論文題目

Physical frailty may predict 2-year prognosis in elderly patients with acute myocardial infarction
（身体的フレイルは高齢心筋梗塞患者の退院後 2 年以内の予後を予測する）

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Abstract

【Background】

Physical frailty is reportedly a poor prognostic factor in elderly patients with acute myocardial infarction (AMI). However, many previous reports have not excluded patients who have not been ambulatory and who have heart failure (HF) complications, possibly resulting in an overestimation of the prognostic impact of physical frailty. In this study, we examined the association between physical frailty and post-discharge prognosis in elderly patients with AMI, without a history of HF, and with walking capacity.

【Methods】

This study was a secondary analysis of a multicenter cohort study in Japan. We analyzed 524 patients aged ≥70 years, hospitalized for AMI, capable of walking at discharge, and not complicated by HF. Physical frailty was assessed using the FLAGSHIP frailty score. This assessment comprises four domains: weakness, slowness, physical inactivity, and exhaustion, and the total score is considered the frailty score (0–14 points). A frailty score of ≥9 is considered to indicate physical frailty. The primary outcome is a composite of all-cause mortality and HF rehospitalization within 2 years after discharge. The secondary outcome is all-cause mortality and HF rehospitalization. We also analyzed the association between each physical frailty domain and the composite outcome.

【Results】

A total of 489 patients were included in the analysis. In the crude model, physical frailty was significantly associated with a high risk of the post-discharge composite outcome (hazard ratio

[HR] = 2.45, 95% confidence interval [CI]: 1.28–4.68, p = 0.007) and marginally associated with all-cause mortality (HR = 2.53, 95% CI: 0.98–6.57, p = 0.056) and HF rehospitalization (HR = 2.02, 95% CI: 0.90–4.53, p = 0.088). After adjusting for confounders, physical frailty showed a significant association with an increased risk of the composite outcome (HR = 2.09, 95% CI: 1.03–4.22, p = 0.040). The risk of HF rehospitalization was increased with physical frailty, but this association was not statistically significant (HR = 2.14, 95% CI: 0.84–5.44, p = 0.110) in the multivariate analysis. Physical frailty was not associated with an increased risk of all-cause mortality (HR = 1.45, 95% CI: 0.49–4.26, p = 0.501). Among the domains of physical frailty, weakness and exhaustion showed marginal associations with an increased risk of the composite outcome (weakness: HR = 1.95, 95% CI: 0.99–3.83, p = 0.052; exhaustion: HR = 1.86, 95% CI: 0.93–3.71, p = 0.077), whereas the others did not show any association with an increased risk of the composite outcome (slowness: HR = 1.32, 95% CI: 0.66–2.65, p = 0.435; physical inactivity: HR = 1.47, 95% CI: 0.76–2.83, p = 0.251).

【Conclusions】

This study demonstrated a correlation between physical frailty and a poor prognosis in elderly patients hospitalized for AMI without a history of HF who were capable of walking. The findings suggest that a physical frailty assessment serves as a stratification tool to identify high-risk individuals for post-discharge clinical events among elderly patients with AMI, without a history of HF, and with intact walking ability.

要旨

【背景】

身体的フレイルは急性心筋梗塞（Acute myocardial infarction: AMI）を発症した高齢患者の予後不良因子としてメタ解析で報告されている。しかし、歩行が不可能な身体機能障害例や心不全を合併した重症例が取り込まれており、高齢 AMI 患者における身体的フレイルと予後との関連は十分に検討されていない。本研究では、心不全を合併していない歩行可能な高齢 AMI 患者を対象に、身体的フレイルと退院後の予後との関連を検討した。

【方法】

本研究は多施設前向きコホート研究の二次研究として実施した。AMI で入院した 70 歳以上の患者で心不全を合併していない歩行可能例 524 名を対象とした。身体的フレイルは、握力低下、歩行速度低下、易疲労性、身体不活動の評価に基づく FLAGSHIP フレイルスコアを用い、退院時に評価した。本スコアは 0〜14 点で、点数が高いほどフレイルは重度であり、心不全の予後不良と関連する。本研究では 9 点以上を身体的フレイルありと定義した。主要アウトカムは退院後 2 年以内の全死亡と心不全発症の複合アウトカムとし、副次的アウトカムは全死亡、心不全発症とした。また、副次的に身体的フレイルの各ドメインと複合アウトカムとの関連を検討した。

【結果】

524 名のうち、心不全既往のある者や研究アウトカムならびに身体的フレイル指標に欠損のある者を除外した、489 名が解析対象となった（年齢の中央値 : 76 歳、男性 : 72.4%）。単変量解析の結果、身体的フレイルは複合アウトカムと有意な関連を認め（ハザード比 =

2.45，95%信頼区間： 1.28–4.68，p = 0.007）、心不全発症（ハザード比 = 2.02、95%信頼区間：0.90–4.53，p = 0.088）、全死亡（ハザード比 = 2.53，95%信頼区間：0.98–6.57，p = 0.056）と関連がある傾向を示した。年齢、性別ならびに単変量解析で p 値が 0.2 未満であった因子で調整した結果、身体的フレイルは複合アウトカムと有意な関連を認めたが（ハザード比 = 2.09，95％信頼区間：1.03–4.22，p = 0.040）、心不全発症（ハザード比 = 2.14，95％信頼区間：0.84–5.44，p = 0.110）、全死亡（ハザード比 = 1.45，95％信頼区間：0.49–4.26，p = 0.501）とは統計学的に有意な関連を認めなかった。

また、身体的フレイルの各ドメインにおいて、年齢、性別で調整した結果、筋力低下と易疲労性は複合アウトカムと関連がある傾向を示したが（筋力低下：ハザード比 = 1.95，95%信頼区間：0.99–3.83，p = 0.052；易疲労性：ハザード比 = 1.86，95%信頼区間：0.93–3.71，p = 0.077）、その他のドメインは関連を認めなかった（歩行速度低下：ハザード比 = 1.32，95%信頼区間：0.66–2.65，p = 0.435；身体不活動：ハザード比 = 1.47，95%信頼区間：0.76–2.83，p = 0.251)。

【結語】

心不全を合併していない歩行可能な高齢 AMI 患者において、身体的フレイルは退院後の複合アウトカムの発生リスク上昇と有意に関連した。本研究結果は、心不全を合併していない歩行可能な高齢 AMI 患者において、身体的フレイル評価が退院後のイベント発生の高リスク集団を層別化するのに有用である可能性を示唆している。

I. Introduction

With the rapid aging of the Japanese population, patients with acute myocardial infarctions (AMI) aged ≥70 years account for approximately 40% of the male population and 70% of the female population.[1] Compared to young patients, elderly patients with AMI constitute a high-risk population for heart failure (HF) and the development of heart disease and mortality;[2,3] therefore, it is important to prevent HF onset in elderly patients with AMI as secondary prevention. Recent guidelines on HF have defined HF as "a clinical syndrome consisting of dyspnea, malaise, swelling, and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart."[4] Furthermore, according to the ACC/AHA Heart Failure Classification, Stage B HF is defined as a structural heart disease characterized by increased filling pressure and elevated biomarker expressions but without symptoms of HF.[5] The treatment goal for stage B HF events, such as AMI, is the prevention of symptomatic HF development, i.e., progression to stage C HF.[4,5] Therefore, long-term disease management, including preventing progression to stage C HF, is a major clinical concern for secondary HF prevention in elderly patients with AMI.

