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One-year clinical outcomes in older patients with non-ST elevation acute coronary syndrome undergoing coronary angiography: An analysis of the ICON1 study☆

Jonathan Batty [a,b,1,2], Weiliang Qiu [c,3], Sophie Gu [a,b,2], Hannah Sinclair [b,2], Murugapathy Veerasamy [b,2], Benjamin Beska [a,b,2], Dermot Neely [d,3], Gary Ford [e,3], Vijay Kunadian [a,b,*,4], On behalf of ICON-1 Study Investigators

[a] Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[b] Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, UK
[c] Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[d] Department of Biochemistry, Newcastle upon Tyne Hospitals NHS Foundations Trust, Newcastle upon Tyne, UK
[e] Oxford University Hospitals NHS Foundation Trust, Oxford, UK

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ABSTRACT

Aims: The aim of this prospective, observational study was to identify predictors of adverse outcome at one year, following invasive care of older patients with non-ST-elevation acute coronary syndrome (NSTEACS) according to frailty status.
Methods: Older patients (aged ≥ 75 years), presenting with NSTEACS, undergoing invasive coronary angiography with a view to revascularisation, underwent assessment of frailty, cognition, functional status and quality of life. Participants were categorised as robust, pre-frail or frail using the Fried criteria. The primary outcome comprised a composite of all-cause mortality, myocardial infarction, stroke, unplanned revascularisation and major bleeding, at one year. Cox proportional hazards regression was used to derive a multivariate risk score.
Results: Overall, the composite endpoint was observed in 81 participants (29%). There was a significant difference in the occurrence of the primary outcome in the 3 frailty groups (robust 18.0%, pre-frail 27.5% and frail 39%; $p = 0.03$; hazard ratio (HR) for frail vs. robust: 2.79, 95% Confidence Interval [CI] 1.28–6.08). Fried frailty classification, age (categorised as ≥85 years), raised Killip class, systolic blood pressure on admission, history of peripheral vascular disease (PVD), problems dressing self and implantation of a bare metal stent were identified as predictors of adverse events at one year, with a C-statistic of 0.77 (95% CI 0.71–0.83). A point-based clinical risk score (FRAIL-HEART) was defined, which had a C-statistic of 0.70 (95% CI 0.63–0.77) and significantly outperformed the GRACE 2 score.
Conclusion: Frailty is associated with adverse clinical outcomes, following invasive management of older patients with NSTEACS. The derived risk models may enable improved risk stratification in practice.

1. Introduction

Despite the development of contemporary treatment strategies, including early invasive revascularisation, dual antiplatelet therapy and intensive risk factor reduction, acute coronary syndrome (ACS) remains a leading cause of mortality among patients aged over 75 years [1,2]. Evidence-based British, European and North American guidelines advocate that all older patients with non-ST-elevation ACS (NSTEACS) should undergo assessment for discretionary invasive revascularisation [3–5]. The importance of a patient-centred approach is emphasised with evaluation of comorbidity, cognition, functional status and life expectancy, although no specific, evidence-based risk model is recommended.

The performance of conventional ACS risk scores in older patients is suboptimal [6]. Such models are predictive of mortality, but do not take account of other morbidity outcomes which are of importance in this age group, such as myocardial infarction (MI), stroke, major bleeding and quality of life. Although age constitutes the single greatest risk

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* Corresponding author at: Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, 4th Floor, William Leech Building, Newcastle upon Tyne NE2 4HH, UK.
E-mail address: vijay.kunadian@newcastle.ac.uk (V. Kunadian).
[1] First author.
[2] Clinical Research Fellows.
[3] Co-investigators.
[4] Chief Investigator and Senior Author.

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factor for adverse outcome, many age-related factors are heterogeneous; leading to poor discrimination within an older population. Frailty is a complex, clinical phenotype; defined as a vulnerability to physiological stressors as a consequence of age-associated decline in resilience and reserve [7]. The frailty phenotype commonly manifests as slowness, weakness, reduced activity, low energy levels and unintended weight loss. Frail, older patients with ACS may be at greater long-term risk of adverse events, compared with their robust counterparts [8]. Given the paucity of data regarding risk stratification in older patients, the aim of this prospective cohort study was to determine the prevalence of the frailty phenotype and identify predictors of adverse outcome at one year, in patients aged 75 and older undergoing invasive management for NSTEACS.

2. Methods

2.1. Study design

The study to Improve Clinical Outcomes in high-risk patieNts with acute coronary syndrome (ICON-1) is a multi-centre, observational, prospective cohort study. The full protocol has previously been published [9]. The ICON-1 study was approved by Local Ethics Committees and the National Research Ethics Service (12/NE/0160) and was conducted in accordance with the Declaration of Helsinki. The written, informed consent of all participants was required. ICON-1 was prospectively registered with the United Kingdom Clinical Research Network (UKCRN; ID 12742) and ClinicalTrials.gov (NCT01933581).

