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Detection of coronary artery calcifications with low-dose thoracic computed tomography and cardiovascular events in liver transplant recipients.

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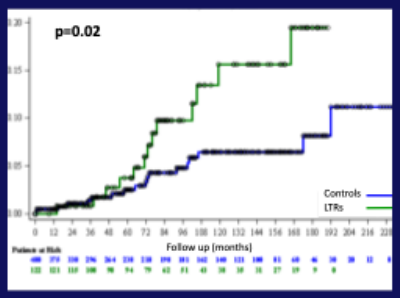
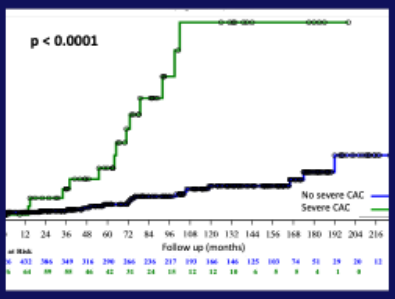
Detection of coronary artery calcifications with low-dose thoracic computed tomography and cardiovascular events in liver transplant recipients.

Liver transplant recipients had more CV complications than controls

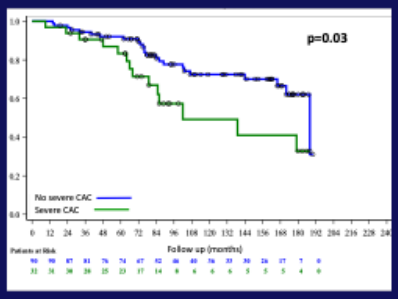
Liver transplant recipients and matched controls]



Severe coronary calcifications predict the risk of CV complications



LT recipients with severe coronary calcifications have lower survival



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Detection of coronary artery calcifications with low-dose thoracic computed tomography and cardiovascular events in liver transplant recipients

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List of abbreviations:

LTR: Liver transplant recipient.

CV: Cardiovascular

LDCT: Low-dose compute tomography.

CAC: Coronary artery calcification.

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I-ELCAP: International Early Cancer Action Project.

ACE: Adverse cardiovascular event.

SD: Standard deviation.

IQR: Interquartile range.

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Investigation: MCL, PRPL, MI, AE, MS, FR.

Formal analysis: MCL, PRPL, GB, JIH.

Visualization: MC, GB, JIH.

Writing original draft: MC, GB, JIH.

Writing (review & editing): all the authors.

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Lay summary

Lung cancer and cardiovascular complications are frequent causes of death of liver transplant recipients. Low-dose computed tomography allows early detection of lung cancer with a low radiation exposure and avoiding the use of contrast medium. We have found that low-dose compute tomography allows the detection of coronary artery calcifications and that they are more frequent and severe in liver transplant recipients. Furthermore, coronary artery calcifications are very useful for prediciting the risk of cardiovascular complications, and liver transplant recipients with severe coronary calcifications had a reduced survival. So, low-dose computed tomography may be useful for the screening of lung cancer and for the risk assessment of cardiovascular complications in liver transplant recipients who smoke.

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Abstract

Introduction. Low-dose computed tomography (LDCT) is useful for lung cancer screening in liver transplant recipients (LTR). It could also be useful for the detection of coronary artery calcifications (CAC) and for predicting the risk of adverse cardiovascular events (ACE). The aim of this study was to evaluate whether LDCT performed for post-transplant lung cancer screening can identify CAC burden and predict the development of ACEs in LTR. Patients and methods. 124 LTR and 485 matched controls were included. Controls were matched for age, sex, smoking history, and presence of emphysema. CAC was assessed on baseline LDCT using a semiquantitative score (0–12); scores ≥ 7 classified as severe. Results. LTRs exhibited a higher prevalence of arterial hypertension, diabetes mellitus and hypercholesterolemia than controls. LTRs also had a greater proportion of severe CAC (26.2% vs. 9.2%, $p < 0.0001$). Liver transplantation, arterial hypertension, and age ≥ 60 years were independently associated with severe CAC. Among LTRs, severe CAC was associated with lower survival. During follow-up, LTRs experienced a higher incidence of ACEs (10.7% vs. 3.7%, $p = 0.02$). Severe CAC, age above 60 years, and hypercolesterolemia were independently associated with an increased risk of ACEs, whereas liver transplantation itself was not. Conclusion. LDCT enables the detection of severe CAC in LTRs, which is associated with an increased risk of ACEs and reduced survival, thus supporting the use of LDCT both for lung cancer screening and for cardiovascular risk stratification in LTRs who smoke with a low radiation exposure and without the need of contrast medium.

