ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2022) **11**, 89–98
https://doi.org/10.1093/ehjacc/zuab114

ORIGINAL SCIENTIFIC PAPER
Acute Coronary Syndromes

Clinical Frailty Scale classes are independently associated with 6-month mortality for patients after acute myocardial infarction

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Received 24 August 2021; revised 9 November 2021; editorial decision 12 November 2021; accepted 19 November 2021; online publish-ahead-of-print 14 December 2021

Aims Data on the prognostic value of frailty to guide clinical decision-making for patients with myocardial infarction (MI) are scarce. To analyse the association between frailty classification, treatment patterns, in-hospital outcomes, and 6-month mortality in a large population of patients with MI.

Methods and results An observational, multicentre study with a retrospective analysis of prospectively collected data using the SWEDEHEART registry. In total, 3381 MI patients with a level of frailty assessed using the Clinical Frailty Scale (CFS-9) were included. Of these patients, 2509 (74.2%) were classified as non-vulnerable non-frail (CFS 1–3), 446 (13.2%) were vulnerable non-frail (CFS 4), and 426 (12.6%) were frail (CFS 5–9). Frailty and non-frail vulnerability were associated with worse in-hospital outcomes compared with non-frailty, i.e. higher rates of mortality (13.4% vs. 4.0% vs. 1.8%), cardiogenic shock (4.7% vs. 2.5% vs. 1.9%), and major bleeding (4.5% vs. 2.7% vs. 1.1%) (all $P < 0.001$), and less frequent use of evidence-based therapies. In Cox regression analyses, frailty was strongly and independently associated with 6-month mortality compared with non-frailty, after adjustment for age, sex, the GRACE risk score components, and other potential risk factors [hazard ratio (HR) 3.32, 95% confidence interval (CI) 2.30–4.79]. A similar pattern was seen for vulnerable non-frail patients (fully adjusted HR 2.07, 95% CI 1.41–3.02).

Conclusion Frailty assessed with the CFS was independently and strongly associated with all-cause 6-month mortality, also after comprehensive adjustment for baseline differences in other risk factors. Similarly, non-frail vulnerability was independently associated with higher mortality compared with those with preserved functional ability.

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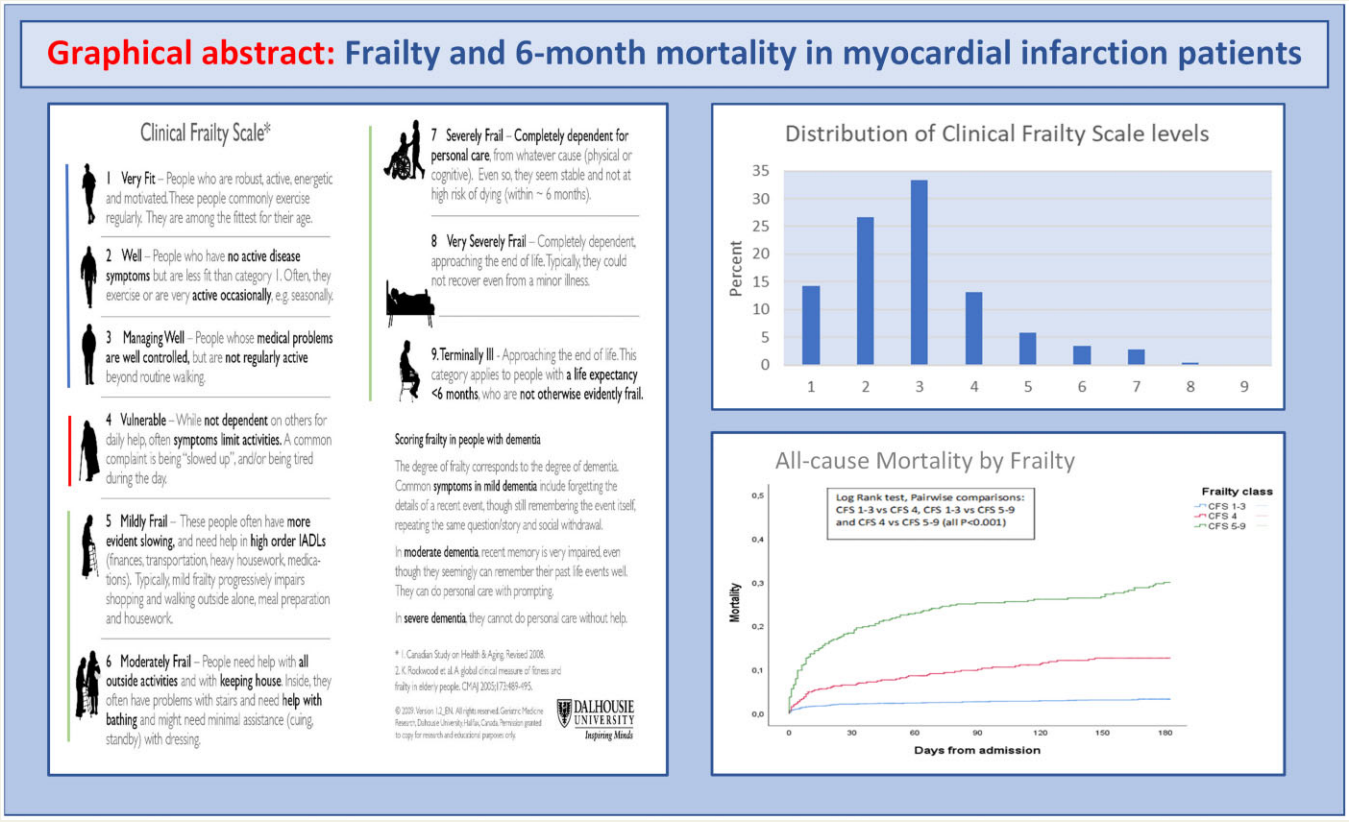
Graphical Abstract



