The Comprehensive Rheumatologic Assessment of Frailty (CRAF): development and validation of a multidimensional frailty screening tool in patients with rheumatoid arthritis

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Abstract

Objective

Frailty is a topic that is gaining more and more interest in rheumatology. The aims of this study were to develop and preliminarily validate a frailty index dedicated to rheumatoid arthritis (RA) called the Comprehensive Rheumatologic Assessment of Frailty (CRAF).

Methods

Ten major frailty domains of CRAF were identified: nutritional status, weakness, falls, comorbidity, polypharmacy, social activity, pain, fatigue, physical function, and depression. Convergent validity was evaluated correlating the scores of the CRAF with the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI). Discriminant validity was assessed using receiver operating characteristic (ROC) curve analysis. Multivariate logistic regression model procedure was used to assess the relative contribution of the individual determinants on the CRAF.

Results

Among the 219 RA patients, 79 (36.1%) were defined as non-frail (CRAF ≤0.12), 63 (28.8%) mild frail (0.12 <CRAF ≤0.24), 34 (15.5%) moderate frail (0.24 <CRAF ≤0.36), and 43 (19.6%) severe frail (CRAF >0.36). In testing for convergent validity, a significant correlation was found between CRAF and SHARE-FI (p <0.0001). The discriminatory power of CRAF was higher than those of the SHARE-FI (difference between areas under the ROC curves=0.0853± 0.0282. Variables associated with frailty at the multivariate analysis were advanced age and high disease activity (both at p<0.0001).

Conclusion

The CRAF demonstrated a robust validity and good discriminant accuracy. Implementation of the frailty assessment into the routine rheumatological practice could represent a major advance in RA care.

Key words

frailty, rheumatoid arthritis, aging, disease activity

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Introduction

Rheumatoid arthritis (RA) is a disease characterised by chronic joint inflammation, which overall results in a functional limitation and reduced performance. A limitation of functional capacity can in turn result in increased frailty (1). Frailty can be defined as "the loss of resources in several domains leading to the inability to respond to physical or psychological stress" (2). Frailty is a condition whereby the individuals are vulnerable to adverse events and less favourable outcomes (3). Frailty is associated with falls, cognitive impairment, hospitalisation, institutionalisation and death, as well as adverse responses to chemotherapy, to surgical intervention, and to recovery after emergency department discharge (4-9). The prevalence of frailty increases with age: it ranges from 7% to 10% in those aged over 65 years and to 20–40% among octogenarians (10).

Compared to the geriatric population in general, frailty in the context of chronic inflammatory joint disease is a relatively under-researched topic (1, 11-13). Haider and colleagues demonstrated that frailty is present in 15% of RA patients younger than 65 years whereas 30% are found to be prefrail (1).

Although there are no universally accepted frailty criteria (2, 14), the main methods of evaluation are two: Fried's criteria (10), and the Frailty Index (FI) (15). Fried and coworkers operationalised the phenotypic model in the Cardiovascular Health Study and defined three categories: frail (three or more criteria present), pre-frail (one or two criteria present), and non-frail (none of the criteria present) (10). The main advantage of this model is that it requires the evaluation of only five parameters, making its calculation rather rapid. The main criticism, however, is that this model is a predominantly physical conceptualisation, identifying the frailty as a wasting process and recognising in the loss of skeletal muscle mass (sarcopenia) as the key pathophysiological feature, and omitting disorders of cognition and mood (10). Conversely, the FI is based on the cumulative deficit approach, relying on a more holistic perspective: frailty can be assessed by evaluating a larger number of non-specified age-associated health deficits (15-18). FI ranges from 0 (none of the deficits present) to 1 (all deficits present), with the cut-off points for frailty levels identified as: non-frail (0 to ≤0.12), mild frail (>0.12 to ≤0.24), moderate frail (>0.24 to ≤0.36) and severe frail (>0.36) (3).

In recent years, the FI has been recognised as the most valuable frailty assessment model (20-23). However, the tool is complex, the psychometric properties need to be explored far more extensively and it has not been validated in the rheumatological setting (21, 23).

Given these limitations, the estimation of frailty in patients with chronic inflammatory arthropaties is difficult to perform in daily clinical practice.

The main objectives of this study are to develop and validate in a preliminary way a tool to assess frailty, dedicated to RA patients and easy to use in clinical practice, called Comprehensive Rheumatologic Assessment of Frailty (CRAF).

Materials and methods

For the development of a multidimensional tool in constructing a measure of frailty, the conceptual framework of deficit accumulation has been adopted (22), following a series of major steps, such as: (*i*) development of a provisional pool of variables related to frailty, (*ii*) variables reduction, and (*iii*) pilot testing of the CRAF index in real-life conditions.

Creation of the CRAF index

The variables included in the CRAF were generated using a Delphi procedure (24), and the general methodology applied in this study has been previously adopted (25-28). Basing on the Gobbens frailty theory model (29), the authors discussed and selected 34 variables from the existing frailty appraisal tools. Subsequently, applying the Lynn's process for content validation, 39 specialists (the expert group, respectively 19 rheumatologists, 6 rehabilitation medicine, 6 geriatrics, 3 ortopaedics, 6 neurologists, and 2 internal medicine specialists) were invited to rate the importance of each variable in the measurment of frailty in RA pa-

tients. The importance of each variable was scored on a Likert scale from one to four: 1 = irrelevant; 2 = slightly relevant; 3 = quite relevant; 4 = very relevant.

To be considered in CRAF, the variables had to have a mean score >3.0 ("quite relevant") by more than the 80% of the expert group (Table I). The top ten ranked variables are listed in Table II. The group of experts established that the nutritional status (considering body mass index [BMI] as an indicator of nutritional status), weakness, falls, comorbidity, polypharmacy, social activity, pain, fatigue, physical function, and depression were the variables most associated with the risk of frailty in RA patients.

