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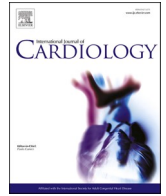
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## Coronary artery calcium assessment on non-gated chest CT to optimize pre-operative cardiac screening in liver transplantation

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### ABSTRACT

**Background:** Guidelines recommend standard pre-operative cardiac screening in all liver transplantation (LT) recipients, despite the relatively low prevalence of obstructive coronary artery disease. Most LT recipients often have non-gated computed tomography (CT) performed of the chest and abdomen. This study evaluated the ability of coronary artery calcification (CAC) assessment on consecutively available scans, to identify a selection of low-risk patients, in whom further cardiac imaging can be safely withheld.

**Methods:** LT recipients with prior non-gated CT chest-abdomen were included. CAC was visually scored on a semi-quantitative ordinal scale. Stress myocardial perfusion, coronary CT angiography (CCTA) and invasive coronary angiography (ICA) were used as golden standard. The sensitivity and specificity of CAC to exclude and predict obstructive CAD were assessed. In addition, peri- and postoperative mortality and cardiac events were analyzed.

**Results:** 149 LT recipients (ranged 31–71 years) were included. In 75% of patients, no CAC and mild CAC could rule out obstructive CAD on CCTA and ICA with 100% certainty. The threshold of mild CAC had a sensitivity of 100% for both CCTA and ICA and a specificity of 91% and 68%, respectively. None of the patients with no or mild calcifications experienced peri- and post-operative cardiac events or died of cardiac causes.

**Conclusion:** Visual evaluation of CAC on prior non-gated CT can accurately and safely exclude obstructive CAD in LT recipients. Incorporation of these already available data can optimize cardiac screening, by safely withholding or correctly allocating dedicated cardiac imaging in LT recipients. Thereby, reducing patients' test burden and save health care expenses.

### 1. Introduction

Current guidelines [1–3] classify patients undergoing liver transplantation (LT) as the highest surgical risk group for cardiovascular death, myocardial infarction, and stroke. Studies have demonstrated that >40% of early post-operative mortality is caused by cardiovascular diseases [4,5]. Herein, coronary artery disease (CAD) has been shown to play an important role [6,7]. Conversely, the prevalence of obstructive CAD and ischemia appears to be relatively low [8], which questions the importance and efficiency of a comprehensive pre-operative cardiovascular screening in all LT candidates.

No current consensus exists on the optimal pre-operative cardiac screening strategy. The accuracy of ischemia detection (with e.g., myocardial stress perfusion) for screening in LT candidates has been debated [8–12]. Other alternatives are coronary computed tomography (CT) angiography or invasive coronary angiography (ICA). However, intravenous contrast and nitroglycerin administration can be undesirable in patients with hemodynamic derangements and coinciding renal failure in a large proportion of LT candidates. With ICA other complications (e.g., bleeding, vascular complications) can arise. A well performing gatekeeper investigation would enable patient-tailored additional cardiac imaging and withholding imaging where safely

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possible.

LT candidates often have non-cardiac (i.e., non-electrocardiogram gated) CTs performed of the thorax and abdomen as follow-up of their liver disease. Patients' coronary artery calcium (CAC) can be accurately assessed on these earlier acquired scans, which is a reliable technique [13–15]. CAC is an indicator of patients' CAD-burden and has proven to be predictive of significant stenosis requiring revascularization [16] and post-operative mortality in LT patients [17]. Conversely, the absence of CAC strongly correlates with event-free survival [17,18].

We hypothesize that these non-gated scans could serve as a gatekeeper to select LT candidates at risk of CAD, who should undergo additional pre-operative cardiac screening. The current study explores the ability of visual CAC assessment on non-gated CT, to rule out obstructive CAD and guide allocation of dedicated cardiac imaging in LT candidates.

## 2. Methods

For this analysis we retrospectively screened 470 consecutive patients who underwent cardiac pre-operative screening before liver transplantation between 2008 and 2023 at the Leiden University Medical Center (LUMC). Patients were included when they received cardiac screening with coronary CT angiography (CCTA), myocardial stress perfusion or invasive coronary angiography (ICA) and underwent a subsequent liver transplantation. Patients were excluded when they were aged <30 years, as the prevalence of CAC in younger patients appears low [19]. Furthermore, patients were excluded when they had a history of coronary artery disease including myocardial infarction, had prior coronary intervention before their cardiac evaluation or had a prior liver transplantation before 2008. The remaining patients were screened for the availability of a non-gated CT of the chest prior to their pre-operative cardiac screening. If patients had a CT performed >7 years prior to the pre-operative cardiac screening, they were excluded. This is based on the previously established warranty for CAC on cardiac CT with the Agatston score [20,21]. According to these studies, physicians should consider re-evaluation of patients' CAC every 3 to 7 years.

Ultimately, 149 patients were included. This selection of patients is depicted in Supplemental file (Fig. 1).

The hospital's ethical review board waived the need for informed consent.

Furthermore, patients' medical records were screened for the presence of cardiac risk factors (e.g., diabetes mellitus, smoking), post-operative immunosuppressive medication, family history and underlying liver disease. Pre-LT liver disease severity was determined based on the Child-Pugh Score (CPS) [22] and Model of End-stage Liver Disease (MELD) [23] score.

### 2.1. Pre-liver transplantation screening

As part of cardiac screening pre-LT, patients either underwent non-invasive cardiac imaging or ICA. All patients with diabetes mellitus were perceived as high-risk patients for coronary artery disease [24,25]. Therefore, all these patients underwent invasive coronary angiography. Non-invasive cardiac imaging was performed with a Coronary CT Angiography (CCTA) or stress myocardial perfusion scintigraphy (Myoview) at the discretion of the cardiologist.

CCTA was performed with a 320-slice scanners (Canon Medical Systems, The Netherlands) and patients were scanned according to a previously prescribed protocol [26], in line with current guidelines from the Society of Cardiovascular Computed Tomography. Patients were screened for coronary atherosclerosis, with plaque categorized as calcified and non-calcified. Obstructive CAD was defined as stenosis for which ICA was recommended (i.e.  $\geq 70\%$ ), according to the Coronary Artery Disease-Reporting and Data System (CADRADS) [27]. Extensive calcifications herein can form a challenge as they increase the risk of overestimation of atherosclerotic lesions and false positive results [28].

