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Frailty scale with the best prediction of mortality in individuals diagnosed with acute coronary syndrome: systematic review and meta-analysis

Letycia Netto de Paula Cunha[1,✉], Samara Vieira de Oliveira[2], Taline Lazzarin[1], Lara Lívia Santos da Silva[2], Marcos Ferreira Minicucci[1], Nara Aline Costa[2]

1. Faculty of Medicine, Botucatu Medical School, São Paulo State University (UNESP), Botucatu, São Paulo, Brazil;
2. Faculty of Nutrition, Federal University of Goiás (UFG), Goiânia, Goiás, Brazil
✉ Correspondence to: letycia.cunha@unesp.br
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ABSTRACT

Background Acute Coronary Syndrome (ACS) is a major cause of hospitalizations and deaths worldwide. Conditions such as frailty worsen these outcomes. Frailty assessment improves risk stratification, complements scores and favors personalized treatments. However, there are numerous tools available for assessing frailty, and there is still no consensus on which would be the most recommended in conditions such as ACS. The objective was to evaluate which frailty diagnostic scale has the best predictive value for mortality in individuals with ACS.

Methods This meta-analysis was conducted using Medline, Embase, and Cochrane, with a search conducted on March 5, 2024. Studies that met the PECOS criteria were included: adult and elderly individuals diagnosed with ACS, frailty assessment determined by a scale, mortality registry and intervention studies or prospective and retrospective cohorts. The risk of bias and quality of evidence were assessed by two researchers using the Joana Briggs Institute Case Series tool and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system, respectively. The meta-analysis was conducted using Review Manager software and subgroup analyses using R software.

Results The results of the meta-analysis indicate that frailty is associated with a significantly higher risk of mortality in patients with ACS ($P < 0.001$). However, the results of the meta-regression did not indicate a significant difference between the five scales evaluated ($P = 0.227$). The choice of scale, therefore, can be based on other factors such as practicality and availability of resources, without compromising the prognosis.

Conclusion Individuals with ACS and frailty have a higher chance of mortality, and all scales evaluated showed good predictive value, with no statistical difference. We suggest that the Clinical Frailty Scale (CFS) is suitable for hospital settings and acute conditions, such as ACS.

It is estimated that around 7 million people are affected by Acute Coronary Syndrome (ACS),[1,2] representing approximately 1 million hospitalizations in the United States of America (USA) and 80,000 in the United Kingdom (UK).[3] In Brazil, around 43% of mortality from cardiovascular causes are attributed to ACS.[4] The treatment of patients with ACS represents a major economic challenge for healthcare systems, due to the complexity and resources required.[5] In addition, the high rate of readmissions due to complications or lack of adherence to treatment worsens the scenario.[6] Lack of adequate treatment also contributes to the development of other conditions, further increasing costs and the impact on the patient.[7]

Conditions such as frailty[8,9] may intensify negative outcomes in ACS, such as reduced recovery capacity and increased mortality risk.[10,11] Frailty is characterized by greater physiological vulnerability resulting from impaired functionality and is closely associated with negative outcomes such as longer hospital stays, readmissions, bleeding, functional decline and mortality.[9,12] Currently, two theoretical models are most commonly used to

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identify frailty: the physical phenotype model and the cumulative deficit model.[9,13] The first model considers fragility by physical and measurable parameters, being the most used.[9] However, there are difficulties in its application, especially in the hospital environment.[14,15] The second model assesses frailty by adding together the individual's deficiencies, comorbidities and conditions, creating an index, and is more recommended in acute or critical conditions, due to its easy applicability.[13,16]

In this sense, the inclusion of frailty assessment has contributed to improving the risk stratification of individuals with ACS, complementing scores widely recognized in the literature and favoring the adoption of personalized treatment strategies, with a focus on improving prognosis.[10,17-19] However, there is a wide variety of tools for assessing frailty, and there is still no consensus on which method is most appropriate, mainly due to the heterogeneity of studies that address this condition as an object of research.[14,15] Considering the lack of consensus on the standardization of the tool, as well as the importance of early diagnosis of frailty, the objective of this meta-analysis was to evaluate which frailty diagnostic scale has the best predictive value for mortality in individuals with ACS.