Some variables (nutritional status, polypharmacy, and social activity) were considered as trichotomous levels (0, 0.5, 1.0); while other variables, such as comorbidity and those related to the patient's perspective (pain, fatigue, physical function, and depression) were assigned five (0, 0.25, 0.5, 0.75 and 1.0) to six levels (0, 0.2, 0.4, 0.6, 0.8 and 1.0), to reflect differences in severity.

Regarding the nutritional status, overweight and normal weight were combined and coded 0, based on evidence that some excess weight can be protective (31). In line with previous studies, obesity was coded 0.5 (32) while underweight was 1.0 (17).

Weakness was assessed by handgrip strength, using an electronic grip device (a five force sensors [FSR-402] manufactured by Interlink Electronics, connected to an Arduino Mega 2560). Two consecutive measurements were recorded from the left and right hands. The highest of the four was selected (this variable was considered as continuous). The measurement of hand grip strength has been recommended as an indicator of overall muscle strength and as a biomarker of general health status (33, 34). According to the available data for grip strength, to define weakness it has been generally used a T-score ≤-2 (equivalent to 19 kg in females and 32 kg in males, or weaker) (35, 36), while a T-score ≤-2.5 (equivalent to 16 kg in females and 27 kg in males) has been applied in patients suffering from coexisting osteoporosis (37).

Table I. The list of the 34 variables coming from the frailty assessment tools. The first 10 variables are those retained in the final Comprehensive Rheumatologic Assessment of Frailty (CRAF).

Variable	Frequency (%)	Mean relevance scores	Frequency importance product (FIP)*
1. Nutritional status (BMI)	93%	3.87	359.91
2. Weakness (handgrip strength)	92%	3.77	346.84
3. Falls	90%	3.55	319.50
4. Comorbidity (RDCI score)	91%	3.25	295.75
5. Medications/Polypharmacy	89%	3.31	294.59
6. Social activity	88%	3.30	290.40
7. Pain	93%	3.11	289.23
8. Fatigue	89%	3.21	285.69
9. Physical function	88%	3.22	283.36
10. Depressive symptoms	89%	3.16	281.24
11. Change in sleep	79%	3.49	275.71
12. Memory changes	79%	3.11	245.69
13. Slow walking speed	79%	3.09	244.11
14. Cognitive impairment	79%	3.03	239.37
15. Needing assistance with ADLs	79%	3.02	238.58
16. Immobilisation	75%	3.08	231.00
17. Abnormal laboratory values	72%	2.90	208.80
18. Balance problems	71%	2.98	205.19
19. Anxiety	78%	2.62	204.36
20. Visual impairment	73%	2.76	201.48
21. Health compared to 1 year ago	74%	2.63	194.62
22. Gender	72%	2.56	184.32
23. Unable to drive	68%	2.56	174.08
24. Frequency of health use	65%	2.65	172.25
25. Educational level	58%	2.78	161.24
26. Marital status	65%	2.43	157.95
27. Help taking medication	72%	2.18	156.96
28. Hearing impairment	70%	2.23	156.10
29. Life satisfaction	60%	2.54	152.40
30. Help with finances	62%	1.87	115.94
31. Speech problems	61%	1.87	114.07
32. Cataract operation	57%	1.98	112.86
33. Smoking status	56%	1.89	105.84
34. Race/ethnicity	59%	1.75	103.25

*FIP: mean relevance score x frequency.

Falls have been defined as unintentional events, with the result that the person is lying on the floor, the ground or other lower level. The number of falls during the last 12 months was registered (38). The question was formulated as follows: "Have you experienced a fall in the past 12 months?". In the literature, falls are the major marker of instability and RA patients (39).

Comorbidities have been recognised as a significant contributor to the development of frailty (40-44). The Rheumatic Diseases Comorbidity Index (RDCI) was used to identify the load of comorbidities. RDCI was created from patients with RA, osteoarthritis, systemic lupus erythematosus, or fibromyalgia (45). The formula is the following: RDCI = 2* lung disease and [2* ((myocardial infarction, other cardiovascular disease, or stroke)) or 1* hypertension] and 1* (ulcer or other gastrointestinal disease) and 1 for each of the following conditions: diabetes, fracture, depression and cancer (44). To generate a frailty score, comorbidity scores were re-scaled to 0 to 1 (score 0), 2 to 3 (score 0.25), 4 to 5 (score 0.50), 6 to 7 (score 0.75) and score >7 (score =1.0).

Multimorbidity and the concomitant utilisation use of multiple medications (polypharmacy), is common in the RA population. Polypharmacy is associated with adverse outcomes including frailty, mortality, falls, adverse drug reactions, increased length of stay in hospital and readmission to hospital soon after discharge (46, 47). The most commonly reported category of definitions for polypharmacy and associated terms was numerical only. The ques-

tion was formulated as follows: "What medications are you currently taking?". In line with previous studies polypharmacy was defined as five medications or more frailty (48-50), scored 1, while the use of three or four medications was scored 0.5.

To assess the social activities, the item number 20 of the 36-Item Short Form Health Survey (SF36) (51) were rescaled to three (0, 0.5 and 1.0) levels. The question was formulated as follows: "during the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?".

Pain, fatigue, physical function, and depression are also recognised as contributors to frailty by both patients and the group of experts (52-54). These variables are strongly recommended measures both of Outcome Measures in Rheumatology (OMERACT) Patient Perspective Workshop and of American College of Rheumatologists (ACR)/ European League Against Rheumatism classification criteria (EULAR) task force (55, 56). The measurement of these four parameters has proved to be of extreme relevance in rheumatology (57). In the CRAF, the rating of all these four variables has been assigned in six levels (0, 0.2, 0.4, 0.6, 0.8 and 1). Finally, the calculation of the CRAF is based on the sum of the ten variables divided by ten: the score ranges between 0.0 (no deficit present) to 1.0 (all deficits present). The CRAF cut-off points have been established using Clegg's criteria (3), as follow: score ≤0.12 represents patients without frailty; score >0.12 and ≤0.24 represents patients with mild frailty; score >0.24 and ≤0.36 represents patients with moderate frailty; score >0.36 represents patients with severe frailty.

