The Journal of Frailty & Aging 15 (2026) 100164

Contents lists available at ScienceDirect

The Journal of Frailty & Aging

journal homepage: www.elsevier.com/locate/tjfa

Original Research

Phenotypes of frailty and their mortality and disability implications

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ARTICLE INFO

Keywords:
Frailty
Geriatric syndrome
Frailty tools
Mortality risk
Disability

ABSTRACT

Background: Frailty is a geriatric syndrome defined as increased vulnerability to stressors due to dysfunction in multiple physiological systems, measured by different tools.
Objectives: To assess whether participants characterized as frail by multiple scales simultaneously have differentiated risks.
Design: Prospective population-based cohort study.
Setting and participants: Community-dwelling adults from the first wave of The Toledo Study for Healthy Aging (TSHA), including a total of 1.563 participants with a mean age of 74.51 years. Frailty was assessed using three tools: the Frailty Index (FI), the Fried Phenotype, and the Frailty Trait Scale (FTS-5). Eight groups were defined based on the presence or absence of frailty according to these scales. Associations between frailty categories and outcomes were evaluated using multivariate Cox proportional hazards models for mortality and logistic regression models for incident and worsening disability.
Results: The FTS-5 scale identified the highest number of frail participants, suggesting it may be the most sensitive tool for detecting early physiological changes related to aging. Risk of adverse events varied depending on the specific combination of frailty criteria met. Individuals classified as frail by both FTS-5 and FI exhibited the highest mortality risk, exceeding that of participants frail on all three scales. Regarding worsening health or disability, the highest risk was among those frails on all three scales, followed closely by the FTS-5-FI group.
Conclusion: Our findings highlight variability in frailty assessment, showing that different instruments capture complementary aspects of frailty and that their combined use may improve risk stratification.

1. Introduction

Frailty is a geriatric syndrome with a high prevalence among older adults. It is defined as a state of increased vulnerability to stressors caused by dysfunction in multiple physiological systems. This condition leads to a reduction in biological reserves and the body's adaptive capacity to maintain homeostasis when challenged with stressors. This condition is the result of accumulated deficits, often associated with age and other variables, predisposing individuals to adverse outcomes such as falls, an increased risk of disability, hospitalization, and mortality [1].

The concept of frailty emerged several decades ago. While there is some agreement on the concept of frailty, there are some dissimilitude between conceptual frameworks**.** Its operationalization remains far from unanimous, and there are multiple measures of frailty that show significant differences in terms of the dimensions included, number of items, scope, and other factors [2]. This disparity in the constructs of the scales leads to inconsistencies in the results of frailty studies across different settings: 1) In epidemiological studies, a high degree of variability has been observed in the impact of frailty within populations [3]. 2) In conventional clinical practice, the lack of consensus on the

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https://doi.org/10.1016/j.tjfa.2026.100164
Received 14 December 2025; Received in revised form 9 April 2026; Accepted 6 May 2026
Available online 6 June 2026

diagnosis of frailty among different scales creates uncertainty about the practical applicability of these measures [4]. And, finally, 3) in research, this lack of standardization complicates the ability to identify and extrapolate findings.

At the individual level, each scale identifies individuals at high risk of adverse health events consistent with frailty models. However, agreement among these scales in classifying patients as frail is low, with concordance rates reaching as low as 20 % in some cases. There are many factors that may explain this lack of agreement among these scales are numerous and include differences in the domains assessed, varying criteria, and cut-off points that may not be suitable for evaluating different populations, among other factors [5]. Additionally, the origins of frailty are diverse, and each scale may identify a different frailty phenotype [3]. This raises the question of which scale is most appropriate for measuring frailty. Although there are studies assessing the concordance between different scales, no study has yet explored the sources of this lack of agreement [6].

When focusing on frailty scales that use different domains, there are two main approaches for assessing frailty: one based primarily on physical performance and body composition criteria, for which the Frailty Phenotype (FP) or Frailty Trait Scale (FTS-5) are commonly used, and another defined by the accumulation of deficits, such as the VIG FRAIL scale or the Frailty Index (FI) [7]. Neither scale has been established as superior to the other, however, given the differences between the measurements used by each scale, is a key challenge in assessing frailty with multiple tools. Some individuals may be identified as frail by multiple tools at the same time, while others may be classified as frail by only one, which highlights the potential for inconsistent classification.

