Title page

Title:

Outcome-Specific Thresholds and Clinically Relevant Changes in Frailty: Evidence from a Population-Based Longitudinal Cohort

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Abstract

Background: The use of the Frailty Phenotype in clinical settings is hampered by its difficulty in defining outcome-specific risk trajectories, monitor longitudinal changes, and quantify the size of those changes to achieve clinical impact

Objective: To assess risk trajectories defining outcome-specific thresholds and slopes of risk, and to determine Minimal Clinically Important Differences (MCIDs) in frailty scores to guide personalized clinical targets.

Design, Setting and subjects: Prospective community-dwelling cohort of people ≥65 years).

Methods: Frailty was determined at baseline (wave 1) and after 5.02 years (wave 2) using the Frailty Trait Scale (FTS; n=1811) and its shorter 5-items form (FTS 5 (n=1597). Primary outcomes assessed at wave 2 were worsening disability (median follow-up 5.02 years), hospitalization (3.3), and mortality (5.4). For MCIDs analyses, time-to-event outcomes assessed at wave 3 were 2.99, 4.18 and 6.77 years, respectively. Cox proportional hazards models and logistic regression were used.

Results: A continuous dose-response association was observed between frailty scores and all outcomes, with distinct thresholds, slopes, and saturation points. Disability risk increased since a FTS score of 25/100 (or 10/50 for FTS5); hospitalization risk since 40/100 (15/50 FTS5); and mortality risk since 50/100 (25/50 FTS5). MCID analyses showed increases in frailty scores associated with higher risk of all outcomes, whereas reductions protected against hospitalization [FTS≥10.3: HR 0.74 (95%CI, 0.56-0.99); FTS5≥6.5: 0.74 (0.55-0.996)] and mortality [FTS≥4.5: HR 0.65 (95%CI, 0.45-0.95); FTS5≥1.0: 0.65 (0.45-0.93)].

Conclusions: Frailty Phenotype scores show characteristics that make them useful in clinical settings, contributing to the personalized approach to old frail patients.

Word count: 250

Key words: frailty, mortality, hospitalization, disability, MCID.

Key points

- The Frailty Trait Scale (FTS and FTS 5-item) demonstrated a continuous dose-response with disability, hospitalization and mortality.
- Distinct thresholds depending upon the outcome, with specific slopes, and saturation points were observed.
- Small reductions in scores were associated with reduced risk of hospitalization and mortality, but not for disability.
- FTS and FTS5 are sensitive to change and useful for monitoring changes and guiding timely, individualized interventions.

Text

Introduction

Frailty is a highly prevalent[1–3] age-associated syndrome characterized by increased vulnerability to stressors and a heightened risk of adverse outcomes[4,5], including disability[6–8], hospitalization[9–11], and mortality[12–14]. Despite increasing recognition of its clinical importance in older adults' care, its operationalization and implementation in routine clinical practice remains challenging[15–18]. This difficulty stems mainly from the lack of agreement on the optimal diagnostic tool(s)[19–21], the limited ability to monitor progression or improvement over time[4,22–24], and the paucity of data on outcome-specific risk thresholds that could guide timely interventions in terms of changes in the clinical risk [25,26].

The two most widely used conceptual frameworks are the deficit accumulation[27] and the Frailty Phenotype [28], from which the most common tools are derived: the Frailty Index (FI)[27,29] and the Fried´s Frailty Phenotype (FFP) [28], respectively. On the one hand, the FI, provides a continuous score which has shown to predict risks in a graded manner,[30,31] reflecting this characteristic of frailty [27,29]. However, it includes comorbidity and disability-entities that, while often related, are conceptually distinct from frailty itself [4,32]. In contrast, the FP has solid biological causative theory[33] and aims to distinguish frailty from comorbidity and disability[32]. However, this categorical approach (by classifying individuals as robust, prefrail or frail) [28] presents important limitations. First, transforming a presumably continuous construct into watertight, rigid categories may impede to distinguish between individuals qualified within the same frailty category but at potential different risks of developing different events. Second, the dichotomous scoring of its items and its final categorical nature limit its utility in capturing subtle but clinically relevant improvements or worsening, greatly reducing its usefulness in clinical practice for monitoring the response to interventions[15,16,34] or its natural evolution in epidemiological studies. In this sense, this information would provide clear risk thresholds, intervention targets and a practical way to monitor the evolution and responses to interventions in older adults.[19]

Therefore, the present study aimed (1) to confirm the continuous nature of the risks (disability, hospitalization, and death) associated to frailty according to the existence of new tools to assess the Frailty Phenotype concept, (2) to assess whether these risks follow outcome-specific thresholds and slopes across the frailty spectrum and (3) to determine the minimally clinically important differences (MCIDs) in frailty associated with each of these outcomes.

Methods

The Toledo Study for Healthy Ageing[35] (TSHA) is a prospective, population-based cohort study designed to investigate the determinants, interactions, and consequences of frailty and disability in individuals aged ≥65 years residing in the province of Toledo, Spain. The study conforms to STROBE guidelines[36]. Ethical approval for the study was granted by the local ethics committee, and all participants provided written informed consent.

