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Clinical Research

Temporary postoperative myocardial injury and long-term survival in liver transplant patients with coronary artery disease

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Background: Coronary artery disease (CAD) is increasing worldwide due to the aging population and cardiometabolic syndrome. However, the extent of postoperative myocardial injury, the most common cause of death during the 30 days after noncardiac surgery, remains unclear with respect to liver transplant (LT) patients with CAD. We examined the link between post-LT high sensitivity cardiac troponin I (hs_cTnI) and long-term survival according to liver disease severity.

Methods: Consecutive patients who underwent LT (n = 3,220) from 2010 to 2020 were evaluated retrospectively. CAD was defined as a history of coronary artery bypass surgery or percutaneous intervention, or previous myocardial infarction. Peak hs_cTnI levels within 30 days post-transplant were compared in patients with and without CAD. The primary endpoint was defined as an all-cause mortality at 12 years following LT. Secondary endpoints include peak hs_cTnI level within post-transplant 30 days and 30-day mortality. Survival analysis was performed using the Kaplan–Meier method.

Results: CAD patients (n = 264, 8.2%) had higher peak hs_cTnI levels within 30 days post-LT than those without CAD (median [interquartile]: 0.068 [0.030–0.154] vs. 0.087 [0.037–0.203] ng/ml, respectively; P = 0.004); however, the mortality rate was comparable (14.7% vs. 14.8%, respectively, P = 0.999), at 12 years, and 1.9% vs. 1.1% (P = 0.522) at 30 days, respectively, at 30 days. Subgroup analysis with stratified liver disease severity identified a similar risk of long-term mortality.

Conclusions: Although the peak hs_cTnI level within 30 days was higher in revascularized or treated CAD patients after LT compared those without CAD, long-term mortality rates at 12 years and 30-day mortality rate were comparable.

Keywords: Coronary artery disease; Liver transplant; Mortality; Troponin I.

INTRODUCTION

The prevalence of coronary artery disease (CAD) is rising worldwide due to an increase in coronary risk factors such as aging, obesity, diabetes, and cardiometabolic syndrome [1,2]. About 25% of liver transplantation (LT) candidates with traditional coronary risk factors may have a moderate degree of CAD (stenosis ≥ 50%), even though they are asymptom-

atic [2,3]. However, there is a consensus that CAD should not be regarded as an absolute contraindication to LT if patients are treated appropriately [3,4].

Cardiac death or postoperative myocardial injury is the leading cause of death within the first 30 days after noncardiac surgery [5–7]. Similarly, in the modern era of LT, cardiovascular events are the leading cause of early and late mortality [8]. However, the extent of myocardial injury or damage, as assessed by measurement of high sensitivity cardiac troponin I (hs_cTnI) after LT, in patients with CAD remains unclear.

In the current study, we first examined the extent of hs_cTnI increase within 30-day after LT in the patients with CAD. We then compared long-term mortality and 30-day mortality in the patients with and without CAD. In the subgroup analysis, we observed the long-term mortality across the stratification of liver disease severity, because high model for end-stage liver disease (MELD) score may affect the outcomes of CAD patients.

MATERIALS AND METHODS

Study population

A total of 4,432 consecutive, prospectively registered patients who underwent LT from January 2010 to February 2020 were enrolled. Of these, 1,212 were excluded for the following reasons: 227 were < 18 years old, 180 underwent retransplantation after rejection of the initial graft, 131 had acute fulminant liver failure, 130 had toxic hepatitis, and 544 had incomplete hs_cTnI data. Finally, 3,220 patients were included in the analysis (Fig. 1).

Data collection

Baseline demographic characteristics, laboratory, and perioperative variables related to LT were collected using fully computerized database extraction software (ABLE, Asan Biomedical Research Environment). The study design and a waiver of informed consent from participants were approved by the Institutional Review Board (no 2022-0511).

The MELD score, a known index of liver disease severity, was calculated using variables measured during hospitalization for LT. When variables were measured repeatedly, they were updated at the time of LT.