Keywords: Cardiovascular complications. Liver transplantation. Low-dose computed tomography.

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Key points.

What was previously known: Cardiovascular complications are a frequent cause of death. Low-dose computed tomography allows early detection of lung cancer.

What was the study contribution: Liver transplant recipients have a high prevalence of coronary artery calcifications, as compared with matched non-transplanted controls. The detection of severe coronary artery calcifications predicts cardiovascular complications and are associated to a reduced survival of liver transplant recipients.

How the results influence clinical practice: Low-dose computed tomography may be useful for early detection of lung cancer and severe coronary artery calcifications. This detection may lead to a more intense treatment to reduce the risk of cardiovascular complications.

Conflicts of interest: Nothing to report.

Inclusion and diversity declaration: We support inclusive, diverse, and equitable research.

AI usage statement: Generative AI and AI-Assisted technologies have not been used in the generation of this work or in the writing process.

Data availability statement: Dasta supporting the study findings are available from the corresponding author upon request.

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Introduction

Refinements in surgical techniques, advances in immunosuppressive and anti-infective therapies, combined with decades of clinical experience have substantially improved survival outcomes following liver transplantation. Current 1- and 5-year post-transplant survival rates approach 90% and 80%, respectively, in many centers (1-3). However, improvements in long-term survival beyond the first post-transplant year have not progressed at the same rate (4). Among liver transplant recipients (LTRs), *de novo* malignancies and cardiovascular (CV) disease are two leading causes of late mortality (5,6). Tobacco smoking represents a major shared risk factor for both outcomes (7-11).

Early intervention has been shown to improve the management of CV risk factors (12), with evidence suggesting a potential reduction in the incidence of *de novo* CV events in LTRs. On the other hand, screening with low-dose computed tomography (LDCT) has enabled the detection of lung cancer at an early stage in more than 80% of high-risk LTRs with significant smoking histories (13). Quantification of coronary artery calcification (CAC), calculated on a standard chest computed tomography, has been validated as a tool for CV risk assessment, with pre-transplant CAC scores providing prognostic value for early cardiac risk stratification (14).

The present study aimed to determine whether LDCT performed for post-transplant lung cancer screening can also predict subsequent CV complications, and whether LTRs exhibit a higher CAC burden compared to smoking-matched individuals undergoing lung cancer screening but who did not receive a liver transplant.

Patients and Methods

Patients

A retrospective study was conducted including all LTRs who participated in the lung cancer screening program at our institution between 2007 and 2021. Eligibility criteria for enrollment were based on the International Early Lung Cancer Action Project (I-ELCAP) protocol and included: (1) age greater than 40 years; (2) smoking history exceeding 10 pack-years; (3) current smokers or former smokers who had quit less

than 10 years before enrollment; and (4) absence of clinical symptoms suggestive of lung cancer at the time of inclusion.

For each LTR, four control participants were selected from the I-ELCAP cohort. Controls were non-transplanted individuals matched to the LTRs according to sex, age (+/- 10 years), smoking history (+/- 10 pack-years), current smoking status at the time of enrollment, and presence or absence of emphysema, as documented in the baseline LDCT scan report.

Computed Tomography

The I-ELCAP screening protocol included annual LDCT examinations, with shorter follow-up intervals when pulmonary nodules were detected (13). All examinations were performed using a 64-row multidetector CT scanner (SOMATOM Sensation 64; Siemens Healthineers, Forchheim, Germany).