Data collection was conducted by trained and certified professionals, either at participants' home or their local health centre. For the purposes of this part of the analysis, we utilized data from the first (2006 to 2009) second (2011 to 2013) waves of the study.

Study variables

Frailty

Frailty was evaluated using three instruments: the Frailty Trait Scale (FTS)[37], its abbreviated 5-item version (FTS5)[38] and the FP.

FTS[37] comprises 12 items grouped into seven physiological domains: nervous system function, physical activity, muscle weakness, endurance, slowness, energy balance, and nutrition. Most items are scored on a 0 to 4 scale (with 0 representing optimal function and 4 the worst performance), except for the "chair stand test", which is scored from 0 to 5. A total frailty score is calculated when participants completed at least 10 items, and this score is subsequently standardized on a 0 to 100 scale, where higher scores indicate greater frailty.

FTS5[38] evaluates five core domains: energy balance and nutrition (body mass index-BMI), physical activity levels (Physical Activity Scale for the Elderly, PASE[39]), balance (progressive Romberg test[40]), muscle strength (grip strength[41]), and gait speed (3-metre walk test). Each domain is scored from 0 to 10, with higher scores denoting worse performance. The total frailty score is obtained by summing the individual domain scores. The test is considered valid only in participants completing the five domains.

FP [28] assesses frailty status through the presence of five domains: unintentional weight loss, exhaustion, muscle weakness, slow walking speed and low physical activity. FP cut-off points were fitted to our population.[35] According to this tool, individuals are categorized as robust (meeting 0 criteria), prefrail (meeting 1 or 2 criteria) and frail (meeting ≥3 criteria).

The Frailty Index (FI) was built incorporating 40 items, according to Searle et al[29]. Items and scoring system are provide in Supplementary Table X. A total score ranging from 0 to 100 were obtained. Subjects were considered frail if the score was ≥0.275.

Comentado [AÁ1]: Confirmar por Jose.

Comorbidity assessment

Comorbidity was evaluated at baseline using the Charlson Comorbidity Index [42].

Main outcomes

Mortality

Vital status and dates of death were ascertained through linkage with the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare) and supplemented by telephone contact with designated family members. The latest update of mortality data was conducted in November 2013, with a median follow-up of 5.4 years (range: 0.04-6.92 years).

Hospitalization

Data on hospital admissions were retrieved from the administrative database of the Hospital Complex of Toledo. Follow-up for hospitalization outcomes extended until December 2011, yielding a median follow-up of 3.3 years (range: 0.04-4.81 years).

Worsening disability

Disability was assessed using the Katz Index[43] of Independence in Activities of Daily Living. A transition to a fewer score at follow-up was defined as worsening disability. Participants were followed for a median period of 5.02 years (range: 4.1-5.9 years).

Minimally Clinically Important Difference (MCID)

To determine the MCID in frailty scores (defined as the smallest measurable change perceived as beneficial or harmful for each one of the outcomes), we analyzed paired frailty data from the baseline (Wave 1) and the follow up visits (Wave 2). Participants without a follow-up frailty assessment were excluded from this part of the analysis (Figure 1).

MCID thresholds of frailty status were estimated in relation to each outcome (i.e., mortality, hospitalization, and disability), as estimated in the Wave 3 of the TSHA (2015-2017) for hospitalization (December 2016) and disability (March 2017) and by the data about vital status provided by the Spanish National Death Index for mortality (March 2019). Median follow-up times were: 6.77 years for mortality (range: 0.27-7.50), 4.18 years for hospitalization (range: 0.02-5.25), and 2.99 years for disability (range: 2.00-5.40).

Statistical analysis

Descriptive statistics are presented as means with standard deviations (SD) for continuous variables and counts with percentages for categorical variables. Unadjusted P for trend was computed across frailty categories.

To explore both the associations of frailty scores with death and hospitalization and to run MCID analyses Cox proportional hazard regression models were applied, while logistic regression models were used to test the associations between frailty-related parameters and worsening disability. Covariates included in

all models were age, sex, Charlson Comorbidity Index, and number of medications. For each frailty instrument, only participants with complete data at baseline for all variables included in the model were analyzed.

Finally, to group the participants in categories to make their frailty status characterization as easy as possible, we employed classification tree analysis to determine optimal cut-off points for categorizing the FTS and FTS5 scores. To ensure adequate statistical power, a constraint was applied whereby each resulting category was required to include a minimum of 100 participants. For ease of clinical interpretation, cut-off values were subsequently rounded. The resulting categories were labelled as: Robust – individuals with no associated risks; Prefrail – subdivided into mild prefrail (associated with risk for one adverse outcome), severe prefrail (associated with risk for two outcomes); and Frail – individuals with risk for all outcomes, either modest (frail) or pronounced (severe frail) in magnitude. According to FTS scores five frailty categories were described: Robust (n=231; 12.76%), Mild Prefrail (n=577; 31.86%), Severe Prefrail (n=414; 22.86%), Frail (n=286; 15.79%) and Severe Frail (n=303; 16.73%). When FTS5 was used the categories were established as follows: Robust (n=180; 11.27%), Mild Prefrail (n=288; 18.03%), Severe Prefrail (n=714; 44.71%), Frail (n=254; 15.90%) and Severe Frail (n=161; 10.08%).

