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Original Article

Combined assessment of frailty and nutritional status can be a prognostic indicator after percutaneous coronary intervention

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Abstract

The cardiac prognosis of patients with frailty and malnutrition remains poorly investigated. This study aimed to investigate the impact of frailty and malnutrition on cardiac prognosis by combining the Clinical Frailty Scale (CFS) and the Geriatric Nutritional Risk Index (GNRI) in patients who underwent percutaneous coronary intervention (PCI). In this study, 608 patients who underwent PCI for stable angina pectoris between January 2018 and December 2020 were included. CFS scores of ≥ 4 were defined as high CFS and patients with these scores were considered frail. GNRI scores of ≤ 98.0 were defined as low GNRI and patients with these scores were considered to have malnutrition. Patients were categorized into low-risk (n = 267, low CFS and high GNRI), intermediate-risk (n = 200, high CFS or low GNRI), and high-risk (n = 141, high CFS and low GNRI) groups. Major adverse clinical events (MACEs), including all-cause death, nonfatal myocardial infarction, revascularization, hospitalization for heart failure, and stroke, were assessed. The median follow-up period was 529 days. During the follow-up, MACEs were found in 135 patients. The high-risk group were older (77.0 ± 9.2 vs. 71.4 ± 10.7 vs. 65.0 ± 10.1 years, $p < 0.001$), had higher prevalence rates of chronic kidney disease (61.7% [87/141] vs. 37.5% [75/200] vs. 16.9% [45/267]; $p < 0.001$) and heart failure (47.5% [67/141] vs. 22.5% [45/200] vs. 12.4% [33/267], $p < 0.001$), and had higher C-reactive protein levels (1.64 ± 2.66 vs. 1.00 ± 2.02 vs. 0.34 ± 0.90 mg/dL; $p < 0.001$) than the intermediate-risk and low-risk groups. The high-risk group (hazard ratio

[HR], 4.39; 95% confidence interval [CI], 2.87–6.72; $p < 0.001$) was an independent predictor of MACEs. In conclusion, patients with both frailty and malnutrition had a higher risk of MACEs after PCI than patients with frailty or malnutrition. Post-PCI patients should be evaluated for frailty and malnutrition together.

Keywords: Clinical Frailty Scale; Geriatric Nutritional Risk Index; stable angina pectoris; percutaneous coronary intervention

Introduction

In advanced nations, the number of older patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) is increasing because of the aging of the population [1, 2]. The prevalence of frailty and malnutrition has been increasing with the aging of society [3, 4]. Frailty is defined as a state of increased risk of adverse outcomes and loss of the ability to cope with daily or acute stressors [5]. It is considered to be highly prevalent with increasing age and to confer a high risk for adverse health outcomes [6]. The patients with frailty were associated with ischemic heart disease, carotid artery disease, peripheral artery disease, and heart failure (HF) [7–11]. Malnutrition is associated with an increased risk of mortality [12–14]. Assessing the nutritional status of patients can help predict their survival [15]. Malnutrition causes cardiac cachexia and a significantly worsened prognosis, particularly in patients with chronic HF. Frailty and nutritional assessment should be practical, easy to perform, noninvasive, and applicable at the bedside, with no device requirement. Patients with frailty may have good or poor nutritional status, and examining the prognosis of a group of patients with both frailty and malnutrition would be important. Thus, in this study, we aimed to investigate whether the combined assessment of frailty and nutritional status can be a useful prognostic factor.

Materials and Methods

Study population

This single-center, observational, retrospective cohort study included 608 consecutive patients who underwent PCI for stable angina pectoris at the Toho University Omori Hospital in Tokyo, Japan, between January 2018 and December 2020 (**Figure 1**). The Ethics Committee of the Toho University Medical Center Omori Hospital (approval number: M21293) approved the study protocol. As this was a retrospective study, the participants were informed regarding the study protocol using an opt-out approach on the website of the Toho University Medical Center Omori Hospital.

