ORIGINAL ARTICLE

The predictive value of coronary artery calcium detected by computed tomography in a prospective study on cardiac allograft vasculopathy in heart transplant patients

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SUMMARY

The predictive value of coronary artery calcium (CAC) in heart transplant (HTX) patients is not established. We explored if the absence of CAC on computed tomography (CT) could exclude moderate and severe cardiac allograft vasculopathy [$CAV_{2–3}$; the International Society for Heart and Lung Transplantation (ISHLT) recommended nomenclature] and significant coronary artery stenosis (diameter reduction ≥50%) and predict long-term clinical outcomes. HTX recipients ($n = 133$) were prospectively included and underwent CT for CAC scoring and invasive coronary angiography (ICA) 7.8 ± 5.0 years after HTX. CAC was detected in 73 (55%) patients. The absence of CAC on CT had a negative predictive value of 97% for ISHLT $CAV_{2–3}$ and 88% for significant stenosis on ICA. During 7.5 ± 2.6 years of follow-up after CAC CT ($n = 127$), there were 57 (45%) nonfatal major adverse cardiac events and 23 (18%) deaths or graft losses registered as first events. Patients with CAC had significantly more events ($P = 0.011$). In an adjusted Cox regression analysis, the presence of CAC was significantly associated with a negative outcome (HR 1.8, 95% CI 1.1–3.0; $P = 0.023$). The absence of CAC predicted low prevalences of ISHLT $CAV_{2–3}$ and significant coronary artery stenosis in HTX patients. The presence of CACS was significantly associated with a worse long-term outcome.

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Introduction

Cardiac allograft vasculopathy (CAV) is a major cause of long-term morbidity and mortality in heart transplant (HTX) patients [1]. CAV is typically seen as diffuse and concentric intimal thickening affecting all parts of the coronary artery tree, and more infrequently as proximal focal eccentric lesions, as in coronary atherosclerotic disease [2]. To detect CAV, most HTX patients undergo annual invasive coronary angiography (ICA), which has a small, but not negligible risk of complications.

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The development of CAV is thought to be a part of an inflammatory process with a different etiology than atherosclerosis [3]. The pathophysiology is multifactorial including immunological and nonimmunological factors. The development of calcification in CAV is poorly understood, but calcified and necrotic components increase with time after HTX [4,5].

In a non-HTX population, coronary artery calcium (CAC) is a marker of coronary atherosclerosis [6,7]. In asymptomatic individuals, the absence of CAC excludes significant stenosis and predicts a low risk of future cardiac events [8–10]. In symptomatic patients, the prognostic value of zero CAC is debated [11–17].

The coronary pathology in HTX patients is predominantly of a different etiology than the atherosclerosis in the general population, furthermore, HTX patients may be asymptomatic due to denervation; thus, results from studies of CAC in a general population might not be applicable for HTX patients. A limited number of publications have studied CAC in a HTX population [18–26].

In this study, we evaluated if the absence of CAC in HTX patients can exclude CAV of moderate-to-severe grade ($CAV_{2–3}$) using the International Society for Heart and Lung Transplantation (ISHLT) recommended nomenclature [27], as well as significant stenosis using ICA as the reference standard. We also investigated if CAC may serve as a surrogate marker for long-term outcome using death or graft loss (D/GL), and nonfatal major adverse cardiac events (NF-MACE) as outcome variables.

Patients and methods

Study population

From December 2005 to April 2008, 133 HTX recipients scheduled for routine ICA at their annual follow-up were prospectively enrolled. One computed tomography (CT) scan for CAC scoring was performed within 2 weeks prior to, or during, the first annual follow-up after enrollment. Eligible patients were ≥18 years of age, and the time since transplantation was ≥12 months. Exclusion criteria were pregnancy, atrial fibrillation, severe heart failure, and severe lung disease restricting breath-hold during CT scanning. The study was approved by the Regional Ethics Committee, and all participants provided written informed consent. During the annual follow-up visit at the time of inclusion, the patients' demographics and medical history, medication, biochemistry, and echocardiography were recorded. Donor data, history of cytomegalovirus infection, and transplant rejection episodes (biopsy-proven rejection grade ≥2 and/or antibody-mediated rejection) were obtained from medical records. All patients received immunosuppressive therapy as per local protocol. This consisted of maintenance therapy with prednisolone, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil. No cytotoxic induction therapy was given, and statins were introduced as standard therapy from 1997.

Coronary artery calcium

The patients were examined with either 16- or 64-slice multidetector CT (GE Light Speed Pro16 and VCT; General Electric Healthcare Technologies, Milwaukee, WI, USA) using prospective electrocardiographic triggering, 120 kV, and 300–400 mAs depending on the patient's body weight. The detector configuration was 8 × 2.5 mm with a collimation of 20 mm and a rotation time of 0.35 or 0.40 s. Images were reconstructed with a slice thickness of 2.5 mm at an increment of 2.5 mm. Advantage Windows 4.3 workstation (General Electric Healthcare Technologies, Milwaukee, WI, USA) was used for calculating the CAC score, which was presented as an Agatston score [28]. Calcium scoring was performed by two experienced readers blinded to the ICA results. If there was a discrepancy in scoring between the readers, a consensus reading was performed.

