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The impact of patient-reported frailty on cardiovascular outcomes in elderly patients after non-ST-acute coronary syndrome

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ABSTRACT

Background: As life expectancy increases, the population of older individuals with coronary artery disease and frailty is growing. We aimed to assess the impact of patient-reported frailty on the treatment and prognosis of elderly early survivors of non-ST-elevation acute coronary syndrome (NSTE-ACS).

Methods: Frailty data were obtained from two prospective trials, POPular Age and the POPular Age Registry, which both assessed elderly NSTE-ACS patients. Frailty was assessed one month after admission with the Groningen Frailty Indicator (GFI) and was defined as a GFI-score of 4 or higher. In these early survivors of NSTE-ACS, we assessed differences in treatment and 1-year outcomes between frail and non-frail patients,

Abbreviations: ACS, Acute Coronary Syndrome; DAPT, Dual Antiplatelet Therapy; EQ-5D, EuroQol 5D; GFI, Groningen Frailty Indicator; MACE, Major adverse cardiovascular events; MCS, Mental Component Summary; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCS, Physical Component Summary; PCI, Percutaneous Coronary Intervention; SF-12, Short Form Health Survey 12.

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considering major adverse cardiovascular events (MACE, including cardiovascular mortality, myocardial infarction, and stroke) and major bleeding.

Results: The total study population consisted of 2192 NSTE-ACS patients, aged ≥70 years. The GFI-score was available in 1320 patients (79 ± 5 years, 37% women), of whom 712 (54%) were considered frail. Frail patients were at higher risk for MACE than non-frail patients (9.7% vs. 5.1%, adjusted hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.01–2.43, $p = 0.04$), but not for major bleeding (3.7% vs. 2.8%, adjusted HR 1.23, 95% CI 0.65–2.32, $p = 0.53$). Cubic spline analysis showed a gradual increase of the risk for clinical outcomes with higher GFI-scores.

Conclusions: In elderly NSTE-ACS patients who survived 1-month follow-up, patient-reported frailty was independently associated with a higher risk for 1-year MACE, but not with major bleeding. These findings emphasize the importance of frailty screening for risk stratification in elderly NSTE-ACS patients.

1. Introduction

The growing life expectancy is anticipated to result in a higher prevalence of elderly individuals diagnosed with non-ST-elevation acute coronary syndrome (NSTE-ACS) [1]. These patients often exhibit frailty, which is a complex clinical syndrome that is characterized by reduced physiological reserve and increased vulnerability to stressors [2,3]. It encompasses various domains, including physical, cognitive, and psychosocial aspects. Frailty and cardiovascular disease (CVD) exhibit common risk factors, including advanced age, sedentary lifestyle, unhealthy eating habits, and smoking [3,4]. In older adults with CVD, the prevalence of frailty can be as high as 60%, indicating a significant interplay between frailty and cardiovascular health [5]. Moreover, CVD contributes to the development of frailty through factors such as physical deconditioning and polypharmacy.

On the one hand, frail patients who present with NSTE-ACS less frequently receive invasive treatment and optimal medical therapy, and they have a higher mortality risk [6]. On the other hand, frail patients often present with high-risk disease and may potentially have a relatively greater benefit from invasive treatment. When selecting therapeutic options, clinicians commonly associate classical cardiovascular risk factors, such as advanced age, diabetes, or kidney failure with poorer outcomes. However, frailty has also been identified as a factor that is independently linked to adverse cardiovascular outcomes [7–9]. Unfortunately, in routine clinical practice frailty-related factors, such as impaired psychosocial functioning, are often overlooked. By incorporating objective assessment of frailty with simple tools into clinical routine, healthcare providers may gain insights that are particularly valuable when treating older patients with CVD.

Yet, in elderly NSTE-ACS patients there is a research gap in understanding the impact of patient-reported frailty on cardiovascular outcomes and quality of life in elderly NSTE-ACS patients. Therefore, the main objective of this analysis is to assess the impact of patient-reported frailty on these outcomes, aiming to improve our understanding and therapeutic management of NSTE-ACS in this vulnerable patient population.

2. Methods

2.1. Study design and population

This analysis consists of an assessment of patient-reported frailty from two large trials, the POPular AGE trial and the POPular Age Registry [10,11]. The details on the design, methods and results of the POPular AGE trial have been published previously [12]. In brief, it was an open-label, assessor-blinded, randomized controlled trial performed in 12 centers in the Netherlands between 2013 and 2018. In this study, 1002 patients of 70 years and older were randomized to either clopidogrel, or ticagrelor/prasugrel on top of standard care after NSTE-ACS. The POPular AGE registry was an investigator-initiated, prospective, observational, international, multicenter study of NSTE-ACS patients ≥75 years of age. In this study, 1227 patients were recruited between 2016 and December 2019 at 29 sites in the Netherlands, the United Kingdom, and Austria. In both studies, follow-up duration was 12 months.