Table II summarises the CRAF variables and cut-off points.

Table II. Variables included in the Comprehensive Rheumatologic Assessment of Frailty (CRAF)*

Variable	Description	CRAF value
1. Nutritional status	Normal/overweight: BMI 25–30 kg/m^2	0.00
	Obese: BMI >30 kg/m^2	0.50
	Underweight: BMI <18.5 kg/m^2	1.00
2. Weakness	Handgrip strength (in kg) in men	
	<27 T-score -2.5 or below	1.00
	≤32 T-score -2 or below	0.50
	>32 Normal grip	0.00
	Handgrip strength (in kg) in women	
	<16 T-score -2.5 or below	1.00
	≤19 T-score -2 or below	0.50
	>19 Normal grip	0.00
3. Falls	Falls less than twice in the last 12 months	0.00
	Falls between two and five times in the last 12 months	0.50
	Falls more than five times in the last 12 months	1.00
4. Comorbidity	RDCI score 0–1	0.00
	RDCI score 2–3	0.25
	RDCI score 4–5	0.50
	RDCI score 6–7	0.75
	RDCI score >7	1.00
5. Polypharmacy	Patient uses less than two different medications	0.00
	Patient uses between three and four different medications	0.50
	Patient uses 5 or more different medications	1.00
6. Social activity	Not at all/slightly	0.00
	Moderately	0.50
	Quite a bit/extremely	1.00
7. Pain	Extreme pain	1.00
	Very severe pain	0.80
	Severe pain	0.60
	Moderate pain	0.40
	Mild pain	0.20
	No pain	0.00
8. Fatigue	Extreme fatigue	1.00
	Very severe fatigue	0.80
	Severe fatigue	0.60
	Moderate fatigue	0.40
	Mild fatigue	0.20
	No fatigue	0.00
9. Physical function	Extreme limitation	1.00
	Very severe limitation	0.80
	Severe limitation	0.60
	Moderate limitation	0.40
	Mild limitation	0.20
	No limitation	0.00
10. Depression	Extreme depression	1.00
	Very severe depression	0.80
	Severe depression	0.60
	Moderate depression	0.40
	Mild depression	0.20
	No depression	0.00

*CRAF score ≤0.12=non frailty, >0.12 to ≤0.24=mild frailty, >0.24 to ≤0.36=moderate frailty, >0.36=severe frailty. RDCI: Rheumatic Disease Comorbidity Index; BMI: Body Mass Index.

Pilot testing of the CRAF index in real-life conditions: construct validity

Between April 2016 and December 2018, the cross-sectional evaluation involved 219 consecutive RA patients from the outpatient clinic of an Italian tertiary rheumatology centre (Rheumatological Clinic, Università Politecnica delle Marche, "Carlo Urbani" Hospital, Jesi, Ancona). All the patients with an adult-onset RA, as defined by the ACR/EULAR criteria, have been involved (58). All patients were receiving at least one conventional disease-modifying anti-rheumatic drug (cDMARD) (methotrexate, leflunomide, sulphasala-

Table III. Demographic, laboratory and clinimetric data of the whole cohort (219 rheumatoid arthritis patients).

	Mean	Standard deviations	Median	25th – 75th percentile
Age (years)	58.54	13.28	56.00	48.00 - 70.00
Disease duration (years)	7.37	2.78	7.00	5.00 - 10.00
Educational level (years)	12.23	3.73	13.00	11.00 - 16.00
BMI (kg/m^2)	26.39	4.48	25.5	23.03 - 28.71
RMDI score (0-11)	1.90	2.01	1.00	0.00 - 4.00
HAQ-DI (0-3)	0.92	0.54	0.87	0.62 - 1.00
TJC (0-28)	8.58	4.98	9.00	5.00 - 12.00
SJC (0-28)	5.22	4.24	4.00	2.00 - 8.00
PhGA (0-10)	6.32	1.92	7.00	6.00 - 8.00
PtGA (0-10)	6.32	1.92	7.00	6.00 - 8.00
CRP (mg/dl)	2.74	3.31	1.80	0.72 - 3.30
SDAI (0-86)	27.11	12.61	25.32	24.40 - 27.84
Fatigue (0-1)	0.42	0.25	0.40	0.20 - 0.60
General Health Status (0-1)	0.39	0.23	0.30	0.20 - 0.60
Pain (0-1)	0.46	0.24	0.40	0.20 - 0.70
Physical function (0-1)	0.31	0.23	0.20	0.20 - 0.40
SHS (0-448)	15.42	15.11	12.00	3.25 - 23.00
CRAF Index (0-1)	0.26	0.22	0.18	0.17 - 0.20
SHARE-FI (0-1)	2.03	2.53	1.08	0.29 - 2.48

BMI: Body Mass Index; RDCI: Rheumatic Diseases Comorbidity Index; HAQ-DI: Health Assessment Questionnaires Disability Index; TJC: 28 joint count for tender joints; SJC: 28 joint count for swollen joints; PtGA: patient assessment of disease activity; PhGA: physician assessment of disease activity; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; SHS: Sharp's method as modified by Sharp-van der Heijde Score; CRAF: Comprehensive Rheumatologic Assessment of Frailty; SHARE-FI: SHARE Frailty Instrument.

zine, or hydroxychloroquine), and/or a biological agent (26.9%). Of the 59 patients receiving a biologic agent, 18 (30.5%) were receiving adalimumab, 17 (28.8%) etanercept, 10 (16.9%) golimumab, 7 (11.9%) abatacept, 5 (8.5%) tocilizumab, and 2 (3.4%) infliximab. Thirty-nine patients (17.8%) were taking oral corticosteroids, at a mean prednisone or equivalent dose of 5.3 mg/day (range 2.5–25), and 111 (50.6%) were prescribed non-steroidal anti-inflammatory drugs (NSAIDs) on demand. A comprehensive questionnaire, including socio-demographic data and disease-related variables was administered to all the patients.