Methods

Eligibility Criteria

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[20] and is registered with PROSPERO (registration number CRD42024518509). We sought to include prospective and retrospective intervention and cohort studies that met the following inclusion criteria (PECO): Participants (P): Individuals over 18 years of age, of both sexes, diagnosed with ACS assessed by frailty scale. Exposure (E): frailty diagnosis by scales that consider this condition as a state of increased vulnerability to external stressors.[9] Furthermore, considering that there is still no internationally recognized standard definition for this condition, individuals with frailty can transition between states of severity, we also consider those classified as pre-frail within this group, since they may present compatible clinical manifestations, even if they are not identified as frail by the scales.[8,9] Comparator (C): individuals considered no frail by the scales. Outcomes (O): all-cause mortality.

Exclusion Criteria

Publications prior to December 2012, studies conducted among individuals diagnosed with other cardiovascular conditions were excluded, as well as those that assessed frailty exclusively through objective measures (walking speed, handgrip strength, physical tests such as the short physical performance battery (SPPB), among others). In addition, letters to the editors, reviews, conference abstracts and articles published in languages other than English, in cases where there was no response from the authors after contacting them requesting the English version of the publication, were also excluded.

Search Strategy

The search strategy was developed by an independent researcher (LNPC) and reviewed by a senior researcher experienced in systematic reviews and the topic of interest of the study (MFM). The search was carried out on March 5, 2024 in the Medline, Embase and Cochrane databases. Articles from the reference list of relevant articles or from previously published reviews were not considered.

The main terms included were: "frailty", "tool", "scale", "instrument", "acute coronary syndrome", "acute myocardial infarction", "non-ST-segment elevation myocardial infarction", "ST-segment elevation myocardial infarction" and "unstable angina". The terms were combined with the Boolean operators "AND" and "OR", and specifically, for the Medline database, the terms were used according to the MeSH (Medical Subject Headings) vocabulary. The complete search strategy, considering the databases used, is provided in the Supplementary Material (Table S1).

Study Selection Process

All search results were exported and organized using the Rayyan web tool[21] by two independent researchers (LNPC and SVO). Subsequently, selection process was performed. Conflicts throughout the process of conducting this review were resolved by a third researcher (NAC).

The study selection process was carried out in two stages. After the exclusion of duplicate articles, the first stage consisted of reading the title and abstract, and publications that did not meet the eligibility criteria were excluded. In the second stage, we read the studies included in the first stage in full. Conflicts were resolved by a third researcher (NAC).

Data Extraction

The articles included in the second stage had the following information collected: author, year, country, study design (including sample size, most prevalent sex and age), frailty tool used and diagnostic criteria to define this condition as present, number of individuals considered to have pre-frailty and frailty, total mortality and mortality in individuals with pre-frailty and frailty. The data were extracted by two independent researchers (LNPC and SVO) and recorded in an Excel spreadsheet. Verification and disagreements were resolved by a third researcher (NAC).

We contacted authors by email requesting the full-text manuscript when only abstracts were available, or to obtain the information needed to fill out the data sheet when it was not clear in the publications.

Assessment of Risk of Bias

The risk of bias of the selected studies was assessed using the Joana Briggs Institute Case Series tool.[22] This tool assesses the methodological quality of observational studies that describe a group of patients with specific outcomes or conditions. The checklist contains ten questions, with possible answers: "yes", "no", "unclear" and "not applicable".[22] Two researchers (LNCP and SVO) assessed the risk of bias of the studies, considering it as: low (≥ 70% of "yes" scores), moderate (50% to 69% of "yes" scores) and high (≤ 49% of "yes" scores).[22]

Data Analysis

The results were expressed by scale, number of events and the odds expressed in terms of odds for each scale. The effects were reported as odds ratios (OR) and respective 95% confidence intervals (95% CI). The heterogeneity of the effects between the studies was quantified by the I^2 statistic (I^2 value > 50% indicates high heterogeneity).[23] Subgroup analysis was performed to investigate the influence of the frailty scale on mortality prediction. The adopted model was random effects, considering the heterogeneity between the studies. The subgroups were organized according to the scales used in the included studies. The Review Manager software (version 5.4)[24] and the R software (version 4.3.3) were used for meta-analysis and subgroup analyses, respectively. A P-value < 0.05 was considered statistically significant.

Quality of Evidence

To determine the quality of the evidence presented by the included articles, we used the GRADE system.[25] Each article was graded according to the preferred method into one of four levels: high, moderate, low and very low. GRADE-pro GDT software was employed in this process.

RESULTS

Selection of Articles

A total of 1684 studies were retrieved in the database search. After removing duplicates, 1315 titles and abstracts were evaluated, and 157 studies were selected for full-text reading. Twenty-nine studies were included in this systematic review, and twenty-five studies were also evaluated quantitatively. Figure 1 shows the flow diagram for publication selection.

