or a high CACS may identify patients at highest risk of CVE.[33–36] In our study, that included one of the largest cohorts of LT recipients with CACS, we also observed an independent

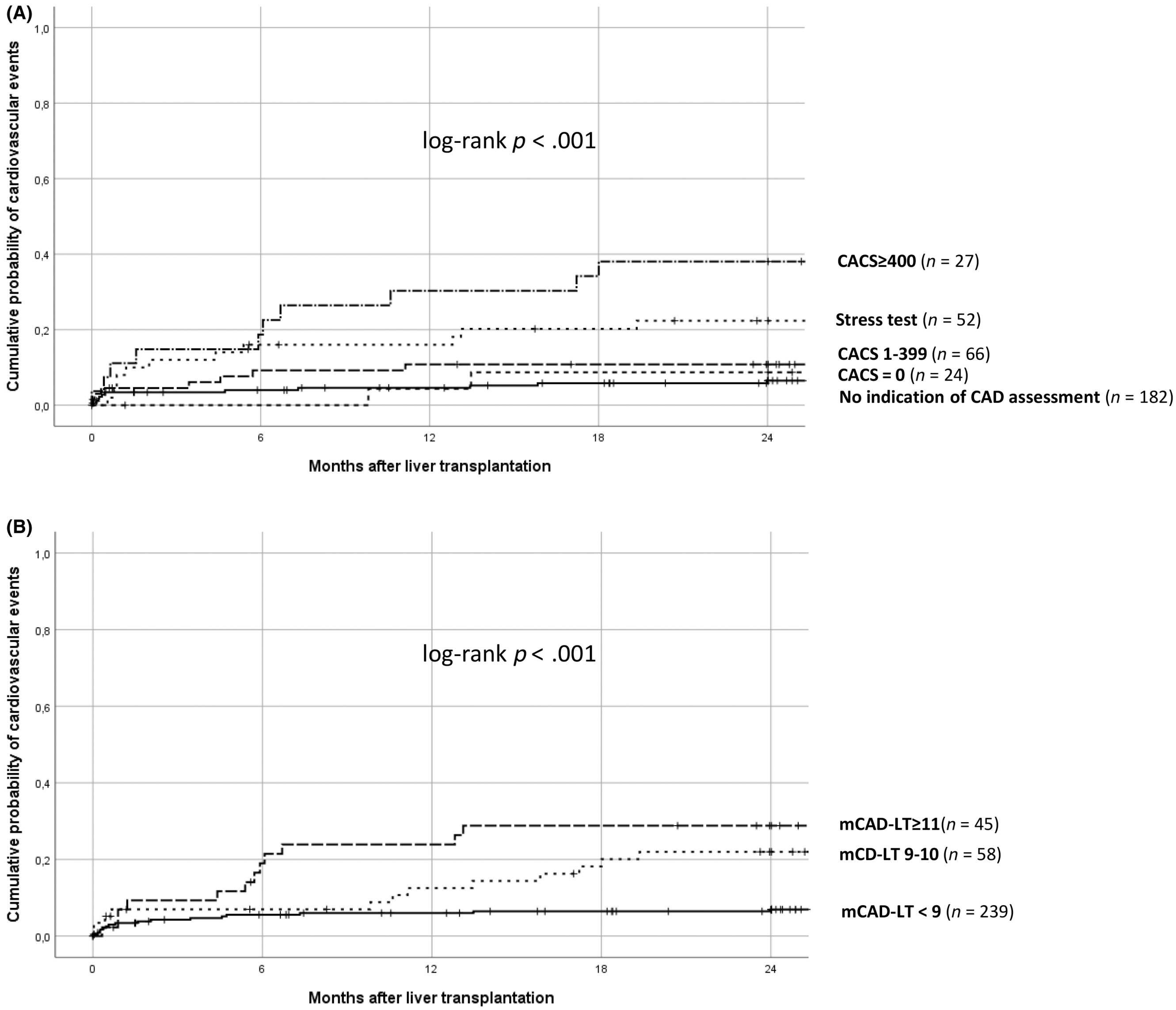

FIGURE 3 Two-year post-liver transplant (LT) cumulative probability of a first cardiovascular event (CVE) according to first-line coronary artery disease assessment test, with coronary artery calcium score (CACS) categorized (A); and to the pre-LT mCAD-LT tertile (B).

association between pre-LT CACS and post-LT CVE, which were particularly incident in patients with CACS≥400. At univariate analysis, significant stenoses in CCTA were also associated with CVE (Figure S1), similar to recent studies that evaluated CCTA findings according to the CAD-RADS system.[37] The lower number of recipients with CCTA, however, did not allow us to perform adjusted analyses. Interestingly, as reported in the literature, most CVE were not ACS. While this may be related to the therapeutic procedures directed to manage CAD, it also possibly reflects the capacity of CACS and CCTA to define the burden of atherosclerosis as a systemic disease, further than CAD.[38] Indeed, this highlights its potential as a tool to adapt the intensity of post-LT interventions to mitigate the risk of CVE.