Angiography and ISHLT CAV classification

The ICA was performed by standard hospital procedure. The coronary arteries were assessed by one reader blinded to the results of the CAC CT and graded as normal or with lumen diameter reduction of <50%, 50–70%, or ≥70%, and affected primary or secondary vessels were noted. Based on the results of the ICA and echocardiography, each patient was classified according to ISHLT CAV recommended nomenclature: not significant (CAV_0), mild (CAV_1), moderate (CAV_2), or severe (CAV_3) [27]. Significant stenosis was defined as ≥50% luminal reduction.

Long-term outcome

The medical records of the patients, which are continuously updated with information from the Norwegian Population Register and computerized medical records, were reviewed in February 2016 to ascertain long-term

outcomes using the same variables as in other studies [29,30]. This included graft survival and NF-MACE defined as acute myocardial infarction, congestive heart failure, need for percutaneous coronary intervention (PCI), coronary artery bypass grafting, cardiac defibrillator placement, cerebral vascular accident, and peripheral vascular disease. The inclusion date was defined as the date of CT scan. Censored date for the outcome graft survival was either the time of D/GL or the date of the patient's last recorded clinical follow-up. A combined outcome was defined as the date of the first event of either a NF-MACE or D/GL or the date of the patient's last recorded clinical follow-up if no adverse event occurred.

Statistics

Categorical variables are presented as frequency (percentage). Continuous variables are presented as mean ± standard deviation or median (interquartile range). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CAC CT were calculated using ISHLT $CAV_{2–3}$ and significant stenosis on ICA as references, respectively. Demographic data, laboratory values, immunosuppressive medication, and outcome data were compared in the groups with and without CAC using independent samples *T*-test for continuous variables, Pearson Chi-Square Test for categorical variables, and log-rank test. The association of CAC with long-term outcomes was examined using Kaplan–Meier plot and Cox regression analysis. Possible confounders were identified. These were variables significantly different in the group with and without CAC, as well as being significantly associated with long-term outcome, either with D/GL and/or with the combined outcome NF-MACE and D/GL. Results from the Cox model are presented as hazard ratios (HR), *P*-values, and 95% confidence intervals (95% CI). The statistical analyses were performed using IBM SPSS Statistics version 21 (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered significant.

Results

One hundred and thirty-three HTX recipients were included, 117 men and 16 women. At the time of CAC CT, the mean age was 56 ± 11 years, mean time interval after HTX was 7.8 ± 5.0 years, and mean allograft age was 42 ± 12 years. The median time interval between ICA and CT was 0 (interquartile range from −15 to 1) days. Demographic and clinical characteristics of the study population are shown in Table 1. The median CAC Agatston score was 1 (interquartile range 0–51). Of the 133 patients examined, 60 (45%) had no CAC (NCAC group) and 73 (55%) had a CAC score >0 (CAC group). The donor age, time since HTX, allograft age, and history of rejection were significantly higher in the CAC group compared with the NCAC group. Otherwise, the groups were comparable (Table 1). The CAC score displayed a continuous increase with allograft age (Fig. 1) and time interval since HTX (Fig. 2), but not with recipient age at time of inclusion (Fig. 3). Donor atherosclerosis, defined as any grade of stenosis detected at the baseline ICA after HTX, was only present in one of 124 patients. For nine patients, the report of the baseline ICA was not available.

CAC score and ISHLT CAV classification

In the total population, there were 69 (52%) CAV_0, 48 (37%) CAV_1, 8 (5%) CAV_2, and 8 (6%) CAV_3 patients using the ISHLT recommended nomenclature. The CAC score increased continuously with the severity of ISHLT CAV (Fig. 4, Table 2). In the NCAC group, two (3.3%) patients had ISHLT $CAV_{2–3}$; while, 14 (19%) in the CAC group had ISHLT $CAV_{2–3}$. The CAC CT had an overall sensitivity, specificity, PPV, and NPV for ISHLT $CAV_{2–3}$ of 88%, 50%, 19%, and 97%, respectively.

CAC score and significant coronary stenosis

Seven (12%) and 13 (18%) patients had significant coronary stenosis confirmed by ICA in the NCAC group and CAC group, respectively. The CAC CT with ICA as a reference had an overall sensitivity, specificity, PPV, and NPV for significant coronary stenosis of 65%, 47%, 18%, and 88%, respectively. Of the 20 patients with significant stenosis, three were treated with PCI and two of them had no CAC.