Characteristics of the Studies

As shown in Table 1, 489,097 participants were included.[26-54] The majority (46.2%) were male and elderly (≥ 65 years).[26-54] Among the studies included,[26-54] most had an observational design and only one was a double-blind randomized clinical trial.[42] The follow-up time varied from the period of hospitalization to up to five years.[26-54] The most widely used frailty scale to assess this condition was the Clinical Frailty Scale (CFS). Thirteen studies[26-38] assessed frailty using only the CFS, three[28,39,40] only the Edmonton Frailty Scale (EFS), four[28,36,41,42] the Fried Criteria (FC), six[28,29,43-46] only the Frail Scale (FS), four[47-50] only the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI). In addition, three studies[28,29,36] assessed frailty by comparing the use of different scales such as FC, EFS, FS and CFS. Scales such as the Claims-Based Frailty Index (CFI),[51] ACTION Frailty Scale,[52] Frailty Index (FI)[53] and, Modified Frailty Index (mFI)[54] are still little studied in SCA, with no more than one study published with each of these tools. Due to the lack of studies for comparison, these works[51-54] were not included in the meta-analysis.

Approximately 93,884 (19.2%) individuals were considered pre-frail or frail by the studies, and 12,947 (13.8%) died in this group.[26-54] The studies were conducted in different regions of the world. Seven[44-50] were carried out in Spain, five[30,34,36,28,41] in the UK, two[35,54] in China,

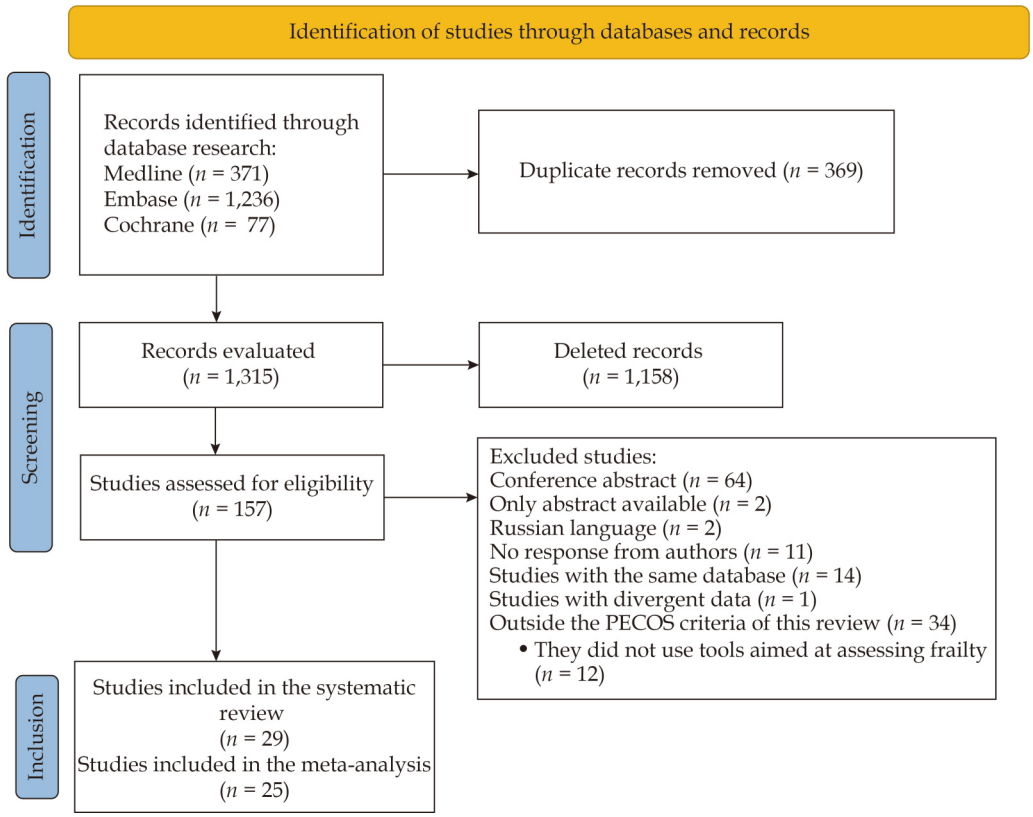


Figure 1 Publication selection flow diagram.

five[26,31,32,37,52] in Japan, two[39,43] in Vietnam, two[27,33] in Sweden, one in the USA,[51] Canada,[40] Poland,[28] Australia,[53] Brazil[29] and one using a sample of fifty-two countries[42] (Table 1).