The aim of this study is to assess whether participants with different frailty characterization, as determined by multiple tools simultaneously, have differentiated risks. For this purpose, we used data from The Toledo Study for Healthy Aging (TSHA) which has comprehensively phenotype participants using three widely used tools: The Frailty Phenotype (FP), Frailty Index (FI), and Fried Frailty Trait Scale (FTS-5).

2. Materials and methods

The Toledo Study for Healthy Aging (TSHA) is a population-based prospective cohort study. Data have been collected in waves conducted every 3–4 years, with the aim of measuring frailty, its characteristics, and its consequences in individuals aged 65 and older living in the province of Toledo (Spain) [8].

The study was conducted in three phases: in the first phase, a team of trained and certified psychologists conducted an in-home interview with the participant, collecting sociodemographic data, comorbidity, quality of life, physical function, social support, and an extensive neuropsychological assessment, among other variables. In the second phase, a certified nurse collected anthropometric data, physical performance measures, blood pressure and heart rate readings, as well as various tests (e.g., ECG, PFR, among others). In the third phase, blood and urine samples were collected after a 12-hour fasting period.

The study complied with the ethical standards outlined in the 1964 Declaration of Helsinki and Spanish biomedical research laws and obtained approval from our Centre's Clinical Research Ethics Committee [ref: 22/2005]. Before data acquisition, informed consent was obtained from all individuals included in this study.

2.1. Participants

This study included 1563 participants from the first wave, who performed the three frailty tools. Figure S1 shows the flow – chart.

2.2. Measurements

2.2.1. Frailty phenotype (Fried)

The frailty phenotype described by Fried and colleagues [3] serves as a standard for assessing frailty. It comprises five criteria: (1) involuntary weight loss over the past year (greater than 4.5 kg), (2) low energy and endurance, assessed using the CES-D survey, (3) grip strength of the dominant hand (measured in kilograms using a Jamar dynamometer, with individuals classified in the lowest quintile of the population based on sex and muscle mass index), (4) gait speed (evaluated by timing a 4.5-meter walk, stratified by height, sex and the lowest quintile), and (5) level of physical activity (classified in the lowest quintile of physical activity using the PASE scale).

Each item is assigned one point, resulting in a total score ranging from 0 to 5. Based on the final score, patients are classified as robust (0 points), pre-frail (1–2 points), or frail ($\geq$3 points).

2.2.2. Frailty index (Rockwood)

The Frailty Scale described by Rockwood, also known as the Frailty Index [9], conceptualizes frailty as an accumulation of deficits present in an individual, characterizing frailty as a multifactorial process.

Based on the approach suggested by Searle et at [10], the TSHA developed a FI based on 40 items [11], including comorbidities, laboratory measurements, physical, psychological, mental, or social signs or symptoms, and disabilities. The score is calculated by dividing the number of deficits identified by the total number of possible deficits, with a score greater than or equal to 0.25 indicating frailty.

2.2.3. Frailty trait scale (FTS −5)

The Frailty Trait Scale (FTS)[11], based on the concept of frailty by Fried and Walston [3], was proposed to capture the multidimensional changes that occur in an individual as they transition from robustness to frailty, incorporating additional domains.

In 2020, a short version of the scale was proposed, which demonstrated similar performance to the long version in predicting adverse outcomes [12]. The FTS-5 consists of five items previously described: body mass index, physical activity measured by the PASE scale, dominant hand strength using the Jamar dynamometer, gait speed over 3 m, and balance assessed through the Romberg test. The score for each item represents a biological trait ranging from 0 to 10, with a cumulative range from 0 to 50 (indicating maximum frailty). The cut-off point that optimizes the sensitivity and specificity of the scale is $>$ 25.

2.4. Frailty categories

We defined eight categories resulting from the combination of frailty statuses from FP, FTS, and FI. Participants were then classified into one of these categories.

2.4.1. Confounding factors

Disability: Disability was assessed by evaluating the ability to perform basic activities of daily living, using the Katz index (which ranks dependency in six activities of daily living: bathing, dressing, toileting, transfers, continence, and feeding). A participant who was considered as disabled if suffered limitation in at least one activity (excluding urinary incontinence) [13].

Polypharmacy: Polypharmacy is defined as the use of five or more active substances daily for at least three months.