2.2. Participants

Patients with NSTEACS, aged ≥65 years, undergoing coronary angiography with a view to revascularisation, were recruited between November 2012 and December 2015 at two tertiary cardiovascular centres: Freeman Hospital, Newcastle upon Tyne, and James Cook University Hospital, Middlesbrough, United Kingdom. Participants were referred from neighbouring district general hospitals, following diagnosis of NSTEACS. Exclusion criteria included 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 coronary angiography (e.g. Takotsubo cardiomyopathy, pulmonary embolism, myocarditis and coronary vasospasm) were excluded. After recruitment commencement, we focussed our recruitment high risk older patients aged 75 and over.

2.3. Protocol and study procedures

All study participants underwent contemporary, guideline-directed medical management and invasive revascularisation at the discretion of the attending cardiologist. Baseline data collection, performed on admission, included participant demographics, medical history and details of coronary angiography and revascularisation, including any periprocedural complications. Cardiovascular status was assessed using the Killip Class, New York Heart Association (NYHA) functional classification and Canadian Cardiovascular Society (CCS) angina grade. The Short Form 36 (SF-36) and EQ5D (EuroQol 5 Domains) health surveys were used to ascertain patient-reported functional status and quality of life [10–12]. Patient-reported health state was ascertained by asking the patient to place a cross on a continuous (1−100) visual analogue scale. Cognitive status was ascertained using the Montreal Cognitive Assessment (MoCA) [13]. All patients underwent assessment for frailty using the Fried Frailty Index, derived from the Cardiovascular Health Study [7]. A score of 0 is categorised as non-frail (robust), 1–2 as pre-frail (intermediate) and ≥3 as frail. The Charlson Co-morbidity Index (CCI) [14] and the Global Risk of Acute Coronary Events (GRACE 2) score were also calculated.

2.4. Outcomes and follow-up

The primary outcome was a composite of myocardial infarction, need for urgent repeat revascularisation, stroke, significant bleeding, and all-cause mortality at one year. Significant bleeding was defined by Bleeding Academic Research Consortium (BARC) criteria (type 2 or greater) [15]. In-hospital complications and outcomes were ascertained on the day of discharge. All 30-day outcomes were ascertained using Summary Care Records, obtained from the regular primary care physician of the study participant. Tertiary centre electronic patient records were used to identify repeat revascularisation procedures, or hospital re-admission, to ensure complete capture of events. One-year outcomes were ascertained at a follow-up clinic appointment, during which repeat blood samples were collected, NYHA and CCS classes were ascertained and frailty, SF-36 and MoCA assessments repeated. If a patient was unable to attend, telephone-based follow-up was performed [16].

2.5. Statistical methods

The power of the study was estimated using the Hsieh and Lavori method, using a type I error rate of 0.05, and outcome rate conservatively estimated at 5% [17,18]. The available sample size provided >80% statistical power to detect an association between covariates and outcomes, with an HR ≥2.0 [9]. A two-tailed p-value < 0.05 was used as the threshold for statistical significance in all analyses. The distribution of each variable was examined by visual inspection of histogram and quantile-quantile plots, and computation of the Shapiro-Wilk statistic. Discrete variables are presented as count (percentage). Continuous variables are presented as mean (standard deviation; SD) if normally distributed, and as median (interquartile range; IQR) otherwise. One-way analysis of variance (ANOVA) was performed for the comparison of normally distributed, continuous variables by frailty category. The Kruskal–Wallis test was performed for non-normally distributed variables. The Chi-square (χ^2) test was used for comparison of discrete variables. When a contingency table contained a cell with less than five counts, Fisher's Exact test was used. For subjects experiencing multiple components of the composite outcome, time-to-first event was used. The Kaplan-Meier method was used to evaluate composite endpoint-free survival by frailty status. The log-rank test was used to evaluate equality of event-free survival.

Multivariate Cox proportional hazards regression, with stepwise backward selection (using a selection p-value of 0.05), using 1000 bootstrap samples with replacement, was performed in an a priori hypothesis-free approach to model building [9]. All variables collected at baseline were eligible to enter the model, including frailty status and components thereof. Variables selected in ≥800 models were included in the final risk model. A simplified, additive, point-based risk score was derived, based on relative weights of regression coefficients in Cox proportional hazards analysis, using the method of Austin et al. [19] Evaluation of model fit was performed, and Harrell's C-statistic was estimated using probit regression, bootstrapping 1000 times. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices were calculated. Stata 14.0 (StataCorp LLC, TX, USA) was used for all analyses. This study is reported in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [20].

3. Results

The study flow chart is shown in Fig. 1. Study participants had a mean ± standard deviation age of 81 ± 4 years, were predominantly male (60%) and had a range of cardiovascular risk factors (Table 1). Of the 280 patients, 50 were classified as robust (17.9%), 153 as pre-frail (54.6) and 77 as frail (27.5%) using the Fried Frailty Index (Table 1). Full details of medical and invasive management are presented in (**Supplemental Table 3**).

