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ORIGINAL ARTICLE
Coronary artery disease

Five-year clinical outcomes in patients with frailty aged ≥75 years with non-ST elevation acute coronary syndrome undergoing invasive management

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Aim Frailty is associated with adverse outcomes in older patients with acute coronary syndrome (ACS). The impact of frailty on long-term clinical outcomes following invasive management of non-ST elevation ACS (NSTEACS) is unknown.

Methods and results The multi-centre Improve Clinical Outcomes in high-risk patieNts with ACS 1 (ICON-1) prospective cohort study consisted of patients aged ≥75 years undergoing coronary angiography following NSTEACS. Patients were categorized by frailty assessed by Canadian Study of Health and Ageing Clinical Frailty Scale (CFS) and Fried criteria. The primary composite endpoint was all-cause mortality, unplanned revascularization, myocardial infarction, stroke, and bleeding. Of 263 patients, 33 (12.5%) were frail, 152 (57.8%) were pre-frail, and 78 (29.7%) were robust according to CFS. By Fried criteria, 70 patients (26.6%, mean age 82.1 years) were frail, 147 (55.9%, mean age 81.3 years) were pre-frail, and 46 (17.5%, mean age 79.9 years) were robust. The composite endpoint was more common at 5 years among patients with frailty according to CFS (frail: 22, 66.7%; pre-frail: 81, 53.3%; robust: 27, 34.6%, $P = 0.003$), with a similar trend when using Fried criteria (frail: 39, 55.7%; pre-frail: 72, 49.0%; robust: 16, 34.8%, $P = 0.085$). Frailty measured with both CFS and Fried criteria was associated with the primary endpoint [age and sex-adjusted hazard ratio (HR) compared with robust groups. CFS: 2.22, 95% confidence interval (CI) 1.23–4.02, $P = 0.008$; Fried: HR 1.81, 95% CI 1.00–3.27, $P = 0.048$].

Conclusion In older patients who underwent angiography following NSTEACS, frailty is associated with an increased risk of the primary composite endpoint at 5 years.

Registration: Clinicaltrials.gov NCT01933581

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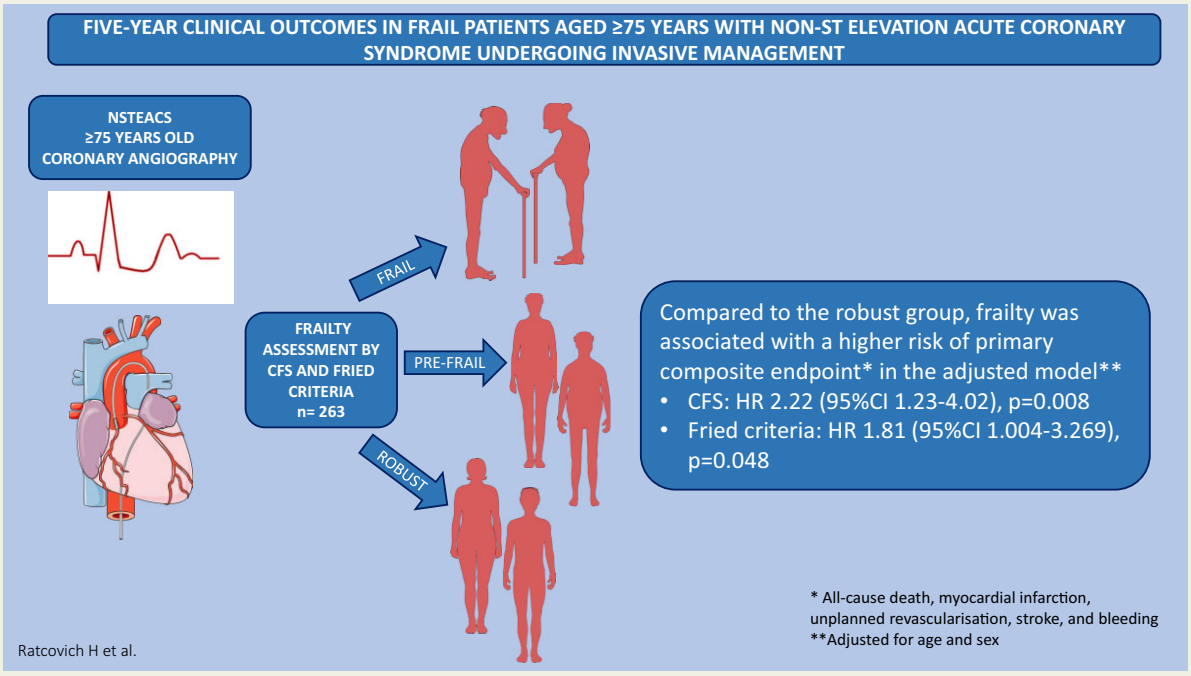
Graphical Abstract



