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Original article

Frailty and adverse outcomes in patients over 65 years old with acute coronary syndrome in a hospital cohort in Medellin, Colombia

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The authors declare no conflict of interest.

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ABSTRACT

Objective. Several studies have demonstrated the association between frailty and worse outcomes in patients with acute coronary syndrome (ACS); however, there is a lack of evidence in Colombia. This study aims to evaluate the association between frailty and the risk of adverse outcomes in patients over 65 years of age diagnosed with ACS. **Materials and Methods.** A prospective cohort study was conducted that included patients over 65 years of age with an indication for coronary arteriography due to ACS diagnosis in a hospital in Medellín, Colombia. Frailty was assessed using the FRAIL scale. The primary outcome was all-cause mortality at 30 days. Secondary outcomes included: length of hospital stay and a composite outcome of in-hospital or 30-day death; contrast-induced nephropathy (CIN); acute heart failure; cardiogenic shock; hemorrhagic complications, and vascular complications. **Results.** A total of 112 patients were included. Frail patients (n = 35, 31.3%) were older, had a lower socioeconomic status, higher GRACE scores, and more severely compromised coronary vessels. A significant association was observed between frailty and 30-day mortality (relative risk [RR] 19.00, 95% confidence interval [CI]: 5.04-72.61; p < 0.001), the composite outcome (RR 4.57, 95% CI: 2.56-8.34; p < 0.001), and longer hospital stays (9 days vs. 5 days in the non-frail group). **Conclusions.** A considerable number of patients over 65 years of age with ACS were frail. Frailty was associated with adverse in-hospital and 30-day outcomes.

Keywords: Frailty; Acute Coronary Syndrome; Frail Elderly; Colombia (Source: MeSH NLM).

RESUMEN

Objetivo. Diversos estudios han demostrado la asociación entre la fragilidad y peores desenlaces en pacientes con síndrome coronario agudo (SCA); sin embargo, hay una falta de evidencia en Colombia. Este estudio tiene como objetivo evaluar la asociación entre la fragilidad y el riesgo de desenlaces adversos en pacientes mayores de 65 años diagnosticados con SCA. **Materiales y métodos.** Se realizó una cohorte prospectiva que incluyó a pacientes mayores de 65 años con indicación de arteriografía coronaria debido a diagnóstico de SCA en un hospital de Medellín, Colombia. La fragilidad se evaluó mediante la escala FRAIL. El desenlace primario fue la mortalidad por cualquier causa a los 30 días. Los desenlaces secundarios incluyeron: duración de la estancia hospitalaria y un desenlace compuesto de muerte intrahospitalaria o a los 30 días; nefropatía inducida por contraste (NIC); insuficiencia cardiaca aguda; choque cardiogénico; complicaciones hemorrágicas, y complicaciones vasculares. **Resultados.** Se incluyeron 112 pacientes. Los pacientes frágiles (n=35, 31,3%) fueron de mayor edad, con un estrato socioeconómico más bajo, un puntaje GRACE más alto y un mayor número de vasos comprometidos en la arteriografía. Se observó una asociación significativa entre la fragilidad y la mortalidad a 30 días (riesgo relativo [RR] 19,00, IC 95%: 5,04-72,61; p<0,001), el desenlace compuesto (RR 4,57, IC 95%: 2,56-8,34; p<0,001), y una mayor estancia hospitalaria (9 días vs. 5 días en el grupo no frágil). **Conclusiones.** Un número considerable de pacientes mayores de 65 años con SCA eran frágiles. La fragilidad se asoció con desenlaces adversos intrahospitalarios y a 30 días.

Palabras clave: Fragilidad; Síndrome Coronario Agudo; Anciano Frágil; Colombia (Fuente: DeCS Bireme).

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and disability in Colombia and worldwide [1,2]. Within this group, acute coronary syndrome (ACS) represents a significant number of hospital admissions, affecting approximately 50% of older adults who suffer heart attacks [3]. The interaction between aging, the number of comorbidities, and polypharmacy can alter the risk-benefit ratio of interventions in patients with ACS. For example, older adults have a higher cardiovascular risk, as well as a greater risk of complications. Moreover, this population is often excluded or underrepresented in clinical trials, which limits the generalizability of the results. Due to this, some groups propose that strict adherence to guidelines in these patients could increase adverse events, while clinical benefits would be limited [4].