Decisions regarding medical therapy, performance of invasive coronary angiography (CAG) and, if indicated, subsequent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were at the discretion of the attending physicians, except for the patients enrolled in the POPular AGE trial, as they were randomized between ticagrelor and clopidogrel [10]. Both studies were conducted according to the principles of the Declaration of Helsinki and was approved by the local Medical Research Ethics Committee. All patients provided written informed consent.

2.2. Data collection

Demographic, clinical and procedural characteristics, and in-hospital and one-year follow-up data were collected. Frailty was evaluated using the Groningen Frailty Indicator (GFI) one month after admission [13]. The GFI measures frailty through a self-assessment questionnaire reflecting their condition in the previous months, and was therefore used as a proxy for baseline frailty scores in this analysis. The questionnaire consists of 15 questions measuring the dimensions of physical and psychosocial vulnerability. All items are dichotomized to calculate the total GFI sum score. A higher GFI sum score indicates a greater level of frailty, with a maximum score of 15. A person is considered to be frail when the GFI sum score is 4 points or higher [13]. Within the GFI-score, there are two major domains: one for physical mobility, with a maximum score of 4, and another for psychosocial functioning, with a maximum score of 5.

At one and twelve months, patients were sent a questionnaire inquiring about current medication use, events, new hospital admissions and quality of life by use of the Short Form Health Survey 12 (SF-12) in the POPular Age registry and EuroQol 5D (EQ-5D) in the POPular Age trial. The SF-12 can be used to calculate the Physical Component Summary (PCS) and Mental Component Summary (MCS) scales. The EQ-5D is a widely used self-reported measure for health-related quality of life and consists of questions comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [14]. The EQ-5D outcome ranges from 1, representing full health, to 0, representing a health state considered as bad as being dead. Values below 0 are possible, and indicate health states that are deemed worse than a state as bad as being dead. To estimate EQ-5D responses based on the available SF-12 data, we employed the method outlined by Gray et al. [15]. Missing questionnaire data at one month were imputed by predictive mean matching when at least one item for the questionnaire was registered.

Cardiovascular events consisted of all-cause death, cardiovascular death, recurrent ACS, stroke, stent thrombosis, transient ischemic attack (TIA) and bleeding (Bleeding Academic Research Consortium [BARC] criteria) at one-year follow-up [16,17]. MACE was defined as a composite of cardiovascular death, MI and stroke. Major bleeding was defined as BARC 3 or 5 bleeding. Net adverse clinical events (NACE) was defined as a composite of all-cause death, MI, stroke, or major bleeding. Treatment strategies were CAG only, PCI, CABG, or pharmacological

treatment only.

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR); categorical variables are presented as frequencies and percentages. Differences in baseline characteristics and events during follow-up between the frail and non-frail patients were tested with chi-square or Fisher exact tests for categorical variables and two-sample *t*-test or Mann-Whitney *U* test for continuous variables. The relationship between GFI-score and EQ-5D index at one month was examined using Pearson's correlation coefficient. Baseline characteristics associated with frailty were identified through logistic regression analysis. We assessed various clinical variables (sex, age, hypercholesterolemia, diabetes, previous MI, previous stroke, peripheral artery disease, kidney failure, chronic obstructive pulmonary disease [COPD], Killip class, use of vitamin-K antagonists (VKA), use of angiotensin converting enzyme [ACE]-inhibitors, use of cholesterol-lowering drugs, use of anti-diabetic drugs, use of diuretics and type of $P2Y_{12}$-inhibitor treatment) in a univariate model. Variables were used in the multivariate model if *p*-values were < 0.05.

Kaplan-Meier curves were plotted to illustrate the cumulative incidence of clinical outcomes over time. Differences in survival functions were compared with the log-rank test. Cox proportional hazard regression analyses were conducted, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. The model was adjusted for relevant clinical variables that demonstrated a significant effect on the multivariate model, as assessed using the change-in-estimate method [18]. Variables with a significant effect on the multivariate model, defined as those with a 5% or greater change in estimate, were included. The Cox proportional hazards models with restrictive cubic splines were used to investigate the association between the height of the GFI and EQ-5D score and clinical outcomes. Both scores were modelled with a four-degree-of-freedom restricted cubic spline with the best possible score as a reference. A plot was created to show the estimated hazard ratios relative to the reference score.

