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Clinical Research

Association Between the Frailty Index and Clinical Outcomes after Coronary Artery Bypass Grafting

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Background: This study investigated the predictive value of the frailty index calculated using laboratory data and vital signs (FI-L) in patients who underwent coronary artery bypass grafting (CABG).
Methods: This study included 508 patients (age 67.3±9.7 years, male 78.0%) who underwent CABG between 2018 and 2021. The FI-L, which estimates patients' frailty based on laboratory data and vital signs, was calculated as the ratio of variables outside the normal range for 32 preoperative parameters. The primary endpoints were operative and medium-term all-cause mortality. The secondary endpoints were early postoperative complications and major adverse cardiac and cerebrovascular events (MACCEs).
Results: The mean FI-L was 20.9%±10.9%. The early mortality rate was 1.6% (n=8). Postoperative complications were atrial fibrillation (n=148, 29.1%), respiratory complications (n=38, 7.5%), and acute kidney injury (n=15, 3.0%). The 1- and 3-year survival rates were 96.0% and 88.7%, and the 1- and 3-year cumulative incidence rates of MACCEs were 4.87% and 8.98%. In multivariable analyses, the FI-L showed statistically significant associations with medium-term all-cause mortality (hazard ratio [HR], 1.042; 95% confidence interval [CI], 1.010–1.076), MACCEs (subdistribution HR, 1.054; 95% CI, 1.030–1.078), atrial fibrillation (odds ratio [OR], 1.02; 95% CI, 1.002–1.039), acute kidney injury (OR, 1.06; 95% CI, 1.014–1.108), and re-operation for bleeding (OR, 1.09; 95% CI, 1.032–1.152). The minimal p-value approach showed that 32% was the best cutoff for the FI-L as a predictor of all-cause mortality post-CABG.
Conclusion: The FI-L was a significant prognostic factor related to all-cause mortality and postoperative complications in patients who underwent CABG.

Keywords: Risk assessment, Coronary artery bypass, Frailty

Introduction

For patients with coronary artery disease, coronary artery bypass grafting (CABG) is recommended as the standard treatment along with percutaneous coronary intervention (PCI) [1,2]. With advances in PCI, the indications for CABG and PCI are being discussed. However, CABG is still the recommended first-line treatment for severe coronary artery diseases, such as 3-vessel disease and left main disease [2-5].

The Society of Thoracic Surgery (STS) score and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) have been widely used to evaluate the risk of cardiac surgery, including CABG, and have been proven to effectively predict postoperative mortality and morbidity [6-8].

In addition to these risk assessment methods, frailty has recently emerged as a factor influencing patients' clinical course after cardiac surgery [9,10]. Among the various tools available to measure patients' frailty, the frailty index calculated using laboratory data and vital signs (FI-L) is an objective and easy-to-use tool to evaluate patients' frailty, because it uses the results of routine preoperative laboratory data, blood pressure, and pulse rate [11]. This study was conducted to elucidate the clinical correlation between frailty scores and surgical outcomes in patients who underwent CABG.

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Methods

Patient characteristics

In total, 519 patients who underwent primary isolated CABG at Seoul National University Hospital between January 2018 and March 2021 were assessed for eligibility. After excluding 11 patients who underwent emergency operations, 508 patients (78.0% male) were enrolled in this study. The mean age at surgery was 67.3±9.7 years. The median STS scores and EuroSCORE II were 1.3 (interquartile range [IQR], 0.9–2.3) and 0.9 (IQR, 0.5–1.5), respectively. The most common comorbidities identified were hypertension (n=337, 66.3%) and diabetes mellitus (n=297, 58.5%) (Table 1).

Operative data

All operations in the study were performed through median sternotomy, except in 20 patients who underwent robot-assisted minimally invasive direct CABG. Off-pump CABG and on-pump beating CABG were performed in 498 patients (98.0%) and 10 patients (2.0%), respectively. The left internal thoracic artery was used in 497 patients (97.8%). The saphenous vein, right internal thoracic artery, and right gastroepiploic artery were used in 434 patients (85.4%), 45 patients (8.9%), and 8 patients (1.6%), respectively. The mean number of distal anastomoses was 3.4±1.1.

