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Coronary artery calcium on standard chest computed tomography predicts cardiovascular events after liver transplantation

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A B S T R A C T

Aims: Cardiac complications are a leading cause of mortality after orthotopic liver transplantation (LT) and pre-operative risk stratification is challenging. We evaluated whether coronary artery calcium (CAC) score calculated on a standard (non-thin layer, non-ECG gated) chest computed tomography (CT) predicted cardiac outcome after LT.
Methods: We included a consecutive series of LT recipients who underwent pre-operative cardiac evaluation including stress-testing or cardiac catheterization in high-risk patients. Patients with a history of coronary artery disease or coronary revascularization were excluded. The CAC score was calculated from the chest CT routinely performed before LT. CAC values were not available at the time of pre-transplant cardiac evaluation and did not affect LT eligibility. The primary end-point included peri-operative arrhythmic cardiac arrest and sustained ventricular arrhythmias; heart failure, myocardial infarction and cardiac death within 1-year after LT.
Results: The study population consisted of 301 patients (median age 56 years, 76% males). At chest CT, 49% had CAC = 0; 27% had CAC = 1–99, 15% had CAC = 100–399 and 9% CAC > 400. The primary end-point incidence increased from 7% in patients with CAC = 0 to 27% in patients with CAC > 400 ($p = 0.007$). At multivariable analysis including traditional risk factors, CAC remained an independent predictor of cardiac events ($p = 0.01$).
Conclusions: CAC score calculated on a standard chest CT stratified the risk of cardiac events in patients who underwent LT after negative pre-transplant cardiac evaluation. These findings suggest that evaluation of CAC from a standard chest CT performed for other reasons can be used as an early cardiac risk stratification tool before LT.

1. Introduction

Cardiac complications are one of the leading causes of mortality after orthotopic liver transplantation (LT), both in the post-operative period, due to the stress imposed by rapid increase of blood pressure and peripheral vascular resistance, and in the long term [1] [2]. For this reason, accurate selection of candidates is crucial to optimize pre-transplant therapy and to apply the most appropriate post-operative care. Unfortunately, cardiovascular risk stratification of LT candidates is particularly challenging because cardiac modifications typical of end-stage cardiac disease, such as high cardiac output and vasodilation, lowers the accuracy of traditional cardiac imaging tests [3].

Abbreviation: CAC, coronary artery calcium; CAD, coronary artery disease; CRI, cardiac risk index; CT, computed tomography; ECG, electrocardiography; LT, orthotopic liver transplantation; RCI, revised cardiac index; SPECT, Single Photon Emission Computed Tomography.

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Several studies have suggested the potential role of coronary artery calcium (CAC) to estimate the cardiovascular risk of patients undergoing LT [4–7]. Other investigations have compared CAC evaluation to non-invasive stress tests (such as exercise testing or nuclear studies) demonstrating its higher correlation with the burden of coronary artery disease [8,9]. Quantification of CAC usually requires dedicated chest computed tomography (CT) scans that are thin-layer (usually slices of 3 mm) and electrocardiography (ECG) gated, in order to minimize motion artifacts from beating heart and to provide better quality images. These scans are not often performed in the daily clinical practice because of longer acquisition time and technical difficulties such as the need for cooperation of patients.

There is evidence that CAC scoring quantified on standard (non-ECG gated and non-thin layer) chest CT examinations, which is routinely performed before LT to exclude contraindications, correlates well with scores obtained from dedicated scans [10,11], and may be of prognostic value in certain subsets of patients such as smokers at high risk for lung cancer [12,13,14]. However, it remains to be established whether CAC quantified on standard chest CT is able in stratifying the risk of cardiovascular complications after LT.

The aim of our study was to evaluate the burden of CAC at pre-transplant CT and its association with peri-operative and within the first year cardiovascular complications after LT. The CAC score was not available at the time of pre-LT cardiac evaluation and did not influence the diagnostic work-up and eligibility decision: for this reason, we were able to assess the additional prognostic value of CAC amount in patients considered eligible to LT according to standard evaluation.

