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Frailty Is Independently Associated With Short-Term Outcomes for Elderly Patients With Non-ST-Segment Elevation Myocardial Infarction

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Background—For the large and growing population of elderly patients with cardiovascular disease, it is important to identify clinically relevant measures of biological age and their contribution to risk. Frailty is an emerging concept in medicine denoting increased vulnerability and decreased physiological reserves. We analyzed the manner in which the variable frailty predicts short-term outcomes for elderly non-ST-segment elevation myocardial infarction patients.

Methods and Results—Patients aged ≥ 75 years, with diagnosed non-ST-segment elevation myocardial infarction were included at 3 centers, and clinical data including judgment of frailty were collected prospectively. Frailty was defined according to the Canadian Study of Health and Aging Clinical Frailty Scale. The impact of the comorbid conditions on risk was quantified by the coronary artery disease-specific index. Of 307 patients, 149 (48.5%) were considered frail. By multiple logistic regression, frailty was found to be strongly and independently associated with risk for the primary composite outcome (death from any cause, myocardial reinfarction, revascularization due to ischemia, hospitalization for any cause, major bleeding, stroke/transient ischemic attack, and need for dialysis up to 1 month after inclusion) (odds ratio, 2.2; 95% confidence interval, 1.3–3.7), in-hospital mortality (odds ratio, 4.6; 95% confidence interval, 1.3–16.8), and 1-month mortality (odds ratio, 4.7; 95% confidence interval, 1.7–13.0).

Conclusions—Frailty is strongly and independently associated with in-hospital mortality, 1-month mortality, prolonged hospital care, and the primary composite outcome. The combined use of frailty and comorbidity may constitute an ultimate risk prediction concept in regard to cardiovascular patients with complex needs.

Clinical Trial Registration—<http://www.clinicaltrials.gov>. Unique identifier: NCT01049997. (*Circulation*. 2011;124:2397-2404.)

Key Words: elderly ■ frailty ■ non-ST-segment elevation acute coronary syndromes ■ outcomes research

In Western countries, the number of elderly patients with complex needs for healthcare is large and growing as a result of demographic and epidemiological causes. The most common diagnostic category for this patient group is cardiovascular disease.^{1–3} A recent scientific statement from the American Heart Association Council emphasized that the evaluation of frailty, comorbidity, and functional status is crucial when elderly patients with non-ST-segment elevation myocardial infarction (NSTEMI) are treated.⁴

Clinical Perspective on p 2404

The present guidelines, based primarily on randomized, controlled trials and systematic reviews, focus on the treatment of defined organ-specific diagnoses (eg, NSTEMI), which makes them difficult to apply to individual patients with multiple comorbidities. Many randomized, controlled

trials^{5,6} exclude elderly patients with specified comorbid conditions, which limits the generalizability of the results to patients in routine practice.^{4,7–12} There is a particular lack of data concerning the long-term adverse outcomes for these patients.¹³ Interactions between normal biological aging processes in the cardiovascular system, age-related pathology, sequelae of heart disease, comorbidity, and polypharmacy can influence the benefit-risk ratio of medical interventions.¹⁴ The increasing cardiovascular risk in elderly patients can increase the benefit of interventions. However, these patients are at higher risk of complications (eg, bleedings, cerebrovascular events, and renal insufficiency).^{4,14} It has been stated that adhering to guidelines in caring for elderly patients with several comorbid conditions may have undesirable effects.¹¹ Given that $\approx 50\%$ of myocardial infarctions afflict patients aged ≥ 75 years,^{3,15,16} the problem does not appear to be minor.

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The Swedish national guidelines for heart disease emphasize that the patient's biological age (ie, biological status and expected length of life) is crucial for decision making.¹⁷ However, there is very limited guidance in regard to how biological age should be estimated and how different comorbid conditions influence the benefit-risk ratio of interventions.

The term *frailty* denotes a multidimensional syndrome characterized by increased vulnerability and decreased physiological reserves.^{18–23} Frailty stratification predicts a patient's risk of death and need for institutional care.^{19,20} There is not a single accepted operational definition.²³ Although frailty instruments have thus far been validated and used mainly in a geriatric context, they have been identified as being potentially relevant for heart patients as well in regard to risk stratification for elderly patients with cardiovascular disease.^{4,14,22,24}

Our aim in this study is to describe patients aged ≥ 75 years with NSTEMI, especially in regard to the variables cardiovascular risk, comorbidity, and frailty, and to analyze the manner in which frailty is associated with short-term outcomes for these patients.