As a part of our institution's routine post-LT cardiac workup since 2008, all LT recipients were assessed with transthoracic echocardiography, coronary computed tomography (CT) angiography, B-type natriuretic peptide and hs_cTnI levels. All recipients, irrespective of signs and symptoms of heart failure/myocardial injury, have their hs_cTnI concentration measured immediately after LT (i.e., on postoperative day [POD] 1); this was repeated at least once on POD2 or POD3 [9,10]. Additionally, when patients suffered signs and symptoms of an adverse cardiovascular event, including myocardial ischemia, within 30 days after LT, hs_cTnI levels were measured and followed-up. In the current study, the peak hs_cTnI level within 30 days after LT was used for analysis. Hs_cTnI was assessed using the ADVIA Centaur XP TnI-Ultra (Siemens Healthcare Diagnostics, USA; the 99th percentile upper reference limit [URL] = 0.04 pg/L; lower limit = 0.006 ng/L).

1. Outcomes and follow-up

Mortality data were collected from the medical records database and the institution's LT Registry, which is updated regularly by the Organ Transplantation Center. The primary endpoint was defined as an all-cause mortality at 12 years following LT and secondary endpoint include 30-day mortality and peak hs_cTnI level within post-transplant 30 days. Liver disease severity was assessed with the stratification of MELD score: MELD score < 16, MELD score 16–30 and MELD score > 30.

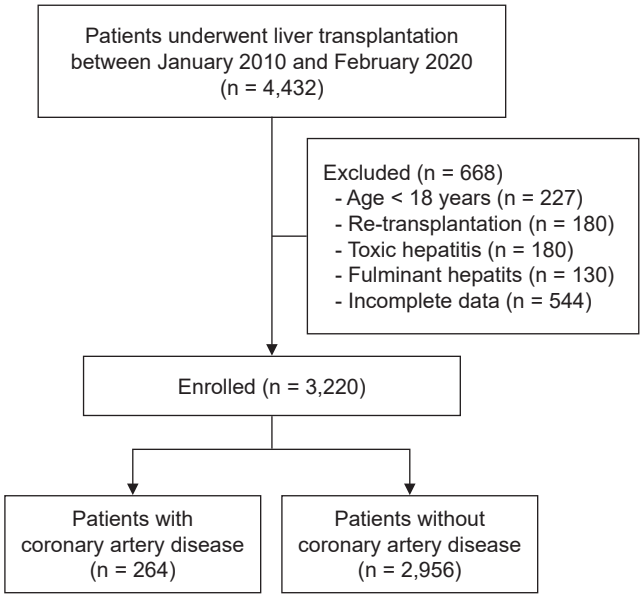

Fig. 1. Flow diagram of current study.

Statistics

Data were expressed as the mean and standard deviation, as the median and interquartile range (for continuous variables), or as numbers and percentages (for categorical variables). Intergroup comparisons were performed using a *t*-test or the Mann–Whitney *U* test (for continuous variables), or the χ^2 test or Fisher's exact test (for categorical variables), as appropriate. Kaplan–Meier survival curves were used to depict the risk of all-cause mortality during the entire follow-up period. To evaluate the relationship between clinical and biochemical parameters, liver disease severity, and mortality events, a Cox proportional multiple regression model was built, and adjusted hazard ratios (HR) were obtained for long-term mortality. Covariates included in long-term survival analysis were age, sex, body mass index, diabetes, hypertension, MELD score, intraoperative red blood cell transfusion, and postreperfusion syndrome and CAD. Statistical analyses were conducted using R (version 4.1.2, R Foundation for Statistical Computing, Austria) with a significance level of 0.05.

RESULTS

Of 3,220 LT recipients included in the study (Table 1), the median age was 54.0 (interquartile, 49, 59) years, and 2,411 (74.9%) were male. The MELD score was 14 (9, 22) (Table 1). The primary causes of liver disease were virus-related liver cirrhosis (65.8%), alcoholic liver disease (22.9%), and others (4.1%).

