Influence of Preadmission Frailty on Short- and Mid-Term Prognoses in Octogenarians With ST-Elevation Myocardial Infarction

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Background: Octogenarians, who are frequently frail, represent a large proportion of patients admitted for ST-segment elevation myocardial infarction (STEMI). We investigated the relationship between frailty, assessed by the Canadian Study of Health and Aging Clinical Frailty Scale (CFS), and short- and mid-term prognoses in octogenarian STEMI patients.

Methods and Results: We used a multicenter registry data of 1,301 patients with STEMI undergoing percutaneous coronary intervention (PCI) between January 2014 and December 2016. Of them, 273 were retrospectively analyzed after categorization into 3 groups based on the preadmission CFS (CFS 1–3, 140 patients; CFS 4–5, 99 patients; and CFS 6–8, 34 patients). We evaluated the influence of CFS on overall mortality at 2 years and on non-home discharge, defined as the composite of in-hospital death and new transfer to a hospital or nursing home. During the study period (median, 565 days), the overall mortality and ratio of non-home discharge increased as CFS increased. After adjustment for multivariable analysis, the severely frail continued to be significantly associated with an increased risk of overall mortality (adjusted hazard ratio 2.37; 95% confidence interval [CI] 1.11–5.05; P=0.026) and non-home discharge (adjusted odds ratio 9.50; 95% CI 3.48–25.99; P<0.001).

Conclusions: Frailty, as assessed by CFS, had an influence on short- and mid-term prognoses in octogenarian patients with STEMI.

Key Words: Frailty; Octogenarians; Prognoses; ST-elevation myocardial infarction
total screened, 273 consecutive octogenarian patients were enrolled in this study after excluding 15 patients who had been in a hospital or nursing home immediately before admission. STEMI was defined as: (a) clinical evidence of ischemia; (b) ECG showing new ST elevation at the J-point in 2 contiguous leads, with cutoff points of $\geq 0.2\text{ mV}$ in men and $\geq 0.15\text{ mV}$ in women in leads V2–V3, or $\geq 0.1\text{ mV}$ in the other leads; and (c) at least 1 high myocardial biomarker level, which was defined as a serum troponin I/T or creatine kinase level above the 99th percentile of the normal reference population during the first 24 h after admission. We excluded patients with suspected STEMI who did not undergo coronary angiography, those who exhibited coronary vasospasm or takotsubo cardiomyopathy, and those who had culprit lesions but did not undergo PCI. The institutional medical ethics committees approved the study in accordance with the Declaration of Helsinki.

Frailty Classification

Patients were categorized into 3 groups based on their preadmission CFS level determined by the validation study. CFS 1–3 (not frail), CFS 4–5 (at risk to mildly frail), and CFS 6–9 (severely frail). The assessment of CFS data was retrospectively performed by at least 2 investigators in each institute between July 2017 and May 2018.

The CFS assessment was conducted with the primary physician, using chart reviews evaluated regarding the preadmission status by the rehabilitation therapists, nurses, and doctors who made first contact with the patients. Rehabilitation therapists made detailed medical records of patient exercise capacity before admission and during rehabilitation. Furthermore, at admission, the nurses and physicians in the emergency department interviewed patients and their relatives and immediately recorded patients’ preadmission life history, including daily activities and cognitive function. In the case of the primary physician not being present, we determined CFS based on the chart review by at least 2 people’s checks.

Study Endpoints

The study endpoint was overall mortality during 2 years as the mid-term prognostic endpoint and non-home discharge as the short-term prognostic endpoint according to the CFS. Non-home discharge was defined as the composite of in-hospital death and new transfer to a hospital or nursing home. We did not set a limit of days in non-home discharge. Furthermore, the independent predictors of each endpoint were evaluated.

Treatment Protocol

Upon admission, patients underwent a rapid evaluation that included sharing their medical history, a physical examination, ECG, chest radiography, echocardiography, and blood tests. In this study, all patients underwent immediate coronary angiography and primary PCI. Written informed consent was given by each patient and/or the patient’s relatives before PCI. None of the patients received systemic thrombolytic therapy. Other therapeutic interventions were performed at the discretion of the attending physician, including blood transfusion for anemia, mechanical ventilation for respiratory failure or shock, the administration of diuretics for congestive heart failure, and administration of inotropes for hypotension or hypoperfusion.

