The assessment of scales of frailty and physical performance improves prediction of major adverse cardiac events in older adults with acute coronary syndrome

Gianluca Campo, MD[ab], Elisa Maietti, MSc[cd], Elisabetta Tonet, MD[b], Simone Biscaglia, MD[b], Albert Ariza-Solè, MD[e], Rita Pavasini, MD[b], Matteo Tebaldi, MD[b], Paolo Cimaglia, MD[b], Giulia Bugani, MD[b], Matteo Serenelli, MD[b], Rossella Ruggiero, MD[b], Francesco Vitali, MD[b], Francesc Formiga, MD[f], Juan Sanchis, MD[g], Marcello Galvani, MD[h], Monica Minarelli, MD[i], Giulia Ricci Lucchi, MD[l], Roberto Ferrari, MD, PhD[ab], Jack Guralnik, MD[m], Stefano Volpato, MD[c]

a: Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy

b: Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona (FE), Italy.

c: Department of Medical Science, University of Ferrara, Ferrara, Italy.

d: Department of Biomedical and Neuromotor Sciences, University of Bologna

e: Coronary Care Unit, Heart Diseases Institute, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain

f: Geriatric Unit, Internal Medicine Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain.

g: Cardiology Department, Hospital Clínico de Valencia, INCLIVA, Universidad de Valencia, CIBER CV, Valencia, Spain

h: Unità Operativa di Cardiologia, Ospedale GB Morgagni, Forlì, Italy

i: Department of Emergency, Division of Cardiology, Delta Hospital, Azienda Unità Sanitaria Locale di Ferrara, Ferrara, Italy

l: Division of Cardiology, S. Maria Delle Croci Hospital, Ravenna, Italy

m: University of Maryland School of Medicine, Baltimore, MD, USA

Address for correspondence:

Stefano Volpato, MD,

Department of Medical Science, University of Ferrara, Ferrara, Italy.

Via Aldo Moro 8, 44124, Cona (Fe), Italy,

Phone: +39(0)532236658

Email: stefano.volpato@unife.it

ABSTRACT

Background: The number of older adults admitted to hospital for acute coronary syndrome (ACS) have increased worldwide. The aim of this study is to determine which scale of frailty or physical performance provides incremental improvements in risk-stratification of older adults after ACS.

Methods: A prospective cohort of 402 older (≥70 years) ACS patients were enrolled. Data about baseline characteristics, Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores were collected. Before hospital discharge, 7 scales of frailty and physical performance were measured. The one-year occurrence of adverse events (cardiac death, reinfarction and cerebrovascular accident [MACCE] and all-cause mortality) were recorded.

Results: Out of the 402 patients, 43 (10.5%) had a MACCE and 35 (8.7%) died. Following adjustment for confounding factors, scales of frailty and physical performance were associated with adverse events. Among the scales, the addition of SPPB produced the highest incremental value over the initial model generated by baseline characteristics both for MACCE (ΔC-statistic 0.043, p=0.04; IDI 0.054, p=0.001; NRI 0.752, p<0.001) and all-cause mortality (ΔC-statistic 0.063, p=0.02; IDI 0.061, p<0.001; NRI 1.022, p<0.001). The addition of SPPB scale on top of GRACE or TIMI risk scores led to a considerable improvement in the prediction of MACCE and all-cause mortality (about 15% and 20%, respectively).

Conclusions: The assessment of the physical performance with SPPB scale before hospital discharge increases the ability to predict adverse events in older ACS patients and may be useful in the clinical decision-making process.

Clinical trial registration: www.clinicaltrials.gov NCT02386124.

KEYWORDS

Acute coronary syndrome, ST-segment elevation myocardial infarction, frailty, short physical performance battery.

INTRODUCTION

Risk assessment after acute coronary syndrome (ACS) is the foundation of the current cardiovascular practices [1-2]. Risk-stratification for the estimation of mortality or reinfarction is based on baseline characteristics or on risk scores, such as the Global Registry of Acute Coronary Events (GRACE) and the Thrombolysis in Myocardial Infarction (TIMI) [1-2]. These risk scores have been validated in population with a mean age around 60 years. With the exclusion of age, they do not include specific variables to evaluate the risk of older ACS patients [3-5]. Nevertheless, several studies showed that in older adults there is a frequent mismatch between "biological" and "chronological" age with substantial clinical implications in terms of mortality and recurrence of adverse events [5]. The scales of frailty and physical performance can help physicians in the assessment of this mismatch, but their integration in daily clinical practice is still far away [3-5].

This study has been designed to determine which scale of frailty or of physical performance provides incremental improvements in risk-stratification in terms of major adverse cardiovascular events (MACCE) and all-cause mortality of older adults after ACS. Firstly, we assessed and compared several scales of frailty and physical performance in a prospective multicenter cohort of older adults admitted to hospital for ACS. Secondly, we investigated their potential incremental prognostic value in predicting adverse events.