Frailty is an age-related geriatric syndrome characterized by a weakened resistance to stressors and decreased physiological reserve,[6] and there are two popular approaches to defining physical frailty.[7] The phenotype model captures the physical symptoms manifested by age-related decline in physiological reserve and is conventionally assessed based on cardiovascular health study criteria consisting of five components: weight loss, weakness, slowness, physical inactivity,

and exhaustion.[8] The deficit model is another widely accepted frailty concept that captures the accumulation of age-related deficits, such as symptoms, signs, illnesses, and disabilities, and is used to evaluate an individual's number of these deficits.[9] In elderly patients with AMI, the prevalence of physical frailty is high compared with community-dwelling elderly people,[10] and physical frailty is reportedly associated with a poor prognosis, such as major bleeding, rehospitalization, and all-cause mortality.[10,11] These factors suggest the clinical significance of frailty in post-AMI disease management, including cardiac rehabilitation.

Many studies have examined the association between physical frailty and a poor prognosis in elderly patients with AMI, whereas only a few reports have excluded patients with stage C HF, that is, symptomatic HF. A study on elderly patients with stage B HF showed that patients with physical frailty were at a 2.83-fold higher risk of developing stage C HF within 6 months.[12] However, the prevalence of myocardial infarction in the patients was only 15%. In addition, few previous studies of elderly patients with AMI did not exclude patients incapable of walking, which contradicts the international consensus that frailty is a pre-disabled stage.[7] Therefore, the influence of physical frailty on a poor prognosis may be overestimated in patients with AMI, and these findings indicate that limited evidence is available on the association between physical frailty and HF development and/or post-AMI mortality.

In this study, we examined the association between physical frailty and a composite outcome of mortality and/or HF rehospitalization in elderly patients with AMI, without a history of HF, and who were capable of walking.

II. Methods

1. Study design and participants

This prospective observational study was performed as a secondary analysis of a multicenter cohort study (FLAGSHIP study) designed to develop frailty-based prognostic criteria in patients with HF[13]. The inclusion criteria of the FLAGSHIP study were as follows: 1) patients hospitalized due to acute HF or worsening chronic HF and capable of walking 20 m at the time of discharge, or 2) patients aged ≥70 years hospitalized for AMI not complicated by HF and capable of walking 20 m at the time of discharge. The ability to walk 20 m did not depend on whether assistance or walking aids were used. Non-ambulatory patients were not included in this cohort, in line with the international consensus that frailty is the pre-disabled stage.[7] The complications associated with HF were determined by cardiologists at each participating center. The exclusion criteria included the presence of one or more of the following: 1) severe cognitive impairment, characterized by a Mini-Mental State Examination (MMSE)[14] score <17 points; 2) severe mental disorder; 3) difficulty in responding to questionnaires; and 4) an assumed short-term mortality (e.g., presence of severe aortic valve stenosis without surgical indication or terminal-stage cancer). We enrolled patients from September 2015 to December 2018, and all registered patients were followed up for 2 years after discharge. The enrollment of patients readmitted to the hospital during the study period was considered to begin at the time of the first hospitalization. The main findings of the primary FLAGSHIP analysis that studied patients hospitalized due to acute HF and worsening chronic HF have been published elsewhere.[15]

Of the patients enrolled in the FLAGSHIP study, the present secondary analysis included patients aged ≥70 years who were hospitalized for AMI not complicated by HF. In the case of AMI not complicated by HF, only patients aged ≥70 years were included in the FLAGSHIP study due to the high prevalence of frailty and the risk of HF onset in elderly AMI populations.[16] We excluded patients with a history of hospitalization for HF treatment and missing data on physical frailty and other endpoints.

The FLAGSHIP study protocol and this analysis were approved by the ethics committee of Nagoya University School of Medicine (approval No. 2014-0421), which complies with the principles of the Declaration of Helsinki. Ethical approval was also obtained from each participating hospital, and all patients provided written informed consent for study participation. This secondary analysis was approved by the ethics committee of the Nagoya University School of Health Sciences (approval No. 22-508).

2. Study follow-up and endpoints

The primary endpoint was a composite of all-cause mortality and HF rehospitalization within 2 years of discharge; the secondary endpoints were all-cause mortality and HF rehospitalization. A follow-up survey was performed for each patient using the medical records from the hospitals where the patients were previously admitted, and HF rehospitalization was determined by cardiologists at each enrolled institute. If patients did not attend follow-up visits at the respective hospitals, prognostic data were obtained from a survey questionnaire mailed directly to the patients every 4

months. The follow-up period was defined as the time from discharge to the main endpoint, or until the last date of event-free survival, as confirmed by medical records or data from the mail survey, or until 2 years after discharge.

3. Assessment of physical frailty

Physical frailty was assessed at discharge using the frailty score presented in the primary analysis of the FLAGSHIP study.[15] This physical frailty assessment was proposed with reference to the frailty domains included in the phenotype model,[8] and the score could be calculated using objective measurements collected within 10 minutes.[15]

The physical frailty assessment comprised four domains: weakness, slowness, physical inactivity, and exhaustion. Weakness and slowness were assessed based on the grip strength and usual walking speed, respectively, of the patients. Grip strength was measured using a Jamar dynamometer (Digital Hand Dynamometer, DHD-1, SAEHAN Corporation, South Korea) set at the second handle position at discharge. Two attempts were made with each hand, and the maximum value for each hand was recorded. A 10-meter walkway was used to measure the usual walking time, and the lower of the two values was used. Physical inactivity was assessed using the Self-Efficacy for Walking-7 (SEW-7) scale, which has a moderate-to-strong correlation with accelerometer-measured step counts and a moderate correlation with vigorous physical activity.[17] SEW-7 is scored from 7 to 35 points, with a lower score corresponding to less physical activity. Exhaustion was assessed using the Performance Measure for Activities of Daily Living-8 (PMADL-

8) assessment tool,[18] which exhibits a strong negative correlation with peak oxygen uptake.[19] PMADL-8 is scored from 8 to 32 points, with higher scores indicating more severe functional limitations.