Moreover, all patients underwent a clinimetric assessment to establish disease activity (Simplified Disease Activity Index [SDAI]) (59), functional disability (Health Assessment Questionnaires Disability Index [HAQ-DI]) (60), and radiological damage (Sharp's method as modified by Sharp-van der Heijde Score [SHS]) (61). We have also calculated the Survey of Health Ageing and Retirement in Europe Frailty Index (SHARE-FI), a simple and a globally accepted instrument to screen frailty screening in primary care (62).

Composite disease activity indices

Clinical assessments and laboratory investigations comprised the following single items: 28 joint counts for swollen and tender joints (SJC and TJC, respectively), patient assessment of disease activity (PtGA) and physician global assessment of disease activity (PhGA) on 0–10 numerical rating scales, C-reactive protein (CRP) (mg/dl). These variables were used to compute the SDAI and define disease activity: high disease activity is defined as a SDAI >26, moderate activity as a SDAI >11 and ≤26, low activity as a SDAI ≤11 and >3.3, and remission as a SDAI ≤3.3 (59).

Functional disability

The HAQ-DI evaluates the difficulty in performing daily life activities in eight domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, activities (60). For each action, patients have to rate the level of difficulty over the past week on a 4-point scale (0 = no difficulty; 3 = unable to perform), is then considered the highest score of each domain, the scores are added and divided by eight. To HAQ-DI final score ranges from 0 to 3, with higher scores indicating worse disability.

Radiographic assessment

Radiological damage to the hands, wrists and feet has been assessed by an experienced radiologist (MC) (63), according to SHS. The SHS method assesses erosions and joint space narrowing separately, and ranges from 0 to 448. Thirty-two joints in the hands and 12 in the feet are scored for erosions, with a maximum score of 5 per joint in the hands and 10 per joint in the feet. Joint space narrowing was graded from 0 to 4 in 30 joints in the hands and in 12 joints in the feet (61).

SHARE-FI

The SHARE-FI has been developed on a large European population cohort, is easy to calculate, and gives an immediate estimate of the frailty of the subject. It is freely accessible online (http://www.biomedcentral.com/1471-2318/10/57/additional), and it is based on a phenotypic approach considering fatigue, low appetite, weakness by handgrip strength, difficulties walking or climbing stairs, and low physical activity) (62). A recent systematic review considering frailty screening tools in the primary care setting identified SHARE-FI as a promising instrument (23).

A detailed discussion of the various instruments listed above is beyond the scope of this work and for further information please refer to the respective bibliographic references.

Statistical analysis

Continuous data were presented as means with standard deviations (SDs) or medians and interquartile ranges (IQR), depending on the distribution of the data (tested with the Kolmogorov–Smirnov test). Categorical data were presented as proportions. Demographic and clinical measures were compared using Mann-Whitney U-test or Kruskal-Wallis test for continuous variables, and chi-square analysis for discontinuous variables.

The prevalence of frailty was calculated for CRAF based on Clegg's criteria (3). The construct validity of the CRAF was examined in two ways. Firstly, it has been examined the convergent validity by correlating the scores of the CRAF with those of the SHARE-FI and

other clinical measures applied in the study. The Spearman's rho correlation coefficient was used to quantify these relationships. Correlations >0.90 were interpreted as very high, 0.70–0.89 as high, 0.50–0.69 as moderate, 0.26–0.49 as low, and ≤0.25 as little if any correlation (64). Secondly, it has been analyzed the receiver operating characteristic (ROC) curve to explore the discriminative accuracy of the CRAF and SHARE-FI, to distinguish frail and non-frail patients and using the patient opinion on symptoms state (PASS) as external criterion (65). PASS were recorded as a "yes" or "no" answer to the anchor question: "Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider that your current state is satisfactory?" (66, 67). The area under the ROC curve (AUC) was calculated to quantify the discriminative accuracy. According to Sweets and colleagues, AUCs from 0.50 to 0.70 represent poor accuracy, those from 0.70 and 0.90 are "useful for some purposes", and higher values represent high accuracy (68). From the ROC curve analysis it has been obtained the optimal cut-off point corresponding to the maximum sum of sensitivity and specificity.

Finally, in order to assess the relative contribution of the individual determinants (covariates) such as age, sex, disease duration, level of education, HAQ-DI, and SHS score on the CRAF (as the dependent variable), multivariate logistic regression models procedure has been used. Analysis with backward elimination included variables that yielded *p*-values of 0.1 or lower in the initial univariate analysis. *p*-values <0.05 were considered statistically significant.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

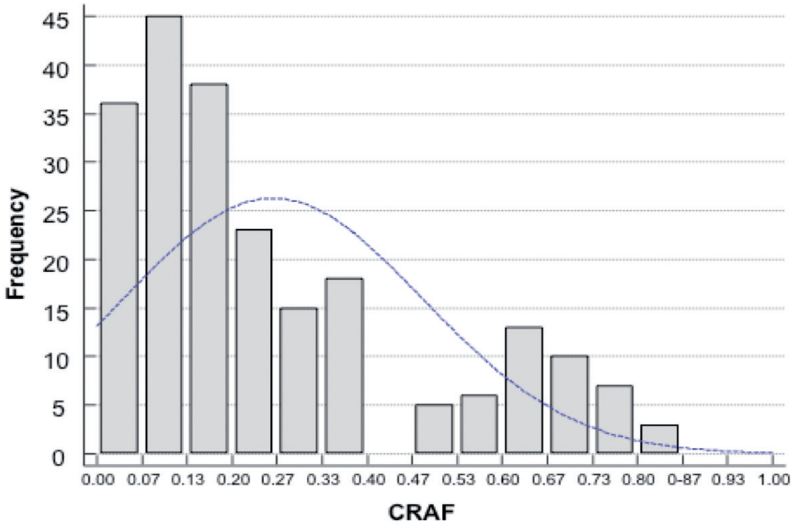

Fig. 1. Distribution of the CRAF scores in the whole cohort (219 rheumatoid arthritis patients).