The Clinical Frailty Scale (CFS) is reproduced with permission from Professor Kenneth Rockwood.

Keywords Myocardial infarction • Clinical Frailty Scale • Risk prediction • Mortality

Introduction

Worldwide, there is a large and growing group of older individuals, including patients with complex needs. The most common diagnostic category among these individuals is cardiovascular disease.[1] The present clinical guidelines, based primarily on randomized clinical trials (RCTs) and systematic reviews, focus on the treatment of defined organ-specific diagnoses, e.g. myocardial infarction (MI). These recommendations are based on studies of populations with generally low risk, challenging their applicability to individuals with multiple or severe comorbidities or frailty.[2,3] The problem does not appear to be minor, given that approximately 50% of all MIs occur in patients who are over the age of 75 years, of whom a large proportion are diagnosed with comorbidities.[3]

Consecutive annual reports from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry illustrate the problem in real-world patients with a considerable proportion of older adults. Compared with younger patients, older adults receive considerably less pharmacological and invasive treatment after an MI and with a very large variation between hospitals.[4] For example, the proportion of non-ST-elevation myocardial infarction (NSTEMI) patients over the age of 80 undergoing coronary angiography within 3 days ranges from 20% to 90% between hospitals.

Guidelines and statements regarding the treatment of heart disease have emphasized that the patient's biological age, i.e. the expected remaining life years based on biological status, not the date of birth, is crucial for decision-making.[5–7] The term *frailty* denotes a multi-dimensional syndrome characterized by increased vulnerability and reduced physiological reserves,[8,9] which may be used as a marker of biological age, distinct from chronological age. There are several different instruments for frailty assessment, but the Canadian Study of Health and Ageing (CSHA) Clinical Frailty Scale (CFS) is probably the most commonly used in an acute care context.[7,9,10]

Frailty instruments have been advocated as relevant for risk stratification, especially in elderly patients with NSTEMI.[8,11–14] We previously reported the importance of frailty for short-term (1 month), medium-term (1 year), and long-term (>5 years) outcomes in a relatively small NSTEMI population[9,16] over the age of 75 years. However, published data on the prognostic value of frailty, its capacity to predict adverse outcomes including complications and the

potential to guide clinical decision-making for patients with MI are scarce, and much larger studies are needed.[10]

Aims

To analyse the association between frailty classification, treatment patterns, in-hospital outcomes, and 6-month mortality in a large population of patients with MI. We hypothesized that frailty (CFS 5–9) and non-frail vulnerability (CFS 4), using the CFS instrument, was independently associated with 6-month mortality.

Methods

Study population and data sources

For the current analysis, we used data prospectively collected from the SWEDEHEART registry, a nationwide quality registry, collecting information on patients hospitalized with suspected MI in accordance with the fourth universal definition of MI[11]: individual patient demographics, medical history, medications before admission, management during hospital stay, treatment at discharge, and final diagnoses. Information on mortality was obtained from the Swedish population registry, a nationwide registry with information on vital status for all Swedish residents. For details of the registry, see the website (http://www.ucr.uu.se/swedeheart/). The SWEDEHEART registry is regularly monitored, with over 95% agreement between registered information and the patients' medical records.[12]

On 1 November 2017, the 9-level version of CFS (CFS-9) was introduced in the SWEDEHEART registry at five pilot hospitals and was later made a mandatory variable at all hospitals on 1 January 2020. For the current analysis, we included all patients with MI and a registered level of frailty between 1 November 2017 and 31 December 2019 from the pilot hospitals (three university hospitals and two county hospitals). There were no exclusion criteria, other than the absence of a Swedish unique 12-digit personal identification number, to ensure complete follow-up.

Data collection and variable selection

The CFS is a 9-level scale (CFS-9, version 1.2) derived from the accumulated deficit model of frailty, and it has been validated against the Frailty Index[13] (Supplementary material online, *Figure S1*). It provides a simple, global, clinical measure of biological age, combining the degree of illness, comorbidity, disability, and cognitive impairment. In a position paper from the Acute Cardiovascular Care Association [European Society of Cardiology (ESC)], the CFS was proposed to be probably the most useful available measurement of frailty acutely.[14] It has shown good predictive validity and prognostic power and is easy to use in clinical practice.[15,10,20] In a previous study, the performance of the CFS (for prediction of 30-day mortality in emergency department patients 65 years or older) was reported as the area under the curve at 0.81 [95% confidence interval (CI) 0.77–0.85].[16]

The evaluation of the patients' level of frailty was based on a bedside judgement undertaken by the registered nurses regarding frailty and other clinical information including the records in the patient file. The instruction was to reflect the level of frailty 2 weeks before hospitalization to avoid assessed declines due to the hospitalization itself.

