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Routine invasive strategy and frailty burden in non-ST-segment elevation acute myocardial infarction

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ABSTRACT

Objective To assess the prognostic impact of a routine invasive strategy according to the frailty burden in patients with non-ST-segment elevation myocardial infarction (NSTEMI) from the MOSCA-FRAIL clinical trial.

Methods The MOSCA-FRAIL trial randomized 167 frail patients, defined by a Clinical Frailty Scale (CFS) ≥ 4, with NSTEMI to an invasive or conservative strategy. The primary endpoint was the number of days alive and out of hospital (DAOH) one year after discharge. For this subanalysis, we compared the impact of an invasive strategy on the outcomes between vulnerable (CFS = 4, n = 43) and frail (CFS > 4, n = 124) patients.

Results Compared to vulnerable patients, frail patients presented lower values of DAOH (289.8 *vs.* 320.6, P = 0.146), more readmissions (1.03 *vs.* 0.58, P = 0.046) and higher number of days spent at the hospital during the first year (10.8 *vs.* 3.8, P = 0.014). The causes of readmission were mostly non-cardiac (56%). Among vulnerable patients, DAOH were similar regardless of strategy (invasive *vs.* conservative: 325.7 *vs.* 314.7, P = 0.684). Among frailest patients, the invasive group tended to have less DAOH (267.7 *vs.* 311.1, P = 0.117). Indeed, patients with CFS > 4, invasively managed lived 29 days less than their conservative counterparts. In contrast, there were no differences in the subgroup with CFS = 4.

Conclusions Adult patients with frailty and NSTEMI showed different prognosis according to the degree of frailty. A routine invasive strategy does not improve outcomes and might be harmful to the frailest patients.

Current guidelines strongly recommend a routine early invasive strategy in high-risk patients with non-ST-segment elevation myocardial infarction (NSTEMI).[1] However, there is scant and conflicting information about the impact of an invasive strategy on older patients.[2–6] Some data suggest that the be-

nefit might be significantly reduced, or even disappear, in patients with a high burden of comorbidities or establis hed frailty criteria.[7,8]

Recently, the MOSCA-FRAIL clinical trial randomized frail patients with NSTEMI aged ≥ 70 years to a routine invasive strategy or an initial conservative strategy.[9] The invasive approach failed to increase the number of days alive and out of hospital (DAOH) during the first year after admission. Importantly, readmissions and mortality were mainly due to non-cardiac causes. These facts may be considered potential reasons for the lack of benefit from the invasive strategy.

Frailty and comorbidity often overlap with other geriatric syndromes.[10,11] In this sense, patients with higher frailty scores tend to have some physical and cognitive disabilities, comorbidities, and malnutrition. These more complex patients are at higher risk for developing cardiovascular and non-cardiac events and overall mortality. We speculated that the invasive strategy's impact might differ across the frailty burden. Therefore, the main aim of this subanalysis was to assess, among patients from the MOSCA-FRAIL clinical trial database, the association between the degree of frailty status and the prognostic impact of a routine invasive strategy.

METHODS

Study Population

The MOSCA-FRAIL clinical trial was a multicenter, prospective, randomized, open-label trial that was conducted in older adult patients with frailty and NSTEMI (ClinicalTrials.gov identifier: NCT03208153).[9] The trial included 167 patients with the following criteria: (1) NSTEMI, defined by symptoms consistent with acute myocardial ischemia, absence of persistent ST-segment elevation, and troponin elevation (according to the local laboratory troponin assay); (2) age ≥ 70 years; and (3) frailty defined by 4 points or greater on the Clinical Frailty Scale (CFS).[12] Exclusion criteria were prior known nonrevascularizable coronary artery disease, significant concomitant nonischemic heart disease, inability to understand/sign informed consent (patients or relatives), and life expectancy less than 12 months. In addition, the attending physician should believe that the participation of the patient in the study was reasonable. Participants were randomized in a 1:1 ratio within 48 h of admission to: (1) routine invasive strategy, consisting of coronary angiography within 72 h of admission with coronary revascularization if deemed appropriate; or (2) conservative strategy, consisting of medical therapy only, although cardiac catheterization was allowed in the case of recurrent ischemia during the index hospitalization. Medical treatment was optimized according to the clinical practice guidelines recommendations for all patients.[1] When the percutaneous coronary intervention was performed, the type of stent implanted was left to the judgment of the treating cardiologist, although encouraging the use drug eluting stents.