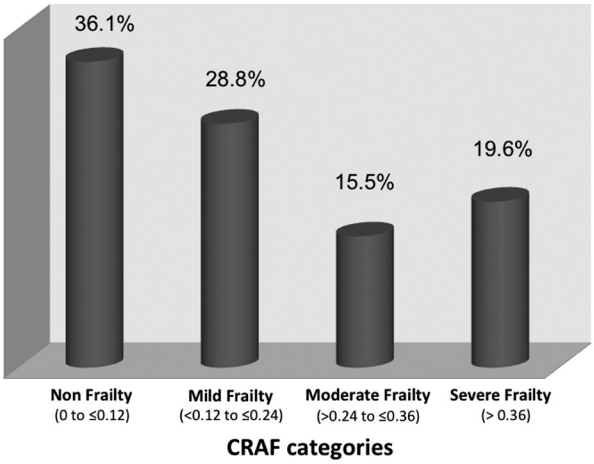

Fig. 2. Percentage distribution of frailty categories in rheumatoid arthritis patients.

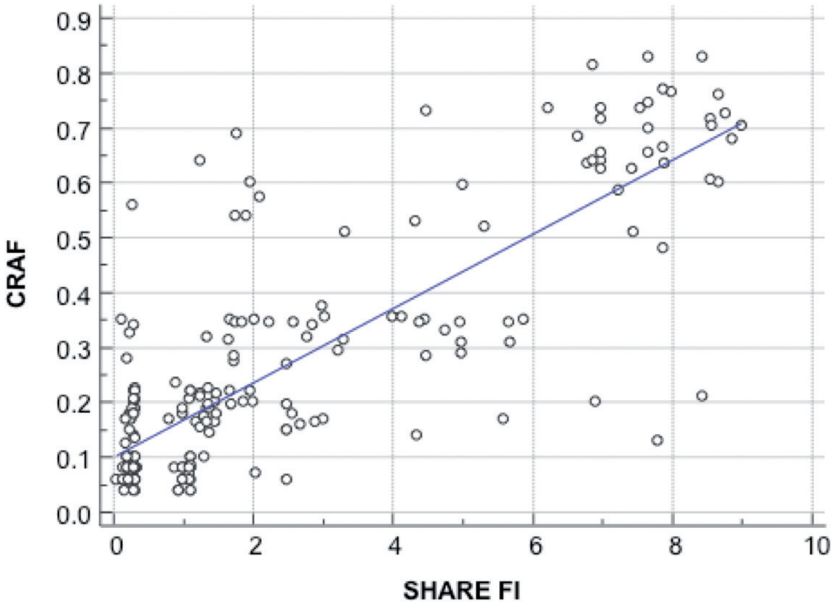

Fig. 3. Scatter plot of the CRAF values *versus* SHARE-FI scores. The analysis indicates a highly significant degree ($p<0.0001$).

Table IV. Convergent validity between instruments: correlation table (Spearman rank correlation coefficient).

	SDAI (0-86)	CRAF (0-1)	Disease duration (years)	Educational level (years)	HAQ-DI (0-3)	SHS (0-448)	SHARE-FI (0-1)
Age (years)	0.560 <0.0001	0.687 <0.0001	0.185 0.0061	-0.185 0.0009	0.522 <0.0001	0.108 0.1095	0.562 <0.0001
SDAI (0-86)		0.634 <0.0001	0.278 0.0001	-0.009 0.1955	0.694 <0.0001	0.061 0.1635	0.622 <0.0001
CRAF (0-1)			0.256 0.0001	-0.200 0.0029	0.700 <0.0001	0.117 0.0850	0.712 <0.0001
Disease duration (years)				-0.084 0.2137	0.236 0.0004	0.706 <0.0001	0.229 0.0006
Educational level (years)					-0.054 0.4251	-0.010 0.8813 219	-0.207 0.0002
HAQ-DI (0-3)						0.067 0.3258	0.550 <0.0001
SHS (0-448)							0.071 0.2987

SDAI: Simplified Disease Activity Index; CRAF: Comprehensive Rheumatologic Assessment of Frailty; HAQ-DI: Health Assessment Questionnaires Disability Index; SHS: Sharp's method as modified by Sharp-van der Heijde Score; SHARE-FI: SHARE Frailty Instrument.

Table V. Factors associated with frailty in multivariate analysis.

Independent variables	Coefficient	Standard error	t	*p*-value
(Constant)	-0.4325			
Age (years)	0.009861	0.0008886	11.097	<0.0001
Disease duration (years)	0.00007498	0.004292	0.0175	0.9861
Educational level (years)	-0.004629	0.002465	-1.878	0.0618
Gender	0.01967	0.01899	1.036	0.3014
SDAI (0-86)	0.005485	0.0008989	6.102	<0.0001
SHS (0-448)	0.0007286	0.0007538	0.966	0.3349

SDAI: Simplified Disease Activity Index; SHS: Sharp's method as modified by Sharp-van der Heijde Score.

Results

Characteristics of the study population

The characteristics of the study population are described in Table III. Briefly, the population consisted of 219 RA patients, 167 women (76.3%) and 52 men (23.7%). The mean value (SD) of age was 58.54 (13.28) years, disease duration 7.37 (2.78) years, and BMI 26.39 (4.48) kg/m^2. The mean (SD) SDAI was 27.11 (12.61), with 13 patients fulfilling the definition of remission, 23 of low disease activity, 90 of moderate disease activity, and 93 of high disease activity. The mean (SD) HAQ-DI 0.92 (0.54).

Of the 219 subjects enrolled, 148 (67.6%) reported 1 or more medical comorbidities, mostly cardiovascular (23.7%), respiratory (15.9%), and metabolic (13.7%) disorders. Polypharmacy was very common in our study population, with the 55.7% of the subjects receiving five medications per day or more, and the 13.7% receiving 10 medications per day or more. The mean number of medications received per day was 5.8 (SD 3.3; min = 0; max = 14).