2. Methods

The study analyzed patients with end-stage liver disease who underwent LT at Padua Hospital between January 2013 and May 2018. The study was approved by the Medical Ethics Committees of the University of Padua. Because of the retrospective and observational nature of the study no consent was required. The data that support the findings of this study are available from the corresponding Author upon reasonable request. Exclusion criteria included age < 18 years, known obstructive coronary artery disease (CAD), previous surgical or percutaneous coronary revascularization, previous myocardial infarction, or CT with inadequate quality for CAC quantification. To improve the reliability of the results, we also excluded patients who underwent chest CT more than 6 months before transplantation.

2.1. Pre-transplant cardiological evaluation

Pre-transplantation data were collected from in-hospital and outpatient clinical evaluation, as well as data available on digital medical records of our Hospital. When other main etiological factors of liver disease (HBV, HCV, alcohol, autoimmune diseases) were excluded, the origin of cirrhosis was classified as metabolic or cryptogenic based on clinical probability. The group of metabolic cirrhosis was mainly composed of obese patients with associated metabolic syndrome and included those with non-alcoholic fatty liver disease.

Data systematically collected at pre-transplant cardiological evaluation included history (especially data of special interest for cardiological risk stratification), clinical evaluation, chest X ray, electrocardiogram (ECG), basal trans-thoracic echocardiography. Further examinations, such as ECG-stress test, physical or pharmacological stress echocardiography and invasive cardiac catheterization including coronary angiography and measurement of pulmonary pression, were reserved to selected candidates based on the results of first-level investigations. Although indications to stress testing to rule out CAD were not standardized at the time of the study, they were typically based on the presence of multiple CAD risk factors (male gender, diabetes, active smoking, hypertension, dyslipidemia, age > 60 year-old) or of ≥1 clinical risk factors according to the "Revised cardiac risk index" (CRI), also known as "LEE score" (chronic kidney disease, diabetes mellitus requiring insulin therapy, history of heart failure, angina pectoris, history of stroke or transient ischemic attack), as suggested by the European Society of Cardiology guidelines for cardiovascular risk stratification before non-cardiac surgery [15]. In case of positive stress testing, regional left ventricular wall motion abnormalities (suspected of ischemic origin) or high probability of pulmonary hypertension at baseline echocardiography, cardiac catheterization with coronary angiography was performed.

Data on the degree of CAC were not available at the time of pre-transplant cardiac evaluation and did not influence the diagnostic work-up and transplant eligibility decision.

2.2. Coronary artery calcium score quantification

Pre-LT thoraco-abdominal standard CT was performed in all patients before LT for exclusion of contraindications (particularly malignancy). Coronary artery calcium score was quantified with post-processing analysis of the standard thoracic 6-mm CT scan images (DICOM files) using Calcium Scoring Plugin of the software Horos Project™, version 3.0 (horosproject.com). CAC was quantified using an Agatston scoring method, and classified as none (0), mild (1–99), moderate (100–399) and severe (≥ 400) (Fig. 1).

2.3. Definition of outcome

Outcome information were obtained from surgical and anesthesiologic records, follow-up outpatient evaluations, available digital medical records of our Hospital and/or telephonic communication. The primary end-point was a combination of intra-operative cardiac arrest due to ventricular arrhythmias, cardiac death or non-fatal major cardiovascular complications (heart failure requiring hospitalization, sustained ventricular tachycardia or ventricular fibrillation, acute myocardial infarction) that occurred in the first year following LT. Secondary outcomes were the single type of events.

2.4. Statistical analysis

Categorical variables were presented as counts (%) and compared using the Fisher exact test or the chi-squared test. As normality could not be assumed for any variables, continuous variables were presented as median (1st-3rd quartiles) and compared with non-parametric tests such as the rank sum test (two groups) or the Kruskal-Wallis test (multiple groups). Age, gender, risk factors for CAD and the presence of ≥1 clinical risk factors according to the Revised CRI were input in a univariate logistic regression analysis to evaluate the association with the outcome considered; variables with significant proportion difference at baselines were included in a multivariable logistic regression analysis. The evaluation of the improvement in the model fitting after the inclusion of the CAC score compared to the Revised CRI score alone was performed using the likelihood test with the Akaike criterion [16]. Furthermore, the Net Reclassification Improvement was estimated by comparing the model with only the Revised CRI and the model with both the Revised CRI and the CAC scores [17]. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using R Studio Software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

During the study period, 421 patients underwent LT. Of those, 88 were excluded because standard thoracic CT had been performed more than 6 months before transplant; 19 because the CT had inadequate quality for CAC quantification and 13 because of a known history of ischemic heart disease. Thus, the final sample included 301 patients. There were no significant differences in main clinical characteristics between patients who were and were not included.