CAC score and long-term outcome

All participants were followed to the time of D/GL (52) or to their last clinical follow-up (81) with an overall mean follow-up time of 7.5 ± 2.6 (range 0.3–10) years after CAC CT. For one patient, the date of death was recorded, but other clinical follow-up data were missing. This patient was excluded from the combined outcome analysis, as were five other patients diagnosed and treated for heart failure prior to inclusion. In the remaining 127 patients, there were 57 cases with

Table 1. Demographic and clinical characteristics of the study population according to the presence or absence of coronary artery calcium (CAC; n = 133).

Characteristic	CAC = 0 (n = 60)	CAC > 0 (n = 73)	P-value
Demographics			
Recipient age (years)	55 ± 12	55 ± 13	0.941
Recipient male gender	51 (85%)	66 (90%)	0.340
Allograft age (years)	38 ± 12	46 ± 10	<0.001
Body mass index (kg/m²)	27 ± 4	26 ± 4	0.799
Medical history			
Recipient age at time of HTX (years)	49 ± 14	46 ± 14	0.287
Time since HTX (years)	5.9 ± 4.2	8.5 ± 5.0	0.002
Etiology heart failure			
Cardiomyopathy	32 (53%)	30 (41%)	0.159
Coronary artery disease	19 (32%)	33 (45%)	0.111
Hypertension*	42 (70%)	45 (62%)	0.313
Diabetes mellitus	9 (15%)	13 (18%)	0.664
Current smoker	9 (15%)	16 (22%)	0.310
Rejection†	15 (25%)	31 (43%)	0.035
CMV treated	11 (18%)	22 (30%)	0.129
Medication			
Immunosuppression			
Mycophenolate Mofetil	26 (43%)	27 (37%)	0.457
Azathioprine	33 (55%)	39 (53%)	0.856
Cyclosporine	56 (93%)	68 (93%)	0.967
Tacrolimus	4 (7%)	4 (6%)	0.774
Everolimus	3 (5%)	3 (4%)	0.806
Prednisolone	59 (98%)	69 (95%)	0.250
Statins	52 (87%)	68 (93%)	0.210
Biochemistry			
Creatinine (μmol/l)	101 ± 31	113 ± 46	0.068
eGFR (ml/min/1.73 m²)	69 ± 20	63 ± 19	0.064
Low-density lipoprotein (mmol/l)	3.1 ± 0.9	3.0 ± 0.9	0.511
Total cholesterol (mmol/l)	5.3 ± 1.0	5.1 ± 0.9	0.197
Donor characteristics			
Donor male gender	33 (55%)	50 (69%)	0.052
Donor age (years)	32 ± 13	37 ± 12	0.014
Ischemic time (min)	159 ± 13	139 ± 74	0.145

CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate, as measured by the MDRD formula.

Data expressed as number (percentage) or as mean ± standard deviation, as appropriate. All variables reported, except for donor characteristics, are from the time of inclusion, that is, the date of annual follow-up at time of CAC CT.

*Hypertension was defined as treated with medication.

†Biopsy-proven rejection grade ≥2 and/or antibody-mediated rejection.

NF-MACE and 23 cases with D/GL registered as first events. During follow-up, 49 (71%) patients in the CAC group experienced NF-MACE or D/GL versus 31 (53%) in the NCAC group (log-rank test, P = 0.011); while, D/GL occurred in 34 (47%) and 18 (30%) patients in the two groups, respectively (log-rank test, P = 0.029, Table 3).

Unadjusted Cox regression analysis and Kaplan–Meier plots showed a significant association between the presence of CAC and a worse outcome both for D/GL alone (HR 1.9, 95% CI 1.1–3.3; P = 0.032) and for the combined outcome of either NF-MACE or D/GL (HR 1.8, 95% CI 1.1–2.8; P = 0.016) (Table 4, Fig. 5).

Male donor, time interval between TX and inclusion, and creatinine >150 μmol/l (variable dichotomized; dominant influence by the 95% percentile) were confounders significantly associated with D/GL and/or with the combined outcome and were also significantly different in the groups with and without CAC (P < 0.10). The CAC and these three variables were included simultaneously in a Cox regression model (Table 4), which showed the presence of CAC to be significantly

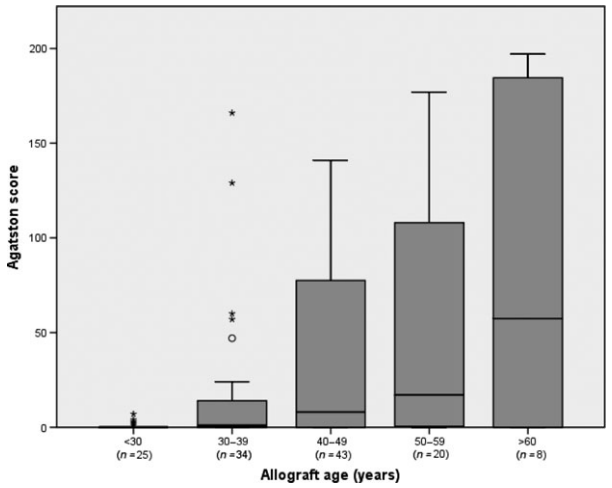

Figure 1 Agatston score according to different allograft age groups at time of inclusion.