Fig. 1 presents the estimates of central tendency and distribution of score for CRAF in the whole cohort. CRAF values were non-normally distributed (Kolmogorov-Smirnov test). The median of CRAF index was 0.18 (25–75 percentiles 0.17-0.20) (Table III).

Prevalence of frailty

Among the 219 RA patients, 79 (36.1%) subjects were defined non-frail (CRAF ≤0.12), 63 (28.8%) were defined having a mild frailty (CRAF >0.12 and ≤0.24), 34 (15.5%) were defined having a moderate frailty (CRAF >0.24 and ≤0.36), while the remaining 43 patients (19.6%) were defined having a severe frailty (CRAF >0.36) (Fig. 2), with the CRAF median values significantly different (Kruskal-Wallis test corrected for ties Ht = 202.94; $p<0.0001$) among the four categories. Applying the 0.24 cut-off point (moderate and severe frailty), the estimated prevalence of frailty in RA patients is the 35.1%. As expected, the percentage of frailty increases with age (18.3% in the 50s to 57.1% at age 75s or older).

Construct validity of the CRAF

In testing for convergent validity between instruments (Table IV), it has been found a significant correlation between CRAF and disease activity (SDAI, $p<0.0001$), functional capacity (HAQ-DI, $p<0.0001$), and in addition between CRAF and disease duration ($p=0.0006$) and the level of education ($p=0.0002$) (Table IV).

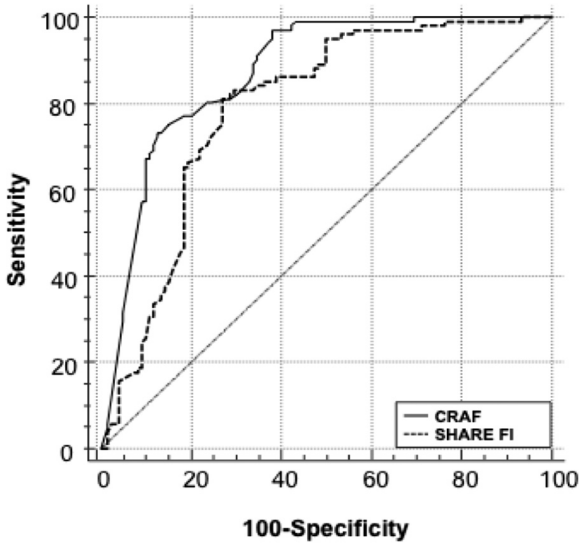

Fig. 4. Receiver operating characteristic (ROC) curve analysis for the CRAF and the SHARE-FI.

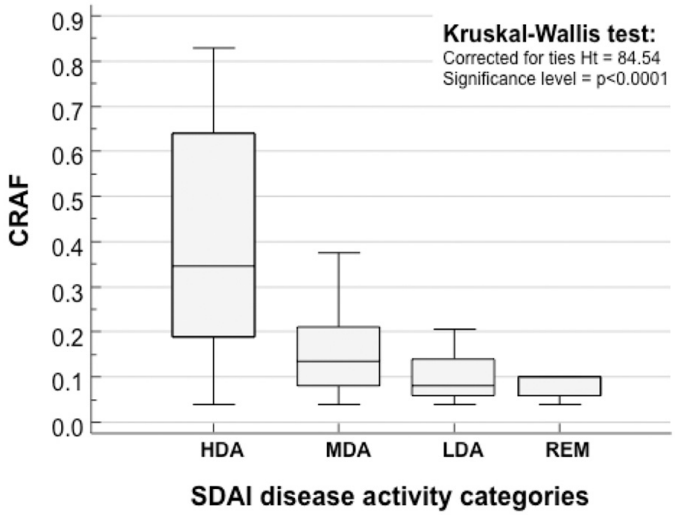

Fig. 5. Box-Whisker plots showing the relation between the CRAF scores and the disease activity states by SDAI, and *p*-values for comparison (Kruskal-Wallis test). The horizontal line in each box in the two top graphs represents the median, and the box height represents the interquartile range. HDA: High disease activity; MDA: moderate disease activity; LDA: low disease activity and REM: remission.

Of special interest, the high correlation between the CRAF and the SHARE-FI at the bivariate analysis (two-tailed Spearman's rank correlation coefficient: 0.712, $p<0.0001$) (Fig. 3).

ROC curve analysis

Fig. 4 shows the ROC curve analysis for the CRAF and the SHARE-FI scores which was carried out to assess the ability for discriminating between frail and non-frail patients for multiple cut-off points. The AUC for CRAF was 0.873 (95% confidence intervals [CI] 0.822–0.914), whereas for the SHARE-FI was 0.788 (95% CI 0.728–0.841). The AUC-ROC curves difference of the two tools was significant (0.0853, 95% CI 0.031–0.141, $p=0.0025$).

Variables associated with CRAF

Factors associated with frailty in multivariate analysis are listed in Table V. They were advanced age and high degree of disease activity measured by SDAI (both at $p<0.0001$). Disease activity was found to be the only clinical RA parameter significantly related to CRAF. Gender, educational level, disease duration and radiographic damage were variables not significantly associated with frailty.

Finally, the CRAF scores were significantly correlated with the four disease activity states of the SDAI ($p<0.0001$) (Fig. 5).

Discussion

In this study we have shown the realisation and completed the preliminary validation of a new tool for the evaluation of frailty in RA patients. To the best of our knowledge, no instruments dedicated to RA have ever been developed before. It has also been revealed that frailty affects a significant proportion of RA patients.

The prevalence of frailty among RA patients is useful information for health and social programme planning. From a medical point of view, the term 'frail' identifies patients with a reduced capacity to effectively compensate for external stresses. As a result, a frail patient is at greater risk of worse outcomes, including prolonged hospitalisation, institutionalisation, increased disability and even greater risk of death (1, 3, 69). Based on the cut-offs identified in this study, it is estimated that 35.1% of RA patients are moderately or severely frail. A percentage of this kind could concern about 100,000 patients in Italy (70). This prevalence of frailty in a non-geriatric cohort is greater than in other studies (1, 12, 69), including studies that have involved patients with at least 10 years more of age (71, 72).