Definitions

All laboratory data were measured on admission. In this study, hypertension was defined as systolic blood pressure (BP) of ≥ 140 mmHg, diastolic BP of ≥ 90 mmHg, or the administration of antihypertensive drugs. Diabetes was defined as fasting blood glucose levels of ≥ 126 mg/dL, casual blood glucose levels of ≥ 200 mg/dL, HbA1c (NGSP) levels of ≥ 6.5%, or the administration of antidiabetic drugs. Dyslipidemia was defined as triglyceride levels of ≥ 150 mg/dL, low-density lipoprotein cholesterol (LDL-C) levels of ≥ 140 mg/dL, high-density lipoprotein cholesterol levels of < 40 mg/dL, or the administration of statins. The estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine (Cr) level and age during admission. Furthermore, chronic kidney disease (CKD) was defined

as baseline eGFR of < 60 mL/min/1.73 m^2.

Frailty was assessed using the Clinical Frailty Scale (CFS) of the Canadian Study of Health and Aging. The CFS does not require special measurements and is classified into nine levels, ranging from 1 (very fit) to 9 (terminally ill) [16]. Each patient was assessed using the CFS after performing PCI. In this study, a CFS score of 4 was used as the cutoff value, and CFS scores of ≥ 4 were defined as high CFS and patients with these scores were considered frail.

The Geriatric Nutritional Risk Index (GNRI) is a tool for assessing nutritional status. The assessment of nutritional status using the GNRI is useful for risk stratification among older patients and those undergoing hemodialysis [17, 18]. According to a previous study [19], the GNRI was calculated using the following formula:

GNRI = (14.89 × serum albumin [g/dL]) + (41.7 × [actual body weight/ideal body weight])

Ideal body weight (kg) = (height [m])^2 × 22 kg/m^2

When the actual body weight exceeded the ideal body weight, the ratio of actual body weight to ideal body weight was set to 1. The actual body weight was measured on admission, and dry weight was determined in patients undergoing hemodialysis. The GNRI was classified into four grades of nutrition-related risks: major risk (GNRI: < 82), moderate risk (GNRI: 82 to < 92), low risk (GNRI: 92 to ≤98), and no risk (GNRI: > 98). The GNRI was calculated

using the albumin levels and physical findings on admission. In this study, a GNRI score of 98.0 was used as the cutoff value, and GNRI scores of ≤ 98.0 were defined as low GNRI and patients with these scores were considered to have malnutrition.

The patients were categorized into low-risk (n = 267, low CFS and high GNRI), intermediate-risk (n = 200, high CFS or low GNRI), and high-risk (n = 141, high CFS and low GNRI) groups [20].

Outcomes

The primary endpoint was major adverse clinical events (MACEs), including all-cause death, nonfatal myocardial infarction, revascularization, hospitalization for HF, and stroke. Patient outcomes were compared among the three groups.

Statistical analysis

Regarding patient characteristics and the number of events, continuous and categorical variables were presented as means ± standard deviations and numbers (%), and the differences between the groups were tested using one-way analysis of variance and chi-square test, respectively. The cumulative incidence of composite endpoints was assessed using the Kaplan–Meier curves, and group differences were compared using the log-rank test. Furthermore, the effect of the MACEs on the high-risk group was examined using univariate

and multivariate Cox proportional hazard models, in which hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. For the multivariate analysis, we selected variables with a p-value of < 0.01 in the univariate models and common risk factors for coronary artery disease and HF. All statistical data were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions that are frequently used in biostatistics.

Results

Baseline characteristics

The baseline characteristics of these patients are presented in **Table 1**. The high-risk group had a significantly older population (77.0 ± 9.2 vs. 71.4 ± 10.7 vs. 65.0 ± 10.1 years, $p < 0.001$). Regarding atherosclerotic risk factors, the high-risk group had significantly higher prevalence rates of CKD (61.7% [87/141] vs. 37.5% [75/200] vs. 16.9% [45/267], $p < 0.001$), hemodialysis (24.8% [35/141] vs. 12.0% [24/200] vs. 3.0% [8/267], $p < 0.001$), and HF (47.5% [67/141] vs. 22.5% [45/200] vs. 12.4% [33/267], $p < 0.001$) and had a significantly lower prevalence rate of dyslipidemia (58.2% [82/141] vs. 80.0% [160/200] vs. 88.4% [236/267], $p < 0.001$) than the intermediate- and low-risk groups. The high-risk group had

significantly higher levels of C-reactive protein (CRP) (1.64 ± 2.66 vs. 1.00 ± 2.02 vs. 0.34 ± 0.90 mg/dL, $p < 0.001$), Cr (2.35 ± 2.46 vs. 1.81 ± 2.33 vs. 1.11 ± 1.22 mg/dL, $p < 0.001$), and brain natriuretic peptide (BNP) (586.6 ± 813.2 vs. 256.2 ± 395.0 vs. 100.9 ± 171.2 pg/mL, $p < 0.001$), and significantly lower levels of eGFR (40.6 ± 24.7 vs. 54.0 ± 39.3 vs. 64.0 ± 18.8 mL/min/1.73 m^2, $p < 0.001$) and hemoglobin (11.3 ± 2.0 vs. 12.5 ± 1.7 vs. 14.0 ± 1.6 g/dL, $p < 0.001$) than the intermediate- and low-risk groups.