METHODS

Study design

The "Frailty in elderly patients receiving cardiac interventional procedures" (FRASER) is a multicentre, investigator-driven, prospective study involving consecutive older adults admitted to hospital for ACS [6]. The detailed protocol of the study has been previously published [6]. The study enrolled inpatient and was conducted in an hospital setting [6]. Three public hospitals of the Emilia-Romagna (Italy) were involved [6]. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all gave informed written consent. This study was registered (www.clinicaltrials.gov with identifier NCT02386124) and approved by the ethical review boards at the participating hospitals.

Study population

Inclusion criteria were: i) age ≥70 years; ii) hospital admission for ACS receiving coronary artery angiography ± percutaneous coronary intervention (PCI) [6]. Exclusion criteria were: short portable mental status questionnaire (SPMSQ) <4, inability to stand upright, life expectancy <3 months, surgical coronary revascularization, inability to be sent home [6]. The patient management was at the discretion of the attending physician and followed the current guidelines and the institutional protocols.

Study measurements and assessment of frailty or physical performance

A large amount of clinical and management data, including demographics, previous medical history, comorbidities, laboratory data and treatments, were collected. Seven scales of frailty or of physical performance were compared: frailty - as defined by Fried's phenotype,

handgrip strength, short physical performance battery (SPPB), Rockwood clinical frailty scale (CFS), Columbia frailty index, Multidimensional Prognostic Index (MPI) and Edmonton frail scale [7-13]. The inclusion in the study, as well as the collection of scales, were performed as soon as possible after the mobilization of the patient. The assessment of scales of frailty and physical performance was performed by an ad hoc team composed of a study physician and a study assistant, adequately trained to perform the tests following standardized protocols. The order of execution of the scales was variable depending on the patient. The scales including measures of physical performance were alternated with those based on questions or on anamnestic details. The overall assessment of the seven scales required around 45-60 minutes. No adverse events occurred during the assessment of the scales. Only in 3 cases, the patients asked to stop the assessment which it was successfully repeated and completed the day after.

TIMI and GRACE risk scores

The TIMI and GRACE risk scores were previously reported and validated for both in-hospital and long-term occurrence of adverse events. The calculation was performed by an ad hoc team blinded to outcome and result of scales of frailty and physical performance, with the available online calculator [1-2].

Clinical follow-up, study endpoints and definitions

The outpatient visits were planned for six and twelve months from the hospital discharge. Source documentation regarding each adverse event was collected. In this analysis we considered two endpoints: i) the one-year occurrence of cardiac death, reinfarction and cerebrovascular accident (MACCE); and ii) the one-year occurrence of all-cause mortality. All deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. The diagnosis of myocardial infarction (MI) required a combination of

symptoms, ECG changes and significant increase in cardiac markers (troponin). Cerebrovascular accidents (CVA) were defined as the clinical diagnosis of stroke and transient ischemic attacks. The clinical events committee, whose members were unaware of the patients' frailty assessment, centrally evaluated all events.

Sample size calculation and statistical analysis.

A detailed description of sample size calculation and statistical analysis have been previously reported [6]. Continuous data were tested for normal distribution with the Kolmogorov–Smirnov test. Normally distributed values were presented as mean ± SD and compared by t test and one-way ANOVA; otherwise median value [interquartile range, IQR], the Mann–Whitney U and Kruskal–Wallis tests were used. Categorical variables were summarized in terms of counts and percentages and were compared by using the Pearson's chi-squared test or the Fisher's exact test, as appropriate. All variables included in Table 1 were tested using a univariate logistic regression as predictors of events. Variables showing a p-value <0.1 were included in the multivariable model. Independent predictors among baseline characteristics were selected with backward stepwise modelling approach. Variables remaining significant at a threshold p-value ≤0.05 were retained as final predictors. Model performance was assessed using metrics of discrimination (Harrel's C statistic) and the Hosmer-Lemeshow goodness of fit test. To assess the incremental predictive value, each frailty scale was added to the multivariable model generated by baseline characteristics and the following indices were calculated: Δ C-statistic, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) [14]. C-statistic describes the probability that a randomly selected patient who experienced an event had a higher risk score than a patient who had not experienced the event [14]. Δ C-statistic represents the increase in probability in the comparison of two scores [14]. IDI ranges between 0 and 1 and can be interpreted as equivalent to the increase in

average sensitivity given no changes in specificity [14]. NRI focuses on reclassification and is calculated summing up two components: “event NRI”, ie the net proportions of individual with increase in predicted probability among those who will develop the event, and the “non-event NRI” ie the net proportions of individual with decrease in predicted probability among those who will not develop the event [14]. NRI ranges from 0 to 2, with more positive values indicating greater improvement in predicting probabilities [14]. Lastly, we assessed the additional value on top of GRACE and TIMI risk scores of the scale showing the best performance in the above-mentioned comparison. All tests are two-sided, and the statistical significance was defined as $p<0.05$. All analyses were performed with Stata 13 and with R 3.5.0 by the staff (EM) of the Center for Clinical Epidemiology (University of Ferrara, Ferrara, Italy). Among the authors, GC had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

