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Assessment of muscle fatigability using isometric repetitive handgrip strength in frail older adults. A cross-sectional study

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Abstract

Background Fatigue has a significant impact on physical performance and quality of life in older adults, but is subjectively assessed in the Fried phenotype, so early deterioration may be overlooked. This study explores whether repetitive handgrip strength (HGS) provides an objective method of differentiating levels of frailty by comparing fatigue and recovery ratios with subjective measures and their correlations with frailty indicators.

Methods Participants ($n = 217$) were included based on mobility and cognitive function (MMSE > 17), with exclusions for neuromuscular disease or hand injury. The protocol consisted of two 10-maximal grip assessments one hour apart, calculating fatigue ratios 1 and 2 (maximum/mean force) at each session and recovery ratios between sessions. Logistic regression analysed associations between Fried's criteria components (Unintentional Weight Loss, Exhaustion Single Question, Multidimensional Fatigue Inventory (MFI), Short Physical Performance Battery (SPPB), Physical Activity Scale for the Elderly (PASE), standard Maximum HGS, Fatigue Ratio, and Recovery Ratio).

Results Among the participants (58 non-frail, 68 pre-frail, 91 frail; ages 74.7, 79.4, 83.8 years), significant differences were found for Fatigue Ratio 1 of 1.12 (non-frail), 1.23 (pre-frail), 1.40 (frail), Fatigue Ratio 2 of 1.12, 1.21, 1.45, and Recovery Ratio of 1.03, 1.01, 0.90, respectively. Fatigue Ratios 1, 2 and Recovery correlated more strongly with frailty status ($r = 0.67$, 0.69, -0.68) than MFI ($r = 0.50$), standard maximum HGS ($r = -0.51$) or a single fatigue question ($r = 0.21$). In logistic regression for predicting fatigue (MFI), Fatigue Ratio (OR = 1.51, $p < 0.001$) and Recovery Ratio (OR = 0.83, $p = 0.022$) were stronger predictors than single-question fatigue (OR = 1.15, $p = 0.047$) and maximum HGS. For predicting frailty, physical performance (SPPB) was the strongest predictor (OR = 0.72, $p < 0.001$), followed by Fatigue Ratio 1 (OR = 1.28, $p < 0.001$), with a higher Recovery Ratio reducing frailty risk (OR = 0.86, $p = 0.050$).

Conclusion The repetitive HGS protocol is equivalent to the SPPB in assessing frailty and outperforms standard HGS and subjective fatigue measures. This objective method supports the identification of frailty by measuring strength, fatigue resistance and recovery capacity.

Keywords Fatigue, Recovery, Handgrip strength, Frailty

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Background

In an ageing society, the accurate assessment of frailty is becoming increasingly important [1]. This geriatric syndrome affects 10–20% of older adults aged 65 + and over 40% of those aged 80+, leading to an increased risk of adverse health outcomes such as falls, hospitalisation, disability and mortality. The associated healthcare burden and reduced quality of life emphasise the need for early detection and intervention [2, 3]. Many common assessment methods, such as Fried's Phenotype, SHARE-FI, FRAIL Scale, Tilburg Frailty Indicator, and Frailty Index, include fatigue as a central component. However, these methods are mainly based on subjective assessments, often in the form of single question assessments [4]. Fatigue is a complex phenomenon that manifests as reduced mental and physical performance and a persistent feeling of exhaustion [5]. Its effects are far-reaching, affecting functional status, daily activities, physical exercise and social participation. Fatigue can also increase morbidity and has been associated with higher mortality rates [6, 7]. Although fatigue presents as both an objective symptom and a subjective feeling [5], studies have highlighted the need for objective measures [8, 9]. Studies show that objective measurement techniques for quantifying neuromuscular fatigue allow more accurate detection of fatigue phenomena and their effects. These methods can detect changes in muscle performance and recovery before they become manifest in subjective perception [8, 10]. Such objective measurements could contribute to a more comprehensive understanding of fatigue processes and their systemic effects [11]. The repetitive isometric maximum handgrip strength (HGS) protocol, which consists of 10 repetitions of 3-second maximum grips with 5-second rest intervals, has been shown to be a robust biomarker of muscle fatigue and performance decline in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-COVID-19 syndrome, providing a reliable indicator of disease severity and progression [12, 13]. The results showed significant differences between the patient groups and healthy controls, suggesting that this method could be a valuable tool for detecting subtle transitions between different stages of ageing, from robust older adults to those who are pre-frail or frail. These transitions are often not sensitively detected by simple maximal strength tests, such as those used in Fried's Frailty Assessment and other frailty assessments, or by subjective assessments with a single fatigue question [14, 15]. However, it remains to be investigated whether this method can be applied to older adults at all stages of ageing, from robust to pre-frail to frail, to detect and monitor early functional decline.

As mentioned above, this introduces us to another central component of frailty assessment, the measurement of maximum HGS. As an integral part of many established frailty assessments, the maximum HGS of two to three repetitions with prolonged pauses is a fundamental parameter for quantifying muscle function [16]. However, this method may not be sensitive enough to effectively capture age-related changes in strength, endurance and fatigue resistance [17]. Studies have shown that the ability to maintain strength over time and the ability to recover are better predictors of daily activity performance in older adults [14, 18]. Fatigue resistance and recovery capacity are crucial for fall prevention, as even individuals with normal maximal HGS may be at increased risk of falling [19]. Changes in muscular endurance and recovery often occur earlier than changes in maximal strength, making them important early indicators of frailty [17]. In addition, measures of endurance and recovery are more sensitive to training interventions, highlighting their importance in assessing rehabilitation outcomes [20]. Therefore, maximal strength may be incorrectly generalised by equating low max. HGS with poor muscle function and vice versa. Consequently, maximal HGS may be an incomplete measure of muscle function and a measure of muscle weakness [21]. To understand these complex relationships between muscle function, fatigue and frailty, it is crucial to examine the underlying physiological mechanisms at play. The observed declines in muscle function, such as reduced endurance and fatigue resistance, are the result of complex underlying physiological processes. These changes are closely associated with underlying physiological alterations, including mitochondrial dysfunction and reduced capillary networks, which impair muscle energy production and oxygen supply [22, 23]. Additionally, chronic inflammation plays a significant role, with elevated levels of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β exacerbating muscle degradation and inhibiting growth. These cytokines also disrupt mitochondrial energy processes and contribute to fatigue through their effects on the nervous system. The resulting elevation in C-reactive protein further amplifies the inflammatory response, leading to a self-perpetuating cycle of inflammation, muscle loss, and fatigue [24, 25]. Furthermore, the age-related transition from fast-twitch to slow-twitch muscle fibres contributes to a reduction in muscle strength and endurance [26]. These findings emphasise the importance of assessing not only maximal HGS but also endurance, fatigue resistance and recovery capacity when assessing muscle function in older adults. Such a comprehensive approach may provide a more objective and sensitive indicator of the multifactorial pathophysiological changes associated with frailty and increasing fatigue than relying solely on maximal HGS and self-reported fatigue.