Methods

Study Sample

Between October 2009 and June 2010, we included evaluable patients aged ≥ 75 years with diagnosed NSTEMI treated at Linköping University Hospital and the county hospitals in Trollhättan (NÄL-Uddevalle) and Jönköping (Ryhov). The patients received care in 1 or more of the following hospital units: cardiology, acute medicine, geriatrics, and other areas of internal medicine.

This is an observational study addressing a study instrument (Clinical Frailty Scale) that has not been used previously to predict risk of short-term outcomes for NSTEMI patients. It was therefore difficult to estimate a clinically relevant difference regarding outcomes for frail versus nonfrail elderly patients. We estimated that ≈ 300 patients should be included.

Despite the aforementioned issues, before the study we tried to estimate the expected percentages of primary outcome events for frail and nonfrail NSTEMI patients aged ≥ 75 years. We approximated these 2 groups of patients with the percentages of outcome events of the Global Registry of Acute Coronary Events (GRACE) (30%) and the Virtual Coordinating Center for Global Collaborative Cardiovascular Research (VIGOUR) (15%) populations aged ≥ 75 years, respectively.⁴

Given this rough estimation, a chosen level of significance of 5%, and a power of 80%, we determined that ≈ 260 patients should be included.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and the latest version of the Good Clinical Practice Guidelines. The study was undertaken after the protocol and its appendices had received full approval from the Independent Ethics Committee in Linköping.

Data Collection and Variable Selection

Patients aged ≥ 75 years with diagnosed NSTEMI according to their attending physicians were included consecutively.

The Canadian Study of Health and Aging Clinical Frailty Scale is a 7-point scale with good predictive validity (regarding death and need for institutional care) and prognostic power that relies on clinical judgment¹⁹ (Figure 1). It is a global clinical measure of biological age, and it combines comorbidity, disability, and cognitive impairment. First, 3 independent translations of the Canadian Study

1	Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well – without active disease, but less fit than people in category 1.
3	Well, with treated comorbid disease – disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.
5	Mildly frail – with limited dependence on others for instrumental activities of daily living
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

(Rockwood, K. et al. (2005). A global clinical measure of fitness and frailty in elderly people. *CMAJ* 173(5): 489-95.)

Figure 1. The Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS). Reproduced from Rockwood et al¹⁹ with permission of the publisher. Copyright © CMAJ, 2005.

of Health and Aging Clinical Frailty Scale from English into Swedish were done by 2 translation agencies and the principal investigator. On the basis of these translations, a consensus-based choice of an appropriate translation was performed in a group consisting of 1 physician, 1 nurse, 1 physiotherapist, and 1 occupational therapist. The resulting consensus version in Swedish was retranslated into English, which finally was compared with the original English version. Before start of the study, the study nurses underwent training regarding assessment of frailty. Then they individually assessed the frailty of 30 patients. An intraclass correlation test²⁵ showed that the interrater reliability regarding the study nurses' judgment of frailty was very good at the individual level (intraclass correlation 2-way random consistency [30 cases, 4 raters], single measure: 0.97; 95% confidence interval [CI], 0.94–0.98%). An intraclass correlation coefficient of ≥ 0.75 has been defined previously as indicating a good degree of agreement between the raters.²⁶

If the inclusion criteria were fulfilled and the patient had given informed consent, evaluation of the patient's degree of frailty was based on bedside judgment regarding frailty and other clinical information, including the records in the patient file. If a patient was unable to give informed consent but there was sufficient clinical information including the records in the patient file, evaluation of the patient's degree of frailty was based on this information only (ie, without bedside judgment). A few patients who fulfilled the inclusion criteria while evidently not fulfilling any of the exclusion criteria were for some reason not evaluated during the hospital care episode. For these cases, the evaluation of frailty was based on the records in the patient file and/or information obtained via a telephone call to the patient, after the patient had provided written consent via a letter. After permission from the hospital board was received, a computer-based screening of the hospital's diagnosis register was performed intermittently to detect potentially eligible but already discharged NSTEMI patients.