Data Definitions and Data Collection

Hypertension was defined as current or previous treatment with antihypertensive medication. Diabetes mellitus was defined as current or previous treatment with antidiabetic medication.
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was defined in this study as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². We calculated the eGFR according to the Japanese equation: eGFR (mL/min/1.73 m²) = 194 × serum creatinine −1.094 × age −0.287 × 0.739 (if female). Previous MI, congestive heart failure, ischemic

| Table 1. Baseline Patient Characteristics According to CFS |
|---------------------------------------------------------------|
| Overall (n=273) | CFS 1–3 (n=140) | CFS 4–5 (n=99) | CFS 6–8 (n=34) | P value |
| Clinical characteristics |
| Age, years | 84.6±3.8 | 83.7±3.1 | 85.4±4.1 | 85.7±4.6 | 0.001 |
| Male, n (%) | 126 (46.2) | 75 (53.6) | 38 (38.4) | 13 (38.2) | 0.59 |
| Body mass index, kg/m² | 22.1 (20.1–24.5) | 22.6 (20.7–24.7) | 21.7 (19.9–24.8) | 21.5 (18.1–22.2) | 0.001 |
| Body mass index <20 kg/m², n (%) | 58 (21.8) | 22 (15.9) | 24 (25.0) | 12 (37.5) | 0.018 |
| Prior heart failure, n (%) | 11 (4.0) | 4 (2.9) | 5 (5.1) | 2 (5.9) |
| Prior MI, n (%) | 26 (9.5) | 14 (10.0) | 10 (10.1) | 2 (5.9) |
| Prior PCI, n (%) | 35 (12.8) | 15 (10.7) | 18 (18.2) | 2 (5.9) |
| Prior CABG, n (%) | 4 (1.5) | 3 (2.1) | 1 (1.0) | 0 (0) |
| Prior ischemic stroke, n (%) | 28 (10.3) | 10 (7.1) | 9 (9.1) | 9 (26.5) |
| Prior intracranial bleeding, n (%) | 6 (2.2) | 2 (1.4) | 2 (2.0) | 2 (5.9) |
| Prior gastrointestinal bleeding, n (%) | 5 (1.8) | 2 (1.4) | 1 (1.0) | 2 (5.9) |
| Prior PAD, n (%) | 18 (6.6) | 7 (5.0) | 6 (6.1) | 5 (15.6) |
| Dyslipidemia, n (%) | 137 (50.2) | 73 (52.1) | 53 (53.5) | 11 (32.4) |
| Diabetes mellitus, n (%) | 87 (31.9) | 42 (30.0) | 35 (35.4) | 10 (29.4) |
| Hypertension, n (%) | 189 (69.2) | 95 (67.9) | 69 (69.7) | 25 (72.6) |
| Current smoking, n (%) | 34 (12.5) | 17 (12.1) | 17 (17.2) | 0 (0) |
| CKD, n (%) | 167 (61.2) | 79 (56.4) | 69 (69.7) | 19 (55.9) |

Admission data

| | Overall | CFS 1–3 | CFS 4–5 | CFS 6–8 | P value |
| Clinical characteristics |

Systolic blood pressure, mmHg | 131.9±41.5 | 134.2±42.3 | 127.9±39.6 | 134.4±44.0 | 0.48 |
| Diastolic blood pressure, mmHg | 72.8±24.1 | 73.7±24.5 | 70.5±22.0 | 76.0±28.0 | 0.44 |
| Heart rate, beats/min | 75.8±25.5 | 75.5±27.1 | 74.8±22.8 | 79.8±26.8 | 0.60 |
| Killip class | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) | 1.0 (1.0–2.0) | 1.0 (1.0–2.3) | 0.34 |
| Killip class ≥3, n (%) | 55 (20.1) | 25 (17.9) | 22 (22.2) | 8 (23.5) | 0.62 |

Laboratory data on admission

Hemoglobin, g/dL | 12.4±1.9 | 12.7±1.9 | 12.0±1.8 | 12.1±2.1 | 0.017 |
eGFR, mL/min/1.73 m² | 51.5±21.5 | 53.9±20.6 | 47.9±21.2 | 51.7±25.2 | 0.10 |
| Albumin, g/dL | 3.8 (3.4–4.1) | 3.9 (3.5–4.1) | 3.7 (3.4–4.1) | 3.5 (3.3–4.0) | 0.015 |
| Albumin <3.5 g/dL, n (%) | 73 (27.2) | 27 (20.0) | 29 (29.3) | 17 (50.0) | 0.002 |
| White blood cell count, ×10³/μL | 8.5 (6.9–10.5) | 8.3 (6.4–10.3) | 8.5 (6.9–10.5) | 9.4 (7.5–11.7) | 0.046 |
| CRP, mg/dL | 0.2 (0.1–1.1) | 0.2 (0.1–0.9) | 0.2 (0.1–0.8) | 0.8 (0.2–1.4) | 0.35 |
| Blood glucose, mg/dL | 167.0 (135.0–208.5) | 160.0 (135.0–205.0) | 178.0 (135.0–225.0) | 164.5 (130.0–220.3) | 0.98 |
| HbA1c, % | 5.9 (5.6–6.5) | 5.9 (5.6–5.9) | 5.8 (5.5–6.7) | 5.8 (5.5–6.4) | 0.93 |
| Peak CK, IU/L | 1,086.0 (323.0–2,395.0) | 1,336.5 (663.0–2,430.0) | 1,581.5 (692.0–2,963.0) | 1,778.0 (436.5–2,569.0) | 0.13 |
| LVEF, % | 56.0 (45.0–62.0) | 56.7 (45.6–62.9) | 56.0 (46.0–64.0) | 50.5 (43.8–60.0) | 0.23 |

