Comparison of the prognostic value of frailty assessment tools in patients aged ≥ 65 years hospitalized in a cardiac care unit with acute coronary syndrome

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https://doi.org/10.11909/j.issn.1671-5411.2022.05.010

ABSTRACT

BACKGROUND   Frailty is associated with adverse events in elderly patients with acute coronary syndrome (ACS). Our aim was to compare the prognostic value of four frailty scales in patients aged ≥ 65 years hospitalized with ACS in a cardiac care unit (CCU).

METHODS   Patients aged ≥ 65 years with ACS were included. Frailty was assessed using the Fried frailty scale (reference standard), the Edmonton Frail Scale (EFS), the FRAIL scale, and the Clinical frailty scale (CFS). The primary end point was all-cause mortality and the secondary end point was unscheduled rehospitalization.

RESULTS   One hundred and seventy four patients aged ≥ 65 years with ACS were recruited. The median follow-up was 637.5 days. Frailty was identified in 41.4%, 40.2%, 39.1% and 36.3% patients by the Fried frailty scale, EFS, FRAIL scale and CFS, respectively. The agreement coefficients were 0.88, 0.86, and 0.79 for the FRAIL scale, EFS and CFS, respectively. In the Cox regression model, frailty was associated with all-cause mortality regardless of the scale used (univariate: hazard ratio [HR] 95% CI = 10.5, 2.4–46.8 Fried frailty scale; 12.0, 2.7–53.4 FRAIL scale; 7.1, 2.0–25.2 EFS; 8.3, 2.4–29.6 CFS. Multivariate: HR = 5.1, 1.1–23.8 Fried frailty scale; 5.7, 1.2–26.8 FRAIL scale; 3.7, 1.0–14.0 EFS; 4.2, 1.1–15.9 CFS). The FRAIL scale had the highest HR. In the univariate analysis, frailty was associated with unscheduled rehospitalization (HR = 3.2, 1.7–6.0 Fried frailty scale; 3.4, 1.8–6.3 FRAIL scale; 3.5, 1.8–6.6 EFS; 3.1, 1.7–5.8 CFS). In the multivariate analysis, only the EFS independently predicted unscheduled rehospitalization (HR = 2.2, 1.1–4.63).

CONCLUSIONS   Frailty assessed by the Fried frailty scale, FRAIL scale, EFS and CFS is associated with all-cause mortality and unscheduled rehospitalization in elderly patients hospitalized in a CCU with ACS. The adjusted HR of the FRAIL scale for all-cause mortality was the highest among the scales compared, whereas the EFS was an independent predictor of unscheduled rehospitalization. These data should be taken into consideration when choosing a frailty assessment tool.

Cardiovascular diseases, including ischemic heart disease, are the leading cause of death globally.[1] Age is one of the strongest predictors of adverse events in patients with coronary artery disease (CAD) and acute coronary syndrome (ACS). Over 60% of all people admitted to hospital with ACS are elderly and this population is projected to rise.[2–5] Older patients with co-morbidities, and physical and cognitive disabilities are often excluded from clinical trials; therefore, current evidence-based recommendations are not applicable for these patients.[6] For ACS risk stratification in this population, we should also take into consideration geriatric syndromes, most importantly frailty.[7] Frailty is a loss of physiological reserves, which leads to a failure of homeostasis following stressful events and causes vulnerability to adverse outcomes, such as falls, hospitalizations or mortality. An example of a stressful event is ACS.[8,9] Current studies and structured literature reviews have shown that frailty is common in older people with ACS. The frailty prevalence is estimated at

5%–48%, with a median prevalence of 31.5%.[10,11] Moreover, frailty syndrome is an independent predictor of mortality and adverse events in ACS patients, and the relationship has been demonstrated by many studies using different frailty assessment tools.[12,13] There are many valid and reliable tools to identify frailty and there is evidence of usefulness for some of them in patients with ACS.[9,14] However, it remains unclear which tool is the best for detecting frailty in ACS patients that are hospitalized in a cardiac care unit (CCU).

The aim of this study is to compare the prognostic value of four different frailty scales in ACS patients aged ≥ 65 years who are hospitalized in a CCU, and to identify the most valuable frailty scale in these patients.

METHODS

Participants

This is a single-center prospective cohort study. Patients aged ≥ 65 years with diagnosed ACS were included. ACS was defined as one of three conditions: unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), according to the European Society of Cardiology guidelines.[15] Exclusion criteria included a refusal to participate, inability to give consent, and any substantial visual, hearing or speech impairments that precluded a frailty assessment. Patients were recruited from the Department of Intensive Cardiac Therapy at the National Institute of Cardiology in Warsaw. The study protocol was approved by the Bioethics Committee and all participants signed informed consent forms.

Data Collection

The demographic and clinical characteristics of the participants were recorded. Details on medical history, previous medications and comorbidities were collected through interviews and patient medical files. Comorbidities included hypertension, diabetes mellitus, atrial fibrillation (AF), hyperlipidemia/hypercholesterolemia, congestive heart failure (CHF), valvular heart disease, previous coronary heart disease (including previous myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting), cere-

brovascular disease, peripheral vascular disease, chronic pulmonary disease, chronic kidney disease (CKD), and a history of cancer. Frailty was assessed as soon as possible after admission with the exception of the physical tests, which were performed immediately after patients' bed restrictions were removed. Physical tests were performed by a team of physical therapists from the National Institute of Cardiology. Four validated frailty scales were used: (1) the Fried frailty scale (as a reference scale); (2) the Edmonton Frail Scale (EFS); (3) the FRAIL scale; and (4) the Clinical Frailty Scale (CFS).

The Fried frailty scale consists of five criteria: (1) weight loss: self-reported unintentional weight loss (≥ 4.5 kg in the last year). (2) Exhaustion: identified by using two questions from the Center of Epidemiologic Studies-Depression (CES-D): "How often in the last week did you feel that everything you did was an effort?" and "How often in the last week did you feel that you could not get going?". Participants answering "a moderate amount of the time (3–4 days)" or "most of the time" to either of these questions were categorized as frail by the exhaustion criterion. (3) Low physical activity: Based on the short version of the Minnesota Leisure Time Activity questionnaire. Physical activity was considered low if total physical activity was < 383 kcal/week (men) and < 270 kcal/week (women). (4) Walk time, stratified by gender and height: Time required to walk 4.57 m in a straight line. (5) Grip strength, stratified by gender and body mass index (BMI) quartiles: assessed using a handgrip strength dynamometer.