3.1. In-hospital and 30-day outcomes

Although there was no overall difference between major procedural complications by frailty status ($p = 0.30$), vascular access complications were more common in frail participants (0, 1.3 and 5.2% in the robust, pre-frail and frail groups, respectively; $p = 0.05$; Table 2). The overall length of stay did not differ between frailty class (7.1, 6.8 and 9.8 days, respectively; $p = 0.16$). At 30 days, the primary composite endpoint did not differ between the frailty groups (8.0, 7.8 and 13.0% of robust, pre-frail and frail groups, respectively; $p = 0.46$).

3.2. One-year outcomes

Outcome status at one year was ascertained in 279 participants (99.6%). Overall, the composite endpoint was observed in 81 participants (29%). There was a significant difference in the occurrence of primary outcome in the 3 groups (robust 18.0%, pre-frail 27.5% and frail 39%; $p = 0.03$) (Table 2). Frailty was associated with a hazard ratio (HR) of 2.79 (95% confidence intervals [CI]: 1.28–6.08, $p = 0.01$) for the primary endpoint, compared with the robust group (Fig. 2). Death was more common among frail participants (13%), compared with pre-frail and robust participants (3.3 and 2%, respectively, $p = 0.01$; HR frail vs. robust 6.93, 95% CI 0.89–54.14). MI occurred more frequently in frail patients (20.3%), compared with pre-frail and robust patients (8.8 and 6.1%, respectively, $p = 0.03$; HR frail vs. robust 3.18, 95% CI 0.92–11.1). Repeat all-cause hospitalisation occurred in 10 robust (20.4%), 48 pre-frail (34.0%) and 29 frail participants (34.4%, $p = 0.02$; HR for frail vs. robust: 2.20, 95% CI 1.07–4.52).