The final study population consisted of 402 older adults (Figure 1). Baseline characteristics are detailed in Table 1. The median [IQR] age was 78 [74-82] years with a range from 70 to 96 years. Coronary artery angiography was performed one [1-2] day after hospital admission. Almost the whole study population (n=392, 98%) received successful PCI. Median time of inclusion in the study was five [4-7] days after hospital admission. Main findings of scales of frailty or physical performance are reported in Table 2. Median hospital stay was seven [5-9] days. The one-year follow-up was complete in all patients.

Major adverse cardio- and cerebro-vascular events

After one-year, 21 (5%) patients died for cardiac cause. Eighteen (4.5%) and seven (2%) experienced respectively MI and CVA. Overall, 43 (10.5%) patients reached the composite endpoint MACCE. Several baseline variables and the scales of frailty or physical performance were related to 1-year MACCE (Table 1 and 2). At multivariable analysis including baseline characteristics, the independent predictors of MACCE were STEMI, hemoglobin, albumin and loop diuretic (Table 3). Model resulted well calibrated (Hosmer-Lemeshow goodness of fit test p=0.91) and with a good discrimination ability (AUC=0.775). After the adjustment for confounding factors, the scales of frailty and physical performance remained related to one-year MACCE (Table 4). The SPPB showed the highest incremental value. The addition of SPPB improved of 4.3% the ability to discriminate patients experiencing MACCE (ΔC-statistic 0.043, p=0.04) (Table 4). IDI resulted of 0.054 (p=0.001), then the addition of SPPB increased of 5.4% the average sensitivity, without changes in specificity (Table 4). Including SPPB, the net gain in reclassification was 35% for patients who experienced MACCE and 40% for patients free from MACCE (NRI 0.752, p<0.001) (Table 4).

All-cause mortality

Thirty-five (9%) patients died after the inclusion in the study. Several baseline characteristics and all scales of frailty and physical performance were associated to one-year all-cause mortality (Tables 1 and 2). Age, albumin and hemoglobin emerged as independent predictors of all-cause death (Table 3). Model resulted well calibrated (Hosmer-Lemeshow goodness of fit test p=0.64) and with a good discrimination ability (AUC=0.786). After the adjustment for confounding factors, SPPB, Edmonton and Fried scales remained associated to all-cause mortality (Table 4). The SPPB showed the greatest incremental value (Table 4). The addition of SPPB to baseline predictive model improved of 6.3% the ability to discriminate those who died (ΔC-statistic 0.063, p=0.02) (Table 4). Including SPPB, the average sensitivity improved of 6.1%, without changes in specificity (IDI 0.061) and the net improvement in predicted probabilities was gained for 60% of deceased patients and 42.2% of alive patients (NRI=1.02 p<0.001) (Table 4).

Incremental value of SPPB scale over GRACE and TIMI risk scores

GRACE and TIMI risk scores predicted MACCE (OR 1.02, 95%CI 1.01-1.04 and OR 1.41, 95%CI 1.14-1.75, respectively) and all-cause mortality (OR 1.03, 95%CI 1.01-1.05 and OR 1.72, 95%CI 1.36-2.17, respectively). The integration of SPPB guaranteed a significant improvement in the discrimination ability of both risk scores (Figure 2). The ability of the GRACE and TIMI risk scores to discriminate patients with MACCE improved of 14.3% (ΔC-statistic 0.143, p<0.001) and 15.8% (ΔC-statistic 0.158, p<0.001), respectively. Similarly, the ability to discriminate those who died improved of 17.6% (ΔC-statistic 0.176, p<0.001) and 19.3% (ΔC-statistic 0.193, p<0.001), respectively. The analysis regarding IDI and NRI values was consistent (Figure 2).

DISCUSSION

The main findings of the study can be summarized as follows:

i) The commonly available scales to measure frailty or physical performance predict adverse events in older adults admitted to hospital for ACS.

ii) SPPB scale, a standardized assessment of the physical performance, shows the greatest incremental value when added to a model containing baseline clinical/laboratory variables.

iii) The addition of SPPB improves of about 15% the prognostic ability of GRACE and TIMI risk scores.