To provide a smoothed visual representation of the dose–response relationship between frailty scores and adverse outcomes, we employed the piecewise cubic Hermite interpolation method.

All analyses were conducted using R statistical software, version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). P-value was set at level <0.05.

Results

Descriptive Characteristics of the Study Population

A total of 1811 individuals were included in the FTS analysis, (mean age 75.19±5.92 years; 44.01% men). Their baseline characteristics are presented in Table 1. For the FTS5 analyses, 1597 participants were assessed (mean age 74.57±5.63 years; 44.08% men) (Table 2).

Frailty severity was significantly associated with age, comorbidity burden, medication use, women sex, and disability, regardless of the frailty assessment method, as well as the incidence rates of disability, hospitalization and mortality (*P* for trend <0.001).

Associations between frailty scores and negative health outcomes

A consistent and graded dose–response relationship was observed between frailty severity and the risk of worsening disability, hospitalization, and mortality.

Using the FTS, each 5-point increase was associated with a 21% (95%CI 1.16-1.26) increase in mortality risk, 7% (1.03-1.11) increase in the risk of hospitalization, and 16% (1.10-1.22) increase in the likelihood of worsening disability.

Similarly, for FTS5, every 2.5-point increment corresponded to a 21% (95%CI 1.15-1.28) increase in mortality risk, a 13% (95%CI 1.08-1.18) increase in hospitalization risk, and an 18% (1.12-1.24) increase in the probability of worsening disability.

Associations between frailty categories and negative health outcomes

FTS categories and outcomes

When we distributed our population according to the defined categories using the FTS (Table 3), the risk of worsening disability became significantly elevated at scores above 25 [OR (95%CI): 1.81 (1.04-3.17); *P*=.0372], with a clear escalation across more severe categories. Odds ratios ranged from 3.04 to 4.92, reflecting progressively higher risk as frailty worsened. The risk of hospitalization was significantly increased in categories scoring above 40, with hazard ratios ranging from 1.74 to 2.11. Regarding mortality, the risk was significantly elevated in categories with scores above 50 [Frail: HR (95%CI): 2.78 (1.43-5.39); p = 0.0026; and Severe Frail: HR (95%CI): 4.81 (2.49-9.30); *P*<.0001].

Furthermore, when we use this type of analyses it becomes evident that the relationship is not linear and is different for each outcome. While disability increases along a modest slope with a tendency to achieve a plateau, hospitalization shows a more modest increase reaching a plateau quite early. Finally, mortality risk increases sharply without any apparent attenuation (Fig 1).

FTS5 categories and outcomes

Using the FTS5 categorization, the odds of worsening disability rose markedly from the Mild Prefrail (FTS5 >10 to 15) to Severe Frail categories, with ORs ranging from 2.06 to 7.04 (Table 4). The risk of hospitalization increased significantly in categories with scores above 15, with HRs between 2.05 and 2.99. As for mortality, elevated risks were observed in the higher categories [Frail: HR (95%CI): 2.73 (1.26-5.93); *P*=.0111; and Severe Frail: HR (95%CI): 4.99 (2.27-10.99); *P*=.0001].

Similar slopes that the one observed for the FTS were observed (Fig 2).

FP categories and outcomes

Prefrail individuals exhibited a 33% and 111% higher risk of hospitalization and mortality, respectively, compared to their robust counterparts (Supplementary Table 2). However, although there seems to be an association with the risk of worsening disability, it does not reach a statistical significance (*P*=.097). In contrast, frail individuals demonstrated an elevated risk of both worsening disability and mortality, although no significant association was observed with hospitalization (*P* =.18).

Minimally Clinically Important Difference (MCID)

Increments in frailty scores, as measured by both the FTS and FTS5, were consistently associated with a heightened risk of adverse outcomes. Specifically, an increase of ≥2.1 (FTS) or ≥5.5 (FTS5) points was linked to a significantly elevated risk of mortality by 39% and 52%, respectively. Even relatively modest increases (≥0.9 points in FTS and ≥1.0 point in FTS5) were significantly associated with an increased risk of hospitalization, suggesting the tools' sensitivity to early deterioration. In terms of worsening disability, increases of ≥15 (FTS) or ≥3 (FTS5) points were both associated with approximately 1.5-fold greater odds of developing new disability, underscoring the progressive risk gradient linked to frailty severity across both instruments (Table 5).