Comorbidity (Charlson Index): The Charlson Index is a tool designed to quantify the burden of comorbidities in patients with chronic medical conditions. This index is used to adjust the risk of mortality based on the presence and severity of specific chronic diseases [14]. Each disease included in the index is categorized with a weighted value according to its impact on mortality. The conditions considered in the index include cardiovascular diseases, respiratory diseases, diabetes, cancer, among others.

Cardiovascular disease: Cardiovascular disease included self-reported myocardial infarction, heart failure or angina pectoris.

Cerebrovascular disease: Cerebrovascular disease included self-reported stroke and transient ischemic attacks.

2.4.2. Outcomes

Death: All-cause mortality was assessed using data from the Spanish National Death Index (Ministry of Health, Consumer Affairs, and Social Welfare).

Incident and worsening disability: Individuals were classified as having incident disability when onset of the first disability occurred and worsening as the onset of a new disability in the Katz Index during follow up.

2.5. Statistical analysis

Descriptive statistics are presented as mean (standard deviation) for continuous variables and N (percentage) for discrete and categorical variables. Differences between groups were tested using the Kruskal-Wallis and Chi-squared tests.

To assess the association between frailty categories and outcomes, we used multivariate Cox proportional hazards regression models for death and multivariate logistic regression models for incident and worsening disability. 3 successive nested models were estimated: (1) raw model, (2) adjusted for age and gender, (3) Charlson and polypharmacy. Additionally, for death we estimated a fourth model including disability.

ROC curves and the corresponding AUC were constructed to evaluate discrimination using predicted risk from Cox proportional hazards models for 5-year mortality and logistic regression models for incident and worsening disability during follow-up using M3. Additionally, we included a base model adjusted only for confounders.

Analyses were performed using a complete-case approach, including only participants with no missing values for the variables of interest, and conducted with the R statistical package for Windows (Vienna, Austria), version 4.1.2. The significance level was set at 0.05.

3. Results

We analyzed a sample of 1563 participants with a mean age of 74.51 years (SD ± 5.59), and 687 (43.95 %) were men. Among these participants, 12.67 % presented cardiovascular disease, and 4.23 % experienced cardiovascular disease. Additionally, 50.22 % were hypertensive, 19.39 % were diabetic, and 8.19 % showed respiratory diseases. Survival analysis of the sample showed a 5-year mortality rate of 9.98 %. The prevalence of disability in one or more basic activities of daily living was 6.97 %, with an incident disability rate of 10.22 % (Table 1).

3.1. Agreement between frailty categories

Figure S2 shows the Venn diagram corresponding to the eight categories that were identified based on the presence or absence of frailty as determined by the different scales. It was observed that 1094 participants were classified as non-frail by all scales. Targeting frail individuals, 401 were identified as frail by the FTS-5, 223 (more than 50 %) were classified as frail by only this tool; 228 were classified as frail according to the FI, of which 55 (24 %) were frail only by this scale. The total number of individuals classified as frail by the Fried was 121, with being frail individually only 2 (1.6 %). Collectively, 97 were classified as frail by two scales (16 by FRIED and FTS-5, 11 by FRIED and FI, and 70 by FTS-5 and FI) and 92 were identified as frail by all three scales. This shows that the most inclusive scale was FTS-5 which also was the scale with the highest prevalence individually (more than 50 %) while the most specific was the Fried Phenotype.

Descriptive statistics of each category is shown in Table 1. All variables showed statistically significant differences between groups.

The distribution of comorbidity, cardiovascular risk factors, polypharmacy, disability, and mortality for frail and non-frail participants

Table 1
Descriptive statistics.