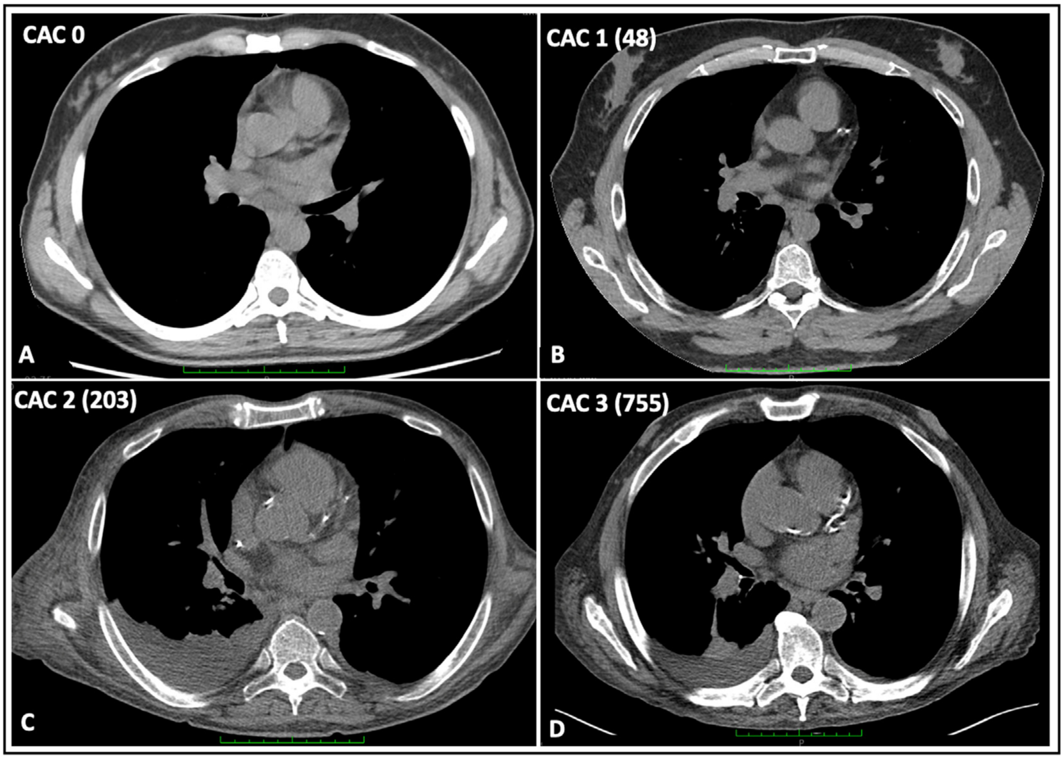

Fig. 1. Representative example of the different coronary artery calcium (CAC) categories at standard chest computed tomography. A: No coronary calcium (CAC = 0); B: Mild coronary calcifications (CAC = 48); C: moderate coronary calcifications (CAC = 203); D: severe coronary calcifications (CAC = 755).

3.1. Baseline characteristics and preoperative cardiac evaluation

Baseline characteristics of the study population are summarized in Table 1. The median age at transplant was 57 years, with a predominance of male sex (76%). The most common underlying liver disease was HCV-related cirrhosis, followed by HBV and alcoholic. The median Child Pugh and Meld score at transplantation were, respectively, 7 and 15.

Preoperative cardiac evaluation results are listed in Table 2. Based on pre-transplant cardiac evaluation, 68 patients underwent one or more inducible-ischemia noninvasive tests (27 stress ECG, 17 dipyridamole-stress echocardiography, 8 dobutamine-stress echocardiography, 28 cardiac SPECT). Of those, 1 stress ECG (3%) and 3 cardiac SPECT (11%) resulted abnormal. These 4 patients underwent invasive coronary angiography that, by inclusion criteria, resulted negative.