Therefore, the aim of this study was to explore the potential of the 10 × 3 s HGS protocol to differentiate between non-frail, pre-frail and frail older adults. The

study examined (1) differences between frailty groups in terms of strength, fatigue and recovery; (2) the relationship between objectively measured muscle fatigue and subjectively perceived fatigue; (3) the correlation of these measures with established frailty indicators; and (4) the predictive power of the repetitive maximal isometric HGS protocol in determining frailty status. It was hypothesised that this protocol would provide a more sensitive method of detecting frailty than conventional single measures of maximal HGS or single questions about exhaustion/fatigue.

Methods

Study design and participants

This cross-sectional study was conducted over a six-month period, from January to June 2024, at two residential care homes in Vienna. It was carried out in accordance with the Declaration of Helsinki and received ethical approval from the Clinical Research Ethics Board of Vienna (EK-23-082-0523).

Participants

This study used a convenience sample from two Vienna residential care homes, where among 281 residents, potential participants were screened for eligibility. Inclusion criteria required individuals to be at least 65 years old, be able to either walk independently or with the use of assistive devices, provide signed informed consent, and have sufficient knowledge of German or English to understand the questionnaires and physical performance tests. Participants with cognitive impairment, as identified by a Mini Mental State Examination (MMSE) score ≤ 17, were excluded because of the potential difficulties in following instructions and maintaining concentration during unfamiliar procedures [27]. In addition, individuals with severe rheumatoid arthritis, carpal tunnel syndrome, advanced osteoarthritis, significant paralysis or stroke sequelae, recent hand injury, severe neuromuscular disorders, or other conditions that strongly affect HGS were excluded to avoid confounding effects on HGS measurements. Forty-seven residents were excluded due to: cognitive impairment ($n = 16$), hand-related conditions ($n = 10$), inability to walk even with assistance ($n = 9$), and insufficient language skills ($n = 12$). Of the 234 eligible residents, 217 agreed to participate (77.2% of total resident population), while 17 declined due to unwillingness to undergo physical examinations.

Frailty status

The frailty status of study participants was determined using a modified, more stringent version of Fried's frailty phenotype criteria [28]. As described in the introduction, these criteria include unintentional weight loss, exhaustion/fatigue, weakness, slow walking speed and low physical activity. To improve the assessment of physical function, the Short Physical Performance Battery (SPPB) was used instead of the walking speed test, which improved the accuracy of identifying frailty [29]. Based on these criteria, participants were classified as non-frail if they met none of the specified criteria, pre-frail if they met one or two, and frail if they met three or more.

- Unintentional Weight Loss: Participants' unintentional weight loss was assessed using a combination of medical records and face-to-face interviews. Specifically, they were asked whether they had lost more than 10 pounds (4.5 kg) or 5% of their body weight in the previous 12 months, a threshold for significant unintentional weight loss.
- Exhaustion/Fatigue: Fatigue was assessed by asking participants, "In the past month, have you had too little energy to do things you wanted to do?" A positive response met the fatigue criterion.
- Weakness: Muscle weakness was assessed by measuring HGS using a digital hand dynamometer (CAMRY, model: SCACAM-EH101) according to standardised procedures [30]. For familiarisation and to reduce the likelihood of technical errors, for both the standard and repeat HGS measurements, the participants familiarised themselves with the dynamometer by picking up the HGS device and pressing twice before the start of the tests, followed by a minimum of 3 min rest before the actual test. Participants, seated with elbows flexed at 90 degrees and forearms in neutral position, squeezed the dynamometer as hard as possible for 3 s, with three trials per hand and 1-minute rest between measurements. Compensatory movements were discouraged and instructions were repeated as necessary. The dynamometer was calibrated daily prior to testing to ensure measurement accuracy. The highest value (kg) from each trial was recorded. Weakness was defined as HGS < 27 kg for men and < 16 kg for women according to EWGSOP2 guidelines [31].
- Physical Performance: The SPPB was used to assess physical performance and consisted of three components: balance tests, a 4-metre walking speed test and a chair-stand test. Each component was scored from 0 to 4, with a total score of 0 to 12. A score below 7 indicated frailty, reflecting an increased risk of disability and mortality [29].
- Low Physical Activity: Physical activity levels were quantified using the Physical Activity Scale for the Elderly (PASE), which assesses activities such as walking, exercise, housework, gardening and caregiving. The PASE score, which ranges from 0 to 793, reflects the frequency, duration and intensity of

activities performed in the past week, with higher scores indicating greater physical activity. Thresholds for low physical activity were set based on the study by Auyeung et al. [32] with values of 0-56.4 for men and 0-58.8 for women, below which individuals were classified as frail.

Procedure

All measurements were carried out by two physiotherapists, each with more than five years' experience in geriatric and rehabilitation assessment. The physiotherapists were randomly assigned to perform the measurements on different participants to ensure that the assessments were performed in a random and unbiased manner. Measurements were taken in the morning under standardised conditions, including consistent flooring, lighting and room size. First, all physical measurements, such as SPPB and maximum HGS, were performed in a randomised order, followed by the administration of questionnaires (PASE, unintentional weight loss, fatigue/exhaustion). The first round of the 10 × 3 s HGS test was then carried out. An interval timer application was used to maintain the requisite intervals (3 s of maximum grip strength, followed by 5 s of rest). Subsequently, the Multidimensional Fatigue Inventory (MFI) and Athens Insomnia Scale (AIS) questionnaires were administered. One hour later, the second round of the 10 × 3 s HGS test was performed.

The following measurements and calculations have been carried out to assess the handgrip force and the associated fatigue and recovery parameters.

• Fmax (Round 1 and round 2)
Formula: Fmax [kg]. Explanation: Maximum HGS within one session (ten repeat trials).

• Fmean (Round 1 and round 2)
Formula: ∑10pulls/10. Explanation: Mean HGS of all ten trials.

• fatigue ratio (assessment of fatigability)
Formula: Fmax / Fmean. Explanation: Higher values indicate a stronger decrease in force during one session.

• recovery ratio (assessment of recoverability)
Formula: Fmean2 / Fmean1. Explanation: Higher value indicates better recovery after two measurements.

Co variables

To comprehensively assess the relationship between objective measures of HGS and other components of frailty with fatigue, we used the MFI. The MFI is a well-validated 20-item self-report instrument specifically designed to capture the multidimensional nature of fatigue. It includes five distinct subscales: General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation and Mental Fatigue. Each item is rated on a five-point Likert scale, with higher scores indicating more severe fatigue. The total MFI score ranges from 20 to 100 points, with higher scores reflecting greater levels of fatigue [33].

In view of the potential confounding effect of sleep disorders on fatigue, the Athens Insomnia Scale (AIS) was also administered. The AIS is an additional validated self-report measure of sleep disturbance. The scale comprises eight questions, which address various aspects of sleep and daytime functioning. These include difficulties in initiating sleep, nocturnal awakenings, duration of sleep, quality of sleep, and daytime sleepiness. Each item is scored on a four-point scale, ranging from 0 (no problems) to 3 (severe problems), with a total score of 6 or above indicating the presence of clinically significant sleep disturbance [34]. In addition, we collected key demographic and clinical information from medical records, including age, sex, body mass index (BMI), and comorbidities as assessed by the Charlson Comorbidity Index (CCI) and Mini Mental State Examination (MMSE). This comprehensive approach allowed us to account for potential confounding variables while examining the complex interactions between physical frailty and fatigue in our study population.