For sensitivity analysis, we performed analyses in a cohort of patients without imputed data and a cohort excluding patients with events during the first month. Differences in outcomes between clopidogrel and ticagrelor were only assessed in patients included in the POPular AGE trial, as due to randomization this comparison was not influenced by selection bias and unmeasured confounding. In this sub-analysis, we abstained from calculating *p*-values to mitigate the issue of multiple testing. A two tailed *p*-value <0.05 was used for statistical significance. All analyses were performed using R statistical software version 3.4.2.

3. Results

3.1. Baseline characteristics

Of 2192 NSTE-ACS patients ≥70 years, at least one item of the GFI-score was available in 1320 patients (79 ± 5 years, 37% women) who represented the study population of our present study (Supplementary Fig. 1). Of the study patients, 821 (62%) were from the POPular AGE trial and 499 (38%) from the POPular AGE registry. In 389 patients (29%), at least one item of the GFI-score was missing. Frailty (i.e., a GFI-score of 4 or higher) was present in 712 (54%) patients. Frailty was more common in patients from the POPular AGE registry (61%) as compared to POPular AGE trial participants (41%). Baseline variables are outlined in Table 1. Frail patients were older, more often female, and had a higher incidence of comorbidities, including previous MI, peripheral arterial disease, kidney failure, and diabetes. Of the total population, 1027 patients (78%) underwent invasive management, with either PCI ($N = 573$, 43%) or CABG ($N = 149$, 11%).

Table 1
Baseline characteristics of frail versus non-frail patients.

Characteristics	Frail ($N = 712$)	Non-frail ($N = 608$)	*p-value*
Age (median [IQR])	80.00 [77.00, 84.00]	77.00 [75.00, 81.00]	*<0.001*
Female sex (%)	306 (43.0)	186 (30.6)	*<0.001*
BMI (mean (SD))	26.95 (4.37)	26.89 (3.76)	0.816
History of smoking (%)	320 (44.9)	298 (49.0)	0.097
Hypertension (%)	472 (66.3)	393 (64.7)	0.555
Diabetes Mellitus (%)	210 (29.5)	132 (21.7)	*0.001*
Previous MI (%)	224 (31.5)	155 (25.5)	*0.036*
Previous PCI (%)	176 (24.7)	138 (22.7)	0.390
PAD (%)	80 (11.2)	45 (7.4)	*0.018*
Previous stroke (%)	99 (13.9)	62 (10.2)	*0.040*
Previous bleeding (%)	21 (2.9)	15 (2.5)	0.592
Kidney failure (%)	81 (11.4)	29 (4.8)	*<0.001*
COPD (%)	88 (12.4)	50 (8.2)	*0.014*
Malignancy (%)	25 (3.5)	20 (3.3)	0.825
During admission			
Killip class ≥2 (%)	84 (11.8)	51 (8.4)	*0.042*
Heartrate (mean (SD))	77.87 (46.42)	76.91 (20.96)	0.640
ST depression (%)	263 (36.9)	205 (33.7)	0.223
eGFR EPI (median [IQR])	62.00 [46.80, 75.75]	67.10 [54.40, 80.00]	*<0.001*
CAG (%)	506 (71.1)	521 (85.7)	*<0.001*
PCI (%)	257 (36.1)	316 (52.0)	*<0.001*
CABG (%)	74 (10.4)	75 (12.3)	0.266
Medical treatment			
DAPT (%)	437 (61.4)	423 (69.6)	*0.002*
Triple therapy (%)	52 (7.3)	30 (4.9)	0.075
Dual therapy (%)	92 (12.9)	57 (9.4)	*0.042*
DOAC (%)	71 (10.0)	56 (9.2)	0.640
Vitamin-K antagonist (%)	91 (12.8)	45 (7.4)	*0.001*
Aspirin (%)	555 (77.9)	502 (82.6)	*0.036*
Clopidogrel (%)	315 (44.2)	251 (41.3)	0.279
Prasugrel (%)	4 (0.6)	3 (0.5)	0.865
Ticagrelor (%)	279 (39.2)	269 (44.2)	0.063
Beta-blocker (%)	529 (74.3)	454 (74.7)	0.877
ACE inhibitor (%)	355 (49.9)	346 (56.9)	*0.011*
AT-II antagonist (%)	136 (19.1)	111 (18.3)	0.695
Calcium antagonist (%)	210 (29.5)	157 (25.8)	0.138
Cholesterol-lowering drugs(%)	598 (84.0)	537 (88.3)	*0.024*
Diuretics (%)	237 (33.3)	160 (26.3)	*0.006*
PPI (%)	566 (79.5)	498 (81.9)	0.269
Antidiabetic drugs	183 (25.7)	113 (18.6)	*0.005*
Frailty and Quality of Life			
GFI-score (median [IQR])	6.00 [5.00, 8.00]	2.00 [1.00, 3.00]	*<0.001*
GFI – psychosocial component (median [IQR])	3.00 [2.00, 4.00]	0.00 [0.00, 1.00]	*<0.001*
GFI – mobility component (median [IQR])	1.00 [0.00, 2.00]	0.00 [0.00, 0.00]	*<0.001*
EQ-5D (median [IQR])	0.69 [0.55, 0.80]	0.85 [0.76, 1.00]	*<0.001*