In addition to the CFS, a comprehensive geriatric evaluation was performed during hospitalization, assessing the status before admission as follows: (1) frailty was also assessed by the FRAIL scale,[13] a simple, interview based tool which evaluates 5 items (fatigue, resistance, ambulation, concomitant diseases and weight loss). Pre-frailty is defined as the presence of one or two criteria and frailty as the presence of three or more criteria; (2) comorbidity conditions were evaluated with the Charlson index;[14] (3) physical independence was evaluated with the Barthel index;[15] and (4) cognitive function was measured with the Pfeiffer test.[16]

The primary endpoint was the number of DAOH between discharge from the index hospitalization to 1 year. The coprimary endpoint was the composite of major ischemic cardiac events, including cardiac death, reinfarction, or postdischarge revascularization. Cardiac death was defined as any death due to cardiac causes. Unwitnessed death and death of unknown cause were considered cardiac death. Readmissions due to cardiac diagnoses were reinfarction (chest pain with troponin elevation), unstable angina (readmission for ischemic chest pain with normal troponin levels), coronary revascularization not related to readmissions for myocardial infarction or unstable angina, acute heart failure, and other cardiac reasons. Non-cardiac diagnoses for readmission included stroke, bleeding, and other non-cardiac reasons (pulmonary, abdominal, neurologic, diabetes decompensation, infections, neoplasia, peripheral artery disease, falls, urinary, and others). Follow-up was carried out via clinical visit, electronic medical record review, and/or telephone contacts at 6 months and 1 year.

For the purpose of this study, we assessed the clinical profile and outcomes according to the burden of frailty in the 167 patients included in the MOSCA-FRAIL clinical trial.

Statistical Analysis

To conduct the subanalysis, we categorized the CFS sc-

ore as either CFS = 4 or CFS > 4. Then, we compared the clinical characteristics and outcomes among four resulting groups based on frailty burden and the assigned treatment strategy: CFS = 4/conservative (n = 20, 12%), CFS = 4/invasive (n = 23, 13.8%), CFS > 4/conservative (n = 63, 37.7%), and CFS > 4/invasive (n = 61, 36.5%). The results were presented in counts (percentages), mean ± SD, or medians (interquartile range) as appropriate, and the Pearson's chi-squared test or ANOVA tests were used for between-group comparisons. To account for differences at baseline, sex, prior stroke, and prior atrial fibrillation were included in all regression models as adjusting covariates. Additionally, the clustering effect of the centre on patients was considered in all regression models.

We analyzed the primary endpoint (DAOH) as a continuous variable using mixed regression analysis, with the study centre as a random effect. As the study focused on the between-effect of the treatment strategy on CFS = 4 and CFS > 4, we forced the interaction between the two variables in the model. The results were expressed as predicted means (least square means) with 95% CI.

To assess the effect of the invasive strategy on all-cause 1-year mortality, we constructed a Kaplan-Meier curve. However, as the proportional assumption among the four groups was not met, we used the restricted mean survival time to estimate the number of days remaining alive in a 1-year follow-up. The differences between treatment strategies on CFS = 4 and CFS > 4 were estimated using the restricted mean survival time. We analyzed the coprimary composite endpoint using competing risk event analysis, accounting for non-cardiac death as a competing event. We calculated the subdistribution hazard ratio with 95% CI, and included the study centre as the stratification variable due to the multicenter nature of the data.

Finally, we analyzed the number of readmissions using negative binomial regression. We expressed estimates as rates and incidence rate ratios with 95% CI. A two-sided P-value < 0.05 was considered to be statistically significant. All analyses were performed using Stata software version 17.0 (Stata Corp, College Station, TX, USA).

RESULTS

Patient Characteristics and Outcomes

Among a total of 167 patients, 79 patients (46.7%) were male, and the mean age was 85.5 ± 5 years. The distribution of patients across the CFS categories was as follows: CFS = 4 (n = 43, 25.7%), CFS = 5 (n = 72, 43.1%), CFS = 6 (n = 48, 29%), and CFS = 7 (n = 4, 2%). Based on the CFS definition, the patient population was divided into vulnerable (CFS = 4, n = 43) and frail (CFS > 4, n = 124) patients.