Frailty was considered present when 3 or more of the 5 criteria were fulfilled. Pre-frailty was considered present when 1 or 2 of the 5 criteria were fulfilled. Participants with 0 criterion were considered not frail.[8]

The EFS is composed of series of simple questions and tasks that assess several conditions, such as cognitive function (by using the "clock test"), functional independence, previous hospitalization, social support, medications, nutrition, mood, incontinence and functional status (by using the "get up and go" test). Frailty was considered present when the total score was 8–17 points. Pre-frailty was considered present when the total score was 6–7 points. Participants with a total score between 0–5 points were considered not frail.[16,17]

The FRAIL scale is a simple questionnaire that in-

cludes 5 components: fatigue, resistance, ambulation, illness, and loss of weight. The maximum score is 5 and the minimum score is 0. Frailty was considered present when the total score was 3–5 points. Pre-frailty was considered present when the total score was 1–2 points. Participants with a total score of 0 points were considered not frail.[18,19]

The CFS is a 7-point scale that evaluates specific conditions such as comorbidity, functional status and cognition. Frailty was considered present when the patient was assigned to categories 5–7. Prefrailty was present when the patient was assigned to category 4. Patients assigned to categories 1–3 were considered not frail.[20] However, the CFS is now more commonly used as a 9-point scale with the additional subgroups "very severe frailty" and "terminally ill".

All scales are attached in the supplementary material (Supplementary Tables 1–4).

Clinical Outcomes

The primary end point was all-cause mortality and the secondary end point was unscheduled rehospitalization. The information was obtained by contacting the patient or patient's family.

Statistical Analysis

Depending on the distribution of continuous variables as assessed by the Shapiro-Wilk test, the results are shown as either arithmetic means with standard deviations or as median values with interquartile ranges. The significance of differences between the mean values was evaluated using the Student's t-test. Categorical variables are shown as frequencies and percentages. Comparisons of the proportional categorical data from two different groups were performed using the chi-squared test with the Yate's correction for continuity, or the Fisher's exact test if the minimum expected count in the cell was less than 5. Agreement between the binary variables of the paired samples was analyzed using the kappa coefficient and McNemar's test. The relationships between frailty and the other examined variables are listed in Table 1. Outcome (all-cause death and unscheduled rehospitalization) was assessed with the Cox's proportional hazard model using univariate and backward multivariate procedures. The multivariate analysis included variables for which the level of statistical significance in univariate analysis was $P < 0.1$ (Table 2). Variables included in the multivariate analysis of all-cause death were gender, age, BMI, previous CKD, malignant disease, hypercholesterolemia or hyperlipidemia, hemoglobin (Hgb) on admission to hospital, and left ventricular ejection fraction (LVEF) assessed during hospitalization. The variables included in the multivariate analysis of unscheduled rehospitalization were age, previous MI, CHF with EF ≥ 50%, CHF with EF < 50%, previous AF, previous CKD, previous stroke/TIA, Hgb on admission to hospital, LVEF assessed during hospitalization, and coronary angiography results. Each of the analyzed frailty scores were assessed in separate multivariate models. The goodness of fit models were evaluated with Harrell's C-index. A significance level of $P < 0.05$ was required for the variable to remain in the multivariate model. A test for non-proportionality of hazards based on Schoenfeld residuals did not reveal significant violations of the proportionality assumptions. The probabilities of survival and survival free of unscheduled rehospitalization were estimated using the Kaplan–Meier method. The homogeneities of the curves with a different status of frailty syndrome were assessed with the log-rank test. All tests were two-sided and a P-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Baseline Patient Characteristics

A total of 174 patients aged ≥ 65 years with diagnosed ACS were recruited. 78 (44.8%) patients were female and 96 (55.2%) were male. The mean patient age was 74.8 years and the oldest was 96 years. 96 (55.2%) patients were 65–74 years of age, 64 (36.8%) were 75–84 years of age, and 14 (8%) were ≥ 85 years of age. STEMI was diagnosed in 88 (50.6%) patients, NSTEMI in 80 (46%) patients, and UA in 6 (3.4%) patients. The baseline patient characteristics were similar irrespective of the scale used, with a few exceptions (Table 1). Frail patients were more likely to be female, older than non-frail patients, with a mean age of 78 vs. 72 years according to the reference scale (Fried frailty scale, $P < 0.001$), have a lower BMI, a lower level of Hgb on admission to hospital, and a lower LVEF evaluated dur-

Table 1 Baseline patient characteristics.