Table 1. Preoperative characteristics and risk factors in the study population (n=508)

Characteristic	Value
Age (yr)	67.3±9.7
Sex (male)	396 (78.0)
Body mass index (kg/m²)	24.7±3.6
STS score (%)	0.9 (0.5–1.5)
EuroSCORE II (%)	1.3 (0.9–2.3)
Coronary artery disease	
3 VD	361 (71.1)
Left main disease with 3VD	143 (28.2)
Acute coronary syndrome	295 (58.1)
History of percutaneous coronary intervention	127 (25.0)
Risk factors	
Hypertension	337 (66.3)
Diabetes mellitus	297 (58.5)
Dyslipidemia	257 (50.6)
History of stroke	59 (11.6)
Peripheral vascular disease	112 (22.0)
Chronic obstructive pulmonary disease	26 (5.1)
Atrial fibrillation	23 (4.5)
Left ventricular dysfunction (EF <0.35)	45 (8.9)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; 3 VD, three-vessel disease; EF, ejection fraction.

Frailty index calculation and evaluation of clinical outcomes

The FI-L was calculated using the patients' laboratory data and vital signs [11]. It was calculated as the ratio of variables outside the normal range among 32 preoperative parameters, including vital signs (blood pressure, pulse rate) and routine laboratory test results using the last preoperative laboratory test results and vital signs, usually obtained the day before surgery. The formula used was FI-L (%)=(number of variables with abnormal results/number of variables measured)×100 (Table 2). A higher score indicated greater frailty.

Table 2. Frailty-related parameters

Parameter	Normal range
Systolic blood pressure	90–140 (mm Hg)
Diastolic blood pressure	40–60 (mm Hg)
Pulse rate	60–99 (bpm)
Mean arterial pressure	70–105 (mm Hg)
Pulse pressure	30–65 (mm Hg)
Bicarbonate	21–29 (mmol/L)
Calcium	8.8–10.5 (mg/dL)
Phosphorus	2.5–4.5 (mg/dL)
Glucose	70–110 (mg/dL)
Blood urea nitrogen	10–26 (mg/dL)
Uric acid	3.0–7.0 (mg/dL)
Cholesterol	0–240 (mg/dL)
Total protein	6.0–8.0 (g/dL)
Albumin	3.3–5.2 (g/dL)
Total bilirubin	0.2–1.2 (mg/dL)
Alkaline phosphatase	30–115 (U/L)
Lactate dehydrogenase	100–225 (U/L)
Creatinine	0.7–1.4 (mg/dL)
Sodium	135–145 (mEq/L)
C-reactive protein	0–0.5 (mg/dL)
Triglyceride	0–200 (mg/dL)
High-density lipoprotein cholesterol	35–55 (mg/dL)
Hemoglobin	12–16 (g/dL)
Mean cell volume	79–95 (fL)
Red cell distribution width	11.5–14.5 (%)
Platelet	130–400 (1,000 cells/μL)
Segmented neutrophil	50–75 (%)
Glycohemoglobin	4–6.4 (%)
Vitamin B12	200–1,000 (pg/dL)
Vitamin D	19.6–54.3 (ng/dL)
Folate	3–15 (ng/mL)
Iron, refrigerated	50–170 (μg/dL)

The primary endpoints of this study were operative and medium-term all-cause mortality after CABG. Secondary outcomes were early postoperative complications and major adverse cardiac and cerebrovascular events (MACCEs). The definition of operative mortality was all-cause death during index hospitalization or within 30 postoperative days. After discharge, regular follow-up was performed at 3- to 6-month intervals in the outpatient clinic. Patients were contacted by telephone if the last visit did not occur on the scheduled date. In addition, data pertaining to death from any cause or cardiac events were obtained from death certificates provided by Statistics Korea. The definition of cardiac death was death pertaining to cardiac events including sudden death. MACCEs were defined as cardiac death, cerebrovascular accident, non-fatal acute myocardial infarction, and coronary re-intervention, including PCI and redo-CABG. The median follow-up duration was 18.2 months (IQR, 10.8–29.4 months).