In order to assess frailty in a Swedish context with the CFS-9 scale, a rigorous translation process was undertaken based on relevant translation methodology.[17,22] The inter-rater reliability regarding trained nurses' judgement of frailty using the CFS has been previously described as very good.[18]

Prior to the data collection, a manual and an instruction film on the frailty assessment using the CFS, both developed by a focus group including cardiology and geriatric expertise, were developed and shared with regional centres. Five trained SWEDEHEART nurses functioned as support to the local collection of CFS data.

The investigators focused on characteristics likely to be potential confounders when testing the hypothesis such as chronological age, sex, cardiovascular risk score, diabetes, heart failure, renal insufficiency, other comorbidities, previous MI, medications, ejection fraction, and MI type [i.e. ST-elevation myocardial infarction (STEMI) or NSTEMI]. The results from echocardiography, electrocardiograms, laboratory testing, and the registration of anthropometric data were included, according to routine practice within the SWEDEHEART registry.

Clinical outcomes

The primary outcome was death from any cause over 6 months after inclusion. The follow-up time was chosen to harmonize with the well-established and recommended GRACE score. Secondary outcomes were treatment patterns including medications, invasive strategies before discharge, and adverse in-hospital outcomes [i.e. major bleeding, re-infarction and cardiogenic shock (CS)].

Ethics

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version. The study was undertaken after full approval of the protocol and its appendices by the Swedish ethical review authority (D.no. 2020-01708). The study was registered at www.clinicaltrials.gov, ID: NCT04488536.

In accordance with Swedish legislation, patients are informed about their participation and their right to refuse participation or have their data removed, waiving the requirement for individual written informed consent. The checklist of the Strengthening the reporting of observational studies in epidemiology (STROBE) statement was followed.

Statistics

An intraclass correlation test showed that the inter-rater reliability for the CFS classification was excellent [intraclass correlation one-way random absolute agreement (12 cases, 40 raters), single measurement: 0.96; 95% CI 0.93–0.98%]. An intraclass correlation coefficient above 0.90 has previously been defined as indicating an excellent degree of agreement between the raters.[19]

Patients were classified in accordance with their CFS level into three strata: 1–3 (very fit, well, and managing well), 4 (vulnerable), and 5–9 (frail). This classification was based on previous data on the prognostic power of the different frailty levels in a broader clinical context.[20,24,25] Continuous variables are presented as the mean and standard deviation or as the median and interquartile range and categorical variables are presented as counts and percentages. Categorical data were compared using the χ^2 test or Fisher's exact test, while continuous data were compared by using Student's *t*-test or the Mann–Whitney *U* test, depending on whether the variable was normally distributed or not. A *P*-value of <0.05 denotes significance.

With few exceptions, covariates included in the multivariable analyses had a low rate of missing. Left ventricular function had 7.8% missing, smoking 4.5%, Killip class on arrival 3.0%, and haemoglobin 3.0%, while all the other variables had less than 1% missing. Missing values were assumed to be missing at random. A multiple missing values imputation was performed, generating five datasets. Outcome analyses were performed on a pooled dataset.

We used Cox proportional hazard survival analysis to adjust for differences in baseline characteristics between the three CFS classes. Outcomes are presented as hazard ratios (HRs) and 95% CIs. In the first model, frailty was the sole explanatory variable. In the second model, age and sex were added. In the third model, all variables in the GRACE in-hospital and 6-month risk scores[21,27] (systolic blood pressure, heart rate, initial serum creatinine, ST-segment deviation, Killip class, cardiac arrest on arrival, an invasive strategy during index hospitalization, previous left ventricular dysfunction, and history of MI) were added. Finally, in a fourth model, other comorbid conditions not included in the GRACE score [current smoking, previous hypertension, diabetes mellitus, stroke, previous percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG)] and acute MI complications [cardiopulmonary resuscitation (CPR) and CS on arrival and during hospital stay] were added.

In a sensitivity analysis limited to patients discharged alive, evidence-based medications at discharge were entered (aspirin, P2Y12-inhibitor, angiotensin-converting enzyme (ACE)-inhibitor, angiotensin receptor blocker, and beta-blocker). We used non-frail patients as a reference to compare vulnerable non-frail (CFS 4) and frail (CFS 5–9) patients. The assumption of proportional hazard was reviewed by visual inspection of the Kaplan–Meier curves with no sign of violation. Subgroup analyses were performed, including testing for interaction regarding age (>75 years or not) and sex. Statistical analysis was performed using SPSS software, release 23.0 (SPSS Inc).

Results

The study population comprised 3381 MI patients with a registered level of frailty using the CFS identified in the SWEDEHEART registry between November 2017 and December 2019, *Figure 1*.