Assessment of CAC was performed retrospectively on the first LDCT examination of each participant. A single radiologist (MC), blinded to clinical outcomes, evaluated four coronary artery territories: left main coronary artery, left anterior descending artery, left circumflex artery, and right coronary artery. Calcifications were graded using a semiquantitative scoring system as score 0 = no calcification; score 1 = calcification involving <1/3 of the vessel length; score 2 = calcification involving ≥1/3 but <2/3 of the vessel length; score 3 = calcification involving ≥2/3 of the vessel length. The sum of scores across the four arteries provided a total CAC score ranging from 0 to 12 (15). Severe CAC was defined as a total score of 7 or higher. The patients did not undergo any other cardiac testing, unless clinically indicated.

Clinical Events

Adverse cardiovascular events (ACEs) were defined as any of the following: ischemic stroke, acute coronary syndromes (including myocardial infarction and unstable angina), or death of cardiovascular origin, including sudden cardiac death.

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when non-normally distributed. Categorical variables are expressed as absolute values and percentages. Comparison between groups were performed using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables.

Multivariate logistic regression analyses were conducted to identify factors independently associated with severe CAC. Actuarial survival and risk of ACEs were estimated using the Kaplan–Meier method, between-group differences were assessed using the log-rank test. Independent predictors of ACEs were evaluated using multivariate Cox proportional hazards regression analysis, using a forward conditional inclusion of variables, due to the limited number of events. A P value <0.05 was considered statistically significant. Analyses were performed using SAS Enterprise Guide version 8.3 (32-bit) and SPSS version 5.0.

Ethical Considerations

The study was carried out in compliance with the Declaration of Helsinki. All participants provided written informed consent to participate in the I-ELCAP program and to allow the use of their clinical data for research purposes. The study protocol was reviewed and approved by the Research Ethics Committee of the Universidad de Navarra, Spain (CEI-UN 2021.141).

Results

Patients

A total of 124 LTRs were enrolled in the lung cancer screening program. Among the 496 non-transplanted controls, 11 were excluded because of inadequate image quality; thus, the final number of control patients was 485. Baseline demographic and clinical characteristics of both cohorts are presented in Table 1. The two groups were comparable in most aspects, except for a significantly higher prevalence of diabetes mellitus, arterial hypertension, and hypercholesterolemia in the LTR cohort.

Coronary Artery Calcification

Two LTRs and five controls had undergone prior coronary catheterization with stent placement before inclusion in the screening program, and their baseline LDCT scans were therefore not evaluable for CAC. Both LTR had undergone stent placement one year before entering their baseline LDCT (one of them, ten years after LT and the other one, one year before LT). Among the remaining 602 participants, CAC was identified in 97 of 122 LTRs (78.2%) and in 281 of 480 controls (57.9%) ($P < 0.0001$). Severe CAC was present in 32 LTRs (26.2%) and 44 controls (9.2%) ($P < 0.0001$).

Risk factors for severe CAC identified in univariate analysis included liver transplantation, age >60 years, diabetes mellitus, hypercholesterolemia, and arterial hypertension (Table 2). In multivariate analysis, liver transplantation, age >60 years, and arterial hypertension remained independently associated with severe CAC (Table 3).

During follow-up, 39 LTRs died. Cardiovascular or cerebrovascular causes accounted for 9 deaths (23.1%). The presence of severe CAC was associated with significantly reduced overall survival ($P = 0.03$), as shown in Figure 1.

Adverse Cardiovascular Events

Thirteen LTRs (10.7%) and 18 controls (3.7%) experienced an ACE. Two LTR had an ACE on the first year after their baseline LDCT, four of the had it between the second and the fifth years, and seven of the had it more than more than five years later. Actuarial risk analysis demonstrated a significantly higher incidence of ACEs in LTRs compared with controls (Figure 2). Across the entire cohort, ACEs occurred more frequently in patients with severe CAC (Figure 3). In univariate analysis, liver transplantation, age above 60 years, cumulative smoking above 35 pack-years, diabetes mellitus, hypercholesterolemia, arterial hypertension and severe CAC were associated to a higher risk of ACE. In the multivariate Cox regression analysis, severe CAC, age above 60 years, and hypercholesterolemia were independently associated with a markedly increased risk of ACE (Table 4). In contrast, liver transplantation status was not independently associated with ACE risk.