To identify factors that allow for better patient risk stratification, frailty assessment has been suggested. Frailty is a biological condition that implies a reduction in reserve and resistance capacity against stressors, which leads to a loss of homeostasis and increased vulnerability to adverse events [5]. Stratifying patients according to their degree of frailty helps predict mortality, rehospitalizations, and disability, and is also a useful tool in pre-intervention and surgical procedure evaluations [6,7]. In the context of ACS, frailty has been shown to have prognostic value, allowing for risk reclassification and improving clinical decision-making [8-11].

In Latin America, data on the impact of frailty in elderly patients with ACS are scarce. This study aims to determine the association between frailty and in-hospital and 30-day adverse outcomes in patients over 65 years of age who undergo coronary arteriography for ACS.

Materials and methods

Study design, population, and sample

This prospective cohort study was conducted between March 1 and October 1, 2023. Patients over 65 years old admitted to the hemodynamics unit of the Hospital Universitario San Vicente Fundación (HUSVF) in Medellín, with a diagnosis of ACS according to the Fourth Universal Definition of Myocardial Infarction [12], were included. Patients with a confirmed alternative diagnosis, those under anesthesia, with severe cognitive impairment or difficulties in frailty assessment, as well as those who did not agree to participate, were excluded. The selection of pharmacological treatment and strategy (invasive or conservative) was left to the discretion of the treating physician, without considering the result of the FRAIL scale.

The sampling was by convenience. Based on previous studies [8–11] on the association between frailty and short-term mortality in patients over 65 years old with ACS, an incidence of the primary outcome of 10% in the frail group and 2% in the non-frail group was estimated. With a significance level of 5% and 80% power, it was determined that at least 274 patients were needed.

Frailty assessment

The FRAIL scale, recommended by various cardiology and geriatrics scientific societies, validated in Mexico and used in local studies [13–16], was used to assess frailty. This scale consists of 5 items: fatigue, resistance (ability to climb one flight of stairs), ambulation (ability to walk ≥100 m), weight loss (>5% in the last 6 months), and comorbidities (5 or more confirmed diseases). One point is assigned for each positive item. Based on the score, patients were classified as frail (≥3 points), pre-frail (1 or 2 points), and robust (0 points). Frailty was assessed upon admission to the hemodynamics unit in those patients who met the inclusion criteria and provided informed consent. If the patient could not provide consent, but a third party accepted and sufficient data was available, the patient was included.

Data collection and variable selection

Clinical and sociodemographic characteristics were extracted from the electronic medical record and recorded in a Microsoft Excel database. Variables that could act as confounders were included: age, sex, history of cardiovascular disease (CVD), socioeconomic status (6-level classification, with level 1 being the lowest and level 6 the highest), diabetes mellitus, smoking, chronic kidney disease, atrial fibrillation, and history of heart failure. CVD was defined as previous coronary revascularization (surgical or percutaneous), stroke, peripheral arterial disease, or documentation of coronary disease through invasive or non-invasive tests. Upon admission, the GRACE score was calculated and cognitive status was assessed with the Mini-Cog tool (score from 0 to 5, where <3 points indicates possible cognitive impairment). LDL cholesterol, creatinine, and hemoglobin values were recorded at admission, and the glomerular filtration rate (GFR) was estimated using the 2009 CKD-EPI equation. During coronary arteriography, the type of vascular access, culprit vessel, and number of compromised vessels were considered. All patients underwent a transthoracic echocardiogram.

Outcomes

The primary outcome was all-cause mortality at 30 days after discharge. Secondary outcomes included hospital stay and a composite outcome encompassing 30-day mortality, contrast-induced nephropathy (CIN), vascular complications, hemorrhagic complications, acute heart failure, cardiogenic shock, and 30-day rehospitalization.

Exploratory outcomes included the individual components of the composite outcome. CIN was defined according to KDIGO guidelines [17], while bleeding was classified as minor and major according to the BARC consensus [18]. Vascular complications included hematomas, pseudoaneurysms, and periprocedural stroke, according to consensus [19]. Acute heart failure was defined as the onset or worsening of signs of systemic congestion in the presence of structural or functional cardiac dysfunction, and

cardiogenic shock as arterial hypotension (systolic pressure <90 mmHg) with tissue hypoxia, requiring vasopressors or inotropes. Other exploratory outcomes included arrhythmias and atrioventricular blocks according to consensus [20,21], and the need for transfusion.