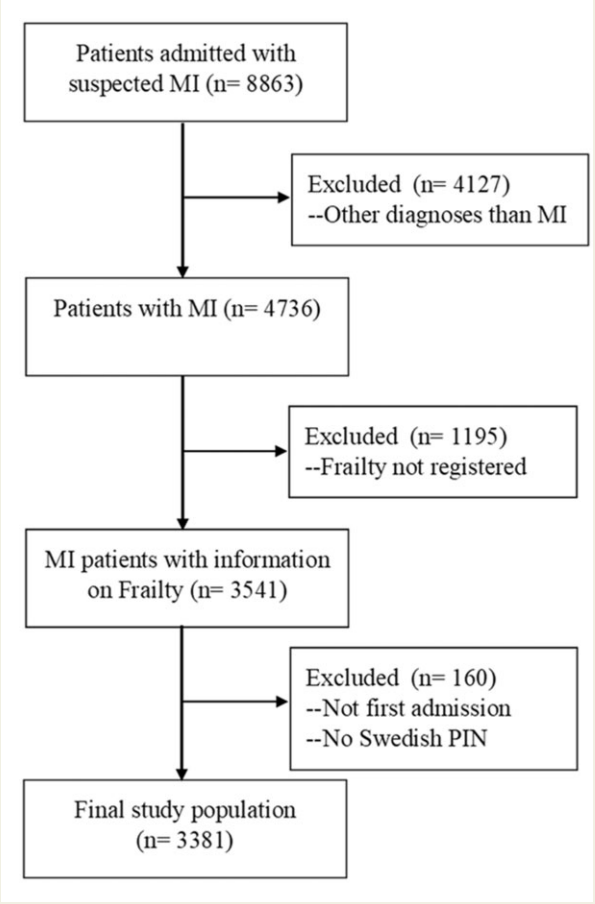


Figure 1 Flow chart.

Of these patients, 2509 (74.2%) were classified as non-frail and non-vulnerable (CFS 1–3), 446 (13.2%) were classified as vulnerable non-frail (CFS 4) and 426 (12.6%) were classified as frail (CFS 5–9). The distribution of patients aged >75 years and ≤75 years by registered level of frailty using the CFS is shown in Supplementary material online, *Figure S2*.

The baseline characteristics are presented in *Table 1*. Frail patients were more often female and older than non-frail patients, with a mean age of 82 years in frail patients, 77 years in vulnerable non-frail patients, and 67 years in non-frail patients ($P < 0.001$). Frail patients presented with a greater burden of comorbidity, including higher rates of diabetes mellitus, hypertension, cerebrovascular disease, previous MI, and previously diagnosed reduced left ventricular ejection fraction (all $P < 0.05$). There were no differences regarding rates of CPR and CS before hospital admission between the groups ($P > 0.05$). Information on missing in baseline characteristics is shown in Supplementary material online, *Table S1*.

Observations, diagnostic measurements, and treatment during hospital stay are presented in *Table 2*. A larger proportion of NSTEMI was reported in frail and vulnerable patients compared with non-frail patients. Regarding laboratory data, frail patients manifested higher levels of creatinine, glucose and C-reactive protein, and lower haemoglobin values compared with non-frail patients. A larger proportion of the frail patients had a reduced left ventricular ejection fraction during hospital stay compared with the non-frail patients ($P < 0.05$). Frailty was associated with less frequent use of coronary angiography and revascularization (PCI and CABG) (all $P < 0.001$). At discharge, a lower proportion of frail patients were prescribed aspirin, potent P2Y12-inhibitors, ACE-inhibitors/A2-blockers, and statins ($P < 0.05$). There was no difference between the groups regarding prescribed beta-blockers ($P = 0.52$), whereas there was a higher proportion of prescribed clopidogrel, anticoagulants, diuretics, and diabetes drugs in frail patients ($P < 0.001$).

In-hospital outcomes are presented in *Table 3*. Frailty was associated with higher rates of in-hospital mortality, CS, major bleeding, and a longer duration of hospital stay (all $P < 0.001$) but not re-infarction ($P = 0.89$). The primary outcome measure, 6-month mortality, occurred in 122 (29.9%) frail patients, in 54 (12.6%) vulnerable non-frail patients, and in 79 (3.3%) non-frail patients without vulnerability (log-rank test $P < 0.001$) assessed by Kaplan–Meier estimates, *Figure 2*.