Variable	All	All 3 scales frail	Fried and FTS5 frail	Fried and FI frail	Fried frail	FTS5 and FI frail	FTS5 frail	FI frail	Non-frail	p-v
N	1563	92	16	11	2	70	223	55	1094	
Age	74.51 (5.59)	79.58 (6.23)	78.69 (6.79)	76.64 (4.84)	82.00 (1.41)	78.63 (5.96)	76.65 (5.50)	75.82 (4.53)	73.22 (4.98)	0.0000
Gender (male)	687 (43.95)	30 (32.61)	4 (25.00)	9 (81.82)	1 (50.00)	16 (22.86)	58 (26.01)	29 (52.73)	540 (49.36)	0.0000
Educative Level										
• No school	1015 (65.36)	63 (68.48)	8 (50.00)	8 (72.73)	1 (50.00)	59 (84.29)	156 (70.91)	47 (87.04)	673 (61.86)	0.0000
• Primary incomplete	271 (17.45)	20 (21.74)	5 (31.25)	1 (9.09)	0 (0.00)	10 (14.29)	34 (15.45)	3 (5.56)	198 (18.20)	
• Primary school or over	267 (17.19)	9 (9.78)	3 (18.75)	2 (18.18)	1 (50.00)	1 (1.43)	30 (13.64)	4 (7.41)	217 (19.94)	
Comorbidities										
• CCV	198 (12.67)	24 (26.09)	0 (0.00)	1 (9.09)	1 (50.00)	17 (24.29)	24 (10.76)	16 (29.09)	115 (10.51)	0.0000
• ACV	66 (4.23)	14 (15.22)	1 (6.25)	0 (0.00)	0 (0.00)	5 (7.25)	6 (2.70)	9 (16.36)	31 (2.84)	0.0000
• DM	303 (19.39)	25 (27.17)	1 (6.25)	5 (45.45)	0 (0.00)	23 (32.86)	47 (21.08)	21 (38.18)	181 (16.54)	0.0001
Charlson Index	1.11 (1.63)	2.13 (2.13)	0.94 (1.29)	2.36 (2.62)	3.50 (2.12)	1.79 (1.89)	0.92 (1.38)	2.56 (2.41)	0.93 (1.47)	0.0000
Num. Drugs	4.32 (2.83)	6.43 (3.08)	5.25 (3.17)	6.27 (3.07)	5.00 (1.41)	6.16 (2.79)	4.67 (2.79)	6.04 (2.91)	3.83 (2.63)	0.0000
Polypharmacy	679 (43.44)	67 (72.83)	8 (50.00)	8 (72.73)	1 (50.00)	50 (71.43)	105 (47.09)	38 (69.09)	402 (36.75)	0.0000
Disability										
Score	4.88 (0.54)	3.80 (1.48)	5.00 (0.00)	4.55 (1.21)	5.00 (0.00)	4.47 (0.86)	4.97 (0.19)	4.69 (0.72)	4.99 (0.10)	0.0000
Disabled	109 (6.97)	52 (56.52)	0 (0.00)	2 (18.18)	0 (0.00)	27 (38.57)	5 (2.24)	12 (21.82)	11 (1.01)	0.0000
Outcomes										
Death	156 (9.98)	31 (33.70)	1 (6.25)	1 (9.09)	0 (0.00)	21 (30.00)	25 (11.21)	13 (23.64)	64 (5.85)	0.0000
Worsening disability	146.00 (11.78)	20.00 (50.00)	5.00 (35.71)	1.00 (14.29)	0.00 (0.00)	20.00 (46.51)	34.00 (20.36)	9.00 (26.47)	57.00 (6.11)	0.0000
Incident disability	121.00 (10.22)	11.00 (52.38)	5.00 (35.71)	1.00 (14.29)	0.00 (0.00)	10.00 (37.04)	33.00 (20.12)	6.00 (23.08)	55.00 (5.95)	0.0000

DM: Diabetes mellitus; **CCV:** Cardiovascular disease; **ACV:** cerebrovascular accident.

according to each tool. Table S1

3.2. Survival analysis

The adjusted hazard ratios (HR) for each group are presented in Table 2. The adjusted HRs were highest for the group frail by FI + FTS-5 (HR 3.87 (95 %CI 2.25, 6.65); $P < 0.005$), followed by all three scales (FP + FI + FTS-5) (HR 2.95 (95 %CI 1.66, 5.27); P-$V = 0.000$), frail only by FI (HR 2.64 (95 %CI 1.39, 5.03); P-$V = 0.003$), and finally, the frail group only by FTS-5 (HR 1.86 (95 %CI 1.15, 3.00); P-$V = 0.011$). Model AUCs ranged from 0.77 (base model) to 0.7983 (frailty categories-model). No statistically significant differences in model performance were observed between the base model and the frailty categories model ($p = 0.3$). (Table S2) Figure S3 shows the ROC curves for the prediction of mortality at 5 years.