Statistical analysis

Statistical analyses were conducted with IBM SPSS ver. 28.0 (IBM Corp., Armonk, NY, USA) and SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). For data presentation, continuous variables were described as the mean with standard deviation for data with normal distribution or the median with IQR for non-normally distributed data. Categorical variables were presented as the number and percentage of participants. Risk factors associated with operative mortality were analyzed using multivariable logistic regression. The validity of the logistic regression model was verified with the Hosmer Lemeshow goodness-of-fit test (p=0.243). The survival rate during the follow-up period was estimated using the Kaplan-Meier method, and risk factors associated with medium-term all-cause mortality were analyzed using a Cox proportional hazards model. The cumulative incidence rates of MACCEs were estimated with non-cardiac death as a competing risk factor for the events. The risk factors for MACCEs were analyzed using the Fine-Gray proportional subdistribution hazard model. Preoperative variables and operation-related factors with a p-value less than 0.10 in univariable analyses were included in multivariable analyses. The optimal cutoff values of continuous variables for predicting time-related events were estimated using the minimal p-value approach [12].

Ethics statement

The institutional review board at Seoul National University Hospital reviewed the protocol of this study and approved it as a retrospective cohort study with minimal risk. The requirement for individual consent was waived according to the institutional guidelines for obtaining consent (approval no., 2108-068-1244).

Results

Early clinical outcomes

The operative mortality rate was 1.6% (n=8). The causes of early death included septic shock (n=3, 0.6%), acute mesenteric ischemia (n=2, 0.4%), pulmonary thromboembolism (n=1, 0.2%), severe limb ischemia (n=1, 0.2%), and intractable native coronary artery spasm (n=1, 0.2%). Postoperative complications included atrial fibrillation (n=148, 29.1%), respiratory complications (n=38, 7.5%), acute kidney injury (n=15, 3.0%), and re-operation for bleeding (n=10, 2.0%) (Table 3).

Medium-term clinical outcomes

Late death occurred in 23 patients. The 1- and 3-year overall survival rates were 96.0% and 88.7%, respectively (Fig. 1A). During the follow-up period, MACCEs occurred in 28 patients. Cardiac death, non-fatal acute myocardial infarction, coronary re-intervention, and cerebrovascular accident occurred in 9, 1, 12, and 7 patients, respectively. The 1- and 3-year cumulative incidence rates of MACCEs were 4.87% (95% confidence interval [CI], 3.16–7.1) and 8.98% (95% CI, 6.13–12.4), respectively (Fig. 1B).

Impact of FI-L on primary and secondary endpoints

The mean FI-L of the study patients was 20.9%±10.9%

Table 3. Early clinical outcomes (n=508)

Variable	No. (%)
Operative mortality	8 (1.6)
Postoperative complication	
Atrial fibrillation	148 (29.1)
Respiratory complications	38 (7.5)
Acute kidney injury	15 (3.0)
Re-operation for bleeding	10 (2.0)
Low cardiac output syndrome	9 (1.8)
Perioperative myocardial infarction	6 (1.2)
Mediastinitis	4 (0.8)
Stroke	1 (0.2)

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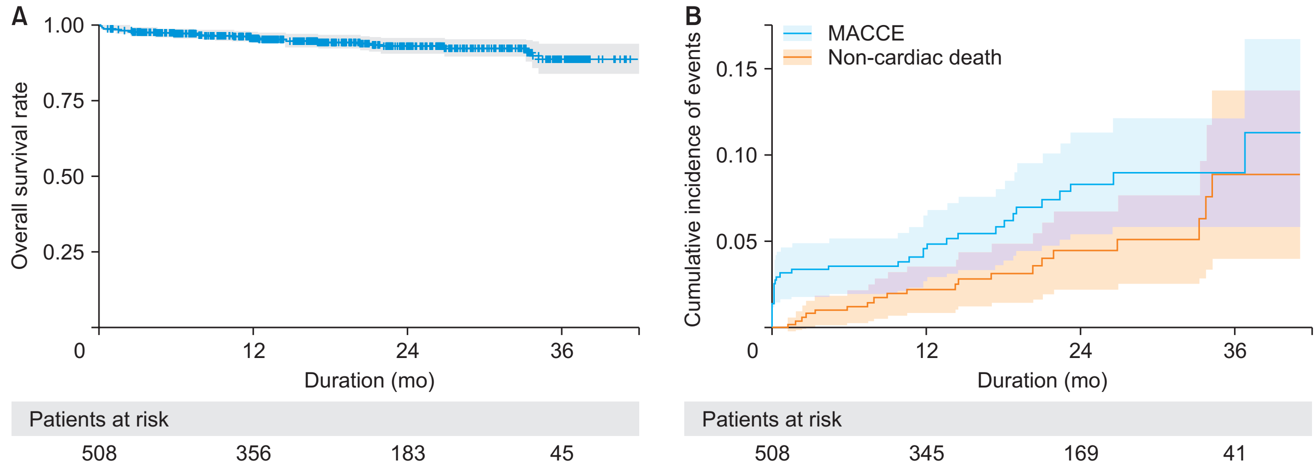