Variables	Fried frailty scale			FRAIL scale			Edmonton Frail Scale			Clinical Frailty Scale		
	Non-frail (n = 102)	Frail (n = 72)	P-value	Non-frail (n = 106)	Frail (n = 68)	P-value	Non-frail (n = 104)	Frail (n = 70)	P-value	Non-frail (n = 111)	Frail (n = 68)	P value
Female	34 (33.3%)	44 (61.1%)	< 0.001	39 (36.8%)	39 (57.4%)	0.012	36 (34.6%)	42 (60.0%)	0.001	40 (36.0%)	38 (60.3%)	< 0.001
Age, yrs	72.1 ± 5.6	78.3 ± 8.0	< 0.001	71.8 ± 5.1	79.2 ± 8.0	< 0.001	72.3 ± 5.7	78.2 ± 8.1	< 0.001	72.1 ± 5.6	79.1 ± 8.0	< 0.001
BMI, kg/m^2	27.7 ± 4.4	25.3 ± 4.2	< 0.001	27.7 ± 4.4	25.2 ± 4.2	< 0.001	27.6 ± 4.4	25.3 ± 4.2	< 0.001	27.4 ± 4.4	25.5 ± 4.3	0.009
Type of ACS			0.095			0.141			0.238			0.322
STEMI	58 (56.9%)	30 (41.67%)		59 (55.7%)	29 (42.6%)		58 (55.8%)	30 (42.9%)		58 (52.2%)	30 (47.6%)	
NSTEMI	42 (41.2%)	38 (52.78%)		45 (42.4%)	35 (51.5%)		43 (41.3%)	37 (52.9%)		51 (45.9%)	29 (46.0%)	
UA	2 (1.9%)	4 (5.56%)		2 (1.9%)	4 (5.9%)		3 (2.9%)	3 (4.3%)		2 (1.8%)	4 (6.3%)	
Coronary angiography			0.002			0.008			0.018			0.026
No significant lesions	2 (2.0%)	7 (10%)		3 (2.8%)	6 (9.1%)		2 (1.9%)	7 (10.3%)		3 (2.7%)	6 (9.7%)	
Single-vessel disease	30 (29.4%)	7 (10%)		30 (28.3%)	7 (10.6%)		28 (26.9%)	9 (13.2%)		29 (26.4%)	8 (12.9%)	
Two-vessel disease	32 (31.4%)	20 (28,6%)		34 (32.1%)	18 (27.3%)		33 (31.7%)	19 (27.9%)		36 (32.7%)	16 (25.8%)	
Three-vessel disease	38 (37.2%)	36 (51.4%)		39 (36.8%)	35 (53.0%)		41 (39.4%)	33 (48.5%)		42 (38.2%)	32 (51.6%)	
Treatment			0.020			0.013			0.007			0.035
Conservative therapy	15 (14.7%)	20 (27.8%)		15 (14.1%)	20 (29.4%)		14 (13.5%)	21 (30.0%)		17 (15.3%)	18 (28.6%)	
PCI	78 (76.5%)	51 (70.8%)		82 (77.4%)	47 (69.1%)		81 (77.9%)	48 (68.6%)		85 (76.6%)	44 (69.8%)	
CABG	9 (8.8%)	1 (1.4%)		9 (8.5%)	1 (1,5%)		9 (8.6%)	1 (1.4%)		9 (8.1%)	1 (1.6%)	
Treatment			0.034			0.014			0.008			0.036
Conservative therapy	15 (14.7%)	20 (27.8%)		15 (14.1%)	20 (29.4%)		14 (13.5%)	21 (30.0%)		17 (15.3%)	18 (28.6%)	
PCI or CABG	87 (85.3%)	52 (72.2%)		91 (85.8%)	48 (70.6%)		90 (86.5%)	49 (70.0%)		94 (84.7%)	45 (71.4%)	
Hypertension	81 (79.4%)	65 (90.3%)	0.055	85 (80.2%)	61 (89.7%)	0.145	83 (79.8%)	63 (90.0%)	0.073	89 (80.2%)	57 (90.5%)	0.076
Diabetes mellitus	32 (31.4%)	30 (41.7%)	0.163	33 (31.1%)	29 (42.6%)	0.166	33 (31.7%)	29 (41.4%)	0.190	35 (31.5%)	27 (42.9%)	0.134
Previous MI	30 (29.4%)	15 (20.8%)	0.203	30 (28.3%)	15 (22.1%)	0.459	30 (28.8%)	15 (21.4%)	0.273	31 (27.9%)	14 (22.2%)	0.409
Previous PCI	29 (28.4%)	16 (22.2%)	0.366	28 (26.4%)	17 (25.0%)	0.976	29(27.9%)	16 (22.9%)	0.458	31(27.9%)	14 (22.2%)	0.409
Previous CABG	12 (11.8%)	7 (9.7%)	0.671	12 (11.3%)	7 (10.3%)	1.00	12 (11.5%)	7 (10.0%)	0.750	14 (12.6%)	5 (7.9%)	0.342
CHF with EF ≥ 50%	3 (2.9%)	10 (13.9%)	0.007	4 (3.8%)	9 (13.2%)	0.043	3 (2.9%)	10 (14.3%)	0.005	4 (3.6%)	9 (14.3%)	0.015
CHF with EF < 50%	5 (4.9%)	8 (11.1%)	0.125	6 (5.7%)	7 (10.3%)	0.402	6 (5.8%)	7 (10.0%)	0.298	7 (6.3%)	6 (9.5%)	0.550
Previous AF	13 (12.7%)	22 (30.6%)	0.004	13 (12.3%)	22 (32.3%)	0.002	13 (12.5%)	22 (31.4%)	0.002	14 (12.6%)	21 (33.3%)	0.001
Previous CKD	20 (19.6%)	28 (38.9%)	0.005	20 (18.9%)	28 (41.2%)	0.002	22 (21.1%)	26 (37.1%)	0.021	24 (21.6%)	24 (38.1%)	0.019
COPD	10 (9.8%)	9 (12.5%)	0.574	9 (8.5%)	10 (14.7%)	0.200	10 (9.6%)	9 (12.9%)	0.501	8 (7.2%)	11 (17.5%)	0.037
Peripheral artery disease	12 (11.8%)	10 (13.9%)	0.678	12 (11.3%)	10 (14.7%)	0.673	13 (12.5%)	9 (12.9%)	0.945	14 (12.6%)	8 (12.7%)	0.987
Previous stroke/TIA	8 (7.8%)	13 (18.1%)	0.042	7 (6.6%)	14 (20.6%)	0.012	9 (8.7%)	12 (17.1%)	0.092	8 (7.2%)	13 (20.6%)	0.009
Malignant disease	13 (12.7%)	11 (15.3%)	0.633	13 (12.3%)	11 (16.2%)	0.614	12 (11.5%)	12 (17.1%)	0.293	13 (11.7%)	11 (17.5%)	0.291
Hypercholesterolemia or hyperlipidemia	81 (79.4%)	48 (66.7%)	0.059	85 (80.2%)	44 (64.7%)	0.023	83 (79.8%)	46 (65.7%)	0.037	92 (82.9%)	37 (58.7%)	< 0.001
Hgb on admission to hospital, g/dL	13.7 ± 1.7	12.5 ± 1.9	< 0.001	13.7 ± 1.7	12.5 ± 2.0	< 0.001	13.7 ± 1.6	12.5 ± 2.0	< 0.001	13.7 ± 1.6	12.3 ± 2.0	< 0.001
EF assessed during hospitalization,%	49.2 ± 11.8	44.3 ± 13.7	0.011	49.4 ± 11.9	43.7 ± 13.5	0.004	48.8 ± 11.9	44.8 ± 13.7	0.043	48.6 ± 12.2	44.7 ± 13.6	0.053

Data are presented as mean ± SD or n (%). ACS: acute coronary syndrome; AF: atrial fibrillation; BMI: body mass index; CABG: coronary artery bypass grafting; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; Hgb: hemoglobin; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischemic attack; UA: unstable angina.

ing hospitalization (on the CFS the difference was on the verge of statistical significance, *P* = 0.053).