Data are n (%) unless stated otherwise. ACE = angiotensin-converting enzyme; AT-II = angiotensin-II; IQR = interquartile range; BMI = body mass index; CABG = coronary artery bypass grafting; CAG = coronary angiography; COPD = chronic obstructive pulmonary disease; CVA = Cerebrovascular accident; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate (CKD-EPI formula); EQ-5D = EuroQol 5D; GFI = Groningen Frailty Indicator; IQR = interquartile range; kg = kilogram; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; SD = standard deviation; STEMI = ST-elevation myocardial infarction; TIA = Transient Ischemic Attack.

3.2. Frailty and quality of life

The median GFI-score was 4 (IQR 2.00, 6.00). There were no patients with a frailty score above 13. The GFI-scores showed a left-skewed distribution (Supplementary Fig. 2). The median GFI-score was 2 in non-frail patients (IQR 1.00, 3.00) versus 6 (IQR 5.00, 8.00) in frail patients ($p < 0.001$). Coherently, quality of life was higher in the non-frail group than in frail patients (0.85, IQR 0.76–1.00 vs. 0.69, IQR

0.55–0.80; $p < 0.001$). The correlation analysis revealed a significant negative correlation between the GFI and EQ-5D score ($r = -0.53$, p < 0.001, 95% CI [−0.58, −0.50]), indicating a strong inverse relationship (Supplementary Fig. 3). Multivariable logistic regression showed that age (odds ratio [OR] 1.11, 95% CI 1.08–1.14), female sex (OR 1.69, 95% CI 1.32–2.16), diabetes (OR 1.57, 95% CI 1.20–2.05), previous MI (OR 1.28, 95% CI 1.01–1.64), COPD (OR 1.56, 95% CI 1.06–2.31), kidney failure (OR 1.94, 95% CI 1.26–3.09), and use of VKA (OR 1.88, 95% CI 1.27–2.81) were associated with frailty.

3.3. Clinical outcomes across frailty and quality of life

The event rates for MACE was higher in frail patients than in non-frail patients (9.7% vs. 5.1%), while the rate for major or clinically-relevant non-major bleeding showed no statistically significant difference (3.7% vs. 2.8%) (Table 2). Univariable Cox regression analysis showed that both frailty as a binary variable (frail vs. non-frail, HR 2.04, 95% CI 1.33–3.11, $p = 0.001$)) and the GFI-score as a continuous variable (HR 1.11, 95%CI 1.04–1.19, $p = 0.002$) were associated with MACE, but not with major bleeding (2.8% vs. 3.7%, HR 1.34, 95% CI 0.72–2.46, $p = 0.35$). (Table 2). After applying the change-in-estimate method, we identified age and diabetes as the only variables that met the criteria for inclusion in the final multivariable model due to their significant effects. After multivariable adjustment, frailty remained associated with MACE (adjusted HR 1.57, 95% CI 1.02–2.43, $p = 0.04$). The relation between the height of the GFI-score and cardiovascular outcomes is demonstrated in Fig. 1. The graphs show an increasing risk for MACE, major bleeding, and NACE as patients score higher on the GFI-score, also after adjusting for confounders. A Kaplan-Meier analysis showed a significant difference between frail and non-frail patients (log-rank p-value = 0.00078) (Fig. 2). The association between frailty and the individual cardiovascular outcomes were also addressed separately. All-cause mortality showed the strongest association with frailty (adjusted HR 3.27, 95% CI 1.77–6.03, $p < 0.001$), while the association between frailty and CV death was less pronounced (Table 2). Frailty was not associated with higher rates of MI (adjusted HR 1.33, 95% CI 0.79–2.26) or stroke (HR 1.08, 95% CI 0.24–4.74).

When employing different cut-off points for the GFI-score, the relationship between frailty and MACE did not reach statistical significance (cut-off of 3 or higher: adjusted HR 1.30, 95% CI 0.81–2.07, $p = 0.30$; cut-off of 5 or higher: adjusted HR 1.24, 95% CI 0.83–1.86, p = 0.30). When separately assessing the two main components of the GFI-score - the physical mobility and psychosocial functioning score - physical mobility was strongly related to MACE (HR 1.35, 95% CI 1.14–1.61, $p < 0.001$), while psychosocial functioning was not (HR 1.06, 95% CI 0.95–1.19, $p = 0.274$).