In some cases, these "blooming artefacts" complicated determining the stenosis grade. If so, obstructive CAD was based on the clinical decision of the cardiologist reviewing the CCTA. Most (>70%) of these patients received a subsequent ICA.

Stress myocardial perfusion imaging was performed with Single-Photon Emission Computed Tomography (SPECT) (GE Discovery) and the radiopharmaceutical  $^{99m}\text{Tc}$ -tetrofosmin, in line with guidelines from the Society of Cardiovascular Computed Tomography [29,30]. Stress was induced with the pharmacological agent regadenoson or adenosine or with a stress electrocardiogram (X-ECG). Myocardial perfusion defects and wall motion abnormalities were analyzed, and phase analysis was performed (i.e., resting-phase versus stress-phase). Abnormalities in myocardial perfusion with SPECT were indicated by decreased tracer uptake, defined as irreversible (infarction) or reversible (ischemia) perfusion defects.

For ICA, obstructive CAD was defined as a stenosis grade of  $\geq 70\%$ . Performance of fractional flow reserve was at the discretion of the operator, and a fractional flow reserve cut-off value of <0.80 was used as significant obstructive CAD.

### 2.2. Image acquisition and evaluation of non-gated chest CT

Non-gated CTs of the chest were performed as part of routine follow-up on patients' liver disease or other non-cardiac care (e.g., long nodules). The specific scan protocol was different per indication (Canon Medical Systems, The Netherlands). Patients' CAC was visually assessed on standard-dose scans with 1-mm axial slices. This method of visual CAC-assessment on non-gated CT scans has been extensively described and proven accurate [14,15,31,32]. Briefly, the extent of CAC in four main coronary arteries is visually evaluated; the right coronary artery, the left main, the left anterior descending and left circumflex (including secondary branches e.g., diagonals). The extent of CAC is quantified on a semiquantitative ordinal scale ranging from 0 to 12. Subsequently, the patient's total CAC score is categorized based on increasing severity: no (CAC 0), mild (CAC 1 to 3), and severe (CAC 4 to 12). The evaluation time is <1 min and this method has no specific imaging requirements [14,15,31,32] and thus easily applicable.

One reader with >2 years of experience in assessment of CCTA and CAC performed CAC-assessment, blinded for of patients' cardiovascular risk profile and dedicated cardiac imaging outcomes.

In addition, patients were retrospectively followed after LT for the occurrence of peri-operative adverse cardiac events and peri-operative mortality ( $\leq 30$  days post LT). Cardiac events were defined as: cardiac arrest, Cardiac Implantable Electronic Device (CIED) implantation, (non-fatal) myocardial infarction, revascularization, and severe arrhythmia (i.e., ventricular tachycardia (VT) or ventricular fibrillation (VF)). Cardiac mortality was a composite endpoint defined as death caused by cardiac arrest, heart failure, myocardial infarction or severe arrhythmia. Cardiovascular mortality was a composite end-point defined as death caused by stroke, pulmonary embolism and Postreperfusion syndrome [33]; defined as a decrease of >30% in the mean systemic arterial blood pressure within 10 min after reperfusion, with or without a doubling of the norepinephrine dose.

### 2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS, Chicago, Illinois version 29.0. Dichotomous variables were described as numbers (%), and continuous variables were reported as mean  $\pm$  SD or median (interquartile range [IQR]). CAC severity groups were compared using a 1-way analysis of variance or a Kruskal-Wallis test for numerical outcomes and a chi-square test for dichotomous outcomes.

The specificity and sensitivity for a previously established [15,31] cut-off point of mild CAC (i.e., CAC score of  $\leq 3$ ) were determined. To visualize these and determine the Area Under the Curve, receiver operating characteristic (ROC) curves were used. In addition, to confirm

whether exclusion of obstructive CAD based on visual CAC was both accurate and safe, peri-operative mortality and occurrence of peri-operative events were analyzed per CAC-group.

To validate the accuracy and reliability of CAC assessment performed, the interrater reliability analysis and interobserver agreement were analyzed with intra class correlation (ICC) and kappa-statistics.

### 3. Results

Patient characteristics are described in Table 1. The median age was 58 years, and most patients were male (83%). The extent of CAC increased significantly with age ( $p < 0.01$ ). A total of 90 patients showed CAC on their non-gated CT, whom 50 (34%) showed mild calcifications (i.e., CAC 1–3) and 40 (27%) severe calcifications (i.e., CAC 4–12). The remaining patients (40%) had no calcifications (i.e., CAC 0). The number of patients with a history of smoking or diabetes was significantly different between the CAC-groups (resp.  $p = 0.002$  and  $p = 0.048$ ), as expected. Other cardiac comorbidities were distributed equally between the three CAC-groups. The most prevalent liver diseases among this patient cohort were hepatocellular carcinoma (HCC) (59%), hepatitis B (22%), and alcohol-associated liver disease (ALD) (30%). The median Child-Pugh Score (CPS) was 6 and most patients had CPS category A (60%). The median MELD score was 10. Severity of liver diseases was not significantly different between the CAC-groups.

Overall, the median time-interval between the prior performed non-gated CT and cardiac pre-operative screening was 2 months. The maximum time-interval was 6 years and 8 months. Most (91%) of the patients had a non-gated CT performed within 12 months before their cardiac pre-operative screening. In the 13 patients with a non-gated CT performed in >12 months, 7 patients underwent CCTA, 4 patients underwent stress myocardial perfusion and 5 underwent ICA.

In total 60 (40%) patients underwent a CCTA for pre-operative cardiac screening, of which 9 were followed-up with ICA. Stress myocardial perfusion imaging was performed in 38 (26%) patients pre-operatively, of which 6 were followed-up with ICA. A total of 66 (44%) patients were pre-operatively screened with ICA. Outcomes of these dedicated imaging modalities are described in Supplemental file (Table 2).

The interobserver agreement between two readers was excellent with  $\kappa = 0.87$ . The interrater reliability for CAC assessment per vessel and total CAC score ranged between 0.92 and 0.98. The ICC and agreement are described in Supplemental file (Tables 3 and 4).

#### 3.1. CAC and CCTA

In the group of patients who received CCTA as pre-operative screening, 47 patients showed no or only mild calcification on the previously performed non-gated CT. Coincidentally, none of these patients had obstructive CAD. Therefore, the absence of calcifications and mild calcifications had a negative predictive value of 100% for obstructive CAD. The remaining patients ( $n = 13$ ) had severe CAC, of which 7 (54%) had obstructive CAD.