Frail patients had more comorbidities, including higher rates of AF, CHF with preserved EF ≥ 50%

Table 2   Predictors of unscheduled rehospitalization and all-cause death (univariate analysis).

Variables	Death (n = 15)	Survivals (n = 153)	P-value	HR [95% CI]	P-value	Rehosp. (+) (n = 41)	Rehosp. (−) (n = 123)	P-value	HR [95% CI]	P-value
Female	10 (66.7%)	66 (43.1%)	0.081	2.40 [0.82; 7.03]	0.109	22 (53.7%)	50 (40.6%)	0.146	1.48 [0.80; 2.73]	0.213
Age, yrs	78.7 ± 7.7	74.2 ± 7.3	0.022	1.07 [1.01; 1.14]	0.025	78.4 ± 8.2	73.4 ± 6.7	< 0.001	1.08 [1.04; 1.12]	< 0.001
BMI, kg/m^2	25.0 ± 3.8	27.0 ± 4.5	0.098	0.90 [0.79; 1.02]	0.097	26.0 ± 3.3	27.1 ± 4.8	0.105	0.96 [0.89; 1.03]	0.218
Type of ACS										
STEMI	10 (66.7%)	75 (49.2%)	0.372	Reference		17 (41.5%)	63 (51.2%)	0.537	Reference	
NSTEMI	5 (33.3%)	72 (47.1%)		0.54 [0.18; 1.58]	0.260	22 (53.7%)	56 (45.5%)		1.31 [0.70; 2.46]	0.405
UA	0 (0.0%)	6 (3.9%)		NA*	0.992	2 (4.9%)	4 (3.3%)		1.28 [0.30; 5.54]	0.741
Coronary angiography										
I. no significant lesions	2 (13.3%)	6 (4.0%)	0.224	Reference		0 (0.0%)	7 (5.7%)	0.061	Reference (I and II)	
II. single-vessel disease	2 (13.3%)	34 (22.5%)		0.18 [0.02; 1.28]	0.087	5 (12.5%)	30 (24.6%)		Reference (I and II)	
III. multi-vessel disease	11 (73.3%)	111 (73.5%)		0.29 [0.06; 1.32]	0.110	35 (87.5%)	85 (69.7%)		2.62 [1.02; 6.68]	0.044
Treatment										
Conservative therapy	5 (33.3%)	27 (17.6%)	0.246	Reference		8 (19.5%)	22 (17.9%)	0.610	Reference	
PCI	10 (66.7%)	117 (76.5%)		0.49 [0.17; 1.43]	0.193	32 (78.1%)	93 (75.6%)		1.16 [0.53; 2.52]	0.707
CABG	0 (0%)	9 (5.9%)		NA*	0.991	1 (2.4%)	8 (6.5%)		0.43 [0.05; 3.44]	0.427
Treatment										
Conservative therapy	5 (33.3%)	27 (17.7%)	0.166	Reference		8 (19.5%)	22 (17.9%)	0.816	Reference	
PCI or CABG	10 (66.7%)	126 (82.3%)		0.46 [0.16; 1.33]	0.152	33 (80.5%)	101 (82.1%)		1.10 [0.51; 2.39]	0.804
Hypertension	11 (73.3%)	129 (84.3%)	0.281	0.55 [0.17; 1.72]	0.304	37 (90.2%)	101 (82.1%)	0.217	1.84 [0.66; 5.18]	0.245
Diabetes mellitus	5 (33.3%)	54 (35.3%)	0.879	0.92 [0.31; 2.69]	0.877	19 (46.3%)	40 (32.5%)	0.110	1.64 [0.89; 3.02]	0.116
Previous MI	2 (13.3%)	41 (26.8%)	0.359	0.43 [0.10; 1.89]	0.263	16 (39.0%)	29 (23.6%)	0.055	1.78 [0.95; 3.33]	0.073
Previous PCI	2 (13.3%)	41 (26.8%)	0.359	0.44 [0.10; 1.93]	0.275	15 (36.6%)	29 (23.6%)	0.103	1.68 [0.89; 3.17]	0.111
Previous CABG	1 (6.7%)	17 (11.1%)	1.000	0.65 [0.09; 4.96]	0.680	3 (7.3%)	15 (12.2%)	0.566	0.72 [0.22; 2.34]	0.587
CHF with EF ≥ 50%	2 (13.3%)	10 (6.5%)	0.291	2.12 [0.48; 9.40]	0.322	9 (21.9%)	3 (2.4%)	< 0.001	4.59 [2.17; 9.74]	< 0.001
CHF with EF < 50%	1 (6.7%)	11 (7.2%)	1.000	0.94 [0.12; 7.15]	0.953	6 (14.6%)	6 (4.9%)	0.075	2.36 [0.99; 5.62]	0.052
Previous AF	5 (33.3%)	26 (17.0%)	0.157	2.23 [0.76; 6.55]	0.142	14 (34.1%)	17 (13.8%)	0.004	2.30 [1.21; 4.40]	0.011
Previous CKD	7 (46.7%)	39 (25.5%)	0.125	2.42 [0.88; 6.66]	0.088	18 (43.9%)	27 (21.9%)	0.006	2.31 [1.25; 4.30]	0.008
COPD	2 (13.3%)	15 (9.8%)	0.651	1.41 [0.32; 6.23]	0.654	6 (14.6%)	12 (9.8%)	0.395	1.33 [0.56; 3.16]	0.524
Peripheral artery disease	2 (13.3%)	18 (11.8%)	0.694	1.18 [0.27; 5.23]	0.828	7 (17.1%)	14 (11.4%)	0.345	1.59 [0.70; 3.58]	0.267
Previous stroke/TIA	3 (20.0%)	18 (11.8%)	0.406	1.81 [0.51; 6.41]	0.395	8 (19.5%)	11 (8.9%)	0.089	2.06 [0.95; 4.46]	0.067
Malignant disease	5 (33.3%)	18 (11.8%)	0.036	3.38 [1.15; 9.89]	0.026	6 (14.6%)	15 (12.2%)	0.686	1.37 [0.58; 3.27]	0.475
Hypercholesterolemia or hyperlipidemia	6 (40.0%)	119 (77.8%)	0.003	0.21 [0.08; 0.60]	0.003	33 (80.5%)	92 (74.8%)	0.458	1.52 [0.70; 3.30]	0.292
Hgb on admission to hospital, g/dL	11.6 ± 1.4	13.3 ± 1.8	< 0.001	0.69 [0.56; 0.85]	< 0.001	12.8 ± 2.1	13.5 ± 1.7	0.020	0.84 [0.73; 0.97]	0.021
EF assessed during hospitalization, %	39.1 ± 13.2	48.5 ± 12.3	0.006	0.95 [0.91; 0.99]	0.008	42.3 ± 13.8	49.6 ± 11.4	< 0.001	0.96 [0.94; 0.99]	0.002