The relationship between quality of life and cardiovascular outcomes is shown in Supplementary Fig. 4.

As the EQ-5D score decreased, the risk significantly increased of experiencing the adverse cardiovascular outcomes MACE, major bleeding, and NACE.

Table 2
Cardiovascular outcomes in the total population and in non-frail versus frail patients.

	Total (N = 1320)	Frail (N = 712)	Non-frail (N = 608)	Hazard ratio (95% CI)[a]	P-value
MACE: CV death, MI or stroke	100 (7.6)	69 (9.7)	31 (5.1)	1.57 (1.02–2.43)	0.04
NACE: All-cause death, MI, stroke, or 3–5 BARC bleeding	179 (13.6)	125 (17.6)	54 (8.9)	1.77 (1.27–2.45)	<0.001
All-cause death	73 (5.5)	60 (8.4)	13 (2.1)	3.27 (1.77–6.03)	<0.001
CV death	29 (2.2)	24 (3.4)	5 (0.8)	2.85 (1.05–7.62)	0.04
MI	64 (4.8)	41 (5.8)	23 (3.8)	1.33 (0.79–2.26)	0.28
Stroke	9 (0.7)	6 (0.8)	3 (0.5)	1.08 (0.24–4.74)	0.92
BARC 2, 3 and 5	177 (13.4)	89 (12.5)	88 (14.5)	0.91 (0.66–1.23)	0.53
BARC 3 and 5	43 (3.3)	26 (3.7)	17 (2.8)	1.23 (0.65–2.32)	0.53

Data are n (%). BARC = bleeding academic research consortium; CV = cardiovascular; FU = follow-up; MACE = Major Adverse Cardiac events; MI = myocardial infarction; NACE = Net Adverse Clinical Events.

[a] Hazard ratio is adjusted for age and diabetes mellitus.

3.4. Invasive versus conservative management

In frail patients, invasive management was strongly associated with a lower incidence of MACE (6.7% vs. 17.0%, adjusted HR 0.40, 95% CI: 0.24–0.65, p < 0.001). Yet, in non-frail patients, invasive management was not associated with a lower risk for MACE (4.8% vs. 6.9%, adjusted HR 0.88, 95% CI: 0.36–2.21, $p = 0.80$). Frailty status alone could not primarily explain this difference in outcome (p-value for interaction = 0.18), indicating that other factors play an important role as well.

3.5. Clopidogrel versus ticagrelor

Among patients from the POPular AGE trial ($N = 392$), there were no differences between those treated with clopidogrel ($N = 206$) or ticagrelor ($N = 186$) at baseline (Supplementary Table 1). Among non-frail patients, there appears to be a larger benefit in MACE with ticagrelor than with clopidogrel (1.8% vs. 7.2%), while the major bleeding rate was 4.5% vs. 3.2%, respectively (Supplementary Table 2). However, among the frail patients, there was an increased major bleeding rate with ticagrelor versus clopidogrel (7.9% vs. 2.5%), yet the MACE rate was still numerically lower in patients treated with ticagrelor (3.9% vs. 7.4%).

4. Discussion

The main findings of the present study are that (1) frailty is common among elderly NSTE-ACS patients who survived one month after a NSTE-ACS, affecting more than half of these patients, (2) frailty is independently associated with 1-year MACE and all-cause death, and (3) the risk for MACE increases gradually with increasing frailty.

As life expectancy continues to rise globally, the burden of cardiovascular diseases in the elderly population is also expected to increase. Understanding how frailty influences the clinical course, quality of life, and management decisions in NSTE-ACS patients is paramount for optimizing medical care in this vulnerable group. Our study is one of the largest to date to assess patient-reported frailty within a cohort of elderly NSTE-ACS patients, and it is the first to do this using the validated GFI questionnaire. Our data show that frailty, as defined by a GFI-score of 4 or higher, is highly prevalent in elderly NSTE-ACS patients with 54% of all patients being defined as frail. This is in line with other, mainly observational, studies, that assessed frailty in elderly ACS patients [19,20].