Fig. 1. (A) A Kaplan-Meier curve for overall survival and (B) a cumulative incidence function for major adverse cardiac and cerebrovascular events (MACCEs).

Table 4. Risk factor analysis for operative mortality

Variable	Univariable analysis p-value	Multivariable analysis	
		Odds ratio (95% CI)	p-value
Sex (female)	0.072	4.914 (1.081–22.222)	0.039
Age	0.493		
STS score	0.494		
EuroSCORE II	<0.001	1.229 (1.112–1.359)	<0.001
FI-L[a)]	0.054	-	-
Hypertension	0.817		
Diabetes mellitus	0.350		
Dyslipidemia	0.973		
History of stroke	0.937		
Peripheral vascular disease	0.072	4.791 (1.032–22.235)	0.045
Chronic obstructive pulmonary disease	>0.999		
Atrial fibrillation[a)]	0.017	-	-
Left ventricular dysfunction (EF <35%)[a)]	0.012	-	-
History of coronary intervention	>0.999		
Acute coronary syndrome	0.361		
On-pump beating CABG	0.999		
Use of the left internal thoracic artery	0.999		
No. of anastomoses	0.457		

CI, confidence interval; STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FI-L, frailty index based on laboratory data and vital signs; EF, ejection fraction; CABG, coronary artery bypass grafting.
[a)]Variables were included in the multivariable analysis but were dropped during stepwise analysis.

(range, 0%–56.3%). The multivariable logistic regression model showed that sex, EuroSCORE II, and peripheral vascular disease were significant risk factors associated with operative mortality (Table 4). The FI-L showed a significant association with all-cause mortality, with a hazard ratio (HR) of 1.042 (95% CI, 1.010–1.076) in the Cox proportional hazards analysis (Table 5).

Among the postoperative complications, the FI-L showed significant associations with atrial fibrillation (OR, 1.02; 95% CI, 1.002–1.039), acute kidney injury (OR, 1.06; 95% CI, 1.014–1.108), and reoperation for bleeding (OR, 1.09; 95% CI, 1.032–1.152) in each multivariable analysis. The FI-L was a significant risk factor related to MACCEs, with a subdistribution HR (sHR) of 1.054 (95% CI, 1.030–1.078) in the Fine–Gray proportional subdistribution hazard model analysis (Table 6).

Table 5. Risk factor analysis for overall survival

Variable	Univariable analysis (p-value)	Multivariable analysis	
		Hazard ratio (95% CI)	p-value
Sex (female)	0.687		
Age	0.001	1.054 (1.003–1.106)	0.036
STS score[a)]	0.041	-	-
EuroSCORE II	<0.001	1.121 (1.051–1.196)	<0.001
FI-L	<0.001	1.042 (1.010–1.076)	0.010
Hypertension	0.827		
Diabetes mellitus	0.932		
Dyslipidemia[a)]	0.017	-	-
History of stroke[a)]	0.037	-	-
Peripheral vascular disease	<0.001	3.472 (1.621–7.435)	0.001
Chronic obstructive pulmonary disease	0.314		
Atrial fibrillation[a)]	0.007	-	-
Left ventricular dysfunction (EF <35%)[a)]	<0.001	-	-
History of coronary intervention[a)]	0.074	-	-
Acute coronary syndrome	0.204		
On-pump beating CABG[a)]	0.038	-	-
Use of the left internal thoracic artery	0.863		
No. of anastomoses	0.437		

CI, confidence interval; STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FI-L, frailty index based on laboratory data and vital signs; EF, ejection fraction; CABG, coronary artery bypass grafting.
[a)]Variables were included in the multivariable analysis but were dropped out during stepwise analysis.