In clinical practice, our results would suggest that both pre-LT CT-based tests and mCAD-LT may help tailor the intensity of post-LT therapeutic interventions on CVR. Specifically, patients with pre-LT CACS≥400, high mCAD-LT/CAD-LT score or significant stenosis in CCTA would require a focused intense management, including exquisite control of blood pressure,[39] early use of statins[40] and careful weight management.[41] With regard to immunosuppressant treatment, more studies are needed to evaluate the impact of different immunosuppressive regimens in the risk of CVE and progression of atherosclerosis.[42,43] Although this was not the purpose of the study, undergoing stress test as first-line CAD screening test was also associated with a higher risk of CVE, likely reflecting baseline risk of these patients as shown in Table 1.

We also contribute to the literature regarding ICA in patients with cirrhosis. In line with other data,[44] we found ICA to be overall safer than what may be expected. We used a radial approach to minimize risks, and interventions were performed by cardiologists with expertise in procedures in patients with cirrhosis. In addition, some patients received second-generation drug-eluting stents, which should be considered of choice in this population as they permit a shorter period of DAPT if needed.[45,46]

Our study has limitations, including the retrospective design that, as mentioned above, did not permit us to assess the original CAD-LT score. In addition, we evaluated our own clinical practice protocol with its specific criteria to guide the different screening tests, which may not be applicable to other centres. In particular, we do not perform CCTA neither patients with CACS = 0, as absence of calcified atherosclerosis is associated with extremely good CV outcomes (even if it does not exclude non-calcified atherosclerosis), nor in patients with CACS≥400, as the high calcification interferes CCTA. Nevertheless, CCTA can be performed even in patients with very high CACS. Finally, a validation cohort would have been ideal to confirm our results. On the other hand, the fact that we included a large cohort, comprising not only actual LT recipients or waitlisted patients but all patients considered for LT, is a significant strength. Indeed, the large cohort studied permitted us to describe the pre-LT diagnostic characteristics of imaging and clinical tests, and also to evaluate their accuracy to predict post-LT CVE in a real-life, clinical practice setting. In addition, this is the first study that compares in the same cohort CT-based tests and a novel clinical score (with a slight modification) that had no external validation to date. Finally, the type of post-LT CVE included in the different studies is controversial. For this reason, we performed a subanalysis on ASCV-CVE, excluding arrhythmia and heart failure.

In conclusion, our study shows that mCAD-LT score and CT-based coronary tests identify LT candidates with significant CAD, but they all tend to overestimate its presence. While this is probably acceptable considering the aim of CAD screening in LT candidates, further efforts are necessary to optimize such screening. Furthermore, both mCAD-LT score and CT-based tests predict post-LT CVE and can consequently be used to improve the clinical management of CVR after LT.

ACKNOWLEDGEMENTS

We thank Dr. Miquel Navasa for his insightful comments and suggestions.

FUNDING INFORMATION

AGAUR 2021 SGR 01332 (AM, FRCB-IDIBAPS GRC Imatge Molecular en Medicina Nuclear); AGAUR 2021 SGR 01331 (GC, PR, JC, FRCB-IDIBAPS GRC Hepatologia Recerca Clínica). JC and GP were supported by a grant from the Asociación Española para el estudio del Hígado 'Beca de intensificación para investigadores' and by Instituto de Salud Carlos III co-financed by the European Union (FEDER/FSE) (PI22/01234).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Clinical Research Ethical Committee of Hospital Clinic, Barcelona, Spain (HCB/2022/0310). Patient informed consent was waived.

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How to cite this article: Pagano G, Sastre L, Blasi A, et al. CACS, CCTA and mCAD-LT score in the pre-transplant assessment of coronary artery disease and the prediction of post-transplant cardiovascular events. *Liver Int*. 2024;44:1912-1923. doi:10.1111/liv.15926