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Keywords Frailty • Ageing • Acute coronary syndrome • NSTEACS

Introduction

Cardiovascular disease is common in older adults, who comprise a large and increasing proportion of the population,[1] and in whom cardiovascular risk factors are often under-recognized.[2] However, older people are often excluded from clinical trials,[3–5] which leads to a gap in evidence to guide the clinical management of older patients with acute coronary syndrome (ACS).[6] Age is an established risk factor for ACS, and older people more commonly present with non-ST elevation ACS (NSTEACS)[7] and are more likely to live with frailty than younger adults. Frailty describes a loss of biological resilience to stressors and is increasingly recognized as an important factor in the management of older people with cardiovascular disease.[8,9]

Previous studies have shown that older patients with NSTEACS have a high prevalence of undiagnosed cognitive impairment, which is associated with recurrent myocardial infarction (MI).[10] After ACS, patients living with frailty tend to have longer hospital stays, less often receive coronary angiography,[11,12] and have a higher 1-year mortality rate compared with those without frailty.[13] However, in patients that survive to 1 year after invasive treatment of NSTEACS, those that are frail or pre-frail report a proportionally larger improvement in health-related quality of life than robust patients.[14] Although those with frailty tend to have more severe angiographic disease,[15] frailty is not associated with a reduction in the short-term procedural success of percutaneous coronary intervention (PCI).[16] Yet the impact of frailty on long-term clinical outcomes following invasive management of non-ST elevation ACS (NSTEACS) is unknown.[6,8] In this study, we report clinical outcomes of older patients 5 years after invasive management of NSTEACS, according to their frailty status at admission.

Methods

The study to Improve Clinical Outcomes in high-risk patieNts with ACS (ICON-1) is a multi-centre, prospective cohort study. The full protocol has previously been published.[17] The 5-year follow-up study was approved by the Research Ethics Committee (REC 12/NE/0160) and was conducted in accordance with the Declaration of Helsinki. Written, informed consent of all participants was obtained. The ICON-1 was prospectively registered with the United Kingdom Clinical Research Network (UKCRN; ID 12742) and ClinicalTrials.gov (NCT01933581).

Study population

Patients with NSTEACS and aged ≥75 years that were referred for invasive angiography at two high volume PCI centres: Freeman Hospital, Newcastle upon Tyne (receiving patients referred from six district hospitals) and James Cook University Hospital, Middlesbrough (receiving patients referred from five district hospitals) were recruited between November 2012 and December 2015. All patients underwent coronary angiography and received guideline-recommended management of NSTEACS. Patients were diagnosed based on clinical symptoms, electrocardiography criteria and high-sensitivity troponin testing, in line with contemporary NSTEACS guidelines.[18] Exclusion criteria were the presence of cardiogenic shock, primary arrhythmia, co-existing significant valvular heart disease, malignancy (with life expectancy ≤1 year), active

infection (pneumonia, urinary tract infection, or sepsis of other cause), and inability to provide informed consent (due to lack of capacity, visual impairment, or language difficulties). Patients with alternative diagnoses after angiography (Takotsubo cardiomyopathy, pulmonary embolism, myocarditis, and coronary vasospasm) were excluded.

Frailty assessments

Frailty was assessed using the Canadian Study of Health and Ageing Clinical Frailty Scale (CFS)[19] and the Fried criteria[20] by experienced members of the research team consisting of principal investigators, research fellows, and research nurses. The CFS reflects the clinician's scaled judgement of activities of daily living, comorbidity impact, and dependency. Scores 1–7 are graded from 'very fit' to 'severely frail' (see Supplementary material online, *Table S1A*). Patients with a CFS score of 1–2 were classified as robust, 3–4 as pre-frail, and 5–7 as frail. The Fried criteria includes self-reported weight loss, physical energy, and low physical activity, and an objective assessment of grip strength and walking speed (see Supplementary material online, *Table S1B*). A score of 0 is categorized as non-frail (robust), 1–2 as pre-frail (intermediate), and $\geq$3 as frail.