Association of Fragility with Mortality by Scales

In general, the presence of frailty was a risk factor for mortality regardless of the scale used to assess adults or elderly individuals with ACS ($P < 0.001$). A 4.6-fold higher risk of mortality was observed in individuals living with frailty, when compared to non-frail individuals (OR: 4.60; 95% CI: 3.62-5.86). However, it was possible to verify high heterogeneity ($I^2 = 63\%$) among the studies (Figure 2).

Given the high heterogeneity identified in the meta-analysis, a meta-regression was performed to explore possible sources of this variability. Specifically, it was assessed whether the type of scale used in each study could explain part of the observed heterogeneity. The results showed that the CFS presented the highest odds ratio (OR) among all the scales evaluated. However, this difference did not reach statistical significance in predicting mortality (OR = 4.50; 95% CI: 3.71–5.46; $P = 0.228$) (Figure 3). In addition, the subgroup analysis by type of scale did not result in a significant reduction in heterogeneity, which remained high ($I^2 = 63.4\%$) (Figure 3).

Risk of Bias from Study

Almost all studies presented low risk of bias considering the domains of the tool used.[22] Only two studies[26,28] were considered to have a moderate risk of bias (Figure 4). The risk of bias was influenced by the lack of information regarding sociodemographic characteristics and the criteria used for the diagnosis of ACS. Supplementary Table 2 presents in detail the assessment of the risk of bias of the included studies.

Quality of Evidence from Study

Of the 25 studies included in the meta-analysis, the assessment of the quality of evidence was conducted using the GRADE system for the 24 cohort studies, as they represent the majority of the evidence base and have similar methodological characteristics. The only randomized clinical trial was not included in this assessment, as its inclusion together with observational studies could compromise the homogeneous application of the GRADE

Table 1 Summary of characteristics of included studies.