The cut-off value and assigned score for each physical frailty domain were determined based on the prognosis of HF in the main analysis of the FLAGSHIP study as follows: weakness = grip strength <30 kg for men and <17.5 kg for women, 5 points; slowness = usual walking speed <0.98 m/s, 4 points; physical inactivity = SEW-7 ≤20 points, 3 points; and exhaustion = PMADL-8 ≥21 points, 2 points. The score of each domain was weighted by multivariate analysis for prognostic prediction, and the total score was considered the frailty score (0–14 points).[15] Based on the frailty score, physical frailty was classified into four categories as follows: Category I, ≤3 points; Category II, 4–8; Category III, 9–12; and Category IV, 14. The score of 13 points did not exist in calculation. In this study, Category III and IV, that is, a frailty score ≥9 was considered to indicate physical frailty.

4. Data collection

Patient characteristics, including age, sex, body mass index, and clinical characteristics (co-morbidities and medications at discharge), were obtained from medical records. Echocardiographic and biochemical data were collected immediately before discharge. Simpson's method was used to calculate the left ventricular ejection fraction (LVEF) by two-dimensional echocardiography. An LVEF <40% was considered low.[5,20] Biochemical data (levels of brain natriuretic peptide [BNP],

N-terminal [NT]-proBNP, hemoglobin, estimated glomerular filtration rate [eGFR], low-density lipoprotein cholesterol, triglyceride [TG], serum albumin, and high-sensitivity C-reactive protein [hs-CRP]) were also collected. A BNP level ≥200 pg/mL or NT-proBNP level ≥900 pg/mL was considered to represent a high BNP level.[21] A hemoglobin level <13 g/dL in men or <12 g/dL in women was indicative of anemia.[22] Global cognitive function was assessed using the MMSE,[14] which is a standard, 11-question test with scores from 0 to 30. Depression was assessed using a 5-item Geriatric Depression Scale questionnaire (score: 0–5) and indicated by a score ≥2 points.[23]

5. Statistical methods

Continuous variables were expressed as medians within an interquartile range (IQR), and categorical variables were reported as percentages. Patient characteristics were compared using the Mann-Whitney test, and categorical variables were analyzed using the Chi-square test for data obtained from patients with and without physical frailty.

The cumulative incidence rates for the composite outcome and all-cause mortality were calculated using the Kaplan-Meier survival method, with comparisons between patients with and without physical frailty being performed using the log-rank test. To account for competing risks, the cumulative incidence of HF rehospitalization was compared between patients with and without physical frailty using Gray's test. The proportional hazards assumption was assessed using the Schoenfeld residuals test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the composite outcome and all-cause mortality were calculated using a Cox proportional hazards model, and the

HR for HF rehospitalization was calculated using the Fine and Gray method to account for competing risks. A multivariable model adjusted for age, sex, and variables with a *p*-value <0.2 in univariate analysis was used to assess the association between the study outcomes and physical frailty. The cumulative incidence rates and HRs were also calculated by frailty category, frailty score, and LVEF. As the secondary analysis, the association between each physical frailty domain and the composite outcome was assessed using a Cox proportional hazards model adjusted for age and sex.

The proportion of missing data was 0%–5% for most variables. To avoid bias caused by the exclusion of patients with missing data, the missing values of covariates were ascribed through multiple imputations by chained equations.[24] Parameter estimates and CIs were obtained by combining 20 imputed datasets.[24] Statistical analyses were performed using Stata version 17 (Stata Corporation, College Station, Texas, USA). A *p*-value <0.05 indicated statistical significance, and a *p*-value < 0.10 indicated marginal significance.

III. Results

Four hundred and eighty-nine elderly patients hospitalized for AMI were included in this secondary analysis (Figure 1). The median age was 76 years (IQR: 72–80 years), and men comprised 72.4% of the population. The prevalence of physical frailty was 26.6%, and frailty categories I to IV were 43.2%, 30.3%, 18.4%, and 8.2%, respectively. The characteristics of patients with and without physical frailty are presented in Table 1. Compared to patients without physical frailty, patients

with physical frailty were older and more often women, with a higher prevalence of hypertension, anemia, use of diuretic drugs, and depression, a lower eGFR, albumin level, and MMSE score, and a higher hs-CRP level.

Thirty-seven composite outcomes occurred during 905.7 person-years of follow-up (including 24 rehospitalization events owing to HF, six cardiac deaths (including the deaths of three patients after HF readmission), and 10 non-cardiac deaths). The median duration from discharge to the time of HF rehospitalization was 208 days (IQR: 66–545 days), and the median duration to the time of all-cause mortality was 484 days (IQR: 184–586 days). Figure 2 shows the cumulative incidence rates for the study endpoints according to physical frailty. Patients with physical frailty showed significantly higher cumulative incidence rates of the composite outcome and all-cause mortality than patients without physical frailty. Patients with physical frailty also showed a marginally higher cumulative incidence rate of HF rehospitalization.

The results of the hazards regression model are presented in Table 2. In the univariate model, physical frailty was significantly associated with a high risk of the post-discharge composite outcome (HR = 2.45, 95% CI: 1.28–4.68, p = 0.007) and marginally associated with all-cause mortality (HR = 2.53, 95% CI: 0.98–6.57, p = 0.056) and HF rehospitalization (HR = 2.02, 95% CI: 0.90–4.53, p = 0.088). After adjusting for age, gender, and the above variables with a p-value <0.20 in the univariate analysis, the association between physical frailty and the composite outcome remained statistically significant (HR = 2.09, 95% CI: 1.03–4.22, p = 0.040). The association between physical frailty and HF rehospitalization was not statistically significant after adjustment

for the confounding factors (HR = 2.14, 95% CI: 0.84–5.44, p = 0.110). This result was unchanged following further adjustment for the use of diuretic drugs (HR = 2.17, 95% CI: 0.83–5.69, p = 0.116). The correlation between physical frailty and all-cause mortality was not statistically significant after adjustment for the confounding factors (HR = 1.45, 95% CI: 0.49–4.26, p = 0.501).

Figure 3 shows the cumulative incidence rates for the composite outcome according to frailty categories. It was observed that the cumulative incidence rates were different for Category I, II and Category III, IV. The results of the hazard ratios of physical frailty for the composite outcome at different cut-off value for the physical frailty determination are presented in Table 3. The association between physical frailty and the composite outcome was statistically significant when the cut-off value for physical frailty was a frailty score > 9 to 11 points after adjusting for confounding factors (≥9 points: HR = 2.09, 95% CI: 1.03–4.22, p = 0.040; ≥10 points: HR = 2.46, 95% CI: 1.20–5.02, p = 0.013; ≥11 points: HR = 2.41, 95% CI: 1.14–5.09).