The sensitivity of CAC  $\leq 3$  as cut-off value was 100% to exclude obstructive CAD. The specificity for this threshold was 91%. Both the sensitivity and specificity are visualized in a ROC curve depicted in Fig. 1. The AUC was 0.956.

Of interest, in 7 patients with severe CAC the CCTA was difficult to read due to “blooming artefacts”. In 5 patients a subsequent ICA was performed, of which 3 patients had obstructive CAD and 2 did not. Furthermore, in the 7 patients who had a non-gated CT performed in >12 months before CCTA, the absence of calcifications and mild calcifications had a negative predictive value of 100% for obstructive CAD. Therefore, no difference in negative predictive power was observed between patients with short (i.e.,  $\leq 12$  months) and long (i.e., >12 months) time-interval.

**Table 1**

Baseline characteristics of study population,  $N = 149^*$ .

	All (n = 149)	None (n = 59)	Mild (n = 50)	Severe (n = 40)	P-value
Age, years	58 (51–63)	52 (46–60)	61 (54–66)	61 (56–65)	<0.01
Sex, men, %	123 (82.6)	45 (76.3)	43 (86.0)	35 (87.5)	0.258
BMI, kg/m <sup>2</sup>	26.9 ± 4.4	26.3 ± 4.3	27.2 ± 4.3	27.2 ± 4.6	0.443
Comorbidities					
Hypertension** (%)	66 (44.3)	20 (33.9)	23 (46.0)	23 (57.5)	0.065
Diabetes, %	59 (39.6)	18 (30.5)	19 (38.0)	22 (55.0)	0.048
Hypercholesterolemia** (%)	24 (16.1)	9 (15.3)	9 (18.0)	6 (15.0)	0.905
ESRD/CKD (%)	11 (7.4)	4 (6.8)	2 (4.0)	5 (12.5)	0.301
Family history of CAD	29 (19.5)	12 (20.3)	8 (15.7)	9 (23.1)	0.500
Obesity (%)	31 (20.8)	10 (16.9)	11 (22.0)	10 (25.0)	0.423
History of smoking (%)					
Yes	87 (58.4)	24 (40.7)	30 (60.0)	33 (83.0)	0.002
History of Liver diseases (%)					
Hepatitis B	32 (21.5)	18 (30.5)	9 (18.0)	5 (12.5)	0.077
Hepatitis C	25 (16.8)	7 (11.9)	13 (26.0)	5 (12.5)	0.101
Hepatitis D	1 (0.7)	1 (1.7)	0 (0.0)	0 (0.0)	0.464
Primary Biliary Cholangitis (PBC)	2 (1.3)	1 (1.7)	1 (2.0)	0 (0.0)	0.683
Primary Sclerosing Cholangitis (PSC)	14 (9.4)	11 (18.6)	3 (6.0)	0 (0.0)	0.005
Alcohol-associated liver disease (ALD)	45 (30.2)	7 (11.9)	12 (24.0)	26 (65.0)	<0.001
Hepatocellular carcinoma	88 (59.1)	27 (45.8)	33 (64.0)	29 (72.5)	0.020
Polycystic liver disease	7 (4.7)	4 (6.8)	2 (4.0)	1 (2.5)	0.589
Cryptogenic Cirrhosis	6 (4.0)	1 (1.7)	3 (6.0)	2 (5.0)	0.489
Metabolic dysfunction associated steatotic hepatitis (MASH)	18 (12.1)	7 (11.9)	7 (14.0)	4 (10.0)	0.844
Sickle cell disease	2 (1.3)	2 (3.4)	0 (0.0)	0 (0.0)	0.213
Autoimmune hepatitis	6 (4.0)	3 (5.1)	3 (6.0)	0 (0.0)	0.308
Alpha 1 antitrypsin deficiency	4 (2.7)	2 (3.4)	1 (2.0)	1 (2.5)	0.902
Acute liver failure on tuberculostatics	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.5)	0.254
Wilson's disease	2 (1.3)	1 (1.7)	1 (2.0)	0 (0.0)	0.683
Cholangiocarcinoma	4 (2.7)	2 (3.4)	1 (2.0)	1 (2.5)	0.902
Child-Pugh score	4 (2.7)	2 (3.4)	1 (2.0)	1 (2.6)	0.897
CPS A	6 (5–8) 88 (59.5)	5 (5–8) 38 (64.4)	6 (5–8) 31 (62.0)	7 (5–9) 19 (48.7)	0.112 0.480
CPS B	33 (22.3)	10 (16.9)	12 (24.0)	11 (28.2)	
CPS C	27 (18.2)	11 (18.6)	7 (14.0)	9 (23.1)	
Model of End-stage Liver Disease (MELD)	10 (7–14)	9 (7–13)	11 (7–14)	10 (8–17)	0.290

AF = Atrial fibrillation, AFI = Atrial flutter, Abn = Abnormalities, BMI = Body mass index, CAD = Coronary artery disease, CKD = Chronic kidney disease, CVA/TIA = Cerebrovascular accident/Transient ischemic attack, ESRD = End-stage renal disease, PE = Pulmonary embolism.

\* All data are presented as mean ± SD, median (IQR) or as number (%).

\*\* Hypertension: a systolic blood pressure > 130 mmHg or a diastolic blood pressure > 80 mmHg or taking medication for hypertension, Hypercholesterolemia: total cholesterol >200 mg/dL or ratio >5 to 1.

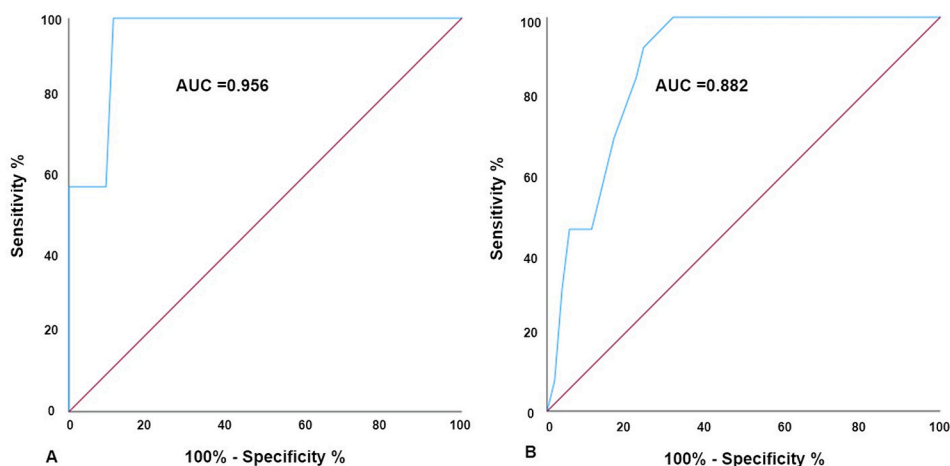


Fig. 1. Receiver operating characteristic (ROC) curves.