Table 6. Risk factor analysis for major adverse cardiac and cerebrovascular events

Variable	Univariable analysis (p-value)	Multivariable analysis	
		sHR (95% CI)	p-value
Sex (female)	0.596		
Age	0.113		
STS score[a)]	0.053	-	-
EuroSCORE II[a)]	<0.001	-	-
FI-L	<0.001	1.054 (1.030–1.078)	<0.001
Hypertension	0.862		
Diabetes mellitus	0.110		
Dyslipidemia	0.230		
History of stroke	0.216		
Peripheral vascular disease[a)]	0.013	-	-
Chronic obstructive pulmonary disease[a)]	0.099		
Atrial fibrillation	0.016	3.118 (1.280–7.596)	0.012
Left ventricular dysfunction (EF <35%)[a)]	0.019	-	-
History of coronary intervention	0.153		
Acute coronary syndrome	0.393		
On-pump beating CABG	0.590		
Use of the left internal thoracic artery	0.765		
No. of anastomoses	0.805		

sHR, subdistribution hazard ratio; CI, confidence interval; STS, Society of Thoracic Surgeons; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FI-L, frailty index based on laboratory data and vital signs; EF, ejection fraction; CABG, coronary artery bypass grafting.
[a)]Variables were included in the multivariable analysis but were dropped during stepwise analysis.

An FI-L of 32% was the best cutoff to predict the medium-term all-cause mortality after CABG according to the minimum p-value approach (Fig. 2). There were significant differences in all-cause mortality and MACCEs between the group with an FI-L >32%, and the group with an FI-L ≤32% (p<0.001 for both) (Fig. 3).

Discussion

This study had 2 main findings. First, the FI-L was shown to be a significant risk factor associated with medium-term all-cause mortality, MACCEs, and early postoperative complications in patients who underwent CABG. Second, frailty in CABG patients was defined as an FI-L more than 32%.

Since CABG was first introduced in the 1950s, surgical techniques and perioperative care have been advanced. However, old age remains a concern when performing cardiac surgery, including CABG [13], and current risk prediction models, such as the STS score and EuroSCORE II, include age as a factor for risk calculation [6,7]. In contrast, previous studies have shown that cardiac surgery could be performed with low risk, even in elderly patients [14-16]. This discrepancy might be explained by the concept of frailty, which refers to the loss of the body's ability to maintain homeostasis in response to external stressful events. Frailty, rather than chronological age, might affect clinical outcomes after surgical treatment [11].

Previous studies have suggested various scales for discriminating frailty in patients [9]. These included various indicators of frailty, such as the modified Fried frailty criteria, the Katz index of independence in activities of daily living, the modified multidimensional geriatric assessment, and the modified geriatric baseline examination. These frailty indicators use questionnaires, physical examination of functional performance, subjective assessment of physicians, and some laboratory tests to evaluate patients' frailty. In this study, the FI-L was adopted to measure patients' frailty, and the study results revealed its association with early- and medium-term clinical outcomes after CABG. Because the FI-L consists of 32 frailty parameters, including 5 parameters derived from vital signs and 27 parameters from laboratory tests, it is objective, easy to measure, and can be adopted during the routine preoperative evaluation of patients. The clinical usefulness of the FI-L in assessing patients' frailty and its association with operative outcomes after cardiac surgery has been demonstrated in previous studies [17-19]. In the present study, it was significantly associated with important postoperative complications such as atrial fibrillation, acute kidney injury, re-operation for bleeding, and medium-term MACCEs, although it was not a significant factor for operative mortality. However, the relatively small number of operative mortality

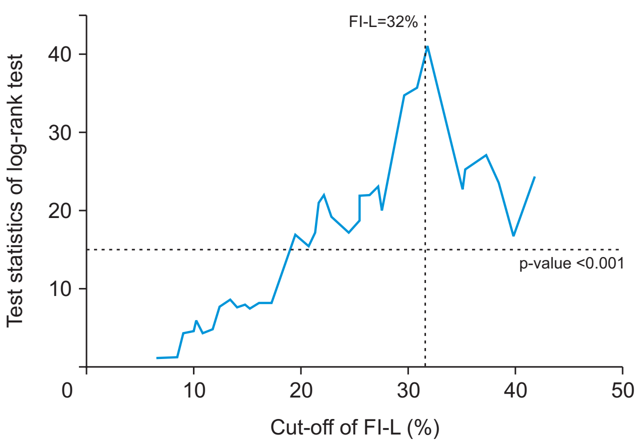

Fig. 2. A test statistic for each cutoff value of the frailty index based on laboratory data and vital signs (FI-L) in the log-rank test.