In Cox regression analyses, frailty was independently associated with 6-month mortality, after adjustment for age and sex (HR 5.85, 95% CI 4.24–8.09) compared with non-frailty. Further adjustment with the GRACE cardiovascular risk score components (HR 3.29, 95% CI 2.32–4.67) and GRACE score plus other potential confounders including medical history and acute MI complications confirmed the result (HR 3.32, 95% CI 2.30–4.79). A similar pattern was seen for vulnerable, non-frail patients. After adjustment for age and sex, vulnerability was associated with 6-month mortality with an HR of

Table 1 Baseline patient characteristics

CFS level	Non-frail (CFS 1–3)	Vulnerable non-frail (CFS 4)	Frail (CFS 5–9)	*P*-value
Patients, *n*	2509	446	426	
Demographics				
Age, years, median, (IQR)	67 (16)	77 (13)	82 (13)	<0.001
Age groups				
≤59 years	691 (27.5)	33 (7.4)	13 (3.1)	<0.001
60–69 years	737 (29.4)	69 (15.5)	42 (9.9)	
70–79 years	746 (29.7)	151 (33.9)	126 (29.6)	
≥80 years	335 (13.4)	193 (43.3)	245 (57.5)	
Female sex	610 (24.3)	178 (39.9)	206 (48.4)	<0.001
BMI, median, (IQR)	26.8 (5.4)	26.7 (6.2)	25.4 (6.5)	<0.001
Medical history				
Current smoker	531 (21.9)	78 (18.4)	48 (12.6)	<0.001
History of diabetes mellitus	478 (19.1)	133 (29.9)	141 (33.1)	<0.001
History of hypertension	1309 (52.3)	325 (73.2)	326 (76.9)	<0.001
Previous stroke	76 (3)	53 (11.9)	85 (20)	<0.001
Previous MI	428 (17.1)	161 (36.2)	163 (38.6)	<0.001
Previous PCI	354 (14.1)	123 (27.6)	103 (24.3)	<0.001
Previous CABG	124 (5)	54 (12.1)	46 (10.8)	<0.001
Previously known reduced LVEF				
Slightly reduced (40–49%)	72 (2.9)	35 (8.2)	35 (8.5)	<0.001
Moderately reduced (30–39%)	31 (1.3)	16 (3.7)	31 (7.5)	
Severely reduced (<30%)	9 (0.4)	10 (2.3)	18 (4.4)	
Findings and status on admission				
CPR (out of hospital)	81 (3.2)	8 (1.8)	8 (1.9)	0.11
Cardiogenic chock (admission)	29 (1.2)	7 (1.6)	10 (2.3)	0.13
Cause of admission				
Chest pain	2299 (91.6)	360 (80.7)	295 (69.2)	<0.001
Dyspnoea	79 (3.1)	46 (10.3)	59 (13.8)	
Cardiac arrest	54 (2.2)	5 (1.1)	7 (1.6)	
Other	77 (3.1)	35 (7.8)	65 (15.3)	
Systolic blood pressure (mean, SD)	149 (27.3)	148 (31.3)	137 (30.7)	<0.001
Heart rate (median, IQR)	76 (24)	81 (28)	87 (29)	<0.001
Medications at admission				
Aspirin	571 (22.8)	199 (44.6)	161 (38)	<0.001
Other platelet inhibitor	108 (4.3)	44 (9.9)	48 (11.4)	<0.001
Oral anticoagulation	153 (6.1)	83 (18.7)	100 (24)	<0.001
Beta-blocker	642 (25.6)	215 (48.4)	235 (55.6)	<0.001
ACE-I or ARB	860 (34.4)	206 (46.3)	190 (44.9)	<0.001
Statin	632 (25.3)	185 (41.5)	165 (39)	<0.001
Diabetes drug (oral)	315 (12.6)	76 (17)	64 (15)	0.06
Diabetes drug (insulin)	191 (7.6)	77 (17.3)	88 (20.7)	<0.001
Diuretic	271 (10.8)	150 (33.6)	167 (39.2)	<0.001

Results are presented as numbers and percentages unless otherwise indicated.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CFS, Clinical Frailty Scale; CPR, cardiopulmonary resuscitation; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

2.66 (95% CI 1.85–3.82). The result was confirmed after adjustment for GRACE score variables (HR 2.09, 95% CI 1.45–3.03) and full adjustment for baseline differences (HR 2.07, 95% CI 1.41–3.02), *Figure 3*.

In a sensitivity analysis restricted to patients discharged alive, evidence-based discharge medication was added to the adjustment model, with similar and consistent results. Both frailty (HR 3.38, 95% CI 2.03–5.65) and vulnerability (HR 2.64, 95% CI 1.60–4.35) were

Table 2 Observations, diagnostic measures and treatment actions during hospitalization