A: ROC curve for coronary artery calcium to exclude obstructive coronary artery disease on coronary computed tomography angiography.

B: ROC curve for coronary artery calcium to exclude obstructive coronary artery disease on invasive coronary angiography.

### 3.2. CAC and stress myocardial perfusion

In the group of patients who underwent stress myocardial perfusion imaging ( $n = 38$ , 26%) as pre-operative screening, 16 had no calcifications and 14 had mild calcifications. According to stress myocardial perfusion, 5 of the patients with no or mild calcifications had reversible perfusion defects (i.e., ischemia) and one patient had irreversible perfusion defects (i.e., infarction). Therefore, the negative predictive value of no or mild calcifications was 80% with stress myocardial perfusion as reference standard. However, 5 of these patients were followed-up with ICA and none had obstructive CAD, indicating that the perfusion defects observed in patients without severe CAC with stress myocardial perfusion were false positive.

A total of 8 patients had severe CAC, of which 2 patients showed ischemia with stress myocardial perfusion. These patients received a follow-up ICA, which confirmatively showed obstructive CAD.

Due to the false positive results in patients with no or mild calcification, the efficiency of performing stress myocardial perfusion in these patients could be questioned. The reclassification performance in these patients was low, as reclassification of patients with an initial low risk (i.e., no-mild CAC) to a higher risk after apparent perfusion defects, appeared to be incorrect. The “reclass-benefit” would therefore be low. However, patients who had severe CAC were initially considered as high-risk patients for obstructive CAD. Down-reclassification of these patients’ risk after the absence of perfusion defects appeared correct, as none of these patients experienced peri-operative cardiac events. The “reclass-benefit” in these patients would therefore be high.

Of interest, no difference in negative predictive power was observed between patients with short ( $n = 34$ ) and long time-interval ( $n = 4$ ).

### 3.3. CAC and ICA

In the group of patients who underwent ICA ( $n = 66$ , 44%) as pre-operative screening, 18 had no calcifications and 18 had mild calcification. All of these 36 (55%) patients had no obstructive CAD. Thus, the negative predictive value of no or mild calcification was 100%.

The remaining 30 patients had severe CAC of which 43% had obstructive CAD.

The sensitivity of  $CAC \leq 3$  as cut-off value was 100% to exclude obstructive CAD. The specificity for this threshold was 68%. Both the sensitivity and specificity are visualized in a ROC curve depicted in Fig. 1. The AUC was 0.882.

Of interest, no difference in negative predictive power was observed between patients with short ( $n = 51$ ) and long time-interval ( $n = 5$ ).

### 3.4. Peri-operative mortality and cardiac events

The peri-operative mortality is described in Table 2. Out of 149 patients followed after LT, 4 (<3%) patients died peri-operatively (within 30 days). None of these deaths had a cardiac cause. Two patients died from postreperfusion syndrome [33], as previously described in the Methods section. The other two patients died because of graft failure or multi-organ failure.

Only one patient (<1%) experienced a non-lethal peri-operative cardiac event. This patient had severe CAC on non-gated CT and received pre-operative revascularization. However, one day after transplantation this patient had an in-hospital cardiac arrest (IHCA) due to VF.

### 3.5. Translation to clinical practice

These results are summarized in a decision tree, depicted in Fig. 2. Herein, a proposed algorithm based on CAC on non-gated CT to guide allocation of dedicated cardiac imaging in LT candidates, is explained.

In Supplementary file (Fig. 2) a few case examples of patients with increasing CAC severity on non-gated CT are depicted.

Table 2  
Peri-operative mortality ( $\leq 30$  days).

	N	%
All-cause mortality	4	100
Cardiac death (n = 0)		
Cardiac arrest	0	0
Heart failure	0	0
Myocardial Infarction	0	0
Severe arrhythmia <sup>a</sup>	0	0
Cardiovascular death (n = 2)		
Pulmonary Embolism	0	0
Stroke	0	0
Postreperfusion syndrome <sup>b</sup>	2	50
Non-cardiovascular death (n = 2)		
Graft failure	1	25
Multi organ failure due to major blood loss	1	25

<sup>a</sup> Defined as ventricular tachycardia (VT) or ventricular fibrillation (VF).

<sup>b</sup> Defined as a decrease of >30% in the mean systemic arterial blood pressure within 10 min after reperfusion, with or without a doubling of the norepinephrine dose.