LTR had a significantly reduced survival, as compared with controls (Figure 4). Thirty-nine LTR and 19 controls died during follow-up. The main causes of death in the LTR

group were infectious diseases (16 cases; 41%) and ACE (9 cases; 23%). In the control group, the main causes of death were unknown (7 cases; 37%) and lung cancer (5 cases; 26%).

Discussion

This study observed a higher prevalence of CAC and ACEs among LTRs compared with an age and smoking matched control population. Furthermore, severe CAC detected on LDCT was strongly predictive of future ACEs and was associated with reduced survival in this patient population, a fact that underscores the elevated cardiovascular risk inherent to LTRs.

The identification of patients at elevated risk for cardiovascular complications is of particular clinical importance in LTRs, owing to their increased susceptibility to ACEs.

Consistent with previous reports, LTRs in our study showed a higher prevalence of diabetes mellitus, hypercholesterolemia, and arterial hypertension compared with controls (16,17). These comorbidities likely contributed to the higher prevalence of CAC and incidence of ACEs observed in this cohort. Another notable finding was that LTRs exhibited a higher prevalence of severe CAC even after adjusting for conventional cardiovascular risk factors, which may be related to additional unmeasured contributors, such as chronic kidney disease (18). This high risk is partly related to immunosuppression, and different types of immunosuppression may also have different effects on these risk factors (19). Our results are in line with earlier studies reporting a high prevalence of CAC in LTRs and a robust association between CAC and post-transplant cardiovascular complications (14,18,20-22). Importantly, we found that severe CAC identified in post-transplant LDCT predicted ACEs and reduced survival, in contrast to Su et al. (23), who did not observe an association between pre-transplant CAC and long-term survival.

A key methodological difference between studies lies in imaging protocols. Quantification of CAC is traditionally performed using dedicated ECG-gated cardiac CT acquisition with 3-mm slice thickness, applying the Agatston scoring method (24). In the pre-transplant evaluation setting, non-ECG-gated 6-mm CT scans have often been

used. In our study, CAC was assessed using LDCT scans, which provided sufficient discriminatory power to identify high-risk patients, with the advantage of lower radiation exposure. This suggests that LDCT may serve as a practical and efficient tool for simultaneous lung cancer screening and cardiovascular risk assessment, without the need of an additional specific cardiac CT acquisition for CAC quantification.

Prior work has shown that multidisciplinary management of cardiovascular risk factors in LTRs can reduce the incidence of complications (12). We therefore believe that detection of severe CAC on LDCT justifies intensified risk factor modification strategies to prevent ACEs in this high-risk group.

These strategies may include optimization of blood pressure and glycemic control, aggressive lipid-lowering therapy, lifestyle modification, smoking cessation, and, when necessary, referral to cardiology for further functional or invasive evaluation (25,26). Importantly, a proactive, multidisciplinary approach ensures individualized care that addresses the complex interplay between liver disease, immunosuppression, and cardiovascular health (27). From a clinical standpoint, early recognition of severe CAC provides a unique opportunity to intensify these strategies. Recent recommendations from experts in the field underline the importance of the detection of severe CAC in the management of cardiovascular risk factors, leading to the initiation of high-intensity statin therapy or aspirin in certain patients (28). Anyway, it should be emphasized that the first step in the prevention of cardiovascular disease and post-transplant malignancy should be smoking cessation.

