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Preoperative coronary calcium score is predictive of early postoperative cardiovascular complications in liver transplant recipients

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Editor's key points

- Patients undergoing liver transplantation have a high incidence of coronary artery disease and cardiovascular complications are common.
- In this retrospective study, a high coronary calcium score determined by coronary CT was associated with cardiovascular complications after liver transplant.
- Prospective data in an external cohort are required to confirm these findings.

Background. Coronary computed tomographic angiography (coronary CT) is a non-invasive test for diagnosis of cardiac function. Coronary calcium scores determined by coronary CT are associated with cardiovascular risk factors. However, no studies have investigated the association between coronary calcium scores and cardiovascular complications after liver transplantation (LT). We therefore evaluated the utility of preoperative coronary calcium scores for predicting early postoperative cardiovascular complications in LT recipients.

Methods. Between 2010 and 2012, 443 LT recipients were analysed retrospectively. Preoperative cardiovascular assessments, including coronary CT, were performed. A coronary calcium score >400 was defined as a positive finding. Predictive factors of early postoperative cardiovascular complications were evaluated by univariate and multivariate analyses. Major cardiovascular complications occurring during a period of 1 month after LT were noted.

Results. Of the 443 patients, 38 (8.6%) experienced one or more cardiovascular complications. Positive coronary CT findings were seen in 11 (2.5%) patients. In the multivariate analysis, a coronary calcium score >400 {odds ratio (OR)=4.62 [95% confidence interval (CI): 1.14–18.72], P=0.032} and female sex [OR=2.76 (1.37–5.57), P=0.005] were predictive of cardiovascular complications.

Conclusions. A preoperative coronary calcium score of >400 predicted cardiovascular complications occurring 1 month after LT, suggesting that preoperative evaluation of coronary calcium scores could help predict early postoperative cardiovascular complications in LT recipients.

Keywords: coronary CT; early postoperative cardiovascular complications; liver transplantation

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Liver transplantation (LT) is the curative therapy for patients with advanced liver disease.[1] Cardiovascular complications are a leading cause of death after LT. The reported incidence of cardiovascular complications after LT ranges from 25 to 70%, and these complications are regarded as a major cause of postoperative morbidity and mortality in LT recipients.[2–4] Furthermore, LT recipients are at high risk of cardiac diseases such as coronary artery disease (CAD).[5] Therefore, accurate preoperative cardiac examinations should be performed to prevent postoperative cardiovascular complications. However, the optimal method to evaluate such cardiovascular risks in LT recipients remains controversial.[6 7]

A preoperative cardiac evaluation includes electrocardiography (ECG), echocardiography, and thallium single photon emission computed tomography (thallium SPECT).[6 7] Generally, when an abnormal finding is detected using these methods, a further investigation using coronary angiography (CAG) can be performed. However, preoperative cardiac evaluations such as ECG, echocardiography, and thallium SPECT cannot be effective because of their relatively low sensitivity to detect CAD in LT recipients.[8 9] In contrast with these evaluating tools, CAG was identified as a good diagnostic and preventive modality with reduction of overall all-cause mortality and also the incidence of both fatal and non-fatal myocardial infarction in LT recipients.[10] Nevertheless, CAG may not be an appropriate screening test for patients with relatively advanced liver diseases, because coagulation abnormalities can increase the risk of bleeding during CAG.[11]

To address the aforementioned drawbacks, coronary computed tomographic angiography (coronary CT) has been suggested as a non-invasive imaging test for diagnosis of cardiac function, because it has the advantage of being able to identify

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coronary vessel wall characteristics and stenosis.[12] Coronary calcium scores, obtained from coronary CT, are a particularly useful determinant of the prevalence of CAD in LT candidates.[13] Several previous studies report a significant correlation between coronary calcium scores and known cardiovascular risk factors in LT recipients.[14 15] In addition, a coronary calcium score of >400 is significantly associated with CAD on CAG in LT recipients.[16–18] However, no studies have investigated the association between coronary calcium scores and cardiovascular complications after LT.

We therefore evaluated the usefulness of preoperative coronary calcium scores assessed by coronary CT for predicting early postoperative cardiovascular complications in LT recipients. To this end, we evaluated the ability of a coronary calcium score of >400 to predict major cardiovascular complications occurring within 1 month of LT.

