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SHORT COMMUNICATION

Reliability of fr-AGILE tool to evaluate multidimensional frailty in hospital settings for older adults with COVID-19

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Abstract

Aims The study assesses the reliability of fr-AGILE, a validated rapid tool used for the evaluation of multidimensional frailty in older adults hospitalized with COVID-19.

Methods Two different staff members independently assessed the presence of frailty in 144 patients aged ≥ 65 years affected by COVID-19 using the fr-AGILE tool. The internal consistency of fr-AGILE was evaluated by examining the item-total correlations and the Kuder–Richardson (KR) formula. The inter-rater reliability was evaluated using linear weighted kappa.

Results Multidimensional frailty severity increases with age and is associated to higher use of non-invasive ventilation ($p = 0.025$), total severity score on chest tomography ($p = 0.001$) and in-hospital mortality ($p = 0.032$). Fr-AGILE showed good internal consistency (KR-20 = 0.742) and excellent inter-rater reliability (weighted kappa = 0.752 and 0.878 for frailty score and frailty degree, respectively).

Conclusions fr-AGILE tool can quickly identify and quantify multidimensional frailty in hospital settings for older patient affected by COVID-19.

Keywords Multidimensional frailty · Frailty evaluation tool · COVID-19

Introduction

Multidimensional frailty is considered a dynamic state affecting an older adult who experiences losses in one or more domains of human functioning (physical, mental, nutritional, and social) which increases the risk of adverse outcomes [1]. According to this definition, the most used tool for multidimensional frailty recognition is the "Rockwood deficit–accumulation frailty index" (FI), expressed as the ratio between defects found in a patient and the total number of defects investigated, including symptoms, social characteristics, clinical signs, diseases, disabilities and laboratory or instrumental abnormalities [2]. Several studies have shown that FI is more predictive of adverse clinical outcomes than other tools in both hospital and community settings [3]. Recently, we have developed and validated an Italian modified version of FI, the Italian Frailty index (IFi) [4].

Despite the numerous advantages and reliability, frailty identification tools developed on deficit index model found its greatest limitation in prolonged administration time, requiring a complete multidimensional assessment that needs about 60 min for each patient under examination. To overcome this limitation, we have recently created and validated a rapid tool for the evaluation of multidimensional frailty called "fr-AGILE" that has been proved to be reliable with a diagnostic power comparable to that of the IFi with a high predictive value on adverse clinical outcomes, and more importantly, with a consumption time less than 5 min [5].

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In the 2019 Coronavirus disease (COVID-19) pandemic, multidimensional frailty has been identified as one of the most relevant prognostic determinants in the management of the elderly patient [6]. However, the identification and quantization of multidimensional frailty in COVID-19 context is problematic especially for the excessive length of time that is necessary to define it. Therefore, because of high biological risks of health workers involved in COVID-19 setting, the assessment of multidimensional frailty status should be necessarily rapid [5].

Thus, the aim of this study is to assess the reliability of fr-AGILE, a validated and rapid tool for identification and quantization of multidimensional frailty in COVID-19 hospital settings.

Methods

Study population

One hundred and forty-four patients aged ≥ 65 years hospitalized in the departments of "COVID Internal Medicine" and "COVID Infectious Diseases" of the "Azienda Ospedaliera Universitaria—Federico II" in Naples (Italy) were consecutively enrolled in the study from November 2020 to November 2021.

COVID-19 assessment

Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) infection was diagnosed by real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. All patients underwent a chest computed tomography (TC). Quantification of pulmonary inflammation was made by the total severity score (TSS), an evaluation method which scores the severity of inflammation on CT images based on summing up degree of acute lung lesion involvement of each lobe [7]. Blood biomarkers of disease severity [C-reactive protein (CRP), interleukine-6 (IL-6), D-dimer and Neutrophile to Lymphocyte Ratio (NLR)] were measured at the admission. Patients have been systematically evaluated for super-infectious complications in case of clinical worsening or clinical suspicion with culture tests of biological fluids and blood determination of procalcitonin and galactomannan. Medical history record was analyzed for the presence of hypertension (previous medical diagnosis, antihypertensive pharmacological treatment, or blood pressure ≥ 140/90 mmHg), diabetes and obesity.