Medications on admission

The high-risk group had a significantly higher proportion of patients using diuretics (40.4% [57/141] vs. 24.5% [49/200] vs. 9.7% [26/267], $p < 0.001$) and had a significantly lower proportion of patients administering statins (61.0% [86/141] vs. 73.5% [147/200] vs. 74.2% [198/267], $p = 0.015$) than the intermediate- and low-risk groups.

Clinical outcomes

The median follow-up period was 529 days. During the follow-up, 135 cases of composite endpoints were identified. **Table 2** shows the details of the MACEs. The high-risk group had a significantly higher incidence rate of MACEs (51.8% [73/141] vs. 22.0% [44/200] vs. 6.7% [18/267], $p < 0.001$). **Figure 2** illustrates the Kaplan–Meier curves for the MACEs. The curves showed that the incidence of MACEs was significantly higher in the high-risk group

than in the intermediate-risk ($p < 0.001$) and low-risk groups ($p < 0.001$). In the multivariate Cox hazard model adjusted for the high-risk group, age, male sex, and CKD, HF, and Hb levels, and statin therapy were the independent predictors of MACEs (HR, 4.39; 95% CI, 2.87–6.72; $p < 0.001$), males (HR, 1.67; 95% CI, 1.02–2.73; $p = 0.041$), and HF (HR, 1.48; 95% CI, 1.02–2.16; $p = 0.040$) (**Table 3**).

Discussion

The major findings of this study are as follows: (1) the high-risk group showed high incidence of MACEs; and (2) the high-risk group, intermediate-risk group, males, and HF were independent predictors of MACEs after PCI.

In this study, patients in the high-risk group were older, had high prevalence rates of CKD and HF, and had high BNP levels. Older patients [21] and patients with CKD [22], HF, low LVEF [23], and high BNP levels [24] have poor outcomes after PCI. An assessment of patients' frailty and nutritional status may be useful in screening high-risk patients with the abovementioned factors.

Frailty was associated with major adverse outcomes in this study. Patients with CFS scores of ≥ 5 are defined as frail, and with a CFS score of 4 are considered as pre-frail. A pre-frail state is also associated with central adiposity, long-term glycemic control, and indicators of inflammation. Furthermore, this state is a risk factor for cardiovascular diseases

[25]. Oxidative stress markers, such as lipoprotein phospholipase A2, isoprostanes, malonaldehyde, 8-hydroxy-20-deoxyguanosine, reactive oxygen metabolite derivatives, and protein carbonylation levels, have been implicated in frailty [26, 27]. These factors may be associated with the prognosis of patients with frailty. The early detection of frailty with the risk of developing adverse events and early intervention may improve prognosis [28].

CRP was not an independent risk factor of MACEs in this study. However, the high-risk group exhibited significantly higher CRP levels than the intermediate-group and low-risk groups on admssion. Older patients often present with diseases that increase the levels of inflammatory markers in the blood [29]. High levels of inflammatory cytokines, such as CRP, interleukin-6, and tumor necrosis factor-α, are associated with decreased appetite in older patients [30]. Chronic inflammation decreases albumin production, resulting in malnutrition [31]. Malnutrition leads to loss of muscle mass, resulting in loss of muscle strength and a walking dysfunction called sarcopenia [32]. Decreased activity and energy expenditure lead to chronic malnutrition, which further accelerates sarcopenia. Fried et al. proposed this vicious cycle as the frail cycle [6]. Additionally, inflammation plays a central role in all processes of atherosclerosis [33]. High levels of inflammatory cytokines cause damage to vascular endothelial cells. Consequently, macrophages infiltrate the blood vessels, resulting in atherosclerosis.