Table 1 compares the baseline clinical characteristics of patients according to their frailty status. The age was not significantly different. However, patients with a higher burden of frailty were more frequently women, had a higher proportion of prior stroke and a trend towards more prior atrial fibrillation. As expected, patients with CFS > 4 presented a significantly poorer functional status measured with Barthel index.

The proportion of patients assigned to a routine invasive strategy was not significantly different between frailty groups (Table 2). Despite similar findings in the coronary angiogram, patients with CFS = 4 underwent more commonly revascularization procedures than those with CFS > 4. No significant differences were observed regarding medical treatment at discharge (Table 2).

Patients with CFS > 4 presented a non-significant trend to lower values of DAOH (289.8 *vs.* 320.6, P = 0.146), a higher number of readmissions per patient (1.03 *vs.* 0.58, P = 0.046) and a significantly higher number of days spent at the hospital during the first year (10.8 *vs.* 3.8, P = 0.014). Likewise, a non-significant trend to a higher number of patients with CFS ≥ 5 died [32/124 (25.8%) *vs.* 6/43 (14%), P = 0.110]. The proportion of patients suffering the composite of myocardial infarction, revascularization or cardiac death was not significantly different (P = 0.940).

Impact of a Routine Invasive Strategy According to Frailty Categories

Overall, the mean DAOH was 297 ± 119 days. A total of 38 patients (23%) died. Non-cardiac reasons accounted for 58% of the deaths. Mortality was mostly non-cardiac only among frail patients (62.5%) compared to CFS = 4 patients (33.3%). There were a total of 153 readmissions, 86 readmissions (56%) because of non-cardiac reasons. Infections, bleeding episodes, and stroke were the most common reasons for non-cardiac readmission.

The clinical characteristics by frailty and randomization subgroups are shown in supplemental material, Table 1S. Baseline differences were only in sex, prior stroke and prior atrial fibrillation. So, the comparison between subgroups was adjusted for these variables.

The invasive strategy did not significantly change the DAOH (14 days more with the invasive management, 95% CI: -53–81, P = 0.68) among patients with CFS = 4. However, in the subgroup with CFS > 4, patients with invasive

Table 1 Baseline clinical characteristics and geriatric profile according to frailty burden status.

Variable	Vulnerable (*n* = 43)	Frail (*n* = 124)	*P*-value
Baseline clinical characteristics			
Age, yrs	85.4 ± 5	85.6 ± 5	0.870
Male	26 (60.5%)	53 (42.7%)	0.045
Hypertension	38 (88.4%)	115 (92.7%)	0.373
Dyslipidemia	32 (74.4%)	96 (77.4%)	0.689
Diabetes mellitus	27 (62.8%)	66 (53.2%)	0.277
Peripheral artery disease	6 (14%)	12 (9.7%)	0.301
Prior stroke	2 (4.7%)	28 (22.6%)	0.030
Smoking status			0.143
Never smoker	26 (60.5%)	86 (69.4%)	
Prior smoker	17 (39.5%)	33 (26.6%)	
Active smoker	0	5 (4%)	
Chronic kidney disease	15 (34.9%)	59 (47.6%)	0.149
Prior myocardial infarction	12 (27.9%)	39 (31.5%)	0.664
Prior percutaneous coronary intervention	14 (32.6%)	38 (30.6%)	0.815
Prior heart failure	6 (14%)	23 (18.5%)	0.493
Prior atrial fibrillation	7 (16.3%)	38 (30.6%)	0.067
Killip class at admission II	8 (18.6%)	31 (25%)	0.169
Normal electrocardiogram at admission	15 (34.9%)	38 (30.6%)	0.607
Systolic blood pressure, mmHg	142 ± 28	139 ± 24	0.526
Heart rate, beat/min	78 ± 16	79 ± 19	0.827
Haemoglobin	12.6 ± 2	12.3 ± 2	0.227
Creatinin	1.28 ± 1	1.36 ± 0.7	0.581
Geriatric syndromes			
Charlson index	2.7 ± 2	2.8 ± 2	0.784
Barthel index	95 ± 5	68 ± 21	< 0.001
Pfeiffer test	1.4 ± 1	2.1 ± 2	0.115
FRAIL scale	1.8 ± 1	2.8 ± 1	< 0.001