Table 1. Demographics and Perioperative Variables According to CAD

Variable	CAD (–) (n = 2,956)	CAD (+) (n = 264)	Total (n = 3,220)	P value
Demographics				
Age (yr)	54 (48, 59)	57 (53, 62)	54 (49, 59)	< 0.001
Male	2,178 (73.7)	233 (88.3)	2,411 (74.9)	< 0.001
Body mass index (kg/m^2)	24.2 (21.9, 26.5)	24.7 (22.4, 27.0)	24.2 (22.0, 26.6)	0.059
MELD score	14 (9, 23)	13 (9, 20)	14 (9, 22)	0.221
Cardiovascular disease	379 (12.8)	264 (100.0)	643 (20.0)	< 0.001
Diabetes mellitus	680 (23.0)	113 (42.8)	793 (24.6)	< 0.001
Hypertension	511 (17.3)	79 (29.9)	590 (18.3)	< 0.001
Varix bleeding	51 (1.7)	3 (1.1)	54 (1.7)	0.643
Intractable ascites	863 (29.2)	88 (33.3)	951 (29.5)	0.180
Pre-LT RRT	229 (7.7)	23 (8.7)	252 (7.8)	0.660
Pre-LT vasopressor use	128 (4.3)	10 (3.8)	138 (4.3)	0.796
Pre-LT ventilator use	172 (5.8)	8 (3.0)	180 (5.6)	0.080
Etiology of liver cirrhosis				
Viral cirrhosis	1,966 (66.5)	153 (58.0)	2,119 (65.8)	0.006
Alcoholic cirrhosis	657 (22.2)	80 (30.3)	737 (22.9)	0.004
Biliary cirrhosis	120 (4.1)	2 (0.8)	122 (3.8)	0.012
Other disease	10 (0.3)	1 (0.4)	11 (0.3)	1.000
Laboratory findings				
Total bilirubin	2.0 (1.0, 6.5)	1.8 (0.9, 4.2)	2.0 (1.0, 6.3)	0.040
Prothrombin time, INR	1.42 (1.20, 1.81)	1.38 (1.17, 1.71)	1.41 (1.20, 1.79)	0.147
Creatinine (mg/dl)	0.79 (0.64, 1.00)	0.80 (0.67, 1.06)	0.80 (0.64, 1.01)	0.114
Serum sodium (mEq/L)	139 (135, 141)	138 (135, 141)	139 (135, 141)	0.240
Intraoperative variables				
pRBC transfusion	8 (3, 16)	9 (4, 17)	8 (3, 16)	0.013
Postreperfusion syndrome	1,737 (58.8)	179 (67.8)	1,916 (59.5)	0.005
Outcome after LT				
30-day mortality	56 (1.9)	3 (1.1)	59 (1.8)	0.522
Overall mortality	434 (14.7)	39 (14.8)	473 (14.7)	1.000

Values are presented as median (1Q, 3Q) or number (%). CAD: coronary artery disease, MELD: model for end-stage liver disease, LT: liver transplantation, RRT: renal replacement therapy, pRBC: packed red blood cells, INR: international normalized ratio.

CAD patients

CAD patients (n = 264, 8.2%) were older, and had a higher prevalence of diabetes, hypertension, alcoholic cirrhosis, and a history of previous cardiovascular disease including stroke; however, the pretransplant MELD score for CAD and non-CAD patients was similar. Intraoperatively, patients with CAD required transfusion of more red blood cells (median [interquartile], 9.0 [4.0, 17.0] vs. 8.0 [3.0, 16.0] units, P = 0.013) and were more likely to suffer from postreperfusion syndrome (67.8% vs. 58.8%, P = 0.005). Following LT, patients with CAD had higher peak hs_cTnI levels within 30 days of LT than those without CAD (0.087 [0.037, 0.203] vs. 0.068 [0.030, 0.154] ng/ml, respectively; P = 0.004).

30 day and long-term mortality

All-cause mortality (14.7% vs. 14.8%, P = 0.999, Fig. 2) at 12 years and at 30 days (1.9% vs. 1.1%, P = 0.522) was similar for patients with and without CAD.

When patients are grouped with peak hs_cTnI > 0.04 ng/ml and hs_cTnI ≤ 0.04 ng/ml level within 30 days of LT, patients with CAD did not show differences in mortality compared with those without CAD (Fig. 3).

In multivariable Cox proportional HR analysis, CAD did not remain as an important determinant for long-term survival, as expected in the univariate analysis (Fig. 4).

Subgroup analysis after stratification according to liver disease severity (MELD score < 16, 16–30, or > 30) revealed a comparable risk of long-term mortality (log-rank P = 0.41, P = 0.89, and P = 0.52, respectively) (Fig. 5).