A reduction of ≥4.5 points (FTS) and of ≥1 point (FTS5) during follow-up was significantly associated with a reduced risk of mortality. In the case of hospitalization, the thresholds for clinically meaningful improvement were higher: 10.3 points (FTS) and 6.5 points (FTS5), respectively. However, no score reduction in either tool was found to be significantly associated with a reduced risk of worsening disability (Table 5).

These findings reinforce the importance of detecting even modest changes in frailty scores, as such variations may reflect clinically meaningful shifts in an individual's risk trajectory.

Discussion

The main findings of the present study reveal a graded and continued association between two frailty scales (FTS and FTS5) and the risk of disability, hospital admission, and mortality. Furthermore, we find different thresholds from which the risk begins to increase for each one of the different outcomes considered, following a stepwise distribution: worsening disability, hospitalization and, finally, mortality. Additionally, changes in frailty status are linked to either an increase or a reduction in the risk of the adverse health outcomes explored, drawing targets to monitor the spontaneous evolution of the risks or the response to interventions, helping to the decision-making process.

In our study, gradual increases in both FTS and FTS5 scores were consistently associated with elevated risks of mortality, hospitalization, and disability, underscoring their clinical relevance across a continuum of risk. Worthy to note, the slopes of risk are different for each one of the outcomes, highlighting that although all of them are consequences of the syndrome they do not show the same weight at any time or at any score. While prefrailty is mainly linked since its earliest stages to an increase of the risk of disability and hospitalization, this is not true for mortality. On the other hand, frailty is mainly linked to disability and the risk of death, with a modest increased risk for hospitalization in comparison to the risk conferred by prefrailty. Finally, while the risk of disability and death do not seem to reach a maximum, hospitalization risk reaches a plateau. This longitudinal perspective enables more personalized care strategies, grounded in both the severity and progression of frailty.[12]

Spontaneous impairments in frailty status were linked to an increased risk in all the outcomes, with different thresholds for each one, while reductions in frailty scores were associated with decreased risks of both mortality and hospitalization. Although previous studies have estimated the MCID for frailty

scores,[44–48] they assessed changes in frailty scores through changes between two waves[44–46], while we used three waves, making possible to analyze how the changes between first and second wave impact on the risk to suffer the outcome in the third wave. Finally, while the follow-up in those studies took one year in our case it had a duration ranging from three to near seven years, strengthening the meaning of this finding by giving it a potential clinical usefulness.

Our findings were obtained using two instruments that were designed to overcome some of the pitfalls of more classical instruments which may reduce the sensitivity needed to detect subtle but clinically significant changes in risk, potentially leading to misclassification and missed opportunities for early intervention [10,21,49]. In our cohort, 75.5% (FTS) and 80.0% (FTS5) of individuals classified as robust by the FP showed an increased risk according to both FTS-based classifications. Similarly, 44.3% (FTS) and 37.7% (FTS5) of those individuals categorized as prefrail by the FP were identified as frail according to the FTS tools suggesting an underestimation of risk when using the FP. These findings resemble those previously published in our cohort, where FTS5 showed better prognostic performance than the FP[38], and support the predictive validity of FTS and FTS5 as multidimensional frailty instruments that also may serve for tracking frailty trajectories over time and its consequences. In this same regard the main differences in the categorization of risk between FP and FTS versions was detected in the prefrailty category, where roughly two third of those classified as prefrail by FP had a similar risk of those classified as robust by FTS, while the other third showed risks similar to those classified as frail by FTS. Due to its simplicity, strong predictive capacity, and rapid administration time (<7 minutes)[49], the FTS5 may be particularly useful for routine use in primary care and residential care settings.[10]

Strengths and limitations

This study has several strengths, including a large and representative sample of Spanish community-dwelling older adults, the inclusion of frailty instruments validated in this and other populations, a long follow-up and rigorous ascertainment of negative health events. However, certain limitations should be considered. The study has been carried out in community-dwelling older people. Thus, our results can vary in other settings, including hospital and care homes, where the changes in frailty status are of the utmost interest [49,50]. Moreover, FTS5 applicability may be limited in some clinical settings like Emergency Rooms or Acute Care Units [49], since this tool needs a full assessment of all the items to provide a valid score. In our cohort, FTS5 could not be applied in 12% of participants. Notably, individuals for whom FTS5 could not be calculated were older and exhibited higher levels of comorbidity, baseline disability, and incidence of adverse outcomes (Supplementary Table 3). In contrast, the original FTS can accommodate missing data on up to three items (25%), similar to the approach used in the Frailty Index[37].

Conclusions

Frailty Phenotype is associated with adverse outcomes in a continuous, non-linear manner. The presence of separate thresholds, clinical categories and trajectories for the risk of every outcome jointly to the determination of MCDIs for each one raise opportunities for a differential and targeted management of frail and prefrail patients and its monitoring. The use of categorical tools has hampered the approach to frailty through the Frailty Phenotype framework in the clinical practice. FTS and FTS5 can overcome this barrier into healthcare practice.

Word count: 2987

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Tables

Table 1. Characteristics of the sample according to the FTS score categories.