Lesion characteristics

LMT, n (%) | 17 (6.2) | 10 (7.1) | 6 (6.1) | 1 (2.9) | 0.66 |
| LAD, n (%) | 103 (37.7) | 51 (36.4) | 37 (37.4) | 15 (44.1) | 0.71 |
| LCx, n (%) | 23 (8.4) | 9 (6.4) | 10 (10.1) | 4 (11.8) | 0.46 |
| RCA, n (%) | 118 (43.2) | 62 (44.3) | 43 (43.4) | 13 (38.2) | 0.81 |
| 2VD, n (%) | 12 (4.4) | 8 (5.7) | 3 (3.0) | 1 (2.9) | 0.55 |

Time to reperfusion

Onset to reperfusion time, h | 3.5 (2.4–7.0) | 3.5 (2.5–9.0) | 4.4 (2.5–9.0) | 3.8 (3.0–5.8) | 0.28 |

Data are number (%) or mean ± SD. Data are also presented as median (Q1–Q3). CABS, coronary artery bypass grafting; CFS, clinical frailty scale; CK, creatine kinase; CKMB, creatine kinase MB; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LAD, left anterior descending artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; LMT, left main trunk; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; 2VD, 2- vessel disease; LAD+LCx/LAD+RCA/RCA+LCx.

medication (insulin or oral hypoglycemic drugs) or a hemoglobin A1c level ≥6.5%, in accordance with the National Glycohemoglobin Standardization Program. Dyslipidemia was defined as current or previous treatment with antidysslipidemic medication. Chronic kidney disease was defined in this study as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². We calculated the eGFR according to the Japanese equation: eGFR (mL/min/1.73 m²) = 194 × serum creatinine −1.094 × age −0.287 × 0.739 (if female). Previous MI, congestive heart failure, ischemic
stroke, intracranial bleeding, gastrointestinal bleeding, peripheral artery disease (PAD), PCI, and coronary artery bypass grafting were recorded based on interviews with the patients and/or their relatives. The time from the onset of MI to reperfusion was recorded. The recorded laboratory findings included the baseline white blood cell count and levels of C-reactive protein (CRP), hemoglobin, blood glucose, hemoglobin A1c, peak creatine kinase, peak creatine kinase MB isoenzyme, and albumin. The echocardiographic findings included the left ventricular ejection fraction (LVEF). The Killip classification was determined from the physical examination and systolic blood pressure.

Clinical data were collected during hospital visits or by telephone interviews with the patients and their relatives at 6-month intervals.

**Statistical Analysis**

Continuous variables are expressed as mean±standard deviation (SD) or median and interquartile range (IQR: 25–75%). Categorical variables are expressed as number and percentages. Comparisons of clinical, echocardiographic, angiographic, and procedure-related characteristics were performed using the chi-square test for categorical covariates, one-way analysis of variance for continuous variables.
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Body mass index (BMI), prior heart failure, Killip classification, target lesion in right coronary artery (RCA), albumin, hemoglobin, and CRP and patients' age and sex. An assessment of proportional hazard assumption in the Cox regression analysis on overall mortality was also performed using a backward stepwise selection method. Logistic regression analysis was performed to detect the independent predictors of non-home discharge. Logarithmic transformation was performed for non-normally distributed variables. The covariates that were introduced into the multivariate logistic model were predictors associated with non-home discharge (P<0.05) [CFS, BMI, age, prior ischemic stroke, Killip classification, CKD, target lesion in left main trunk (LMT), albumin, hemoglobin, and CRP].