Telephone follow-up was conducted at 30 days to assess vital status and rehospitalizations.

Statistical analysis

Categorical variables are presented as absolute frequencies and percentages, while continuous variables are expressed as medians and interquartile ranges. To evaluate the association between frailty and 30-day mortality, as well as with exploratory outcomes, a quasi-Poisson model with logarithmic link function was used to estimate the risk ratio (RR) and its 95% confidence interval (CI). The analysis was adjusted for age, sex, smoking, history of coronary heart disease, socioeconomic status, medical management, and diabetes. The selection of these confounders was made through discussion among the researchers and the construction of a directed acyclic graph (Supplementary Material) [22]. Differences in hospital stay were evaluated using the difference in rank-biserial coefficient (rank rbiserial) as a measure of effect size. A value greater than 0.40 was considered a "large" difference. The composite outcome was analyzed with a quasi-Poisson model using quasi-likelihood parameter estimates, and the relative risk (RR) with its 95% CI was calculated. R software was used for data analysis.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and current guidelines for good research practices. Approval was obtained from the ethics and research committee of the Hospital Universitario San Vicente Fundación (HUSVF) in Medellín.

Results

Between March 1 and October 1, 2023, 280 procedures were performed in the Hemodynamics Laboratory of the Hospital Universitario San Vicente Fundación (HUSVF) in Medellín. 112 patients were included in the study **(Figure 1)**. A total of 35 (31.3%) patients were classified as frail, 56 (50%) as pre-frail, and 21 (18.8%) as robust. Patients were grouped into two categories: frail (n=35; 31.3%) and non-frail (which included pre-frail and robust) (n=77; 68.8%).

Clinical and sociodemographic characteristics are presented in **Table 1**. Frail patients (FP) had a median age of 78 years, while non-frail patients (NFP) had a median age of 73 years. FP had higher GRACE scores (median of 185 vs. 137 in NFP) and lower Mini-Cog scores (median of 2 points vs. 4 in NFP). Hemoglobin and LDL cholesterol levels were similar in both groups, but FP showed a lower GFR (median of 57 mL/min/1.73 m^2 vs. 77 mL/min/1.73 m^2 in NFP). Additionally, FP presented a higher number of compromised vessels (median of 3 vessels vs. 2 vessels in NFP) and a lower ejection fraction (median of 38% vs. 49% in NFP).

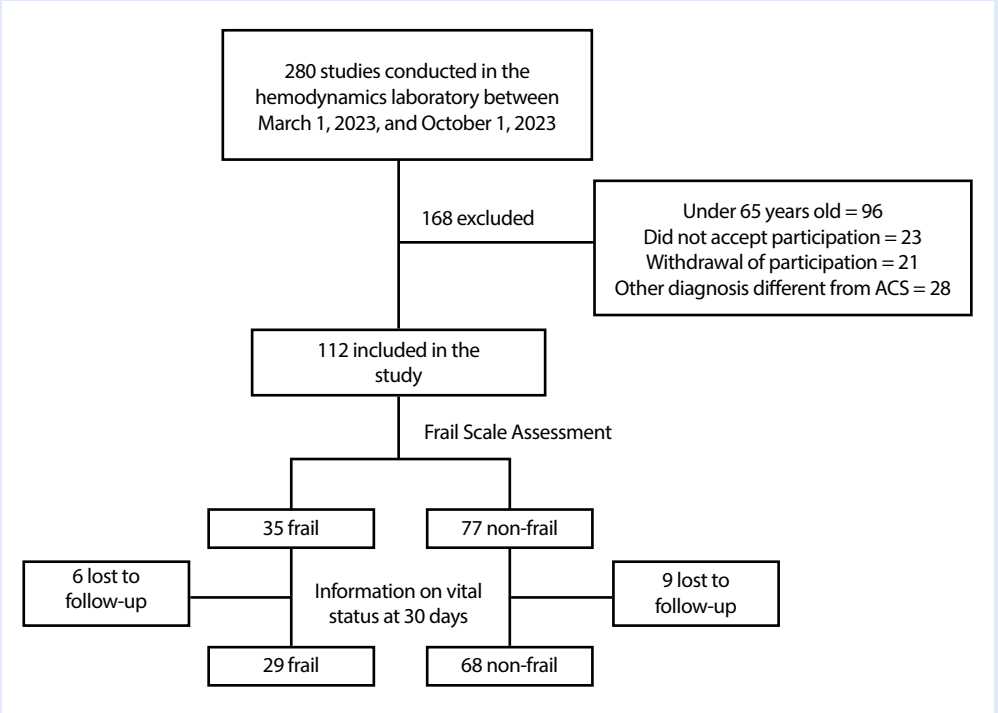

Figure 1. Flowchart of participant selection in the study.