Variable	all	[0-25]	(25-40]	(40-50]	(50-60]	(60-100]	
N	1811	231	577	414	286	303	
Age[A]	75.19 (5.92)	70.89 (3.69)	73.28 (4.97)	75.18 (5.22)	77.40 (5.79)	80.02 (5.84)	**<0.0001**
Men[B]	797 (44.01)	143 (61.90)	290 (50.26)	173 (41.79)	97 (33.92)	94 (31.02)	**<0.0001**
Charlson Index[B]							
0	833 (46.00)	134 (58.01)	301 (52.17)	185 (44.69)	121 (42.31)	92 (30.36)	**<0.0001**
1	467 (25.79)	51 (22.08)	144 (24.96)	108 (26.09)	85 (29.72)	79 (26.07)	
2	266 (14.69)	32 (13.85)	62 (10.75)	69 (16.67)	42 (14.69)	61 (20.13)	
>2	245 (13.53)	14 (6.06)	70 (12.13)	52 (12.56)	38 (13.29)	71 (23.43)	
Number of drugs[B]							
0-1	287 (15.85)	77 (33.33)	118 (20.45)	55 (13.29)	25 (8.74)	12 (3.96)	**<0.0001**
2-3	494 (27.28)	71 (30.74)	173 (29.98)	122 (29.47)	65 (22.73)	63 (20.79)	
4-5	435 (24.02)	46 (19.91)	133 (23.05)	107 (25.85)	75 (26.22)	74 (24.42)	
>5	595 (32.85)	37 (16.02)	153 (26.52)	130 (31.40)	121 (42.31)	154 (50.83)	
Disability[B]	348 (19.41)	9 (3.91)	49 (8.55)	64 (15.65)	75 (26.69)	151 (50.33)	**<0.0001**
Frailty status (within categories)[B]							
Robust	807 (46.95)	198 (86.84)	382 (67.85)	172 (43.65)	49 (18.15)	6 (2.27)	**<0.0001**
Prefrail	747 (43.46)	30 (13.16)	177 (31.44)	209 (53.05)	190 (70.37)	141 (53.41)	
Frail	165 (9.60)	0 (0.00)	4 (0.71)	13 (3.30)	31 (11.48)	117 (44.32)	
Main outcomes[B]							
Death	316 (17.45)	11 (4.76)	44 (7.63)	54 (13.04)	69 (24.13)	138 (45.54)	**<0.0001**
Hospitalization	414 (22.86)	26 (11.26)	104 (18.02)	104 (25.12)	83 (29.02)	97 (32.01)	**<0.0001**
Inc. Disability	393 (28.62)	17 (8.63)	97 (19.40)	109 (33.13)	86 (44.56)	84 (54.55)	**<0.0001**

A=mean (SD); B=N (%). In bold: p-value <0.05. FTS: Frailty Trait Scale.

Table 2. Characteristics of the sample according to the FTS5 score categories.

Variable	All	[0-10]	(10-15]	(15-25]	(25-30]	(30-50]	
N	1597	180	288	714	254	161	
Age[A]	74.57 (5.63)	70.91 (3.38)	72.20 (4.42)	74.55 (5.29)	77.28 (5.47)	78.70 (6.48)	**<0.0001**
Men[B]	704 (44.08)	118 (65.56)	159 (55.21)	315 (44.12)	73 (28.74)	39 (24.22)	**<0.0001**
Charlson Index[B]							
0	757 (47.40)	91 (50.56)	161 (55.90)	339 (47.48)	115 (45.28)	51 (31.68)	**<0.0001**
1	402 (25.17)	51 (28.33)	71 (24.65)	173 (24.23)	65 (25.59)	42 (26.09)	
2	236 (14.78)	26 (14.44)	25 (8.68)	110 (15.41)	38 (14.96)	37 (22.98)	
>2	202 (12.65)	12 (6.67)	31 (10.77)	92 (12.89)	36 (14.17)	31 (19.25)	
Number of drugs[B]							
0-1	272 (17.03)	60 (33.33)	75 (26.04)	103 (14.43)	21 (8.27)	13 (8.07)	**<0.0001**
2-3	436 (27.30)	50 (27.78)	82 (28.47)	209 (29.27)	68 (26.77)	27 (16.77)	
4-5	387 (24.23)	39 (21.67)	65 (22.57)	175 (24.51)	67 (26.38)	41 (25.47)	
>5	502 (31.44)	31 (17.22)	66 (22.92)	227 (31.79)	98 (38.58)	80 (49.69)	
Disability[B]	248 (15.69)	6 (3.39)	17 (5.90)	87 (12.32)	58 (23.20)	80 (50.00)	**<0.0001**
Frailty status (within categories) [B]							
Robust	787 (49.97)	158 (89.27)	237 (82.29)	347 (49.22)	39 (15.60)	6 (3.87)	**<0.0001**
Prefrail	665 (42.22)	19 (10.73)	51 (17.71)	344 (48.79)	173 (69.20)	78 (50.32)	
Frail	123 (7.81)	0 (0.00)	0 (0.00)	14 (1.99)	38 (15.20)	71 (45.81)	
Main outcomes[B]							
Death	225 (14.09)	8 (4.44)	21 (7.29)	77 (10.78)	57 (22.44)	62 (38.51)	**<0.0001**
Hospitalization	346 (21.67)	18 (10.00)	40 (13.89)	164 (22.97)	78 (30.71)	46 (28.57)	**<0.0001**
Inc. Disability	342 (27.27)	11 (7.19)	41 (16.60)	87 (12.32)	78 (43.09)	48 (53.33)	**<0.0001**

A=mean (SD); B=N (%). In bold: p-value <0.05. FTS5: Frailty Trait Scale 5-item.