Author, year	Country	Study design, follow-up period	Sample (total *n*, sex, age)	Frailty (tool, diagnostic criteria for pre- frailty and frailty)	Total mortality	Mortality in pre- frail and frail individuals
Alegre, *et al.* 2018	Spain	Cohort; 12 months follow-up	*N* = 532; 61.7% male; age 84.3 ± 4 years	FS ≥ 3 points; *n* = 145	75	34
Anand, *et al.*, 2020	United Kingdom	Cohort; 12 months follow-up	*N* = 198; 58% male; 79 ± 6 years	CFS ≥ 5 points; *n* = 40	33	19
Batty, *et al.*, 2018	United Kingdom	Cohort; 12 months follow-up	*N* = 280; 60% male; 81 ± 4 years	FC ≥ 3 criteria; *n* = 77	18	10
Bernal, *et al.*, 2017	Spain	Cohort; during hospital admission	*N* = 254; 57.5% male; 82.1 ± 4.5 years	FS ≥ 3 points; *n* = 42	21	9
Calvo, *et al.*, 2019	Spain	Cohort; during hospital admission	*N* = 259; 57.9% male; 82.6 years old	FS ≥ 3 points; *n* = 51	18	11
Damluji, *et al.*, 2019	USA	Cohort; during hospital admission	*N* = 469,390; 53.2% female; 82.3 (75-89) years old	CFI score 0.2; *n* = 89,820	48,347	11,856
Ekerstad, *et al.*, 2018	Sweden	Cohort; mean follow-up 6.7 years	N= 307; 51.1% male; 75-79 years old	CFS ≥ 5 points; *n* = 149	213	128
Ekerstad, *et al.*, 2022	Sweden	Cohort; 6 months follow-up	*N* = 3,381; 70.6% male; 71 (61-79) years old	CFS ≥ 5 points; *n* = 426	255	122
Graham, *et al.*, 2013	Canada	Cohort; 12 months follow-up	*N* = 183; 54.1% female; no age record	EFS ≥ 7 points; *n* = 55	13	7
Kang, *et al.*, 2015	China	Cohort; 4 months follow-up	*N* = 352; 57.7% male; 74 years old	CFS ≥ 5 points; *n* = 152	18	16
Kurobe, *et al.*, 2021	Japan	Cohort; mean follow-up 47.9 months	*N* = 266; 77% male; no age record	CFS ≥ 5 points; *n* = 59	15	10
Murali-Krishnan, *et al.*, 2015	United Kingdom	Cohort; 12 months follow-up	*N* = 746; 70% male; 62 ± 12 years old	CFS ≥ 5 points; *n* = 81	31	11
Nguyen, *et al.*, 2019	Vietnam	Cohort; 30-day follow-up	*N* = 324; 60.8% male; 73.5 ± 8.3 years	EFS ≥ 7 points; *n* = 156	68	53
Nishihira, *et al.*, 2021	Japan	Cohort; 12 months follow-up	*N* = 546; 52.2% female; 84.5 (82-88) years old	ACTION Frailty Scale ≥ 3 points; *n* = 152	184	69
Nowak, *et al.*, 2022	Poland	Cohort; mean follow-up 637.5 days	*N* = 174; 55.2% male; 74.8 years old	FC ≥ 3 criteria; EFS ≥ 7 points; FS ≥ 3 points; CFS: ≥ 5 points; FC: 72; EFS: 70; FS: 68; CFS: 68	15	FC: 13; EFS: 12; FS: 13; CFS: 12
Patel, *et al.*, 2018	Australia	Cohort; follow-up up to 6 months after hospital discharge	*N* = 3,944; no record of sex and age	Adaptation FI score ≥ 0.25; *n* = 1,049	423	202
Pham, *et al.*, 2023	Vietnam	Cohort; during hospital admission	*N* = 116; 65.5% male; 72.91 ± 6.22 years old	FS ≥ 3 points; *n* = 38	2	1
Ramos, *et al.*, 2022	Brazil	Cohort; follow-up up to 3 months after hospital discharge	*N* = 111; 61.3% male; 62.3 ± 12.4 years	FS ≥ 3 points; CFS: ≥ 5 points; FS: 76; CFS: 23	13	FS: 10; CFS: 7
Ratcovich, *et al*, 2022	United Kingdom	Cohort; 5-year follow-up	*N* = 263; 61.2% male; 81.2 ± 4.1 years	FC ≥ 3 criteria; CFS: ≥ 5 points; FC: 70; CFS: 33	82	FC: 30; CFS:17
Ratcovich, *et al*, 2024	United Kingdom	Cohort; 12 months follow-up	*N* = 455; 66.3% male; no age record	CFS ≥ 5 points; *n* = 69	67	21
Salinas, *et al*, 2017	Spain	Cohort; 6 months follow-up	*N* = 234; 59.4% male; no age record	SHARE-FI ≥ 6 points; *n* = 94	28	19
Salinas, *et al.*, 2018	Spain	Cohort; 12 months follow-up	*N* = 285; 60% male; 82.5 years old	SHARE-FI ≥ 6 points; *n* = 109	55	38
Salinas (a), *et al.*, 2016	Spain	Cohort; follow-up up to 30 days after hospital discharge	*N* = 190; 60.5% male; 82.7 ± 5.1 years	SHARE-FI ≥ 6 points; *n* = 72	10	6

Continued

Author, year	Country	Study design, follow-up period	Sample (total *n*, sex, age)	Frailty (tool, diagnostic criteria for pre- frailty and frailty)	Total mortality	Mortality in pre- frail and frail individuals
Salinas (b), *et al.*, 2016	Spain	Cohort; follow-up during hospital stay	*N* = 202; 60% male; 82 (79-86) years old	SHARE-FI ≥ 6 points; *n* = 71	7	6
Tashiro, *et al.*, 2022	Japan	Cohort; during hospital admission	*N* = 244; 52% female; 84.4 ± 3.7 years	CFS ≥ 5 points; *n* = 72	28	20
White, *et al.*, 2016	52 countries (Europe, Latin and North America, Asia, Africa and Oceania)	Double-blind randomized clinical trial; 30 months follow-up	*N* = 4,996; 53.4% male; no age record	FC ≥ 3 criteria; *n* = 237	1,111	86
Yoshioka, *et al.*, 2019	Japan	Cohort; mean follow-up 474 days	*N* = 354; 76.6% male; 69.8 ± 12.4 years	CFS ≥ 5 points; *n* = 11	39	5
Yoshioka, *et al.*, 2019	Japan	Cohort; 2-year follow-up	*N* = 273; 53.8% female; 84.6 ± 3.8 years	CFS ≥ 5 points; *n* = 34	65	14
Zong, *et al.*, 2023	China	Cohort; mean follow-up 31.98±10.92 days	*N* = 238; % 52.5 female; 81.17 ± 4.3 years	mFI ≥ 0.27 points; *n* = 143	74	60

CFS: clinical frailty scale; FS: frail scale; FC: Fried Criteria; USA: United States; SHARE-FI: Survey of Health, Aging and Retirement in Europe Frailty Index; CFI: Claims-Based Frailty Index; EFS: Edmonton Frailty Scale; FI: Frailty Index; mFI: Modified Frailty Index.