Figure 4 shows the cumulative incidence rates for the composite outcome based on physical frailty by LVEF, and Table 4 shows the results of the hazard ratios of physical frailty for the composite outcome by LVEF. The cumulative incidence rates and risk of the composite outcome increased with physical frailty in severe AMI patients, that is, LVEF <50%, but the association was not statistically significant (LVEF ≥50%: HR = 2.39, 95% CI: 0.99–5.77, p = 0.054; LVEF <50%: HR = 2.54, 95% CI: 0.84–7.73, p = 0.099).

Figure 5 shows the association between each physical frailty domain and the composite outcome. Weakness and exhaustion exhibited marginal associations with an increased risk of the

endpoint (weakness: HR = 1.95, 95% CI: 0.99–3.83, p = 0.052; exhaustion: HR = 1.86, 95% CI: 0.93–3.71, p = 0.077); the others did not show (slowness: HR = 1.32, 95% CI: 0.66–2.65, p = 0.435; physical inactivity: HR = 1.47, 95% CI: 0.76–2.83, p = 0.251) any associations.

IV. Discussion

We investigated the association between physical frailty and the composite outcome of all-cause mortality and HF rehospitalization within 2 years of discharge in elderly patients with AMI, without a history of HF, and with ambulatory capacity. We found that physical frailty was associated with a poor prognosis in elderly patients hospitalized for AMI. To our knowledge, this is the first study to report that physical frailty provides information on prognosis, including the likelihood of new-onset HF, in ambulatory elderly patients with AMI not complicated by symptomatic HF. The results of this study suggest the clinical importance of a physical frailty assessment for long-term disease management in ambulatory elderly patients with AMI not complicated by HF.

In this study, ambulatory patients with physical frailty without a history of HF exhibited a 2.09-fold higher risk of the composite outcome within 2 years of discharge. In a recent meta-analysis including non-ambulatory patients, physical frailty patients with AMI reportedly had a 3.24-fold higher risk of all-cause mortality.[25] However, there is a consensus that frailty is the pre-disabled stage;[7] elderly participants with severe functional impairments beyond frailty should thus be excluded from studies on physical frailty. Although the association between physical frailty and

the composite outcome was weakened by the exclusion of non-ambulatory patients and patients with AMI not complicated by HF in this study, the association was statistically significant. Furthermore, in ambulatory community-dwelling elderly people, elderly with physical frailty reportedly had a 2.24-fold risk of death within 3 years.[8] When analyzed by LVEF in this study, the cumulative incidence rates and risk of the composite outcome increased with physical frailty in severe AMI patients, that is LVEF <50%, suggesting that the association between physical frailty and prognosis may differ by the severity of AMI. Because the present study included a large number of patients with not severe AMI whose background was similar to that of community-dwelling elderly people, the risk of the composite outcome in all patients with AMI may be comparable to that of ambulatory community-dwelling elderly people. The findings presented here provide additional evidence of the clinical significance to assess physical frailty even among patients without a history of HF who are capable of walking. This is considered a strength of the study.

Several potential mechanisms affect the prognostic impact of physical frailty in AMI. First, the pathological mechanisms underlying physical frailty involve chronic inflammation and high insulin resistance, which are also common risk factors for the development of HF.[26,27] A previous study reported that physical frailty was a risk factor for HF onset even in the general elderly population.[28] The presence of physical frailty may indicate susceptibility to HF via these pathological mechanisms. Another possible explanation is the relationship of physical frailty with endothelial dysfunction[29] and activated inflammatory responses,[30] of which are two known molecular mechanisms underlying atherosclerosis development. In a recent meta-analysis of elderly

individuals, physical frailty was shown to be an independent risk factor for the development of coronary artery disease.[31] Thus, physical frailty may accelerate the progression of atherosclerosis, leading to a poor prognosis for AMI. Finally, sarcopenia, a core component of physical frailty, is a potential risk factor for HF with preserved ejection fraction (HFpEF). In addition to muscle loss, the impairment of energy metabolism in skeletal muscles, metabolic or endocrine abnormalities, and hormonal changes have been documented in cases of sarcopenia.[32] These factors have been considered underlying causes of HFpEF development and have emerged as potential therapeutic targets.[33] In a cross-sectional study, diastolic dysfunction was observed more frequently in community-dwelling older adults with sarcopenia than in older adults without sarcopenia.[34] In the present study, 72.6% of patients had a preserved LVEF ≥50% at discharge. Although the LVEF was not recorded during HF rehospitalization, the subset of individuals requiring HF rehospitalization may have included a certain proportion of individuals with HFpEF. However, supporting data for the above hypotheses were not obtained in the present study; further studies are warranted to examine the suitability of physical frailty as a therapeutic target for secondary prevention after AMI.

In this study, a frail score ≥9 was considered to indicate physical frailty, but analyses were also performed at different cut-off values for the physical frailty determination. It was observed that the cumulative incidence rates were different for Category I, II, and Category III, IV, that is frailty score ≥9 points. Furthermore, in the multivariate analysis, the association between physical frailty and the composite outcome was statistically significant when the frailty score was ≥9 to ≥

11 points. Therefore, we think that a frailty score of ≥9 points, which was defined as physical frailty in this study was appropriate.

Each physical frailty domain was not individually associated with the study outcome, indicating the importance of a multidimensional assessment of frailty. Our results are consistent with those of a previous study in which a comprehensive frailty assessment based on the phenotype model was found to be more predictive of hospitalization risk than a single assessment of each domain in community-dwelling elderly individuals.[35] Thus, a frailty assessment with multiple domains is likely to yield favorable risk stratification. However, the cut-off for each domain in this study was validated by the primary FLAGSHIP outcome-based analysis in patients with HF,[15] which possibly attenuated the prognostic accuracy for AMI not complicated by HF. Therefore, there is scope for the development of an optimal frailty-based risk prediction system in a population with AMI. This can be a topic for future investigations since the sample size of the study was small and did not allow the identification of an AMI-specific cut-off value for each frailty domain.

Our study has a few limitations. First, we could not discuss the usefulness of this frailty score compared with conventional frailty assessments because other frailty assessments were not evaluated. Second, the follow-up period was insufficient for observing the study outcomes in patients with AMI not complicated by HF, which may have reduced the statistical power of the results. The predictive value of frailty for specific clinical events needs to be further evaluated in future studies with a larger sample size and longer follow-up periods. Third, selection bias may have been introduced because only consecutive ambulatory patients who provided informed consent

were included in the FLAGSHIP study. Fourth, the association between frailty and prognosis was not analyzed in patients aged <70 years, since the FLAGSHIP study did not include this younger population. Fifth, there may be potential confounders not measured in this study, including malignancy, the history of previous AMI, and the classification of AMI. Finally, the causal relationship between physical frailty and prognosis, including the development of HF and all-cause mortality, will need to be established through intervention studies.

Further, it is necessary to investigate the effect of improvements from physical frailty intervention, such as cardiac rehabilitation, on the prognosis of elderly patients with AMI in the future.