Data are presented as mean ± SD or *n* (%). *NA: due to the small number of observations. ACS: acute coronary syndrome; AF: atrial fibrillation; BMI: body mass index; CABG: coronary artery bypass grafting; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; EF: ejection fraction; Hgb: hemoglobin; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischemic attack; UA: unstable angina.

and CKD, whereas the incidence of hypercholesterolemia/hyperlipidemia was substantially lower (on the Fried frailty scale the difference was on the verge of statistical significance, P = 0.059). According to most of the scales (Fried frailty scale, FRAIL scale, CFS), frail patients had higher rates of previous stroke and TIA, except on the EFS (P = 0.092). On one scale (CFS), frail patients had slightly higher rates of chronic obstructive pulmonary disease, but the difference was marginal (P = 0.037). Frail patients were more likely to have multi-vessel disease and were more often qualified for conservative therapy.

Frailty Assessment

Figure 1 shows the differences in frailty detection between the FRAIL scale, EFS and CFS compared with the Fried frailty scale as a reference standard. Of the 174 patients, frailty was identified in 72 (41.4%) by the Fried frailty scale, 70 (40.2%) by the EFS, 68 (39.1%) by the FRAIL scale, and 63 (36.3%) by the CFS. The agreement coefficients were high for each scale and were 0.88, 0.86, 0.79 for the FRAIL scale, EFS and CFS, respectively. McNemar's test showed that frailty was statistically significantly more often identified using the Fried frailty

scale compared to the CFS (P = 0.029). In contrast, there were no statistically significant differences between the Fried frailty scale compared and the FRAIL scale (P = 0.206) or EFS (P = 0.564).

Association of Frailty with All-cause Mortality and Unscheduled Rehospitalization

Patients were followed up by telephone consultation. The follow-up period ranged from 80–945 days and the median follow-up time was 637.5 days. Six patients were lost prior to follow-up. During the follow up period, 15 patients died (8 patients in hospital) and 41 patients had an unscheduled hospitalization. Frailty was associated with all-cause mortality regardless of the scale used and the association was demonstrated in both the univariate and multivariate Cox regression models. In both analyses, the FRAIL scale had the highest HR (univariate analysis: HR = 10.5, 95% CI: 2.4–46.8, P < 0.001 for the Fried frailty scale; 12.0, 2.7–53.4, P < 0.001 for the FRAIL scale; 7.1, 2.0–25.2, P < 0.001 for the EFS; 8.3, 2.4–29.6, P < 0.001 for the CFS; multivariate analysis: HR = 5.1, 95% CI: 1.1–23.8, P = 0.037 for the Fried frailty scale; 5.7, 1.2–26.8, P =

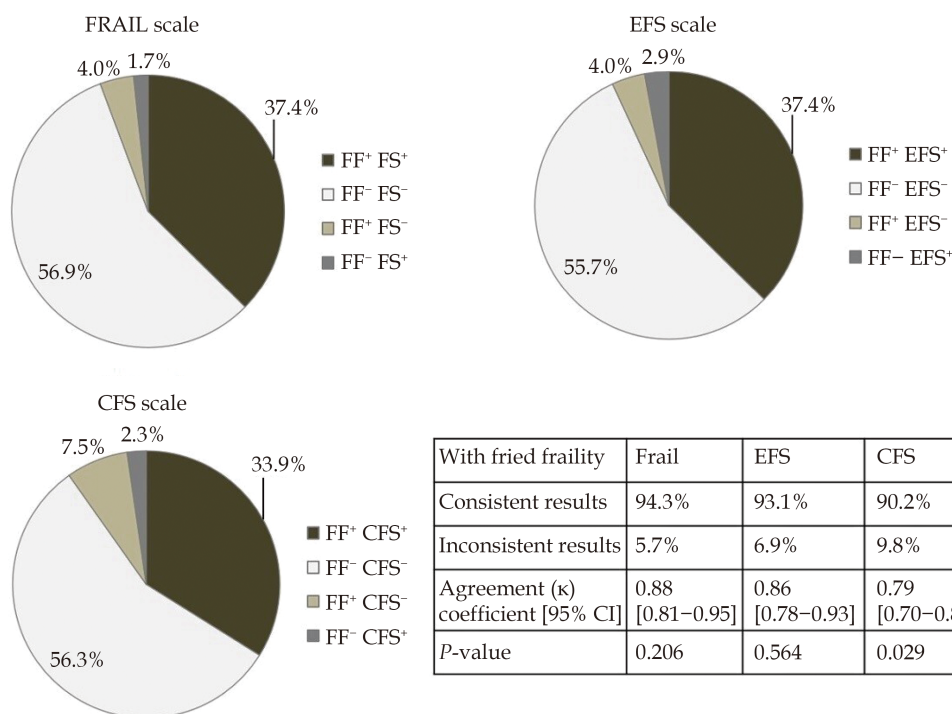| With fried frailty	Frail	EFS	CFS
Consistent results	94.3%	93.1%	90.2%
Inconsistent results	5.7%	6.9%	9.8%
Agreement (κ) coefficient [95% CI]	0.88 [0.81−0.95]	0.86 [0.78−0.93]	0.79 [0.70−0.89]
P-value	0.206	0.564	0.029

Figure 1   Comparison of the scales abilities to detect frailty. The Fried frailty scale is used as a reference standard (total number of frail patients: 72 [41.4%]). CFS: Clinical Frailty Scale; EFS: Edmonton Frail Scale; FF: Fried frailty scale; FS: FRAIL scale. "+" frailty occurred, "−" frailty not occurred.