Baseline characteristics were reported by frailty category, including patient demographics, medical history [diabetes, hypertension, hypercholesterolaemia, renal impairment, previous MI, angina, previous coronary intervention, transient ischemic attack (TIA) or stroke, osteoarthritis or rheumatoid arthritis, peptic ulcer disease, chronic obstructive pulmonary disease (COPD)], findings at admission—heart rate, systolic blood pressure, left ventricular ejection fraction (LVEF), New York Heart Association Functional (NYHA) class, The Global Registry of Acute Coronary Events (GRACE) 2.0 score, Charlson comorbidity index (CCI), and Canadian Cardiovascular Society Angina score (CCS), creatinine, haemoglobin, peak Troponin, high-sensitivity C-reactive protein, non-ACS diagnosis, in-hospital treatment [PCI, coronary artery bypass graft (CABG), medical treatment only], angiographic procedure duration, periprocedural complications, length of stay, and medications at discharge.

Follow-up and clinical outcomes

Five-year follow-up data were collected using the Summary Care Records, National Health Service (NHS) Digital, and tertiary centre hospital electronic patient records. Summary care records are an electronic synthesis of important patient information, created from primary care physician medical records.

The primary outcome was a composite of all-cause mortality, MI, stroke, repeat unplanned revascularization, and significant bleeding [defined as Bleeding Academic Research Consortium (BARC) type 2 or greater].[21] In participants where more than one component of the composite outcome occurred, time-to-first-event was used and all patients were censored at 5 years. The individual elements of the primary composite outcome were analysed separately as secondary outcomes.

Statistical analysis

Categorical variables are summarized by number (*n*) and percentages (%) and compared with χ^2 test. Continuous variables were checked for normality and presented as mean $\pm$ standard deviation or median (interquartile range) and compared with *T*-test or Wilcoxon rank-sum test for variables with normal or non-normal distribution respectively. A *P*-value $\leq$0.05 was considered significant.

Kaplan–Meier survival analysis was used for time to primary outcome and time to all-cause mortality according to frailty group. To investigate whether a potential difference between frailty groups was driven by the mortality rates in the first year, landmark analysis was used to investigate the number of new events after 1-year follow-up until 5-year follow-up. Data are presented as cumulative events and compared with the log-rank test.

Associations between frailty and the primary endpoint as well as all-cause mortality were assessed with Cox proportional hazard model tests, presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazard assumption was assessed with the Schoenfeld residuals test for all variables included in the model. If a patient had more than one event during the follow-up period (MI, new unplanned revascularization, stroke, bleeding, or all-cause death) only the first event counted in the primary composite endpoint. Analyses were performed in R® version 3.6.1.

Results

Of 300 participants in the ICON1 study, 263 (87.7%) completed 5-year follow-up, had frailty assessments at baseline, and were included in this analysis (see Supplementary material online, *Figure S1*). When CFS was used, 33 patients (12.5%) were frail, 152 (57.8%) as pre-frail and 78 (29.7%) as robust. According to Fried criteria, 70 patients (26.6%) were frail, 147 patients (55.9%) were pre-frail, and 46 patients (17.5%) were robust (see Supplementary material online, *Figure S2*). Twenty-five patients had frailty according to both CFS and Fried criteria (see Supplementary material online, *Figure S3*).

Baseline characteristics according to frailty group

When frailty was measured by CFS, patients with frailty were significantly older, more often female, and had more frequently a history of diabetes, hypertension, renal impairment, previous MI, previous angina, PCI, TIA or stroke, COPD, bleeding problems, and anaemia. At the time of admission, patients had significantly more often a Killip class $\geq$2, higher NYHA class, higher GRACE 2.0 score, higher CCI and higher CCS score, as well as lower haemoglobin (*Table 1*). Patients with frailty had a longer length of stay than robust patients. There were no differences in the invasive treatment or pharmacological therapy at discharge, except for nicorandil and isosorbide mononitrate which were more frequently prescribed to patients with frailty (Supplementary material online, *Table S2*).

When assessed using the Fried criteria, patients with frailty were older than pre-frail and robust patients, and more commonly had a history of stroke or TIA and anaemia (Supplementary material online, *Table S3*). At the time of admission, patients with frailty by Fried criteria had a significantly lower median LVEF and lower haemoglobin, and higher mean GRACE score compared with pre-frail and robust patients. There were no differences between the groups in the proportion of patients that were treated with PCI or in the frequency of PCI complications (Supplementary material online, *Table S4*).