The findings about the relation between frailty and clinical outcomes provide important insights into the prognostic implications of frailty in elderly NSTE-ACS patients. Although it is known that frailty is a strong predictor for all-cause mortality, our data demonstrates that frail patients also had a significantly higher risk of MACE [7,21]. Interestingly, our study did not find a significant association between patient-reported frailty based on the GFI and major bleeding events. There are two other large trials that looked at the impact of frailty on bleeding In a study by Patel et al., frailty, assessed through a frailty index based on a variety of baseline variables, exhibited a significant association solely with in-hospital major bleeding among STEMI patients, with no observed

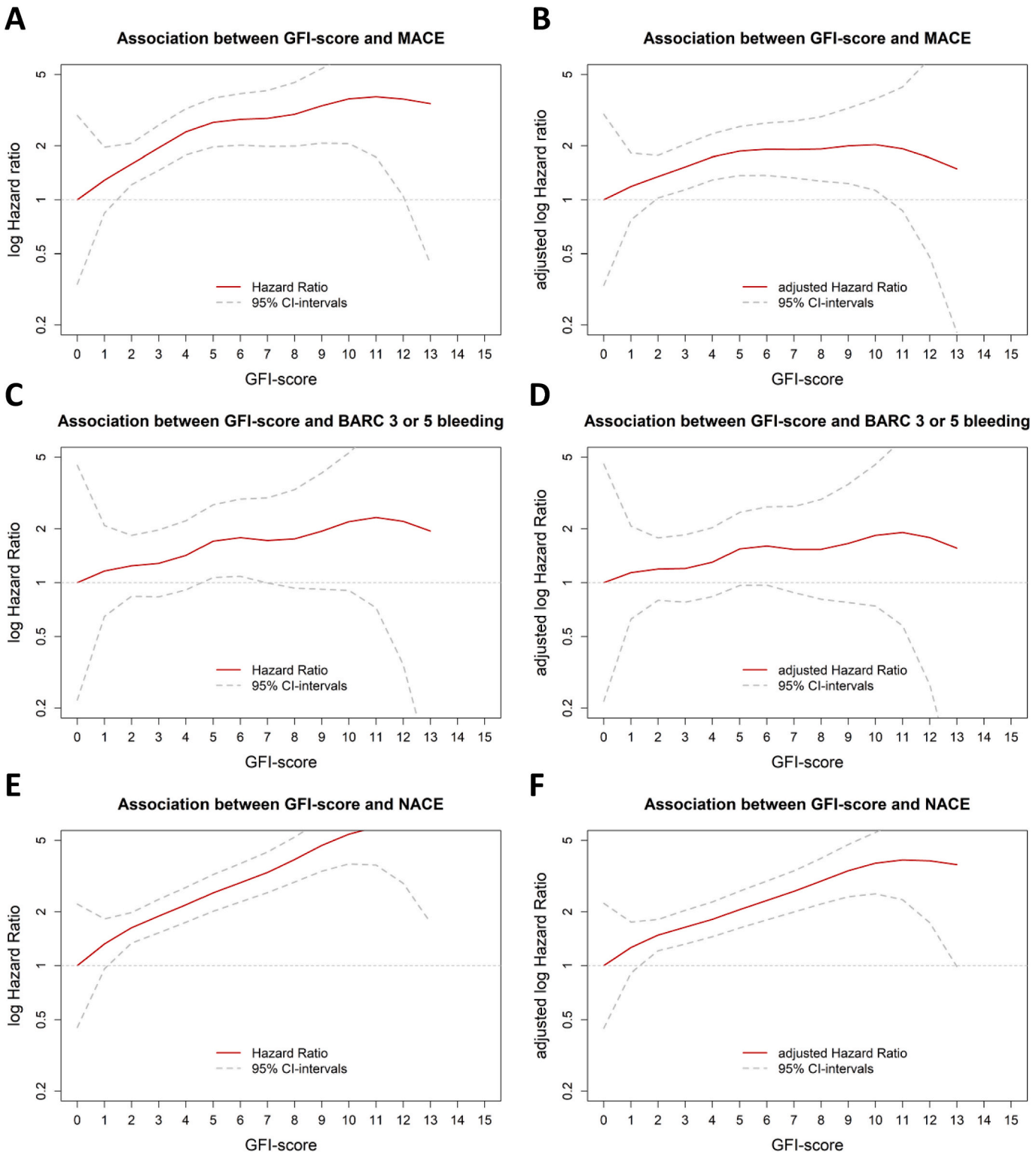

Fig. 1. Cubic spline plots showing the relation between the height of the Groningen Frailty Indicator (GFI) score and major adverse cardiovascular events (MACE), BARC 3 or 5 bleeding and net adverse clinical events (NACE). A. Unadjusted association between the GFI-score and MACE; B. Adjusted association between the GFI-score and MACE; C. Unadjusted association between the GFI-score and BARC 3 or 5 bleeding; D. Adjusted association between the GFI-score and BARC 3 or 5 bleeding; E. Unadjusted association between the GFI-score and NACE; F. Adjusted association between the GFI-score and NACE.

correlation in NSTE-ACS patients [22]. In the TRILOGY ACS study, frailty was assessed using a self-reported questionnaire. [8] The study failed to find evidence of an association between frailty and bleeding. A meta-analysis including both trials did show an independent association between frailty and bleeding, however the included studies were very heterogeneous and primarily assessed in-hospital bleeding [23]. While there is no clear explanation the lack of an association between frailty and bleeding, it may be related to the lower activity levels, less intensive antithrombotic treatment and higher discontinuation rates in frail patients, lowering their exposure to bleeding.