Frailty and malnutrition are known to be strongly interrelated [34]. The patients in the high-risk group in the present study are frail and malnourished and at high risk of MACEs. The intermediate-risk group in the present study comprises patients who were either frail or malnourished. Patients who were frail but still well-nourished were at a risk of becoming malnourished in the future [34]. Patients with frailty exhibit poor appetite, difficulties with chewing and swallowing, and decreased food intake, all of which leads to malnutrition. Conversely, patients who were malnourished but not frail were considered to be at a risk of future frailty. This is because malnutrition causes decreased protein synthesis and muscle loss, resulting in decreased muscle mass and strength. Hence, an assessment of both frailty and nutritional status may be effective in reducing risk of MACEs by enabling earlier intervention. The CFS and GNRI used in this study are useful because they are simple, inexpensive, and can be quickly implemented by non-specialist staff.

Patients with malnutrition and no frailty need to improve their nutrition to avoid becoming frail. In addition, patients who are frail but well-nourished need to maintain their nutritional status. There are several possible approaches to treat patients with frailty and malnutrition. The administration of aspirin, statins, and metformin indirectly reduce CRP levels [35, 36]. In this study, the high-risk group had low LDL-C levels and a low proportion of patients administering statins. Even in patients who are malnourished and have low LDL-C levels, the administration of statins may be necessary to prevent adverse outcomes. It has

been reported that increases in body weight and skeletal muscle mass do not necessarily improve physical function [37]. Therefore, multidisciplinary treatment with anti-inflammatory, metabolic, and appetite-improving medications; nutritional therapy; and appropriate exercise is needed [38]. It is important to assess both frailty and nutritional status when screening high-risk patients and those who may be at high risk in the future and to provide early therapeutic intervention.

Limitations

This study has several limitations. First, this observational study had a small sample size. Second, we measured the CFS and GNRI only once at baseline. Therefore, the temporal changes in the CFS and GNRI during the clinical course were not considered.

Conclusion

In conclusion, patients with both frailty and malnutrition had a higher risk of MACEs after PCI than patients with frailty or malnutrition. Post-PCI patients should be evaluated for frailty and malnutrition together.

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Conflict of interest

The authors declare no conflicts of interest.

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Figure legends

Figure 1. Study population

CFS, Clinical Frailty Scale; GNRI, Geriatric Nutritional Risk Index; PCI, percutaneous coronary intervention

Figure 2. Kaplan–Meier curves for major adverse clinical event

Figure 1

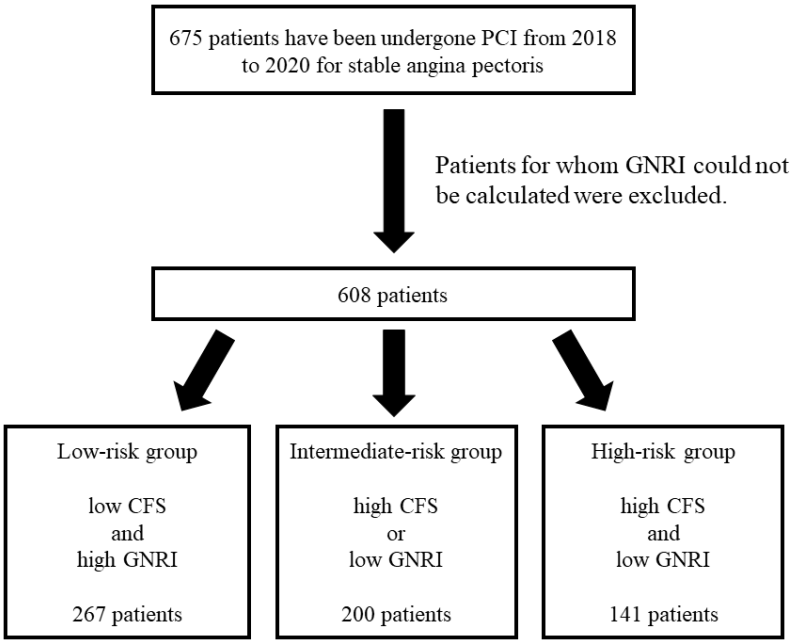
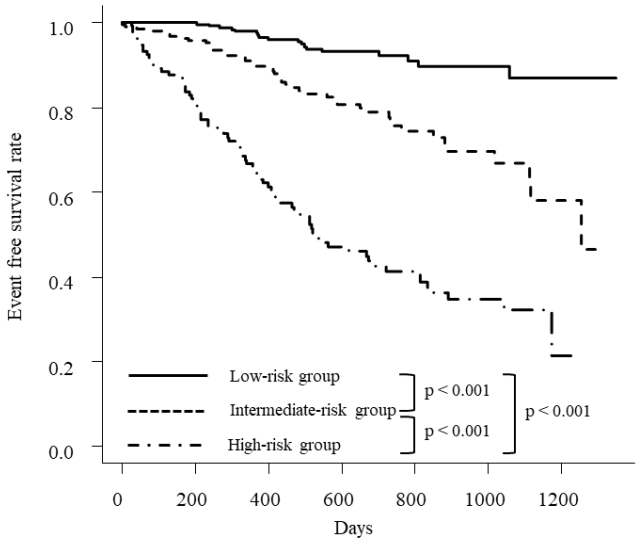