Frailty and the primary composite endpoint at 5 years

Patients with frailty had a higher incidence of the primary composite endpoint as measured by CFS or the Fried criteria (*Table 2* and *Figure 1*). The risk of the primary composite endpoint was almost doubled in patients with frailty compared with robust patients

Table 1 Baseline characteristics for the population stratified by clinical frailty scale

Variable	Total ($n = 263$)	Frail ($n = 33$)	Pre-frail ($n = 152$)	Robust ($n = 78$)	*P*-value
Age, years, mean (SD)	81.2 (4.1)	83.2 (4.8)	81.4 (3.8)	80.2 (4.1)	0.001
Female, *n* (%)	102 (38.8)	20 (60.6)	65 (42.8)	17 (21.8)	<0.001
Body mass index, kg/m^2, mean (SD)	26.9 (4.4)	27.7 (4.3)	27.3 (4.9)	25.8 (3.1)	0.024
Current smoker, *n* (%)	18 (6.8)	2 (6.1)	15 (9.9)	1 (1.3)	0.05
Ex-smoker, *n* (%)	134 (51.0)	17 (51.5)	83 (54.6)	34 (43.6)	0.285
Never smoked, *n* (%)	109 (41.4)	14 (42.4)	54 (35.5)	41 (52.6)	0.045
Diabetes, *n* (%)	69 (26.2)	8 (24.2)	53 (34.9)	8 (10.3)	<0.001
Hypertension, *n* (%)	192 (73.0)	27 (81.8)	117 (77.0)	48 (61.5)	0.021
Hypercholesterolaemia, *n* (%)	152 (57.8)	22 (66.7)	86 (56.6)	44 (56.4)	0.544
Renal impairment, *n* (%)	57 (21.7)	13 (39.4)	34 (22.4)	10 (12.8)	0.008
Previous myocardial infarction, *n* (%)	87 (33.1)	20 (60.6)	55 (36.2)	12 (15.4)	<0.001
Previous angina, *n* (%)	116 (44.1)	22 (66.7)	74 (48.7)	20 (25.6)	<0.001
Previous PCI, *n* (%)	54 (20.5)	12 (36.4)	32 (21.1)	10 (12.8)	0.019
Previous CABG, *n* (%)	17 (6.5)	5 (15.2)	7 (4.6)	5 (6.4)	0.083
Previous TIA or stroke, *n* (%)	45 (17.1)	10 (30.3)	28 (18.4)	7 (9.0)	0.020
Osteoarthritis/rheumatoid arthritis, *n* (%)	37 (14.1)	6 (18.2)	24 (15.8)	7 (9.0)	0.285
Peptic ulcer disease, *n* (%)	14 (5.3)	1 (3.0)	10 (6.6)	3 (3.8)	0.561
COPD, *n* (%)	51 (19.4)	8 (24.2)	38 (25.0)	5 (6.4)	0.003
Malignancy, *n* (%)	25 (9.5)	4 (12.1)	13 (8.6)	8 (10.3)	0.789
Bleeding problems, *n* (%)	8 (3.0)	3 (9.1)	5 (3.3)	0 (0.0)	0.037
Anaemia, *n* (%)	23 (8.7)	7 (21.2)	15 (9.9)	1 (1.3)	0.002
Family history of IHD, *n* (%)	76 (29.1)	12 (36.4)	42 (27.6)	22 (28.9)	0.606
Heart rate, b.p.m., median (IQR)	70 (62–83)	75 (65.5–84.0)	72 (62–84)	68 (61.5–77.0)	0.091
Systolic blood pressure, mmHg, mean (SD)	144.9 (25.6)	143.9 (30.2)	144.1 (26.4)	146.8 (22.1)	0.755
LVEF, %, median (IQR)	55 (45–55)	55 (45–55)	50 (40–55)	55 (50–55)	0.012
Killip class ≥2, *n* (%)	32 (13.4)	9 (29.0)	18 (13.2)	5 (6.9)	0.010
NYHA class, *n* (%)					<0.001
1	111 (42.2)	5 (15.2)	44 (28.9)	62 (79.5)	
2	99 (37.6)	8 (24.2)	75 (49.3)	16 (20.5)	
3	52 (19.8)	19 (57.6)	33 (21.7)	0 (0.0)	
4	1 (0.4)	1 (3.0)	0 (0.0)	0 (0.0)	
GRACE score, mean (SD)	131.9 (19.3)	139.9 (22.6)	133.3 (19.5)	126 (15.4)	0.001
CCI score, median (IQR)	5 (4–7)	6 (5–8)	5 (4–7)	4 (3–5)	<0.001
CCS score, *n* (%)					<0.001
0	79 (30.0)	3 (9.1)	29 (37.2)	47 (30.9)	
1	98 (37.3)	11 (33.3)	35 (44.9)	52 (34.2)	
2	47 (17.9)	7 (21.2)	7 (9.0)	33 (21.7)	
3	32 (12.2)	8 (24.2)	6 (7.7)	18 (11.8)	
4	7 (2.7)	4 (12.1)	1 (1.3)	2 (1.3)	
Creatinine, μmol/L, median (IQR)	97 (80.0–119.5)	102 (86–128)	98 (79–114)	97 (79.2–125.8)	0.556
Haemoglobin, g/dL, median (IQR)	13.1 (11.7–14.3)	12.4 (10.6–13.2)	13.9 (12.7–15.0)	12.9 (11.6–14.2)	<0.001
Peak Troponin, ng/L, median (IQR)	111 (36.0–405.5)	77 (31–277)	147.5 (44.5–443.0)	97.5 (33.0–405.2)	0.359
hsCRP, mg/L, median (IQR)	1.4 (0.6–3.3)	2.1 (0.7–5.0)	1.1 (0.5–2.2)	1.8 (0.7–3.6)	0.110
NSTEMI, *n* (%)	211 (80.2)	28 (84.8)	66 (84.6)	117 (77.0)	0.300
Unstable angina pectoris, *n* (%)	52 (19.8)	5 (15.2)	12 (15.4)	35 (23.0)	0.300
Frailty measurements					
Weight loss during a 1-year period, *n* (%)	70 (26.6)	10 (30.3)	10 (12.8)	50 (32.9)	0.004
Energy loss, *n* (%)	79 (30.0)	18 (54.5)	5 (6.4)	56 (36.8)	<0.001
Low physical energy, *n* (%)	88 (33.5)	25 (75.8)	2 (2.6)	61 (40.1)	<0.001
Weakness (reduced hand grip strength), *n* (%)	174 (66.4)	27 (81.8)	37 (48.1)	110 (72.4)	<0.001
Slow walking speed (TUG), *n* (%)	41 (15.7)	18 (56.2)	1 (1.3)	22 (14.5)	<0.001