There were 2 exclusion criteria: (1) if the patient was not willing to participate or (2) if the patient was not evaluable because of communication problems and insufficient clinical information to enable a judgment of frailty.

Other demographic and clinical patient characteristics that were thought to be potential confounders when the hypothesis was tested were the following: chronological age, sex, cardiovascular risk, myocardial infarction classification, ejection fraction, diabetes mellitus, previous myocardial infarction, and comorbidities. Multimorbidity is defined as “the co-occurrence of multiple chronic or acute diseases and medical conditions within one person.”²⁷ Comorbidity is defined in the same way, although in relation to a specific index condition²⁸ (eg, NSTEMI).

Cardiovascular risk was assessed according to the Fast Revascularization during Instability in Coronary artery disease II (FRISC II) score,^{17,29} which takes into account the following parameters denoting high risk: positive biochemical markers (troponins), ECG signs of myocardial ischemia, previous myocardial infarction, diabetes

Risk factor	Integer coefficient
Current smoker	1
Hypertension	1
History of CVA/TIA	1
DM	2
DM with sequelae	3
COPD	2
PVD	2
Tumour/lymphoma/leukemia	2
Moderate to severe renal disease*	7
Metastatic cancer	5

* Defined as creatinine >3 mg/dl (29)

Figure 2. The coronary artery disease (CAD)-specific index. The integer coefficients are summed, and the resulting score denotes risk group, as follows: 0 to 1, low risk; 2 to 3, moderate risk; and ≥ 4 , high risk. CVA indicates cerebrovascular accident; TIA, transient ischemic attack; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; and PVD, peripheral vascular disease. From Sachdev et al³⁵ with permission of the publisher. Copyright © 2004, Elsevier.

mellitus, chronological age >70 years, male sex, and inflammatory activation.

The presence of 3 or 4 of the aforementioned parameters implies moderate cardiovascular risk, whereas the presence of ≥ 5 implies high cardiovascular risk. The myocardial infarction was classified according to the Joint European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation Task Force consensus statement.³⁰ Echocardiography, ECGs, laboratory testing, and registration of anthropometric data were done according to routine practice. Those comorbidities with a supposed potential to change the benefit-risk ratio of intervention were registered, as follows: diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure (CHF), renal impairment, cerebrovascular disease, peripheral vascular disease, malignant disease, anemia, and dementia. Information was abstracted from the patients' medical records. When ≥ 1 of the following conditions was present, the patient was considered to have severe comorbidity: severe degree of comorbidity according to consensus definitions,^{31–34} malignant disease, a complication of diabetes mellitus,¹³ and an acute severe comorbid condition (ie, bleeding, stroke, septic infection, pneumonia).¹² Furthermore, the supposed impact of the comorbid conditions on risk was quantified by the coronary artery disease (CAD)-specific index³⁵ (Figure 2).

The physician who made the decision to perform or not to perform coronary angiography was asked to present his or her reasons for the decision via the case report form.

Follow-up was done 1 month after the time of inclusion via the patient files and the Causes of Death Register.

The Linköping Academic Research Center group at Linköping University Hospital performed study monitoring 3 times from study start until the first follow-up.

Clinical Outcomes

The primary outcome in this study was the composite of death from any cause, myocardial reinfarction, revascularization due to ischemia, hospitalization for any cause, major bleeding, stroke/transient ischemic attack, and need for dialysis up to 1 month after inclusion. The secondary outcome was the composite of major bleeding, stroke/transient ischemic attack, and need for dialysis up to 1 month after inclusion.

A bleeding was defined as major if 1 of the following was present: intracranial bleeding, retroperitoneal bleeding, blood transfusion, hemoglobin decrease >3 g/dL with overt cause, or hemoglobin decrease >4 g/dL without overt source.³⁶

