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Frailty Tools for Assessment of Long-term Prognosis After Acute Coronary Syndrome

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Abstract

Objective: To evaluate the 5 components of the Fried frailty phenotype (self-reported unintentional weight loss, physical activity questionnaire, gait speed, grip strength, and self-reported exhaustion) for long-term outcomes in elderly survivors of acute coronary syndrome.

Methods: A total of 342 consecutive patients (from October 1, 2010, to February 1, 2012) were included. The 5 components of the Fried score and albumin concentration, as malnutrition index, were assessed before hospital discharge. Patients were followed up until April 2020 (median follow-up, 8.7 years). The end point was postdischarge all-cause mortality.

Results: Mean ± SD age was 77±7 years and mean ± SD Fried score was 2.0±1.1 points. A total of 216 (63%) patients died. After adjusting for clinical covariates, the Fried phenotype was associated with mortality (per points, hazard ratio [HR], 1.35; 95% CI, 1.17 to 1.57; $P<.001$). Among Fried components, physical activity (HR, 2.21; 95% CI, 1.34 to 3.65; $P=.002$) and gait speed (HR, 1.77; 95% CI, 1.29 to 2.43; $P<.001$) were the deficits independendtly associated with mortality. Albumin level provided further prognostic information (per increase in g/dL; HR, 0.63, 95% CI, 0.45 to 0.88; $P=.007$). The model adding the components of the Fried score and albumin level to the clinical model showed the highest risk reclassification (integrated discrimination improvement, 0.040; 95% CI, 0.018 to 0.075; $P=.001$; continuous net reclassification improvement, 0.291; 95% CI, 0.132 to 0.397; $P=.001$) in comparison with the model using clinical covariates alone.

Conclusion: Frailty assessment using the Fried phenotype has prognostic value for long-term mortality in elderly survivors of acute coronary syndrome. Physical activity and gait speed are the predictive components of the Fried score. Albumin level provides incremental prognostic information.

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Frailty status can be assessed with instruments based on physical performance or questionnaires about functional deficit accumulation.[1] Among the first tools, the Fried phenotype has been widely used in elderly people.[2] In the acute phase of acute coronary syndrome, clinical conditions limit performance of physical tests, so functional deficit accumulation tests are recommended.[3,4] However, in the predischarge phase, physical tests might allow a more thorough frailty assessment. The Fried score has demonstrated prognostic value after acute coronary syndrome and acute cardiac diseases.[5-9]

The Fried phenotype consists of 5 components: self-reported unintentional weight loss, physical activity, gait speed, grip strength, and exhaustion. The contribution of each component to overall prognosis assessment after acute coronary syndrome has not been previously investigated. In the present study, we investigated the prognostic value of the Fried scale and its components for long-term mortality in elderly patients after acute coronary syndrome. Identification of the most relevant items in the Fried scale might simplify frailty assessment in these patients.

METHODS

Patient Population

The study population consisted of 342 consecutive patients hospitalized for acute coronary syndrome (either ST-segment elevation or non–ST-segment elevation acute coronary syndrome), who were older than 65 years, from October 1, 2010, to February 1, 2012, at Hospital Clínico Universitario in Valencia, Spain. A detailed description of this cohort is reported elsewhere.[5] On the day before hospital discharge, frailty status was assessed using the Fried score.[2,5] Parameters were unintentional weight loss (self-reported unintentional weight loss >4.5 kg during the preceding year), low physical activity (Minnesota Leisure Time Activity questionnaire), slowness (time to walk 4.57 m), weakness (grip strength using a hand-held isometric dynamometer), and exhaustion (self-reported based on 2 questions from the Center for Epidemiological Studies–Depression scale). Each parameter was categorized as 0 or 1 point according to the Fried definitions; therefore, the score ranged from 0 to 5 points. In addition, albumin level was also determined as index of malnutrition. The study was reviewed and approved by the Clinical Research Ethics Committee of the University Hospital Clinic in Valencia.