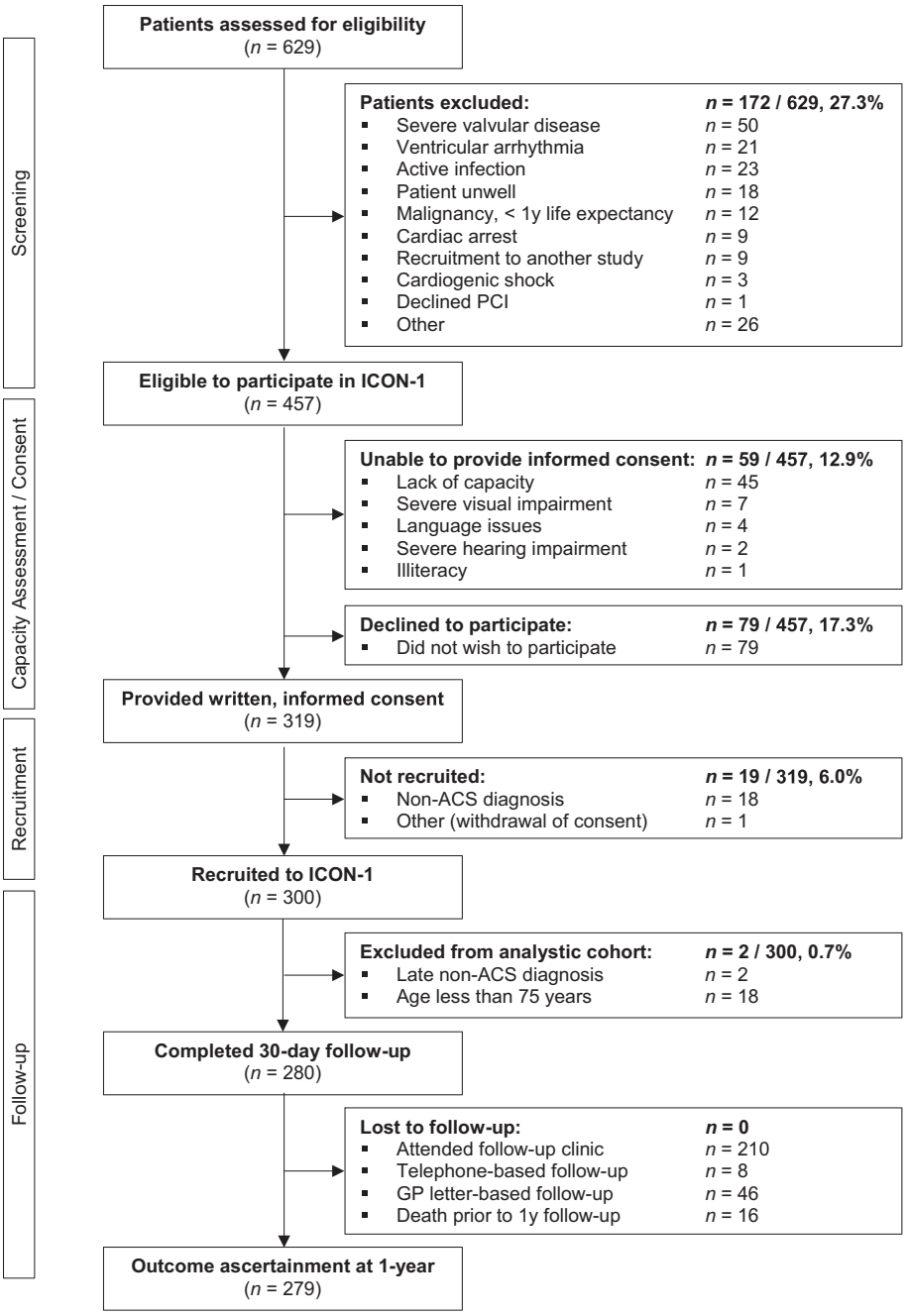

Fig. 1. Flow diagram of ICON-1 screening and recruitment. Abbreviations: ACS - acute coronary syndrome, CABG - coronary artery bypass graft. PCI - percutaneous coronary intervention.

3.3. Predictors of 1-year outcome

Using bootstrapped resampling of the cohort over 1000 iterations and backward stepwise selection, 7 variables were robustly associated with the one-year primary outcome, in ≥80% of models (**Supplemental Table 4**). These were: Fried frailty classification, age (categorised as ≥85 years), systolic blood pressure on admission, raised Killip class on admission, history of peripheral vascular disease (PVD), problems dressing self, and implantation of a bare metal stent. Implantation of a bare metal stent was infrequent (1.8% of the study population). As the aim was to develop a risk score capable of estimating risk prior to coronary angiography, bare metal stent implantation was excluded from subsequent predictive modelling. A simplified, point-based score (FRAIL-HEART) was defined, assigning simplified integer weights to each category (**Supplemental Table 5**).

Linear regression was used to identify predictors of patient-reported health state at one year, controlling for baseline health state. Significant predictors of health state included NYHA class (β coefficient $= -7.07$, $p < 0.001$), history of previous MI ($\beta = -6.0$, $p = 0.02$) and low levels of physical activity ($\beta = -6.13$, $p = 0.02$). Frailty status was not a significant predictor of health state at one year ($p = 1.00$).

3.4. Evaluation of model discrimination

The inclusion of all 6 covariates in a Cox proportional hazard regression model resulted in a C-statistic of 0.77 (95% CI 0.71–0.83) for the primary outcome, and 0.80 (95% CI 0.70–0.91) for all-cause mortality. For comparison, the GRACE 2 score predicted the primary outcome with a C-statistic of 0.48 (95% CI 0.40–0.56), and all-cause mortality with a C-statistic of 0.52 (95% CI 0.35–0.69). The FRAIL-HEART score

Table 1
Baseline characteristics at recruitment to ICON-1.