Table 1. Baseline Patient Characteristics

Variable, n (%)	Nonfrail (n=158)	Frail (n=149)	P
Mean age, y	83	85	0.0003
Female sex	69 (43.7)	81 (54.4)	0.068
Diabetes mellitus	29 (18.4)	41 (27.5)	0.058
COPD	8 (5.1)	19 (12.8)	0.025
Congestive heart failure	25 (15.8)	56 (37.6)	<0.0001
Severe renal impairment*	26 (16.5)	56 (37.6)	<0.0001
Peripheral vascular disease	9 (5.7)	18 (12.1)	0.068
Cerebrovascular disease	26 (16.5)	50 (33.6)	0.0006
Dementia	9 (5.7)	41 (27.5)	<0.0001
Anemia	51 (32.3)	84 (56.4)	<0.0001
Malignant disease	20 (12.7)	25 (16.8)	0.336
Previous myocardial infarction	59 (37.3)	70 (47.0)	0.106
Type 2 myocardial infarction†	50 (31.7)	56 (37.6)	0.283
Medium or high cardiovascular risk	136 (86.1)	140 (94.0)	0.024
High CAD index score	36 (22.8)	62 (41.6)	0.0006

COPD indicates chronic obstructive pulmonary disease; CAD, coronary artery disease.

*Defined as glomerular filtration rate <30.³¹

†Myocardial infarction secondary to ischemia due to either increased O₂ demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension).³⁰

Stroke and transient ischemic attack were defined according to a consensus statement.³⁷

Statistical Analysis

Statistical analysis was performed via SPSS version 19.0 and SAS version 9.1.3. Categorical data were analyzed by use of the Fisher exact test or the χ^2 test, and continuous data were compared with the Student *t* test. The association of frailty with the primary composite outcome was examined by multiple logistic regression models adjusted for relevant prognostic variables (age, sex, previous myocardial infarction, ejection fraction, presence or absence of diabetes mellitus, cardiovascular risk, classification of myocardial infarction, and comorbidities [ie, the score according to the CAD index]). All 2-way interactions between frailty and the other independent variables were tested to validate the findings of the regression model. The regression model including possible statistically significant interactions was evaluated with a likelihood ratio test. All independent variables included in the models were analyzed for possible collinearity with a variance inflation factor test. Variance inflation factor values of ≥ 2.5 were considered to indicate collinearity.³⁸ A premise for the logistic regression models was the standard guideline that they should not estimate >1 β coefficient for approximately every 10 observations in the smaller group.

Results

Baseline Characteristics

Between October 2009 and June 2010, we included 307 evaluable patients aged ≥ 75 years with diagnosed NSTEMI treated at Linköping University Hospital and the county hospitals in Trollhättan (NÄL-Uddevalla) and Jönköping (Ryhov). In all, 275 patients were evaluated during the hospital care episodes. Thirty-two patients were evaluated after having provided written consent via a letter (ie, after the hospital care episode); of these patients, 2 were evaluated by telephone interview.

Table 2. Outcomes (Unadjusted)

Variable, n (%)	Nonfrail (n=158)	Frail (n=149)	P
Primary composite outcome*	43 (27.2)	68 (45.6)	0.0009
Mortality, 1 mo	5 (3.2)	23 (15.4)	0.0002
Mortality, in-hospital	3 (1.9)	15 (10.1)	0.003
Major bleeding, stroke/TIA, or need for dialysis, in-hospital	6 (3.8)	14 (9.4)	0.063
No. of bed days	7.5	13.4	<0.0001
Coronary angiography, 1 mo	73 (46.2)	23 (15.4)	<0.0001
Revascularization, 1 mo	48 (30.4)	10 (6.7)	<0.0001
	Nonfrail (n=155)	Frail (n=134)	
Rehospitalization, 1 mo	34 (21.9)	40 (29.9)	0.138
Reinfarction, 1 mo	8 (5.2)	10 (7.5)	0.470
Major bleeding, stroke/TIA, or need for dialysis, 1 mo	5 (3.2)	2 (1.5)	0.456

*Primary composite outcome denotes the composite of death from any cause, myocardial reinfarction, revascularization due to ischemia, hospitalization for any cause, major bleeding, stroke/transient ischemic attack (TIA), and need for dialysis up to 1 month after inclusion.

Of these 307 patients, 149 (48.5%) were considered frail according to the study instrument (5–7 on the scale), and 75 (24.1%) were considered moderately or severely frail (6–7 on the scale).

The baseline characteristics are presented in Table 1. Frail patients were slightly older than nonfrail patients, with a mean age of 85 years versus 83 years ($P=0.0003$), although the age range was similar in both groups. Frail patients presented with a greater burden of comorbidity, including higher rates of chronic obstructive pulmonary disease, CHF, severe renal impairment, cerebrovascular disease, anemia, and dementia. They also had higher CAD index and cardiovascular risk scores (all $P<0.05$; Table 1). Furthermore, 78.5% of the frail patients presented with 1 or more severe comorbid conditions compared with 43.0% of the nonfrail patients. The 2 groups did not differ significantly regarding other characteristics. Age was used as a continuous variable, whereas the others were used as categorical variables.