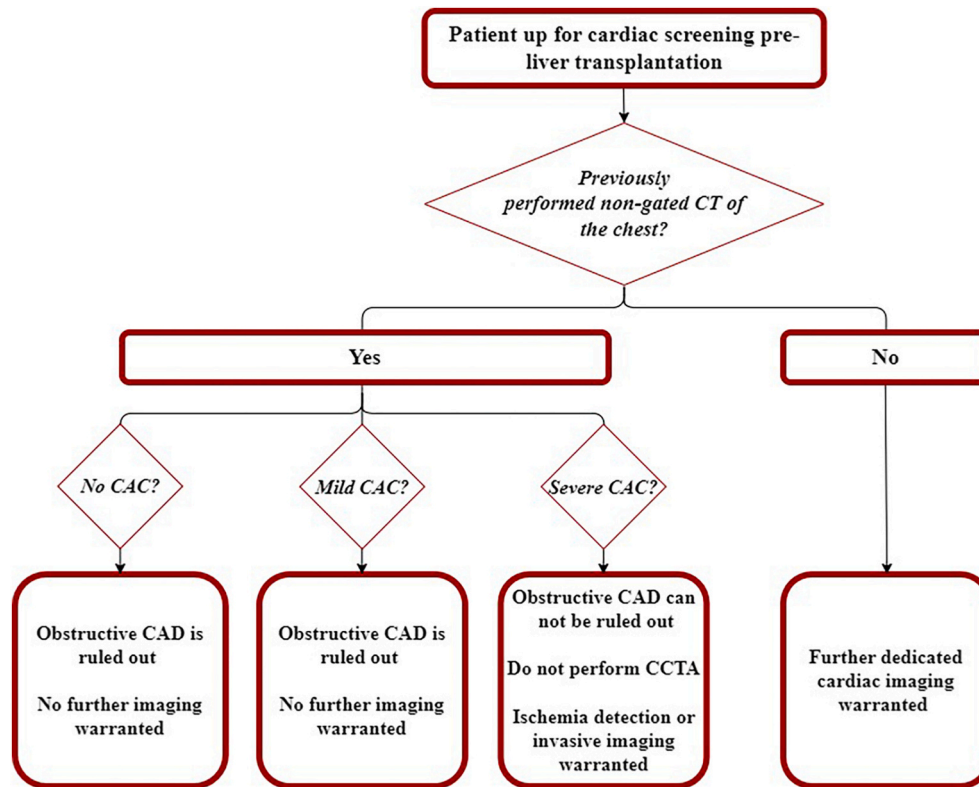


Fig. 2. Decision tree dedicated cardiac screening pre-liver transplantation\*.

\* CAC = Coronary artery calcium, CAD = Coronary artery disease, CT = Computed tomography.

#### 4. Discussion

The present study explored the ability of visual CAC assessment on non-gated chest CT to rule out obstructive CAD and guide withholding or allocation of dedicated cardiac imaging in LT candidates. Although the association between CAC assessed on standard CT and prognosis after LT has previously been described, to the best of our knowledge, we are the first to evaluate the value of visual CAC assessment on non-gated CT to guide pre-operative screening in LT candidates.

The negative predictive value of no or mild calcifications (i.e., a CAC score of 0–3) for obstructive CAD on CCTA and ICA was 100%. The threshold of  $CAC \leq 3$  has previously been established in other populations [15,31]. In our study population, this threshold yielded a sensitivity of 100% and specificity of 91% on CCTA. For ICA, these values were respectively 100% and 68%. Our results suggest that additional dedicated cardiac imaging could have been safely withheld in ~75% (i.e., patients with CAC 0–3,  $n = 109$ ) of the patients by simply reviewing already available data on their CAC-extent. As the negative predictive value of no or mild CAC was 100% for obstructive CAD and none of these patients died peri-operatively due to cardiac causes.

There is an evident relation between CAD and mortality in LT recipients [4,5]. Therefore, cardiac screening is warranted [6]. However, the question remains whether dedicated cardiac screening is necessary in all LT candidates. Furthermore, if screening is warranted which imaging modality would be most efficient?

Previous studies on CAC assessment in LT candidates and recipients report a relatively low prevalence of severe CAC and obstructive CAD. Kong et al. [18] evaluated CAC on ECG-gated CT as a predictor of peri- and post-operative adverse events (e.g., myocardial infarction) in LT candidates. Of the 443 LT candidates, only 11 patients had severe CAC (i.e., an Agatston score > 400). These patients had a fourfold increased risk of cardiac events within 30 days after LT, as compared to patients with no or mild CAC. According to multivariable analysis female sex and

severe CAC were the only significant predictors of cardiac events. Of interest, the classic risk factors for CAD e.g., diabetes mellitus or smoking, were not independently significantly predictive. Zorzi et al. [17] evaluated the relation between prognosis of LT candidates and CAC on non-gated CT, with 1-year follow-up. They evaluated 301 patients (median age 56, 76% male) of whom 26 (only 9%) had severe CAC (i.e., Agatston score > 400). The cardiac event incidence in patients without CAC was 7% versus 27% in patients with severe CAC ( $p = 0.007$ ).

When compared to other populations, the low prevalence of obstructive CAD in LT candidates can be demonstrated as well. Duvall et al. [8] explored the diagnostic yield of stress myocardial perfusion with SPECT for screening in LT candidates as compared to non-LT candidates. They demonstrated similar results as our study. Although patients with end-stage liver disease are considered a high-risk population for post-operative cardiovascular events, the prevalence of ischemia with abnormal perfusion on SPECT is relatively low, and obstructive CAD on subsequent ICA even lower. For these reasons, stress myocardial perfusion had a low diagnostic yield. Duvall et al. reported that only 7.8% of patients had perfusion defects and 1% had obstructive CAD. The prevalence of perfusion defects in non-LT candidates was 34.4% and 85% of these patients had obstructive CAD on ICA. Another explanation may be the lack of response to the administered drugs (e.g. regadenoson) to elicit myocardial ischemia in patients with liver cirrhosis due to cardiac modifications such as high cardiac output and vasodilation [12].

Despite the reported low prevalence of ischemia and obstructive CAD, current guidelines still recommend extensive cardiac screening in all LT candidates. Currently, ICA is recommended in all patients with diabetes mellitus as they are thought to have an increased risk of CAD. However, Zorzi et al. previously demonstrated that diabetes mellitus was not significantly predictive of cardiac events and mortality. In our study, all patients with diabetes mellitus underwent ICA, although retrospectively 55% had no or mild calcifications on prior non-gated CT

and therefore a low a-priori chance of having obstructive CAD. This extensive screening approach is not only time-consuming and expensive, but can lead to complications as well e.g., bleeding or vascular complications with ICA. The results of our study and the previously mentioned studies demonstrate that additional ischemia or CAD screening may not be warranted in patients with cardiac risk factors (e.g., diabetes mellitus) but without severe CAC. Therefore, screening could safely be withheld in the majority of patients (i.e., with no or mild CAC). CAC on non-gated CT can thus be used as a risk-tool for cardiovascular risk and as a gatekeeper for cardiac screening.

Two studies previously demonstrated that CAC can be used as a risk tool for prediction of obstructive CAD in LT candidates. Kemmer et al. [16] reported a strong association between severe CAC on cardiac CT and obstructive CAD on ICA ( $p = 0.02$ ) in 58 LT candidates. West et al. [34] demonstrated a similar relation between a high Agatston score on non-cardiac CT and obstructive CAD ( $p = 0.006$ ) in 54 LT candidates. The results of these studies coincide with the findings of our study, although we aimed to test our hypothesis of a strong negative power of no-mild CAC for obstructive CAD and peri-operative cardiac events.

In terms of the most optimal imaging modality, we observed that severe calcifications interfered with the determination of stenosis on CCTA due to blooming artefacts [28]. This often led to subsequent performance of ICA. Stress myocardial perfusion however, could accurately exclude ischemia and by extension obstructive CAD in patients with severe CAC. Conversely, the diagnostic accuracy of ischemia testing appeared reduced in patients with no or mild calcifications, as the a-priori chance of obstructive CAD is low in patients with a low CAD-burden (i.e., CAC 0–3). Thus, performance of ischemia detection and ICA would be best allocated in patient with a high CAD-burden (i.e., a high CAC score of  $>3$ ). This has been demonstrated in other patient populations as well [35].