3.2. Coronary artery calcium score quantification

Of the 301 patients analyzed, 147 (49%) had no coronary artery calcium; 82 patients (27%) had a mild CAC score (with a value between 1 and 99), 46 (15%) a medium CAC score (between 100 and 399); and 26 (9%) high levels of CAC (>400). A comparison of the baseline characteristics of LT recipients listed according to the CAC score thresholds at chest CT scan is shown in Table 3. Age, male gender, hypertension and diabetes correlated significantly with a higher CAC burden.

3.3. Outcome

Of the 301 LT recipients, 42 (14%) died within one year, mostly for non-cardiovascular causes (21 for infective complications, 4 for liver failure, 5 for neoplasia, 7 for other complications); 19 (6%) patients underwent urgent or emergent re-transplantation. Cardiac outcomes and their incidence are listed in Table 4. The combined cardiovascular outcome was met by 37 (12%) patients: of those, 5 (2%) experienced multiple complications. Specifically, 7 (2%) patients experienced intra-operative cardiac arrest due to malignant arrhythmias (ventricular fibrillation or unstable ventricular tachycardia), fatal in two cases, 30 (10%) patients developed one or more cardiovascular complications during the 1-year follow-up period, and 3 (1%) died for cardiovascular causes after the transplant. Twenty-one of the 37 patients who met the primary endpoint (57%), experienced the outcome within 30 days after LT.

3.4. Predictors of adverse cardiac outcome

Table 5 shows the association between cardiac outcomes and the different CAC score thresholds. The probability of meeting the primary outcome, as well as the secondary endpoints of non-fatal cardiac complications and cardiovascular death, were significantly associated with the CAC score. A sub-analysis including only the events that occurred within 30 days showed that CAC score categories remained associated with the primary outcome ($p = 0.03$).

Table 6 shows univariable and multivariable analysis for predictors of the primary combined end-point. At univariable analysis, age at the time of LT, CAC category and the presence of ≥1 clinical risk factors according to the Revised CRI predicted the end-point. At multivariable analysis, CAC category and the presence of ≥1 clinical risk factors according to the Revised CRI remained significant. A significant improvement in the fitting of the model that included both the Revised CRI and the CAC category was detected (p-value 0.03) compared to the model with only the Revised CRI (Net Reclassification Improvement = 0.50, $p = 0.003$).

4. Discussion

Coronary artery calcium quantification requires a dedicated (ECG-gated, thin-layer) CT that may not be available at the time of cardiology consultation for assessment of suitability to LT: for this reason, we

Table 1
Baseline characteristics of the 301 liver transplant recipients.

Variables	Value
Age at transplant (years)	57 [50–63]
Sex, male	230 (76)
Obesity	49 (16)
Diabetes mellitus	76 (25)
Dyslipidemia	14 (5)
Arterial hypertension	111 (37)
Smoking history	
Past smoking	83 (28)
Active smoking	69 (23)
Familiar history of CAD	24 (8)
Chronic kidney disease	16 (5)
Previous stroke or TIA	5 (2)
Underlying liver disease	
HCV-related liver cirrhosis	111 (37)
HCV + HBV-related liver cirrhosis	6 (2)
HBV-related liver cirrhosis	45 (15)
HBV + HDV-related liver cirrhosis	12 (4)
Alcoholic liver cirrhosis	54 (18)
Metabolic liver cirrhosis	17 (6)
Cryptogenic liver cirrhosis	15 (5)
Cholestatic liver cirrhosis, n (%)	15 (5)
Other/Mixed disease, n (%)	24 (8)
History of alcohol abuse, n (%)	84 (28)
Hepatocellular carcinoma, n (%)	169 (56)
GI bleeding, n (%)	45 (15)
Hepatic encephalopathy, n (%)	90 (30)
History of ascites, n (%)	177 (59)
Child-Pugh score at transplant	7 [6–10]
MELD score at transplant	15 [10–24]

Data are expressed as median (1st-3rd quartiles) or number (percentage). CAD: coronary artery disease; GI: gastro-intestinal; MELD: Model for End-Stage Liver Disease; TIA: transient ischemic attack. Obesity was defined as BMI (body mass index) > 30 kg/m2. Diabetes mellitus was defined according to the 2019 American Diabetes Association recommendations as fasting glucose levels >125 mg/dl on two different days, HbA1c > 6.5% or ongoing antidiabetic drug treatment. Dyslipidemia was defined as LDL value above 130 mg/dl, ongoing lipid lowering therapy or diagnosis of familiar hypercholesterolemia. Arterial hypertension was defined as blood pressure ≥ 140/90 mmHg or a history of hypertension with ongoing medical therapy. Chronic kidney disease was defined as an estimated creatinine clearance <60 ml/min/1.73m^2 calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Table 2
Cardiological pre-transplant evaluation.