675 patients have been undergone PCI from 2018 to 2020 for stable angina pectoris
Patients for whom GNRI could not be calculated were excluded.
608 patients
Low-risk group
low CFS
and
high GNRI
267 patients
Intermediate-risk group
high CFS
or
low GNRI
200 patients
High-risk group
high CFS
and
low GNRI
141 patients

Figure 2



Number at risk

Low-risk group	267	245	202	132	74	41	12
Intermediate-risk group	200	170	141	92	57	29	7
High-risk group	141	99	65	43	33	16	2

Table 1. Characteristics of the patients

	High-risk group (n = 141)	Intermediate-risk group (n = 200)	Low-risk group (n = 267)	p value
Baseline characteristics				
Age, years	77.0 ± 9.2	71.4 ± 10.7	65.0 ± 10.1	<0.001
Male, n (%)	93 (66.0)	157 (78.5)	232 (86.9)	<0.001
Height, cm	158.9 ± 9.3	162.3 ± 8.4	166.0 ± 8.2	<0.001
Body weight, kg	56.2 ± 12.6	62.9 ± 12.7	70.9 ± 13.7	<0.001
BMI, kg/m²	22.1 ± 3.8	23.7 ± 3.7	25.6 ± 3.7	<0.001
GNRI	88.0 ± 7.4	95.3 ± 8.5	104.2 ± 4.0	<0.001
CFS	4.8 ± 1.1	3.6 ± 0.9	2.7 ± 0.5	<0.001
Comorbidity				
Hypertension, n (%)	97 (68.8)	160 (80.0)	199 (74.5)	0.060
Dyslipidemia, n (%)	82 (58.2)	160 (80.0)	236 (88.4)	<0.001
Diabetes, n (%)	76 (53.9)	100 (50.0)	118 (44.2)	0.150
Current smoker, n (%)	31 (22.0)	58 (29.0)	94 (35.2)	0.015
Chronic kidney disease, n (%)	87 (61.7)	75 (37.5)	45 (16.9)	<0.001
Hemodialysis, n (%)	35 (24.8)	24 (12.0)	8 (3.0)	<0.001
Prior PCI, n (%)	52 (36.9)	94 (47.0)	115 (43.1)	0.181
Prior CABG, n (%)	9 (6.4)	8 (4.0)	12 (4.5)	0.591
Prior AMI, n (%)	53 (37.6)	86 (43.0)	107 (40.1)	0.601
Heart Failure, n (%)	67 (47.5)	45 (22.5)	33 (12.4)	<0.001
Stroke, n (%)	21 (14.9)	22 (11.0)	15 (5.6)	0.005
Atrial fibrillation, n (%)	27 (19.1)	21 (10.5)	33 (12.4)	0.064
Echocardiography				
LVEF, %	54.0 ± 15.5	57.9 ± 13.5	61.3 ± 12.2	<0.001
Laboratory data on admission				
CRP, mg/dL	1.64 ± 2.66	1.00 ± 2.02	0.34 ± 0.90	<0.001
Total protein, g/dL	6.9 ± 0.7	7.1 ± 0.6	7.4 ± 0.5	<0.001
Albumin, g/dL	3.3 ± 0.4	3.7 ± 0.5	4.2 ± 0.3	<0.001