Fr-AGILE

A full description of the Fr-AGILE can be found in the original study [5]. Briefly Fr-AGILE was built by selecting among the 40 items of Italian version of Frailty Index the 10 ones most predictive of mortality, to homogeneously represent the four domains of "multidimensional" frailty: physical, mental, nutritional, and socio-economic. The total score ranged from 0 to 10, with higher score indicate more frailty. The Fr-AGILE scores were divided into degree: absent (0), light (1–3), moderate (4–7) and severe frailty (8–10). Fr-Agile items are sown in Table 2.

Fr-AGILE statistical analysis and reliability

According to Park et al. [8], to assess the reliability of fr-AGILE tool, the sample size was determined by considering the number of participants about 5 times the number of items; since the fr-AGILE tool included 10 items the number of participants was more than 50.

Two different staff members (rater 1 and rater 2), independently and "blinded" for each other results, assessed the patient at admission (within the first 24 h on the hospital ward) using the fr-AGILE index with input directly from patients, and if not possible from caregivers. The second rater could obtain the information either from the patient himself or from the caregiver regardless of the method used by the first rater. The inter-rater reliability of the fr-AGILE was evaluated using linear weighted kappa assuming a kappa value ≥ 0.80 as an efficient agreement. The internal consistency of fr-AGILE was evaluated by examining the Kuder–Richardson (KR)-20 test and by item-total correlations. KR-20 coefficient is a measure of internal consistency reliability for a test with binary variables (yes or not). It ranges from 0 to 1, where 0 is "no" reliability and 1 is "perfect reliability"; values above 0.7 show reasonable convergence of the items. The item-total correlation test is performed to check if any item of the test can assess the same concept measured by the other items included. Item correlation less than 0.20 was considered weak with poor clinical applicability; between 0.20 and 0.40 was considered moderate; and greater than 0.40 was considered strong. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables as percentages, respectively. Continuous variables across groups were analyzed by ANOVA test and corrected by Bonferroni's post hoc test while and Chi-square test was used to evaluate categorical variables. Significance level was set at alpha = 0.05 for all analysis. Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY USA).

Results

The demographic and clinical laboratory characteristics of our sample are shown in Table 1. The sample average Fr-AGILE score was 3.9 ± 2.5. Thirteen patients were classified

Table 1 Demographic and clinic characteristics of the study sample stratified for multidimensional frailty degree

Variables	All $n=144$	Multidimensional frailty				p for trend
		No frail $n=13$	**Light** $n=52$	**Moderate** $n=64$	**Severe** $n=15$	
Fr-AGILE score	3.9 ± 2.5	0.0 ± 0.0	1.8 ± 0.9	5.4 ± 1.2	8.7 ± 0.7	< 0.001
Age	76.5 ± 8.4	68.9 ± 2.7	73.9 ± 5.0	78.6 ± 7.9	87.9 ± 7.2	< 0.001
Sex (M %)	56.2	61.5	69.2	48.4	40.0	0.042
NIV (%)	56.9	46.2	51.9	54.7	93.3	0.025
Average hospital stay	29.4 ± 14.8	20.8 ± 6.2	26.2 ± 14.4	31.4 ± 16.4	22.2 ± 12.6	0.421
Superinfection (%)	39.6	15.4	26.9	50.0	60.0	< 0.001
IL-6, pg/mL	74.5 ± 260.5	74.0 ± 34.6	98.4 ± 240.2	40.2 ± 28.4	30.4 ± 21.4	0.496
D-dimer, mg/L	2.6 ± 6.0	1.1 ± 1.6	3.2 ± 8.8	2.5 ± 3.8	1.5 ± 1.3	0.816
NLR	4.2 ± 7.4	3.2 ± 2.7	4.7 ± 2.4	4.9 ± 2.9	4.5 ± 2.9	0.741
CRP, mg/L	49.4 ± 95.2	63.2 ± 48.3	51.2 ± 50.4	44.2 ± 65.9	40.3 ± 84,2	0.749
TTS chest tomography	8.4 ± 3.9	5.5 ± 4.5	7.9 ± 4.2	9.4 ± 3.6	15.0 ± 4.2	< 0.001
Hypertension (%)	79.8	53.8	76.9	84.3	93.3	0.041
Diabetes (%)	45.1	38.5	48.1	43.8	46.7	0.942
Obesity (%)	37.5	38.5	34.6	42.2	26.7	0.132
In-hospital mortality (%)	16.0	7.7	9.6	17.2	40.0	0.032