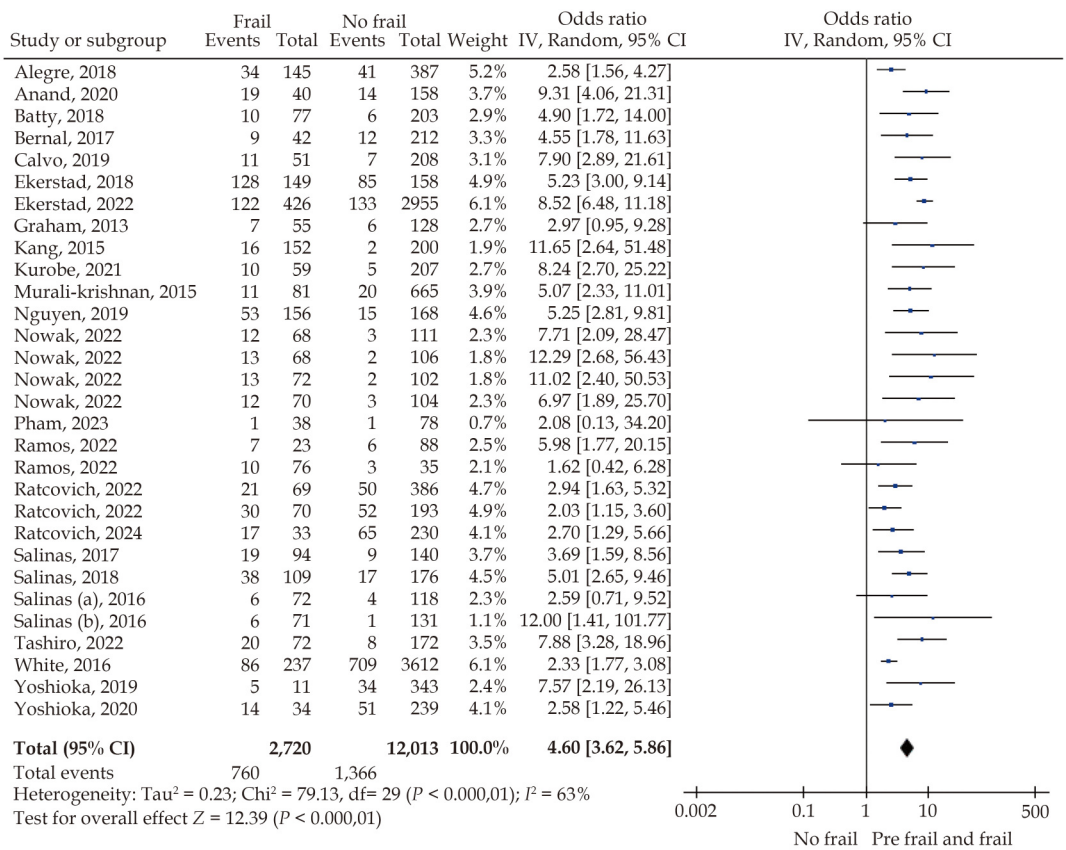


Figure 2 Forest plot association of frailty with mortality by scales.