	Fried index category			*p*-Value
	Robust ($n = 50$)	Pre-frail ($n = 153$)	Frail ($n = 77$)	
Demographics				
Age, years (SD)	79.7 (3.8)	81.2 (4.0)	81.7 (4.2)	0.019*
Female, *n* (%)	14 (28.0)	59 (38.6)	39 (50.7)	0.034*
IMD, decile (IQR)	5 (4)	5 (5)	4 (5)	0.266
IDAOPI, decile (IQR)	5 (3)	5 (4)	4 (5.5)	0.212
Clinical measures				
Height, m (SD)	1.69 (0.10)	1.66 (0.10)	1.63 (0.10)	0.002**
Weight, kg (SD)	77.9 (11.1)	73.8 (14.0)	71.9 (14.8)	0.049*
BMI, kg m^{-2} (SD)	27.3 (3.4)	27.0 (4.8)	27.1 (5.0)	0.014*
Systolic BP, mm Hg (SD)	152.3 (24.2)	143.0 (24.4)	142.2 (27.2)	0.065
NYHA functional class, *n* (%):				
1 - No limitation of activity	30 (60.0)	69 (45.1)	20 (26.0)	<0.001**
2 - Slight limitation of activity	16 (32.0)	59 (38.6)	33 (42.9)	
3 - Marked limitation of activity	4 (8.0)	25 (16.3)	23 (29.9)	
4 - Unable to carry out activity	0 (0.0)	0 (0.0)	1 (1.3)	
GRACE score, points (SD)	124.1 (14.3)	131.3 (19.1)	137.3 (20.5)	0.001**
Medical history				
Diabetes, *n* (%)	7 (14.0)	42 (27.5)	22 (28.6)	0.113
Hypertension, *n* (%)	35 (70.0)	108 (70.6)	63 (81.8)	0.157
Hyperlipidaemia, *n* (%)	28 (56.0)	89 (58.2)	45 (58.4)	0.972
Renal impairment, *n* (%)	5 (10.0)	33 (21.6)	20 (26.0)	0.079
Previous MI, *n* (%)	12 (24.0)	48 (31.4)	34 (44.2)	0.045*
Previous angina, *n* (%)	16 (32.0)	68 (44.4)	38 (49.4)	0.150
Previous PCI, *n* (%)	9 (18.0)	27 (17.7)	22 (28.6)	0.149
Previous CABG, *n* (%)	2 (4.0)	9 (5.9)	6 (7.8)	0.747
HF, *n* (%)	1 (2.0)	10 (6.5)	13 (16.9)	0.006**
AF, *n* (%)	7 (14.0)	18 (11.8)	15 (19.5)	0.282
PVD, *n* (%)	3 (6.0)	16 (10.5)	8 (10.4)	0.651
Previous TIA/stroke, *n* (%)	3 (6.0)	23 (15.0)	21 (27.3)	0.005**
Osteoarthritis, *n* (%)	2 (4.0)	17 (11.1)	17 (22.1)	0.008**
Peptic ulcer disease, *n* (%)	2 (4.0)	9 (5.9)	3 (3.9)	0.872
COPD, *n* (%)	5 (10.0)	28 (18.3)	19 (24.7)	0.115
Malignancy, *n* (%)	5 (10.0)	15 (9.8)	6 (7.8)	0.886
Bleeding problems, *n* (%)	0 (0.0)	4 (2.6)	4 (5.2)	0.254
Anaemia, *n* (%)	0 (0.0)	13 (8.5)	10 (13.0)	0.017*
Smoking status				
Current smoker, *n* (%)	2 (4.0)	10 (6.6)	7 (9.1)	0.586
Ex-smoker, *n* (%)	28 (56.0)	70 (45.8)	44 (57.1)	0.237
Never-smoker, *n* (%)	20 (40.0)	73 (47.7)	26 (33.8)	0.151
Frailty indices				
Fried index components				
Shrinking criterion, *n* (%)	0.0 (0.0)	31 (20.3)	44 (57.1)	<0.001**
Low physical endurance, *n* (%)	0.0 (0.0)	31 (20.3)	55 (71.4)	<0.001**
Low physical activity, *n* (%)	0.0 (0.0)	32 (20.9)	65 (84.4)	<0.001**
Weakness, *n* (%)	0.0 (0.0)	115 (75.7)	69 (89.6)	<0.001**
Slow walking speed, *n* (%)	0.0 (0.0)	9 (6.0)	33 (43.4)	<0.001**
Rockwood score, *n* (%)				
1–2	33 (66.0)	51 (33.3)	1 (1.3)	<0.001**
3–4	16 (32.0)	95 (62.1)	49 (63.6)	
5–7	1 (2.0)	7 (4.6)	27 (35.1)	
Quality of life and co-morbidity				
MoCA, points (SD)	25.7 (3.2)	25.6 (2.7)	23.7 (4.0)	0.002**
SF-36 PCS, points (SD)	42.1 (11.1)	37.6 (11.1)	27.4 (8.2)	<0.001**
SF-36 MCS, points (SD)	51.6 (9.7)	50.8 (9.9)	49.5 (9.8)	0.397
Health state, % (SD)	73.0 (12.6)	66.3 (17.8)	59.2 (18.6)	<0.001**
Charlson index, points (SD)	4.5 (1.3)	5.4 (1.8)	5.9 (1.6)	<0.001**
Blood results				
Haemoglobin, g L^{-1} (SD)	140 (16)	130 (19)	125 (18)	<0.001**
Creatinine, μmol L^{-1} (SD)	88.6 (23.7)	102.0 (32.3)	105.0 (42.3)	0.998
Total cholesterol, mmol L^{-1} (SD)	4.3 (1.1)	4.2 (1.3)	4.3 (1.1)	0.849
hsCRP, mg L^{-1} (SD)	6.3 (10.8)	13.8 (38.0)	11.3 (17.9)	0.071
Troponin T, ng L^{-1} (SD)	385 (499)	488 (893)	479 (1348)	0.146
eGFR, mL min^{-1} 1.73 m^{-2} (SD)	58.4 (16.7)	53.2 (18.7)	50.7 (20.5)	0.078

Abbreviations: AF - atrial fibrillation, BMI - body mass index, BP - blood pressure, CABG - coronary artery bypass graft, COPD - chronic obstructive pulmonary disease, EQ - EuroQol form, GRACE - Global Registry of Acute Coronary Events, HF - heart failure, IDAOPI - Income Deprivation Affecting Older People Index, IMD - Index of Multiple Deprivation, IQR - interquartile range, MCS - mental component summary, MI - myocardial infarction, MoCA - Montreal Cognitive Assessment, NYHA - New York Heart Association class, PCI - percutaneous coronary intervention, PCS - physical component summary, PVD - peripheral vascular disease, SD - standard deviation, SF-36 - short form 36, TIA - transient ischaemic attack, eGFR - estimated glomerular filtration rate, hsCRP - C-reactive protein Asterisks (*) denote statistical significance at the $p < 0.05$ level, double asterisk (**) denotes significance at the $p < 0.01$ level.

had a C-statistic of 0.70 (95% CI 0.63–0.77) for the primary outcome (**Supplemental Fig. 3a**) and 0.66 (95% CI 0.54–0.78) for all-cause mortality. Comparing the full regression model with the GRACE 2 score, the NRI was 0.73 (95% CI 0.46–1.02), with an IDI of 0.26 (95% CI 0.16–0.37) for the primary outcome. The *p*-value for equality of the C-statistic for these two models is 1.2×10^{-6}. Comparing the full

Table 2
In-hospital complications, 30-day and 1-year outcomes, stratified by frailty status.