Table 1. Clinical and sociodemographic characteristics of study participants

Characteristic	Frail, n (%) (n=35)	Non-frail, n (%) (n=77)	Total, n (%) (n=112)
Age*	78 (75-80.5)	73.0 (69.0-76.0)	75.0 (70.8-78.0)
Female sex	18 (51.4)	33 (42.9)	51 (45.5)
Socioeconomic strata			
1 (lowest)	12 (34.3)	22 (28.6)	34 (30.4)
2	12 (34.3)	23 (29.9)	35 (31.3)
3	10 (28.6)	26 (33.8)	36 (32.1)
4	1 (2.9)	4 (5.2)	5 (4.5)
5	0 (0)	2 (2.6)	2 (1.8)
6 (highest)	0 (0)	0 (0)	0 (0)
Diagnosis			
Non-ST elevation ACS	19 (54.3)	37 (48.1)	56 (50.0)
ST elevation ACS	15 (42.9)	33 (42.9)	48 (42.9)
Unstable Angina	1 (2.9)	7 (9.1)	8 (7.1)
Time from symptom onset to hemodynamics laboratory *	48 (18-72)	46 (24-72)	48 (24-72)
Mini-Cog*	2.0 (2.0-3.0)	4.0 (3.0-5.0)	3.50 (2.00-5.00)
GRACE*	185 (162-217)	137 (122-158)	145 (127-177)
Comorbidities			
Diabetes mellitus	11 (31.4)	23 (29.9)	34 (30.4)
Dyslipidemia	17 (48.6)	34 (44.2)	51 (45.5)
Smoking	17 (48.6)	42 (54.5)	59 (52.7)
Heart failure	1 (2.9)	1 (1.3)	2 (1.8)
Chronic kidney disease	4 (11.4)	5 (6.5)	9 (8.0)
Atrial fibrillation	1 (2.9)	1 (1.3)	2 (1.8)
Cardiovascular disease history			
Coronary disease	5 (14.3)	12 (15.6)	17 (15.2)
Stroke	5 (14.3)	0 (0)	5 (4.5)
History of surgical revascularization	0 (0)	2 (2.6)	2 (1.8)
History of stent revascularization	3 (8.6)	8 (10.4)	11 (9.8)
Ejection fraction*	38.0 (31.0-50.5)	49.0 (38.0-56.0)	46.5 (35.0-55.0)
Culprit vessel			
No lesions	3 (8.6)	2 (2.6)	5 (4.5)
Left anterior descending artery	19 (54.3)	36 (46.8)	55 (49.1)
Right coronary artery	9 (25.7)	24 (31.2)	33 (29.5)
Circumflex artery	3 (8.6)	12 (15.6)	15 (13.4)
Left main artery	1 (2.9)	1 (1.3)	2 (1.8)
Posterolateral	0 (0)	1 (1.3)	1 (0.9)
Diagonal	0 (0)	1 (1.3)	1 (0.9)
Number of vessels*	3.00 (1.50-3.00)	2.00 (1.00-3.00)	2.00 (1.00-3.00)
Hemoglobin *	12.8 (12.0-14.0)	13.6 (12.1-15.0)	13.4 (12.0-14.6)
LDL Cholesterol *	95 (66-125)	107 (80.8-126)	100 (74-127)
Creatinine *	1.00 (0.740-1.40)	0.910 (0.760-1.10)	0.945 (0.748-1.20)
GFR *	57.0 (40.5-83)	77.0 (62.0-88.0)	74.0 (54.0-87.0)

ACS: Acute Coronary Syndrome, GFR: Glomerular Filtration Rate.
* The values shown correspond to the median and interquartile range (Q1-Q2).