Statistics

Descriptive statistics were used to summarise the demographic and physical characteristics of the participants, with means and standard deviations (SD) calculated for continuous variables, frequencies and percentages for categorical variables. Paired t-tests were used to compare the first and second round within groups for different grip strength parameters (Fmax, Fmean, Fatigue and Recovery Ratio). Analysis of variance (ANOVA) was used to analyse differences between groups (non-frail, pre-frail, frail). Pearson correlation coefficients were calculated to detect linear correlations, while Spearman rank correlation coefficients were used for non-linear correlations. To explore the relationship between subjectively measured fatigue, assessed using the MFI, and objectively measured parameters such as the Fatigue Ratio, Recovery Ratio, and the variables used to assess Fried's Phenotype (unintentional weight loss, single question on exhaustion/fatigue, SPPB score, PASE score, standard maximum HGS), several statistical methods were applied.

Initially, Receiver Operating Characteristic (ROC) curves and the area under the ROC curve (AUC) were used to determine optimal cut-off values for the MFI scores. These cut-offs were intended to indicate the presence of fatigue concerning different stages of frailty. Two specific comparisons were made: (A) frail vs. non-frail/pre-frail individuals and (B) pre-frail/frail vs. non-frail

individuals. The ROC analysis aimed to identify the point values that best distinguished between the groups, with the point on the ROC curve closest to (0, 1) being selected as the optimal cut-off to balance sensitivity and specificity. To internally validate the results, a bootstrapping method with 1000 replications was performed. This allowed for the estimation of the variability of statistical measures and the assessment of the reliability of the observed associations and diagnostic performance metrics.

Before the main analyses, multicollinearity was checked using variance inflation factors (VIF). For models in which either the MFI or the Fried phenotype classification (i.e. non-frail, pre-frail or frail) was the dependent variable, the independent variables included the components contributing to the Fried phenotype classification (see above), Fatigue Ratio 1, Fatigue Ratio 2, and the Recovery Ratio. A VIF threshold of <2.5 was set. Since Fatigue Ratio 2 had VIF values of 4.1, it was excluded due to high collinearity. Finally, two types of regression analysis were conducted. First, binary logistic regression was used to assess the association between the dependent variable MFI cut-offs from the ROC analysis (≤ 43 vs. ≥ 44 points and ≤ 50 vs. ≥ 51 points) and the independent variables (Fried's Phenotype and, in particular, Fatigue Ratio and Recovery Ratio). Ordinal logistic regression (PLUM, Polytomous Universal Model, link function logit) was then performed with Fried's phenotype (non-frail, pre-frail, frail) as the dependent variable to determine the predictive associations with the independent Fried's phenotype variables (as described above), the MFI, and the newly measured parameters, Fatigue Ratio and Recovery Ratio, to determine which variable best predicted frailty status. Analyses were adjusted accordingly. Model 1 was adjusted for age and sex, while model 2 was additionally adjusted for the AIS, the CCI, and the MMSE. Odds ratios (OR) and 95% confidence intervals (CI) were reported for the logistic regression analyses. No missing data were observed in the dataset. Due to the exploratory nature of the study, p-values were not adjusted for multiple comparisons, as the focus was on identifying potential associations rather than confirming predefined hypotheses. This limitation should be considered when interpreting the results. All analyses were performed with SPSS version 27.0 (IBM Corp., Armonk, NY).

Table 1 Participants' characteristics according to frailty severity

Variables	Total ($n=217$)	Non-frail ($n=58$)	Pre-frail ($n=68$)	Frail ($n=91$)
Age, mean (SD)	80.0 (4.3)	74.7 (2.1)	79.4 (2.8)	83.8 (3.6)
Gender, n (%)				
Female	143 (65.9)	31 (53.4)	45 (66.2)	67 (73.6)
Male	74 (34.1)	27 (46.6)	23 (33.8)	24 (26.4)
BMI, mean (SD)	24.3 (2.9)	25.1 (1.9)	24.5 (3.1)	23.7 (3.2)
Number of medication, median (Q1- Q3)	7 (5–9)	5 (4–6)	6 (5–8)	9 (8–11)
Charlson Comorbidity Index, mean (SD)	2.3 (1.2)	1.2 (0.4)	2.0 (0.6)	3.3 (1.1)
MMSE Score, mean (SD)	27.0 (2.2)	29.2 (0.9)	27.4 (1.3)	25.4 (1.9)
AIS Score mean (SD)	7.9 (2.1)	6.7 (1.9)	8.3 (2.5)	7.8 (2.2)
MFI Score, mean (SD)	53.2 (10.6)	40.1 (3.5)	44.3 (8.2)	58.8 (6.5)
Fried's Phenotype components				
Unintentional Weight Loss, n (%)				
Yes	34 (15.7)	0	8 (8.8)	26 (28.6)
No	183 (84.3)	58 (100.0)	60 (91.2)	65 (71.4)
Exhaustion/Fatigue, n (%)				
Yes	107 (49.3)	16 (27.6)	37 (54.4)	60 (65.9)
No	110 (50.7)	42 (72.4)	31 (45.6)	31 (34.1)
SPPB Score, mean (SD)	7.9 (3.2)	11.4 (0.8)	9.5 (0.9)	5.3 (1.5)
PASE Score, mean (SD)	76.3 (52.5)	135.9 (54.2)	82.1 (23.7)	34.0 (15.1)
Maximum HGS, mean (SD),	21.9 (7.9)	29.1(6.4)	22.9 (5.3)	16.5 (5.4)

Note BMI = Body Mass Index, MMSE = Mini Mental State Examination, PASE = Physical Activity Scale for the Elderly,

MFI = Multidimensional Fatigue Inventory, SPPB = Short Physical Performance Battery, Maximum HGS from 3 Rounds

Results

The study comprised a total of 217 participants, of whom 58 were classified as non-frail, 68 as pre-frail, and 91 as frail. The average age increased with frailty: 74.7 years for non-frail, 79.4 years for pre-frail and 83.8 years for frail participants. Women made up 65.9% of the total, with almost 75% in the frail group. Physical performance (SPPB) and activity level (PASE) decreased progressively with frailty severity, while fatigue (MFI) increased. Mean SPPB scores were 11.4 (non-frail), 9.5 (pre-frail) and 5.3 (frail). Similarly, PASE scores decreased from 135.9 (non-frail) to 82.1 (pre-frail) and 34.0 (frail), while MFI scores increased from 40.1 (non-frail) to 44.3 (pre-frail) and 58.8 (frail). In terms of standard measured HGS, the non-frail group had a median Fmax of 26.10 kg (Q1-Q3: 23.51–35.44), the pre-frail group had 22.34 kg (Q1-Q3: 17.93–25.26) and the frail group had the lowest median Fmax of 14.24 kg (Q1-Q3: 12.12–22.37). More details can be found in Table 1.