NLR neutrophil-to-lymphocyte ratio, *NIV* non-invasive ventilation, *IL-6* interleukin-6, *CRP* C-reactive protein, *TTS* Total Severity Score

Table 2 Prevalence of Fr-AGILE items stratified for multidimensional frailty degree with item-total correlations and internal consistency (KR-20)

Items	All $n=144$	Multidimensional frailty				p for trend	Item total correlation	KR-20 after item deleted
		No frail $n=13$	Light $n=52$	Moderate $n=65$	Severe $n=15$			
1 Feel everything is an effort (%)	54.1	0.0	25.6	69.2	86.6	< 0.001	0.452	0.690
2 Help up/downstairs (%)	63.8	0.0	42.3	84.6	100	< 0.001	0.455	0.692
3 Grip strength[a] (%)	63.1	0.0	42.3	83.0	100	< 0.001	0.443	0.694
4 Temporal orientation deficit[b] (%)	33.3	0.0	11.5	46.1	80.0	< 0.001	0.424	0.701
5 Delayed recall deficit[c] (%)	34.0	0.0	7.6	49.2	86.6	< 0.001	0.435	0.711
6 Feel depressed (%)	30.5	0.0	15.3	38.4	73.3	< 0.001	0.210	0.732
7 Weight loss over 4.5 kg in the last year (%)	8.3	0.0	1.9	7.6	40.0	< 0.001	0.310	0.716
8 Help in eating (%)	22.2	0.0	11.5	26.15	60.0	< 0.001	0.171	0.746
9 Financial helps from family members (%)	43.3	0.0	15.3	60.0	80.0	< 0.001	0.485	0.711
10 Physical help from family members (%)	34.0	0.0	9.6	44.6	100	< 0.001	0.545	0.698

[a] ≤ 27 kg in men, ≤ 16 kg in women at hand-held dynamometer

[b] The subject does not refer the exact date (day/month/year)

[c] The words "bread-house-cat" are referred to the subject at the beginning of the questionnaire and then asked to the subject at this time of the questionnaire

All the binary variables have been coded using "0" to indicate the absence and "1" the presence of a deficit, except for the items 9 and 10 where the absence of help corresponds to "1" and the presence of help to "0"

as "no frail" while the mean Fr-AGILE score in the severe frailty group was 8.7 ± 0.7. The average age of the study group was 76.5 ± 8.4. A greater male prevalence in subjects hospitalized for COVID-19 was observed in study sample (56.2%), while more severe degrees of frailty were found in female sex. Higher degrees of frailty were associated with higher TSS score (p for trend < 0.001), a more frequent use of Non-Invasive Ventilation (NIV) (p for trend 0.025), a higher superinfection rate (p for trend < 0.001) and in-hospital mortality (p for trend 0.032).