Outcomes

Unadjusted 1-Month Outcomes

Among frail patients, mortality, prolonged number of bed days, and the primary composite outcome were more prevalent than among nonfrail patients (all $P<0.05$; Table 2).

Frailty was associated with increased fulfillment of the primary composite outcome (nonfrail, $n=43$ [27.2%]; frail, $n=68$ [45.6%]; $P<0.001$; Table 2). Other factors associated in a univariate manner with increased fulfilling of the primary composite outcome included CHF, anemia, diagnosed hemodynamic instability during the hospital care episode, cardiovascular risk, and CAD index score (all $P<0.05$; data not shown).

Frailty was associated with increased 1-month mortality (nonfrail, $n=5$ [3.2%]; frail, $n=23$ [15.4%]; $P<0.0001$; Table 2). Other factors associated in a univariate manner with

Table 3. Risk-Adjusted Impact of Frailty on the Primary Composite Outcome

	Odds Ratio (95% CI)	P
Age, y		0.34
75–79	Reference	
80–84	1.19 (0.62–2.30)	0.60
≥85	0.76 (0.39–1.49)	0.43
Gender		0.48
Male	Reference	
Female	0.82 (0.47–1.41)	0.48
Ejection fraction		0.58
>40%	Reference	
≤40%	1.11 (0.58–2.14)	0.75
Not recorded	1.37 (0.76–2.44)	0.30
Cardiovascular risk		0.26
Low	Reference	
Moderate	1.74 (0.64–4.72)	0.28
Severe	2.49 (0.81–7.63)	0.12
Frailty		
Nonfrail	Reference	
Frail	2.17 (1.28–3.67)	0.0041
CAD index		0.049
Low	Reference	
Moderate	0.57 (0.29–1.13)	0.11
Severe	1.36 (0.76–2.45)	0.31

CI indicates confidence interval; CAD, coronary artery disease. The independent variables were tested for collinearity with the use of the variance inflation factor. All variables had a variance inflation factor value <2.5, which does not indicate collinearity.

increased 1-month mortality included CAD index score, ejection fraction, CHF, dementia, anemia, and diagnosed hemodynamic instability during the hospital care episode (all $P<0.05$; data not shown).

Furthermore, frailty was associated with increased in-hospital mortality (nonfrail, $n=3$ [1.9%]; frail, $n=15$ [10.1%]; $P=0.003$; Table 2). Other factors associated in a univariate manner with increased in-hospital mortality included CAD index score, dementia, anemia, CHF, and hemodynamic instability.

Frailty was associated with prolonged hospital care in univariate analyses (nonfrail, 7.5 bed days; frail, 13.4 bed days; $P<0.0001$; Table 2).

Adjusted 1-Month Outcomes

Frailty was independently associated with risk for the primary composite outcome by multiple regression analyses (odds ratio [OR], 2.2; 95% CI, 1.3–3.7; Table 3), as was the CAD index score ($P=0.049$). No other factor was associated with the composite outcome in adjusted analysis.

An analysis regarding the potential interaction between frailty and any of the other described independent variables showed that the predictive strength of frailty regarding the primary composite outcome was influenced by the CAD index score. For frail patients, the OR for the primary outcome was 4.7 (95% CI, 1.3–16.9) for patients with moderately high scores, 6.0 (95% CI, 2.3–15.6) for patients

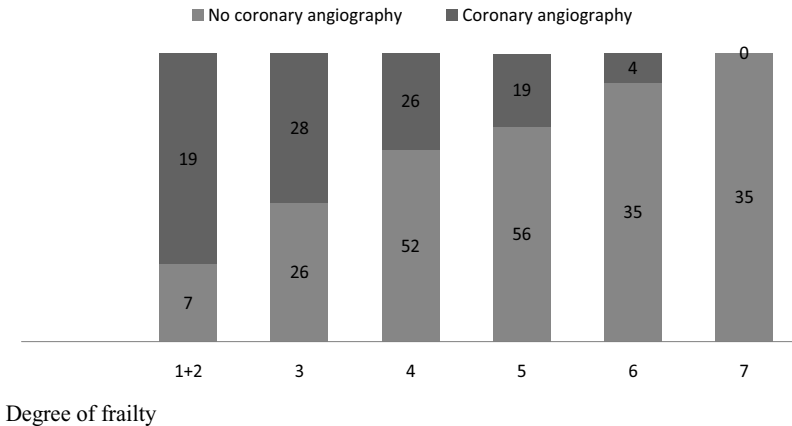


Figure 3. The proportion of patients in each frailty stage not undergoing coronary angiography. The numbers denote numbers of patients.