Methods

Patients

This was a single-centre, retrospective observational study of 443 patients who underwent LT at Asan Medical Center, Seoul, Korea, between 2010 and 2012. The following groups of patients were excluded from the study: (i) patients under 20 years of age, (ii) patients who did not undergo coronary CT before LT, (iii) patients who suffered significant cardiovascular events such as a myocardial infarction, or had a history of coronary angioplasty before LT, and (iv) patients who did not check troponin I assay in the postoperative period (Fig. 1). Medical records were reviewed and cardiovascular complications that occurred within 1 month of the LT were noted. The study protocol was approved by the Institutional Review Board of Asan Medical Center.

Routine cardiac evaluation

In our institution, routine preoperative cardiac assessments consist of an ECG, echocardiography, and thallium SPECT. On echocardiography, the presence of decreased left ventricle function (decreased ejection fraction), regional wall motion abnormality, significant valvular disease, or pulmonary hypertension were categorized as abnormal findings. On thallium SPECT, the presence of a medium or large wall perfusion defect was regarded as an abnormal finding. Preoperative ECG and corrected QT (QTc) interval were also evaluated.

Coronary CT

Coronary CT scans using dual-source CTs (Somatom® Definition Flash or Somatom® Definition, Siemens Medical Solutions, Forchheim, Germany) were performed as part of the routine cardiac evaluations (Fig. 2). Coronary calcium scores were calculated with an automated, computerized software program using an Agatston scoring method.[19]

Total coronary artery calcification was classified as none (0), minimal (1–10), mild (11–100), moderate (101–400), or severe (>400) according to the total coronary calcium score.[20] In the present study, patients with a coronary calcium score >400 were assigned to a positive coronary CT group, while patients with a coronary calcium score ≤400 were assigned to the negative coronary CT group.[16–18]

Coronary angiography

Invasive CAG was performed to identify significant CAD in the positive coronary CT group before LT. The presence of significant stenosis in at least one coronary artery was regarded as a positive finding. However, based on the physician's assessment, some patients with severe coagulopathy did not undergo invasive CAG because of the risk of bleeding.

Posttransplant follow-up

In our institution, the combination of two or three different maintenance immunosuppressive drugs is used for the prevention of rejection after operation. The i.v. calcineurin inhibitors (tacrolimus and cyclosporine) are mainly used during hospital stay. Steroid such as methylprednisolone is almost universally used. Most recipients are also discharged with the oral tacrolimus as a primary immunosuppressant, with steroids which are gradually tapered and weaned in the following months. In addition, mycophenolate mofetil such as azathioprine is also commonly used to reduce tacrolimus dose and

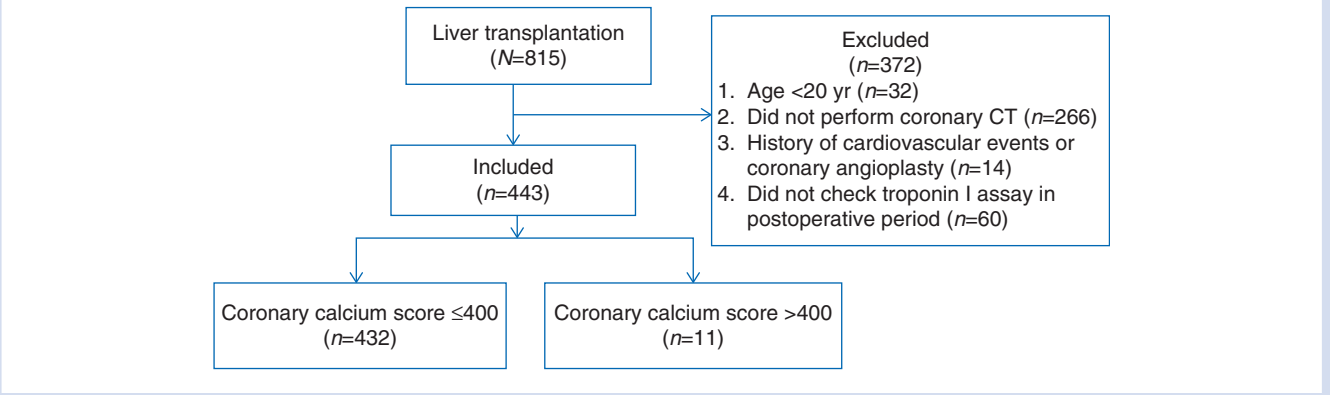

Fig 1 Flow chart of study participants. Coronary CT, coronary computed tomographic angiography.