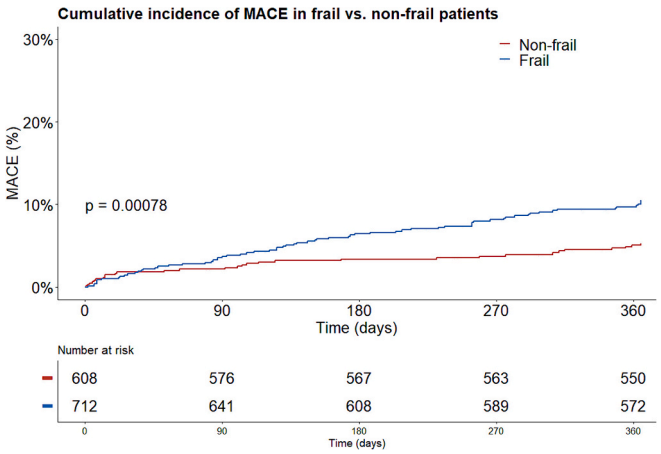

Fig. 2. Kaplan Meier time to event curves for major adverse cardiovascular events for frail and non-frail patients. The graph shows the incidence of major adverse cardiovascular events (MACE) for patients classified as frail or non-frail.

The increased risk of MACE in frail patients suggests that clinicians could use frailty assessment as part of the risk stratification process for NSTE-ACS patients [24]. In addition, the relationship between GFI-score and MACE exhibited a gradual progression, which suggests that employing a specific cut-off value for the GFI-score may not be the optimal approach. Converting a score into a binary outcome carries the risk of losing valuable information and nuances in the data. Therefore, clinicians should consider the full range of this scale to better gauge the risk of an individual patient. Our study is the first to show this clear gradual association between a frailty score and prognosis in patients with NSTE-ACS. This finding is, however, supported by data from the TRILOGY ACS study showing a gradual increased risk for cardiovascular events from normal to pre-frail to frail [8].

4.1. *Frailty and medical management*

Extensive RCT and registry data have shown that early invasive therapy (i.e., CAG) yields superior clinical outcomes in elderly patients with NSTE-ACS compared to more conservative approaches [11,25,26]. The findings of our current post-hoc study highlight the relative beneficial effect of invasive therapy in frail patients. While the support for a formal integration of frailty into clinical decision-making tools may still be somewhat weak, Heart Teams do consider frailty in daily clinical practice when discussing the treatment of individual elderly patients. This requires well-balanced decisions. On the one hand, the significant reduction of MACE in frail patients who were invasively managed may highlight the potential for proportionately greater clinical benefits in elderly frail patients (with inherently higher risk of cardiovascular events) [27,28]. On the other hand, the substantial relative reduction in MACE may result from sound clinical decision-making, including to refrain from invasive management in patients with an unfavorable prognosis. In contrary to our results, the LONGEVO-SCA registry did not find a reduction of ischemic events when frail NSTE-ACS patients were treated invasively [29]. Although this complicates the interpretation of these results, the differences in outcomes may be explained by variations in the definition of outcomes, population, frailty assessment, and the timing of frailty status determination.

The POPular Age trial showed that clopidogrel is a favorable alternative to ticagrelor as it reduced bleeding while being non-inferior regarding the net clinical benefit outcome [10]. The subgroup analysis, performed in a relatively small patient population, suggests that the favorable benefit of clopidogrel may be more pronounced in frail patients. The findings of the current study should be considered as hypothesis-generating; yet, as demonstrated by the Frail-Atrial Fibrillation (FRAIL-AF) trial, the efficacy and safety of universally adopted therapies may differ in frail populations [30]. In (pre-)frail older patients (GFI $\geq$ 3), VKA treatment was shown to reduce bleeding rates, as compared to direct-acting oral anticoagulants (DOACs), without an associated reduction in thromboembolic complications, indicating that findings of landmark trials may not consistently be extrapolated to elderly and frail patient populations. Despite VKA being more frequently used among frail patients, possibly due to the enrollment period dating from several years ago and the higher age in this group, its influence on the study results is likely minimal given the low rates of VKA and DOAC use in our population.