| Preadmission CFS / Patient no. | Age (years) | Sex | Target lesion | Cause of death | Duration from PCI (days) |
|-------------------------------|-------------|-----|---------------|----------------|-------------------------|
| Not frail                      |             |     |               |                |                         |
| 1                             | 80          | M   | LAD           | Sudden death   | 324                     |
| 2                             | 82          | M   | LAD           | Sudden death   | 118                     |
| 3                             | 82          | F   | RCA           | Sudden death   | 242                     |
| 4                             | 86          | M   | RCA           | Sudden death   | 173                     |
| 5                             | 82          | F   | LAD           | Heart failure  | 347                     |
| 6                             | 83          | F   | RCA           | Heart failure  | 315                     |
| 7                             | 82          | M   | LAD           | Fatal arrhythmia | 250              |
| 8                             | 83          | F   | LAD           | Infection      | 43                      |
| 9                             | 85          | F   | RCA           | Infection      | 542                     |
| 10                            | 86          | F   | LMT           | Infection      | 260                     |
| 11                            | 81          | M   | RCA           | Infection      | 454                     |
| 12                            | 81          | F   | LCx           | Infection      | 135                     |
| 13                            | 84          | F   | 2VD (LAD+LCx) | Unknown        | 104                     |
| Mildly frail                   |             |     |               |                |                         |
| 1                             | 83          | M   | RCA           | Sudden death   | 307                     |
| 2                             | 86          | F   | RCA           | Heart failure  | 672                     |
| 3                             | 87          | F   | LCx           | Heart failure  | 214                     |
| 4                             | 91          | F   | LAD           | Heart failure  | 76                      |
| 5                             | 80          | M   | LAD           | Infection      | 43                      |
| 6                             | 84          | F   | LAD           | Infection      | 373                     |
| 7                             | 91          | F   | LAD           | Infection      | 151                     |
| 8                             | 85          | M   | LAD           | Cerebral infarction | 550          |
| 9                             | 86          | F   | LAD           | Cerebral hemorrhage | 313          |
| 10                            | 87          | M   | RCA           | Cerebral hemorrhage | 708          |
| 11                            | 82          | F   | RCA           | Malignancy     | 161                     |
| 12                            | 85          | F   | LAD           | Malignancy     | 96                      |
| 13                            | 80          | M   | LAD           | Unknown        | 68                      |
| 14                            | 83          | F   | LAD           | Unknown        | 35                      |
| 15                            | 84          | M   | RCA           | Unknown        | 57                      |
| 16                            | 84          | F   | LAD           | Unknown        | 499                     |
| 17                            | 92          | F   | LAD           | Unknown        | 150                     |
| 18                            | 94          | M   | RCA           | Unknown        | 96                      |
| Severely frail                |             |     |               |                |                         |
| 1                             | 85          | F   | RCA           | Sudden death   | 25                      |
| 2                             | 94          | F   | RCA           | Heart failure  | 549                     |
| 3                             | 80          | M   | RCA           | Malignancy     | 697                     |
| 4                             | 86          | M   | LAD           | Asthenia       | 333                     |
| 5                             | 87          | F   | LAD           | Asthenia       | 83                      |
| 6                             | 82          | F   | LAD           | Unknown        | 379                     |

Abbreviations as in Table 1.
WBC, CRP, and blood glucose] and the patient’s sex. Similarly, these parameters were assessed by the backward stepwise selection method. The results are reported as adjusted hazard ratios (HR) or odds ratios (OR) with associated 95% confidence intervals (CIs). All statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA) and R ver. 3.5.1 (The R Project for Statistical Computing, http://www.R-project.org/). All P-values were two-tailed, and results with P<0.05 were considered to be statistically significant for all analyses.

Results

Baseline Characteristics of the Overall Population

A total of 273 octogenarian patients with STEMI were treated with PCI in our registry during the study period. The median clinical follow-up was 565 days (1st to 3rd quartile: 255–730 days). The number of patients who were followed more than 1 year was 251 (91.9%). The remaining 22 patients could not be contacted during hospital visit or by telephone.

The percentage of patients in each CFS classification was as follows: CFS 1–3, 51.3%; CFS 4–5, 36.3%; and CFS 6–8, 12.5%. There were no patients with CFS 9 in this study (Figure 1). The baseline clinical, laboratory, and procedural characteristics according to the CFS are shown in Table 1. This cohort had a mean age of 84.6±3.8 years and 46.2% were men. A total of 69.2% of the cohort had hypertension, 31.9% diabetes mellitus, and 50.2% dyslipidemia. The median time from onset to reperfusion was 3.5 h (1st to 3rd quartile: 2.4–7.0 h). In this cohort, 20.1% were classified as Killip class III or IV. Among the 3 CFS study groups, significant differences were observed for mean age, sex, BMI, prior ischemic stroke, prior PAD, current smoking, hemoglobin level, serum albumin level, and white blood cell count.