3.3. Disability

When analyzing worsening disability, individuals in the group frail by all three scales had a higher odds ratio (OR 8.91 (95 %CI 3.92, 20.26); P-V = 0.000) compared to the other groups, followed by the group of patients classified as frail by both FI and FTS-5 (OR 8.45 (95 %CI 3.99, 17.88); P-V = 0.000), and lastly, those classified by a single scale, with ORs of 4.45 ((95 %CI 1.80, 11.02); P-V = 0.001) and 2.34 (95 %CI 1.41, 3.89); P-V = 0.001) for FI and FTS-5, respectively (Table 3). Model AUCs ranged from 0.7972 (base model) to 0.837 (frailty categories-model). No statistically significant differences in model performance we observed between the base model and frailty categories model ($p = 0.058$).

Table 2
Odds of mortality by frailty classification using combinations of frailty tools.

Joint				
	M1 HR (95 %CI); pv	**M2** HR (95 %CI); pv	**M3** HR (95 %CI); pv	**M4** HR (95 %CI); pv
All 3 scales frail	6.87 (4.47, 10.55); P-V = 0.000	4.83 (3.02, 7.73); P-V = 0.000	3.64 (2.20, 6.01); P-V = 0.000	2.95 (1.66, 5.27); P-V = 0.000
Fried and FTS5 frail	1.09 (0.15, 7.86); P-V = 0.931	0.97 (0.13, 7.05); P-V = 0.976	0.96 (0.13, 6.99); P-V = 0.968	0.97 (0.13, 7.08); P-V = 0.978
Fried and FI frail	1.56 (0.22, 11.25); P-V = 0.659	0.90 (0.12, 6.47); P-V = 0.913	0.74 (0.10, 5.37); P-V = 0.766	0.70 (0.10, 5.05); P-V = 0.720
FTS5 and FI frail	5.85 (3.57, 9.58); P-V = 0.000	4.93 (2.92, 8.32); P-V = 0.000	4.08 (2.39, 6.98); P-V = 0.000	3.87 (2.25, 6.65); P-V = 0.000
FTS5 frail	1.98 (1.24, 3.14); P-V = 0.004	1.86 (1.15, 3.00); P-V = 0.011	1.85 (1.15, 2.99); P-V = 0.012	1.86 (1.15, 3.00); P-V = 0.011
FI frail	4.61 (2.54, 8.37); P-V = 0.000	4.01 (2.21, 7.29); P-V = 0.000	2.77 (1.46, 5.25); P-V = 0.002	2.64 (1.39, 5.03); P-V = 0.003
Marginal				
	M1 HR (95 %CI); pv	**M2** HR (95 %CI); pv	**M3** HR (95 %CI); pv	**M4** HR (95 %CI); pv
Fried	3.67 (2.50, 5.39); P-V = 0.000	2.34 (1.56, 3.52); P-V = 0.000	1.73 (1.14, 2.64); P-V = 0.011	1.29 (0.78, 2.13); P-V = 0.328
FTS5	3.11 (2.27, 4.26); P-V = 0.000	2.59 (1.83, 3.66); P-V = 0.000	2.32 (1.63, 3.30); P-V = 0.000	2.11 (1.47, 3.05); P-V = 0.000
FI	4.92 (3.58, 6.76); P-V = 0.000	3.65 (2.61, 5.11); P-V = 0.000	2.80 (1.93, 4.06); P-V = 0.000	2.51 (1.68, 3.76); P-V = 0.000

HR: Hazard Ratio; **CI:** Confidence Interval; **M1:** Unadjusted; **M2:** Adjusted for age and sex; **M3:** Adjusted for age, sex, Charlson Index, and polypharmacy; **M4:** Adjusted for age, sex, Charlson Index, polypharmacy, and disability; **FTS5:** Frailty Trait Scale; **FI:** Frailty index.

Table 3
Odds of worsening disability by frailty classification using different combinations of frailty tools.