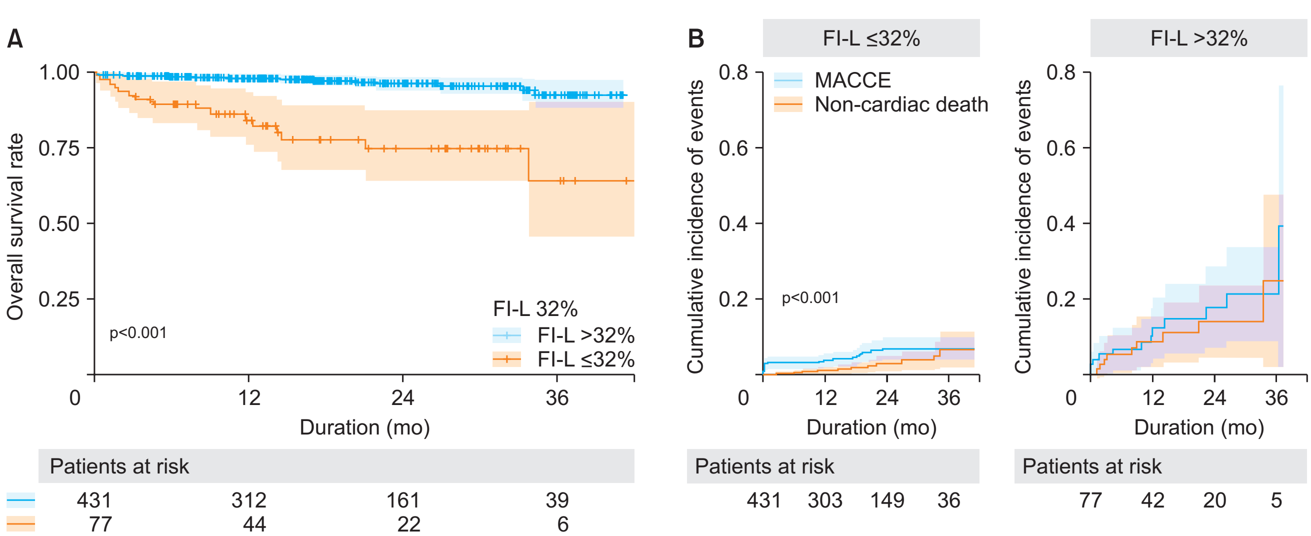

Fig. 3. (A) Kaplan–Meier curves for overall survival and (B) cumulative incidence functions for major adverse cardiac and cerebrovascular events (MACCEs) according to the cutoff value of the frailty index based on laboratory data and vital signs (FI-L).

events in this study might have weakened the statistical power of the risk factor analysis for operative mortality. Because the FI-L is associated with adverse clinical outcomes such as all-cause mortality and MACCEs, efforts should be made to optimize patients' medical care, including timely evaluations during outpatient clinic visits, particularly for patients with a high FI-L.

In addition to the clinical implications of the FI-L, we adopted the minimal p-value approach to identify the optimal cutoff point that differentiates clinical outcomes after CABG, and 32% was found to be the best cutoff value for the FI-L to predict worse clinical outcomes after CABG.

This study had some limitations that should be recognized. First, the present study was designed as a retrospective observational cohort study and was performed at a single institution. Second, the follow-up duration of the study population was relatively short, and the study population was relatively small. Frailty parameters have been routinely measured at our institution since January 2018; therefore, the longest follow-up period was 40 months. Future studies should focus on the analysis of long-term outcomes. Third, as mentioned previously, the number of events for operative mortality was relatively small, which could have weakened the statistical power of the risk factor analysis. Fourth, each component of MACCEs was not separately analyzed because the number of events for each component was relatively small.

In conclusion, in addition to chronological age, the frailty of patients is significantly associated with clinical outcomes after CABG. Therefore, combining frailty scores with current risk prediction models might be helpful in the decision-making process for patients who have coronary artery disease.

Conflict of interest

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

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