Variables	Value
Baseline ECG	
Normal	66 (22)
ST-deviation at baseline ECG	6 (2)
Corrected QT value, Bazett formula (msec)	448 [430–465]
Baseline echocardiography	
Ejection fraction (%)	63 [60–68]
LV end-diastolic volume, biplanar (ml/m2)	58 [48–70]
RV end-diastolic area (mm2)	16 [11−20]
RV FAC (%)	47 [41–52]
TAPSE (mm)	25 [21–29]
PAPs (mmHg)	29 [25–33]
Abnormal diastolic function	
Grade 1	72 (89)
Grade 2	9 (11)
Ascending aorta pathology	24 (8)
Pericardial effusion	15 (5)
More than mild valvular heart disease	30 (10)

Data are expressed as median (1st-3rd quartiles) or number (percentage). ECG: electrocardiography; FAC: fractional area change; LV: left ventricle; PAPs: systolic pulmonary artery pression; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion.

evaluated whether CAC calculated on a standard chest CT performed for other reasons (mainly to exclude malignancies) remains of prognostic value. Although the association between CAC calculated on a dedicated (thin-layer) CT scan has already been described [4–7], to the best of our knowledge we evaluated for the first time the prognostic role of CAC on standard CT for risk stratification after LT.

The study population consisted of a consecutive cohort of patients who underwent OLT with no history of CAD or coronary revascularization. These patients had been evaluated by a cardiologist before OLT with a resting echocardiography; in case of abnormal findings or high risk of CAD, further investigations such as non-invasive stress-imaging or invasive cardiac catheterization were performed. However, CAC score was not known at the time of evaluation: for this reason, we were able to assess the additional prognostic value of CAC amount in patients considered eligible to OLT according to standard evaluation.

4.1. Role of the CAC quantification for risk stratification of LT candidates

A common consensus regarding the methodology of CAD screening in pre-LT patients is lacking[3]. Standard tools for cardiac risk stratification include clinical evaluation, ECG and basal echocardiography; further investigations (anatomical or functional) are generally reserved to selected patients, depending on their characteristics. In particular, while the American Heart Association Guidelines suggest to consider traditional CAD risk factors (such as age, hypertension, dyslipidemia, smoking) to identify patients who should undergo stress testing to rule out myocardial ischemia before LT, the European Society of Cardiology endorses the use of the Revised CRI, which is specifically designed to estimate the risk of adverse cardiac outcomes in non-cardiac surgery [15,18].

One major finding of this study was that, despite systematic pre-transplant cardiac evaluation including resting echocardiography in all patients and stress-imaging in selected cases, 37 out of 301 LT recipients (12%) without known CAD developed serious cardiovascular complications during the peri-operative period and the first year of follow-up (including acute myocardial infarction, heart failure requiring hospitalization and life-threatening arrhythmias) and 5 (2%) died for cardiac reasons.

Several studies have investigated the potential role of CAC quantification, which does not require contrast medium, to improve cardiovascular risk stratification of patients undergoing LT. Kong and colleagues [4] reported a significant association between high levels of CAC score (>400) and early cardiovascular complications after LT. McAvoy el al. [19] demonstrated a significant relationship between CAC score and cardiovascular risk factors in LT recipients. Jodocy and colleagues [20] also described positive coronary CT findings (CAC >300) as a useful non-invasive measure of the prevalence of CAD in LT recipients during a post-transplant follow-up of 15 months.

4.2. Coronary artery calcium on standard chest CT

Quantification of CAC requires dedicated 3-mm sliced ECG-gated chest CT scans that may not be available in the daily clinical practice. Other investigations have already evaluated the possibility of quantifying CAC on standard (non-gated, non-thin-layer) chest CT examinations, with a good correlation with quantification obtained from dedicated gated scans [10,11]. Moreover, the prognostic value in specific subsets of patients has been demonstrated, such as in smokers at high risk for lung cancer [12–14].