Continued

Table 1 ***Continued***

Variable	Total ($n=263$)	Frail ($n=33$)	Pre-frail ($n=152$)	Robust ($n=78$)	*P*-value
Fried criteria*, *n* (%)					<0.001
Robust	46 (17.5)	1 (3.0)	29 (37.2)	16 (10.5)	
Pre-frail	147 (55.9)	7 (21.2)	48 (61.5)	92 (60.5)	
Frail	70 (26.6)	25 (75.8)	1 (1.3)	44 (28.9)	

Categorical variables are summarized by number (*n*) and percentages (%). Continuous variables are presented as mean ± standard deviation (SD) or median (IQR). A fried criteria score of 0 is categorized as robust, 1–2 as pre-frail and ≥3 as frail.
ACS, acute coronary syndrome; CCI, Charleston comorbidity index; CCS, Canadian Cardiovascular Society; CFS, clinical frailty scale; GRACE, The Global Registry of Acute Coronary Events; hsCRP, high sensitive C-reactive protein; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NSTEMI,, non-ST elevation myocardial infarction; NYHA, New York Heart Association Functional Classification; TIA, Transient ischaemic attack; TUG, Timed up and go test.
* = A fried criteria score of 0 is categorized as robust, 1–2 as pre-frail and ≥3 as frail.

Table 2 Five-year outcomes stratified by frailty status according to clinical frailty scale and Fried criteria

CFS	Total at 5 years ($n=263$)	Frail ($n=33$)	Pre-frail ($n=152$)	Robust ($n=78$)	*P*-value
Primary endpoint					
Composite endpoint	127 (48.3)	22 (66.7)	81 (53.3)	27 (34.6)	0.002
Secondary endpoints					
All-cause mortality	82 (31.2)	17 (51.5)	51 (33.6)	14 (17.9)	0.001
Myocardial infarction	36 (13.7)	9 (27.3)	27 (17.8)	7 (9.0)	0.013
Stroke	10 (3.8)	2 (6.1)	5 (3.3)	3 (3.8)	0.752
Repeat unplanned Revascularization (PCI/CABG)	33 (12.5)	8 (24.2)	20 (13.2)	5 (6.4)	0.033
Bleeding	27 (10.3)	5 (15.2)	16 (10.5)	6 (7.7)	0.490
Fried criteria	**Total at 5 years ($n=263$)**	**Frail ($n=70$)**	**Pre-frail ($n=147$)**	**Robust ($n=46$)**	***P*-value**
Primary endpoint					
Composite endpoint	127 (48.3)	39 (55.7)	72 (49.0)	16 (34.8)	0.085
Secondary endpoints					
All-cause mortality	82 (31.2)	30 (42.9)	46 (31.3)	6 (13.0)	0.003
Myocardial infarction	36 (13.7)	14 (20.0)	25 (17.0)	4 (8.7)	0.294
Stroke	10 (3.8)	4 (5.7)	3 (2.0)	3 (6.5)	0.237
Repeat unplanned Revascularization (PCI/CABG)	33 (12.5)	11 (15.7)	18 (12.2)	4 (8.7)	0.529
Bleeding	27 (10.3)	8 (11.4)	13 (8.8)	6 (13.0)	0.667