Table 2 describes the intervention-related characteristics. 51.4% of FP were treated conservatively, compared to 95.5% of NFP who were treated invasively. Most patients underwent percutaneous revascularization, the most common access was radial, and 41.1% required tirofiban infusion. There were no differences between groups in the number of stents implanted.

Table 3 shows the frequency of in-hospital adverse outcomes and their association with frailty. The occurrence of the primary outcome in FP was 22.8% compared to 4.8% in NFP. Frailty was associated with a higher risk of primary outcome in the adjusted analysis (adjusted RR 19.00, 95% CI: 5.04-72.61; p < 0.001). An increased risk of experiencing the composite outcome was also observed (adjusted RR 4.57, 95% CI: 2.56-8.34; p < 0.001). Additionally, as shown in **Figure 2**, FP had longer hospital stays (median of 9 days vs. 5 days in NFP; rank rbiserial = 0.46, 95% CI: 0.26-0.62). The Supplementary Material details the outcomes and specific causes of mortality.

An exploratory analysis on the management strategy (invasive vs. conservative) and outcomes according to the degree of frailty was conducted (Supplementary Material). FP managed conservatively, compared to those treated with an invasive strategy, had fewer bleeding-related complications (16.7% vs. 47.1%), cardiogenic shock (22.2% vs. 41.2%), 30-day mortality (16.7% vs. 29.4%), and shorter hospital stay (median of 8 days vs. 12 days). In NFP, the occurrence of complications was low and the only death occurred in a patient with evolved infarction (>48 h) complicated by cardiogenic shock.

Discussion

This study found an association between frailty and the risk of in-hospital and 30-day adverse outcomes in patients over 65 years old with ACS. Thus, 31.3% of patients were classified as frail, and there were no differences in comorbidities, except for a history of stroke and GFR, which was lower in frail patients. Frailty was independently associated with in-hospital and 30-day mortality, longer hospital stay, bleeding-related complications, CIN, acute heart failure, and cardiogenic shock.

The results of this study are consistent with those reported in other cohorts, although the occurrence of the primary outcome in the frail group was higher than expected (22.8% vs. 4.8% in the non-frail group). In 2011, Ekerstad *et al.* were the first to report the association between frailty and in-hospital and 30-day mortality in patients with ACS, with mortality rates of 10.1% and 15.4% in frail patients, respectively [9]. Similar results were observed in the cohort of Kang *et al.* (2015) and Alonso Salinas *et al.* (2016), who reported the relationship between frailty and short-term mortality [8,11]. In 2018, Patel *et al.* published the results of an Australian cohort of 3,944 patients over 65 years old with ACS, showing the association between frailty and in-hospital mortality (10% vs. 4.9% in non-frail patients) [10].

Unlike other cohorts, no significant differences were found in patient comorbidities. Generally, frail patients present more comorbidities and complications [23]. This could be due to the limited size of our sample and the characteristics of the FRAIL scale, in which comorbidities represent only 1 of the 5 items. However, the association between frailty and adverse outcomes was maintained, which supports the idea that frailty encompasses factors beyond comorbidities. Additionally, frailty was associated with greater cognitive impairment; in this cohort, frail patients had lower Mini-Cog scores. Cognitive impairment is common in elderly patients with ACS and is associated with a higher likelihood of adverse events in the first year [24].

Regarding angiographic characteristics, frail patients had more compromised vessels and were more frequently treated conservatively (51.4% vs. 4.5%). Frail patients with non-ST-elevation ACS (NSTEACS) present more complex and severe

Table 2. Intervention-related characteristics

Characteristic	Frail, n (%) (n=35)	Non-frail, n (%) (n=77)	Total, n (%) (n=112)
Medical management	18 (51.4)	4 (5.2)	22 (19.6)
Revascularization			
Surgical *	2 (5.7)	8 (10.4)	10 (8.9)
Balloon Angioplasty + Stent	15 (42.8)	65 (84.4)	80 (71.4)
Access			
Radial	26 (74.2)	63 (81.8)	89 (79.4)
Femoral	6 (17.1)	14 (18.2)	20 (17.9)
Radial + femoral	3 (8.6)	0 (0)	3 (2.7)
Number of stents **	2 (1-3.25)	2 (1-3)	2 (1-3)
Tirofiban	13 (37.1)	33 (42.9)	46 (41.1)

* 1 patient from the frail group and 2 from the non-frail group initially underwent percutaneous revascularization and subsequently surgical revascularization.
** The values shown correspond to the median and interquartile range (Q1-Q2).