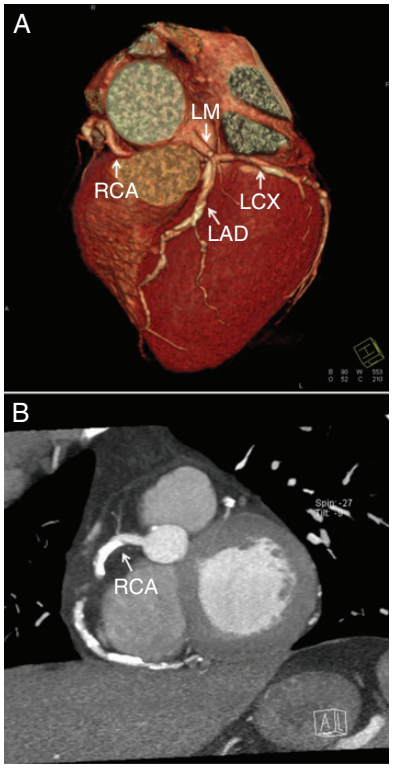

Fig 2 Multiple calcified plaques present on the coronary arteries of a liver transplant recipient, as shown by coronary computed tomographic angiography (A: short-axis view; B: volume-rendered image). The total coronary calcium score is 2601 in this patient [right coronary artery (RCA): 1611; left anterior descending coronary artery (LAD): 746; left circumflex coronary artery (LCX): 228; left main coronary artery (LM): 16].

side-effects such as nephrotoxicity, hypertension, and hyperlipidaemia.[21] Smoking was strictly prohibited after LT. For LT recipients showing serum total cholesterol >240 mg dl^{-1} or suboptimal lipid profiles with other risk factors for CAD, various statin agents were administered.

Data collection

All cardiovascular complications that occurred within 1 month of the LT were recorded. Records from the general ward and intensive care units, which were available on computerized databases, were analysed. Potential risk factors of postoperative cardiovascular complications included age, sex, BMI, diabetes mellitus, smoking history, statins therapy, diuretics use, QT_C interval, Child-Turcotte-Pugh (CTP) score, Model of End-Stage Liver Disease (MELD) score, graft weight, graft ischaemic time, and operation type (single living donor, dual living donor, or cadaveric donor).

Clinical endpoints

The main clinical endpoint was to evaluate whether a calcium score of >400 in coronary CT could predict the occurrence of cardiovascular complications occurring within 1 month of the LT. Postoperative cardiovascular complications were assessed according to the following definitions: a non-fatal myocardial infarction (medical records, ECG findings, and elevated troponin I >0.2 ng ml^{-1}), serious arrhythmia (ventricular tachycardia, ventricular fibrillation, or heart block requiring treatment), and cardiac death (because of fatal myocardial infarction or heart failure).[22]

Statistical analysis

Liver transplant recipients were categorized into two groups: the cardiovascular complications group (recipients with early postoperative cardiovascular complications) and the no cardiovascular complications group (recipients without complications). Categorical data are presented as a number (percentage) and were compared using the chi-square test or Fisher's exact test as appropriate. Continuous data are expressed as the mean (SD) or median (interquartile range) and were compared using a *t*-test or Mann–Whitney *U*-test as appropriate. Factors were input as independent variables into univariate logistic regression analysis. Variables with a *P*-value of <0.1 on the univariate logistic regression analysis were included in a stepwise multivariate logistic regression analysis to evaluate variables that independently predict major cardiovascular complications 1 month after LT. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 18.0, SPSS, Inc., Chicago, IL, USA).

Results

Of the 815 patients who underwent LT during the study period, 443 patients were included in the study (Fig. 1). Patient characteristic data including coronary calcium score are listed in Table 1. Coronary CT was performed on all 443 patients with no complications. The total mean coronary calcium score was 42 (195), and 319 (72%), 27 (6%), 61 (14%), 25 (5.5%), and 11 (2.5%) patients were categorized into the no, minimal, mild, moderate, or severe calcification groups, respectively. Figure 2 shows a coronary CT from a liver transplant recipient with multiple calcified coronary artery plaques.