Data are presented as means ± SD or *n* (%).

management tended to have less DAOH (-31 days, 95% CI: -71–8, $P = 0.11$, Figure 1; $P_{interaction} = 0.26$). Total mortality tended to be higher in patients with CFS > 4 and invasive management ($P = 0.16$, Figure 2). Indeed, within the subgroup with CFS > 4, patients invasively managed lived 29 days less (95% CI: -53–-6) than their conservative counterparts (Figure 2). In contrast, there were no differences between the invasive and conservative strategies in the subgroup with CFS = 4 (-4 days, 95% CI: -50–43).

Finally, no significant differences were observed in the incidence of the coprimary endpoint consisting of cardiac death, myocardial infarction or postdischarge revascularization according to treatment strategy regardless frailty categories (Figure 3).

DISCUSSION

The main findings from this study suggest that patients with higher degrees of frailty had a different clinical profile, with a higher burden of comorbidities, poorer functional status and poorer prognosis, with a higher rate of readmissions, mortality and lower DAOH. Overall, a routine invasive strategy did not improve outcomes. Notably, the impact of a routine invasive strategy seems to change according to frailty status, with a trend to be harmful in the frailest patients.

Data regarding the potential benefit of a routine early invasive strategy among elderly patients with NSTEMI are controversial. While it seems to reduce cardiovascular even-

Table 2 Angiographic data and treatment at discharge according to frailty burden status.

Variable	Vulnerable (*n* = 43)	Frail (*n* = 124)	*P*-value
Angiographic data			
Assignment to an invasive strategy	23 (53.5%)	61 (49.2%)	0.627
Angiography performed	26 (60.5%)	65 (52.4%)	0.361
Number of vessels diseased			0.270
0	2 (7.7%)	15 (23.1%)	
1	11 (42.3%)	16 (24.6%)	
2	3 (11.5%)	11 (16.9%)	
3	10 (38.5%)	23 (35.3%)	
Left main coronary artery disease	5 (20.8%)	9 (16.7%)	0.441
Percutaneous coronary intervention during the admission	21 (48.8%)	35 (28.2%)	0.014
Coronary artery bypass grafting during the admission	1 (2.3%)	1 (0.8%)	0.450
Revascularization during the admission	22 (51.2%)	36 (29%)	0.009
Treatment at discharge			
Acetilsalicylic acid	39 (90.7%)	103 (83.1%)	0.162
Clopidogrel	28 (65.2%)	84 (67.7%)	0.726
Ticagrelor	5 (11.6%)	10 (8.1%)	0.537
Direct anticoagulants	6 (14%)	21 (16.9%)	0.642
Vitamin K antagonists	3 (7%)	16 (12.9%)	0.405
Dual antiplatelet therapy	33 (76.7%)	81 (65.3%)	0.147
Triple therapy	2 (4.7%)	15 (12.1%)	0.132