In Table 2; Fig. 1, all 217 participants completed a maximum HGS measurement (standard), followed by ten consecutive maximal HGS measurements (initial) and a repeated test after 60 min. Non-frail participants had a median Fmax Standard of 26.10 kg (Q1–Q3: 23.51–35.44), with an initial median Fmax1 of 24.86 kg (Q1–Q3: 23.60–35.38), which increased significantly to 27.50 kg (Q1–Q3: 23.90–36.00) after one hour ($p<0.001$). Pre-frail participants had a median Fmax Standard of 22.34 kg (Q1–Q3: 17.93–25.26), with an initial Fmax1 of 23.05 kg

Table 2 Results of different functional health variables in HGS (Fmax, Fmean, fatigue and recovery)

Variables	Non-frail (*n* = 58)	*p*-value within groups*	Pre-frail (*n* = 68)	*p*-value within groups*	Frail (*n* = 91)	*p*-value within groups*	*p*-value between groups**
Fmax Standard kg, median (Q1 – Q3)	26.10 (23.51–35.44)	< 0.001	22.34 (17.93–25.26)	< 0.001	14.24 (12.12–22.37)	< 0.001	< 0.001
Fmax1 kg, median, (Q1 – Q3)	24.86 (23.60–35.38)		23.05 (18.30–26.30)		15.60 (12.70–23.00)		< 0.001
Fmax2 kg, median, (Q1 – Q3)	27.5 (23.90–36.00)		22.10 (18.15–25.05)		13.50 (11.40–21.00)		< 0.001
Fmean1 kg, median, (Q1 – Q3)	22.89 (20.68–31.15)	< 0.001	17.22 (14.24–21.85)	0.940	10.59 (8.22–17.32)	< 0.001	< 0.001
Fmean2 kg, median, (Q1 – Q3)	23.27 (20.39–32.58)		17.74 (13.58–21.35)		9.36 (7.21–16.86)		< 0.001
Fatigue Ratio1 kg, median, (Q1 – Q3)	1.12 (1.09–1.15)	0.180	1.23 (1.14–1.33)	0.168	1.40 (1.26–1.57)	0.005	< 0.001
Fatigue Ratio2 kg, median, (Q1 – Q3)	1.12 (1.10–1.18)		1.21 (1.12–1.32)		1.45 (1.27–1.61)		< 0.001
Recovery Ratio kg, median, (Q1 – Q3)	1.03 (1.00–1.06)		1.01 (0.91–1.06)		0.90 (0.79–0.95)		< 0.001

Note * A paired t-test was used to compare measurements within each group (non-frail, pre-frail, frail) between the two time points

** ANOVA was used to assess differences between groups at one time point

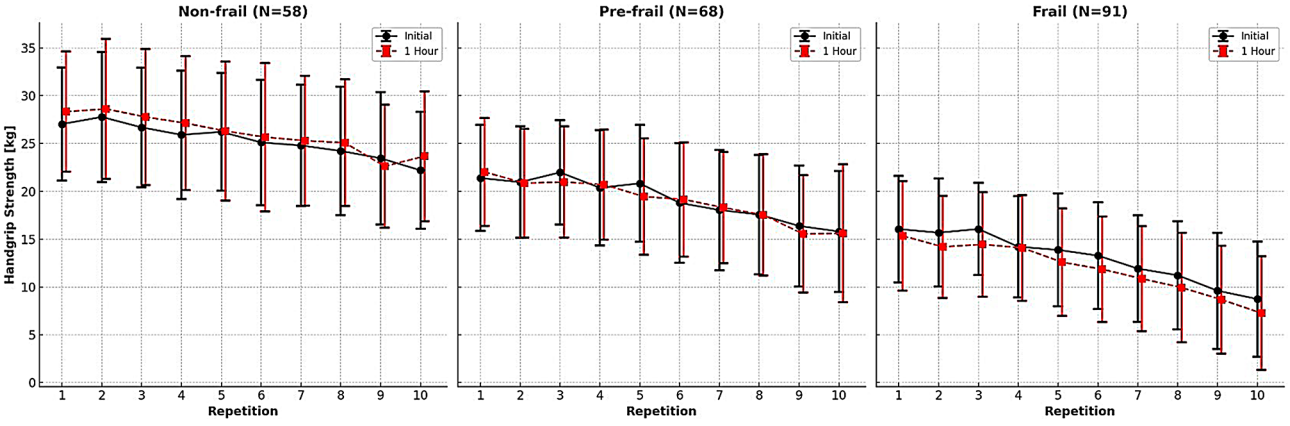


Fig. 1 Note: HGS (kg) over 10 repetitions for the non-frail, pre-frail and frail groups, measured at baseline (black, round marks represent mean values) and after 1 h (red, square marks represent mean values). Error bars indicate the standard deviation

(Q1–Q3: 18.30–26.30), which slightly decreased to 22.10 kg (Q1–Q3: 18.15–25.05) after one hour ($p = 0.144$). Frail participants had the lowest median Fmax Standard at 14.24 kg (Q1–Q3: 12.12–22.37), with an initial Fmax1 of 15.60 kg (Q1–Q3: 12.70–23.00), which further decreased to 13.50 kg (Q1–Q3: 11.40–21.00) after one hour ($p < 0.001$). The median Fmean1 for non-frail participants was 22.89 kg and increased slightly to 23.27 kg. For the pre-frail participants, Fmean1 was 17.22 kg and increased minimally to 17.74 kg ($p = 0.940$). Frail participants had an Fmean1 of 10.59 kg, which decreased to 9.36 kg after one hour ($p < 0.001$). Again, the differences between the groups were significant ($p < 0.001$). The Fatigue Ratio for non-frail participants was 1.12 at both time points ($p = 0.180$). Pre-frail participants had a Fatigue Ratio of 1.23, which decreased slightly to 1.21 after one hour ($p = 0.168$). Frail participants had the highest Fatigue Ratio of 1.40, which increased to 1.45 after one hour ($p = 0.005$). The differences between the groups were also significant ($p < 0.001$). The Recovery Ratio for non-frail participants was 1.03, for pre-frail 1.01 and for frail 0.90. The differences between the groups were also significant ($p < 0.001$). Please refer to Table 2; Figs. 1 and 2 for further details. For further details on the issue of gender differences, please refer to the figure and the table in Annex A.

The correlation heatmap in Fig. 3 shows that the strongest correlations with the Fried phenotype classification are a negative correlation with the SPPB score (r = -0.68) and the Recovery Ratio (r = -0.68), followed by the PASE score (r = -0.59). These results suggest that lower physical performance, recovery and activity levels are strongly associated with higher frailty. In addition, there are strong positive correlations between the Fried phenotype