This study has several limitations. First, it was conducted at a single center, which may restrict the generalizability of the findings. For instance, the proportion of patients with metabolic-associated steatotic liver disease was very low in our study and this liver disease is growing as an indication of liver transplantation in the last decades (29). Second, only persons who smoke or had smoked were included, and therefore the results may not be extrapolated to non-smoking populations. In the period of the study, the number of patients who were followed in our liver transplant program was 350-400, approximately. Nonetheless, the relatively large cohort size, the inclusion of a matched control group, and the blinded centralized radiologic assessment strengthen the validity of our observations. While the Agatston scoring method may provide a

more precise quantification of CAC than the ordinal scoring system employed here, its application requires additional hardware, specialized software, and increased radiation exposure. In contrast, ordinal scoring is simple to implement, offers a semiquantitative balance between visual estimation and Agatston scoring, requires no additional resources, and has been shown to yield both diagnostic and prognostic information (30). The absence of comparison of our results with the Agatston scoring method may also be considered a limitation of the study. At last, the retrospective and observational design of this study limits the availability of certain data (such of body mass index of the control patients) and the ability to infer causality. Future research could evaluate whether tailoring treatment strategies based on CAC detected by LDCT translates into improved outcomes in LTRs.

The results of our study suggest that the evaluation of CAC with LDCT could be beneficial in those patients who undergo lung cancer screening. Its potential usefulness in the evaluation of CAC in other LTR could also be of interest, mainly if they have not undergone a study of CAC previously. Anyway, some questions have to be answered in future studies, such as the selection of patients who could benefit of these studies, its applicability in patients who are not smokers, and the need of repeat testing.

In conclusion, LTRs show a markedly higher prevalence of severe CAC, which is strongly associated with increased risk of ACEs and reduced survival. LDCT screening offers a valuable dual role in this population, enabling both early detection of lung cancer and identification of patients at high risk for cardiovascular events. Therefore, the integration of LDCT (including CAC assessment) in the follow-up of LTRs could facilitate early CV risk stratification and guide preventive interventions in LTRs.

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Table 1. Patient demographic and clinical characteristics.

	LTR*	Controls	p value
Number	124	485	
Male Female	110 (88.7%) 14 (11.3%)	429 (88.4%) 56 (11.6%)	0.94
Age (years)**	59.8 ± 8.8	58.8 ± 9.4	0.15
Body mass index (kg/m^2)**	27.3 ± 4.0		
Diabetes Mellitus	70 (56.5%)	51 (10.5%)	< 0.0001
Arterial hypertension	94 (75.8%)	126 (26.0%)	< 0.0001
Hypercholesterolemia	53 (42.7%)	126 (27.0%)	0.0003
Smoking history (pack-years)***	36,5 (23.5-50)	36.9 (22.5-52.5)	0.79
Active smoking	65 (52.4%)	255 (52.6%)	0.97
Emphysema	57 (46.0%)	219 (45.2%)	0.87
Time since liver transplantation (months)***	36 (12.8-75)		
Indication of liver transplantation Alcoholic liver disease Hepatitis C Other indications****	 75 (60%) 33 (26%) 16 (14%)		

*LTR: Liver transplant recipients

**Expressed as mean ± standard deviation

*** Expressed as median (interquartile range)

****Hepatitis B (6 patients), primary biliary cirrhosis (2 patients), primary sclerosing cholangitis (2 patients), metabolic-associated steatotic liver disease (1 patient), hereditary hemochromatosis (1 patient), familial amyloidotic polyneuropathy (1 patient), nodular regenerative hyperplasia (1 patient), metastases of neuroendocrine tumor (1 patient).

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Table 2. Risk factors associated with severe coronary artery calcification (univariate and multivariate analysis)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)*	p value	OR (95% CI)*	p value
Male sex	1.32 (0.58-3.00)	0.51		
Age ≥ 60 years	4.18 (2.40-7.31)	< 0.001	3.44 (1.91-6.19)	<0.001
Liver transplant	3.61 (2.17-6.02)	< 0.001	2.08 (1.1-3.94)	0.02
Smoking ≥ 35 pack-years	1.57 (0.96-2.59)	0.07	1.22 (0.71-2.09)	0.47
Diabetes mellitus	3.19 (1.90-5.35)	< 0.001	1.39 (0.73-2.63)	0.31
Hypercholesterolemia	1.87 (1.14-3.08)	0.01	1.24 (0.71-2.18)	0.45
Arterial hypertension	3.83 (2.31-6.36)	< 0.001	2.05 (1.12-3.73)	0.02