#### 4.1. Proposed algorithm for future pre-operative cardiac screening of LTX candidates

Choosing the optimal approach for cardiac pre-operative screening of LT candidates should mostly be based on the a-priori chance of a patient having obstructive CAD. As most patients are asymptomatic, the extent of CAC could be a good indicator of patients CAD-burden. This could help determine the a-priori chance of having obstructive CAD per patient specifically. Patients with no or mild calcifications have a low CAD-burden, therefore the chance of obstructive CAD and by extension ischemia are relatively low. Performance of ICA or ischemia detection will lead to a low diagnostic yield. Conversely, in patients with severe CAC i.e., a high CAD-burden, the chances of obstructive CAD and ischemia are higher. The threshold of a visual calcium score  $\leq 3$  accurately rules out obstructive CAD and a CAC score of  $>3$ , can indicate performance of stress myocardial perfusion or invasive coronary angiography.

We would therefore recommend a tiered strategy for cardiac screening, starting with the evaluation of patients' CAC-extent on non-cardiac CT of the chest and abdomen, visualizing the entire heart i.e., coronary tree. This method of CAC assessment would be possible on all types of non-gated CT of the chest, even for example with attenuation CT of SPECT or PET-CT. Previous studies have found an excellent agreement between visual CAC assessment and the Agatston score [12]. However, the slice-thickness of these scans can vary and could influence the accuracy of CAC assessment (i.e., large slice thickness ( $>3$  mm) increases the risk of underestimation of patients' CAC extent).

#### 4.2. Limitations

This study population has a relatively small sample size ( $n = 149$ ). This is due to relatively strict exclusion criteria (Supplemental file (Fig. 1)), as only patients who received a liver transplant were included. In addition, sometimes patients were excluded because they had non-

gated CTs on which only a part of the heart i.e., the coronary tree was visualized. Potentially, standardizing incorporation of patients' whole heart with CT thorax-abdomen would increase the number of patients with usable non-gated CT and streamline performance of dedicated cardiac imaging.

The female sex is relatively underrepresented in this study (27%). This is similar to previous studies, who demonstrated an over-representation of male sex as well. In the study by Kong et al. [18] only 21% were female, the same percentage as in the study by West et al. [34] This disparity based on sex has been previously reported in LT candidates and LT patients [36–38]. A recent study by Locke et al. reported that women are 14.4% less likely to receive a liver transplant from a deceased organ donor as compared to men [39]. Our study only comprises patients who were both screened and received a transplant, thus explaining the relative under representation of women in this study. However, in both sexes no and mild CAC yielded the same negative predictive value for obstructive CAD (i.e., 100%).

The prevalence of patients with HCC is relatively high in this study. Plausible is that patients with HCC are screened more regularly with CT scans than patients with other liver pathologies. This forms a relative bias of our study population. However, these patients with HCC are known to have a relative higher cardiovascular risk profile. Cirrhosis is present in  $\sim 90\%$  of patients with HCC [40] and is associated with CAD [41]. Even in these high-risk patients the absence of CAC could rule out obstructive CAD with 100% and safely.

## 5. Conclusion

We observed that the evaluation of CAC on non-gated CT can accurately identify a selection of low-risk patients in whom further cardiac imaging is safely withheld. Furthermore, patients' CAC-extent can be used as a tool to guide allocation of dedicated cardiac imaging, as performance of ICA or stress myocardial perfusion is most efficient in patients with severe CAC. When available, the incorporation of visual CAC assessment on non-gated CT can reduce test-burden and reduce risk of complications. Ultimately, this could save health care expenses and time. Potentially, the integration of this tiered strategy for cardiac screening, starting with the evaluation of patients' CAC-extent on non-cardiac CT, in the new guidelines on non-cardiovascular surgery can lead to a consensus on the optimal approach for cardiovascular screening in LT candidates.

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## CRediT authorship contribution statement

**Roos A. Groen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fei Lynn Barbero:** Data curation. **Susan E. Fischer:** Writing – review & editing, Data curation. **Paul R.M. van Dijkman:** Writing – review & editing, Supervision. **Jeroen J. Bax:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Maarten E. Tushuizen:** Conceptualization, Supervision, Visualization, Writing – review & editing. **J. Wouter Jukema:** Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Minneke J. Coenraad:** Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Michiel A. de Graaf:** Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

## Declaration of competing interest

There is no conflict of interest for the present manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2024.132015>.