Over the last years, a number of tools have been developed to assess frailty. Many of these tools include estimates of weights that ponder some variables more than others (73). Certain weights preclude the generalisability of other populations (19, 74).

An advantage of the frailty phenotype is the measurement of only five variables (unintentional weight loss, weak grip strength, self-reported exhaustion, slowness and low physical activity level), which makes the fragility assessment relatively rapid (10). An alternative method of measuring frailty is to count the number of deficits accumulated from a given list and divide it by the number of deficits on that list, resulting in a 0–1 score called FI (17). There are currently no universally accepted FI cut-offs. A previous work used 0.21, 0.25 and 0.35 for community seniors (19.75–77). Rockwood and colleagues

proposed scores below 0.08 as "non-frailty" and scores above 0.25 as "frailty", considering intermediate scores as "pre-frailty" (19). In another study by Rockwood and coworkers have been proposed values of FI ≤0.03 as 'relatively fit', 0.03 <FI ≤0.10 as 'less fit', 0.10 <FI ≤0.21 as 'less fit', 0.21 <FI ≤0.45 as 'frail', and FI ≥0.45 as 'more frail' (76). In the present study, CRAF cut-off points have been classified using the Clegg criteria (3).

RA predisposes to many of the factors that make up the definition of the model of cumulative deficit of frailty (78-80). Which factors to include in the definition of frailty is a controversial topic with important implications. For example, while some authors have included disability and functional decline as a component of frailty (16, 22), others consider these two parameters as a result (81). However, it is significant to note that disability and frailty are different entities, and being disabled is not a prerequisite for frailty (40).

In 2010, Romero-Ortuno and colleagues proposed a new frailty screening tool for primary care: the SHARE-FI (82). The SHARE-FI has been applied to large-scale health survey data in several countries (73, 75, 83, 84). However, it has never been validated in patients with RA and under 50 years of age.

The present study has attempted to fill the gap caused by the absence of dedicated tools for RA. The methodology for the implementation of the CRAF was based on established methods, starting from a survey of 39 specialists who were asked to give importance to the various domains potentially responsible for fragility in patients with RA: nutritional status, weakness, falls, comorbidity, polypharmacy, social activity, pain, fatigue, physical function, and depression.

For nutrition, overweight and normal weight have been combined and coded at 0, on the basis of evidence that a small excess weight can be protective (31, 32). Underweight was coded 1.0, in line with previous studies that revealed that low weight elderly people are at higher risk of disease and death, while obesity was coded 0.5 (32). Excess adipose tissue has been identified as a potential risk factor for fragility in both cohorts of elderly and chronic diseases (85). Obesity can also be associated with sarcopenia (sarcopenic obesity), and even in this case the altered lean mass/fat mass ratio is associated with frailty in the elderly (86, 87). Sarcopenia increases the risk of falls and consequently fractures, hinders the ability to perform daily activities, is associated with heart and respiratory diseases, cognitive deficits, can lead to loss of autonomy or the need for long-term care (16, 87).

Impairment of grip strength during RA may be important, and has been shown to correlate with activity and duration of disease (88-91). Measuring grip strenght is simple and economical. However, its accurate measurement requires the use of a calibrated electronic gripper, with interpretative values from appropriate reference populations (92). The current recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP) use as reference values those of -2 standard deviations (19 kg in females and 32 kg in males) from the mean reference value (35, 87). For a more conservative diagnosis the use of -2.5 standard deviations (equivalent to 16 kg in females and 27 kg in males) is suggested (35, 93-97).

Falls are an important indicator of instability. Although there are data suggesting that RA patients, regardless of age, are at high risk of falling (39, 94), a higher prevalence of falls has been demonstrated in RA patients over 65 years of age than in younger patients (95), also giving RA patients an increased risk of death (98).

Patients with RA are also at greater risk of developing comorbidity (99), and consequently more exposed to polypharmacy. Polypharmacy in turn increases the risk of inappropriate prescriptions, drug and drug interactions (100, 101), and thus the risk of adverse health events (102-104). The polypharmacy is therefore considered as a risk factor for frailty in various instruments (22, 49, 105, 106). Muntinga and colleagues have stated that polypharmacy is a necessary requirement for frailty (107).

Pain, fatigue, physical function and depression are other important indicators from the patient's point of view (55, 56). Pain limits the ability to walk, increasing the risk of falls and consequently can precipitate fragility (108, 109). Disability remains one of the most important consequences of RA (60). Persistent inflammation can cause joint deformities, muscle atrophy and subsequent muscle weakness, decreasing capacities in all activities require gripping strenght (110). The prevalence of fatigue in RA has been reported to be 40-80% (111,112). The importance of fatigue in RA is underlined by the fact that fatigue is a predictor of reduced quality of life, deterioration of physical and mental health, and premature mortality (53).

A coexisting depression has an overall negative impact on the health of patients with RA (20,113). It has been estimated that 16.7% of patients with RA meet the diagnostic criteria for major depression disorder. Chronic pain is a risk factor in the development of depression (115). Depressive symptoms translate into increased disability, resulting in frailty (116). Conversely, depression can be an early symptom of frailty (117).

In the implementation and preliminary validation of CRAF, certain limits should be mentioned. This is a cross-sectional study, and no data were available from a comparative control group of individuals without RA. Frailty can be a dynamic process with a fluctuating pattern. In addition, the cut-offs of many of the multiple-level variables included in the CRAF have been arbitrarily defined. A prospective and multi-centre assessment will be needed to fully define the consistency of CRAF.