A number of variables were collected from clinical assessment (age, sex, coronary risk factors, history of ischemic heart disease, prior hospitalization for heart failure, admission heart rate and blood pressure, and Killip class), electrocardiograms (ST-segment deviation and atrial fibrillation at admission), routine blood tests (high-sensitivity troponin T level, admission hemoglobin level, and glomerular filtration rate), and echocardiograms (left ventricular ejection fraction). The Global Registry of Acute Coronary Events (GRACE) score for 6-month mortality was also calculated.

End Points

The end point was all-cause mortality, beginning the follow-up period at hospital discharge. Patients were followed up until April 2020. Seven patients were lost to follow-up. Median follow-up was 8.7 (interquartile interval, 8.3-9.1) years for the survivors and 5.6 (interquartile interval, 2.4-8.5 years) for the entire patient population. We registered information on end point from the hospital files or outpatient department. In patients who failed to return to the hospital or outpatient department, the information was obtained by contacting the patient or general physician.

Statistical Analyses

Continuous variables were expressed as mean ± SD and compared using unpaired *t* test, whereas categorical variables were expressed as absolute values and compared using χ^2 test. First we investigated the unadjusted contribution of each component of the Fried score as well as albumin level (as malnutrition index) for predicting mortality using Cox regression analysis. The hazard ratio (HR) and 95% CI were calculated.

Next we built Cox regression multivariable models (backward method) for all-cause mortality, adjusted for clinical covariates found to be related to mortality in the univariate analysis. Three models were built, including the Fried score (number of points), separately introducing the 5 components of the Fried score instead of the complete score, and adding albumin level. The incremental prognostic information provided by each model over the clinical model was evaluated by discrimination accuracy (Harrell C statistic), calibration metrics (Gronnesby and Borgen test), and risk reclassification using the integrated discrimination improvement (IDI) and continuous net reclassification improvement (cNRI) indexes.

Statistical analysis was performed using SPSS, version 26.0 software (SPSS, Inc) and R package, version 0.4 (Hajime Uno, Harvard University, Massachusetts, USA)

RESULTS

Patient Population

Table 1 presents characteristics of the patient population. Mean age was 77±7 years, and 196 (57%) were men. Mean Fried score was 2.0±1.1 points (range, 0-5). The prevalence of each deficit in the Fried scale was as follows (Figure, top): unintentional weight loss (n=29; 8.5%), low physical activity (n=21; 6.1%), slowness (n=177; 51.8%), weakness (n=283; 82.7%), and exhaustion (n=175; 51.2%). Mean albumin concentration was 3.73±0.46 g/dL (to convert to g/L, multiply

TABLE 1. Patient Characteristics (N=342)[a,b]	
Age (y), mean ± SD	77±7
Male sex, no. (%)	196 (57)
Body mass index (kg/m^2), mean ± SD	27.1±4.0
Current smoker, no. (%)	34 (10)
Hypertension, no. (%)	283 (83)
Hypercholesterolemia, no. (%)	200 (58)
Diabetes mellitus, no. (%)	144 (42)
Previous myocardial infarction, no. (%)	119 (35)
Previous percutaneous coronary intervention, no. (%)	66 (19)
Previous coronary bypass surgery, no. (%)	27 (7.9)
Previous admission for heart failure, no. (%)	52 (15.2)
Peripheral artery disease, no. (%)	33 (9.6)
Previous stroke, no. (%)	44 (13)
Chronic lung disease, no. (%)	58 (17)
Admission systolic blood pressure (mm Hg), mean ± SD	142±33
Killip class ≥2, no. (%)	101 (30)
ST-segment elevation, no. (%)	71 (21)
Admission atrial fibrillation (ventricular rate <100 beats/min), no. (%)	43 (13)
Troponin elevation, no. (%)	314 (92)
Hemoglobin (g/dL), mean ± SD	12.5±1.8
Glomerular filtration rate (mL/min/1.73 m^2), mean ± SD	51.5±14.5
Left ventricular ejection fraction at discharge (%), mean ± SD	53.8±13.3
Coronary angiogram at the index episode, no. (%)	275 (80)
In-hospital revascularization, no. (%)	152 (44)
GRACE score (points), mean ± SD	137±25
Fried score (points), mean ± SD	2.0±1.1
Albumin (g/dL), mean ± SD	3.73±0.46