The administration time of the fr-AGILE test was 2.9 ± 1.4 min. The prevalence of Fr-AGILE items, stratified

for frailty degree and domain of multidimensional frailty is listed in Table 2. As expected, increasing degrees of frailty corresponded to a higher percentage of positivity for each of the 10 items score. Specifically, in subjects with severe frailty degree, a percentage of 100% was found in items that explore the physical domain of frailty ("need for help to climb and descend stairs" and "grip strength") as well as the socio-economic domain ("absence of physical help from family members"). When analyzing internal consistency of fr-AGILE, KR-20 value was 0.742. When separately examining the domain scores, KR-20 was 0.652 for the physical, 0.422 for the mental, 0.534 for nutritional and 0.444 for the social. The KR-20 after deletion of each item ranged from 0.690 to 0.746 and the item-total correlation of Fr-AGILE ranged from 0.171 to 0.545 (Table 2). Finally, the Fr-AGILE score showed excellent inter-rater reliability: weighted kappa for frailty score was 0.752 (95% confidence interval 0.715–0.874) while for frailty degree 0.878 (95% confidence interval 0.799–0.952). In Fig. 1 are shown frequency distribution of ratings fr-AGILE score assessment in the sample study: no significant differences were observed between rater 1 and 2.

Discussion

The study established a good level of reliability of the fr-AGILE score in hospitalized elderly patients with COVID-19. The results suggest that the fr-AGILE, developed in an outpatient setting, is also a fast and reliable tool that allows, in a very short time (≈ 3 min) to identify and quantify multidimensional frailty in a specific and complex hospital settings, as a COVID ward. This is an important confirmation for a clinical context in which the multidimensional frailty assessment is often dependent on information derived from the caregiver and where the acute state of illness can introduce important "recall" bias in proportion to the complexity of the test.

In the current pandemic scenario, to facilitate appropriate management of the patient and ensure a correct allocation of resources, the state of frailty is crucial [6]. Current NICE guidelines recommend frailty assessment as the first step in managing the patient with COVID-19 upon hospital admission [9]. The recommendation promotes the use of the "Clinical Frailty Scale (CFS)" developed on the Rockwood's FI, which provides nine pictograms and short clinical descriptions to evaluate patients on a scale from 1 ("very fit") to 9 ("terminally ill") and it is associated with mortality in a meta-analysis on a pooled sample of 3817 patients with COVID-19 [10]. Although intuitive, CFS is based on a subjective clinical judgment and on extensive multidimensional evaluation that require a long-time of administration [11]. In contrast, although Rockwood's FI evaluates frailty status in an extensive graded manner making a more precise risk prediction than other evaluation methods, it is very time-consuming tool and it needs a previous comprehensive geriatric assessment (CGA), difficult to achieve in a high biological risk environment. In this context, the use of "electronic FI" could be feasible and convenient also in a COVID setting [12]. Although it has not been proven significant difference between frailty phenotype (FP) and FI in evaluating COVID-19 patients [13], it should be underlined that FP is limited to a one-dimensional assessment and not applicable to disabled older patients in hospital setting due