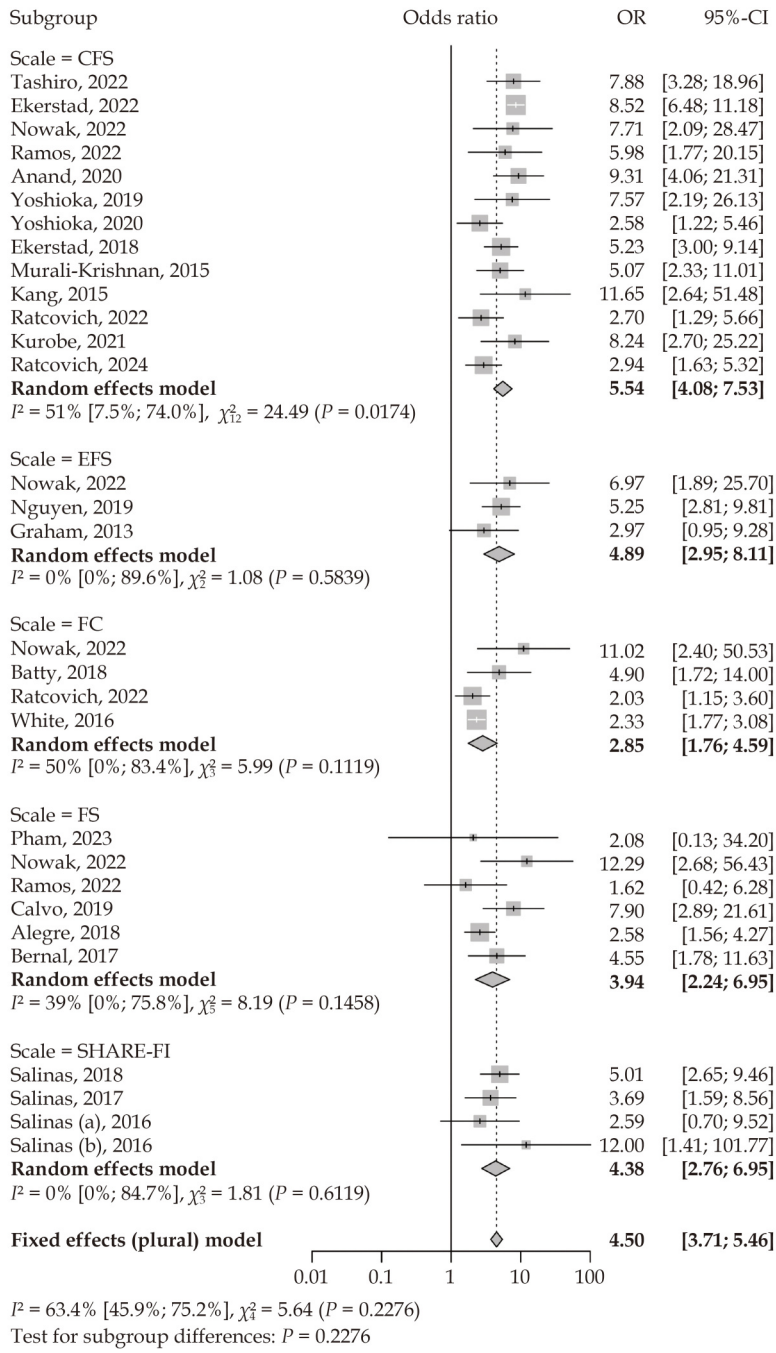


Figure 3 Subgroup analysis (scales) considering the prediction for mortality. CFS: Clinical Frailty Scale; EFS: Edmonton Frailty Scale; FC: Fried Criteria; FS: Frail Scale; SHARE-FI: Survey of Health, Aging and Retirement in Europe Frailty Index.

criteria, given the difference in design and initial level of quality of evidence.

The result shows that despite the magnitude of the observed effect, the certainty of the evidence was classified as very low (Table S3). The high heterogeneity between the studies, and the absence of direct comparisons between the different frailty scales used by the included studies, may have influenced this result.

DISCUSSION

Summary of Evidence

Our study aimed to evaluate which scale for diagnos-

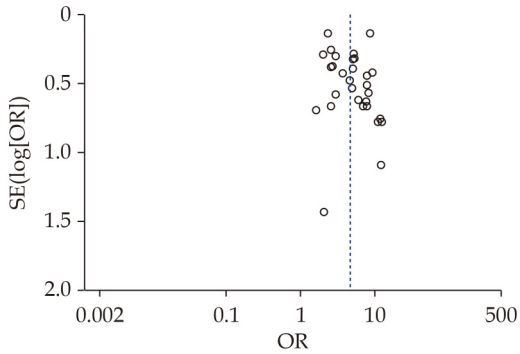


Figure 4 Funnel plot for evaluating publication bias in studies included in the meta-analysis.

ing frailty has the best predictive value for estimating mortality in individuals diagnosed with ACS. Our results showed that all the scales evaluated had good predictive value and that there was no statistically significant difference between them. Therefore, the use of any of these scales is reliable in predicting mortality in ACS. We suggest that given the severity of the patients and the reliability of the methods, the use of easy-to-use bedside tools such as the CFS can be prioritized. Furthermore, we highlight that the diversity of subjective and objective criteria used in each scale may have influenced the prevalence rates of frailty (3.1%-68.5%). This condition associated with the number of outcomes may have influenced the lack of association between the type of scale adopted and the prediction of mortality.