[a]GRACE = Global Registry of Acute Coronary Events.
[b]SI conversion factors: To convert albumin and hemoglobin values to g/L, multiply by 10.

by 10). During follow-up, 216 patients (63%) died.

Determinants of Long-term Mortality

In the undjusted analysis, the continuous Fried score (points) was related to mortality (HR, 1.71, 95% CI, 1.50 to 1.94; *P*<.001). According to the standard Fried criteria, 24 patients were robust (0 point), 197 were prefrail (0-1 point), and 121 were frail (3-5 points). Mortality risk increased across Fried categories (robust: reference; prefrail: HR, 3.58; 95% CI, 1.46 to 8.76; *P*<.01; frail: HR, 7.76; 95% CI, 3.15 to 19.09; *P*<.0001). The Supplemental Table (available online at https://mcpiqojournal.org) shows the unadjusted analysis of the individual components of the Fried score. Low physical activity, slowness, weakness, and exhaustion were associated with all-cause mortality, whereas unintentional weight loss was not significant. However, abumin level evidenced a strong association with all-cause mortality (HR, 0.53; 95% CI, 0.39 to 0.73; *P*<.001).

Table 2 presents the clinical variables independently related to all-cause mortality (age, diabetes, prior admission for heart failure, prior stroke, peripheral artery disease, admission Killip class ≥2, atrial fibrillation, hemoglobin level, glomerular filtration rate, left ventricular ejection fraction, and in-hospital revascularization). After adjusting for these clinical covariates, the Fried score predicted mortality (per points, HR, 1.35; 95% CI, 1.17 to 1.57; *P*<.001;Table 2). When testing the individual components of the Fried score,

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low physical activity (HR. 2.21; 95% CI, 1.34 to 3.65; *P*=.002) and slowness (HR, 1.77; 95% CI, 1.29 to 2.43; *P*<.001) were the deficits significantly associated with mortality, whereas weight loss, weakness, and exhaustion lacked significant predictive value (Figure, bottom; Table 3). However, the addition of albumin level over the latter model provided further significant information (per increase in g/dL; HR, 0.63; 95% CI, 0.45 to 0.88; *P*=.007; C statistic of the model, 0.745; Gronnesby & Borgen test, *P*=.77).

Table 3 shows risk reclassification indexes after adding the Fried score, Fried components, and Fried components together with albumin level to the predictive clinical model. Frailty tools significantly reclassified risk. The model using the components of the Fried score together with albumin level performed the best in all parameters (integrated discrimination improvement , 0.040; 95% CI, 0.018 to 0.075; *P*=.001; continuous net reclassification improvement, 0.291; 95% CI, 0.132 to 0.397; *P*=.001).