In recent years, several studies have dealt with frailty in coronary patients [3-13, 15-18]. Despite consensus about the need for risk-stratification tools oriented to older patients, the integration of frailty and/or physical performance measurements in daily clinical practice has not been brought about yet. [3-5]. This is due to a number of reasons. Firstly, frailty or reduced physical performance do not have a universal definition. Secondly, their prevalence and the effect size vary across studies and a clear and unique assessment are lacking. Thirdly, the identification of the correct timing to apply the assessment of frailty or physical performance is debatable in an acute scenario. Several Authors suggested to define the frailty status before an acute event [10,15]. Alternatively, physical performance can be assessed at the time of hospital discharge. Both approaches show advantages and drawbacks, and studies reporting a direct comparison are lacking. Valuable studies applied different scales to stratify patients with symptomatic aortic stenosis eligible for transcatheter aortic valve implantation (TAVI) and/or aortic valve replacement (AVR) [16-18]. This clinical condition represents an ideal scenario for the assessment of frailty or physical performance because the number of patients is limited, and several exams are necessary to plan the intervention. This is not

transferable to the ACS setting, where the number of patients is huge and constantly increasing worldwide and where the usual frailty assessment is only an 'eyeballing' of the patient on a subjective basis to exclude extreme conditions suggesting a conservative management.

The FRASER study aimed to overcome these limitations. A population of older ACS patients receiving the best available treatment according to the current guidelines was enrolled. Immediately after mobilization, a few days after hospital admission and invasive coronary procedures, the main available scales of frailty and physical performance were assessed. We found that the impairment of the physical performance emerged as a central determiner of vulnerable health status in older ACS patients. The scale showing the best performance (namely SPPB) was that in which physical performance was objectively assessed and entirely contributed to the final score. We may not exclude that the decision to measure frailty after mobilization may have influenced these findings, emphasizing the scales with a direct measurement of the physical performance. Similarly, it plausible that we did not capture the steady-state status of the physical performance. Nevertheless, other studies showed similar results. In the FRAILTY-AVR study [16], the Essential Frailty Toolset (EFT) emerged as the best tool for the stratification of patients undergoing TAVI or AVR. Two of the five points of the EFT are assigned to the ability to perform or not 5 chair rises [16]. The 5-meter gait speed emerged as predictor of mortality and rehospitalization in more than 8000 patients undergoing cardiac surgery [18]. The FRASER study confirmed the association between physical performance and adverse events. What is the natural course of physical performance of the elderly before and after an ACS is not clear. However, our data suggest that the assessment before hospital discharge may be a reliable mirror of the patient's status and it is strongly associated with the functional recovery and outcome.

The clinical implications of this study are numerous. The SPPB score demonstrated to improve the clinicians' ability to identify older adults who, despite the guideline-based treatment, still had a higher probability of poor prognosis. This improvement in the risk-stratification is consistent regardless endpoints (MACCE or mortality), clinical presentation and reference model (validated risk scores or baseline characteristics). The SPPB is an acceptable compromise in terms of feasibility and reliability between the tools for the assessment of frailty and physical performance. It is relatively simple, quick (about 10 minutes), inexpensive. It is longer and complex as compared to grip strength or gait speed alone, but its assessment does not require the presence of physicians. Adequately trained nurses can perform SPPB and report the final value in the patient's file. Obviously, this better risk stratification becomes helpful for physician if related to changes in the medical management of the patients themselves. It can be argued that a complete coronary revascularization or a more aggressive antithrombotic and lipid-lowering therapy might improve their outcome. Otherwise, a closer follow-up as well as a diet supplementation might be related to a reduction of adverse events. The implementation of specific physical activity programs tailored on SPPB values could be taken into consideration. Indeed, the physical performance should be considered a modifiable risk factor. The Lifestyle Intervention and Independence for Elders (LIFE) trial showed benefit from a structured, moderate-intensity physical activity program in vulnerable older adults [19-20]. The effectiveness of physical activity intervention in older adults immediately after ACS has been less investigated and randomized clinical trials are currently ongoing (NCT03021044) [21].

Study limitations

This study has some limitations that should be pointed out. Although the estimation of the sample size calculation has been respected, the overall number of patients should be

considered as limited. Some issues related inclusion/exclusion criteria should be mentioned. The study included patients from one country (Italy). Participating centers were public hospitals. The patients who were not discharged home were excluded. These issues may represent a bias in the selection of the study population. Furthermore, all patients were admitted to Cardiology Units and most of our patients were invasively managed. Therefore, the applicability of our findings should be confirmed in a larger, multi-national scenario and should be translated with caution to patients admitted to other departments and/or undergoing conservative management. Information about the frailty status before hospital admission is lacking. We are not able to establish the relationship between frailty status and physical performance before and after the ACS event, although it is highly probable a strong and direct association. Finally, we are unable to clarify if the measurement of a singular item of physical performance (i.e. gait speed) carries the same prognostic information of more complex scales. Nevertheless, previous studies suggested a benefit from the measurement of more comprehensive scales and the overall impact, in terms of logistic and time, is slightly greater [22].

Conclusions

The study showed that scales of frailty and physical performance might enhance the chance to predict worse prognosis in older adults after an ACS. The physical performance, as assessed by SPPB score, could improve the clinical evaluation and could support a tailored decision-making process.