Summarized by number (*n*) and percentages (%).
CABG, coronary artery bypass grafting; CFS, clinical frailty scale; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention.

(CFS: HR 2.55, 95% CI 1.44–4.50, $P=0.001$; Fried criteria: HR 1.96, 95% CI 1.10–3.51, $P=0.023$). The association remained after adjustment for age and sex (CFS: HR 2.22, 95% CI 1.23–4.02, $P=0.008$; Fried criteria: HR 1.81, 95% CI 1.00–3.27, $P=0.048$; *Table 3*).

Frailty and the secondary endpoints at 5 years

Among patients with frailty assessed by CFS, there were significantly higher all-cause mortalities, as well as more MI events and unplanned repeat revascularization, but no differences in the occurrence of stroke or bleeding. Patients with frailty assessed by Fried criteria had a significantly higher all-cause mortality rate at 5 years compared with pre-frail and robust patients. There were no significant differences in the occurrence of MI, repeated unplanned revascularization, stroke, or bleeding events (*Table 2* and *Figure 2*).

Frailty and pre-frailty were associated with increased risk of all-cause mortality (CFS: HR 3.89, 95% CI 1.91–7.89 $P<0.001$; Fried criteria: HR 4.25, 95% CI 1.77–10.22 $P=0.001$) and (CFS: HR 2.09, 95% CI 1.16–3.77 $P=0.015$; Fried criteria: HR 2.55, 95% CI 1.09–5.98 $P=0.031$) compared with robust patients. The association was sustained after adjustment for age and sex for both frailty (CFS: HR 3.27, 95% CI 1.53–6.96, $P=0.002$; Fried: HR 3.57, 95% CI 1.47–8.65, $P=0.005$) and pre-frailty (CFS: HR 2.05, 95% CI 1.12–3.73, $P=0.019$; Fried: HR 2.35, 95% CI 1.003–5.520, $P=0.049$), compared with

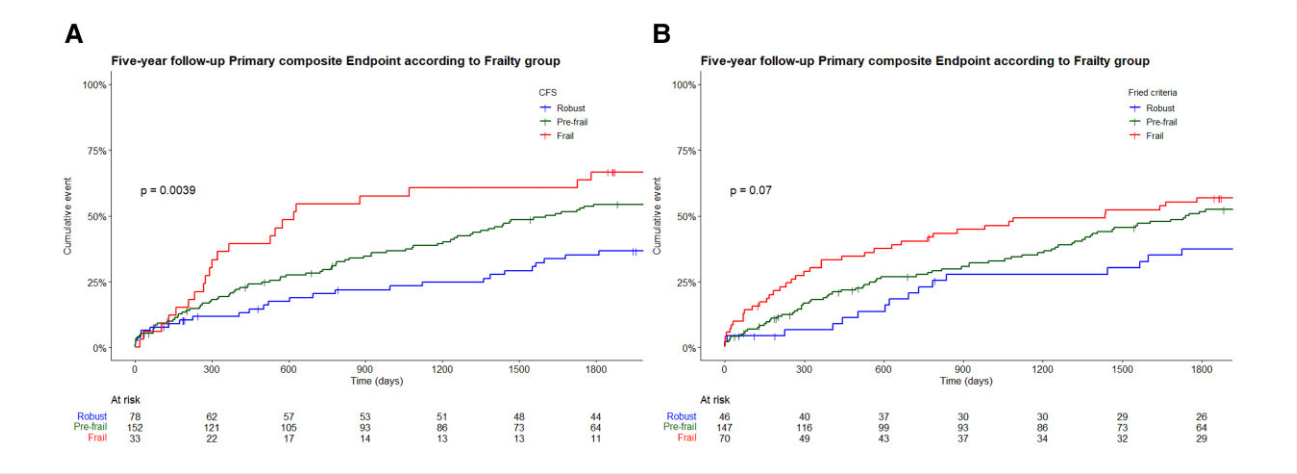

Figure 1 Kaplan–Meier of the composite primary endpoint by frailty category: (*A*) clinical frailty scale and (*B*) Fried criteria. CFS, clinical frailty scale.