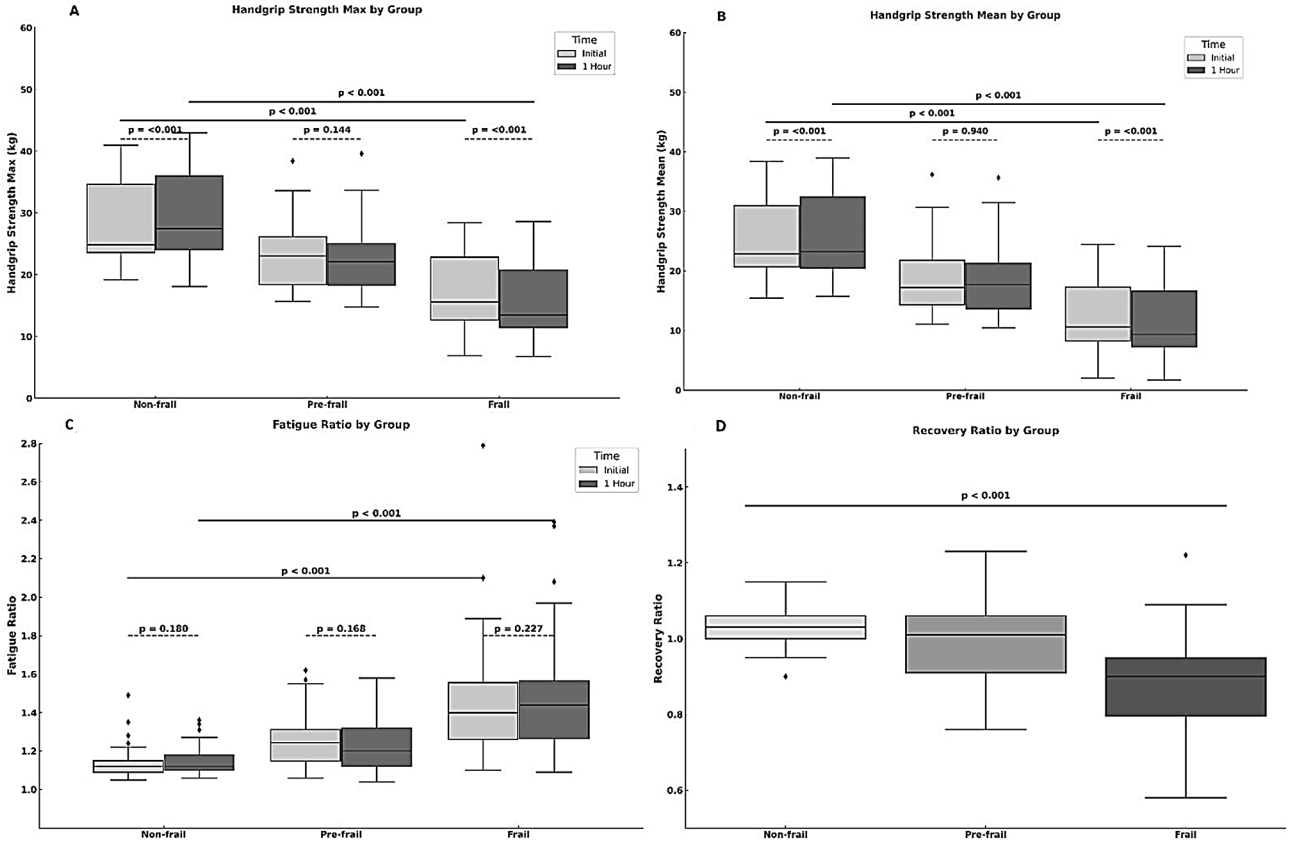


Fig. 2 Results of different functional health variables in HGS (Fmax, Fmean, fatigue and recovery). Note: Figure A shows the maximum grip strength, while Figure B shows the mean grip strength. Figure C shows the fatigue ratio and Figure D shows the recovery ratio. These figures compare data from the three groups: Non-frail, Pre-frail and Frail. Measurements were taken at two different time points – initially (round 1), represented by light grey boxes, and after one hour (round 2), represented by dark grey boxes. The box plots reflect the 10th to 90th percentiles, with outliers marked by individual data points. Comparisons within groups over time were made using a paired t-test, and differences between groups were analysed using ANOV

classification and Fatigue Ratios 1 and 2 ($r = 0.69$ and $r = 0.67$, respectively), suggesting that higher fatigue on repeated measures is associated with increased frailty. For the MFI score, the strongest correlations are negative correlations with the Recovery Ratio (r = -0.63) and the SPPB score (r = -0.43), indicating that poor recovery and physical performance are associated with higher levels of fatigue. In addition, there are positive correlations between the MFI and Fatigue Ratios 1 and 2 ($r = 0.61$ and $r = 0.60$ respectively), showing that greater fatigue is strongly associated with greater self-reported fatigue.

The ROC curves in Fig. 4 show that MFI scores effectively distinguish between frailty levels. For frail vs. non-frail/pre-frail individuals, the AUC was 0.83 (95% CI: 0.77–0.88) with an optimal threshold of 44 points (sensitivity: 81%, specificity: 79%). For pre-frail/frail vs. non-frail individuals, the AUC was 0.89 (95% CI: 0.83–0.92) with an optimal threshold of 51 points (sensitivity: 85%, specificity: 84%). Bootstrapped curves (grey) confirmed the robustness of these results.

Table 3 shows the results of logistic regression analyses investigating the influence of different functional health variables on the MFI and Fried's Phenotype, focusing on the results of multivariable model 2. Multidimensional Fatigue Inventory (MFI) ≥ 44 points: Each unit increase in Fatigue Ratio 1 was associated with a 51% increased likelihood of exceeding the MFI threshold (OR: 1.51, 95% CI: 1.29–2.16, $p < 0.001$). Each unit increase in Recovery Ratio decreased this likelihood by 17% (95% CI: 0.70–0.98, $p = 0.022$). Additionally, responding "yes" to the Exhaustion/Fatigue Single Question was associated with a 15% increased likelihood of exceeding the MFI threshold (95% CI: 1.02–1.77, $p = 0.047$). Multidimensional Fatigue Inventory (MFI) ≥ 51 points: Each unit increase in Fatigue Ratio 1 was associated with a 44% increased likelihood of exceeding this threshold (95% CI: 1.15–2.11, $p < 0.001$). Each unit increase in SPPB score decreased the odds by 24% (95% CI: 0.64–0.92, $p < 0.001$). Additionally, each unit increase in Recovery Ratio decreased the odds by 13% (95% CI: 0.75–0.97, $p = 0.025$). Notably, answering 'yes' to the single question on exhaustion/fatigue was no longer significantly associated with exceeding the MFI threshold (OR: 1.31, 95% CI: 0.94–1.83, $p = 0.099$). Fried's Phenotype: Each one-point increase in SPPB score was