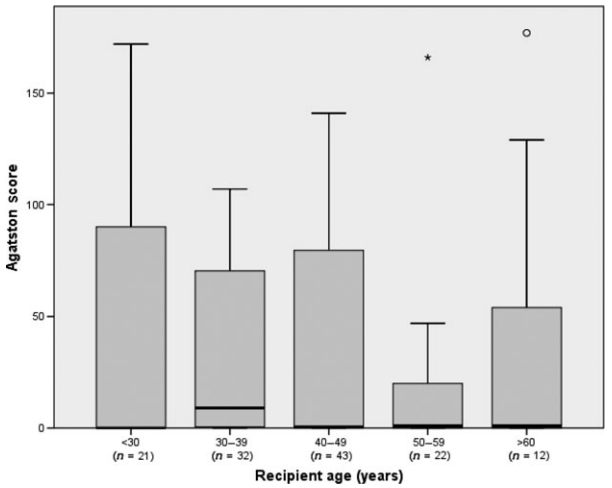

Figure 3 Agatston score according to different recipient age groups at time of inclusion.

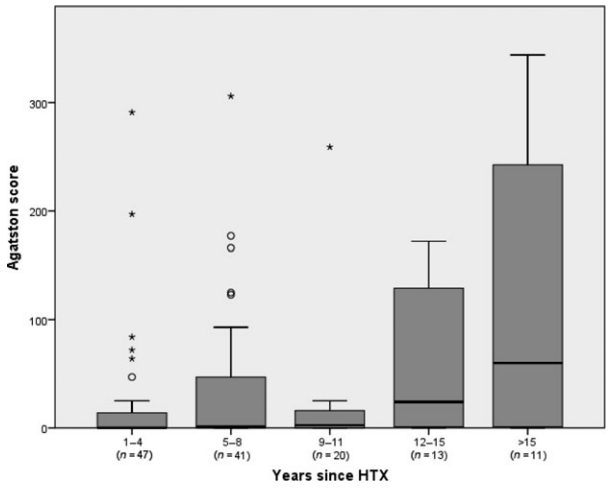

Figure 2 Agatston score according to different time intervals since heart transplantation at time of inclusion.

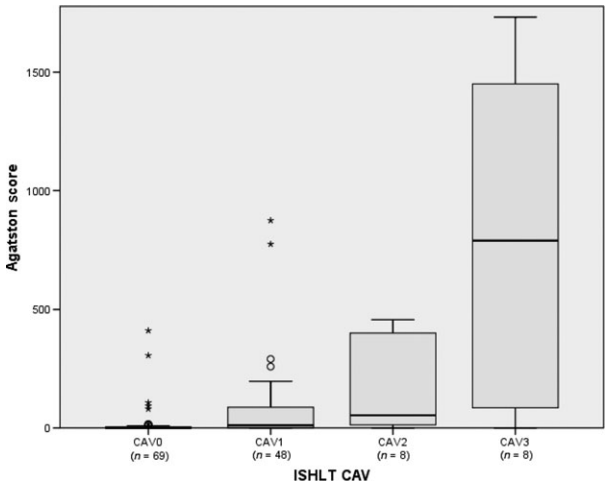

Figure 4 Agatston score according to the International Society for Heart and Lung Transplantation's (ISHLT) recommended nomenclature for cardiac allograft vasculopathy (CAV).

associated with the combined outcome NF-MACE and D/GL (HR 1.8, 95% CI 1.1–3.0; $P = 0.023$), but not with D/GL alone (HR 1.7, 95% CI 0.93–3.2; $P = 0.081$). We checked for nonproportional hazards in the multivariable model using the proportional hazard assumption test with Schoenfeld residuals and found no significant time dependent effects.

Discussion

The major findings in the present study were that the absence of CAC on CT predicts low prevalences of ISHLT $CAV_{2–3}$ and significant coronary artery stenosis on a concurrent ICA with NPVs of 97% and 88%, respectively. In a follow-up period of up to 10 years, the presence of CAC was significantly associated with a worse combined long-term outcome of NF-MACE and D/GL.

To our knowledge, this is the first study to assess the prognostic value of CAC CT using the ISHLT CAV nomenclature, which is based on the combination of coronary visualization and allograft function [27]. We found that CAC continuously increased with the severity of ISHLT classified CAV. The prognostic value of excluding ISHLT $CAV_{2–3}$ has been demonstrated by Prada-Delgado *et al.* [31]. In their retrospective study, they reported that CAV_2 and CAV_3 detected at 1 year after HTX were associated with poor prognosis.

Table 2. Agatston score by ISHLT CAV nomenclature.