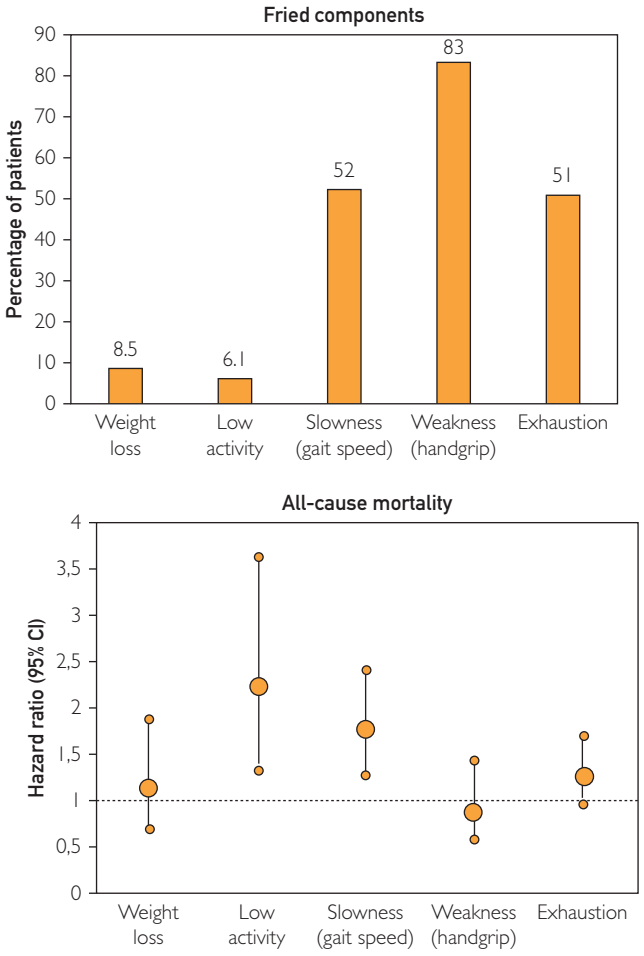

FIGURE. Top, Frequency of the Fried components in the patient population. Bottom, Predictive value of the Fried components for long-term mortality. Hazard ratios adjusted for the predictive clinical covariates: age, diabetes, prior admission for heart failure, prior stroke, peripheral artery disease, admission Killip class 2 or higher, atrial fibrillation, hemoglobin (in g/dL), glomerular filtration rate (in mL/min/1.73 m^2), left ventricular ejection fraction, and revascularization.

DISCUSSION

The main findings of the present study were as follows. 1) Frailty status defined by the Fried score was associated with long-term mortality after acute coronary syndrome in elderly patients. 2) Among the Fried components, physical activity and gait speed were the significant predictors on top of clinical data. 3) Albumin level, as malnutrition index, added further information over the Fried tools.

Fried Scale and Its Components

The Fried scale identifies frailty based on 5 components: self-reported weight loss, low physical activity, slowness, weakness, and exhaustion. Of these, low physical activity (using the Minnesota Leisure Time Activity questionnaire) and slowness (time to walk 4.57 m) retained the greatest value for risk assessment on top of clinical data and the most relevant comorbid conditions.[10] Physical activity questionnaires are tools used for classifying level of physical activity. The Minnesota Leisure Time Activity questionnaire was developed to quantify the level of exercise that would produce a protective effect against coronary heart disease.[11] It has been validated for predicting outcomes in individuals free of prior clinical cardiovascular disease in the general population and in the elderly.[12-14] Gait speed has been shown to reflect the health and functional status of multiple organ systems, including the cardiovascular, pulmonary, nervous, and musculoskeletal systems.[15,16] Its prognostic implications have been demonstrated in many scenarios, such as the general population, elderly population, acute coronary syndrome, and cardiac surgery.[16-19] Grip strength was found to be a marker of mortality risk in patients with cardiac disorders.[20]

TABLE 2. Predictive Models for All-Cause Mortality (n=216)[a,b]