Based on these data, we quantified CAC score using standard chest CT scans images, which was an examination performed in all candidates of our Hospital as part of the pre-transplant clinical investigations, in order to exclude contraindications (particularly malignancy). This strategy represented one of the main strengths of our study, because it did not require dedicated chest CT scan or the use of iodine contrast medium. The rate of inadequate quality CT for CAC quantification was low (4.5%), suggesting the feasibility of using previously acquired standard chest CT images in the majority of cases.

In our LT recipients, cardiac complications and cardiovascular death were significantly associated with the CAC value, independently from

Table 3
Baseline characteristics of liver transplant recipients according to the CAC score thresholds.

	CALCIUM SCORE				
	0 ($n = 147$)	1–99 ($n = 82$)	100–399 ($n = 46$)	> 400 ($n = 26$)	p
Age (years)	53 [45–60]	59 [55–65]	62 [55–66]	63 [58–66]	<0.001
Sex, male	99 (67)	68 (83)	38 (83)	25 (96)	0.002
Hypertension	44 (30)	30 (36)	20 (46)	17 (65)	0.004
DM	26 (18)	24 (29)	11 (24)	15 (58)	<0.001
Dyslipidemia	4 (3)	7 (8)	1 (2)	2 (9)	0.16
CKD	4 (3)	4 (5)	6 (14)	2 (9)	0.05
Previous stroke/TIA	2 (2)	1 (1)	1 (2)	1 (4)	0.80
Active smoking	33 (23)	24 (29)	8 (17)	4 (15)	0.35
EF (%)	63 [60–68]	63 [60–67]	64 [60–69]	60 [58–66]	0.51
Revised CRI	21 (14)4	20 (24)	12 (26)	9 (35)	0.04

Data are expressed as median (1st-3rd quartiles) or number (percentage) as appropriate. CKD: chronic kidney disease; CRI: cardiac risk index; DM: diabetes mellitus; EF: ejection fraction; TIA: transient ischemic attack.

Table 4
Cardiac complications and outcomes.

Outcome	$N = 301$
Cardiac death	5 (2)
Intraoperative cardiac arrest	7 (2)
Non-fatal cardiac complications after transplantation	30 (10)
Major arrhythmias	2 (1)
Acute myocardial infarction	12 (4)
Heart failure	16 (5)

Data are expressed as number (percentage).

other significant factors such as age or chronic kidney disease. In particular, the combined end-point was met by 7% of patients with no coronary calcifications (CAC = 0) versus 27% of patients with diffuse calcifications (CAC > 400). At regression analysis for predictors of the end-point, only CAC score and the presence of ≥1 clinical risk factors included in the Revised CRI, but not traditional risk factors for CAD, remained independent predictors of the end-point. A risk stratification model including both the CAC category and Revised CRI clinical risk factors significantly improved the predictive ability compared to the Revised CRI alone.

These findings suggest that CAC may be a strong risk factor in the pre-operative cardiological evaluation of LT candidates even if calculated on a standard chest CT. In particular, addition of CAC burden to traditional risk factors increases the chances to identify patients at-risk of an adverse cardiac outcome at the time of cardiac screening for potential eligibility to LT. For these reasons, when assessing cardiac risk in LT candidates, it could be of added value to consider the CAC value, when a chest CT-scan is available, together with patients' history and the “classical” risk factors. The goal is to better select those who may need further investigations before becoming eligible to LT.

4.3. Study limitations

The study has some limitations that should be acknowledged, including the retrospective design and the relatively small number of

Table 6
Univariate and multivariate regression analysis for predictors of the combined cardiovascular outcome.