*Odds ratio (95% confidence interval)

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Table 3. Risk factors associated with adverse cardiovascular events (univariate and multivariate analysis)*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)**	p value	OR (95% CI)**	p value
Age ≥ 60 years	2.90 (1.34-6.31)	0.007	2.54 (1.11-5.80)	0.03
Liver transplant	2.25 (1.09-4.63)	0.03		
Severe CAC***	6.79 (3.26-14.14)	< 0.001	5.20 (2.45-11.05)	< 0.001
Diabetes mellitus	2.22 (1.07-4.58)	0.03		
Hypercholesterolemia	2.61 (1.29-5.31)	0.008	2.27 (1.10-4.68)	0.03
Arterial hypertension	3.00 (1.42-6.32)	0.004		

*Only variables that entered multivariate analysis are shown

**Odds ratio (95% confidence interval)

***Coronary artery calcification.

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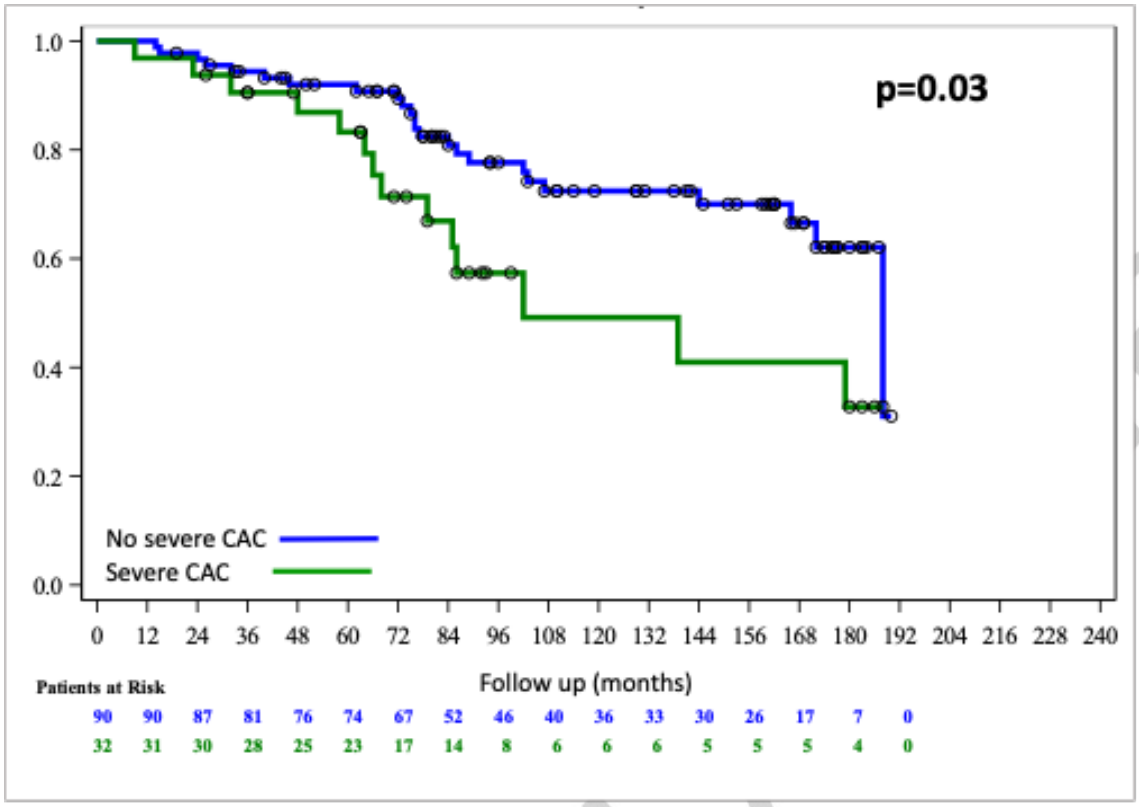

Figure 1. Overall survival of liver transplant recipients after initiation of lung cancer screening, stratified by the presence or absence of severe coronary artery calcification on baseline low-dose computed tomography. CAC: coronary artery calcifications.