Covariates	Clinical Model		Clinical Model + Fried Score (points)		Clinical Model + Fried Components	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.06 (1.03-1.08)	<.001	1.05 (1.03-1.08)	<.010	1.06 (1.03-1.08)	<.001
Diabetes	1.32 (0.99-1.75)	.06	1.30 (0.98-1.71)	.07	1.33 (1.01-1.75)	.05
Prior admission for heart failure	1.48 (1.02-2.14)	.04	1.39 (0.96-2.01)	.09	1.23 (0.84-1.81)	.28
Prior stroke	1.56 (1.07-2.26)	.02	1.49 (1.03-2.16)	.04	1.50 (1.04-2.17)	.03
Peripheral artery disease	1.75 (1.14-2.69)	.02	1.66 (1.08-2.56)	.02	1.86 (1.22-2.85)	.004
Admission Killip class ≥2	1.81 (1.32-2.49)	<.001	1.72 (1.25-2.38)	.001	1.82 (1.34-2.49)	<.001
Atrial fibrillation	1.56 (1.07-2.29)	.03	1.45 (0.99-2.12)	.06	1.44 (0.99-2.10)	.06
Hemoglobin (per increase in g/dL)	0.92 (0.85-0.99)	.04	0.95 (0.88-1.03)	.19	0.96 (0.88-1.04)	.27
GFR (per increase in 5 mL/min/1.73 m^2)	0.96 (0.91-1.0)	.08	0.96 (0.91-1.01)	.08	0.97 (0.93-1.02)	.24
LVEF (per increase in 5%)	0.93 (0.88-0.99)	.02	0.94 (0.89-0.99)	.03	0.94 (0.89-0.99)	.03
Revascularization	0.66 (0.49-0.88)	.005	0.69 (0.52-0.93)	.02	0.68 (0.51-0.91)	.009
Frailty						
Fried score (per increase in points)			1.35 (1.17-1.57)	0.001		
Weight loss					1.17 (0.72-1.90)	.53
Low activity					2.21 (1.34-3.65)	.002
Slowness					1.77 (1.29-2.43)	<.001
Weakness					0.93 (0.60-1.45)	.75
Exhaustion					1.30 (0.98-1.71)	.08
C Statistic	0.735		0.741		0.745	
Gronnesby & Borgen test (*P*)	0.77		0.72		0.89	

[a]GFR = glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction.
[b]SI conversion factors: To convert hemoglobin values to g/L, multiply by 10.

However, we observed a much weaker association with outcomes than other physical tests. This has also been observed in other studies.[17] Exhaustion is defined by the modified 10-item Center for Epidemiological Studies—Depression scale, which ascertains depressive symptoms.[21] Inability to respond properly to the questionnaire is a potential explanation for the low predictive value found in our study.

TABLE 3. Risk Reclassification for Mortality After Adding the Fried Score, Fried Components, and Fried Components Together With Albumin to the Predictive Clinical Model

	Fried Score	Fried Components	Fried Components + Albumin
IDI	0.025 (0.006-0.046); *P* =.007	0.031 (0.008-0.068); *P* =.001	0.040 (0.018-0.075); *P*=.001
Event	0.009	0.0113	0.0123
Nonevent	−0.0163	−0.0200	−0.0281
cNRI	0.186 (0.071-0.300); *P*=.001	0.244 (0.094-0.373;) *P*=.001	0.291 (0.132-0.397); *P*=.001
Event	0.5752	0.5855	0.6002
Nonevent	0.3889	0.3413	0.3095

cNRI = continuous net reclassification improvement; IDI = integrated discrimination improvement.

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Self-reported weight loss, a surrogate for nutritional status, failed to have an impact on prognosis. In contrast, albumin level was associated with mortality and improved the performance of the predictive model. Conceivably, weight control was inadequate in some patients, limiting its value as nutrition marker.[22] Our findings suggest that albumin level is advisable for frailty assessment. Some frailty scales incorporate albumin level instead of self-reported weight loss as nutritional marker.[23]

Limitations

The Fried score was determined in the convalescence phase of acute coronary syndrome in all patients. This must be taken into account when extrapolating the results of the study to other different populations.

CONCLUSION

Frailty assessment using the Fried score is a marker of long-term mortality in elderly survivors after acute coronary syndrome. The Fried score components with predictive value on top of clinical data are physical activity and gait speed. In addition, albumin concentration provides further prognostic information. Hence, measuring only these parameters might simplify frailty assessment in these patients.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at https://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **cNRI** = continuous net reclassification improvement; **GRACE** = Global Registry of Acute Coronary Events; **HR** = hazard ratio; **IDI** = integrated discrimination improvement

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