The physical frailty phenotype has been the most widely used tool in the diagnosis of frailty in various health conditions.[14] However, the characteristics of individuals and the assessment environment may influence the application of this method. Recent studies recommend the use of CFS to assess frailty in acute settings, such as in critically ill or hospitalized patients.[16,55,56] This recommendation is based on the ease of application, low cost and speed in obtaining results, allowing early identification of frailty in these patients, contributing to the optimization of treatment and to making more assertive clinical decisions.[56]

In this meta-analysis, the most widely used scale in the studies was the CFS.[26-38] This tool consists of a clinical judgment scale composed of nine items that analyze the impact of health conditions, cognition and mobility on the ability to perform activities of daily living and instrumental activities of daily living. Higher scores indicate worse functional status and the presence of frailty.[16]

It is known that the relationship between frailty and mortality is already well established in the literature in different cardiovascular conditions.[57-59] In acute conditions such as ACS, frailty has also been shown to be an independent risk factor for mortality,[10] so the European Society of Cardiology (ESC) emphasizes the importance of evaluating this condition in these patients.[60] In this meta-analysis, frailty increased the chance of mortality in terms of odds in individuals living with frailty by 4.6 times, when compared to non-frail individuals. In another meta-analysis also conducted with individuals with ACS followed during the period of hospitalization and for more than 5 years, they identified that the relative risk of mortality in individuals living with frailty was 2.3 times higher when compared to non-frail individuals.[61] In contrast, a recent meta-analysis that included elderly patients with acute myocardial infarction did not identify a statistically significant association in relation to the presence of frailty and mortality ($P = 0.285$).[62]

The difference in our meta-analysis was the proposal to identify which frailty scale has the best predictive value for mortality. With such a determination, there could be advances in the standardization of the type of tool used, with the aim of favoring the results obtained regarding the global prevalence and also stimulating the development of care therapies that can be widely adopted. The confusion in the concept of frailty and other conditions such as sarcopenia, reduced functional capacity and geriatric conditions contribute to the improper use of diagnostic tools.[7,8,14] Because these conditions are similar in terms of their pathophysiological mechanisms and complications, they are often mistakenly confused and do not consider the differences in diagnostic and definition criteria.[14] Despite the synergy and possibility of overlap between such nutritional conditions, it is worth highlighting that frailty is considered a more serious condition, with a lower probability of recovery.[63] In this sense, the use of the appropriate tool for diagnosing frailty becomes essential to minimize the chance of false negative diagnoses.[14]

In our study, during the eligibility assessment process, twelve articles[64-75] were excluded because they did not use recognized tools for the diagnosis of frailty, with the tools most used by the included studies being CFS,[16] EFS,[76] FC,[9] FS[77] and, SHARE-FI.[78] Of these tools, FS derives from the physical frailty phenotype model, however, its assessment is entirely self-reported and subjective.[77] The EFS, FC and SHARE-FI scales are considered mixed models with objective, subjective and self-report assessments.[9,76,78] The CFS is the only tool derived

from the cumulative deficit model[16] which was included in this meta-analysis. Thus, even though in our study it was not possible to identify any preponderance between the tools in predicting mortality, our evidence reinforces the importance of evaluating this condition in ACS and supports the ESC recommendations.[60]

Limitations

Among the limitations of this study, we highlight the small number of randomized clinical studies and the wide use of different tools for the diagnosis of frailty, which may have over- or underestimated this condition. In addition, the great heterogeneity between the studies may have influenced the results obtained. However, the tools evaluated contemplate the most widely used concepts of frailty currently, demonstrating that all tools are capable of predicting negative outcomes in this population.

In conclusion, patients with ACS living with frailty had a mortality rate almost five times higher than patients with the same condition but non-frail. Among the five frailty assessment scales included, all showed good predictive value for mortality, but without statistically significant difference between them.

DISCLOSURE

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Declaration of Interests

None.

Authors' contributions

L.N.P. Cunha: investigation, methodology, reviewer, writing; S.V. Oliveira: investigation, methodology, reviewer, writing; T. Lazzarin: investigation, methodology, reviewer, writing; L.L.S. Silva: methodology, expert critical review for intellectual improvement; M.F. Minicucci: expert critical review for intellectual improvement; N.A. Costa: expert critical review for intellectual improvement, project administration, and supervision.

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