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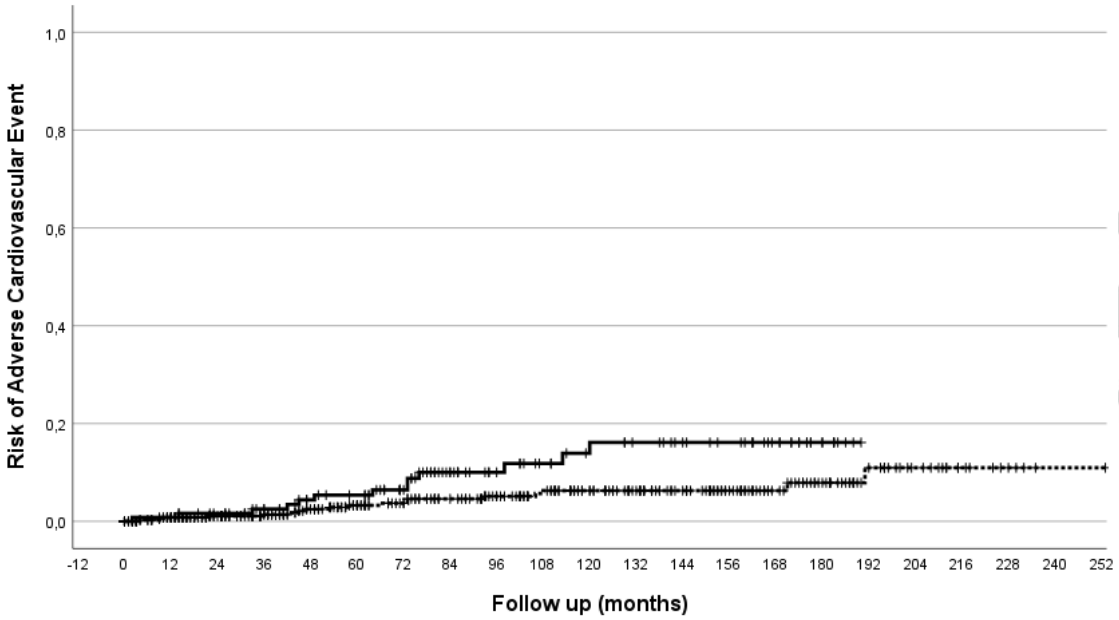

Figure 2. Actuarial risk of adverse cardiovascular events in liver transplant recipients and controls (dotted line). Differences between both groups were statistically significant (p=0.02).