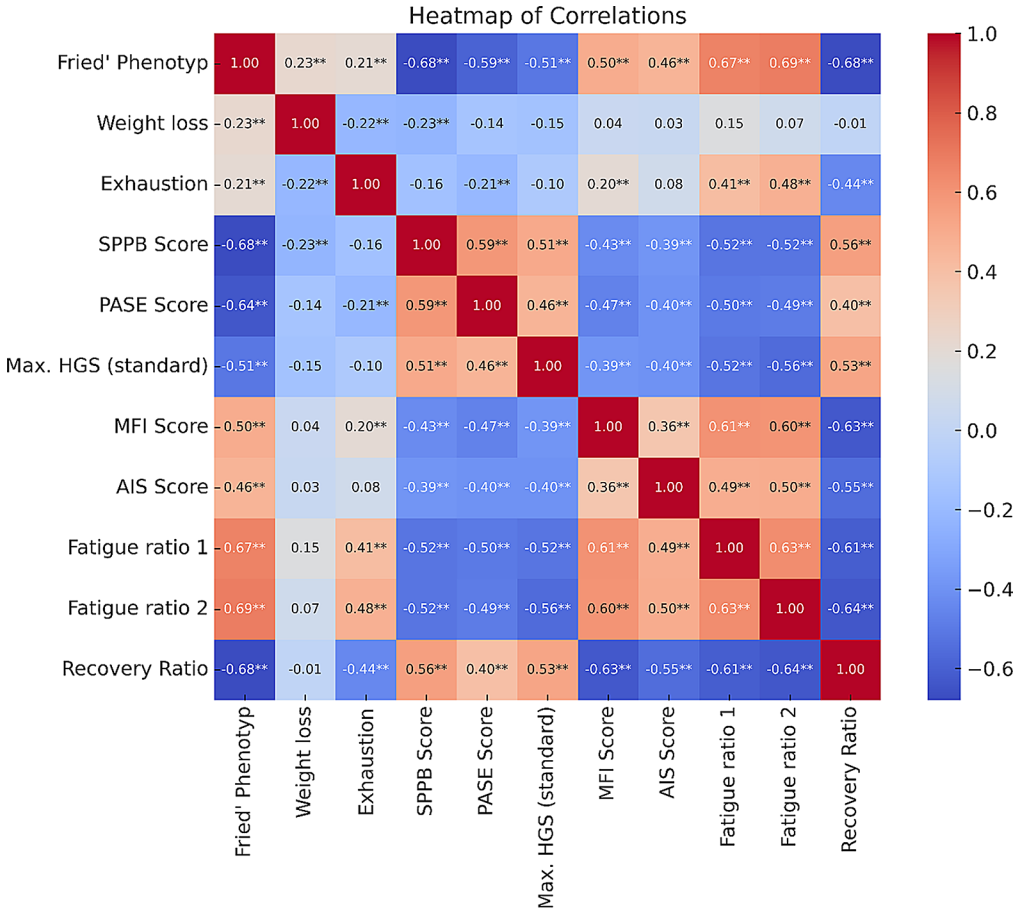


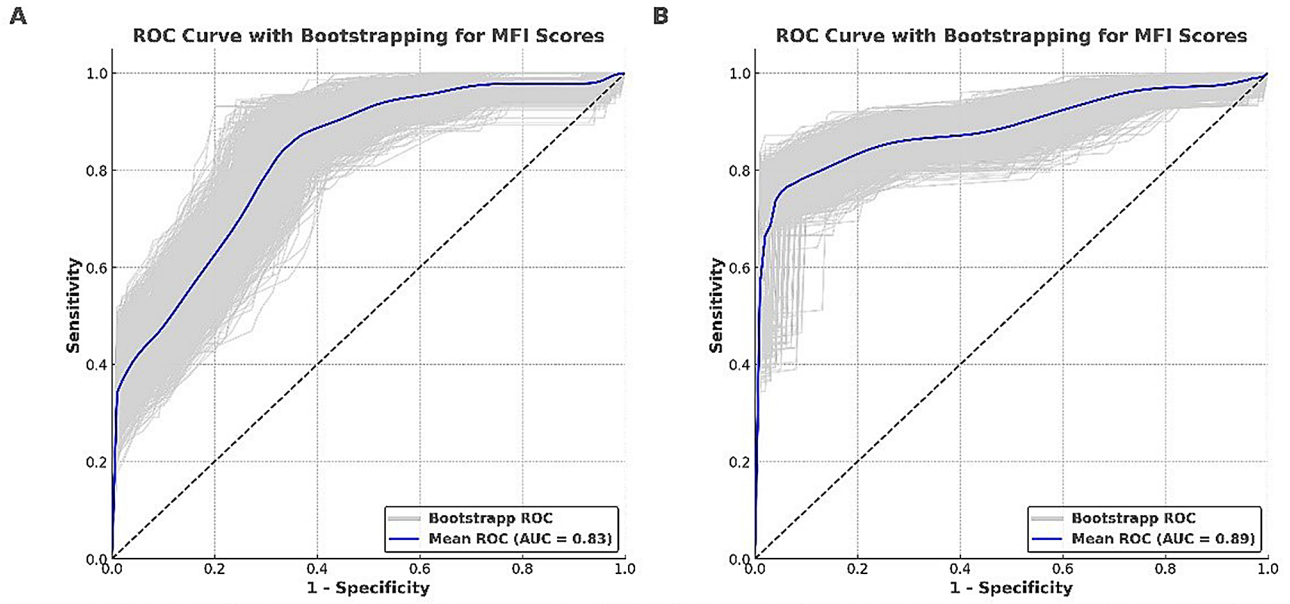
Fig. 3 Correlation Heatmap. Note p value* = <0.05; **= <0.001. MMSE = Mini Mental State Examination, PASE = Physical Activity Scale for the Elderly, MFI = Multidimensional Fatigue Inventory, SPPB = Short Physical Performance Battery, Max HGS (standard) = Maximum HGS from 3 Rounds

associated with a 29% lower likelihood of being classified into a higher frailty category (95% CI: 0.51–0.84, $p < 0.001$). Each unit increase in Fatigue Ratio 1 was associated with a 28% increased likelihood of being classified in a higher frailty category (95% CI: 1.24–2.17, $p < 0.001$). Additionally, each unit increase in Recovery Ratio decreased the odds of being classified into a higher frailty category by 14% (95% CI: 0.71–1.00, $p = 0.050$). While the PASE showed a trend toward significance in Model 1, it was no longer significant after fully adjustment in Model 2 (OR: 0.88, 95% CI: 0.70–1.02, $p = 0.075$). Variables that were not found to be significant for exceeding MFI thresholds in all adjusted models included unintentional weight loss, maximum HGS and PASE. For Fried's Phenotype, unintentional weight loss, maximum HGS, MFI score, PASE and the single question on exhaustion/fatigue were not found to be significantly associated in all adjusted models.

Discussion

This study investigated the use of a repetitive maximal isometric HGS protocol in 217 older adults at different stages of frailty. The protocol, consisting of 10 repetitions of 3-second maximum grips with 5-second rests, performed at two time points, showed significant differences between frailty groups in strength, fatigue and recovery.

The observed differences may be due to underlying physiological mechanisms involving a complex interplay between cellular and systemic processes. Central to this is mitochondrial dysfunction, which leads to reduced ATP production and impaired energy availability [35]. In frail individuals, this manifests itself in reduced aerobic capacity and limited mitochondrial reserve, resulting in more accelerated fatigue during repeated maximal exercise [36]. The inflammatory milieu characteristic of frailty further increases fatigue by disrupting excitation-contraction coupling and delaying recovery. These processes are exacerbated by significant metabolic changes, including impaired glucose homeostasis and insulin resistance, which particularly affect skeletal muscle tissue [35]. The age-related decline in muscle function is characterised



Analyse	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)
A (Frail vs. Non-frail/Pre-frail)	0.83 (0.77 - 0.88)	51	0.83 (0.74 - 0.88)	0.77 (0.69 - 0.84)
B (Pre-frail/Frail vs Non-frail)	0.89 (0.79 - 0.91)	44	0.79 (0.72 - 0.84)	0.81 (0.73 - 0.89)

Fig. 4 Roc Curve. Note: This figure presents Receiver Operating Characteristic (ROC) curve analyses with bootstrapping for MFI (Muscle Function Index) scores. It compares: **A**) Frail vs. Non-frail/Pre-frail individuals **B**) Pre-frail/Frail vs. Non-frail individuals. The graphs show bootstrapped ROC curves (grey lines) and mean ROC curves (blue lines) for both scenarios. The table below provides the Area under the Curve (AUC) with 95% confidence intervals, optimal thresholds, and corresponding sensitivity and specificity values for each comparison

by a shift from fast-twitch (type II) to slow-twitch (type I) muscle fibres, combined with impaired motor unit recruitment, leading to reduced muscle strength and endurance [37]. This loss of muscle mass, or sarcopenia, is primarily due to a reduction in motor units and atrophy of the remaining fibres. Other neuromuscular changes include reduced motor unit firing rates, less stable neuromuscular junctions and altered calcium handling [22]. Together, these factors contribute to reduced maximal strength, slower contractile velocity and increased fatigability [38].