Clinical Outcomes

During the follow-up period, 65 patients died after PCI. As the severity of frailty increased, overall mortality also significantly increased (Figure 2). In-hospital outcomes are shown in Table 2. After discharge, 37 patients died (13 with CFS 1–3, 18 with CFS 4–5, 6 with CFS 6–8). The causes of death are shown in Table 3.

A total of 64 patients were not discharged home, and in-hospital mortality and the possibility of discharge to home significantly worsened as the severity of frailty increased (Figure 3).

Prognostic Factors of Each Clinical Outcome

Regarding overall mortality, Cox multivariate regression analysis identified severe frailty (at risk to mildly frail: adjusted HR 1.81; 95% CI 0.99–3.36; P=0.056, severely frail: adjusted HR 2.37; 95% CI 1.11–5.05; P=0.026), lower BMI (adjusted HR 0.88; 95% CI 0.81–0.95; P=0.001), Killip class ≥3 (adjusted HR 2.20; 95% CI 1.26–3.83; P=0.006), prior heart failure (adjusted HR 2.88; 95% CI 1.22–6.77; P=0.015), and target lesion in the RCA (adjusted HR 0.53; 95% CI 0.31–0.93; P=0.026) as independent predictors of mid-term death (Table 4). Similarly, regarding non-home discharge as a short-term prognosis, multivariate analysis identified severe frailty (at risk to mildly frail: adjusted OR 1.99; 95% CI 0.86–4.63; P=0.11, severely frail: adjusted OR 9.50; 95% CI 3.48–25.99; P<0.001), Killip class ≥3 (adjusted OR 4.42; 95% CI 1.99–9.84; P<0.001), higher CRP (adjusted OR 1.30; 95% CI 1.05–1.59; P=0.014), and target lesion in the LMT (adjusted OR 5.06; 95% CI 1.38–18.55; P=0.015) as independent predictors of non-home discharge (Table 5).

Discussion

The aim of this study was to evaluate the association of CFS with clinical outcomes of octogenarian patients with STEMI. There are 3 important findings from this study. First, the data demonstrated that the overall mortality at 2 years increased as the severity of frailty measured by the CFS increased among octogenarians undergoing PCI for STEMI. Second, the data showed that another frailty-associated parameter, BMI, was also associated with an increased risk of overall mortality. Third, the data suggested the potential prognostic value of CFS for short-term risk stratification among octogenarians undergoing PCI for STEMI.

To the best of our knowledge, this is the first multicenter study to show that the CFS level was independently associated with mid-term mortality among octogenarian STEMI patients undergoing PCI.

Figure 3. Distribution of in-hospital outcome according to the Clinical Frailty Scale (CFS) classification in all patients.
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Frailty parameters must be evaluated by a functional physical test and checklists associated with lifestyle, which are useful for predicting outcomes. However, it can be difficult to evaluate these parameters in the emergency setting. On the other hand, CFS is a simple and effective semiquantitative marker for a baseline objective and non-invasive assessment of patients' characteristics. Frailty can be conceptualized as a phenotype of weight loss, fatigue, and weakness, or a multidimensional state of vulnerability arising from a complex interplay of biological, cognitive, and social factors.

Indeed, the significance of the CFS has been supported by research conducted by Shimura et al, who identified a positive correlation between the CFS and several other indicators of frailty, including BMI <20 kg/m², serum albumin level <3.5 g/dL, gait speed, and grip strength in patients with severe aortic stenosis.

Furthermore, our study clearly showed that risk classification using the CFS is applicable to the Asian octogenarian population with STEMI. Importantly, this study demonstrated that the CFS level had greater prognostic value for overall mortality in patients with STEMI than other characteristics such as renal dysfunction, diabetes mellitus, female sex, and older age, which have previously been reported to have a significant impact on prognosis in patients with acute coronary syndrome (ACS).

In terms of risk stratification in elderly people with ACS, there are several well-established approaches to predicting prognosis that incorporate health and function. For example, gait speed is well known to predict an increased risk of cardiovascular events in patients with STEMI; however, it should be mentioned that the assessment of gait speed takes time and effort, and it is sometimes difficult to evaluate very frail patients. In addition to gait speed, other frailty parameters must be evaluated by a functional physical test and checklists associated with lifestyle, which are useful for predicting outcomes. However, it can be difficult to evaluate these parameters in the emergency setting. On the other hand, CFS is a simple and effective semiquantitative marker for a baseline objective and non-invasive assessment of patients' characteristics. Frailty can be conceptualized as a phenotype of weight loss, fatigue, and weakness, or a multidimensional state of vulnerability arising from a complex interplay of biological, cognitive, and social factors. Indeed, the significance of the CFS has been supported by research conducted by Shimura et al, who identified a positive correlation between the CFS and several other indicators of frailty, including BMI <20 kg/m², serum albumin level <3.5 g/dL, gait speed, and grip strength in patients with severe aortic stenosis.