ISHLT CAV nomenclature	*N* = 133 (%)	Agatston score Median (interquartile range)
CAV_0	69 (52)	0 (0–4)
CAV_1	48 (36)	11 (0–89)
CAV_2	8 (6)	54 (1–429)
CAV_3	8 (6)	789 (45–1501)

ISHLT, International Society for Heart and Lung Transplantation; CAV, cardiac allograft vasculopathy.

Table 3. Long-term outcome variables.

Outcome	CAC = 0	CAC > 0	*P*-value
D/GL (*n* = 133)	18 (30%)	34 (47%)	0.029
Cause of D/GL			
Sudden death	2 (3%)	4 (6%)	0.553
Cardiac-related D/GL*	3 (5%)	7 (10%)	0.318
Malignancy	8 (13%)	8 (11%)	0.675
Other	4 (7%)	11 (15%)	0.127
Unknown	1 (2%)	4 (6%)	0.250
NF-MACE or D/GL (*n* = 127)	31 (53%)	49 (71%)	0.011
NF-MACE first event			
Acute myocardial infarction	2 (3%)	1 (1)	0.460
Heart failure†	4 (7%)	4 (6%)	0.799
Need for percutaneous coronary intervention	16 (28%)	24 (35%)	0.384
Coronary artery bypass grafting	0	0	
Cardiac defibrillator placement	0	0	
Cerebral vascular accident	2 (3%)	2 (3%)	0.860
Peripheral vascular disease	0	2 (3)	0.191

CAC, coronary artery calcium; D/GL, death or graft loss; NF-MACE, nonfatal major cardiac events.

Data expressed as number (percentage).

*Cardiac-related D/GL includes transplant failure, graft sclerosis, and myocardial infarction.

†Heart failure defined as diagnosis and treatment for myocardial dysfunction.

The CAC CT is limited to detecting the calcified and necrotic component of coronary wall pathologies. However, the development of calcifications in CAV is poorly understood. The total atherosclerotic burden in a HTX patient is a composite of donor-mediated disease, CAV, and native atherosclerosis. Both CAV and native atherosclerosis consist of fibrofatty plaques and smooth muscle cell proliferation [32,33]. Calcified lesions are less predominant in CAV, but calcified and necrotic components increase with time after HTX [4], and late CAV has pathophysiological similarities to native coronary atherosclerosis [5]. It is unclear whether this is transformation of fibrofatty intimal proliferation to more malignant calcified and necrotic lesions or infiltration of native atherosclerosis in CAV. In our population, risk factors such as cholesterol levels, smoking, diabetes, and hypertension were not different in the CAC and NCAC groups. Furthermore, the time interval after HTX was significantly longer in the CAC group. This might support the theory of transformation from fibrofatty to calcified and necrotic CAV rather than infiltration of native atherosclerosis driven by regular risk factors. Our finding is contradictory to what Hernandez *et al.* [4] reported; in their study, necrotic core and calcium components detected by intravascular ultrasound (IVUS) virtual histology became more prevalent with time, especially when influenced by cardiovascular risk factors. Von Ziegler *et al.* [25] found CAC continuously increased with allograft age groups, similar to the CAC distribution in different age groups of the general population. Further, within each age group, there was no significant difference in CAC of patients with and without CAV detected by ICA; thus, they hypothesized that CAC represents pre-existing or independently developing de novo atherosclerosis rather than allograft vasculopathy. In our study group, the median CAC score also continuously increased with allograft age (Fig. 1) and the time interval since HTX (Fig. 2). The time interval since HTX was significantly longer in the CAC group than in the NCAC group in our study. This makes it difficult to conclude whether the increase in CAC primarily reflects allograft age, time interval after HTX, or both.

We also evaluated CAC and its association with significant stenosis on ICA. An annual ICA can identify potential significant stenosis eligible for PCI. As ICA is an invasive procedure with a small, but not negligible risk of complications, a screening tool for potential significant stenosis would be of great clinical interest to serve as a gatekeeper for ICA. In this study, we found that the absence of CAC on CT predicts a low prevalence of significant coronary artery stenosis on a concurrent ICA with a NPV of 88%. In two other studies by Barbir *et al.* [18] and Mittal *et al.* [26], a negative CAC CT had NPVs of 95% and 94%, respectively, and a NPV of 99% for a CAC score >55 was reported by Knollmann *et al.* [22]. All three studies predicted stenosis ≥50%. A review by Sarwar *et al.* [8], including 10 255 patients in 18 studies, reported that

Table 4. Long-term outcome results from Cox regression analysis.