Conflict of interest

None

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Table 1. Baseline Characteristics and univariate analysis for the occurrence of adverse events

		MACCE	All-cause mortality
	n=402	**OR (95%CI)**	**OR (95%CI)**
Age, (years)	78±6	1.09 (1.04-1.15)	1.16 (1.09-1.23)
Female sex, no. (%)	137 (34)	3.06 (1.61-5.84)	1.94 (0.97-3.90)
BMI, (Kg/m2)	27±4	0.90 (0.82-0.99)	0.93 (0.84-1.03)
CV risk factors, no. (%)			
Diabetes	120 (30)	1.45 (0.75-2.81)	0.67 (0.30-1.53)
Hypertension	337 (84)	1.21 (0.49-3.01)	1.17 (0.44-3.14)
Hyperlipidemia	215 (53)	0.91 (0.48-1.69)	1.34 (0.66-2.71)
Current smoker	115 (29)	0.84 (0.41-1.73)	0.49 (0.19-1.21)
Medical history, no. (%)			
MI	117 (29)	1.69 (0.88-3.25)	1.49 (0.72-3.07)
PCI	110 (28)	1.32 (0.67-2.61)	1.07 (0.49-2.30)
CABG	41 (10)	0.63 (0.19-2.14)	0.81 (0.24-2.77)
COPD	32 (8)	0.54 (0.12.2.32)	1.56 (0.51-4.74)
PAD	103 (26)	1.46 (0.74-2.89)	1.58 (0.76-3.30)
Clinical presentation			
STEMI, no. (%)	133 (33)	2.3 (1.24-4.4) *	2.6 (1.31-5.3) *
NSTEMI, no. (%)	180 (45)	/	/
UA, no. (%)	89 (22)	/	/
Killip class >I, no. (%)	55 (14)	1.15 (1.04-1.37)	1.25 (1.11-1.77)
Systolic blood pressure, mmHg	141 [118-161]	1.07 (0.97-1.18)	1.07 (0.97-1.18)
Heart rate, bpm	70 [60-82]	1.002 (0.91-1.11)	1.01 (0.91-1.12)
Laboratory data (at inclusion)			
White blood cells, (u/μL)	8±2	1.02 (0.91-1.16)	1.10 (0.97-1.24)
Haemoglobin, (g/dl)	12±2	0.71 (0.59-0.84)	0.68 (0.56-0.83)
Creatinine Clearence, (ml/min)	55 [38-69]	0.97 (0.95-0.99)	0.97 (0.95-0.99)
Albumine, (g/dl)	3.5 [3.2-3.8]	0.24 (0.11-0.53)	0.17 (0.07-0.40)
Troponin T at peak, (ng/dl)	0.9 [0.2-5]	0.99 (0.96-1.01)	0.98 (0.96-1.02)
Angiographic data			
Multi-vessel disease, no (%)	291 (74)	0.86 (0.43-1.73)	0.82 (0.38-1.73)
PCI, no. (%)	392 (98)	1.08 (0.13-8.74)	0.85 (0.11-6.95)
Number of treated lesion	1 [1-2]	1.10 (0.77-1.58)	0.89 (0.58-1.36)
Echocardiographic data			
End-diastolic volume (ml)	102 [85-120]	0.99 (0.98-1.01)	0.99 (0.98-1.01)
LVEF (%)	50±11	0.97 (0.94-0.99)	0.97 (0.94-1.01)
Medical Therapy, no. (%)			
Aspirin	386 (96)	0.37 (0.11-1.18)	0.71 (0.15-3.21)
P2Y12 inhibitor	392 (97)	0.31 (0.08-1.19)	0.42 (0.08-2.01)
Beta-blocker	345 (86)	1.69 (0.58-4.92)	1.84 (0.54-6.22)
ACE inhibitor/A2R antagonist	326 (81)	1.02 (0.45-2.30)	1.44 (0.54-3.84)
Statin	362 (90)	1.08 (0.37-3.22)	0.63 (0.23-1.73)
Loop diuretic	164 (41)	3.44 (1.75-6.73)	2.35 (1.16-4.77)

*: regarding clinical presentation we assessed the predictive role of STEMI vs. other clinical presentation

EP: endpoint. BMI: body mass index. CV: cardiovascular. MI: myocardial infarction. PCI: percutaneous coronary intervention. CABG: coronary artery bypass graft. COPD: chronic obstructive pulmonary disease. PAD: peripheral artery disease. STEMI: ST-segment elevation MI. NSTEMI:non ST-segment elevation MI. UA: unstable angina. LVEF: left ventricular ejection fraction. ACE: angiotensin converting enzyme. A2R: angiotensin 2 receptor.