4.2. *Frailty and quality of life*

Quality of life, based on the EQ-5D, showed a significant negative correlation with the GFI-score, consistent with findings in other studies [31]. This indicates that frailty is linked to reduced self-reported well-being in elderly NSTE-ACS patients. It emphasizes the impact of frailty on not only physical health, but also psychosocial dimensions. This association highlights the importance for a comprehensive geriatric assessment that considers not only traditional cardiovascular risk factors but also the unique vulnerabilities and needs of frail individuals. Incorporating such assessment into routine clinical practice could help identify patients who may require tailored interventions in order to improve their quality of life. In fact, this is addressed in the most recent ACS guidelines by the European Society of Cardiology, which state that assessment of mental well-being with a validated tool and onward psychological referral when appropriate, should be considered (Class IIa, Level of Evidence B) [32].

4.3. *Limitations*

This study has some relevant limitations. When comparing outcomes between frail and non-frail patients, residual confounding is inevitable due to the inherent relation between frailty and both comorbidities and advanced age. When suggesting an independent association between frailty and clinical outcome, mere adjustment for known confounding factors will not completely eradicate bias. Another limitation was the timing of the questionnaires, one month after hospital admission, which we deliberately chose in order to minimize the potential impact of the hospital admission on the patient's response. As patients who passed away within the first month could not respond to the questionnaires, the approach introduced a slight selection bias that resulted in assessing a population with a somewhat lower risk. Nevertheless, as our results are in line with previous studies that assessed frailty at baseline, we do not anticipate that this will detract from the outcomes observed [27]. Furthermore, the imputation of missing data could introduce bias or uncertainty into the findings. Finally, the GFI relies on patient-reported data and does not incorporate objective functional measures that are used in other frailty screening scores [4].

5. Conclusion

In elderly NSTE-ACS patients who survived 1- month follow-up, patient-reported frailty was independently associated with a higher risk for 1-year MACE, but not with major bleeding. These findings emphasize the importance of frailty screening for risk stratification in elderly NSTE-ACS patients.

Ethics approval and consent to participate

The POPular Age was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Medical research Ethics Committees United (MEC-U) (protocol code R13.017 and date of approval: 6th of June 2013). The POPular Age Registry was conducted according to the guidelines of the Declaration of

Helsinki, and approved by the Ethics Committee of Medical research Ethics Committees United (MEC-U) (protocol code W17.021. and date of approval: 28th of February 2016). Informed consent was obtained from all subjects involved in both studies.

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CRediT authorship contribution statement

W.W.A. van den Broek: Writing – original draft, Visualization, Validation, Project administration, Investigation, Formal analysis. **M.E. Gimbel:** Writing – review & Editing, Conceptualization, Methodology, Resources, Validation, Project Administration, Investigation, Funding acquisition. **R.S. Hermanides:** Writing – review & editing, Supervision, Investigation. **C. Runnett:** Writing – review & editing, Supervision, Investigation. **R.F. Storey:** Writing – review & editing, Supervision, Investigation. **P. Knaapen:** Writing – review & editing, Supervision, Investigation. **M.E. Emans:** Writing – review & editing, Supervision, Investigation. **J. Cooke:** Writing – review & editing, Supervision, Investigation. **R.M. Oemrawsingh:** Writing – review & editing, Supervision, Investigation. **G. Galasko:** Writing – review & editing, Supervision, Investigation. **R. Walhout:** Writing – review & editing, Supervision, Investigation, Conceptualization. **C. von Birgelen:** Writing – original draft, Supervision, Investigation. **M.G. Stoel:** Writing – review & editing, Supervision, Investigation. **Paul F.M.M. van Bergen:** Writing – review & editing, Supervision, Investigation. **S.L. Brinckman:** Writing – review & editing, Supervision, Investigation. **I. Aksoy:** Writing – review & editing, Supervision, Investigation. **A. Liem:** Writing – review & editing, Supervision, Investigation. **A.W.J. van't Hof:** Writing – review & editing, Supervision, Investigation. **J.W. Jukema:** Writing – review & editing, Supervision, Investigation. **A.A.C.M. Heestermans:** Writing – review & editing, Supervision, Investigation. **D. Nicastia:** Writing – review & editing, Supervision, Investigation. **H. Alber:** Writing – review & editing, Supervision, Investigation. **D. Austin:** Writing – review & editing, Supervision, Investigation. **A. Nasser:** Writing – review & editing, Supervision, Investigation. **V. Deneer:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **J.M. ten Berg:** Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Dr. D.A.A.M. Schellings served as the principal investigator at the Slingeland Hospital (Department of Cardiology, Doetinchem, the Netherlands) and played a crucial role in both studies conducted at this site. He actively contributed to the trials' execution and manuscript review and editing. Regrettably, Dr. Schellings passed away in 2023 and was unable to provide consent for the latest version of the manuscript and its submission to this journal.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131940.

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