with high scores, and 0.73 (95% CI, 0.3–1.6) for patients with low scores. No other interaction, including age, was found. The value of including an interaction term between frailty and the CAD index in the regression model was evaluated with a likelihood ratio test. This showed that the model was significantly better ($P < 0.001$) when the interaction term was included.

Frailty was independently associated with reduced 1-month survival after adjustment for the CAD index score and cardiovascular risk (OR, 4.7; 95% CI, 1.7–13.0), as was the CAD index score ($P = 0.042$).

Furthermore, frailty was independently associated with prolonged hospital care by *t* test (frail, 13.4 bed days; nonfrail, 7.5 bed days; $P < 0.0001$) and a following multiple linear regression analysis (data not shown). Other factors associated with prolonged hospital care in adjusted analysis were female sex, low ejection fraction, and high cardiovascular risk (all $P < 0.05$; data not shown).

A sensitivity analysis was undertaken to evaluate how alternative groupings of the variable frailty (in the Clinical Frailty Scale, the degree of frailty is prespecified) would influence results. It showed that when patients were stratified into a group including patients who scored 6 or 7 on the scale (moderately or severely frail) versus other patients (1–5 on the scale [ie, including mildly frail patients]), the former group of patients was more likely to fulfill the composite outcome with OR (OR, 2.7; 95% CI, 1.5–4.8). On the other hand, when patients were stratified into a group including patients who scored 4 to 7 on the scale versus other patients (1–3 on the scale), the former group of patients was not more likely to fulfill the composite outcome.

Frail patients were less likely to be treated in intensive cardiac care units than nonfrail patients (nonfrail, $n = 85$ [53.8%]; frail, $n = 52$ [34.9%]; $P < 0.001$). Furthermore, frail patients were less likely to undergo coronary angiography (Table 2) than nonfrail patients (nonfrail, $n = 73$ [46.2%]; frail, $n = 23$ [15.4%]; $P < 0.0001$). Ninety-six of 307 patients underwent coronary angiography. Of these patients, 4 patients were moderately or severely frail, 19 were mildly frail, and 73 were nonfrail (Figure 3). Patients with severe comorbidity were less likely to undergo coronary angiography, whereas neither the cardiovascular risk score nor the CAD-specific index predicted the performance of coronary angiography.

Of 149 frail patients, 23 underwent coronary angiography (Table 4). Of these 23 patients, 10 were revascularized. In addition, of these 23 patients, 9 (39%) had at least 1 primary outcome event, whereas none died before the 1-month follow-up. Of the 10 patients who were revascularized, 4 (40%) had at least 1 primary outcome event, whereas none died before the 1-month follow-up. Of 126 frail patients who did not undergo coronary angiography (and were not revascularized), 59 patients (47%) had at least 1 primary outcome event. Of these 126 patients, 23 (18%) died before the 1-month follow-up.

Table 4. Baseline Characteristics of Frail Patients Who Underwent Cardiac Catheterization and Frail Patients Who Did Not

Variable, n (%)	Coronary Angiography– (n=126)	Coronary Angiography+ (n=23)	P
Mean age, y	86	80	<0.0001
Female sex	71 (56.3)	10 (43.5)	0.266
Diabetes mellitus	35 (27.8)	6 (26.1)	1
COPD	14 (11.1)	5 (21.7)	0.177
Congestive heart failure	50 (39.7)	6 (26.1)	0.250
Severe renal impairment*	49 (38.9)	7 (30.4)	0.492
Peripheral vascular disease	13 (10.3)	5 (21.7)	0.158
Cerebrovascular disease	42 (33.3)	8 (34.8)	1
Dementia	37 (29.4)	4 (17.4)	0.314
Anemia	72 (57.1)	12 (52.2)	0.656
Malignant disease	18 (14.3)	7 (30.4)	0.070
Previous myocardial infarction	58 (46.0)	12 (52.2)	0.653
Type 2 myocardial infarction†	50 (39.7)	6 (26.1)	0.250
Medium or high cardiovascular risk	118 (93.7)	22 (95.7)	1
High CAD index score	50 (39.7)	12 (52.2)	0.358