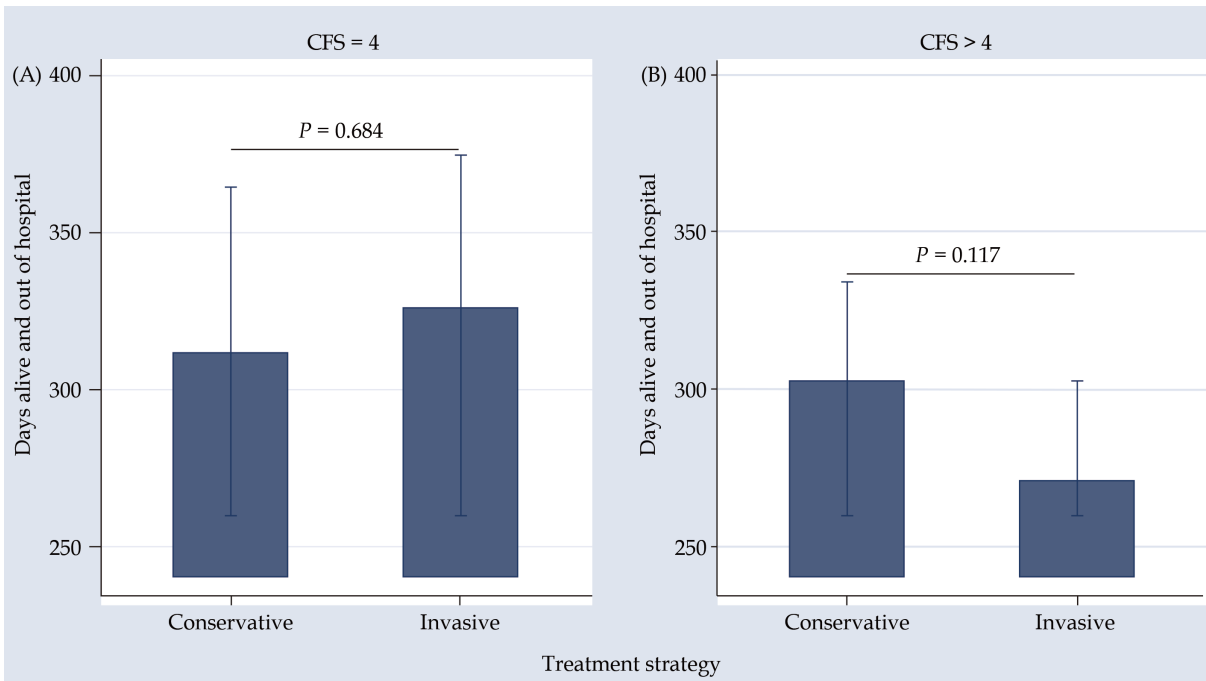

Figure 1 Days alive and out of hospital during the first year after the admission according to treatment strategy in vulnerable patients (A); and in frail patients (B). CFS: Clinical Frailty Scale.

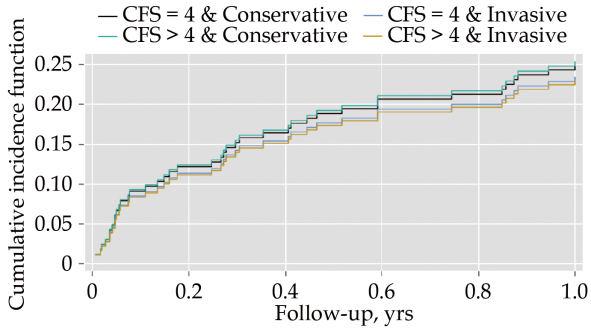

Figure 2 Incidence of mortality according to treatment strategy and degree of frailty. CFS: Clinical Frailty Scale.

ts in highly selected older populations,[2] observational data suggest that patients with a high burden of comorbidity or established frailty criteria may not obtain a significant clinical benefit from an invasive strategy.[7,8] In a previous randomized trial, in patients with two or more relevant comorbidities, there were no differences in the outcomes.[3]

Frailty is receiving a growing interest during the last years for predicting prognosis in older patients with NSTEMI.[17] Importantly, a significantly more conservative management has been described among frail patients.[18,19] It is important to note that patients with higher degrees of frailty also have a high burden of comorbidity, disability and other geriatric syndromes.[10,11] This is a crucial issue since these complex patients are at increased risk of cardiovascular events, non-cardiac readmissions, and mortality.[20–22] The risk of non-cardiac events might preclude obtaining a significant benefit from an invasive strategy during admission. Data from the MOSCA-FRAIL clinical trial[9] strongly supports this hypothesis. Non-cardiac causes accounted for most readmission episodes and mortality. This fact could explain the different impact of the intervention, with a trend to be harmful among patients with CFS > 4. Similar findings were observed at long-term follow-up.[23] These findings highlight the need for a specific, holistic approach to frail patients in future studies. Integrating a specific frailty intervention strategy[24–26] (including education, management of comorbidities, exercise programs and nutrition) might be necessary to improve management and outcomes.

The complexity and high rate of non-cardiac events and readmissions highlight the need for using specific, patient-centred outcomes in clinical trials and registries addressed to elderly patients. In this sense, DAOH[27–29] is a novel clinical outcome encompassing readmissions, mortality and quality of life since being at home is one of the main preferences in this age subgroup. Most clinical trials assessing the impact of an invasive strategy focused on the rate of cardiovascular events. In this sense, using DAOH as the primary outcome in the MOSCA-FRAIL clinical trial allowed us to understand better the complexity of NSTEMI in older adults and how difficult it is to improve outcomes in this context, in particular when frailty coexists.