Our results align with these proposed physiological mechanisms, particularly when examining changes in HGS after one hour. The non-frail participants showed an unexpected improvement in both maximum grip strength (Fmax) and mean grip strength (Fmean). Their mean Fmax increased significantly from 24.86 kg to 27.50 kg ($p < 0.001$), while their median Fmean increased from 22.89 kg to 23.27 kg ($p < 0.001$). In contrast, frail participants experienced a significant decline in both Fmax and Fmean after one hour. Their median Fmax decreased from 15.60 kg to 13.50 kg ($p < 0.001$), while their median Fmean fell from 10.59 kg to 9.36 kg ($p < 0.001$). The pre-frail group showed remarkable stability, with their values remaining largely unchanged. Their median Fmax changed only slightly from 23.05 kg to 22.10 kg ($p = 0.144$), and their median Fmean remained nearly constant with a change from 17.22 kg to 17.74 kg ($p = 0.940$). Furthermore, the stronger significant decrease in grip strength over the ten measurement repetitions in the frail group resulted in a significantly higher Fatigue Ratio compared to the non-frail and pre-frail groups. The median Fatigue Ratio for the frail group increased from 1.40 to 1.45 ($p = 0.022$), while it remained constant at 1.12 in the non-frail group and decreased slightly from 1.23 to 1.21 in the pre-frail group (these changes were not significant). The Recovery Ratio, which indicates better recovery at higher values, showed significant differences between the groups. The non-frail group had the best recovery with a median of 1.03, followed by the pre-frail group with 1.01. In contrast, the frail group, which also had the highest Fatigue Ratio, had the lowest recovery with a median of 0.90. This observation suggests that the repetitive HGS protocol may reveal latent reserves of capacity in healthy older adults, while also revealing reduced fatigue resistance and recovery capacity in frail individuals. The relative stability of performance in the pre-frail group highlights the potential of the protocol to detect subtle gradations along the frailty continuum.

Moreover, an important point to consider is the possible assumption that the maximum HGS during the 10 repetitions (Fmax1 and Fmax2) would be consistently lower than with the standard method. However, this was not the case. In all groups, the maximum HGS was

Table 3 Influence of functional health variables on multidimensional fatigue inventory

Multidimensional Fatigue Inventory (≤ 43 vs. ≥44 [Reference] points)				
	Multivariable Model 1		**Multivariable Model 2**	
Variables	OR (95% CI)	p-value	Or (95% CI)	p-value
Unintentional Weight Loss (Yes)	0.98 (0.56–1.71)	0.889	0.99 (0.48–1.80)	0.915
Exhaustion Single Question (Yes)	1.18 (1.03–1.68)	0.041	1.15 (1.02–1.67)	0.047
SPPB Score	0.89 (0.73–1.08)	0.129	0.90 (0.73–1.12)	0.202
PASE Score	0.95 (0.47–1.93)	0.978	0.91 (0.48–1.86)	0.815
Maximum HGS (standard)	0.95 (0.71–1.27)	0.357	0.96 (0.72–1.30)	0.587
Fatigue Ratio1	1.44 (1.14–2.08)	0.005	1.51 (1.29–2.16)	< 0.001
Recovery Ratio	0.89 (0.76–1.04)	0.106	0.83 (0.70–0.98)	0.022
Multidimensional Fatigue Inventory (≤ 50 vs. ≥51[Reference]points)				
	Multivariable Model 1		**Multivariable Model 2**	
Variables	OR (95% CI)	p-value	Or (95% CI)	p-value
Unintentional Weight Loss (Yes)	0.94 (0.53–1.67)	0.791	0.96 (0.51–1.72)	0.884
Exhaustion Single Question (Yes)	1.27 (0.92–1.76)	0.179	1.31 (0.94–1.83)	0.099
PASE Score	0.95 (0.58–1.55)	0.889	0.92 (0.60–1.38)	0.641
SPPB Score	0.79 (0.71–0.90)	< 0.001	0.76 (0.64–0.92)	< 0.001
Maximum HGS (standard)	0.95 (0.67–1.35)	0.441	0.94 (0.70–1.27)	0.371
Fatigue Ratio1	1.51 (1.23–2.04)	< 0.001	1.44 (1.15–2.11)	< 0.001
Recovery Ratio	0.84 (0.76–0.93)	0.018	0.87 (0.75–0.97)	0.025
Fried's phenotype (0 = non-frail, 1 = pre-frail, 2 = frail)				
	Multivariable Model 1		**Multivariable Model 2**	
Variables	OR (95% CI)	p-value	Or (95% CI)	p-value
Unintentional Weight Loss (Yes)	1.04 (0.56–1.92)	0.945	1.06 (0.57–1.96)	0.902
Exhaustion Single Question (Yes)	1.11 (0.74–1.67)	0.419	1.09 (0.73–1.62)	0.522
SPPB Score	0.75 (0.53–0.86)	0.001	0.71 (0.51–0.84)	< 0.001
PASE Score	0.82 (0.68–0.94)	0.029	0.88 (0.70–1.02)	0.075
Maximum HGS (standard)	0.90 (0.62–1.29)	0.341	0.91 (0.66–1.33)	0.403
Fatigue Ratio1	1.24 (1.20–2.14)	< 0.001	1.28 (1.24–2.17)	< 0.001
Recovery Ratio	0.84 (0.69–0.98)	0.045	0.86 (0.71–1.00)	0.050
MFI Score	1.12 (0.80–1.66)	0.279	1.09 (0.77–1.64)	0.309

Note SPPB = Short Physical Performance Battery, PASE = Physical Activity Scale for the Elderly, Fatigue Ratio = Higher values indicate stronger decrease of force during one session, Recovery Ratio = A higher value is an indication of better recovery after two measurements. MFI = Multidimensional Fatigue Inventory

Model 1: Adjusted for age and sex,

Model 2: Adjusted for sex, age, Athens Insomnia Scale, Charlson Comorbidity Index and Mini Mental State Examination

reached or even exceeded, whether in round 1 (Fmax1) or round 2 (Fmax2). In some cases, the HGS values were even higher than those obtained by the standard method, as shown by the Q1 - Q3 results. This indicates that the 10-repetition protocol can effectively measure maximum HGS better than or at least equal to the standard method of HGS. The ability to maintain or increase force output during repeated efforts demonstrates the potential utility of this method not only for assessing fatigue and recovery, but also for determining maximal HGS. Therefore, the repetitive HGS protocol may be a valuable tool in future studies and clinical assessments to assess both maximal strength and fatigue capacity in a more dynamic context than a standard single measurement.