Table 3. Association between FTS categories and risk of adverse events.

	Death		**Hospitalization**		**Worsening disability**	
Variable	HR (95%CI)	p-value	HR (95%CI)	p-value	OR (95%CI)	p-value
Robust (FTS12 ≤25)	Ref.		Ref.		Ref.	
Mild Prefrail (FTS12 >25-≤40)	1.05 (0.54, 2.05)	0.8895	1.27 (0.82, 1.96)	0.2768	1.81 (1.04, 3.17)	**0.0372**
Severe prefrail (FTS12 >40-≤50)	1.66 (0.85, 3.22)	0.1349	1.74 (1.12, 2.71)	**0.0142**	3.04 (1.72, 5.38)	**0.0001**
Frail (FTS12 >50-≤60)	2.78 (1.43, 5.39)	**0.0026**	1.89 (1.18, 3.02)	**0.0079**	4.14 (2.25, 7.61)	**<0.0001**
Severe frail (FTS12 >60-100)	4.81 (2.49, 9.30)	**<0.0001**	2.11 (1.31, 3.40)	**0.0022**	4.92 (2.59, 9.35)	**<0.0001**

CI: Confidence Interval. FTS: Frailty Trait Scale. HR: Hazard Ratio. FTS: Frailty Trait Scale. In bold: p-value <0.05. Model: adjusted for age, gender, Charlson Index and number of drugs. OR: Odds Ratio.

Table 4. Association between FTS5 categories and risk of adverse events.

	Death		**Hospitalization**		**Worsening disability**	
Variable	HR (95%CI)	p-value	HR (95%CI)	p-value	OR (95%CI)	p-value
Robust (FTS5 ≤10)	Ref.		Ref.		Ref.	
Mild prefrail (FTS5 >10-≤15)	1.34 (0.59, 3.02)	0.4872	1.32 (0.76, 2.31)	0.3298	2.06 (1.01, 4.20)	**0.0454**
Severe prefrail (FTS5 >15-≤25)	1.43 (0.68, 3.01)	0.3507	2.05 (1.24, 3.36)	**0.0048**	2.96 (1.53, 5.72)	**0.0013**
Frail (FTS5 >25-≤30)	2.73 (1.26, 5.93)	**0.0111**	2.76 (1.61, 4.73)	**0.0002**	4.01 (1.95, 8.25)	**0.0002**
Severe Frail (FTS5 >30)	4.99 (2.27, 10.99)	**0.0001**	2.99 (1.66, 5.36)	**0.0002**	7.04 (3.22, 15.42)	**<0.0001**

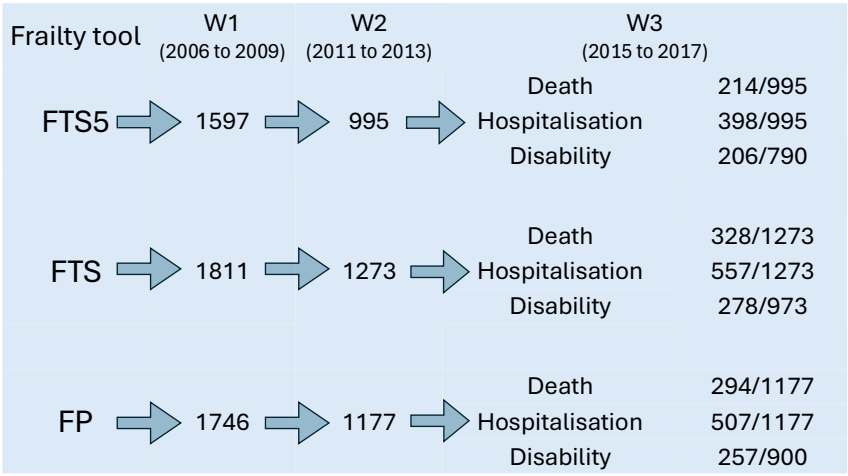
CI: Confidence Interval. FTS: Frailty Trait Scale. HR: Hazard Ratio. FTS5: Frailty Trait Scale 5-items. In bold: p-value <0.05. Model: adjusted for age, gender, Charlson Index and number of drugs. OR: Odds Ratio.

Table 5. Minimally clinically important difference for each frailty tool.