V. Conclusions

In conclusion, physical frailty was associated with a poor prognosis in elderly patients hospitalized for AMI without complications of symptomatic HF or severe physical dysfunction. For secondary prevention in elderly ambulatory patients with AMI, without a history of HF, the assessment of physical frailty may serve as a stratification tool to identify populations at a high risk of post-discharge clinical events.

VI. Acknowledgments

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VII. References

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VIII. Table

Table 1. Comparisons of the characteristics between patients with and without physical frailty.

	Total n=489	Without frailty n=359 (73.4%)	With frailty n=130 (26.6%)	P value
Age (years)	76 [72–80]	75 [72–79]	80 [74–85]	<0.001
Men (%)	72.4%	76.3%	61.5%	0.001
BMI (kg/m^2)	22.6 [20.7–24.8]	22.6 [21.0–24.8]	22.8 [20.1–24.7]	0.436
Co–morbidities				
Hypertension (%)	63.4%	61.0%	70.0%	0.068
Dyslipidemia (%)	52.8%	52.1%	54.6%	0.621
Diabetes mellitus (%)	33.3%	31.8%	37.7%	0.219
Smoking Non (%)	43.1%	42.3%	45.4%	
Past (%)	36.4%	36.5%	36.1%	0.759
Current (%)	20.5%	21.2%	18.5%	
Atrial fibrillation (%)	6.1%	5.6%	7.7%	0.388
COPD (%)	2.5%	2.8%	1.5%	0.431
Anemia (%)	61.3%	58.1%	70.0%	0.017
LVEF (%) < 40	7.4%	7.2%	8.2%	
40–49	20.0%	20.4%	18.8%	0.888
≥ 50	72.6%	72.4%	72.0%	
High BNP level (%)	41.1%	39.8%	44.4%	0.367
eGFR (ml/min/1.73 m^2)	57.8 [47.2–68.0]	59.7 [49.0–68.5]	53.5 [42.5–67.4]	0.006
LDL-C (mg/dL)	89 [70–112]	91 [71–113]	84 [67–111]	0.196
TG (mg/dL)	101 [76–135]	101 [78–134]	99 [70–136]	0.545
Albumin (g/dL)	3.6 [3.2–3.9]	3.6 [3.3–3.9]	3.5 [3.1–3.8]	<0.001
hs-CRP (mg/dL)	0.51 [0.18–1.51]	0.42 [0.17–1.45]	0.76 [0.23–1.72]	0.010
Medication				
Antiplatelet agent (%)	91.0%	90.5%	92.3%	0.544

Anticoagulant agent (%)		28.2%	27.6%	30.0%	0.599
Statin (%)		82.8%	83.8%	80.0%	0.319
Beta blocker (%)		77.7%	77.4%	78.5%	0.810
ACEi/ARB (%)		74.2%	74.4%	73.9%	0.906
Calcium-channel blocker (%)		16.6%	16.2%	17.7%	0.686
Diuretic (%)		21.5%	18.9%	28.5%	0.024
MMSE (points)		28 [26–30]	28 [26–30]	27 [24–29]	<0.001
Depression (%)		27.2%	22.7%	38.5%	<0.001
Usual walking speed (m/s)		1.08 [0.92–1.23]	1.15 [1.04–1.26]	0.85 [0.70–0.95]	<0.001
Grip strength (kg)	All	28.3 [21.4–34.1]	31.1 [24.1–36.0]	22.7 [15.4–27.0]	<0.001
	Men	31.4 [27.1–36.2]	32.9 [29.8–38.2]	26.0 [23.3–28.5]	<0.001
	Women	18.5 [15.3–21.2]	19.8 [18.3–22.5]	14.7 [12.4–16.8]	<0.001
PMADL-8 (points)		17 [12–20]	16 [11–19]	22 [19–25]	<0.001
SEW-7 (points)		22 [17–27]	24 [20–28]	16 [13–20]	<0.001
frailty score (points)		5 [0–9]	3 [0–5]	11 [9–14]	<0.001

Continuous variables are expressed as median and interquartile range.

Anemia was defined as hemoglobin < 13 g/dL in men or < 12 g/dL in women and a high BNP level was defined as BNP ≥ 200 pg/mL or NT-proBNP ≥ 900 pg/mL.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; eGFR, estimated glemerular filtration rate; LDL-C; low density lipoprotein cholesterol, TG; triglyceride, hs-CRP, high sensitive C-reactive protein; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MMSE, Mini-Mental State Examination; PMADL-8, Performance Measure for Activity of Daily Living-8; SEW-7, Self-Efficacy for Walking-7.

Table 2. Univariable and multivariate hazard ratios (95% confidence interval) for the composite outcome, all-cause mortality, and HF rehospitalization within 2 years after discharge.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
A. Composite outcome				
Age (years), per 1 sd	1.09 (0.78–1.52)	0.624	1.03 (0.73–1.47)	0.853
Men	0.80 (0.40–1.59)	0.528	0.95 (0.46–1.95)	0.885
BMI (kg/m^2), per 1 sd	0.94 (0.68–1.31)	0.734	-	
Co-morbidities				
Hypertension	0.75 (0.39–1.44)	0.387	-	
Dyslipidemia	1.50 (0.77–2.91)	0.235	-	
Diabetes mellitus	1.93 (1.01–3.68)	0.045	1.92 (0.98–3.78)	0.058
Smoking	1.02 (0.67–1.56)	0.925	-	
Atrial fibrillation	1.33 (0.41–4.32)	0.639	-	
COPD	NA			
Anemia	1.19 (0.61–2.34)	0.615	-	
Low LVEF	2.16 (0.84–5.59)	0.111	2.36 (0.88–6.37)	0.089
High BNP level	1.10 (0.58–2.12)	0.766	-	
eGFR (ml/min/1.73 m^2), per 1 sd	0.77 (0.56–1.05)	0.097	0.87 (0.63–1.20)	0.382
LDL-C (mg/dL), per 1 sd	1.10 (0.80–1.51)	0.549	-	
TG (mg/dL), per 1 sd	1.22 (0.92–1.65)	0.170	1.18 (0.87–1.59)	0.295
Albumin (g/dL), per 1 sd	1.22 (0.87–1.71)	0.248	-	
hs-CRP (mg/dL), per 1 sd	0.93 (0.65–1.34)	0.706	-	
Medication				
Antiplatelet agent	3.70 (0.51–27.0)	0.197	4.11 (0.56–30.3)	0.166
Anticoagulant agent	1.56 (0.80–3.03)	0.191	1.56 (0.80–3.07)	0.193
Statin	1.35 (0.52–3.45)	0.537	-	