DISCUSSION

In the current study, the peak hs_cTnI level within 30 days after LT was higher in those with CAD; however, we found long-term mortality rates at 12 years were comparable with those of patients without CAD, irrespective of liver disease severity.

We evaluated postoperative peak hs_cTnI levels within 30 days in a large cohort of LT patients, especially those with CAD. Only a few studies have analyzed hs_cTnI levels in the field of LT surgery, despite the importance of post-LT myocardial injury [11].

Myocardial injury after noncardiac surgery (MINS) is defined as myocardial injury/damage caused by ischemia oc-

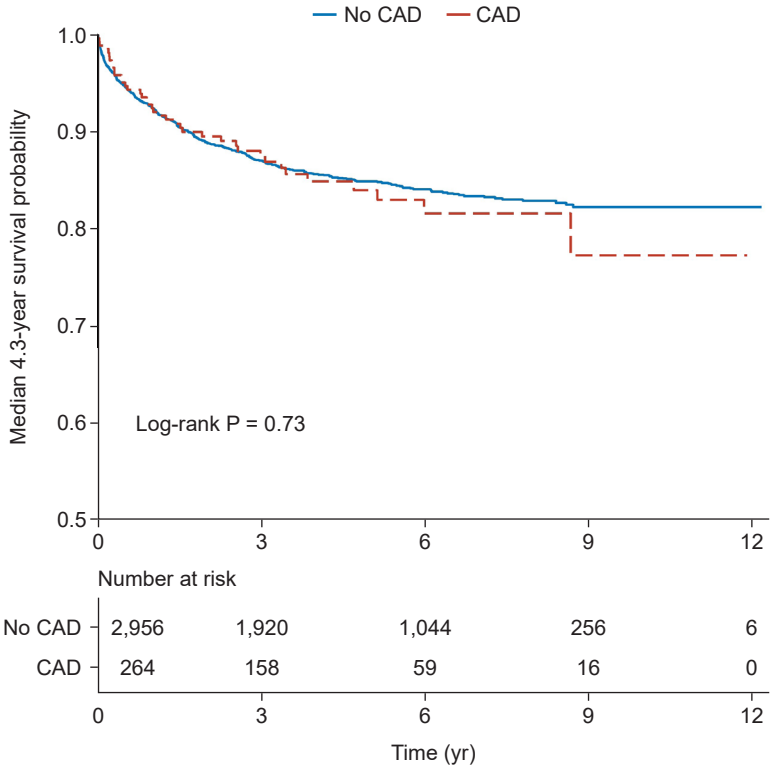

Fig. 2. Kaplan–Meier plot showing cumulative overall survival rate between patients with and without coronary artery disease (CAD).