## References

- L.A. Fleisher, K.E. Fleischmann, A.D. Auerbach, S.A. Barnason, J.A. Beckman, B. Bozkurt, V.G. Davila-Roman, M.D. Gerhard-Herman, T.A. Holly, G.C. Kane, J. E. Marine, M.T. Nelson, C.C. Spencer, A. Thompson, H.H. Ting, B.F. Uretsky, D. N. Wijeyundera, 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, *J. Am. Coll. Cardiol.* 64 (2014) e77–137.
- S.D. Kristensen, J. Knuuti, A. Saraste, S. Anker, H.E. Bøtker, S.D. Hert, I. Ford, J. R. Gonzalez-Juanatey, B. Gorenek, G.R. Heyndrickx, A. Hoes, K. Huber, B. Iung, K. P. Kjeldsen, D. Longrois, T.F. Lüscher, L. Pierard, S. Pocock, S. Price, M. Roffi, P. A. Sirnes, M. Sousa-Uva, V. Voudris, C. Funck-Brentano, 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 Anaesthesiology (ESA), *Eur. Heart J.* 35 (2014) 2383–2431.
- S. Halvorsen, J. Mehilli, S. Cassese, T.S. Hall, M. Abdelhamid, E. Barbato, S. De Hert, I. de Laval, T. Geisler, L. Hinterbuchner, B. Ibanez, R. Lenarczyk, U. R. Mansmann, P. McGreavay, C. Mueller, C. Muneretto, A. Niessner, T.S. Potpara, A. Ristić, L.E. Sade, H. Schirmer, S. Schüpke, H. Sillesen, H. Skulstad, L. Torracca, O. Tutarel, P. Van Der Meer, W. Wojakowski, K. Zacharowski, 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC) endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC), *G. Ital. Cardiol. (Rome)* 24 (2023) e1–e102.
- L.B. VanWagner, B. Lapin, J. Levitsky, J.T. Wilkins, M.M. Abecassis, A.I. Skaro, D. M. Lloyd-Jones, High early cardiovascular mortality after liver transplantation, *Liver Transpl.* 20 (2014) 1306–1316.
- L.B. VanWagner, M. Serper, R. Kang, J. Levitsky, S. Hohmann, M. Abecassis, A. Skaro, D.M. Lloyd-Jones, Factors associated with major adverse cardiovascular events after liver transplantation among a national sample, *Am. J. Transplant.* 16 (2016) 2684–2694.
- X.S. Cheng, L.B. VanWagner, S.P. Costa, D.A. Axelrod, S. Bangalore, S.P. Norman, C.A. Herzog, K.L. Lentine, Emerging evidence on coronary heart disease screening in kidney and liver transplantation candidates: a scientific statement from the American Heart Association: endorsed by the American Society of Transplantation, *Circulation* 146 (2022) e299–e324.
- C.M. Yong, M. Sharma, V. Ochoa, F. Abnousi, J. Roberts, N.M. Bass, C.U. Niemann, S. Shiboski, M. Prasad, M. Tavakol, T.A. Ports, G. Gregoratos, Y. Yeghiazarians, A. J. Boyle, Multivessel coronary artery disease predicts mortality, length of stay, and pressor requirements after liver transplantation, *Liver Transpl.* 16 (2010) 1242–1248.
- W.L. Duvall, A. Singhvi, N. Tripathi, M.J. Henzlova, SPECT myocardial perfusion imaging in liver transplantation candidates, *J. Nucl. Cardiol.* 27 (2020) 254–265.
- B. Baihbhav, C.A. Mahabir, F. Xie, V.K. Shostrom, T.M. McCashland, T.R. Porter, Predictive value of dobutamine stress perfusion echocardiography in contemporary end-stage liver disease, *J. Am. Heart Assoc.* (2017) 6.
- D. Snipelisky, M. Levy, B. Shapiro, Utility of dobutamine stress echocardiography as part of the pre-liver transplant evaluation: an evaluation of its efficacy, *Clin. Cardiol.* 37 (2014) 468–472.
- C.J. Davidson, M. Gheorghide, J.D. Flaherty, M.D. Elliot, S.P. Reddy, N.C. Wang, S.A. Sundaram, S.L. Flamm, A.T. Blei, M.I. Abecassis, R.O. Bonow, Predictive value of stress myocardial perfusion imaging in liver transplant candidates, *Am. J. Cardiol.* 89 (2002) 359–360.
- A. De Gasperi, A. Zorzi, Cardiac evaluation before liver transplantation: a step forward? *J. Hepatol.* 75 (2021) 19–21.
- Y. Htwe, M.D. Cham, C.I. Henschke, H. Hecht, J. Shemesh, M. Liang, W. Tang, A. Jirapatnakul, R. Yip, D.F. Yankelevitz, Coronary artery calcification on low-dose computed tomography: comparison of Agatston and ordinal scores, *Clin. Imaging* 39 (2015) 799–802.
- L. Azour, M.A. Kadoch, T.J. Ward, C.D. Eber, A.H. Jacobi, Estimation of cardiovascular risk on routine chest CT: ordinal coronary artery calcium scoring as an accurate predictor of Agatston score ranges, *J. Cardiovasc. Comput. Tomogr.* 11 (2017) 8–15.
- R.A. Groen, J.W. Jukema, P.R.M. van Dijkman, P.T. Timmermans, J.J. Bax, H. J. Lamb, M.A. de Graaf, Evaluation of clinical applicability of coronary artery calcium assessment on non-gated chest computed tomography, compared with the classic Agatston score on cardiac computed tomography, *Am. J. Cardiol.* 208 (2023) 92–100.
- 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.
- A. Zorzi, G. Brunetti, F. Cardaioli, F. D'Arcangelo, T. Fabris, M. Gambato, S. Iliceto, A. Martini, G. Mattesi, C. Peluso, M. Polacco, C. Sartori, G. Lorenzoni, P. Feltracco, P. Angeli, P. Burra, U. Cillo, P. Pontisso, Coronary artery calcium on standard chest computed tomography predicts cardiovascular events after liver transplantation, *Int. J. Cardiol.* 339 (2021) 219–224.
- Y.G. Kong, J.W. Kang, Y.K. Kim, H. Seo, T.H. Lim, S. Hwang, G.S. Hwang, S.G. Lee, Preoperative coronary calcium score is predictive of early postoperative cardiovascular complications in liver transplant recipients, *Br. J. Anaesth.* 114 (2015) 437–443.
- A.D. Osei, S.M.I. Uddin, O. Dzaye, M.C. Achirica, Z.A. Dardari, O.H. Obisesan, S. Kianoush, M. Mirbolouk, O.A. Orimoloye, L. Shaw, J.A. Rumberger, D. Berman, A. Rozanski, M.D. Miedema, M.J. Budoff, R.S. Vasan, K. Nasir, M.J. Blaha, Predictors of coronary artery calcium among 20–30-year-olds: the coronary artery calcium consortium, *Atherosclerosis* 301 (2020) 65–68.
- O. Dzaye, Z.A. Dardari, M. Cainzos-Achirica, R. Blankstein, A.S. Agatston, M. Duebgen, J. Yeboah, M. Szklo, M.J. Budoff, J.A.C. Lima, R.S. Blumenthal, K. Nasir, M.J. Blaha, Warranty period of a calcium score of zero: comprehensive analysis from MESA, *JACC Cardiovasc. Imaging* 14 (2021) 990–1002.
- J.K. Min, F.Y. Lin, D.S. Gidseg, J.W. Weinsaft, D.S. Berman, L.J. Shaw, A. Rozanski, T.Q. Callister, Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the “warranty period” for remaining normal? *J. Am. Coll. Cardiol.* 55 (2010) 1110–1117.
- R.N. Pugh, I.M. Murray-Lyon, J.L. Dawson, M.C. Pietroni, R. Williams, Transection of the oesophagus for bleeding oesophageal varices, *Br. J. Surg.* 60 (1973) 646–649.
- M. Malinchoc, P.S. Kamath, F.D. Gordon, C.J. Peine, J. Rank, P.C. ter Borg, A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts, *Hepatology* 31 (2000) 864–871.
- D. Mohebbali, A.M. Anagnostopoulos, A. Estrada-Roman, M. Pavlakis, M.P. Curry, M.C. Gavin, Cardiovascular risk assessment in renal and liver transplant candidates: a multidisciplinary institutional standardized approach, *Cardiol. Rev.* 27 (2019) 286–292.
- S. Nagraj, S. Peppas, M.G. Rubianes Guerrero, D.G. Kokkinidis, F.I. Contreras-Yametti, S. Murthy, U.P. Jorde, Cardiac risk stratification of the liver transplant candidate: a comprehensive review, *World J. Transplant.* 12 (2022) 142–156.
- F.R. de Graaf, J.D. Schuijf, J.E. van Velzen, L.J. Kroft, A. de Roos, J.H. Reiber, E. Boersma, M.J. Schalij, F. Spanó, J.W. Jukema, E.E. van der Wall, J.J. Bax, Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease, *Eur. Heart J.* 31 (2010) 1908–1915.
- R.C. Cury, J. Leipsic, S. Abbara, S. Achenbach, D. Berman, M. Bittencourt, M. Budoff, K. Chinnaiyan, A.D. Choi, B. Ghoshhajra, J. Jacobs, L. Kowek, J. Lesser, C. Maroules, G.D. Rubin, F.J. Rybicki, L.J. Shaw, M.C. Williams, E. Williamson, C. S. White, T.C. Villines, R. Blankstein, CAD-RADSTM 2.0–2022 Coronary artery disease - reporting and data system an expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR) and the North America Society of Cardiovascular Imaging (NASCI), *Radiol. Cardiothorac. Imaging* 4 (2022) e220183.
- A. Schubbbaeck, J. Schmid, T. Zimmer, G. Muschiol, M.M. Hell, M. Marwan, S. Achenbach, Influence of the coronary calcium score on the ability to rule out coronary artery stenoses by coronary CT angiography in patients with suspected coronary artery disease, *J. Cardiovasc. Comput. Tomogr.* 10 (2016) 343–350.
- S. Dorbala, M.F. Di Carli, D. Delbeke, S. Abbara, E.G. DePuey, V. Dilisizian, J. Forrester, W. Janowitz, P.A. Kaufmann, J. Mahmarian, S.C. Moore, M.G. Stabin, P. Shreve, SNMMI/ASNC/SCCT guideline for cardiac SPECT/CT and PET/CT 1.0, *J. Nucl. Med.* 54 (2013) 1485–1507.
- A.R. Patel, F. Bamberg, K. Branch, P. Carrascosa, M. Chen, R.C. Cury, B. Ghoshhajra, B. Ko, K. Nieman, F. Pugliese, J. Schoepf, R. Blankstein, Society of cardiovascular computed tomography expert consensus document on myocardial computed tomography perfusion imaging, *J. Cardiovasc. Comput. Tomogr.* 14 (2020) 87–100.
- J. Shemesh, C.I. Henschke, D. Shaham, R. Yip, A.O. Farooqi, M.D. Cham, D. I. McCauley, M. Chen, J.P. Smith, D.M. Libby, M.W. Pasmantier, D.F. Yankelevitz, Ordinal scoring of coronary artery calcifications on low-dose CT scans of the chest is predictive of death from cardiovascular disease, *Radiology* 257 (2010) 541–548.
- R.A. Groen, M.A. de Graaf, J.L. Stöger, P.R.M. van Dijkman, J.W. Jukema, M. J. Schalij, J.J.M. Geelhoed, M.L. Antoni, Coronary calcium score in COVID-19 survivors: association with cardiac injury and cardiac function after 6 weeks, *Am. Heart J. Plus* 27 (2023) 100280.
- R. van Rijn, I.J. Schurink, Y. de Vries, A.P. van den Berg, M. Cortes Cerisuelo, S. Darwish Muraad, J.I. Erdmann, N. Gilbo, R.J. de Haas, N. Heaton, B. van Hoek, V. A.L. Huurman, I. Jochmans, O.B. van Leeuwen, V.E. de Meijer, D. Monbaliu, W. G. Polak, J.J.G. Slangen, R.I. Troisi, A. Vanlander, J. de Jonge, R.J. Porte, Hypothermic machine perfusion in liver transplantation - a randomized trial, *N. Engl. J. Med.* 384 (2021) 1391–1401.
- B.H. West, C.G. Low, B.B. Bista, E.H. Yang, G. Vorobiof, R.W. Busuttill, M.J. Budoff, D. Elashoff, J.M. Tobis, H.M. Honda, Significance of coronary artery calcium found on non-electrocardiogram-gated computed tomography during preoperative evaluation for liver transplant, *Am. J. Cardiol.* 124 (2019) 278–284.
- D. Rijlaarsdam-Hermsen, M. Lo-Kioeng-Shioe, R.T. van Domburg, J.W. Deckers, D. Kuijpers, P.R.M. van Dijkman, Stress-only adenosine CMR improves diagnostic yield in stable symptomatic patients with coronary artery calcium, *JACC Cardiovasc. Imaging* 13 (2020) 1152–1160.