In addition to the CFS level, our study demonstrated...
that another frailty-associated parameter, BMI, was associated with an increased risk of mid-term overall mortality in the multivariate analysis. This further emphasizes the influence of frailty, which is in line with findings of previous reports. Notably, we showed that the rate of discharge to home decreased as the severity of frailty increased, as measured by the CFS. It is possible that there is a close relationship between frailty and non-home discharge in octogenarian patients with STEMI. Sujino et al found that severe frailty and lower BMI were independently associated with non-home discharge in 62 patients.

In agreement with such findings, the present study demonstrated that severe frailty had a significant association with non-home discharge in a larger number of patients. Although sex, cognitive disorder, living alone, caregiver other than spouse, independence in activities of daily living have been previously reported as significant predictors of discharge destination, the CFS is a useful marker of frailty in daily clinical practice when evaluating octogenarian patients with STEMI.

| Table 5. Univariate and Multivariate Regression Analysis for the Association Between Non-Home Discharge (n=64) and Clinical Findings (n=273) |
|---|---|---|
| Factors for predicting | Univariate analysis | Multivariate analysis |
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Patients’ clinical characteristics | | | | | | |
| CFS (1–5) | 1.00 (Ref.) | 1.00 (Ref.) |
| CFS (6–8) | 2.03 | 1.05–3.90 | 0.035 | 1.99 | 0.86–4.63 | 0.11 |
| Age, years | 7.60 | 3.32–17.36 | <0.001 | 9.50 | 3.48–25.99 | <0.001 |
| Male, n (%) | 1.10 | 1.03–1.18 | 0.007 |
| Body mass index, kg/m² | 0.63 | 0.35–1.12 | 0.11 |
| Prior heart failure, n (%) | 0.045 | 0.007–0.29 | 0.001 |
| Prior MI, n (%) | 0.72 | 0.15–3.41 | 0.68 |
| Prior PCI, n (%) | 0.98 | 0.38–2.55 | 0.96 |
| Prior CABG, n (%) | 0.64 | 0.25–1.62 | 0.35 |
| Prior ischemic stroke, n (%) | <0.001 | – | >0.99 |
| Prior PAD, n (%) | 2.78 | 1.24–6.25 | 0.013 |
| Prior heart failure, n (%) | 1.28 | 0.44–3.73 | 0.65 |
| Dyslipidemia, n (%) | 1.27 | 0.72–2.22 | 0.41 |
| Diabetes mellitus, n (%) | 0.72 | 0.39–1.34 | 0.30 |
| Hypertension, n (%) | 0.74 | 0.41–1.33 | 0.31 |
| Current smoking, n (%) | 1.01 | 0.43–2.36 | 0.98 |
| CKD, n (%) | 2.05 | 1.10–3.81 | 0.023 |
| Admission data | | | | | | |
| Killip class ≥3, n (%) | 5.24 | 2.77–9.93 | <0.001 | 4.42 | 1.99–9.84 | <0.001 |
| LMT | 4.11 | 1.52–11.15 | 0.005 | 5.06 | 1.38–18.55 | 0.015 |
| LAD | 0.99 | 0.55–1.76 | 0.97 |
| LCx | 1.17 | 0.44–3.10 | 0.76 |
| RCA | 0.62 | 0.34–1.11 | 0.10 |
| 2-vessel disease | 1.09 | 0.29–4.16 | 0.90 |
| Hemoglobin, g/dL | 0.73 | 0.63–0.86 | <0.001 | 0.84 | 0.69–1.02 | 0.070 |
| Albumin <3.5 g/dL, n (%) | 2.75 | 1.52–4.98 | 0.001 |
| White blood cell count, ×10³/μL | 4.27 | 1.72–10.60 | 0.002 |
| CRP, mg/dL | 1.44 | 1.22–1.71 | <0.001 | 1.30 | 1.05–1.59 | 0.014 |
| Blood glucose, mg/dL | 2.56 | 1.16–5.64 | 0.020 |
| Peak CK, IU/L | 1.12 | 0.90–1.39 | 0.31 |
| Onset to reperfusion time, h | 0.99 | 0.69–1.43 | 0.97 |