As shown in Table 3, the Fatigue Ratio 1 measure (OR: 1.28) shows a similar association with frailty as the SPPB score (OR: 0.71), while the Recovery Ratio also shows an association, but with a lower odds ratio (OR: 0.86). This suggests that repeated isometric HGS (Fatigue Ratio 1) may be more sensitive in identifying frailty than standard maximum HGS (OR: 0.91), which did not show a significant association. A possible explanation for the lack of significance in standard HGS is that a single maximal measurement may not adequately capture cumulative neuromuscular fatigue. Individuals with relatively high baseline strength may still experience significant fatigue or decline with repeated efforts - an aspect that may be missed by a single HGS test. In addition, the cross-sectional nature of our study may have limited our ability to detect smaller but clinically meaningful differences in maximal strength between different stages of frailty. Furthermore, at an MFI threshold of ≥ 44 points, the variables most strongly associated with MFI in the fully adjusted model 2 are the Fatigue Ratio 1 (OR: 1.51),

followed by the Recovery Ratio (OR: 0.83), and the individual fatigue question (OR: 1.15). However, in the fully adjusted model 2, when the threshold is increased to ≥ 51 points, the single exhaustion/fatigue question loses significance (OR 1.31) while Fatigue Ratio 1 (OR: 1.44) continues to show a strong and independent association with the MFI. As noted above, a possible reason for the non-significant result at the higher fatigue thresholds is that a single measure of HGS and a single question about fatigue are unlikely to fully capture the multifactorial nature of fatigue, particularly in older adults who may have multiple comorbidities and varying levels of daily activity. Subjective perceptions of fatigue may also vary according to mood, recent physical exertion or other psychosocial factors that cannot be captured by a single question. Recovery Ratio also remained significantly associated (OR: 0.87). These findings suggest that Fatigue Ratio 1 is the most consistent and reliable predictor of MFI across different thresholds, with Recovery Ratio being particularly relevant at higher levels of fatigue. Additionally, the correlation analysis (see heatmap in Fig. 3) supports these findings, showing that the Fatigue Ratio and Recovery Ratio correlate more strongly with the MFI and Fried phenotype classification than the single exhaustion/fatigue question or the maximum HGS measurement, highlighting their potential as a more effective tool for frailty assessment. The results show that the repetitive HGS protocol assesses not only maximal strength, but also endurance and recovery after repeated efforts. This approach may better capture a wider spectrum of neuromuscular deficits that are critical to everyday physical activity, but often go undetected by single strength measurements that focus solely on maximal strength. Based on these comprehensive assessment capabilities, the protocol demonstrates particular value for three key clinical applications: early identification of pre-frailty through changes in fatigue patterns, monitoring of frailty progression, and evaluation of intervention effectiveness. The ability to detect subtle performance changes provides clinicians with a more sensitive tool for early intervention decisions, especially in individuals who might appear robust based on maximum strength alone.

Frailty assessments such as Fried's Phenotype, Share-FI, the FRAIL scale, the Tilburg Frailty Indicator (TFI), and the Frailty Index (FI) include fatigue as a key component, but rely predominantly on subjective assessments [4, 39]. In contrast, this approach offers the potential to identify an objective biomarker for fatigue in frailty, as has already been established in the context of ME/CFS and Long Covid [12, 13]. Furthermore, the repeated HGS protocol may provide a more realistic assessment of fatigue mechanisms than other commonly used fatigue measures, such as submaximal protocols (e.g. 80% or 60% of maximal voluntary contraction, MVC) [40, 41]. This protocol more closely reflects the types of activities that older people perform on a daily basis, such as repeated standing, climbing stairs or loading and unloading a dishwasher [42, 43]. It more accurately captures the build-up of fatigue during repeated efforts. In contrast, submaximal protocols such as 80% or 60% MVC focus on continuous submaximal effort and allow for systematic recovery through longer rest periods (e.g. 60 s at 80% or 50% MVC). This results in a lower overall level of fatigue [44, 45]. However, the protocol used in this study (10 × 3 s of exercise followed by 5 s of rest) does not allow enough time for the muscles to recover. Studies show that fatigue occurs more quickly during maximal exercise with short rest periods because excitation-contraction coupling - the process that links neural signals to muscle contraction - is impaired more quickly. This leads to a more rapid decline in strength. In contrast, submaximal protocols lead to gradual fatigue because both motor unit activation and metabolic load are lower [40, 41, 45].

Limitation

This study has several limitations. First, due to its cross-sectional design, it is only possible to draw limited conclusions about causality or changes over time. Longitudinal studies are needed to evaluate the predictive validity of the HGS protocol and its effects on the progression of frailty. Second, although biological markers such as TNF-α, IL-6, IL-1β, and CRP were mentioned in the introduction as important factors in muscle wasting and inflammation, these were not measured. Including these markers would have strengthened the evidence for the proposed mechanisms underlying muscle fatigue and frailty. Likewise, measuring muscle mass and composition using techniques such as DXA would have provided a more comprehensive understanding of muscle health and its relationship to frailty. Third, our recruitment of participants from residential care homes may have introduced selection bias, as this sample may not fully represent the broader population of older adults—especially those living independently—thereby limiting the generalizability of the findings. Fourth, although handgrip strength (HGS) is recognized as a reliable and valid measure of muscle function and all tests were conducted by experienced physiotherapists under standardized conditions, minor measurement variations are possible, particularly with ten repetitions. Differences in grip position and participant motivation could have influenced absolute HGS values and thus the comparability across groups. Taken together, these limitations may affect the validity and generalisability of our findings.

Future research

Future research should address the identified limitations and additionally focus on clinical implementation

strategies. This includes establishing clinically relevant thresholds for fatigue and recovery ratios to guide intervention decisions, and practical guidelines for incorporating the repeated HGS protocol into routine geriatric assessment. Research should also evaluate the effectiveness of the protocol as a tool for monitoring rehabilitation progress and investigate its potential for predicting adverse outcomes such as falls or functional decline in clinical practice. Finally, cost-effectiveness studies should investigate the feasibility of implementing this protocol in different health care settings, from primary care to specialised geriatric units.

Conclusion

In comparison to the single measurements employed in Fried's Phenotype, including maximum HGS and the single-question assessment of exhaustion/fatigue, the isometric repetitive HGS protocol offers a more comprehensive and intricate representation of neuromuscular function. This approach is of significant importance for the early detection of frailty, as well as for the longitudinal assessment of frailty status and the evaluation of interventions. By combining strength measurement, fatigue resistance, and recovery ability in a single protocol, it opens up new possibilities for a deeper understanding and more precise assessment of the complex physiological changes associated with frailty.

Abbreviations

AIS	Athens Insomnia Scale
AUC	Area Under the Curve
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
COVID-19	Coronavirus Disease 2019
EWGSOP2	European Working Group on Sarcopenia in Older People 2
Fmax	Maximum Handgrip Strength (erste oder zweite Messung)
Fmean	Mean Handgrip Strength (erste oder zweite Messung)
HGS	Handgrip Strength
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MFI	Multidimensional Fatigue Inventory
MMSE	Mini Mental State Examination
MVC	Maximal Voluntary Contraction
OR	Odds Ratio
PASE	Physical Activity Scale for the Elderly
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SPPB	Short Physical Performance Battery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06239-2.

Supplementary Material 1

Supplementary Material 2

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Author contributions

AK conceived and led the study, wrote the manuscript, and conducted statistical analyses. MR and AL assisted with data collection and analysis. RF supported data analysis and interpretation of results. TW provided statistical consultation. All authors have read and approved the final manuscript.

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Data availability

Data from this study are stored in a secure database accessible only to the research team. Due to ethical restrictions, raw data cannot be shared. This study was not preregistered.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Clinical Research Ethics Board of Vienna (Ethics Approval Number: EK-23-082-0523). All participants provided informed consent.

Consent for publication

All authors consent to the publication of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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