0.027 for the FRAIL scale; 3.7, 1.0–14.0, $P = 0.05$ for the EFS; 4.2, 1.1–15.9, $P = 0.033$ for the CFS). Other independent predictors were a low LVEF assessed during hospitalization and a low Hgb level on admission to hospital (Table 3, Figure 2). In the univariate Cox regression model, frailty was associated with an increased risk of unscheduled rehospitalization regardless of the scale used (HR = 3.2, 95% CI: 1.7–6.0, $P < 0.001$ for the Fried frailty scale; 3.4, 1.8–6.3, $P < 0.001$ for the FRAIL scale; 3.5, 1.8–6.6, $P < 0.001$ for the EFS; 3.1, 1.7–5.8, $P < 0.001$ for the CFS). Multivariate analysis showed that frailty assessed only with the EFS was an independent predictor of unscheduled rehospitalization (HR = 2.2, 95% CI: 1.1–4.5, $P = 0.031$). Other independent predictors were age and CHF with mildly reduced and reduced EF (< 50%; Table 3, Figure 3).

DISCUSSION

The present study confirmed a high prevalence of frailty in elderly patients with ACS, which varied from 36.3–41.4% depending on the scale used. High agreement coefficients denoted the high concordance in frailty identification between the Fried frailty scale (our reference scale) and the FRAIL scale, the EFS, and the CFS. At the same time, McNemar's test showed that frailty was significantly more often identified using the Fried frailty scale compared to the CFS (but not compared to the FRAIL scale or the EFS), indicating that the CFS may underestimate frailty in elderly patients hospitalized in a CCU with ACS. Our study also showed that frailty, regardless of the scale used, was associated with an increased risk of rehospitalization or mortality during the follow-up period. Frailty was asso-

Table 3   Impact of frailty on unscheduled rehospitalization and all-cause death as assessed by the Cox regression model.

	Frail group	Non-frail group	Univariate		Multivariate		
			Frailty: HR (95% CI)	P value	Frailty: HR (95% CI)	P value	Other significant predictors, HR [95% CI], P-value, Harrell's C-index [95% CI]
All-cause Death							
Fried frailty scale N = 68, n = 100	13 (19.1%)	2 (2.0%)	10.5 [2.4–46.8]	< 0.001	5.1 [1.1–23.8]	0.037	EF: 0.94 [0.90–0.98]; P = 0.009 HgB: 0.67 [0.51−0.88]; P = 0.005 Harrell's C-index: 0.86 [0.80−0.92]
FRAIL scale N = 64, n = 104	13 (20.3%)	2 (1.9%)	12.0 [2.7–53.4]	< 0.001	5.7 [1.2–26.8]	0.027	EF: 0.94 [0.90; 0.99]; P = 0.013 HgB: 0.68 [0.51−0.90]; P = 0.007 Harrell's C-index: 0.87 [0.81−0.92]
Edmonton frail scale N = 65, n = 103	12 (18.5%)	3 (2.9%)	7.1 [2.0–25.2]	< 0.001	3.7 [1.0–14.0]	0.050	EF: 0.94 [0.90–0.98], P = 0.004 HgB: 0.67 [0.51−0.88], P = 0.005 Harrell's C-index: 0.87 [0.82−0.93]
Clinical frailty scale N = 59, n = 109	12 (20.3%)	3 (2.75%)	8.3 [2.4–29.6]	< 0.001	4.2 [1.1–15.9]	0.033	EF: 0.94 [0.90–0.98]; P = 0.005 HgB: 0.68 [0.51−0.90], P = 0.007 Harrell's C-index: 0.87 [0.82−0.93]
Unscheduled rehospitalization							
Fried frailty scale N = 64, n = 100	26 (40.6%)	15 (15.0%)	3.2 [1.7–6.0]	< 0.001	-	-	Age: 1.07 [1.03–1.12], P < 0.001 CHF with EF < 50%: 3.68 [1.73–7.82], P < 0.001 Harrell's C-index: 0.70 [0.62–0.79]
FRAIL scale N = 60, n = 104	25 (41.7%)	16 (15.4%)	3.4 [1.8–6.3]	< 0.001	-	-	Age: 1.07 [1.03–1.12], P < 0.001 CHF with EF < 50%: 3.7 [1.8–7.9], P < 0.001 Harrell's C-index: 0.70 [0.62–0.80]
Edmonton Frail Scale N = 61, n = 103	26 (41.6%)	15 (14.6%)	3.5 [1.8–6.6]	< 0.001	2.2 [1.10–4.5]	0.031	Age: 1.05 [1.01–1.09], P = 0.026 CHF with EF < 50%: 3.3 [1.5–7.0], P = 0.002 Harrell's C-index: 0.74 [0.67–0.81]
Clinical Frailty Scale N = 55, n = 109	23 (41.8%)	18 (16.5%)	3.1 [1.7–5.8]	< 0.001	-	-	Age: 1.07 [1.03–1.12], P < 0.001 CHF with EF < 50%: 3.7 [1.7–7.9], P < 0.001 Harrell's C-index: 0.70 [0.62–0.79]