Table 3. In-hospital adverse outcomes and association with frailty

Outcome	Frail	Non-frail	Adjusted RR*	95% CI	p value
30-day mortality**	8/35 (22.9%)	1/77 (1.3%)	19.00	5.04-72.61	<0.001
Composite outcome***	27/35 (77%)	14/77(18.2%)	4.57	2.56-8.34	<0.001
Contrast-induced Nephropathy	11/35(31.4%)	5/77 (6.5%)	6.52	1.56-35.39	0.015
Vascular complications****	7/35 (20%)	6/77 (7.8%)	1.36	0.32-5.69	0.671
In-hospital bleeding****	11/35(31.4%)	1/77(1.3%)	25.54	3.5-815 .53	0.009
Acute heart failure****	9/35(25.7%)	2/77(2.6%)	11.00	2.18-93.93	0.009
30-day hospitalization****	7/35(20%)	3/77(3.9%)	1.38	0.23-8.08	0.720
Cardiogenic shock****	11/35 (31.4%)	1/77 (1.3%)	30.07	7.93-196.81	<0.001

RR: relative risk. CI: confidence interval.
* Model adjusted for age, sex, history of coronary artery disease, smoking, diabetes, socioeconomic status, and medical management.
** Details of each cause of death are provided in the Supplementary Material.
***The composite outcome included: 30-day mortality, contrast-induced nephropathy, any vascular complication, any bleeding, acute heart failure, 30-day hospitalization, and cardiogenic shock. This outcome was calculated as relative risk using a quasi-Poisson model, with quasi-likelihood estimation of the model parameters.
**** The RR for contrast-induced nephropathy, vascular complications, in-hospital bleeding, acute heart failure, and cardiogenic shock was estimated using a quasi-Poisson model.

angiographic characteristics, regardless of age, which increases their risk of mortality, urgent revascularization, infarction, and bleeding during follow-up [25]. Although guidelines recommend an early invasive strategy in high-risk groups, frail patients with ACS tend to be disproportionately affected by these high-risk characteristics. In this cohort, frail patients had a higher GRACE score, and a correlation between the degree of frailty and this score has been demonstrated [26]. However, the GRACE score may overestimate risk in patients over 65 years old. Risk reclassification according to the degree of frailty could improve the accuracy of predictions [27].

Invasive management in elderly patients follows the same recommendations as in the general population; however, variables such as the severity of comorbidities, cognitive impairment, and life expectancy should be considered. In the study by Patel *et al.*, approximately 40% of frail patients were managed conservatively, which is consistent with the results of this cohort [10]. Regarding NSTEACS, five randomized clinical trials have evaluated the efficacy of the invasive strategy in elderly patients, but only two considered frailty and comorbidities. Four studies found no differences, while one reported a reduction in recurrent infarctions and the need for