Frailty Tool	Death			Hospitalization			Worsening disability		
	ΔScore	**HR (95%CI)**	**p-value**	**ΔScore**	**HR (95%CI)**	**p-value**	**ΔScore**	**OR (95%CI)**	**p-value**
FTS12	<-4.5	0.655 (0.450, 0.952)	**0.0265**	<-10.3	0.741 (0.557, 0.986)	**0.0398**	NA	NA	
	Ref [-4.5; 2.1]	1		Ref [-10.3; 0.9]	1		Ref (<=15)	1	
	>2.1	1.385 (1.006, 1.906)	**0.0459**	>0.9	1.240 (1.015, 1.515)	**0.0355**	>15	1.560 (1.051, 2.315)	**0.0272**
FTS5	<-1	0.650 (0.453, 0.933)	**0.0194**	<-6.5	0.741 (0.551, 0.996)	**0.0467**	NA	NA	
	Ref [-1; 5.5]	1		Ref [-6.5; 1]	1	-	Ref (<=3)	1	
	>5.5	1.522 (1.020, 2.272)	**0.0399**	>1	1.268 (1.005, 1.599)	**0.0453**	>3	1.527 (1.031, 2.261)	**0.0345**

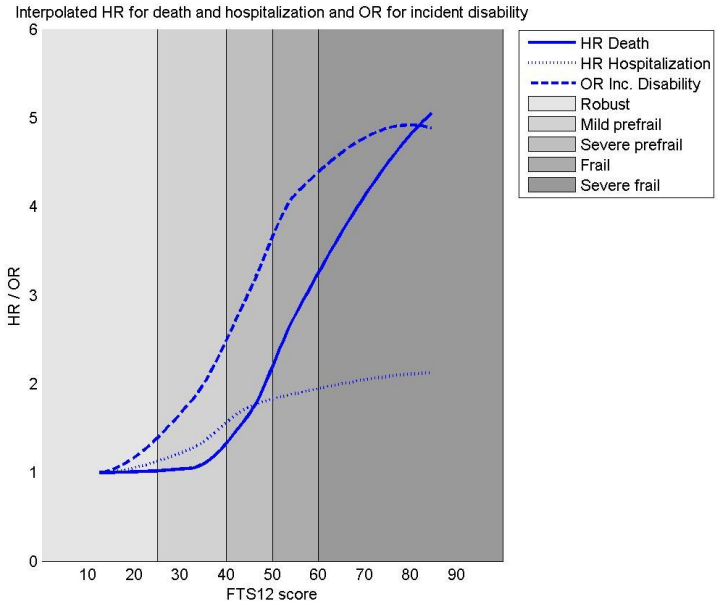
CI: Confidence Interval. FTS: Frailty Trait Scale. HR: Hazard Ratio. FTS: Frailty Trait Scale. In bold: p-value <0.05. Model: adjusted for age, gender, Charlson Index, number of drugs and frailty score (according to each instrument) at baseline. NA: Not Available. OR: Odds Ratio

Figure 1. Number of individuals assessed according to each frailty scale in visits 1 and 2, as well as the number of events recorded, and participants involved in each event.



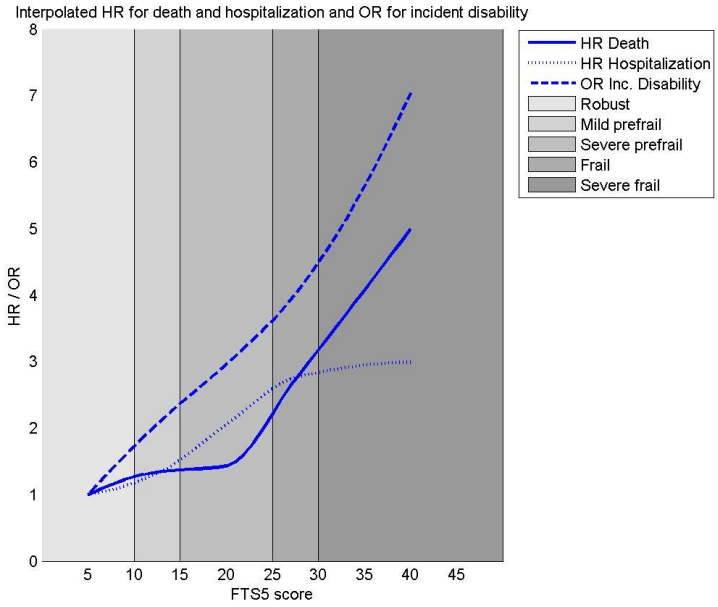
FTS: Frailty Trait Scale. FP: Frailty Phenotype. W: Wave.

Figure 2. Dose-response relationship between FTS categories and adverse events.



FTS: Frailty Trait Scale. OR: Odds Ratio. HR: Hazard Ratio.

Figure 3. Dose-response relationship between FTS5 categories and adverse events.



FTS5: Frailty Trait Scale 5-item. OR: Odds Ratio. HR: Hazard Ratio.