Coronary angiography– indicates frail patients who did not undergo cardiac catheterization; coronary angiography+, frail patients who underwent cardiac catheterization; COPD, chronic obstructive pulmonary disease; and CAD, coronary artery disease.

*Defined as glomerular filtration rate < 30 .³¹

†Myocardial infarction secondary to ischemia due to either increased O_2 demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension).³⁰

Discussion

Our study demonstrates frailty to be independently and strongly associated with risk for adverse short-term clinical outcomes for elderly NSTEMI patients. In this study, 48.5% of the patients were frail, and 24.1% were moderately or severely frail. Frail patients manifested an increased burden of disease, and they were slightly older than nonfrail patients. Furthermore, 1 or more severe comorbidity was manifested by 78.5% of the frail patients and 43.0% of the nonfrail patients. Frailty was independently associated with in-hospital mortality, 1-month mortality, prolonged hospital care, and the primary composite outcome. In particular, frail patients with a high comorbidity burden manifested a markedly increased risk for the primary composite outcome. No other interaction with any independent variable, including age, was found. A sensitivity analysis showed that the association of frailty was similar when the patients were stratified into 1 group including moderately or severely frail, but not mildly frail, patients. Frail patients were less likely to be treated in intensive cardiac care units and to undergo coronary angiography than were nonfrail patients. Frailty, but not cardiovascular risk score or CAD index score, was associated with the performance of coronary angiography.

Our study is a multicenter, prospective observational trial with very few exclusion criteria. Given our aim, which was to describe a representative sample of elderly NSTEMI patients treated in clinical practice (ie, including patients not being treated in coronary care units and patients with secondary coronary ischemia),³⁰ the study design seems appropriate. To our knowledge, this is the first study to demonstrate frailty as a risk factor for adverse short-term clinical outcomes for elderly NSTEMI patients. We did this using an easily applied clinical measure of frailty, which was evaluated before the start of the study and was shown to have very good interrater reliability. The study was carefully monitored at 3 time points.

Because follow-up was done with the use of patient files and the Causes of Death Register, quality of life and burden of symptoms were not measured explicitly. However, rehospitalization for cardiovascular causes indirectly indicates the burden of symptoms. The trial did not have enough statistical power to properly analyze the manner in which frailty influences the short-term benefit of coronary angiography and the possible invasive treatment that can follow.

A geriatric patient cohort has been studied in most frailty studies rather than acute heart patients. These studies have shown that frailty is associated with long-term mortality, hospitalization, and institutionalization for geriatric patients.^{19,21} Our study indicated that frailty is independently associated with short-term outcomes for elderly NSTEMI patients. Furthermore, no other independent variable, with the exception of comorbidity score, was associated with the primary composite outcome in adjusted analysis with the use of multiple regression, which emphasizes the predictive strength of frailty.

Because frailty is an emerging concept, there is not a single accepted definition, and instead there are a variety of operationally defined scales. In our study, 48.5% of the patients were frail, and 24.1% were moderately or severely frail. It has

been estimated that 30% of a community-dwelling population of octogenarians are frail.³⁹ Furthermore, and more relevant in comparison with our study, the prevalence of frailty in an elderly population requiring cardiac care ranges from 27% to 63% depending on the classification scheme.³⁹

We chose to use the Canadian Study of Health and Aging Clinical Frailty Scale because it is based on clinical judgment and is relatively easily applied in a clinical context. There may be other measures of frailty that are more sensitive but that are also more time-consuming and costly to administer.

In regard to the burden of comorbidity in our study, 31.9% of the patients presented with high CAD-specific index scores. This represents a higher proportion than in former studies including patients with CAD and using the same index, in which 16% and 24% of the patients, respectively, presented with high scores.^{13,35} This is not surprising because our study included older patients than in those studies.