		Unadjusted			Adjusted*		
Long-term outcome	Clinical variables	HR	95% CI	*P*-value	HR	95% CI	*P*-value
D/GL	CAC	1.9	1.1–3.3	0.032	1.7	0.93–3.2	0.081
	Male donor	0.63	0.35–1.2	0.137	0.60	0.36–1.3	0.122
	Time since TX (Q4 vs. Q1)	0.47	0.22–1.0	0.054	0.53	0.23–1.2	0.123
	Creatinine >150 μmol/l	4.3	2.2–8.5	<0.001	5.2	2.5–11.1	<0.001
D/GL and NF-MACE	CAC	1.8	1.1–2.8	0.016	1.8	1.1–3.0	0.023
	Male donor	0.59	0.37–0.96	0.034	0.64	0.39–1.1	0.087
	Time since TX (Q4 vs. Q1)	0.94	0.52–1.7	0.826	1.2	0.65–2.3	0.555
	Creatinine >150 μmol/l	1.1	0.51–2.2	0.866	1.0	0.45–2.3	0.987

D/GL, death/graft loss; NF-MACE, nonfatal major adverse cardiac events; CAC, coronary artery calcium; HR, hazard ratio; CI, confidence interval; Q, quartile.

*Adjusted—All variables are included simultaneously in the regression analysis.

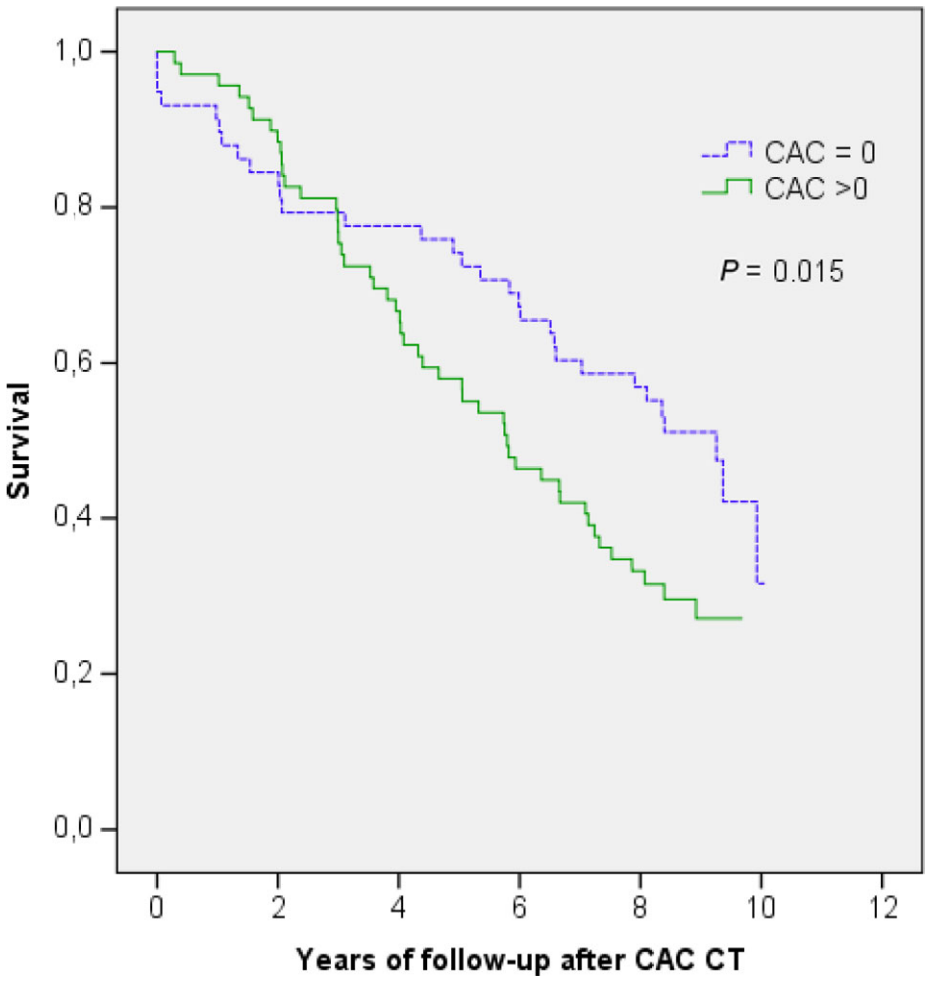

Figure 5 Unadjusted Kaplan–Meier curve of the combined outcome nonfatal major adverse cardiac events (NF-MACE) and death or graft loss (D/GL) according to coronary artery calcium (CAC) group.

the absence of CAC on CT had a NPV of 93% for significant coronary stenosis in the general population. Therefore, our findings are consistent with other publications on CAC and significant stenosis in HTX patients, as well as results from large scale studies of the general population.