Joint			
	M1 OR (95 %CI); pv	**M2** OR (95 %CI); pv	**M3** OR (95 %CI); pv
All 3 scales frail	13.60 (6.41, 28.86); P-V = 0.000	9.02 (4.05, 20.11); P-V = 0.000	8.91 (3.92, 20.26); P-V = 0.000
Fried and FTS5 frail	8.55 (2.77, 26.35); P-V = 0.000	3.99 (1.12, 14.20); P-V = 0.032	4.03 (1.13, 14.31); P-V = 0.031
Fried and FI frail	2.57 (0.30, 21.67); P-V = 0.387	1.62 (0.17, 15.71); P-V = 0.676	1.60 (0.17, 15.51); P-V = 0.684
FTS5 and FI frail	12.54 (6.36, 24.74); P-V = 0.000	8.53 (4.10, 17.74); P-V = 0.000	8.45 (3.99, 17.88); P-V = 0.000
FTS5 frail	3.92 (2.47, 6.23); P-V = 0.000	2.34 (1.41, 3.88); P-V = 0.001	2.34 (1.41, 3.89); P-V = 0.001
FI frail	5.22 (2.29, 11.92); P-V = 0.000	4.55 (1.90, 10.88); P-V = 0.001	4.45 (1.80, 11.02); P-V = 0.001
Marginal			
	M1 OR (95 %CI); pv	**M2** OR (95 %CI); pv	**M3** OR (95 %CI); pv
Fried	4.82 (2.68, 8.66); P-V = 0.000	3.26 (1.73, 6.14); P-V = 0.000	3.05 (1.61, 5.77); P-V = 0.001
FTS5	5.16 (3.56, 7.48); P-V = 0.000	3.23 (2.15, 4.87); P-V = 0.000	3.15 (2.08, 4.76); P-V = 0.000
FI	6.31 (3.97, 10.04); P-V = 0.000	5.12 (3.10, 8.44); P-V = 0.000	5.01 (2.94, 8.52); P-V = 0.000

OR: Odds Ratio; **CI:** Confidence Interval; **M1:** Unadjusted; **M2:** Adjusted for age and sex; **M3:** Adjusted for age, sex, Charlson Index, and polypharmacy. **FTS5:** Frailty Trait Scale; **FI:** Frailty index. All models included basal disability.

(Table S3) Figure S4 shows the ROC curves for the prediction of worsening disability during follow-up.

Finally, we analyzed the risk of incident disability, obtaining similar results to the previous groups. The groups using the FI to classify frail patients showed higher ORs. Frail by all three scales (OR 10.18 (95 %CI 3.88, 26.76); P-V = 0.000), frail by FTS-5 and FI (OR 5.79 (95 %CI 2.33, 14.40); P-V = 0.000), and frail by FI (OR 4.27 (95 %CI 1.49, 12.30); P-V = 0.007), all of which were also statistically significant. Lower ORs were observed in the groups that used only the FTS-5, without FI, for

Table 4
Odds of incident disability by frailty classification using different combinations of frailty tools.

Joint			
	M1 OR (95 %CI); pv	**M2** OR (95 %CI); pv	**M3** OR (95 %CI); pv
All 3 scales frail	17.38 (7.08, 42.69); P-V = 0.000	10.46 (4.01, 27.31); P-V = 0.000	10.18 (3.88, 26.76); P-V = 0.000
Fried and FTS5 frail	8.78 (2.84, 27.08); P-V = 0.000	4.01 (1.12, 14.33); P-V = 0.032	3.98 (1.12, 14.20); P-V = 0.033
Fried and FI frail	2.63 (0.31, 22.26); P-V = 0.374	1.64 (0.17, 15.97); P-V = 0.668	1.60 (0.17, 15.37); P-V = 0.686
FTS5 and FI frail	9.29 (4.06, 21.26); P-V = 0.000	5.97 (2.46, 14.52); P-V = 0.000	5.79 (2.33, 14.40); P-V = 0.000
FTS5 frail	3.98 (2.49, 6.36); P-V = 0.000	2.35 (1.40, 3.93); P-V = 0.001	2.34 (1.40, 3.92); P-V = 0.001
FI frail	4.74 (1.83, 12.28); P-V = 0.001	4.62 (1.70, 12.51); P-V = 0.003	4.27 (1.49, 12.30); P-V = 0.007
Marginal			
	M1 OR (95 %CI); pv	**M2** OR (95 %CI); pv	**M3** OR (95 %CI); pv
Fried	6.78 (3.55, 12.97); P-V = 0.000	4.15 (2.03, 8.48); P-V = 0.000	3.86 (1.90, 7.87); P-V = 0.000
FTS5	5.10 (3.44, 7.55); P-V = 0.000	3.06 (1.98, 4.73); P-V = 0.000	2.99 (1.93, 4.64); P-V = 0.000
FI	5.73 (3.46, 9.50); P-V = 0.000	4.66 (2.70, 8.03); P-V = 0.000	4.47 (2.50, 8.00); P-V = 0.000