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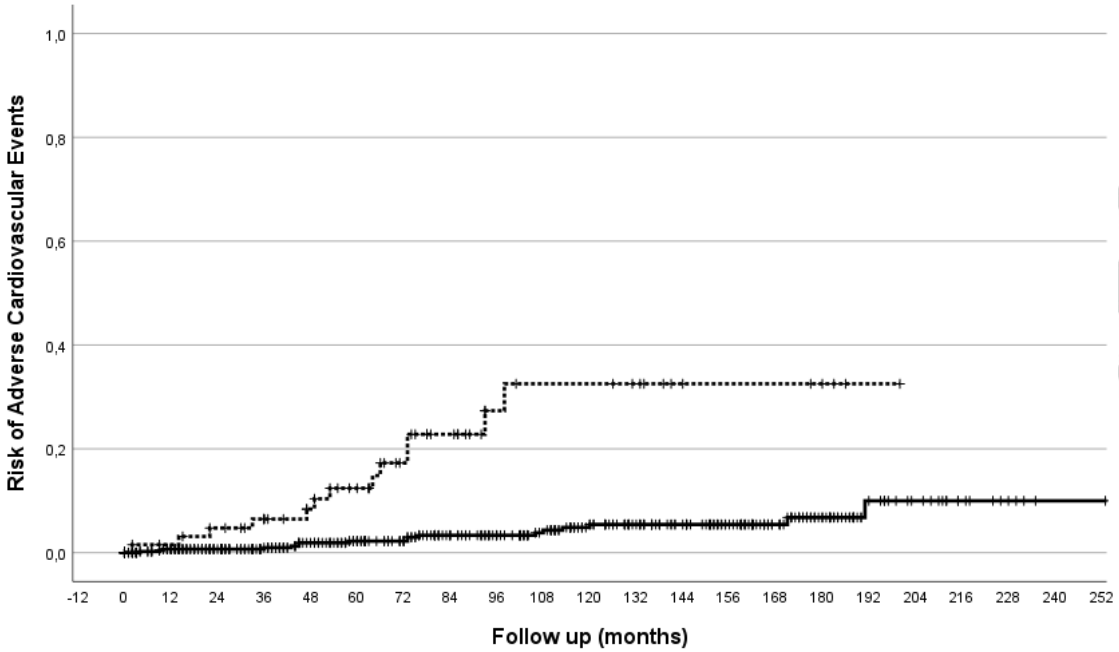

Figure 3. Actuarial risk of adverse cardiovascular events in liver transplant recipients and controls with (dotted line) or without severe coronary artery calcification. Differences between both groups were statistically significant ($p < 0.0001$).

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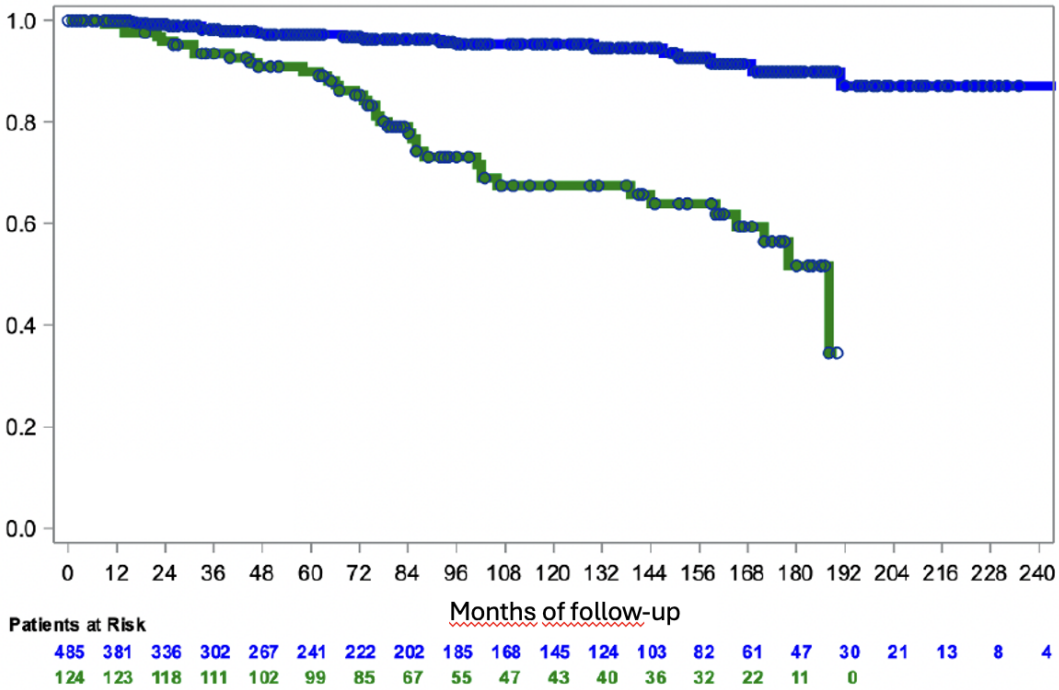

Figure 4. Survival after inclusion in the lung cancer screening of liver transplant recipients (green line) and control (blue line) ($p < 0.001$).