Covariates introduced into the multivariate model were: CFS, age, sex, BMI, prior ischemic stroke, CKD, Killip classification, left main trunk (target lesion), hemoglobin, albumin, WBC, CRP, and blood glucose. Abbreviations as in Tables 1, 4.
Considering these factors, there is a possibility that our findings are important for the management of frail patients with STEMI in the early hospital phase. Further, early intervention for frailty in concert with social support and cardiac rehabilitation should be prioritized in order to support octogenarian patients with STEMI to live as independently as possible, for as long as possible.23,37,38

Study Limitations
First, the study was retrospective in nature. Second, there were no comparative data between STEMI patients with PCI and those without PCI. Third, in this study, we turned the continuous 9-stage CFS level into a 3-stage categorical variable because the data available were relatively few. Considering the inadequate number of enrolled patients, particularly in the high CFS group, large-scale studies are required to confirm the effect of the CFS on clinical outcomes. Fourth, the CFS classification was not evaluated at admission because of the retrospective design, and in cases where the primary physician was absent, we estimated the CFS based on chart review. Therefore, it is possible that the retrospective assessment of CFS with primary physician introduces recall bias, and assessment of CFS by referring to chart review introduces misclassification bias. Fifth, the synergistic effects of social work, home care, and cardiac rehabilitation were not evaluated in this study. Sixth, a significant parameter for both endpoints, LVEF, was not used in the multivariate analysis because this parameter was not available in 16 of the patients in our registry and of these patients, 12 died during hospitalization for STEMI.

Finally, of the 65 patient deaths in this study, 28 (43%) occurred in hospital. It is possible that our assessment of the influence of the CFS on mid-term mortality was affected by the in-hospital mortality rate. In addition, it is well known that elderly patients tend to become frail after hospital admission. Therefore, in the future, the change in frailty level during hospitalization should be investigated to determine more appropriate timing for applying the CFS. Further investigations are required to clarify the indications for PCI in frail patients with STEMI.

Conclusions
CFS level was associated with an increased risk of not only mid-term overall mortality, but also non-home discharge in octogenarian patients with STEMI undergoing PCI.

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None.

References
1. De Felice F, Guerra E, Fiorilli R, Parma A, Musto C, Nazzaro M, et al. One-year clinical outcome of elderly patients undergoing angioplasty for ST-elevation myocardial infarction complicated by cardiogenic shock: The importance of 3-vessel disease and final TIMI-3 flow grade. J Invasive Cardiol 2014; 26: 114–118.
2. Antoniucci D, Valenti R, Santoro GM, Bolognesi L, Moschi G, Trapani M, et al. Systematic primary angioplasty in octogenarian and older patients. Am Heart J 1999; 138: 670–674.
3. Sadeghi HM, Grines CL, Chandra HR, Dixon SR, Boura JA, Dukkipati S, et al. Percutaneous coronary interventions in octogenarians: Glycoprotein Ilb/IIIa receptor inhibitors' safety profile. J Am Coll Cardiol 2003; 42: 428–432.
4. Yamazaki F, Jeong MH, Saito S, Aha Y, Chae SC, Hur SH, et al. Comparison of clinical outcomes between octogenarians and non-octogenarians with acute myocardial infarction in the drug-eluting stent era: Analysis of the Korean Acute Myocardial Infarction Registry. Circ J 2011; 75: 210–216.
5. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: A call to action. J Am Med Dir Assoc 2013; 14: 392–397.
6. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–M156.
7. Clegg A, Young J, Iliffe S, Rikkest MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752–762.
8. Clinical Frailty Scale-Geriatric Medicine Research-Dalhousie University. Faculty of Medicine GMR, Research/Projects, Clinical Frailty Scale. Dalhousie University, Halifax, Canada. http://geriatricresearch.medscience.dal.ca/clicial_frailty_scale.htm (accessed December 3, 2018).
9. Gregorevic KJ, Hubbard RE, Lim WK, Katz B. The clinical frailty scale predicts functional decline and mortality when used by junior medical staff: A prospective cohort study. BMC Geriatr 2016; 16: 117.
10. Negishi Y, Tanaka A, Ishii H, Takagi K, Inoue Y, Uemura Y, et al. Contrast-induced nephropathy and long-term clinical outcomes following percutaneous coronary intervention in patients with advanced renal dysfunction (estimated glomerular filtration rate <$30\text{ml/min}\cdot1.73\text{m}^2$)). Am J Cardiol 2013; 120: 361–367.
11. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119–177.
12. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell, et al. A global clinical measure of fitness and frailty in elderly people. Can Med Assoc J 2005; 173: 489–495.
13. Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes; Diabetes Care 2009; 32: 1327–1334. Clin Biochem 2009; 42: 197–200.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461–470.
15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982–992.
16. Grabowski M, Filipiak KJ, Opolski G, Glowczynska R, Gawalko M, Balsam P, et al. Risk factors for adverse outcomes following percutaneous coronary intervention in patients undergoing primary percutaneous coronary intervention. Cardiol Res 2018; 9: 94–98.
17. Matsuzawa Y, Konishi M, Akiyama E, Suzuki H, Nakayama N, Kiyokuni M, et al. Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol 2017; 61: 1964–1972.
18. Blanco S, Ferrieres J, Bongard V, Toulza O, Sebai F, Billet S, et al. Prognosis impact of frailty assessed by the Edmonton Frail Scale in the setting of acute coronary syndrome in the elderly. Can J Cardiol 2017; 33: 933–939.
19. Alonso Salinas GL, Sanmartin M, Pascual Izzo M, Rincon LM, Pastor Pueyo P, Marco Del Castillo A, et al. Frailty is an independent prognostic marker in elderly patients with myocardial infarction. Clin Cardiol 2017; 40: 923–931.
20. White. 2013; 33: 933–939.
21. Mitrakos A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc 2005; 53: 2184–2189.
22. Graham MM, Galbraith PD, O’Neill D, Rollison DB, Dando C, Norris CM. Frailty and outcome in elderly patients with acute coronary syndrome. J Am Coll Cardiol 2013; 61: 1610–1615.
23. Yoshioka N, Takagi K, Morita Y, Yoshida R, Nagai H, Kanzaki