	Fried index category			*p*-Value
	Robust ($n = 50$)	Pre-frail ($n = 153$)	Frail ($n = 77$)	
In-hospital major complications				
Any major complication, *n* (%)	1 (2.0)	11 (7.2)	7 (9.1)	0.303
GI bleed, *n* (%)	0 (0.0)	1 (0.7)	1 (1.3)	1.000
Unplanned re-intervention PCI, *n* (%)	0 (0.0)	6 (3.9)	0 (0.0)	0.196
Arterial complication, *n* (%)	0 (0.0)	2 (1.3)	4 (5.2)	0.049*
Death, *n* (%)	0 (0.0)	0 (0.0)	1 (1.3)	0.999
Stroke, *n* (%)	1 (2.0)	0 (0.0)	0 (0.0)	0.179
Other, *n* (%)	0 (0.0)	2 (1.3)	1 (1.3)	0.999
30-day outcomes				
Composite, *n* (%)	4 (8.0)	12 (7.8)	10 (13.0)	0.460
Death, *n* (%)	0 (0.0)	0 (0.0)	1 (1.3)	0.454
Myocardial infarction, *n* (%)	2 (4.0)	2 (1.3)	3 (3.9)	0.373
Unplanned revascularisation, *n* (%)	1 (2.0)	3 (2.0)	1 (1.3)	0.931
Stroke, *n* (%)	0 (0.0)	1 (0.7)	1 (1.3)	0.691
Significant bleeding, *n* (%)	1 (2.0)	8 (5.2)	5 (6.5)	0.515
All-cause re-hospitalisation, *n* (%)	3 (6.0)	14 (9.2)	14 (18.2)	0.054
New dialysis requirement, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Institutional care requirement, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
1-year outcomes				
Composite, *n* (%)	9 (18.0)	42 (27.5)	30 (39.0)	0.033*
Death, *n* (%)	1 (2.0)	5 (3.3)	10 (13.0)	0.010*
Myocardial infarction, *n* (%)	3 (6.1)	13 (8.8)	14 (20.3)	0.029*
Unplanned revascularisation, *n* (%)	2 (4.1)	10 (6.8)	10 (14.3)	0.102
Stroke, *n* (%)	1 (2.0)	2 (1.4)	1 (1.5)	1.000
Significant bleeding, *n* (%)	3 (6.1)	24 (16.3)	9 (13.0)	0.210
All-cause re-hospitalisation, *n* (%)	10 (20.4)	48 (34.0)	29 (34.4)	0.017*
New dialysis requirement, *n* (%)	0 (0.0)	0 (0.0)	1 (1.6)	0.449
Institutional care requirement, *n* (%)	0 (0.0)	3 (2.0)	1 (1.3)	1.000
Discontinuation ≥ 1 medication, *n* (%)	18 (36.0)	40 (26.1)	33 (42.9)	0.033*
Discontinuation of aspirin, *n* (%)	5 (10.0)	20 (13.1)	14 (18.2)	0.412
Discontinuation of statin, *n* (%)	6 (12.0)	12 (7.8)	10 (13.0)	0.413
Discontinuation of ACEi/ARB, *n* (%)	8 (16.0)	14 (9.2)	13 (16.9)	0.158
Discontinuation of β-blocker, *n* (%)	6 (12.0)	9 (5.9)	7 (9.1)	0.333
Change in BMI from baseline, kg m^{-2} (MAD)	−0.3 (0.7)	0.1 (1.2)	−0.1 (1.1)	0.587
Change in SF-36 PCS from baseline, points (MAD)	1.6 (7.0)	2.9 (7.2)	5.0 (6.0)	0.292
Change in SF-36 MCS from baseline, points (MAD)	2.2 (5.5)	2.6 (5.5)	1.3 (5.6)	0.796
Change in pain and discomfort score, points (MAD)	0.1 (0.0)	0.0 (0.0)	0.2 (1.0)	0.243
Change in health state from baseline, % (MAD)	−3.1 (10)	1.9 (10)	−2.2 (15)	0.315
Change in MoCA from baseline, points (MAD)	0.2 (3.0)	−0.8 (2.0)	−1.0 (2.0)	0.179

Abbreviations: GI - gastrointestinal, MAD - median absolute deviation, MCS - mental component summary, MoCA - Montreal Cognitive Assessment, PCS - physical component summary, SF-36 - short form 36, TIA - transient ischaemic attack. Asterisks (*) denote statistical significance at the $p < 0.05$ level, double asterisk (**) denotes significance at the $p < 0.01$ level. Note: the composite endpoint only counts the first event; some patients experienced multiple adverse outcomes, e.g. a patient satisfying the composite outcome may have experienced MI, unplanned revascularisation *and* bleeding.

regression model and simple points-based FRAIL-HEART model, the NRI was 0.16 (95% CI −0.17–0.56), and the IDI was 0.07 (95% CI 0.03–0.15). The *p*-value for equality of the C-statistic for these two models was 0.09 (**Supplemental Fig. 3b**).