	Univariable Analysis		Multivariable Analysis	
Variables	OR (95% CI)	p value	OR (95% CI)	p value
Age at transplant	1.06 (1.01–1.10)	0.01	1.04 (0.99–1.09)	0.10
Sex, male	0.88 (0.38–2.02)	0.76		
Hypertension	0.97 (0.46–2.09)	0.96		
Diabetes mellitus	1.47 (0.67–3.18)	0.34		
Dyslipidemia	-*	–		
Active smoking	0.76 (0.31–1.82)	0.52		
CAC category				
0	1	0.01	1	0.02
0–99	1.51 (0.59–3.82)		1.35 (0.53–3.45)	
100–399	3.41 (1.34–8.66)		3.05 (1.18–7.89)	
≥400	4.52 (1.56–13.10)		3.73 (1.25–11.1)	
Revised CRI ≥ 1	3.15 (1.52–6.52)	0.002	2.71 (1.28–5.75)	0.009

CAC: coronary artery calcium; CI: confidence interval; CRI: cardiac risk index; OR: odds ratio.
* the odds ratio could not be calculated as no events occurred in patients with dyslipidemia.

events. While pre-transplant cardiac evaluation was blinded to CAC values, the presence of CAD risk factors and of clinical risk factors according to the Revised CRI potentially influenced the eligibility decision. As the study included only patients who underwent LT, we cannot exclude a selection bias that might affect the generalizability of the results of the risk prediction model to the overall population of LT candidates. Moreover, a subset of patients was excluded because the CT was performed more than 6 months before the event or had inadequate quality for CAC quantification. Finally, we recognize that more than half of cardiac events occurred in the peri-operative period or within the first month when multiple mechanisms other than CAD (e.g. inflammation, blood loss, electrolytic disturbances etc.) can play a major physiopathological role in causing cardiac complications: for this reason, despite the significant association between CAC and early cardiac outcomes, we cannot infer a cause-effect relation.

5. Conclusions

In conclusion, CAC score quantified on standard (non-gated) chest CT was associated with the incidence of perioperative and post-operative (within 1-year) cardiac complications and cardiac death among patients considered eligible for LT after systematic cardiac evaluation blinded to CAC value. Moreover, the CAC score demonstrated additional prognostic value to traditional pre-transplant cardiac assessment based on risk factors, suggesting its potential utility for assessing LT eligibility and need for further testing to rule out CAD. Because CAC assessment does not require contrast medium administration and can be calculated from images of a standard chest CT performed for other reasons, it can be used as an early risk stratification tool. Although precise CAC quantification requires a dedicated software that may not be available at the time of patient evaluation, we can speculate that at least the opposite sides of the spectrum (i.e. no calcifications vs. severe calcifications) may be easily recognized by a quick

Table 5
Associations between cardiac outcomes and different CAC score thresholds.

	CAC = 0 N = 147	CAC = 1–99 N = 82	CAC = 100–399 N = 46	CAC > 400 N = 26	p
Combined end-point	11 (7)	9 (11)	10 (22)	7 (27)	0.007
Perioperative arrhythmic cardiac arrest	3 (2)	3 (4)	0	1 (4)	0.56
Non-fatal cardiac complications	9 (6)	6 (7)	8 (17)	7 (27)	0.002
Cardiac death	0 (0)	2 (2)	2 (4)	1 (4)	0.04

Data are expressed as number (percentage). CAC: coronary artery calcium.

review of the chest CT images with little training. However, further studies are needed to verify the concordance between "calculated" and "visually-assessed" CAC category.

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Declaration of Competing Interest

none.

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References

[1] M. Izzy, L.B. Vanwagner, S.S. Lee, M. Altieri, M. Angirekula, K.D. Watt, Understanding and managing cardiovascular outcomes in liver transplant recipients, Curr Opin Organ Transplant. 24 (2019) 148–155.

[2] G. Therapondos, A.D. Flapan, J.N. Plevris, P.C. Hayes, Cardiac morbidity and mortality related to orthotopic liver transplantation, Liver Transpl. 10 (2004) 1441–1453.

[3] L.B. VanWagner, M.E. Harinstein, J.R. Runo, C. Darling, M. Serper, S. Hall, et al., Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations, Am. J. Transplant. 18 (2018) 30–42.

[4] Y.G. Kong, J.W. Kang, Y.K. Kim, H. Seo, T.H. Lim, S. Hwang, et al., Preoperative coronary calcium score is predictive of early postoperative cardiovascular complications in liver transplant recipients, Br. J. Anaesth. 114 (2015) 437–443.