OR: Odds Ratio; **CI:** Confidence Interval; **M1:** Unadjusted; **M2:** Adjusted for age and sex; **M3:** Adjusted for age, sex, Charlson Index, and polypharmacy. **FTS5:** Frailty Trait Scale; **FI:** Frailty index.

classification: frail by Fried and FTS-5 (OR 3.98 (95 %CI 1.12, 14.20); P-V = 0.033) and frail by FTS-5 (OR 2.34 (95 %CI 1.40, 3.92); P-V = 0.001) (Table 4). Model AUCs ranged from 0.7832 (base model) to 0.8221 (frailty categories-model). No statistically significant differences in model performance we observed between the base model and frailty categories model ($p = 0.1001$). (Table S3) Figure S5 shows the ROC curves for the prediction of incident disability during follow-up.

4. Discussion

The main finding of our study is that the risk of suffering adverse events varies depending on the specific combination of frailty tools met by our participants. Notably, individuals classified as frail within the FTS5-FI group exhibit the highest risk of mortality, surpassing even those classified as frail across all three scales. Conversely, for outcomes such as worsening health or disability, the highest risk is observed among individuals classified as frail by all three scales, followed by those categorized as frail within the FTS5-FI group. It should be noted that almost all individuals classified as frail according to the frailty phenotype (FP) were also classified as frail by either the FTS-5 or the FI, with only two exceptions; therefore, FP contributes minimally to further stratification in this context. Its exclusion confirms that the FTS5–FI category is the one with the highest risk for both outcomes. These findings highlight that different frailty constructs may capture distinct risk profiles depending on the outcome considered.

Another notable finding is that, when analyzing prevalence across the scales, the FTS-5 shows the highest prevalence (26.66 % for FTS-5, 14.59 % for FI, and 7.94 % for FP). This may suggest that the FTS-5 is more sensitive to early physiological changes associated with aging. Consistent with previous evidence, approximately one-third of pre-frail individuals according to the FP were classified as frail by the FTS-5 [12], supporting its ability to detect early stages of functional decline. This may be explained by the fact that the FTS-5 evaluates functional decline across multiple domains using continuous measures, allowing for the identification of more subtle deficits that may not yet meet categorical thresholds in other instruments.

The primary explanation for these findings lies in the different domains assessed by the scales. Importantly, and to clarify a potential misunderstanding, the FI—constructed through the accumulation of deficits including comorbidities, disability, and psychosocial as well as physical components, all coded as present or absent—captures a broad, multidimensional spectrum of vulnerability. This may explain why individuals classified as frail by the FI tend to present poorer outcomes, as the scale may reflect more advanced stages of vulnerability. Furthermore, numerous studies have debated whether the FI predominantly reflects biological age [15].

Although there is substantial overlap between frailty categories, we retained all phenotypes in the analysis to preserve the conceptual differences between instruments and avoid oversimplifying the frailty construct. This decision is further supported by the partial overlap between FP and FTS-5, particularly in common domains such as gait speed, grip strength, and physical activity, as well as by the observation that FP-defined frailty not captured by the FTS-5 may be driven by the other two components, namely unintentional weight loss and exhaustion. These two features may, in turn, be indirectly represented through the broader deficit accumulation captured by the FI.

Other studies suggest that the FTS-5 is capable of progressively capturing how deterioration manifests across the various domains it evaluates, showing an increasing risk of adverse events from early stages [12]. Thus, the simultaneous use of multiple scales and the assessment of different domains are associated with an increased risk of adverse events, as demonstrated in our findings.

These results are consistent with previous studies, such as the Frailtools project [16], which reported that both the Frailty Index and the FTS-5 have good predictive ability for outcomes including mortality and disability. However, rather than identifying a single "best" instrument, our findings support the view that the simultaneous use of different tools provides complementary information and captures distinct aspects of the frailty construct. Although no differences in model performance were observed across the different events, the use of frailty categories allowed for more precise risk stratification.

At this point, the disagreement between instruments should be interpreted not as a limitation, but as a reflection of the multidimensional nature of frailty. In line with previous evidence, including the Frailtools project, the choice of a frailty instrument should be guided by the clinical or research context, as a substantial proportion of patients may not be assessable with certain tools, particularly those relying on physical performance measures in individuals with disability, institutionalized patients, or those who are bedridden [16]. Rather than pursuing a universal "gold standard," our findings support the use of the most appropriate validated instrument or the combined use of complementary instruments according to the specific objective, as this may enhance risk stratification and better capture the heterogeneity of frailty across populations. Subsequent studies have similarly shown that no single instrument is superior across all settings, reinforcing the importance of tailoring frailty assessment to the population and purpose of evaluation [17]. From a clinical perspective, combining instruments may improve risk stratification and support more personalized interventions. Overall, frailty assessment should not be restricted to a single tool, but adapted to the domain of interest, clinical setting, and feasibility of implementation.