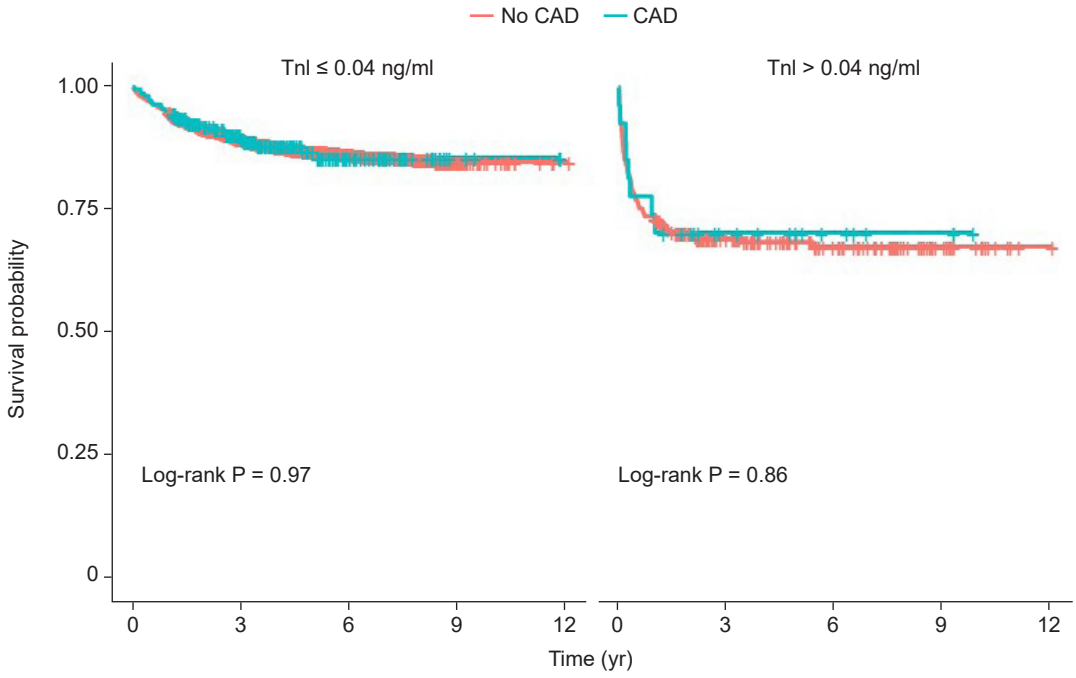

Fig. 3. Impact of coronary artery disease (CAD) prevalence on cumulative overall survival rate between patients with low (≤ 0.04 ng/ml) and high (> 0.04 ng/ml) troponin I (TnI).

curring during or within 30 days after surgery [7]. Among patients undergoing cardiac and noncardiac surgery, peak postoperative troponin levels during the first 3 days post-surgery are significantly associated with 30-day mortality, and a number of studies show that elevated cardiac troponin is an independent predictor of major adverse cardiac events [11,12]. Therefore, perioperative troponin screening is highly recommended because it can identify patients with MINS who are at higher risk for major cardiovascular events after noncardiac surgery. Another study shows that after living-donor LT surgery, myocardial injury detected by elevated hs-cTnI levels immediately after surgery is independently associated with adverse outcomes during hospital stay [11].

LT can be an extremely stressful event for patients with end-stage liver disease because they often suffer from refractory hypotension, tachyarrhythmia, massive bleeding with extreme anemia, inferior vena cava clamping, prolonged vasoplegia with high dose vasopressors, and acute overload of ventricular preload during surgery [9,13,14]. Additionally, afterload increase during the immediate postoperative period transforms silent cardiovascular disease into early heart failure status [15–17]. Therefore, it might not be surprising that CAD patients had higher postoperative hs_cTnI levels. However, the difference was not sufficiently high to discriminate long-term mortality in the current study, suggesting that adequately treated CAD patients may tolerate the stressful event well, as did patients without CAD, resulting in comparable long-term outcomes.

By contrast, a previous retrospective study [10] of 2,118 consecutive LT patients who underwent CAD screening using coronary CT angiography identified unknown obstructive CAD (> 50% narrowing, 9.2% prevalence) in 21.7% of patients with three or more known CAD risk factors listed by the American Heart Association (i.e., diabetes mellitus, hypertension, prior cardiovascular disease, left ventricular hypertrophy, age > 60 years, smoking, and dyslipidemia) [18]. Of these, two-vessel or three-vessel obstructive CAD had a 4.9-fold higher post-LT type 2 myocardial infarction risk than normal coronary vessels [10]. This finding emphasizes the importance of pretransplant identification of unknown CAD, and administration of appropriate treatments such as revascularization.

However, another study evaluated cardiovascular events after LT; patients were stratified according to the presence and severity of CAD, as measured by coronary angiography. The authors found no evidence of a relationship between the presence and severity of CAD and composite cardiovascular events and concluded that the risk of cardiovascular events during the immediate post-transplant period is not associated with the presence or severity of CAD [19].