[5] N. Kemmer, J. Case, S. Chandna, G.W. Neff, The role of coronary calcium score in the risk assessment of liver transplant candidates, Transplant. Proc. 46 (2014) 230–233.

[6] Y.G. Kong, T.Y. Ha, J.W. Kang, S. Hwang, S.G. Lee, Y.K. Kim, Incidence and predictors of increased coronary calcium scores in liver transplant recipients, Transplant. Proc. 47 (2015) 1933–1938.

[7] J. Buggs, S. Aslam, C. Walker, M. Hook, M Matyja T, Rogers E, et al. pre-liver transplant coronary artery disease workup for low-risk patients, Am. Surg. 86 (2020) 976–980.

[8] K. Nieman, T.W. Galema, L.A. Neefjes, A.C. Weustink, P. Musters, A.D. Moelker, et al., Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain, Am. J. Cardiol. 104 (2009) 1499–1504.

[9] A.I. Löffler, J.A. Gonzalez, S.K. Sundararaman, R.C. Mathew, P.T. Norton, K.D. Hagspiel, et al., Coronary computed tomography angiography demonstrates a high burden of coronary artery disease despite low-risk nuclear studies in pre–liver transplant evaluation, Liver Transplant. 26 (2020) 1398–1408.

[10] H.S. Hecht, P. Cronin, M.J. Blaha, M.J. Budoff, E.A. Kazerooni, J. Narula, et al., 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the Society of Cardiovascular Computed Tomography and Society of thoracic radiology, J Cardiovasc Comput Tomogr. 11 (2017) 74–84.

[11] J. Kirsch, I. Buitrago, T.L.H. Mohammed, T. Gao, C.R. Asher, G.M. Novaro, Detection of coronary calcium during standard chest computed tomography correlates with multi-detector computed tomography coronary artery calcium score, Int J Cardiovasc Imaging. 28 (2012) 1249–1256.

[12] P.C. Jacobs, M.J.A. Gondrie, Y. Van Der Graaf, H.J. De Koning, I. Isgum, B. Van Ginneken, et al., Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose ct screening for lung cancer, Am. J. Roentgenol. 198 (2012) 505–511.

[13] Y.K. Kim, Y.M. Sung, S.H. Cho, Y.N. Park, H.Y. Choi, Reliability analysis of visual ranking of coronary artery calcification on low-dose CT of the thorax for lung cancer screening: comparison with ECG-gated calcium scoring CT, Int J Cardiovasc Imaging. 30 (2014) 81–87.

[14] R.A.P. Takx, P.A. De Jong, T. Leiner, M. Oudkerk, H.J. De Koning, C.P. Mol, et al., Automated coronary artery calcification scoring in non-gated chest CT: agreement and reliability, PLoS One 9 (2014), e91239.

[15] S.D. Kristensen, J. Knuuti, A. Saraste, S. Anker, H.E. Bøtker, S. De Hert, et al., 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the joint task force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth, Eur. Heart J. 35 (2014) 2383–2431.

[16] M. Ellison Aaron, J. Gotelli Nicholas, D. Inouye Brian, R. Strong Donald, P values, hypothesis testing, and mdoel selection: it's deja vu all over again, Ecology 95 (3) (2014) 609–610, https://doi.org/10.1890/13-1911.1 published online.

[17] M.J. Pencina, R.B. D'Agostino, K.M. Pencina, Janssens ACJW, P. Greenland, Interpreting incremental value of markers added to risk prediction models, Am J Epidemiol 176 (6) (2012) 473–481.

[18] K.L. Lentine, S.P. Costa, M.R. Weir, J.F. Robb, L.A. Fleisher, B.L. Kasiske, et al., Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, J. Am. Coll. Cardiol. 60 (2012) 434–480.

[19] N.C. McAvoy, N. Kochar, G. McKillop, D.E. Newby, P.C. Hayes, Prevalence of coronary artery calcification in patients undergoing assessment for orthotopic liver transplantation, Liver Transplant. 14 (2008) 1725–1731.

[20] D. Jodocy, S. Abbrederis, I.W. Graziadei, W. Vogel, O. Pachinger, G.M. Feuchtner, et al., Coronary computer tomographic angiography for preoperative risk stratification in patients undergoing liver transplantation, Eur. J. Radiol. 81 (2012) 2260–2264.