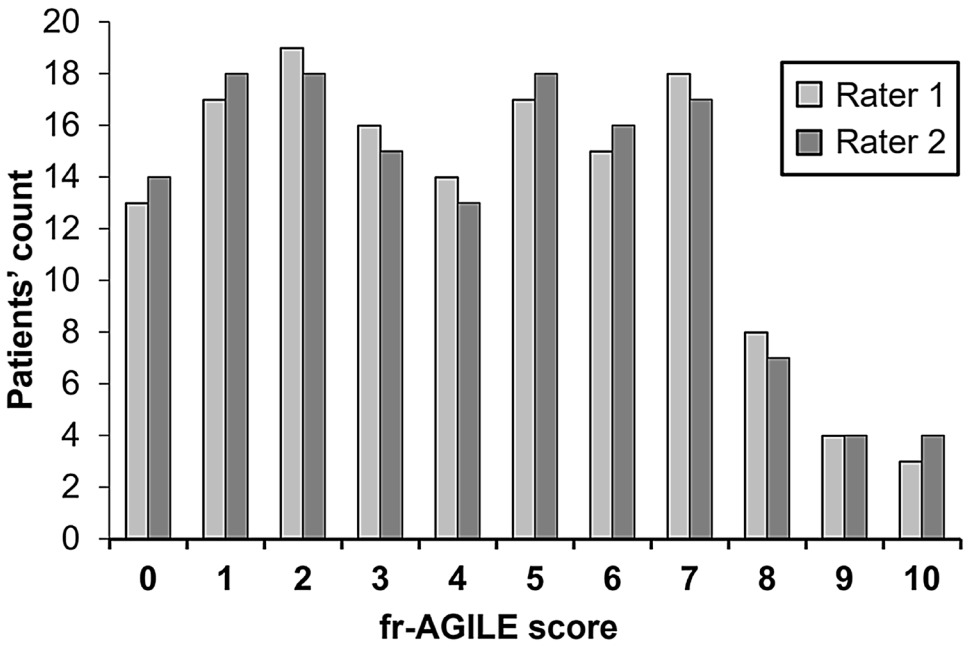

Fig. 1 Frequency distribution of ratings fr-AGILE score assessment in the sample study in raters 1 and 2

the requirement of objective measurement of speed walk. Finally, the FRAIL (Fatigue, Resistance, Ambulation, Illness, Loss of Weight) tool entirely based on patients themselves without any measurement tool does not investigate socio-economic and mental domains of frailty [14].

Most of these limitations encountered by the frailty assessment tools in COVID-19 population are considerably overcome by fr-AGILE. In addition to the speed of execution, essential for reducing the biological risk of healthcare professionals, fr-AGILE clearly evaluates all frailty domains, including items of physical frailty easily performed in any type of patient, also in hospital setting.

When considering multidimensional frailty degree by fr-AGILE assessments, our study demonstrated a good level of agreement between rater 1 and 2 with a weighted kappa of 0.875. We have not analyzed score differences according to the nature of the assessor from different professions because Fr-AGILE items are largely independent of clinical judgment and are based on information reported by the patient and/or care giver and, therefore, can be administered without specific training. Moreover, to have a good internal consistency, KR-20 and item-total correlation coefficient for each item should be greater than 0.7 and 0.2, respectively. Regarding the KR-20, fr-AGILE presents a value of 0.742 while regarding the item-total correlation coefficient, only item 8 ("help in eating") reported a value of 0.171. The poor correlation of this item is probably related to complexity of the deficit analyzed which includes conditions ranging from the inability to prepare a meal to the need to be fed. In addition, item 6 ("feel depressed") and item 7 ("weight loss over 4.5 kg in last year") showed a lower value of correlation probably because found positive only in patients with a more severe frailty degree.

Subjects identified as frail by fr-AGILE score showed a more severe disease experience as demonstrated by a higher value of radiological severity of pneumonia and a higher recourse to NIV, and mortality. In contrast, no significant associations were found between the stratification of frailty severity and biochemical markers of disease severity, such as higher value of NLR, D-Dimer, C-reactive protein, and interleukin-6 levels, often associated with the "cytokine storm" responsible for the most severe forms of disease in younger patients. These results could be justified by the possible deregulation of the immune response in more frailty and older subjects, who are often characterized by anergic responses to infection diseases with a greater predisposition to complications [15]. Accordingly, the association between frailty severity and superinfection may confirm this hypothesis.

Finally, when considering the analysis of the relationship between frailty and comorbidities undoubtedly associated with a worse prognosis of SARS-COv2, a close association between hypertension and frailty was found.

Conclusions

A series of studies suggested that elderly COVID-19 patients have a high incidence of frailty, and frailty is detrimental to COVID-19 prognosis. At present, there is no generally accepted consensuses for the evaluation of frailty in elderly patients with COVID-19. In this scenario, Fr-AGILE could represent the ideal tool to quickly identify and quantify the multidimensional frailty in older adults with COVID-19.

Declarations

Conflict of interest The authors do not have any conflict of interest to declare.

Ethical approval The study was approved by the Institutional Review Boards at University of Naples Federico II.

Statement of human and animal rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Review Boards of the participating institutions and with the 1964 Helsinki.

Informed consent Informed consent for participation was obtained from all participants.

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