BUN, mg/dL	26.7 ± 13.4	21.4 ± 11.3	17.4 ± 5.9	<0.001
Creatinine, mg/dL	2.35 ± 2.46	1.81 ± 2.33	1.11 ± 1.22	<0.001
eGFR, mL/min/1.73 m²	40.6 ± 24.7	54.0 ± 39.3	64.0 ± 18.8	<0.001
Urinary acid, mg/dL	5.7 ± 2.2	5.7 ± 2.0	5.7 ± 1.6	0.938
HbA1c, %	6.4 ± 1.0	6.6 ± 1.4	6.6 ± 1.1	0.209
LDL-C, mg/dL	85.1 ± 33.1	92.2 ± 33.5	93.7 ± 31.2	0.044
Triglyceride, mg/dL	107.8 ± 53.2	125.9 ± 77.1	171.0 ± 195.2	<0.001
BNP, pg/mL	586.6 ± 813.2	256.2 ± 395.0	100.9± 171.2	<0.001
Hemoglobin, g/dL	11.3 ± 2.0	12.5± 1.7	14.0± 1.6	<0.001
Medication on admission				
β-blocker, n (%)	69 (48.9)	116 (58.0)	148 (55.4)	0.248
ACE inhibitor or ARB, n (%)	77 (54.6)	120 (60.0)	154 (57.7)	0.616
Calcium channel blocker, n (%)	54 (38.3)	82 (41.0)	100 (37.5)	0.732
Diuretics, n (%)	57 (40.4)	49 (24.5)	26 (9.7)	<0.001
Antidiabetic drug, n (%)	46 (32.6)	63 (31.5)	87 (32.6)	0.974
Insulin, n (%)	30 (21.3)	32 (16.0)	28 (10.5)	0.011
Statin, n (%)	86 (61.0)	147 (73.5)	198 (74.2)	0.015
Aspirin, n (%)	141 (100.0)	200 (100.0)	267 (100.0)	1.000
$P2Y_{12}$ inhibitor, n (%)	141 (100.0)	200 (100.0)	267 (100.0)	1.000
Angiographic and procedural data				
Multivessel disease, n (%)	107 (75.9)	149 (74.5)	177 (66.3)	0.060
Drug-eluting stent, n (%)	133 (94.3)	186 (93.0)	240 (89.9)	0.256
Drug-coated balloon, n (%)	8 (5.7)	14 (7.0)	27 (10.1)	0.256

ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CFS, clinical frailty scale; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

Table 3. Predictors of major adverse clinical events

	Univariate			Multivariate		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
High-risk group	5.45	3.88–7.67	<0.001	4.39	2.87–6.72	<0.001
Age	1.02	1.00–1.04	0.021	0.99	0.98–1.01	0.488
Male	1.27	0.80–2.00	0.313	1.67	1.02–2.73	0.041
CKD	2.68	1.90–3.76	<0.001	1.38	0.93–2.04	0.110
Heart failure	2.32	1.64–3.28	<0.001	1.48	1.02–2.16	0.040
CRP	1.12	1.05–1.20	<0.001			
Albumin	0.44	0.33–0.59	<0.001			
LDL-C	1.00	0.99–1.00	0.294			
Triglyceride	1.00	0.99–1.00	0.095			
Hemoglobin	0.81	0.74–0.88	<0.001	0.96	0.88–1.06	0.438
Statin	0.59	0.41–0.83	0.003	0.71	0.50–1.03	0.075

CFS, clinical frailty scale; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; GNRI, geriatric nutritional risk index; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol

Table 2. Details of major adverse clinical events

	High-risk group (n = 141)	**Intermediate-risk group (n = 200)**	**Low-risk group (n = 267)**	**p value**
MACEs, n (%)	73 (51.8)	44 (22.0)	18 (6.7)	<0.001
All-cause death, n (%)	37 (26.2)	12 (6.0)	1 (0.4)	<0.001
Cardiac death, n (%)	11 (7.8)	1 (0.5)	0 (0.0)	<0.001
Non-cardiac death, n (%)	26 (18.4)	11 (5.5)	1 (0.4)	<0.001
Nonfatal myocardial infarction, n (%)	1 (0.7)	4 (2.0)	0 (0.0)	0.060
Revascularization, n (%)	12 (8.5)	15 (7.5)	17 (6.4)	0.148
Hospitalization for heart failure, n (%)	14 (9.9)	9 (4.5)	0 (0.0)	<0.001
Stroke, n (%)	9 (6.4)	4 (2.0)	0 (0.0)	<0.001

MACEs, major adverse clinical events