CHF with EF < 50%: congestive heart failure with ejection fraction < 50%; CHF: congestive heart failure; EF: ejection fraction; HR: hazard ratio; Hgb: hemoglobin.
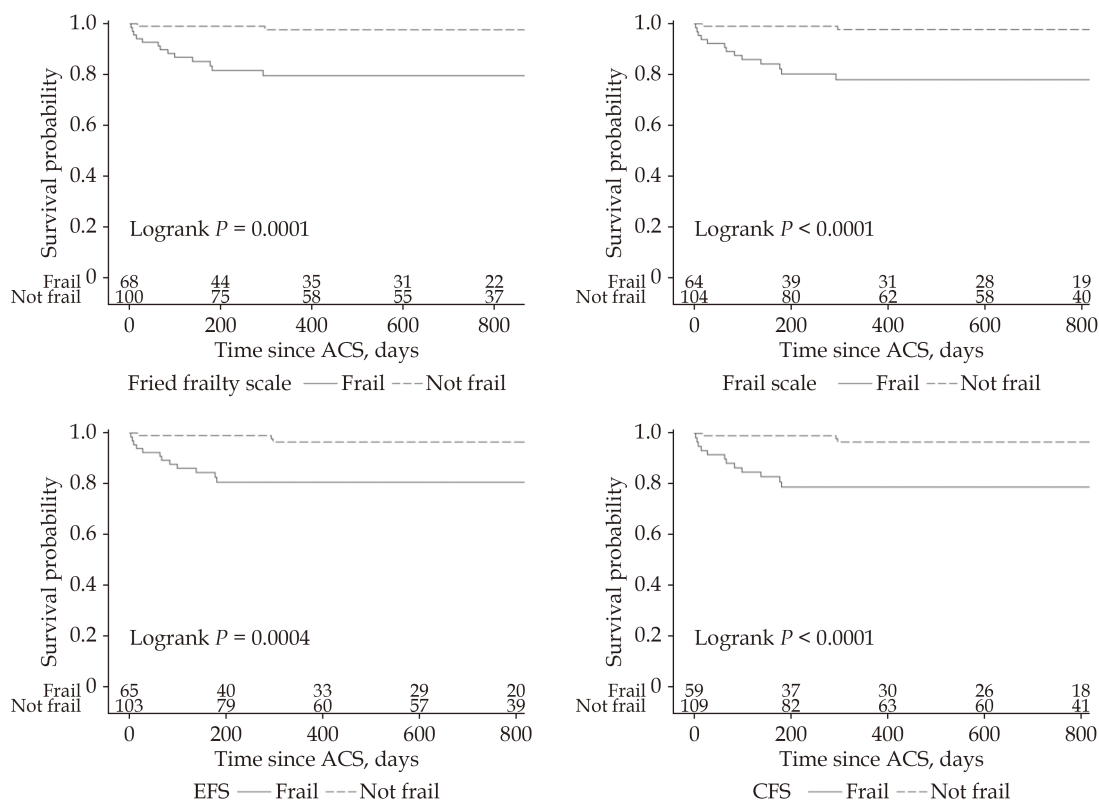
Figure 2   Kaplan–Meier curves. All-cause mortality according to frailty status. ACS: acute coronary syndrome; CFS: Clinical Frailty Scale; EFS: Edmonton Frail Scale.

ciated with all-cause mortality and the association was demonstrated in the univariate and multivariate Cox regression models. In both analyses, the FRAIL scale had the highest HR and it turned out to be the scale that best correlated with mortality in elderly patients hospitalized in a CCU with ACS. Unscheduled rehospitalization occurred 3.1–3.5 times (depending on the scale used) more often in patients with frailty. However, multivariate analysis showed that frailty assessed only with the EFS was an independent predictor of unscheduled rehospitalization.

There are two principal models of frailty: the phenotype model and the cumulative deficit model. The phenotype model was established by Fried and colleagues and considers frailty as poor physical functioning. Frailty criteria are included in the Fried frailty scale and it's the most common frailty screening tool used worldwide, with multidomain evaluation and strong evidence of frailty identification. For these reasons, we chose this scale as a reference standard.[8,9] The Fried frailty scale requires an interview and physical testing; therefore, it can only be conducted in stable, mobile patients. This scale has strong evidence for usefulness in patients with ACS. Frailty assessed by this scale is strongly associated with long-term mortality and an increased risk of MI in elderly patients with CAD, ACS, or in those who underwent PCI.[11,21–25] The cumulative deficit model describes frailty as an accumulation of deficits, including symptoms, signs, abnormal laboratory values, comorbidities and disabilities. On the basis of this conception of frailty, the EFS,[16] the FRAIL scale,[18] and the CFS[20] were established. The CFS and the FRAIL scale are simple tools, based only on interviews without physical testing, and both are easy and fast to perform. The FRAIL scale is comprised of five items and contains multidomain evaluation, including for concomitant illnesses. The FRAIL scale independently predicts in-hospital, short-term and long-term outcomes (mortality and re-admission) in older patients with ACS.[19,26,27] The CFS is a 7-point scale (however, at present, a 9-point scale is more commonly used) and the level of frailty can be assessed by a few, simple questions, according to the description provided for every level. The identification of the category is
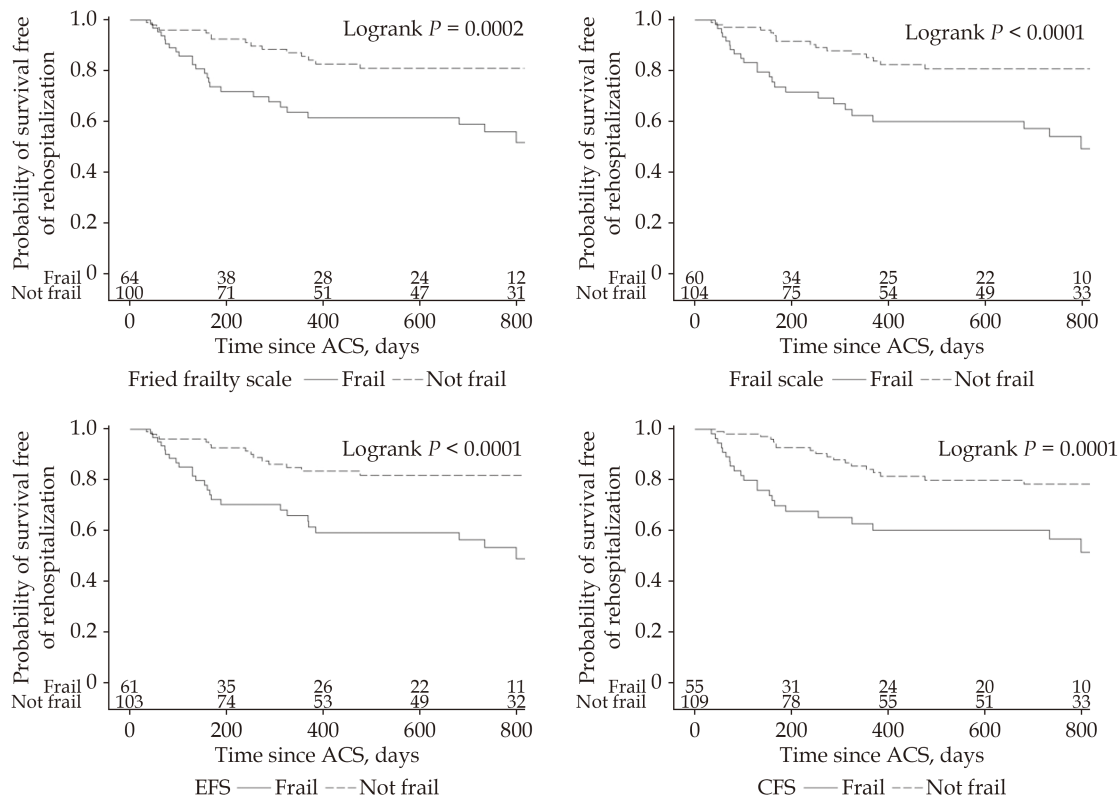
Figure 3   Kaplan–Meier curves. Survival free of unscheduled rehospitalization according to frailty status. ACS: acute coronary syndrome; CFS: Clinical Frailty Scale; EFS: Edmonton Frail Scale.