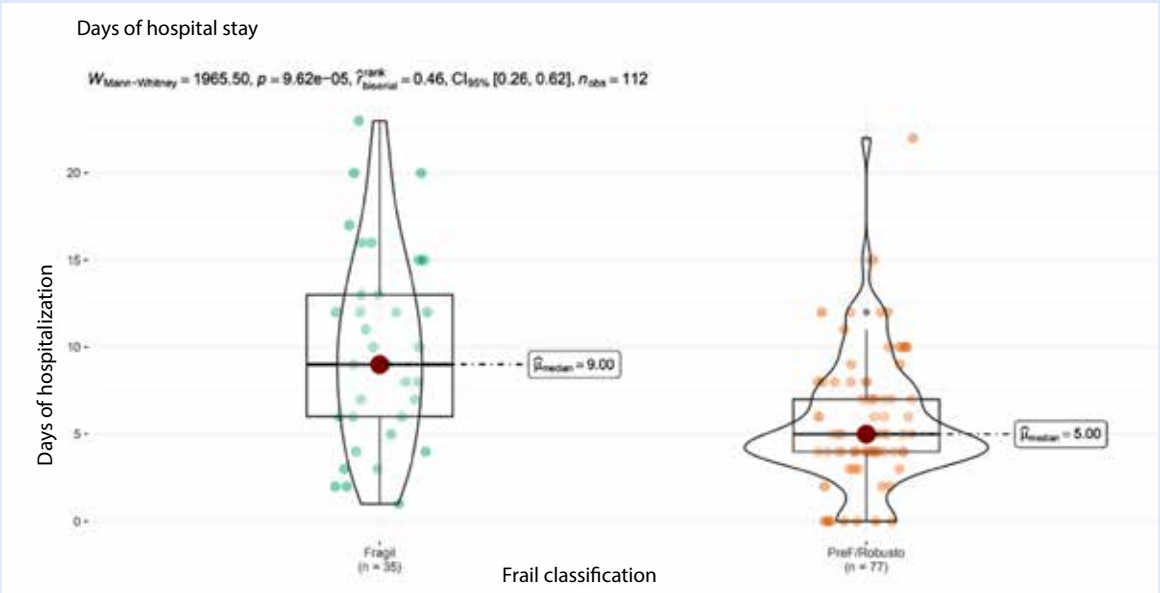

Figura 2. Differences between frailty and length of hospital stay.

urgent revascularization [28]. In patients with ST-elevation ACS, a meta-analysis showed that percutaneous revascularization reduces mortality, reinfarction, and stroke, although no study considered frailty [28]. Furthermore, frail patients present a higher risk of vascular and hemorrhagic complications, CIN, infections, and procedure-related complications. Additionally, the meta-analysis showed that patients over 70 years old treated with an invasive approach have a higher risk of bleeding (Odds ratio [OR] 2.19, 95% CI: 1.12-4.28) [29], and those over 75 years old undergoing coronary arteriography have a higher risk of developing CIN (OR 1.99, 95% CI: 1.75-2.27) [28]. Our data align with previous studies showing that frail patients with ACS have worse short-term outcomes.

When analyzing outcomes according to the management strategy, frail patients treated with an invasive approach presented more adverse outcomes. However, these data are not generalizable due to the comparison not being planned a priori, which could introduce a type I error, in addition to the small sample size. Finally, the main cause of death in this cohort was cardiogenic shock. Elderly patients with ACS have a higher prevalence of cardiogenic shock and worse prognosis compared to younger patients. Additionally, this subgroup is less likely to undergo invasive interventions and more vulnerable to complications derived from critical illness, such as infections, arrhythmias, and gastrointestinal bleeding [30].

Given that frailty is an emerging concept, there is no universally accepted definition or standardized scale for its assessment. In this study, the FRAIL scale was chosen for its ease of application; likewise, it has been validated in Mexico and used in local research [13-16]. Regardless of the method used, frailty has been consistently associated with adverse outcomes, which highlights the need for further evaluation in this field [28].

This study has several limitations. Being a single-center study with a small sample and its observational nature, it is subject to biases, mainly confounding and measurement, since some outcomes depended on clinical records. The collection rate was lower than expected, which explains the wide confidence intervals and limits the precision of the results. The reduced number of patients was also due to the limited time for data collection. Furthermore, the study was conducted in a high-complexity center that is not limited to cardiovascular diseases and with convenience sampling, which prevents the generalization of the results. The FRAIL scale, which includes four self-reported items, could be biased by patient subjectivity. The lack of a standardized scale to assess frailty could also limit the extrapolation of the results. It would be important to expand these observations by applying the same scale to a larger sample and with long-term follow-up, which positions this study as a starting point for future research.

In conclusion, in the present cohort, a significant number of patients over 65 years old with ACS were classified as frail. Frailty was associated with adverse outcomes, both in-hospital and at 30 days. The degree of frailty could be an important prognostic marker in elderly patients with ACS, so its routine assessment could significantly impact clinical decision-making.

Author's Contributions

ANN, ANO, JMSS: conceptualization. **ANN, ANO, VAV, DEPD, JCOU, JADR:** data curation. **ANN, ANO, JMSS:** formal analysis and validation. **ANN, ANO, JMSS:** Writing - Original Draft. **ANN, ANO, VAV, DEPD, JCOU, JADR:** Visualization. **ANN, ANO, JMSS, JCOU, JADR:** Writing - Review & Editing.

All authors had access to the data (including statistical analysis and tables) in the study and accepted responsibility for maintaining the integrity of the data and the accuracy of the data analysis.

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