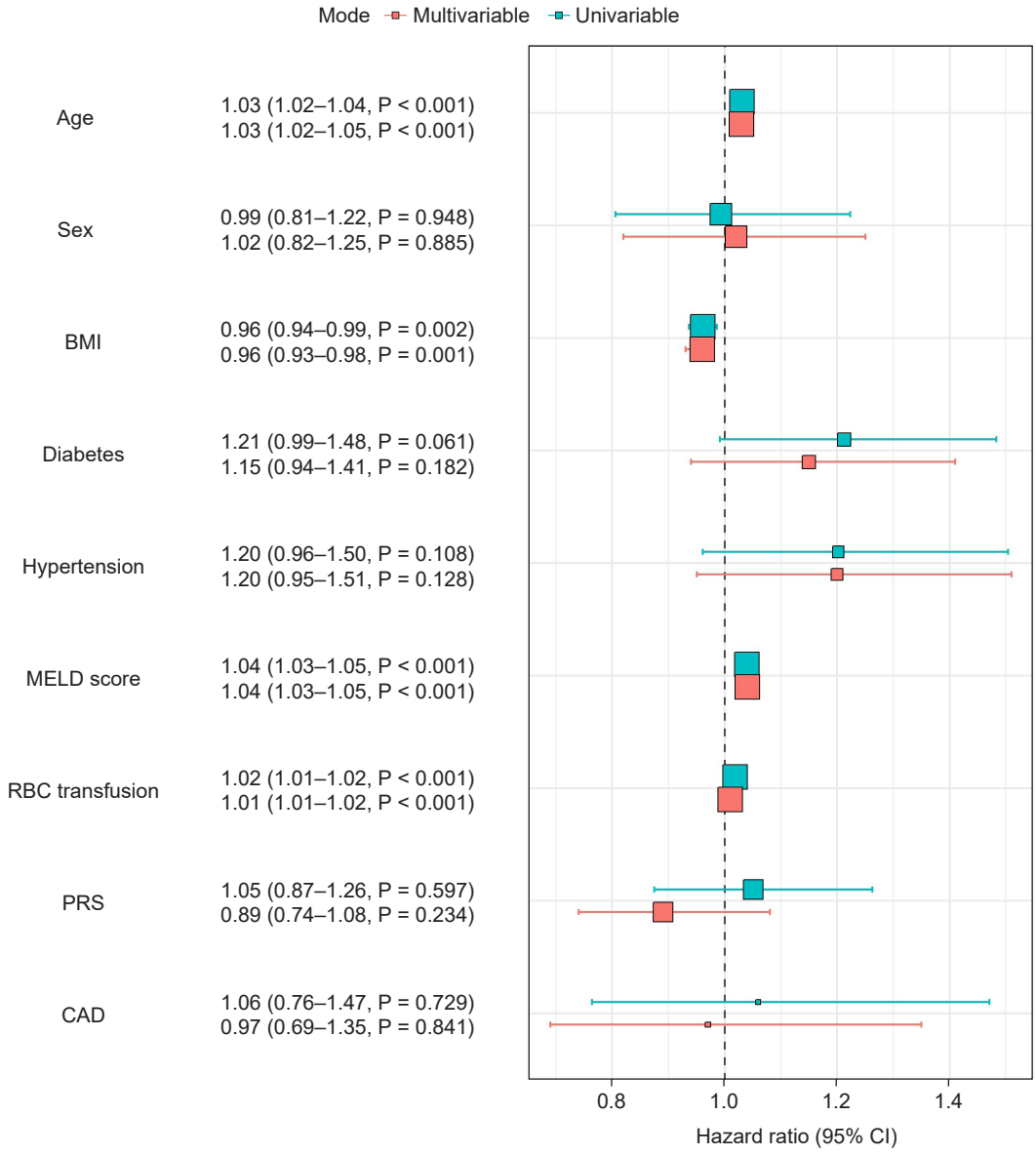

Fig. 4. Uni- and multivariable cox regression analysis with long-term mortality rates at 12 years. BMI: body mass index, MELD: model for end-stage liver disease, RBC: red blood cell, PRS: post-reperfusion syndrome, CAD: coronary artery disease, CI: confidence interval.

Similarly in the Satapathy et al.'s study [4], it was emphasized that listing for LT after appropriate revascularization in the preoperative period in patients with high risk for potential or known CAD would lead to similar post-LT survival compared with those without obstructive CAD irrespective of underlying severity, or extent disease, if appropriately revascularized. In the current study, our definition of patients with CAD was already revascularized or treated patients from old myocardial infraction. Therefore, our results showing comparable long-term outcomes in patients with and without CAD are in line with previous studies [4,20]. Specifically, our comparable long-term results were across the stratification of liver disease severity of MELD score, which importantly affect the critical determinants of post-LT survival.