- [36] J.C. Lai, N.A. Terrault, E. Vittinghoff, S.W. Biggins, Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system, *Am. J. Transplant.* 10 (2010) 2658–2664.
- [37] A.K. Mathur, D.E. Schaubel, Q. Gong, M.K. Guidinger, R.M. Merion, Sex-based disparities in liver transplant rates in the United States, *Am. J. Transplant.* 11 (2011) 1435–1443.
- [38] C.A. Moylan, C.W. Brady, J.L. Johnson, A.D. Smith, J.E. Tuttle-Newhall, A.J. Muir, Disparities in liver transplantation before and after introduction of the MELD score, *Jama* 300 (2008) 2371–2378.
- [39] J.E. Locke, B.A. Shelton, K.M. Olthoff, E.A. Pomfret, K.A. Forde, D. Sawinski, M. Gray, N.L. Ascher, Quantifying sex-based disparities in liver allocation, *JAMA Surg.* 155 (2020) e201129.
- [40] D.A. Herbst, K.R. Reddy, Risk factors for hepatocellular carcinoma, *Clin. Liver Dis. (Hoboken)* 1 (2012) 180–182.
- [41] E. Kalaitzakis, A. Rosengren, T. Skommevik, E. Björnsson, Coronary artery disease in patients with liver cirrhosis, *Dig. Dis. Sci.* 55 (2010) 467–475.