Beta blocker	0.88 (0.42–1.87)	0.749	-	
ACEi/ARB	1.48 (0.65–3.36)	0.354	-	
Calcium-channel blocker	1.39 (0.63–3.03)	0.414	-	
Diuretic	1.39 (0.67–2.87)	0.376	-	
MMSE (points), per 1 sd	1.05 (0.75–1.47)	0.794	-	
Depression	1.17 (0.58–2.37)	0.660	-	
Physical frailty	2.45 (1.28–4.68)	0.007	2.09 (1.03–4.22)	0.040
B. All-cause mortality				
Age (years), per 1 sd	1.28 (0.78–2.11)	0.330	1.66 (0.91–3.04)	0.097
Men	1.26 (0.41–3.85)	0.691	2.08 (0.62–6.94)	0.236
BMI (kg/m^2), per 1 sd	0.98 (0.60–1.58)	0.923	-	
Co-morbidities				
Hypertension	1.40 (0.49–3.98)	0.526	-	
Dyslipidemia	1.00 (0.39–2.60)	0.996	-	
Diabetes mellitus	2.27 (0.88–5.88)	0.092	2.36 (0.80–6.96)	0.121
Smoking	1.09 (0.59–2.02)	0.778	-	
Atrial fibrillation	2.07 (0.47–9.03)	0.335	-	
COPD	NA		-	
Anemia	0.72 (0.28–1.87)	0.499	-	
Low LVEF	2.91 (0.83–10.20)	0.095	4.52 (1.01–20.25)	0.049
High BNP level	0.77 (0.29–2.09)	0.613	-	
eGFR (ml/min/1.73 m^2), per 1 sd	0.73 (0.46–1.15)	0.178	0.92 (0.56–1.51)	0.746
LDL-C (mg/dL), per 1 sd	1.03 (0.63–1.67)	0.912	-	
TG (mg/dL), per 1 sd	1.35 (0.94–1.93)	0.103	1.41 (0.95–2.09)	0.089
Albumin (g/dL), per 1 sd	1.19 (0.74–1.92)	0.469	-	
hs-CRP (mg/dL), per 1 sd	0.95 (0.57–1.61)	0.861	-	
Medication				

Antiplatelet agent	1.60 (0.21–12.1)	0.649	-	
Anticoagulant agent	2.90 (1.12–7.51)	0.029	3.42 (1.22–9.60)	0.019
Statin	0.49 (0.17–1.38)	0.175	0.55 (0.17–1.77)	0.317
Beta blocker	0.70 (0.25–1.99)	0.505	-	
ACEi/ARB	1.12 (0.37–3.44)	0.843	-	
Calcium-channel blocker	2.81 (1.04–7.60)	0.042	3.84 (1.25–11.80)	0.019
Diuretic	2.63 (1.00–6.91)	0.050	2.63 (0.87–8.03)	0.087
MMSE (points), per 1 sd	1.00 (0.62–1.60)	0.990	-	
Depression	1.93 (0.74–5.08)	0.182	1.51 (0.53–4.27)	0.439
Physical frailty	2.53 (0.98–6.57)	0.056	1.45 (0.49–4.26)	0.501
C. HF rehospitalization				
Age (years), per 1 sd	0.97 (0.62–1.52)	0.890	0.90 (0.55–1.47)	0.659
Men	0.64 (0.28–1.46)	0.286	0.70 (0.31–1.59)	0.398
BMI (kg/m^2), per 1 sd	0.90 (0.60–1.35)	0.623	-	
Co-morbidities				
Hypertension	0.68 (0.30–1.51)	0.343	-	
Dyslipidemia	1.82 (0.78–4.25)	0.164	1.58 (0.65–3.86)	0.317
Diabetes mellitus	1.71 (0.77–3.81)	0.189	1.42 (0.60–3.39)	0.429
Smoking	0.96 (0.54–1.71)	0.894	-	
Atrial fibrillation	0.65 (0.09–4.68)	0.668	-	
COPD	NA		-	
Anemia	1.56 (0.65–3.76)	0.322	-	
Low LVEF	1.95 (0.56–6.71)	0.292	-	
High BNP level	1.21 (0.54–2.71)	0.635	-	
eGFR (ml/min/1.73 m^2), per 1 sd	0.81 (0.55–1.18)	0.271	-	
LDL-C (mg/dL), per 1 sd	1.21 (0.86–1.72)	0.275	-	
TG (mg/dL), per 1 sd	1.07 (0.68–1.71)	0.761	-	

Albumin (g/dL), per 1 sd	1.48 (0.82–2.69)	0.194	1.45 (0.83–2.54)	0.195
hs-CRP (mg/dL), per 1 sd	0.79 (0.45–1.38)	0.403	-	
Medication			-	
Antiplatelet agent	2.33 (0.32–17.10)	0.407	-	
Anticoagulant agent	1.04 (0.43–2.51)	0.392	-	
Statin	2.32 (0.55–9.80)	0.254	-	
Beta blocker	0.86 (0.34–2.16)	0.743	-	
ACEi/ARB	1.30 (0.48–3.50)	0.603	-	
Calcium-channel blocker	0.44 (0.11–1.88)	0.271	-	
Diuretic	0.98 (0.36–2.64)	0.962	-	
MMSE (points), per 1 sd	1.02 (0.70–1.51)	0.903	-	
Depression	0.92 (0.37–2.32)	0.864	-	
Physical frailty	2.02 (0.90–4.53)	0.088	2.14 (0.84–5.44)	0.110

HF, heart failure; HR, hazard ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; eGFR, estimated glemerular filtration rate; LDL-C; low density lipoprotein cholesterol, TG; triglyceride, hs-CRP, high sensitive C-reactive protein; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MMSE, Mini-Mental State Examination.

High BNP level was defined as BNP ≥ 200 pg/mL or NT-proBNP ≥ 900 pg/mL.

Low LVEF was defined by LVEF < 40%.

Multivariate analysis includes age, sex, and variables with a p-value < 0.2 in univariate analysis.

NA: Not applicable because no patients with COPD experienced each outcome

Table 3. Univariable and multivariate hazard ratios (95% confidence interval) of physical frailty for the composite outcome within 2 years after discharge at different cut-off values for the physical frailty determination.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
frailty score ≥14 points	2.23 (0.93–5.35)	0.072	2.02 (0.81–5.01)	0.129
frailty score ≥12 points	2.35 (1.11–4.99)	0.025	2.05 (0.93–4.52)	0.073
frailty score ≥11 points	2.63 (1.30–5.33)	0.007	2.41 (1.14–5.09)	0.022
frailty score ≥10 points	2.60 (1.32–5.10)	0.006	2.46 (1.20–5.02)	0.013
frailty score ≥9 points	2.45 (1.28–4.68)	0.007	2.09 (1.03–4.22)	0.040
frailty score ≥8 points	2.21 (1.16–4.21)	0.016	1.77 (0.88–3.56)	0.112
frailty score ≥7 points	1.83 (0.96–3.49)	0.066	1.46 (0.73–2.94)	0.285
frailty score ≥6 points	1.73 (0.91–3.30)	0.096	1.34 (0.67–2.72)	0.404
frailty score ≥5 points	1.81 (0.92–3.56)	0.084	1.57 (0.76–3.23)	0.225
frailty score ≥4 points	1.43 (0.73–2.80)	0.301	1.22 (0.60–2.52)	0.579

HR, hazard ratio; CI, confidence interval.