Supplementary Tables

Supplementary Table 1. Characteristics of the sample according to the Frailty Phenotype categories.

Variable	all	Robust	Prefrail	Frail	
N	1746	809	757	180	
Age[A]	74.98 (5.85)	73.01 (4.92)	75.96 (5.72)	79.66 (6.53)	**<0.0001**
Men[B]	774 (44.33)	363 (44.87)	340 (44.91)	71 (39.44)	**<0.0001**
Charlson Index[B]					
0	799 (45.76)	429 (53.03)	319 (42.14)	51 (28.33)	**<0.0001**
1	446 (25.54)	202 (24.97)	207 (27.34)	37 (20.56)	
2	264 (15.12)	98 (12.11)	123 (16.25)	43 (23.89)	
>2	237 (13.57)	80 (9.89)	108 (14.27)	49 (27.22)	
Number of drugs[B]					
0-1	278 (15.92)	175 (21.63)	92 (12.15)	11 (6.11)	**<0.0001**
2-3	473 (27.09)	241 (29.79)	204 (26.95)	28 (15.56)	
4-5	420 (24.05)	190 (23.49)	194 (25.63)	36 (20.00)	
>5	575 (32.93)	203 (25.09)	267 (35.27)	105 (58.33)	
Disability[B]	322 (18.62)	62 (7.72)	143 (19.12)	117 (65.73)	**<0.0001**
Main outcomes[B]					
Death	296 (16.95)	55 (6.80)	154 (20.34)	87 (48.33)	**<0.0001**
Hospitalization	383 (21.94)	139 (17.18)	197 (26.02)	47 (26.11)	**<0.0001**
Inc. Disability	372 (27.95)	149 (21.41)	178 (31.96)	45 (57.69)	**<0.0001**

A=mean (SD); B=N (%). In bold: p-value <0.05. FTS: Frailty Trait Scale.

Supplementary Table 2. Association between FP categories and risk of adverse events.

	Death		**Hospitalization**		**Worsening disability**	
Variable	HR (95%CI)	p-value	HR (95%CI)	p-value	OR (95%CI)	p-value
Robust	Ref.		Ref.		Ref.	
Prefrail	2.11 (1.54, 2.89)	**<0.0001**	1.33 (1.06, 1.66)	**0.0127**	1.26 (0.96, 1.66)	0.0973
Frail	3.55 (2.42, 5.22)	**<0.0001**	1.28 (0.89, 1.83)	0.1785	2.67 (1.58, 4.51)	**0.0003**

CI: Confidence Interval. FP: Frailty Phenotype. HR: Hazard Ratio. In bold: p-value <0.05. Model: adjusted for age, gender, Charlson Index and number of drugs. OR: Odds Ratio.

Supplementary Table 3. Characteristics of the sample not included in the FTS or FTS5 analyses.

	FTS			**FTS5**		
Variable	Included	Not included	p-value	Included	Not included	p-value
N	1583	228		1583	14	
Age[A]	74.57 (5.62)	79.48 (6.14)	**<0.001**	74.57 (5.62)	74.43 (6.80)	0.980
Men[B]	698 (44.09)	99 (43.42)	0.848	698 (44.09)	6 (42.86)	0.926
Charlson Index[B]						
0	750 (47.38)	83 (36.40)	**0.001**	750 (47.38)	7 (50.00)	0.664
1	401 (25.33)	66 (28.95)		401 (25.33)	1 (7.14)	
2	233 (14.72)	33 (14.47)		233 (14.72)	3 (21.43)	
>2	199 (12.57)	46 (20.18)		199 (12.57)	3 (21.43)	
Number of drugs[B]						
0-1	266 (16.80)	21 (9.21)	**<0.001**	266 (16.80)	6 (42.86)	0.801
2-3	436 (27.54)	58 (25.44)		436 (27.54)	0 (0.00)	
4-5	386 (24.38)	49 (21.49)		386 (24.38)	1 (7.14)	
>5	495 (31.27)	100 (43.86)		495 (31.27)	7 (50.00)	
Disability[B]	246 (15.69)	102 (45.33)	**<0.001**	246 (15.69)	2 (15.38)	0.976
Frailty status (within categories) [B]						
Robust	785 (50.13)	22 (14.38)	**<0.001**	785 (50.13)	2 (22.22)	0.113
Prefrail	659 (42.08)	88 (57.52)		659 (42.08)	6 (66.67)	
Frail	122 (7.79)	43 (28.10)		122 (7.79)	1 (11.11)	
Main outcomes[B]						
Death	223 (14.09)	93 (40.79)	**<0.001**	223 (14.09)	2 (14.29)	0.983
Hospitalization	343 (21.67)	71 (31.14)	**0.002**	343 (21.67)	3 (21.43)	0.983
Worsening Disability	246 (15.69)	102 (45.33)	**<0.001**	246 (15.69)	2 (15.38)	0.284

A=mean (SD); B=N (%). FTS: Frailty Trait Scale. In bold: p-value <0.05. FTS: Frailty Trait Scale.