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25. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of the Clinical Frailty Scale on outcomes after transcatheter aortic valve replacement. Circulation 2017; 135: 2013–2024.

26. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012; 60: 1438–1454.

27. Moscarella E, Spitaleri G, Brugaletta S, Senti Farrarons S, Perigot A, Ortega-Paz L, et al. Impact of body mass index on 5-year clinical outcomes in patients with ST-segment elevation myocardial infarction after everolimus-eluting or bare-metal stent implantation. Am J Cardiol 2017; 120: 1460–1466.

28. Sujino Y, Tamno J, Nakano S, Funada S, Hosoi Y, Senbonmatsu T, et al. Impact of hypoaalbuminemia, frailty, and body mass index on early prognosis in older patients (285 years) with ST-elevation myocardial infarction. J Cardiol 2015; 66: 263–268.

29. Nigam A, Wright RS, Allison TG, Williams BA, Kopecky SL, Reeder GS, et al. Excess weight at time of presentation of myocardial infarction is associated with lower initial mortality risks but higher long-term risks including recurrent re-infarction and cardiac death. Int J Cardiol 2006; 110: 153–159.

30. Knudtson MD, Klein BE, Klein R, Shankar A. Associations with weight loss and subsequent mortality risk. Ann Epidemiol 2005; 15: 483–491.

31. Kang WY, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ, et al. Obesity paradox in Korean patients undergoing primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. J Cardiol 2010; 55: 84–91.

32. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, et al. Impact of body mass index on in-hospital outcomes after percutaneous coronary intervention for ST segment elevation acute myocardial infarction. Circ J 2008; 72: 521–525.

33. El-Menyar A, Zubaid M, AlMahmeed W, Sulaiman K, AlNabti A, Singh R, et al. Killip classification in patients with acute coronary syndrome: Insight from a multicenter registry. Am J Emerg Med 2012; 30: 97–103.

34. Parakh K, Thombs BD, Bhat U, Fauerbach JA, Bush DE, Ziegelstein RC. Long-term significance of Killip class and left ventricular systolic dysfunction. Am J Med 2008; 121: 1015–1018.

35. Pongan E, Dorey JM, Krolak-Salmon P, Federico D, Sellier C, Auguste N, et al. Predictors of discharge destinations and three-month evolution of patients initially hospitalized in a cognitive behavioral unit. J Alzheimers Dis 2017; 60: 1259–1266.

36. Astell AJ, Clark SA, Hartley NT. Predictors of discharge destination for 234 patients admitted to a combined geriatric medicine/old age psychiatry unit. Int J Geriatr Psychiatry 2008; 23: 903–908.

37. George M, Azhar G, Pangle A, Peeler E, Dawson A, Coker R, et al. Feasibility of conducting a 6-month long home-based exercise program with protein supplementation in elderly community-dwelling individuals with heart failure. J Physiother Phys Rehabil, doi:10.4172/2373-0312.1000137.

38. Melsaae DI, Jen T, Mookerji N, Patel A, Lalu MM. Interventions to improve the outcomes of frail people having surgery: A systematic review. PLoS One 2017; 12: e0190071.