The absence of CAC in HTX patients does not, however, definitively exclude the presence of significant stenosis. This is underscored by the finding that two of three patients treated with PCI had no CAC. Manifestation of significant stenosis in patients with no CAC is also documented in a nontransplanted population [11]. Hence, the clinical use CAC CT as a gatekeeper for ICA is of limited value. CAC score used in combination with one or more other markers could potentially increase its clinical value in a HTX population; for example, CAC score in combination with Troponin, probrain natriuretic peptide, and a stable clinical situation. In patients with relative contraindications for ICA, CAC score could be especially valuable, that is, difficult access for invasive procedures, previous coronary dissection or cerebral stroke, severe kidney impairment, or allergy to iodine contrast agent. In such patients, a negative CAC CT could support limiting ICA.

We found the presence of CAC was significantly associated with worse long-term outcome in a follow-up period of up to 10 years. CAC was associated with the combined outcome NF-MACE or D/GL, but not with D/GL alone. The latter could be explained by the high number of noncardiac deaths that do not reflect CAV, as 31 (60%) patients had malignancy or "other" registered as the cause of death. Our CAC long-term outcome results are in line with our finding that CAC reflects the severity of ISHLT CAV. Prada-Delgado *et al.* [31] demonstrated ISHLT CAV severity had a prognostic significance for long-term outcome; similarly, our study showed a relation between the presence of CAC and a worse long-term outcome. To our knowledge, there is only one other study on CAC and long-term outcome in a HTX population. Lazem *et al.* [20] studied CAC as a predictor of cardiac events in 91 subjects with a mean follow-up of 2.12 years and found that CAC was a significant predictor of cardiac events.

One obvious limitation of our study is the sample size, especially compared with the large cohort studies of CAC in the general population. Single-center studies on HTX patients are naturally limited by the number of available patients. Other studies reporting on CAC in HTX recipients included 55–161 patients [18,22,23,25,26]. It is well documented that ICA underestimates CAV in HTX patients compared with IVUS [34], and further studies should include IVUS parameters, including virtual histology, to more precisely detect the evolution of atherosclerosis and the calcified component of the matrix. Our study included patients at any time after HTX, and CAC CT was only performed once. Serial examinations of CAC CT in a cohort of de novo HTX patients could provide valuable knowledge on when to do CAC CT and how to incorporate it in the follow-up of HTX, especially in combination with studies of other CAV markers.

Conclusion

We found the absence of CAC on CT predicts very low prevalences of ISHLT $CAV_{2–3}$ and significant coronary artery stenosis on a concurrent ICA with NPVs of 97% and 88%, respectively; however, it does not definitively exclude the presence of significant stenosis. The presence of CAC was associated with a worse long-term combined outcome of NF-MACE and D/GL in HTX patients during up to 10 years follow-up. The clinical utility of the CAC score should be explored in a larger population and preferably in combination with other markers of CAV.

Authorship

AG: designed the study, performed research, collected CACS, ICA, and clinical data, analyzed data, and wrote the paper. RA: contributed in the design of the study, collected CACS data and contributed to the revision, and approval of the paper. EG: contributed in the collection and analyzing of clinical data and to the writing, revision, and approval of the paper. JJ and TE: contributed in the design of the study and to revision and approval of the paper. LS: contributed to the statistical analysis and to writing and approval of the paper. AA: contributed to the analyses of data and to writing, revision, and approval of the paper. LA: contributed in the design of the study, the collection of ICA data, and the revision and approval of the paper. LG: designed the study, and contributed to the writing, revision, and approval of the paper.

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Conflict of interest

The authors have no conflict of interest to disclose.