Table 3 Association of frailty and the primary endpoint at 5-year follow-up according to clinical frailty scale and Fried criteria

	Unadjusted		Adjusted with age + sex	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CFS				
Robust	Reference		Reference	
Pre-frail	1.69 (1.09–2.64)	0.020	1.63 (1.04–2.55)	0.033
Frail	2.55 (1.44–4.50)	0.001	2.22 (1.23–4.02)	0.008
Fried criteria				
Robust	Reference		Reference	
Pre-frail	1.56 (0.91–2.68)	0.107	1.60 (0.93–2.75)	0.092
Frail	1.96 (1.10–3.51)	0.023	1.81 (1.004–3.269)	0.048

HR, hazard ratio; CI, confidence interval; CFS, clinical frailty scale.

robust patients. Frailty measured by CFS was associated with an increased risk of MI and unplanned repeat revascularization compared with robust patients. There were no significant association between frailty measured by Fried criteria and other secondary outcomes (see Supplementary material online, *Table S5*).

A landmark analysis excluding the first year of follow-up showed that frailty was still associated with a significantly higher risk of mortality at 5 years (Fried criteria: $P = 0.016$, CFS: log-rank $P = 0.001$; Supplementary material online, *Figure S3*).

Discussion

Among older adults with NSTEACS undergoing invasive treatment, frailty measured using the Fried criteria or CFS was associated with the primary composite endpoint, and strongly associated with higher all-cause mortality at 5 years, even after adjustment for age and sex. All-cause mortality was almost 50% among patients with frailty using either frailty assessment tool. To our knowledge this is the first study investigating long-term outcomes based on frailty criteria of older NSTEACS patients undergoing invasive care.

The increased risk of adverse events in patients with frailty has been reported before, but mostly in studies with a short duration of follow-up.[11,16,22,23] In our study, frailty was associated with an increased risk of the primary composite outcome of all-cause death, MI, unplanned repeat revascularization, stroke, and bleeding at 5 years when compared with robust patients. Previous studies that report long-term follow-up mainly included patients that were not referred for invasive treatment. These studies also showed that frailty was associated with adverse outcomes.[24–26] For example, the TRILOGY ACS trial consisted of patients with NSTEACS planned for medical management only ($n = 4996$, age ≥65 years, frailty according to Fried criteria) and found that frailty was associated with

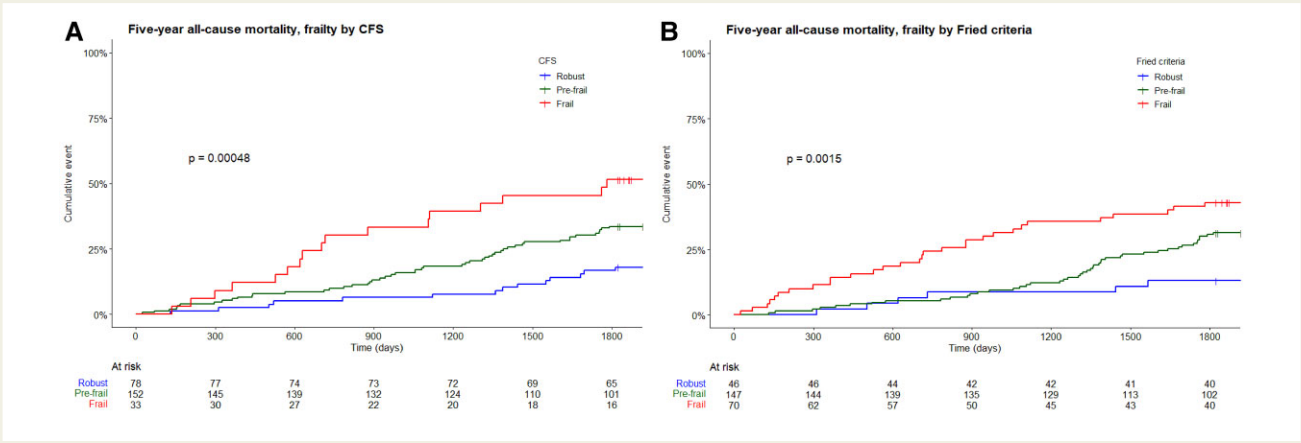

Figure 2 Kaplan–Meier of 5-year all-cause mortality by frailty category: (*A*) clinical frailty scale and (*B*) Fried criteria. CFS, clinical frailty scale.