Of the 443 patients in the study population, 432 (97.5%) had a coronary calcium score of ≤ 400, and were therefore assigned to the negative coronary CT group (Fig. 1). Positive findings on the coronary CT (classified as a coronary calcium score of >400) were seen in 11 (2.5%) patients; of which, 3 underwent CAG. These 3 patients all showed significant stenosis in at least one coronary artery. The first patient had the stenosis at left anterior descending coronary artery (LAD) and right coronary artery (RCA) in coronary CT and thus CAG was performed. In CAG, diffuse stenosis at LAD was observed in the patient. LT was performed after the application of medical treatment. On the sixteenth day after the operation, the patient was diagnosed with paroxysmal atrial fibrillation, requiring another medical treatment. The patient expired in 60 days as a result of unknown cardiac arrest. The second patient had stenosis at LAD and left circumflex coronary artery (LCX) in coronary CT, while stenosis at LAD was observed in CAG. LT was

Table 1 Patient characteristics of 443 liver transplant recipients. Data are expressed as the mean (SD) or number (percentage) as appropriate

Variables	Value
Age (yr)	52.4 (7.7)
Gender (male/female)	349 (79%)/94 (21%)
BMI (kg m^{-2})	23.9 (3.7)
Diabetes mellitus	106 (24%)
Smoking history	144 (33%)
Statins therapy	6 (1%)
Underlying liver disease	
Hepatitis B virus related liver cirrhosis	315 (71%)
Hepatitis C virus related liver cirrhosis	24 (6%)
Alcoholic liver disease	64 (15%)
Non-B Non-C hepatitis	18 (4%)
Toxic hepatitis	6 (1%)
Biliary cirrhosis	6 (1%)
Others	10 (2%)
Severity of liver disease	
Child-Turcotte-Pugh score (A/B/C)	150 (34%)/174 (39%)/119 (27%)
Model for End-Stage Liver Disease score	15.0 (8.2)
Preoperative haematologic profiles	
Haemoglobin (g dl^{-1})	11.0 (2.2)
Platelet (10^3 mm^{-3})	71.7 (50.8)
Prothrombin time (INR)	1.5 (0.5)
Albumin (g dl^{-1})	3.2 (0.6)
Creatinine (mg dl^{-1})	1.01 (1.00)
Coronary calcium score	42 (195)
No (0)	319 (72%)
Minimal (1–10)	27 (6%)
Mild (11–100)	61 (14%)
Moderate (101–400)	25 (5.5%)
Severe (>400)	11 (2.5%)

performed after medical treatment, and no postoperative cardiovascular events were found. The third patient had stenosis at LAD, LCX, and RCA in coronary CT. Although the patient was observed with three-vessel disease in CAG, LT was performed after only medical treatment. No postoperative cardiovascular complications were determined. The remaining 8 of 11 patients did not undergo CAG and were solely treated with medications before LT mainly because of their abnormal coagulation function.

All patients underwent ECG and echocardiography before LT. On echocardiography, 31 (7.0%) patients had abnormal findings. On ECG, the mean QT_C interval was 449.0 (34.1) ms. Thallium SPECT was performed on 410 (92.5%) patients, and a wall perfusion defect was detected in only three (0.7%) patients. Routine cardiac evaluations such as ECG, echocardiography, and thallium SPECT did not predict early postoperative cardiovascular complications in LT recipients. A comparison of the clinical characteristics of LT recipients listed according to the development of cardiovascular complications 1 month after LT is shown in Table 2. In the univariate logistic regression analysis, the following factors were significantly associated with early postoperative cardiovascular complications: a coronary calcium score >400, female sex, and statins therapy (Table 3). In the multivariate logistic regression analysis, predictive factors of major cardiovascular complications after LT were a coronary calcium score >400 and female sex. The risk of cardiovascular complications in LT recipients with a coronary calcium score >400 was 4.62 times that of LT recipients with a coronary calcium score ≤400 (P=0.032; Table 3).

Of the 443 LT recipients, 38 (8.6%) patients developed one or more cardiovascular complications during the 1 month follow-up period. Notably, 24 of the 38 patients experienced a non-fatal myocardial infarction, and 17 patients showed serious arrhythmia requiring immediate treatment. In addition, three of the 38 patients died as a result of cardiovascular complications.

Discussion

The major finding in the present study is that a coronary calcium score of >400 and female sex are useful determinants for predicting early postoperative cardiovascular complications in LT recipients. Cardiovascular complications occur frequently after LT, and an increased incidence of CAD has been consistently reported in patients with end-stage liver disease.[2–4] For these reasons, cardiovascular morbidity and mortality are major concerns in patients undergoing LT. It is therefore very important to predict postoperative cardiovascular complications in LT recipients.[23]

Coronary calcium scores are effective for detecting CAD.[24–26] Calcification of the coronary artery is caused by calcium phosphate, which accumulates in the form of hydroxyapatite. Its formation in atherosclerotic plaques is similar to bone mineralization. Coronary calcium scores are therefore related to measures of coronary luminal narrowing, stenosis severity, and total plaque burden. In addition, the coronary calcium score, which is used as a strong diagnostic determinant of CAD, may be a predictive factor of cardiovascular events in patients without cardiac symptoms because of its high negative predictive value and its independence from traditional coronary risk factors.[27]