A greater FRAIL-HEART score correlated with a greater absolute risk of the primary outcome at 12 months. The reference patient (with a FRAIL-HEART score of 0) is robust, 75–84 years old, without a history of PVD and with no problems dressing, is non-hypotensive and shows no signs of heart failure on presentation. The model-predicted probability of such a patient satisfying the primary outcome is 6.3%. The risk increases in stepwise fashion: 18.2% for score 1–3, 39.1% for score 4–6, 50.0% for score 7–9 and approaching 100% for score 10–12 (**Supplemental Fig. 3b**).

4. Discussion

This study demonstrates that invasive revascularisation was feasible and well tolerated among older patients presenting with NSTEACS, regardless of frailty status. With the exception of vascular complications, which were more common among frail patients, there was no increase in procedure related complications and 30-day clinical outcomes (myocardial infarction, stroke, unplanned repeat revascularization, major bleeding and all-cause mortality) between the frailty groups. However, at 1-year, frailty was associated with adverse clinical outcomes driven by excess mortality, myocardial infarction and all cause re-hospitalisation. Fried frailty classification, age (categorised as ≥85 years), systolic blood pressure on admission, raised Killip class on admission, history of peripheral vascular disease and problems dressing self were significantly associated with one-year primary outcome, leading to the development of the point-based FRAIL-HEART risk score. This performed significantly better than GRACE 2, and was equivalent to the full regression model, in predicting the primary outcome at one year.

All patients enrolled in the ICON-1 study underwent routine coronary angiography; with PCI performed in >80% of cases with a mean age of 81.1 years. Studies of NSTEACS patients of comparable age, such as that by Ekerstad et al. (mean age 83.9 years), report coronary angiography and revascularisation in a much lower proportion of patients (31.3%), with a much greater rate of adverse events at one month [21]. The frailty phenotype and factors relating to frailty (such as inability to independently dress, significant recent weight loss, and low physical endurance and energy levels) were found to be significantly and independently associated with adverse clinical outcome. Using the Fried frailty scale, we identified that approximately one-third of patients aged ≥75 years, undergoing invasive management for non-ST-elevation ACS were frail. Many clinical characteristics, such as age,

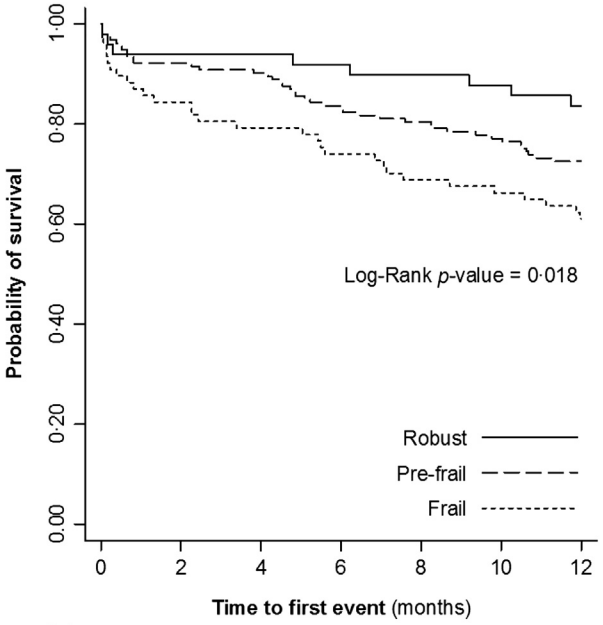

Fig. 2. Kaplan-Meier plot, demonstrating time to primary composite endpoint (death, MI, unplanned revascularisation, stroke, episode of significant bleeding). The numbers at risk, stratified by Fried Frailty group are presented below. The Log-Rank test for equality of survival distributions demonstrates a significant difference between the survival curves ($X^2 = 8.06$, 2 degrees of freedom, $p = 0.018$*). The frail phenotype is associated with a greater likelihood of achieving the primary composite endpoint compared to the robust phenotype (HR 2.16, 95% CI 1.13 to 4.16, $p = 0.021$*) and the pre-frail phenotype (HR 1.42, 95% CI 0.97 to 2.08, $p = 0.071$).

gender, and baseline comorbidity burden were associated with the frailty phenotype, in accordance with previous findings [7,21,22].