based on the judgment of the physician; thus, there is a component of subjective consideration. Frailty assessed by the CFS is strongly and independently associated with in-hospital, 1-month and 1-year mortality, increased length of stay in hospital and unscheduled rehospitalization in elderly patients with ACS.[28–33] The EFS is a moderately complex multidimensional scale, which is based on a series of basic questions and tasks. Similar to the Fried frailty scale, the EFS requires an interview and physical testing, and can only be conducted in stable, mobile patients. Frailty assessed by the EFS is a strong and independent prognostic factor for mid-term and long-term mortality in elderly patients presenting with ACS.[23,34,35] A comparison of the frailty assessment tools is presented in Table 4.

    Frail patients represent a group at high risk of mortality, morbidity and medical complications. Thus, recent studies and reviews have highlighted the importance of frailty assessment for better risk stratification in elderly patients with ACS. Knowledge of a patient's frailty status gives valuable information that may be useful in decision making regarding treatment strategy. At the same time, cur-

rent studies are limited. Most clinical trials exclude this population; therefore, there are no guidelines from randomized controlled trials (RCTs) as to how and when frailty should be assessed, what scales are preferable, and how a frailty diagnosis should impact treatment (revascularization strategy, pharmacological treatment, rehabilitation).[11,13,14,36] Recommendations from the Geriatric Cardiology Section of the Spanish Society of Cardiology suggest the FRAIL scale or CFS to assess frailty in the acute phase of ACS, as they are simple and rapid to complete tools. By contrast, after the acute phase of ACS (24–48 hours after ACS onset), they suggest a more complete frailty assessment, with more extensive tools (e.g., the Fried frailty scale or the EFS).[14] Furthermore, Walker, *et al*.[36], in a paper from the Acute Cardiovascular Care Association, recommend the CFS as a generally useful tool to assess frailty at the time of an acute cardiovascular admission because of its practical use in the acute settings; however, the authors do not specify which tool is most useful in ACS patients.

    In the current study, the adjusted HR of the FRAIL scale for all-cause mortality was the highest

Table 4 Comparison of the frailty assessment tools.[14]

	Evidence for usefulness in ACS	Physical test	Easy and fast to perform	Objective assessment	Practical in the cardiac care unit
Fried frailty scale	+	+	-	+	-
Edmonton frail scale	+	+	-	+	-
Frail scale	+	-	+	+	+
Clinical frailty scale	+	-	+	-	+

ACS: acute coronary syndrome.

among the scales used, whereas the EFS turned out to be an independent predictor of unscheduled rehospitalization. These data should be taken into consideration when choosing a frailty assessment tool in elderly patients hospitalized in a CCU with ACS. Considering mortality as the most important factor, the FRAIL scale seems to be the most prognostically valuable scale, and we suggest this scale should be favored in elderly (≥ 65 years) patients hospitalized in a CCU with ACS. Moreover, our study showed no differences in frailty identification between the FRAIL scale and more comprehensive scales like the Fried frailty scale and the EFS. Therefore, we suggest the FRAIL scale as a useful tool both during and after the acute phase of ACS. The FRAIL scale is simple to use and takes less than 2 min to complete. Thus, it might be an easy and practical tool for everyday use in a CCU.

LIMITATIONS

The current study has several limitations. First, it was a single-center, non-randomized study with a relatively small number of patients. In addition, there is no consensus on the optimal frailty assessment tool in patients with ACS. We chose to compare 4 frailty scales. The Fried frailty scale is one of the most common frailty screening tools used worldwide, with strong evidence of frailty identification. The EFS, the CFS and the FRAIL scale were chosen for their feasibility and practicality. However, there are several different, valid scales with evidence for usefulness in ACS. Further research, especially a RCT, is needed to indicate the optimal frailty scale for elderly patients with ACS.

CONCLUSIONS

The current study demonstrates that frailty assessed by the Fried frailty scale, the FRAIL scale, the EFS and the CFS is strongly associated with an increased risk of all-cause mortality and unscheduled rehospitalization in an elderly population with ACS. Compared to the other scales, the FRAIL scale, turned out to have the best prognostic value and it may be a favored tool for elderly ACS patients in a CCU. However, the EFS better predicts unscheduled rehospitalization.

Acknowledgments

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