Although we recognize the value of established scales such as the FI, our findings support the incorporation of tools that are sensitive to early and potentially reversible functional decline, such as the FTS-5. Rather than replacing the FI, the FTS-5 may complement it in routine clinical practice by capturing functional domains that may be more amenable to intervention, whereas the FI reflects a broader accumulation of deficits, including factors that are less modifiable. This complementary and potentially combined use of instruments could improve the identification of at-risk individuals, enhance risk stratification, and support more targeted preventive strategies, although further studies are needed to confirm this approach.

The main strengths of our study include the large sample size and the extensive experience of the TSHA. In addition, the use of multiple validated frailty instruments allowed a comprehensive comparison of different frailty constructs and their combinations, providing a more nuanced understanding of how frailty is expressed across domains. The availability of clinically relevant outcomes strengthens the applicability of the findings, and the analysis of agreement between instruments addresses an important and underexplored clinical question. Overall, these aspects enhance the robustness and clinical relevance of the results.

Several limitations should be acknowledged. First, although the overall sample size is substantial, some frailty-combination groups include a small number of participants, which may limit the robustness and interpretability of subgroup analyses. As a consequence, residual confounding cannot be ruled out, as some relevant variables (e.g., socioeconomic status, educative level) were not included to maintain model parsimony. Second, potential biases related to self-reported data should be considered. Finally, the study population is drawn from a specific geographic area, which may limit the generalizability of the findings to other settings or populations.

5. Conclusions

Our study shows that the risk of adverse outcomes varies according to the combination of frailty instruments used, highlighting that different tools capture complementary aspects of the frailty construct. Rather than identifying a single optimal instrument, our findings support the view that frailty assessment should be guided by the clinical context and may benefit from the combined use of complementary tools to improve risk stratification. In particular, instruments focused on

functional performance, such as the FTS-5, and multidimensional indices, such as the Frailty Index, provide distinct but complementary information.

Funding

This work was supported by grants [CB16/10/00456 and CB16/10/00464] from the European Union (the Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES) and FEDER funds), [PI15/01305] from the Instituto de Salud Carlos III (Ministerio de Ciencia e Innovación, Spain), [DEP2015-69386-R and RD12/0043] from the Instituto de Salud Carlos III (Ministerio de Economía y Competitividad, Spain), [PI2010/020] from FISCAM (Junta de Comunidades de Castilla-La Mancha, Spain), and [FP7- 305483-2] ("Frailomic Iniciative") from FP7-Health-2012-Innovation (European Union).

Declaration of the use of generative AI and AI-assisted technologies

During the preparation of this manuscript, generative artificial intelligence tools were not used.

Ethical approval

The study complied with the ethical standards outlined in the 1964 Declaration of Helsinki and Spanish biomedical research laws and obtained approval from our Centre's Clinical Research Ethics Committee [ref: 22/2005].

Informed consent

Informed consent has been obtained from all individuals included in this study.

Data statement

Data are not publicly available due to privacy and ethical restrictions.

Conflict of Interest and Authorship Conformation Form: All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

CRediT authorship contribution statement

Lorena Suárez Portugués: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **José A. Carnicero:** Conceptualization, Supervision, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Alonso Sepúlveda Martínez:** Investigation, Writing – review & editing. **Fabio A. Quiñónez Bareiro:** Investigation, Writing – review & editing. **Ana Alfaro Acha:** Writing – review & editing. **Ignacio Ara:** Writing – review & editing. **Leocadio Rodriguez Mañas:** Project administration, Funding acquisition, Resources, Writing – review & editing. **Francisco J. García García:** Project administration, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare no conflicts of interest.

Acknowledgments

We gratefully acknowledge the financial support provided through grants from the Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES) and FEDER funds, the Instituto de Salud Carlos III, FISCAM (Junta de Comunidades de Castilla-La Mancha, Spain), and the FP7-Health-2012-Innovation program (European Union).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100164.

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