In multivariable Cox proportional HR analysis, CAD did not remain significant, however, age, body mass index (BMI), MELD score, and intraoperative red blood cell transfusion remained significant. Of these, although above variables remained are generally expectable for important risk factors of long-term mortality, decreased BMI is interesting. Presumably, it is thought that low BMI might be associated with sarcopenia, which is known risk factors of poor LT outcomes [21]. However, further controlled study

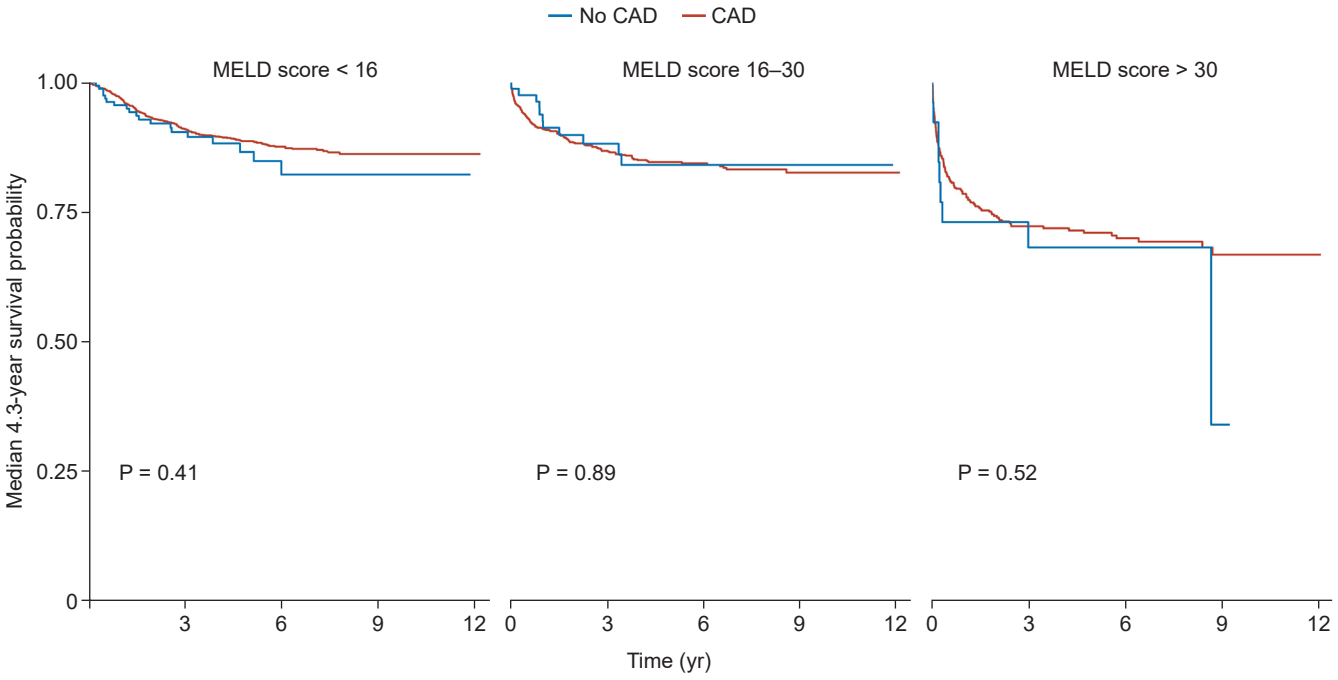

Fig. 5. Kaplan–Meier plot of cumulative overall survival rate between patients with and without coronary artery disease (CAD), in subset of patients with MELD score of < 16, 16–30, or > 30. MELD: model for end-stage liver disease.

will be needed.

The current study has several limitations. Although the study cohort was collected prospectively, the retrospective review of mortality from medical records has limitations. Second, despite the large LT population, our patients are all from a single institution. Therefore, a prospective multicenter study will be needed in the future.

In conclusion, patients with CAD showed transient myocardial injury with slightly higher peak hs_cTnI within 30 days after LT compared with those without CAD, however, long-term mortality rates at 12 years and 30-day mortality rate were comparable.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: J Yang, Gyu-Sam Hwang. Data curation: Jae Hwan Kim, Ji-Woong Yang. Formal analysis: Gyu-Sam Hwang. Methodology: Jae Hwan Kim. Visualization: Hye-Mee Kwon, Ji-Woong Yang. Writing - original draft: Hye-Mee Kwon. Writing -review & editing: Gyu-Sam Hwang. Investigation: Ji-Woong Yang. Software: Hye-Mee Kwon. Supervision: Gyu-Sam Hwang.

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