CFS level	Non-frail (CFS 1–3)	Vulnerable non-frail (CFS 4)	Frail (CFS 5–9)	*P*-value
Patients, *n*	2509	446	426	
Type of MI				
NSTEMI	1321 (52.7)	293 (65.7)	281 (66)	<0.001
STEMI	1188 (47.3)	153 (34.3)	145 (34)	<0.001
Interventions				
Coronary angiography	2427 (96.7)	360 (80.7)	251 (58.9)	<0.001
PCI	2121 (84.5)	293 (65.7)	209 (49.1)	<0.001
CABG	188 (7.5)	22 (4.9)	8 (1.9)	<0.001
Laboratory parameters				
CRP (median, IQR)	4.3 (4.5)	5 (13.6)	10 (34)	<0.001
Glucose (median, IQR)	7 (3)	7.4 (3.4)	7.8 (4.5)	<0.001
Creatinine (median, IQR)	82 (26)	90 (41.3)	97 (63)	<0.001
GFR (CG) (median, IQR)	79 (37.9)	60.3 (42.8)	46.7 (35.3)	<0.001
Haemoglobin (mean, SD)	141.4 (15.6)	132.5 (18)	124.5 (20)	<0.001
Killip classification				
Killip 1	2293 (94.1)	368 (84.4)	311 (77)	<0.001
Killip 2	66 (2.7)	41 (9.4)	59 (14.6)	
Killip 3	16 (0.7)	11 (2.5)	9 (2.2)	
Killip 4	63 (2.6)	16 (3.7)	25 (6.2)	
LVEF				
Normal	1483 (62.7)	193 (47.5)	137 (39.7)	<0.001
Slightly reduced (40–49%)	566 (23.9)	103 (25.4)	84 (24.3)	
Moderately reduced (30–39%)	249 (10.5)	74 (18.2)	75 (21.7)	
Severely reduced (<30%)	68 (2.9)	36 (8.9)	49 (14.2)	
Medications at discharge				
Aspirin	2340 (94.9)	375 (87.6)	283 (76.7)	<0.001
Clopidogrel	391 (15.9)	147 (34.3)	148 (40.1)	<0.001
Potent ADP-I[a]	1790 (72.7)	187 (43.7)	111 (30.1)	<0.001
Anticoagulation	329 (13.4)	119 (27.9)	128 (34.7)	<0.001
Beta-blocker	1993 (80.9)	355 (82.9)	304 (82.4)	0.52
ACE-I or ARB	1973 (80.1)	337 (78.7)	249 (67.5)	<0.001
Statin	2365 (95.9)	369 (86.2)	281 (76.4)	<0.001
Diabetes drug. oral	335 (13.4)	74 (16.6)	49 (11.5)	<0.001
Diabetes drug. insulin	205 (8.2)	71 (15.9)	72 (16.9)	<0.001
Diuretic	334 (13.3)	165 (37)	180 (42.3)	<0.001
Aldosterone inhibition	216 (8.8)	74 (22.1)	45 (12.2)	<0.001

Results are presented as numbers and percentages unless otherwise indicated.
A2-blocker, angiotensin receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; ADP-I, adenosine diphosphate receptor inhibitor; CABG, coronary artery bypass grafting; CFS, Clinical Frailty Scale; CG, Cockcroft–Gault; CRP, C-reactive protein; GFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
[a]Ticagrelor in >99% of potent ADP-I.

independently associated with 6-month mortality compared with non-frailty (CFS 1–3).

Kaplan–Meier estimates after stratification for age (>75 years and ≤75 years) and frailty classification (frail, vulnerable, and non-frail) are shown in Supplementary material online, *Figure S3*. A tripled risk of mortality was observed in frail patients aged ≤75 years compared with non-frail patients aged >75 years. We performed three subgroup analyses. The risk associated with frailty and vulnerability was similar in women and men (*P*-value for interaction 0.46 and 0.95, respectively), in patients older than 75 years or younger (*P*-value for interaction 0.15 and 0.89, respectively) and in patients with STEMI or NSTEMI (*P*-value for interaction 0.72 and 0.83, respectively), Supplementary material online, *Table S2*. Among frail patients, there were longer delays from symptom presentation to PCI compared with non-frail patients, see Supplementary material online, *Table S3*. The characteristics of patients with missing CFS data are summarized side-by-side with those with available CFS data, Supplementary material online, *Table S4*.

Table 3 In-hospital outcomes

CFS level	Non-frail (CFS 1–3)	Vulnerable non-frail (CFS 4)	Frail (CFS 5–9)	*P*-value
Patients, *n*	2509	446	426	
Death	44 (1.8)	18 (4.0)	57 (13.4)	<0.001
Cardiogenic shock	47 (1.9)	11 (2.5)	20 (4.7)	<0.001
Re-infarction	9 (0.4)	2 (0.4)	1 (0.2)	0.87
Major bleeding	27 (1.1)	12 (2.7)	19 (4.5)	<0.001
Duration of stay, days, median (IQR)	3 (2)	4 (4)	5 (5)	<0.001

Results are presented as numbers and percentages unless otherwise indicated.
CFS, Clinical Frailty Scale; IQR, interquartile range.

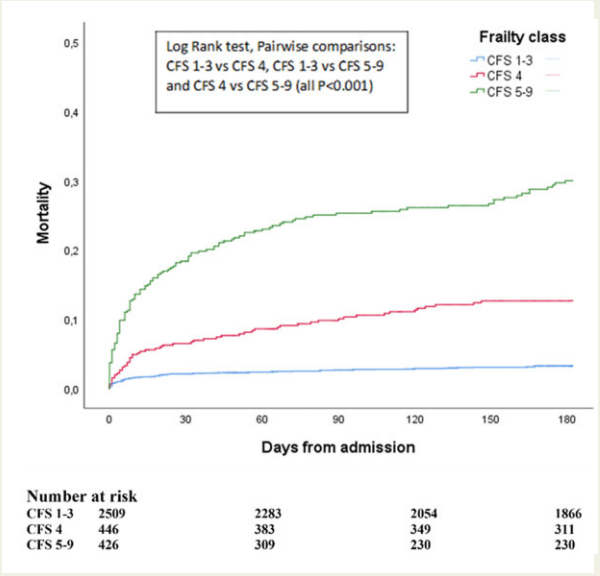


Figure 2 Kaplan–Meier. Association between Clinical Frailty Scale and all-cause mortality.