the composite primary endpoint (cardiovascular death, MI, or stroke) at 30 months after adjustment for baseline characteristics and GRACE score.[24] In another study of patients with NSTEACS aged ≥75 years ($n = 307$, median follow-up 6.7 years, frailty defined using CFS), frailty was independently associated with all-cause mortality, although the study included patients with type II MI, and most patients with frailty did not undergo angiography.[26] In a further study of patients with ACS aged ≥65 years ($n = 342$, NSTEMI diagnosis in 79%, mean age 77 years, frailty by Fried criteria), frailty was associated with higher mortality during a median of 8.7 years follow-up, and while 80% of patients had angiography, only 44% were revascularized. Whether frail patients were more often underwent incomplete revascularization was not reported.[25]

In our study, the 5-year mortality rate was 31%, and it was higher among those with frailty than in robust patients (43 vs. 18%, for CFS). We found that there was no difference in the proportion of patients that were treated with PCI between frailty groups, in contrast to previous studies.[16,27] While there is a clear need for individualized, patient-centred care for older patients with NSTEACS, there is a gap in the existing evidence to guide the optimal management in the context of frailty, including the benefit of a routinely applied invasive strategy.[28,29] The results of the ongoing British Heart Foundation Older Patients With Non-ST SEgmeNt elevatIOn myocaRdial Infarction Randomized Interventional TreAtment trail (SENIOR-RITA, $n = 1600$) will be valuable in evaluating the role of invasive management in older adults with NSTEACS in the context of concomitant frailty.

Our study provides further evidence that biological age (i.e. frailty) is a more important influence on prognosis for older people with NSTEACS than chronological age alone. With an increasing number of older people, routine evaluation of frailty could help to guide the most appropriate treatment strategies and inform prognosis. Risk scoring systems like the GRACE score are widely used to triage patients of all ages with ACS. However, GRACE score is highly influenced by the patient's age, when inclusion of a frailty assessment may offer better model discrimination.[22,24] A routine integration of frailty into prognostication risk tools for better biological age estimation may be a useful next step.[23]

There were some differences in the clinical outcomes of patients with frailty as defined using the CFS and the Fried criteria. While this is to be expected based upon the different models, in this study, we also acknowledge that this is likely to be in part related to relatively small group sizes and therefore wide CIs. Current clinical practice guidelines do not recommend a particular tool in patients with NSTEACS.[6] There are benefits and disadvantages with both tools. The Fried criteria encompass both physical activity (slowness and weakness) as well as self-reported exhaustion, which incorporates the subjective assessment by the patient. In contrast, CFS is assessed by a bedside observation only, which is faster and may be more suitable for a patient in an acute setting and can easily be performed in the emergency departments and cardiology ward.[23] This study did not aim to compare the predictive utility of the two frailty models, and further work is needed to identify whether one scoring system is better than another in predicting outcomes for patients following ACS. However, there are some data that the Fried criteria outperform the CFS for mortality prediction in this setting.[30]

Strengths and limitations

This study uses prospectively collected data with in-person follow-up up to 1 year. Five-year follow-up was carried out via summary care records for robust outcome ascertainment. All frailty assessments were performed by experienced research team members with expertise in frailty assessments, and there are minimal missing data. However, we recognize the limitations of our work. Firstly, although over a quarter of participants were frail, the cohort is unlikely to include the frailest patients in whom invasive treatment was deemed not to be appropriate and were therefore not referred for angiography. Secondly, this is a relatively small study population, which increases the possibility of a type two error.

Conclusion

Among older patients with NSTEACS undergoing coronary angiography, frailty was associated with an increased risk of the primary composite endpoint of all-cause mortality, MI, repeat unplanned

revascularization, stroke, and bleeding at 5 years, even after adjustment for age and sex. The recognition of frailty is important to inform the prognosis of patients with NSTEACS and to identify a population at particular risk of adverse outcomes.

Author contributions

H.R. performed the statistical analyses used in the paper, wrote the draft, multiple revisions and the graphical abstract. B.B., G.M., L.H., J.A.H., H.S., M.V., and C.W. made critical review of the entire manuscript. V.K. made critical review and multiple revisions.

Lead author biography

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Data availability

Data can be provided on request to the Chief Investigator and Sponsor.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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