Furthermore, as many as 60.3% of our study patients manifested 1 or more severe comorbid conditions (eg, severe renal insufficiency or severe dementia). In most evidence-generating randomized controlled trials, such conditions constitute exclusion criteria, which raises questions about the generalizability of the results of those studies to a clinical context including elderly patients with severe comorbidities or frailty.

Despite overlap between frailty and comorbidity, the distinction between the concepts has been stressed in other studies.^{22,40} Although frailty was strongly associated with the composite end point in adjusted analysis with the use of multiple regression, frail patients with a high or moderately high comorbidity burden were at particularly high risk.

Frail patients were less likely to be treated in intensive cardiac care units than nonfrail patients, and, similarly, they were less likely to undergo coronary angiography. Frailty and severe comorbidity were strong negative predictors for performance of coronary angiography, whereas degree of cardiovascular risk did not influence the use of this measure. Clinical decision making for elderly NSTEMI patients seems to be based on factors other than the estimation of cardiovascular risk. This observation could be compared with recommendations in Swedish, European, and American heart guidelines, which rely primarily on cardiovascular risk. However, despite the relatively conservative treatment strategies chosen for frail patients, they had remarkably many hospital bed days in addition to their worse outcomes. Furthermore, the proportion of frail patients who underwent coronary angiography differed between the 3 centers. There are possible alternative interpretations of these findings. One could argue that if frail patients indeed benefit from interventions, more of these patients should undergo coronary angiography to improve outcomes. On the contrary, one could argue that frail NSTEMI patients should be treated in coronary care units to a lesser extent than today because they are not judged to benefit from specific coronary care. In fact, as many as 78.5% of the frail patients manifested 1 or more severe comorbid conditions (eg, acute bleeding, severe renal insufficiency, severe anemia, or severe dementia). Many of these conditions could be considered potential contraindications to invasive procedures.

Clearly, this matter needs further evaluation, although whether it would be possible from an ethical viewpoint to perform an interventional study on the frailest patients is unclear. There is a need for more prospective clinical studies with very few exclusion criteria (if possible, randomized, controlled trials) to study the benefit of interventions for frail cardiovascular patients. Furthermore, we believe that registers should be adapted for elderly NSTEMI patients including relevant measures (ie, frailty) and relevant comorbidities (ie, dementia).

In conclusion, our study indicates that frailty is strongly and independently associated with a risk for short-term outcomes for elderly NSTEMI patients, including in-hospital mortality, 1-month mortality, prolonged hospital care, and the primary composite outcome defined according to the study protocol. Frail patients with a high or moderately high comorbidity burden appeared to be a subgroup at particularly high risk. The disconnect between biological and chronological age has been identified as a major obstacle in applying evidence-based treatments.²² In regard to the large and growing population of elderly patients with cardiovascular disease, it is important to identify clinically relevant measures of biological age and their contribution to risk. The combined use of frailty and comorbidity may constitute an ultimate risk prediction concept in regard to cardiovascular patients with complex needs.

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Disclosures

None.

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CLINICAL PERSPECTIVE

There is sometimes a disconnect between biological and chronological age, and this has been identified as a major obstacle in applying evidence-based treatments. For the large and growing population of elderly patients with cardiovascular disease, it is important to identify clinically relevant measures of biological age and their contribution to risk. Frailty is an emerging concept in medicine denoting increased vulnerability and decreased physiological reserves. Frailty instruments have thus far been validated and used mainly in a geriatric context, in which frailty stratification has been shown to be associated with a patient's risk of death and need for institutional care. We analyzed the manner in which the variable frailty is associated with short-term outcomes for elderly non-ST-segment elevation myocardial infarction patients. Frailty is strongly and independently associated with risk for in-hospital mortality, 1-month mortality, prolonged hospital care, and the primary composite outcome (all-cause death, myocardial reinfarction, revascularization due to ischemia, hospitalization for any cause, major bleeding, stroke/transient ischemic attack, and need for dialysis up to 1 month after inclusion). The combined use of frailty and comorbidity may constitute an ultimate risk prediction concept for cardiovascular patients with complex needs. In clinical decision making, frailty could function as a tool in estimating the patient's benefit-risk ratio associated with a treatment, including the expected lifetime for individual patients and its relation to the overall yield of a treatment. It could enhance decision making in regard to whether to focus on prognostic or symptomatic treatment.