Table 2. Scales of frailty and physical performance and univariate analysis for the occurrence of adverse events

	All n=402	MACCE OR (95%CI)	All-cause mortality OR (95%CI)
Short physical performance battery	8 [5-10]	0.74 (0.66-0.82)	0.67 (0.59-0.77)
- ≥10, no. (%)	148 (37)		
- 4-9, no. (%)	195 (48)		
- ≤3, no. (%)	59 (15)		
Columbia	3 [2-5]	1.32 (1.18-1.47)	1.33 (1.19-1.51)
- ≤3, no. (%)	244 (61)		
- 4, no. (%)	57 (14)		
- 5, no. (%)	33 (8)		
- ≥6, no. (%)	68 (17)		
Edmonton	4 [2-5]	1.48 (1.30-1.69)	1.51 (1.31-1.74)
- ≤5, no. (%)	312 (77)		
- 6, no. (%)	30 (7)		
- 7, no. (%)	25 (6)		
- ≥8, no. (%)	35 (9)		
Grip strength, (Kg)	28 [20-36]	0.92 (0.89-0.96)	0.93 (0.90-0.97)
- female	18 [14-22]		
- male	34 [27-40]		
Fried	2 [0-3]	1.67 (1.32-2.13)	1.93 (1.46-2.56)
- 0, no. (%)	118 (29)		
- 1, no. (%)	82 (21)		
- 2, no. (%)	78 (19)		
- ≥3, no. (%)	124 (31)		
Rockwood CFS	4 [3-5]	1.45 (1.11-1.97)	1.65 (1.18-2.31)
- 1-3, no. (%)	128 (32)		
- 4, no. (%)	142 (35)		
- ≥5, no. (%)	132 (33)		
Multidimensional performance index	0.18 [0.18-0.25]	7.6 (1.20-47)	6.4 (0.70-55)
- class I, no. (%)	389 (97)		
- class II, no. (%)	13 (3)		

CFS: clinical frailty scale

Table 3. Multivariable analysis for the prediction of MACCE and all-cause mortality including baseline characteristics

	model 1		model 2	
	OR (95%CI)	p	OR (95%CI)	p
MACCE				
Age, (years, single change unit)	1.04 (0.97-1.11)	0.2	/	
Female sex	1.70 (0.81-3.55)	0.1	/	
BMI, (Kg/m2, single change unit)	0.94 (0.85-1.04)	0.2	/	
STEMI	1.61 (0.77-3.37)	0.2	2.04 (1.03-4.01)	0.04
Killip class >I	1.18 (0.71-2.65)	0.6	/	
Haemoglobin, (g/dl, single change unit)	0.84 (0.69-10.2)	0.08	0.78 (0.66-0.94)	0.009
Creatinine Clearence, (ml/min, single change unit)	0.99 (0.98-1.02)	0.9	/	
Albumin, (g/dl, single change unit)	0.41 (0.17-0.97)	0.04	0.39 (0.17-0.88)	0.02
LVEF (%, single change unit)	0.98 (0.95-1.01)	0.3	/	
Aspirin	0.36 (0.08-1.59)	0.7	/	
P2Y12 inhibitor	0.75 (0.14-3.86)	0.7	/	
Loop diuretic	2.25 (1.01-503)	0.05	2.89 (1.43-5.82)	0.003
All-cause mortality				
Age, (years, single change unit)	1.11 (1.03-1.19)	0.003	1.12 (1.05-1.19)	<0.001
Female sex	0.93 (0.42-2.06)	0.8	/	
STEMI	2.02 (0.92-4.46)	0.08	/	
Killip class >I	1.10 (0.80-1.95)	0.8	/	
Haemoglobin, (g/dl, single change unit)	0.80 (0.65-0.98)	0.04	0.77 (0.63-0.94)	0.01
Creatinine Clearence, (ml/min, single change unit)	0.99 (0.97-1.01)	0.7	/	
Albumin, (g/dl, single change unit)	0.37 (0.15-0.91)	0.03	0.35 (0.14-0.87)	0.02
LVEF (%, single change unit)	0.99 (0.96-1.03)	0.8	/	
Loop diuretic	1.38 (0.60-3.10)	0.4	/	

model 1: including all variables showing a p-value <0.1 at univariate analysis (Table 1).

model 2: after backward stepwise procedure.

MACCE: major adverse cardio cerebrovascular events. OR: odd ratio. CI: confidence interval. BMI: body mass index. STEMI: ST-segment elevation myocardial infarction. LVEF: left ventricle ejection fraction.