To date, few well-powered studies have evaluated, in randomised fashion, whether an invasive strategy is superior to a conservative approach, in older patients presenting with non-ST-elevation ACS. In one Italian trial early invasive management did not lead to a reduction in the primary composite at one year (a composite of all-cause mortality, MI, disabling stroke, severe bleeding and repeat cardiovascular hospitalisation), although a benefit was observed in troponin positive patients (22% vs. 40%; $p = 0.03$) [23]. In the After-Eighty study, the composite endpoint (myocardial infarction, need for urgent revascularisation, stroke, and death) occurred in 40.6% of patients assigned to the invasive group and 61.4% patients assigned to the conservative group [24]. However, this study excluded high-risk frail patients (only 11% of eligible patients were recruited; the remainder had a short life expectancy, clinical instability, recent bleeding, refused to participate or had logistical contraindications), and did not report quality of life-based outcomes. Only 52% of patients underwent any form of revascularisation. Though our present study sample size is small, the ongoing, multi-centre British Heart Foundation SENIOR-RITA trial aims to definitively answer this question; enrolling 2300 patients aged ≥75 years with NSTEMI, with broad eligibility criteria to prevent preferential selection of robust patients (ClinicalTrials.gov NCT03052036).

In a prospective cohort study by Singh et al., the addition of frailty (as defined by Fried frailty score), co-morbidity and quality of life to the conventional cardiovascular risk factors in the Mayo Clinic Risk Score significantly improved the prognostic ability of the score [25]. Frailty was associated with increased long-term mortality or myocardial infarction (HR 2.45; 95% CI 1.33–4.53) among patients undergoing PCI. Multiple risk prediction models are available to augment clinical decision-making, with regard to identifying those patients with non-ST-elevation ACS that will benefit from invasive revascularisation. However, older patients were systematically under-represented in the derivation and validation cohorts of such models, and as age often forms the primary determinant of risk, such models are less discriminatory *within* the high-risk strata of advanced age. In the context of non-ST-elevation ACS, Angeli et al. demonstrated that one-year mortality in patients aged ≥75 years is predicted by a score comprising five covariates: previous vascular event, haemoglobin levels, eGFR, ischaemic electrocardiography changes and elevated cardiac troponin levels [26]. Although validated in an independent cohort, when applied to ICON-1, their risk score was not predictive of the one-year composite outcome (C-statistic 0.45, 95% CI 0.36–0.53) or all-cause mortality (C-statistic 0.54, 95% CI 0.41–0.67). Additional studies report the association of additional risk scores with both short- and long-term clinical outcomes in unselected older patients undergoing PCI, including GRACE 2 [27,28]. Both the full regression-based and simplified FRAIL-HEART score were discriminative of the primary composite outcome and all-cause mortality in the ICON-1 cohort. The clinical utility of the risk models derived from the ICON-1 study are subject to external validation in an independent cohort of comparable patients. This will permit empirical evaluation of the predictive performance of such models; assessing the effect of model over fitting with regard to the specific case-mix of patients recruited to ICON-1. There were insufficient patients recruited in ICON-1 to permit sub-setting of participants to form nested discovery and validation sub-cohorts with sufficient statistical power. We hope to validate the FRAIL-HEART score in the BHF SENIOR-RITA trial, once recruitment is completed.

4.1. Strengths and limitations

Approximately three-quarters of all patients screened and eligible for inclusion provided informed, written consent to participate; a high participation rate in this age group [16]. Although this study was non-randomised, no difference was observed in the management of robust, pre-frail and frail patients, suggesting that guidelines are being applied equitably, and that management differences are unlikely to account for differences in outcome in this study. Loss to follow-up was very low, which has historically been a problem concerning studies of community-dwelling older patients dependent on follow-up clinic visits.

This study has several limitations. Firstly, ICON-1 recruited older patients with non-ST-elevation ACS referred to a tertiary cardiovascular centre for coronary angiography ± invasive revascularisation. It is likely that the oldest, frailest patients were not referred for invasive management, based on clinical judgements of the futility of such actions, leading to selection bias. Secondly, the primary instrument used to ascertain frailty status is, in part, subjective and thus subject to some degree of inter-observer variability. However, the inclusion of objective measures (e.g. quantification of grip strength, walking speed, body mass index, etc.) improves the reproducibility of the Fried Frailty Index, beyond that of alternative instruments, such as the Rockwood (Canadian Study of Health and Ageing Frailty) Scale [22]. However, such limitations would be expected to weaken, rather than inflate any observed association between frailty and outcome.

5. Conclusions

Invasive revascularisation was well tolerated among older patients with non-ST-elevation ACS, regardless of frailty status. However, frailty was associated with adverse, long-term clinical outcomes, driven by excess mortality, myocardial infarction and all cause re-hospitalisation. The addition of determinants of frailty to conventional risk-stratification models, or application of the FRAIL-HEART risk model, may facilitate improved, patient-centred and evidence-based decision-making, in those aged ≥75 years old undergoing assessment for invasive

revascularisation. Robust, prospective external validation of FRAIL-HEART using an independent cohort is required, which we intend to undertake in the British Heart Foundation SENIOR-RITA trial.

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Disclosures

All authors have reported that they have no relationships with industry relevant to the contents of this paper to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.086.

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