A negative or extremely low coronary calcium score (10 or lower) indicates the absence of a significant coronary obstructive lesion. Thus, no specific further cardiac work-up is required for such patients. A coronary calcium score of 11 to 400 is consistent with mild or moderate atherosclerotic plaque burden, and suggests mild or moderate obstructive coronary artery stenosis.[27 28] Importantly, patients with a coronary calcium score >400 are at a high likelihood of at least one significant coronary artery stenosis.[16–18]

In the present study, 11 (2.5%) of the 443 of the patients had a coronary calcium score >400. In the multivariate logistic regression analysis, a coronary calcium score >400 was a significant factor for predicting early cardiovascular complications

Table 2 Clinical characteristics of liver transplant recipients according to the development of postoperative cardiovascular complications. Data are expressed as the mean (SD), median (interquartile range), or number (percentage) as appropriate. Thallium SPECT, thallium single photon emission computed tomography; QT_C, corrected QT interval on ECG; MELD, Model for End-Stage Liver Disease

Variables	No complications ($n=405$)	Complications ($n=38$)	*P*-value
Coronary calcium score >400	8 (2.0%)	3 (7.9%)	0.059
Thallium SPECT	3 (0.9%)	0 (0%)	1.000
Echocardiography	29 (7.2%)	2 (5.3%)	1.000
Age (yr)	52.4 (7.5)	52.2 (9.8)	0.894
Gender (male/female)	326 (80.5%)/79 (19.5%)	23 (60.5%)/15 (39.5%)	0.004
Body mass index (kg m^{-2})	23.9 (3.7)	23.4 (4.2)	0.433
Diabetes mellitus	93 (23.0%)	13 (34.2%)	0.120
Smoking history	136 (33.6%)	8 (21.1%)	0.115
Statins therapy	4 (1.0%)	2 (5.3%)	0.086
Preoperative diuretics use	243 (60.0%)	21 (55.3%)	0.569
QT_C (ms)	448.7 (34.3)	452.3 (32.1)	0.533
Child-Turcotte-Pugh score	8.0 (2.3)	8.1 (2.1)	0.628
MELD score	15.1 (8.2)	14.5 (8.0)	0.678
Graft ischaemic time (min)	44.0 (34.0–61.0)	44.5 (37.0–64.0)	0.526
Graft weight (g)	730.0 (650.0–830.0)	738.0 (680.0–810.0)	0.610
Donor type			0.774
Cadaveric donor	13 (3.2%)	2 (5.3%)	
Single living donor	353 (87.2%)	33 (86.8%)	
Dual living donor	39 (9.6%)	3 (7.9%)	

Table 3 Univariate and multivariate regression analysis associated with cardiovascular complications during the first month after liver transplantation. OR, odds ratio; CI, confidence interval; thallium SPECT, thallium single photon emission computed tomography; QT_C, corrected QT interval on ECG; MELD, Model for End-Stage Liver Disease

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Coronary calcium score >400	4.25 (1.08–16.76)	0.039	4.62 (1.14–18.72)	0.032
Thallium SPECT	0	0.999		
Echocardiography	0.72 (0.17–3.14)	0.662		
Age	1.00 (0.96–1.04)	0.867		
Gender				
Male	1.00		1.0	
Female	2.69 (1.34–5.39)	0.005	2.76 (1.37–5.57)	0.005
Body mass index	0.96 (0.88–1.06)	0.432		
Diabetes mellitus	1.75 (0.86–3.55)	0.124		
Smoking history	0.53 (0.24–1.18)	0.120		
Statins therapy	5.57 (0.99–31.46)	0.052	4.20 (0.69–25.63)	0.120
Preoperative diuretics use	0.82 (0.42–1.61)	0.570		
QT_C	1.00 (1.00–1.01)	0.531		
Child-Turcotte-Pugh score	1.03 (0.89–1.19)	0.725		
MELD score	1.00 (0.95–1.03)	0.664		
Graft ischaemic time	1.12 (0.61–2.07)	0.709		
Graft weight	1.00 (1.00–1.00)	0.735		
Donor type				
Cadaveric donor	1.00			
Single living donor	0.61 (0.13–2.81)	0.524		
Dual living donor	0.50 (0.08–3.33)	0.474		