The categories for physical frailty based on frailty score were as follows: Category I, ≤3 points; Category II, 4–8; Category III, 9–12; and Category IV, 14. The score of 13 points did not exist in calculation. In this study, a frailty score ≥9 was defined as physical frailty.

Multivariate analysis adjusted for sex, diabetes mellitus, low LVEF, eGFR, TG, antiplatelet and anticoagulant agents.

Table 4. Univariable and multivariate hazard ratios (95% confidence interval) of physical frailty for the composite outcome within 2 years after discharge by LVEF.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
All patients[a]	2.45 (1.28–4.68)	0.007	2.09 (1.03–4.22)	0.040
LVEF ≥50%[b] (n = 341)	2.87 (1.29–6.39)	0.010	2.39 (0.99–5.77)	0.054
LVEF <50%[b] (n = 129)	2.32 (0.84–6.41)	0.103	2.54 (2.84–7.73)	0.099

HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction.

[a]Adjusted for age, sex, diabetes mellitus, low LVEF, eGFR, TG, antiplatelet and anticoagulant agents.

[b]Adjusted for age, sex, diabetes mellitus, eGFR, TG, antiplatelet and anticoagulant agents.

IX. Figure

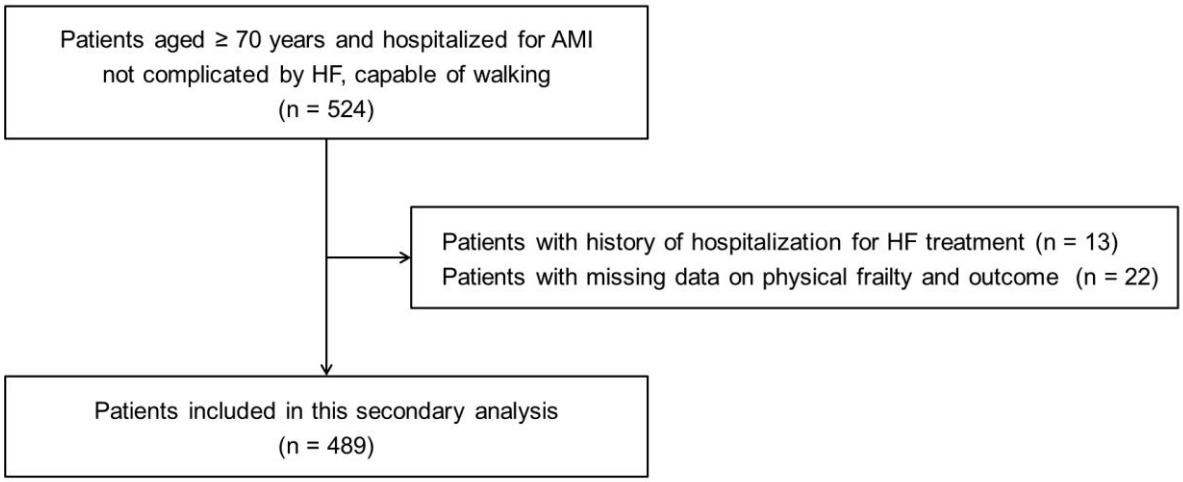

Figure 1. Flow diagram of the patient inclusion method.

AMI, acute myocardial infarction; HF, heart failure.

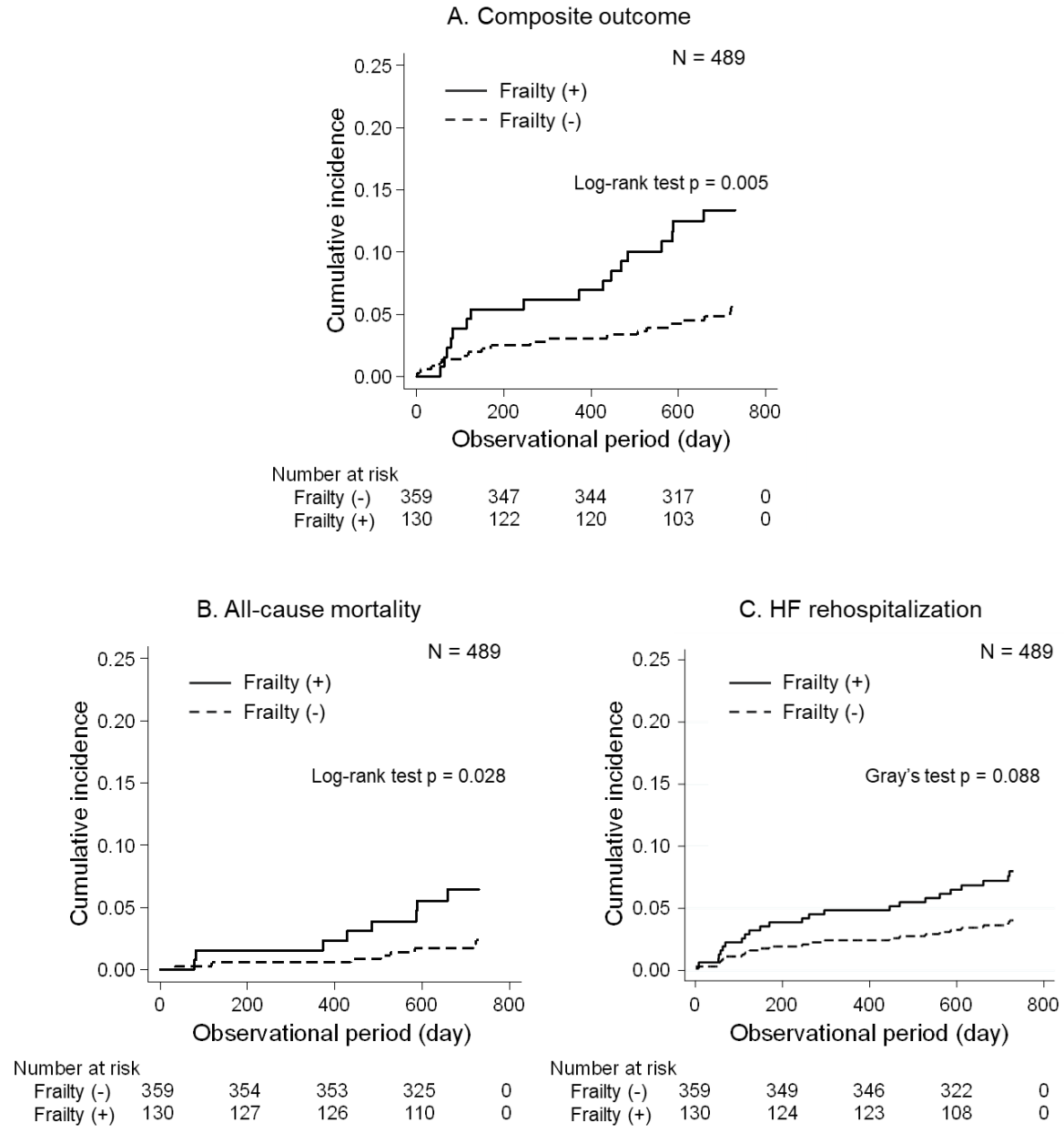

Figure 2. Cumulative incidence rates for the composite outcome, all-cause mortality, and HF rehospitalization within 2 years based on physical frailty.