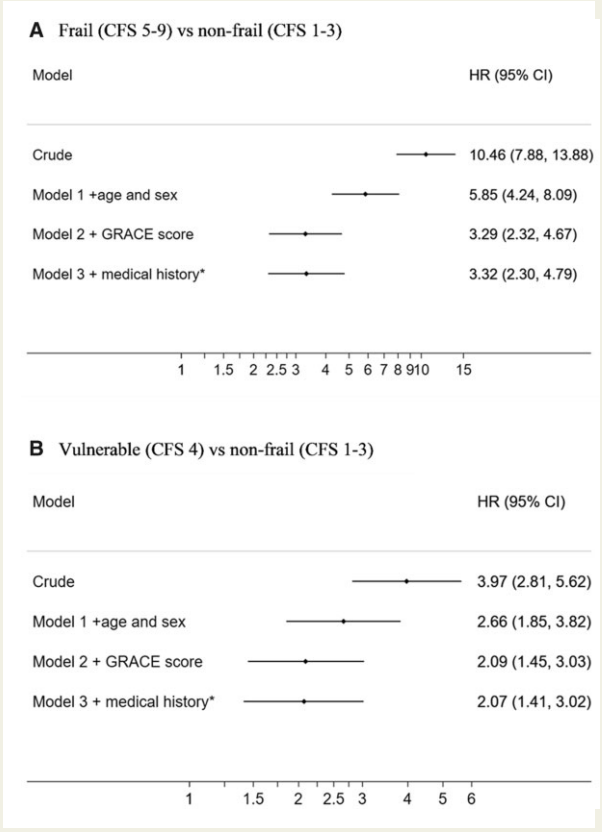


Figure 3 Forest plot. Adjusted association between assessed levels of the Clinical Frailty Scale (CFS) and all-cause 6-month mortality. (*A*) Frail patients (CFS 5–9) vs. non-frail (CFS 1–4) and (*B*) vulnerable patients (CFS 4) vs. non-frail (CFS 1-3) are shown. [a]Medical history denotes other comorbid conditions not included in the GRACE score (current smoking, previous hypertension, diabetes mellitus, stroke, previous percutaneous coronary intervention, and coronary artery bypass graft surgery) and acute myocardial infarction complications (cardiopulmonary resuscitation and cardiogenic shock on arrival and during hospital stay).

Discussion

To our knowledge, this is the first large study to demonstrate that both frailty and vulnerability add important prognostic information beyond a well-established prognostic risk score in patients with MI. Frailty and vulnerability, assessed with the CFS, were independently and strongly associated with all-cause mortality, with curves diverging after discharge and continuing over 6 months of follow-up. A more than triple risk of mortality was observed in frail patients, while the risk in vulnerable non-frail patients was more than double that in non-frail patients. The risk remained significant after comprehensive adjustment for other prognostic factors.

The result was consistent in men and women and in patients older than 75 years or younger, implying good generalizability of the study results. With functional assessments, using an easily applied tool, it is possible to identify those at greatest risk of mortality over follow-up. One-eighth of the population was frail and these patients were older than non-frail patients and presented with a greater burden of comorbidity and a higher cardiovascular risk score. Similarly, approximately one-eighth of the population was assessed as CFS level 4, denoting vulnerable non-frail patients, and these were more ill than

the non-frail patients. There were more reported bleeds and longer hospitalizations during the index hospital stay among the frail patients.

Frailty was associated with a lower use of coronary angiography, PCI and CABG and, at discharge, a smaller proportion of frail patients were prescribed medications recommended in evidence-based guidelines. These observations are in line with previous studies[22,23,26] and could be seen as either a consequence of the inappropriate underuse of evidence-based therapies for frail elderly patients or a reasonable and more conservative strategy for elderly patients in the absence of firm evidence.[23,28–30] Importantly, also after adjustment for an invasive strategy, and including discharge medication in a second analysis, the mortality risk associated with vulnerability and frailty, respectively, persisted.

Among frail patients, there were longer delays from symptom presentation to PCI compared with non-frail patients. Moreover, among frail patients, dyspnoea and unspecific symptoms were more common as initial symptoms compared with non-frail patients. Conversely, chest pain was not as common among frail patients as among non-frail patients. These findings might partly be explained by the fact that the proportions of women and older adults were higher among frail patients. The difference between groups in clinical presentation and the delay to admission and reperfusion might explain part of the differences in outcomes.