Table 4. Multivariable analysis including scales of frailty and physical performance and incremental value.

	adjusted OR (95%CI) *	Δ C-Statistic	p-value	IDI	p-value	NRI	p-value
MACCE							
SPPB	0.79 (0.70-0.89)	0.044	0.04	0.054	0.001	0.752	<0.0001
Columbia	1.17 (1.03-1.33)	0.019	0.2	0.016	0.2	0.248	0.1
Edmonton	1.34 (1.15-1.56)	0.017	0.4	0.073	<0.0001	0.505	0.001
Grip strength, (Kg)	0.96 (0.92-0.99)	0.008	0.6	0.018	0.04	0.316	0.052
Fried	1.36 (1.04-1.79)	0.011	0.5	0.019	0.02	0.319	0.047
Rockwood CFS	1.07 (0.76-1.49)	0.001	0.9	0.001	0.4	0.100	0.5
MPI	1.61 (2.70-9.61)	0.020	0.1	0.020	0.1	0.277	0.08
All-cause mortality							
SPPB	0.74 (0.63-0.85)	0.063	0.02	0.061	<0.0001	1.022	<0.0001
Columbia	1.13 (0.97-1.30)	0.005	0.5	0.013	0.05	0.012	0.9
Edmonton	1.33 (1.13-1.56)	0.037	0.07	0.045	0.004	0.646	0.0003
Grip strength, (Kg)	0.98 (0.94-1.02)	-0.008	0.4	0.010	0.01	0.358	0.047
Fried	1.58 (1.14-2.18)	0.020	0.3	0.033	0.002	0.371	0.035
Rockwood CFS	1.34 (0.94-1.92)	0.005	0.7	0.015	0.08	0.420	0.017
MPI	1.25 (0.01-113)	-0.001	0.5	0.0002	0.78	-0.061	1

*: multivariable analysis obtained after the insertion of the scale in the baseline model (Table 3)

Δ C-Statistic, IDI, NRI: the values are referred for the comparison between the baseline model (Table 3) and the same model with the addition of frailty scale.

IDI: Integrated discrimination improvement. NRI: Net reclassification improvement. OR: odds ratio. SPPB: short physical performance battery. CFS: clinical frailty scale. MPI: multidimensional prognostic index. MACCE: major adverse cardio cerebrovascular event.

FIGURE LEGEND

Figure 1. Study flow-chart

SPMSQ: short portable mental status questionnaire.

Figure 2. Receiver-operator characteristics curves for prediction of MACCE and all-cause mortality for GRACE and TIMI risk scores alone and with the addition of SPPB

A: major adverse cardio- and cerebro-vascular accident (MACCE). B: all-cause mortality. Continue lines: risk score alone. Dotted lines: risk scores with the addition of SPPB. Green lines: GRACE (±SPPB). Red lines: TIMI (±SPPB).

GRACE: global risk of coronary events. TIMI: Thrombolysis in myocardial infarction.