HF, heart failure.

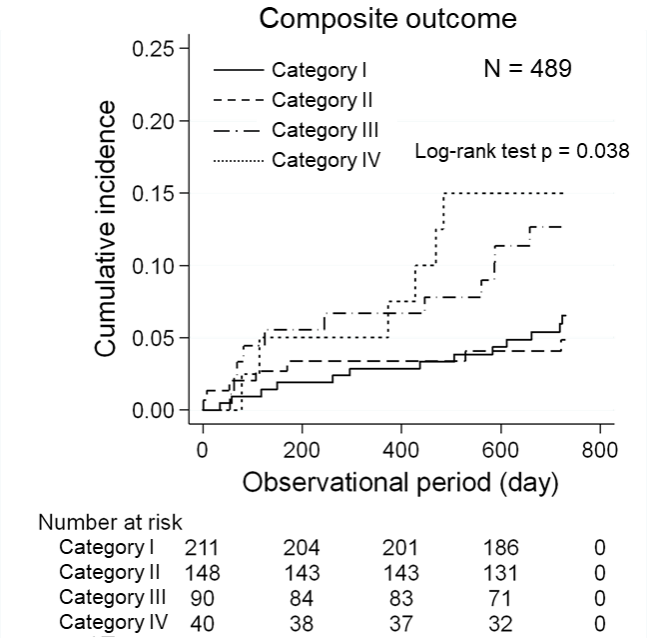

Figure 3. Cumulative incidence rates for the composite outcome within 2 years based on frailty categories.

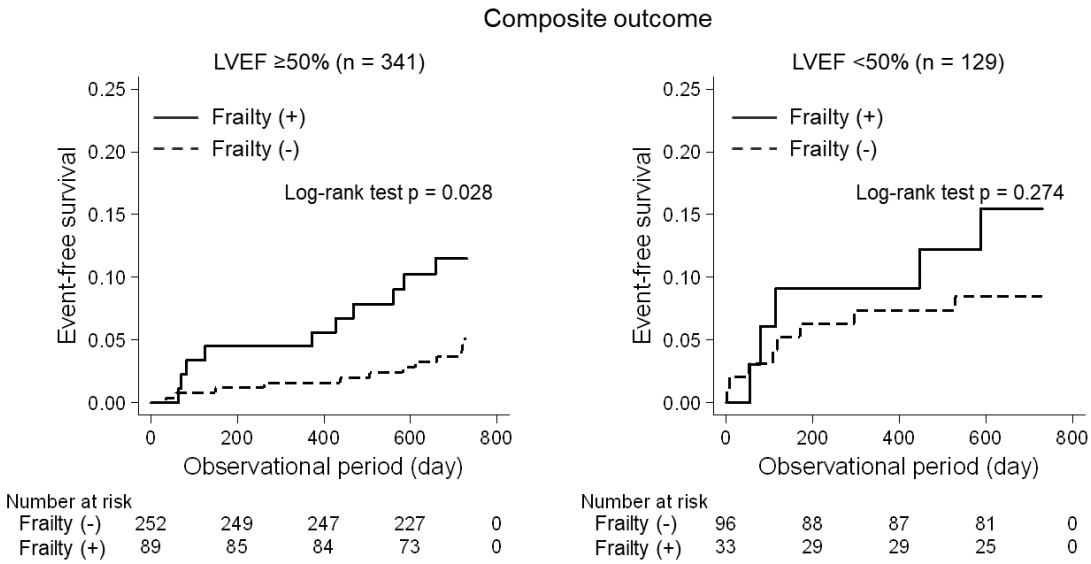

Figure 4. Cumulative incidence rates for the composite outcome within 2 years based on physical frailty by LVEF.

LVEF, left ventricular ejection fraction.

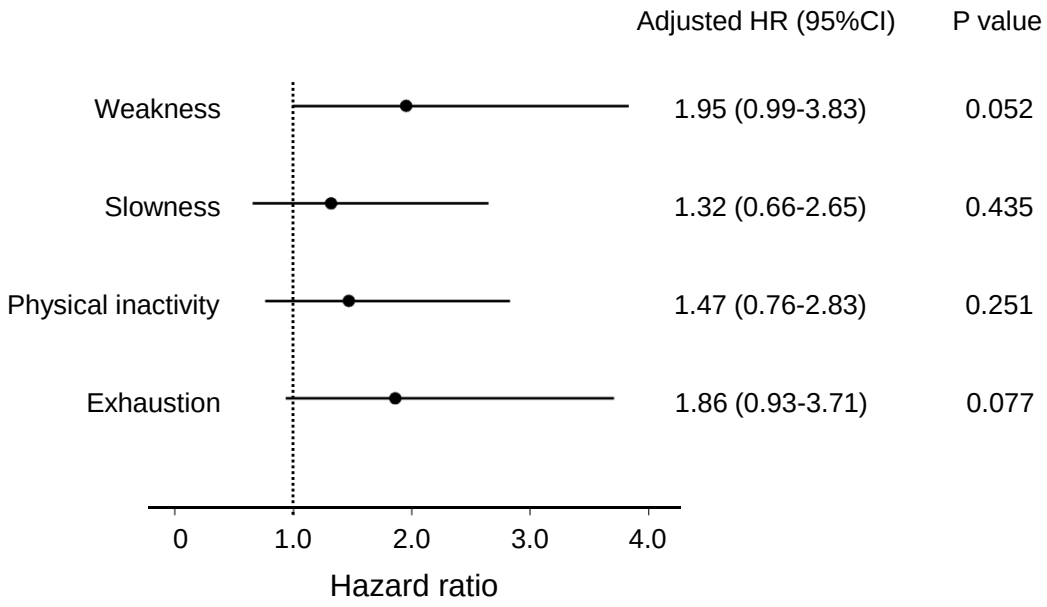

Figure 5. Adjusted hazard ratios of the composite outcome within 2 years associated with the different domains of physical frailty.

HR, hazard ratio.

The hazard ratios were adjusted for age and sex.