Finally, the rate of revascularization deserves to be commented. The cross-over rate across the two treatment arms was low, and less than 10% of patients allocated to the conservative strategy underwent angiography during admission. Interestingly, a significantly lower proportion of patients with a CFS > 4 underwent revascularization despite similar findings in the angiogram. This is a relevant point since the performance of angiography was randomized but not the performance of revascularization procedures. In this sense, the lower rate of revascularization

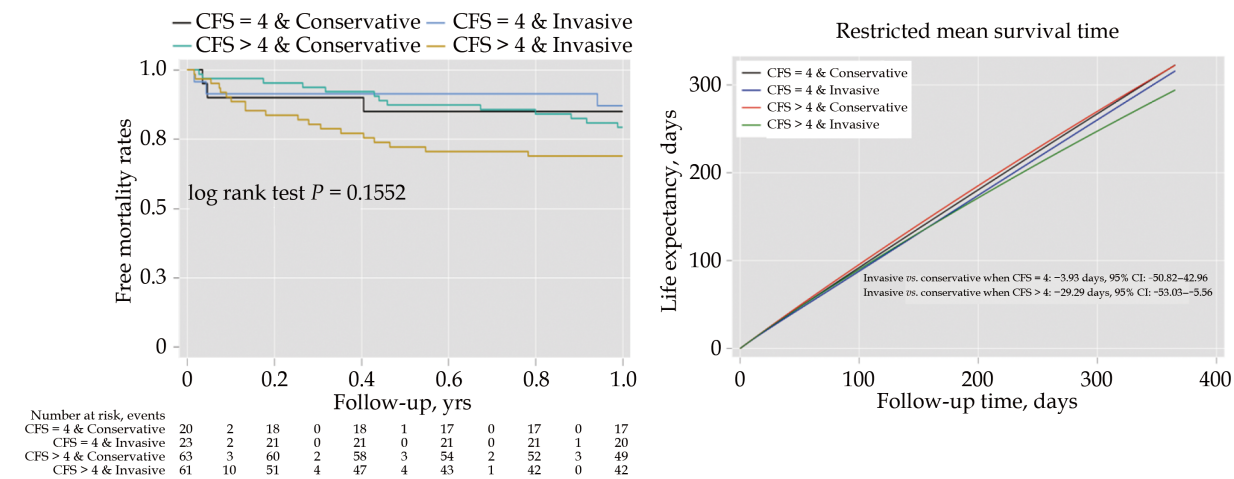

Figure 3 Incidence of the composite of myocardial infarction, need for revascularization and cardiac death at one year according to treatment strategy and degree of frailty. CFS: Clinical Frailty Scale.

among the frailest patients might be due to the perception of less clinical benefit from treating physicians,[8,30] which could also impact prognosis.

LIMITATIONS

This study has some limitations, such as the moderate size of subgroups (due to the fragmentation of the sample) and the open-label design of the trial. Frailty was defined by the CFS, so our result might not be extrapolated to frail patients as defined by other frailty measurement tools. On the other hand, since revascularization was not controlled and left at the physicians' criteria, its impact on outcomes cannot be adequately assessed, and residual confounding cannot be excluded. Therefore, this work should be considered a hypothesis generating study to be confirmed with larger series and properly designed specific clinical trials.

However, despite these limitations, this study retrieves novel and valuable data regarding the clinical profile, outcomes and the impact of a routine invasive strategy in NSTEMI according to the degree of frailty. Future research in this field is warranted, especially regarding long-term outcomes in these patients and the potential impact of an holistic intervention for reducing adverse events in this setting.

CONCLUSIONS

Patients with higher degrees of frailty have different clinical profile and poorer outcomes, with a higher rate of readmissions, mortality and lower DAOH at one year. The impact of a routine invasive strategy seems to change according to frailty status and might be harmful in the frailest patients. These findings highlight the need for an optimal selection of patients and the integration of different tools for reversing frailty along with drug treatments when designing trials for older frail patients with NSTEMI. Improving management and outcomes in these complex patients may lead to significant clinical, economic and social consequences.

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