after LT. These data, together with previous reports,[16–18] suggest that a coronary calcium score >400 should be considered as a cardiovascular risk factor when performing preoperative evaluations in LT recipients. In line with the present results, McAvoy and colleagues[14] reported a significant relationship between coronary calcium scores and cardiovascular risk factors such as age, systolic blood pressure, and the number of coronary vessels involved in LT recipients. They also suggested that the coronary calcium score is a more sensitive measure to detect cardiovascular risk factors in LT patients than the Framingham risk score. Jodocy and colleagues[29] also described positive coronary CT findings (with a coronary calcium score >300) as a useful non-invasive measure of the prevalence of CAD in LT recipients during a post-transplant follow-up period ranging from 9 to 15 months. In patients with chronic renal failure, the coronary calcium score >400 proved to have good diagnostic and prognostic performance to evaluate cardiovascular events.[30] In patients with asymptomatic diabetes, there was a significant association between coronary calcium score >400 and the prevalence of carotid plaque.[31]

In addition, CAG is known to be an important diagnostic tool for assessing cardiovascular events in LT recipients, although it has the risk of bleeding. Maddur and colleagues[10] reported that the increased use of CAG and percutaneous coronary intervention was associated with significant reductions in postoperative myocardial infarction and 1-yr all-cause mortality and also overall all-cause mortality in LT recipients. Furthermore, they also suggested that the CAG can be recommended to evaluate cardiac risks, when indicated, in LT recipients.

We also found that female sex is a reliable predictive factor for cardiovascular complications after LT. In an earlier study by Rumberger and colleagues,[27] the amount of coronary calcium proportionally corresponded to the degree of overall atherosclerotic plaque burden regardless of sex. However, they reported that the atherosclerotic process, regardless of conventional risk assessment, is more premature, accelerated, and aggressive in women than in men. Importantly, they asserted that when using coronary calcium scoring in clinical applications, the variability of the score as a function of sex must be considered. However, further studies are required to clarify the effect of sex on the prediction of postoperative cardiovascular complications.

Fouad and colleagues[13] showed that cardiac complications after LT are common, and emphasized that adverse intraoperative cardiovascular events, previous cardiac disease, and integrated MELD score are independent predictors of cardiac complications during the 6-month period after LT. However, in the present study, the MELD score was not a significant predictive factor of cardiovascular complications occurring 1 month after LT. The reasons underlying the discrepancy between the present results and previous findings are not clear. Possible factors such as LT donor type (living *vs* cadaveric donor) and follow-up period after LT (1 *vs* 6 months) are thought to, at least in part, influence these differences. The relatively low MELD score [15.0 (8.2)] in our patients may also influence the predictive ability of this factor for postoperative cardiovascular complications.

In the present study, other routine cardiac evaluations such as thallium SPECT and echocardiography were not predictive of postoperative cardiovascular complications in LT recipients. At our institution, LT candidates with abnormal thallium or echocardiography findings underwent further cardiac evaluations or were sent to a cardiac specialist. At this point, if additional abnormal findings were found, cardiac interventional procedures or surgical treatment was performed before LT surgery. Therefore, these candidates were excluded from our study, and such patients' treatment procedure likely influenced the results of the study.

There were several limitations to our study, including its retrospective design and the use of medical records from the general ward and intensive care unit. Furthermore, because coronary CT has been performed by clinicians' decision after evaluating the conditions of LT recipients, the coronary CT was not performed in some recipients. Therefore, our retrospective study may be, at least in part, influenced by the inevitable selection bias. Further prospective study would be needed to minimize the selection bias. In addition, the 1-month study period was relatively short. Further studies are therefore needed to assess long-term postoperative cardiovascular complications.

In conclusion, a coronary CT calcium score of >400 and female sex are reliable predictive factors for cardiovascular complications occurring during a period of 1 month after LT. Therefore, these results suggest that the coronary calcium score provides useful information for predicting early postoperative cardiovascular complications in LT recipients. These results also suggest that the coronary CT can be another potentially good screening tool for preoperative cardiovascular evaluation in LT candidates.

Authors' contributions

Y.-G.K.: study design, data collection, data analysis, manuscript preparation, and revision; J.-W.K.: study design, data analysis, manuscript revision, and final approval; Y.-K.K.: conception, study design, data analysis, manuscript preparation, revision, and final approval; H.S.: study design and data collection; T.-H.L.: manuscript revision and final approval; S.H.: manuscript revision and final approval; G.-S.H.: conception, study design, and final approval; S.-G.L.: manuscript revision and final approval.

Declaration of interest

None declared.

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