REFERENCES

1. Lund LH, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Heart Transplantation Report–2015; Focus Theme: Early Graft Failure. *J Heart Lung Transplant* 2015; **34**: 1244.
2. Billingham ME. Cardiac transplant atherosclerosis. *Transplant Proc* 1987; **19**: 19.
3. Chih S, Chong AY, Mielniczuk LM, Bhatt DL, Beanlands RSB. Allograft vasculopathy: the Achilles' heel of heart transplantation. *J Am Coll Cardiol* 2016; **68**: 80.
4. Hernandez JM, Vazquez de Prada JA, Burgos V, *et al.* Virtual histology intravascular ultrasound assessment of cardiac allograft vasculopathy from 1 to 20 years after heart transplantation. *J Heart Lung Transplant* 2009; **28**: 156.
5. Potena L, Masetti M, Sabatino M, *et al.* Interplay of coronary angiography and intravascular ultrasound in predicting long-term outcomes after heart transplantation. *J Heart Lung Transplant* 2015; **34**: 1146.
6. Stary HC, Chandler AB, Dinsmore RE, *et al.* A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 1995; **92**: 1355.
7. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation* 1995; **92**: 2157.
8. Sarwar A, Shaw LJ, Shapiro MD, *et al.* Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging* 2009; **2**: 675.
9. Greenland P, Bonow RO, Brundage BH, *et al.* ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 2007; **115**: 402.
10. Shaw LJ, Giambrone AE, Blaha MJ, *et al.* Long-term prognosis after coronary artery calcification testing in asymptomatic patients: a cohort study. *Ann Intern Med* 2015; **163**: 14.
11. Gottlieb I, Miller JM, Arbab-Zadeh A, *et al.* The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. *J Am Coll Cardiol* 2010; **55**: 627.
12. Rubinshtein R, Gaspar T, Halon DA, Goldstein J, Peled N, Lewis BS. Prevalence and extent of obstructive coronary artery disease in patients with zero or low calcium score undergoing 64-slice cardiac multidetector computed tomography for evaluation of a chest pain syndrome. *Am J Cardiol* 2007; **99**: 472.
13. Kim YJ, Hur J, Lee H-J, *et al.* Meaning of zero coronary calcium score in symptomatic patients referred for coronary computed tomographic angiography. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 776.
14. Hulten E, Bittencourt MS, Ghoshhajra B, *et al.* Incremental prognostic value of coronary artery calcium score versus CT angiography among symptomatic patients without known coronary artery disease. *Atherosclerosis* 2014; **233**: 190.
15. Mittal TK, Pottle A, Nicol E, *et al.* Prevalence of obstructive coronary artery disease and prognosis in patients with stable symptoms and a zero-coronary calcium score. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 922.
16. Villines TC, Hulten EA, Shaw LJ, *et al.* Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography. *J Am Coll Cardiol* 2011; **58**: 2533.
17. Chaikriangkrai K, Velankar P, Schutt R, *et al.* Additive prognostic value of coronary artery calcium score over coronary computed tomographic angiography stenosis assessment in symptomatic patients without known coronary artery disease. *Am J Cardiol* 2015; **115**: 738.
18. Barbir M, Bowker T, Ludman PF, Mitchell AG, Wood D, Yacoub M. Ultrafast computed tomographic scanning for detection of coronary disease in cardiac transplant recipients. *Am J Cardiol* 1994; **74**: 941.
19. Barbir M, Lazem F, Bowker T, *et al.* Determinants of transplant-related coronary calcium detected by ultrafast computed tomography scanning. *Am J Cardiol* 1997; **79**: 1606.
20. Lazem F, Barbir M, Banner N, Ludman P, Mitchell A, Yacoub M. Coronary calcification detected by ultrafast computed tomography is a predictor of cardiac events in heart transplant recipients. *Transplant Proc* 1997; **29**: 572.
21. Shemesh J, Tenenbaum A, Stroh CI, *et al.* Double-helical CT as a new tool for tracking of allograft atherosclerosis in heart transplant recipients. *Invest Radiol* 1999; **34**: 485.
22. Knollmann FD, Bocksch W, Spiegelsberger S, Hetzer R, Felix R, Hummel M. Electron-beam computed tomography in the assessment of coronary artery disease after heart transplantation. *Circulation* 2000; **101**: 2078.
23. Ratliff NB 3rd, Jorgensen CR, Gobel FL, Hodges M, Knickelbine T, Pritzker MR. Lack of usefulness of electron beam computed tomography for detecting coronary allograft vasculopathy. *Am J Cardiol* 2004; **94**: 202.
24. Knollmann FD, Stuhmer F, Lehmkuhl H, Felix R, Hetzer R. Progression of coronary atherosclerosis after heart transplantation on electron-beam computed tomography. *Acad Radiol* 2009; **16**: 194.
25. von Ziegler F, Kaczmarek I, Knez A, *et al.* Coronary calcifications detected by computed tomography are not markers of cardiac allograft vasculopathy. *Transplantation* 2011; **92**: 493.
26. Mittal TK, Panicker MG, Mitchell AG, Banner NR. Cardiac allograft vasculopathy after heart transplantation: electrocardiographically gated cardiac CT angiography for assessment. *Radiology* 2013; **268**: 374.
27. Mehra MR, Crespo-Leiro MG, Dipchand A, *et al.* International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010; **29**: 717.

28. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15**: 827.
29. Kobashigawa JA, Tobis JM, Starling RC, *et al.* Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol* 2005; **45**: 1532.
30. Kittleson MM, Shemin R, Patel JK, *et al.* Donor–recipient sex mismatch portends poor 10-year outcomes in a single-center experience. *J Heart Lung Transplant* 2011; **30**: 1018.
31. Prada-Delgado O, Estévez-Loureiro R, Paniagua-Martín MJ, López-Sainz A, Crespo-Leiro MG. Prevalence and prognostic value of cardiac allograft vasculopathy 1 year after heart transplantation according to the ISHLT recommended nomenclature. *J Heart Lung Transplant* 2012; **31**: 332.
32. Johnson DE, Gao SZ, Schroeder JS, DeCampli WM, Billingham ME. The spectrum of coronary artery pathologic findings in human cardiac allografts. *J Heart Transplant* 1989; **8**: 349.
33. Billingham ME. Histopathology of graft coronary disease. *J Heart Lung Transplant* 1992; **11**: S38.
34. St Goar FG, Pinto FJ, Alderman EL, *et al.* Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. *Circulation* 1992; **85**: 979.