Figure 1

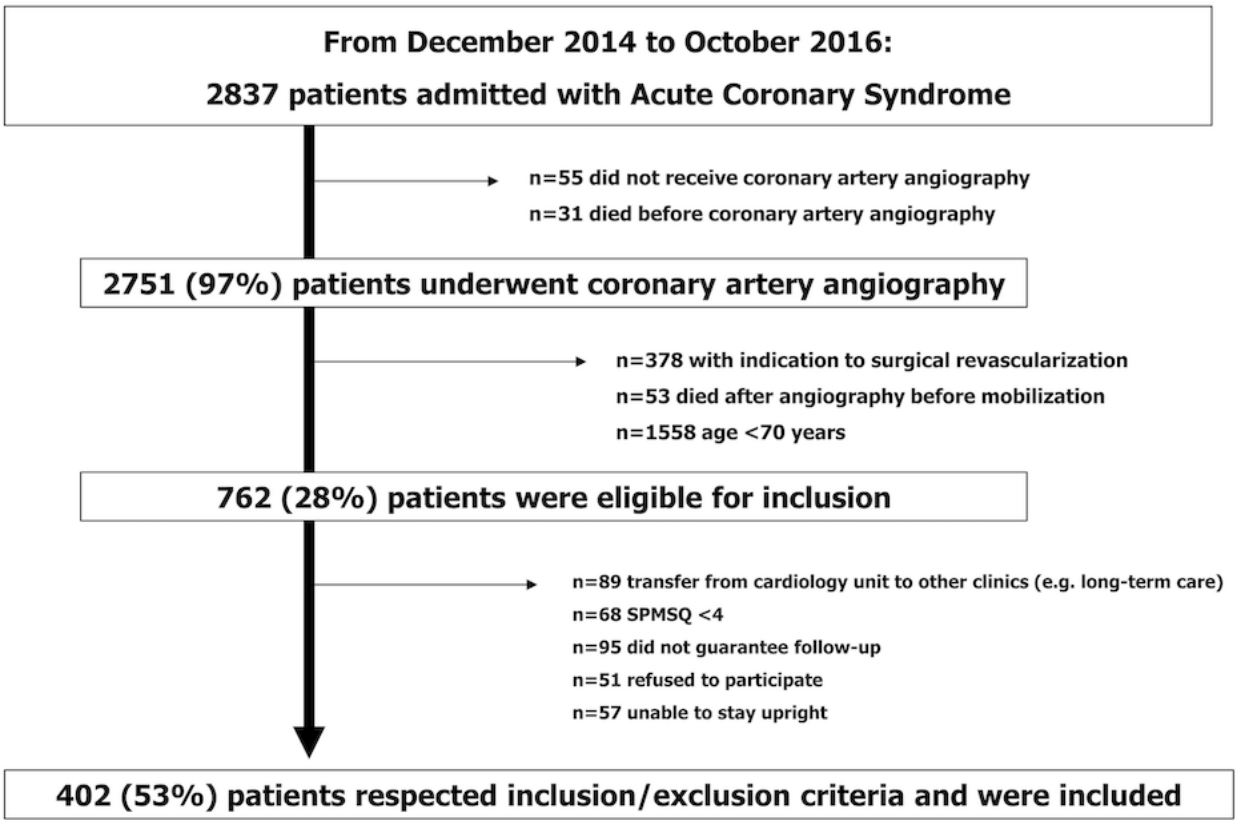
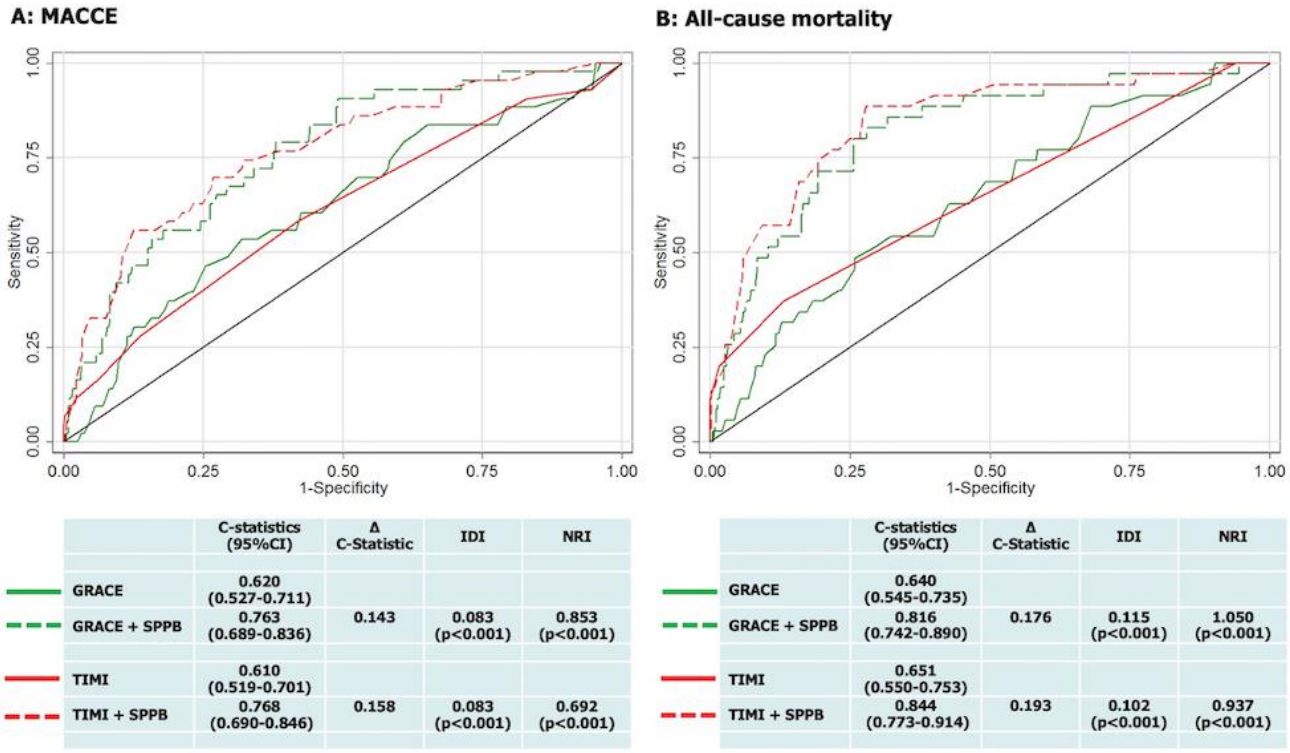


Figure 2



	C-statistics (95%CI)	Δ C-Statistic	IDI	NRI
GRACE	0.620 (0.527-0.711)			
GRACE + SPPB	0.763 (0.689-0.836)	0.143	0.083 (p<0.001)	0.853 (p<0.001)
TIMI	0.610 (0.519-0.701)			
TIMI + SPPB	0.768 (0.690-0.846)	0.158	0.083 (p<0.001)	0.692 (p<0.001)

	C-statistics (95%CI)	Δ C-Statistic	IDI	NRI
GRACE	0.640 (0.545-0.735)			
GRACE + SPPB	0.816 (0.742-0.890)	0.176	0.115 (p<0.001)	1.050 (p<0.001)
TIMI	0.651 (0.550-0.753)			
TIMI + SPPB	0.844 (0.773-0.914)	0.193	0.102 (p<0.001)	0.937 (p<0.001)