The results of our study harmonize with the results of earlier, smaller studies, in which frailty has been reported to be independently associated with short-, mid-, and long-term outcomes for older NSTEMI patients.[24,16,25,25,28,29,31] Similarly, the results are in line with a previous larger study, in which frailty, assessment based on clustering of diagnoses, long hospital stay (>10 days in hospital), and emergency readmission within 30 days of discharge, i.e. administrative data, was associated with all-cause mortality within 30 days of the date of admission.[26] Importantly, in our study, the CFS level 4 was also associated with a significantly worse prognosis compared with CFS levels 1–3, which might be of particular clinical relevance in a prevention context, where the early identification of potentially reversible frailty is of utmost importance. This is in line with the updated CFS version (2.0), in which level 4 ('vulnerable') has been redefined as 'living with very mild frailty'.[27] Scientific statements from the ESC and the American Heart Association (AHA) have stressed that the assessment of frailty and comorbidity is crucial when older patients with acute coronary syndromes are managed.[28,6] A previous, smaller study indicated that information on frailty level improves the discriminatory ability of risk scores, which have been derived from routine cardiovascular parameters,[29] which is confirmed in our much larger study.

The use of the CFS is not particularly time-consuming and is easy to implement in daily clinical practice. It is a global measurement of prior home function and is not prone to declines due to the hospitalization itself or limitations in measurement accuracy as an inpatient. To our knowledge, there are no better validated instruments than the CFS when it comes to the accumulated deficit model of frailty, designed for risk prediction.[30] The CFS may also be used for purposes other than risk prediction, i.e. as a screening instrument in order to identify frail patients suitable for further geriatric evaluation, i.e. a comprehensive geriatric assessment (CGA), in which CFS level 4 might be of particular interest. Frailty does not equate with a desire not to be treated. For older adults with severe frailty, indicating a very poor prognosis, effective symptom management is crucial. However, the potential adverse effects of many interventions are immediate, whereas the benefits of preventive interventions accumulate over time. Hence, it is reasonable that clinical priorities and decision-making vary to some extent with life expectancy. In this respect, some therapies, e.g. CABG, might be futile for individual patients with severe frailty, i.e. high biological age.

To illustrate the importance of frailty, a proxy for biological age, in relation to chronological age, in this analysis, a higher risk of mortality was observed in frail patients aged ≤75 years compared with non-frail patients aged >75 years. For this reason, without frailty, even older adults may have a good prognosis and should be managed accordingly.

Information on long-term prognosis may substantially improve informed decision-making on an individual basis, in elderly patients with MI, where the best available evidence, clinical expertise and patient preferences are integrated. Frailty, as assessed with the CFS, adds important predictive value to the previously advocated and well-established GRACE risk score, which is in line with the results of a previous study.[31] Clinical Frailty Scale assessment may be useful to individually tailor treatment regarding benefits and risks, thereby improve outcomes. However, more research is needed concerning outcomes of different intervention strategies in different frailty strata.

A broader adoption and implementation of the frailty concept in routine cardiovascular clinical practice is warranted. This includes the use of frailty as a risk marker and a condition which should trigger a CGA, in an effort to identify older patients at risk of adverse events and secure rapid follow-up and individualized rehabilitation. We also believe that registries should be further adapted for these patients, including frailty assessments, which has been previously stated.[32]

Limitations

First, quality of life (QoL) and burden of symptoms were not measured. We acknowledge the importance of QoL as an outcome measurement, although life expectancy is of importance for decision-making in an elderly population. In a future study, elderly MI patients should be assessed using an established and validated QoL instrument to inform care. Second, there are no data on post-discharge changes in medication for the patients included in the study, e.g. in primary care. However, given the relatively short follow-up period, it does not seem probable that changes in medications would have had a substantial impact on outcomes. Third, although we adjusted for numerous confounders, unmeasured residual confounding cannot be ruled out. Finally, one-fourth of the patients were not assessed with the CFS and excluded from analysis. A rough non-response analysis showed that these patients were older, had and a larger burden of comorbidity compared with patients with registered CFS. This observation might suggest that these patients would have been assessed with higher CFS scores than non-frail patients. We do not have information on specific reasons for not including these patients. However, most previous risk scores are derived from RCTs, which often exclude a large majority of the whole population.[33] Furthermore, we were unable to account for all relevant non-cardiac medical

problems, since the SWEDEHEART registry only collects a selected set of non-cardiovascular comorbidities. We do not have the necessary data to complete a more structured assessment of comorbidity. However, adding medical history to the GRACE score, age and sex changed the prognostic value of CFS modestly. We recognize that analysis of cause of death might provide additional insight into the relationship between frailty and outcomes in patients with MI, but we are unable to conduct this analysis because of the absence of these data in SWEDEHEART. In addition, we believe all-cause death is the most appropriate primary outcome to assess association with frailty.

Conclusions

In this large study of MI patients, frailty and non-frail vulnerability assessed with the CFS were independently and strongly associated with all-cause mortality. A more than tripled risk of mortality was observed in frail patients versus non-frail and more than doubled risk in vulnerable non-frail versus non-frail patients. The association persisted after adjustment for a well-known post-MI risk score adding global functional status to traditional post-MI risk indicators.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

Conflict of interest: none declared.

Acknowledgements

The authors acknowledge the important work of the coronary care nurses who performed the frailty assessments. The authors also thank Lars Dahlbom for educational efforts during the study period and the extraction of data from the SWEDEHEART register base.

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