References

1. HAIDER S, GRABOVAC I, BERNER C *et al*.: Frailty in seropositive rheumatoid arthritis patients of working age: a cross-sectional study. *Clin Exp Rheumatol* 2019; 37: 585-92.
2. RODRIGUEZ-MANAS L, FEART C, MANN G *et al*.: Searching for an operational definition of frailty: A Delphi method based consensus statement. The Frailty Operative Definition-Consensus Conference Project. *J Gerontol A Biol Sci Med Sci* 2013; 68A: 62-67.
3. CLEGG A, BATES C, YOUNG J *et al*.: Development and validation of an electronic frailty index using routine primary care

electronic health record data. *Age Ageing* 2016; 45: 353-60.
4. HIPPISLEY-COX J, COUPLAND C: Development and validation of QMortality risk prediction algorithm to estimate short term risk of death and assess frailty: cohort study. *BMJ* 2017; 358: j4208.
5. AUYEUNG TW, LEE JS, KWOK T *et al*.: Physical frailty predicts future cognitive decline: A four-year prospective study in 2737 cognitively normal older adults. *J Nutr Health Aging* 2011; 15: 690-94.
6. MITNITSKI A, FALLAH N, ROCKWOOD MR *et al*.: Transitions in cognitive status in relation to frailty in older adults: A comparison of three frailty measures. *J Nutr Health Aging* 2011; 15: 863-67.
7. HURRIA A, TOGAWA K, MOHILE SG *et al*.: Predicting chemotherapy toxicity in older adults with cancer: A prospective multicenter study. *J Clin Oncol* 2011; 29: 3457-65.
8. MAKARY MA, SEGEV DL, PRONOVOST PJ *et al*.: Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; 10: 901-8.
9. HASTINGS SN, PURSER JL, JOHNSON KS *et al*.: Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. *J Am Geriatr Soc* 2008; 56: 1651-57.
10. FRIED LP, TANGEN CM, WALSTON J *et al*.: Frailty in older adults: Evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146-56.
11. CLEUTJENS FAHM, BOONEN AERCH, VAN ONNA MGB: Geriatric syndromes in patients with rheumatoid arthritis: a literature overview. *Clin Exp Rheumatol* 2018 [Epub ahead of print].
12. ANDREWS JS, TRUPIN L, YELIN EH *et al*.: Frailty and reduced physical function go hand in hand in adults with rheumatoid arthritis: a US observational cohort study. *Clin Rheumatol* 2017; 36: 1031-39.
13. SALAFFI F, DI CARLO M, FARAH S, DI DONATO E, CAROTTI M: Prevalence of frailty and its associated factors in patients 6 with rheumatoid arthritis: a cross-sectional analysis. *Clin Rheumatol* 2019; 38: 1823-30.
14. CONROY S: Defining frailty--the Holy Grail of geriatric medicine. *J Nutr Health Aging* 2009; 13: 389.
15. MOORHOUSE P, ROCKWOOD K: Frailty and its quantitative clinical evaluation. *J R Coll Physicians Edinb* 2012; 42: 333-40.
16. MITNITSKI AB, MOGILNER AJ, ROCKWOOD K: Accumulation of deficits as a proxy measure of aging. *Scientific World Journal* 2001; 1: 323-36.
17. SEARLE SD, MITNITSKI A, GAHBAUER EA *et al*.: A standard procedure for creating a frailty index. *BMC Geriatrics* 2008; 8: 24.
18. HOOVER M, ROTERMANN M, SANMARTIN C, BERNIER J: Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. *Health Rep* 2013; 24: 10-17.
19. SONG X, MITNITSKI A, ROCKWOOD K: Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010; 58: 681-87.
20. LI G, PAPAIOANNOU A, THABANE L, CHENG J, ADACHI JD: Frailty change and major osteoporotic fracture in the elderly: data from the Global Longitudinal Study of Osteoporosis in Women 3-Year Hamilton Cohort. *J Bone Miner Res* 2016; 31: 718-24.
21. DE VRIES NM, STAAL JB, VAN RAVENSBERG CD, HOBBELEN JSM, OLDE RIKKERT MGM, NIJHUIS-VAN DER SANDEN MWG: Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011; 10: 104-14.
22. ROCKWOOD K, MITNITSKI A: Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; 27: 17-26.
23. PIALOUX T, GOYARD J, LESOURD B: Screening tools for frailty in primary health care: a systematic review. *Geriatr Gerontol Int* 2012; 12: 189-97.
24. STEWART J, O'HALLORAN C, HARRIGAN P: Identifying appropriate tasks for the preregistration year: modified Delphi technique. *BMJ* 1999; 319: 224-29.
25. SALAFFI F, BAZZICHI L, STANCATI A *et al*.: Development of a functional disability measurement tool to assess early arthritis: the Recent-Onset Arthritis Disability (ROAD) questionnaire. *Clin Exp Rheumatol* 2005; 23: 628-36.
26. SALAFFI F, SILVERI F, STANCATI A, GRASSI W: Development and validation of the osteoporosis prescreening risk assessment (OPERA) tool to facilitate identification of women likely to have low bone density. *Clin Rheumatol* 2005; 24: 203-11.
27. SALAFFI F, DI CARLO M, LUCHETTI MM *et al*.: A validation study of the Simple Psoriatic Arthritis Screening (SiPAS) questionnaire to screen psoriasis patients for psoriatic arthritis. *Clin Exp Rheumatol* 2018; 36: 127-35.
28. DI CARLO M, LUCHETTI MM, BENFAREMO D *et al*.: The DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire: development and preliminary testing of a new tool to screen patients with inflammatory bowel disease for the presence of spondyloarthritis. *Clin Rheumatol* 2018; 37: 1037-44.
29. GOBBENS RJ, VAN ASSEN MA, LUIJKX KG, SCHOLS JM: Testing an integral conceptual model of frailty. *J Adv Nurs* 2012; 68: 2047-60.
30. LYNN MR: Determination and quantification of content validity. *Nursing Res* 1986; 35:382-385.
31. WEISS A, BELOOSESKY Y, BOAZ M *et al*.: Body mass index is inversely related to mortality in elderly subjects. *J Gen Intern Med* 2008; 23: 19-24.
32. GARNER RE, FEENY DH, THOMPSON A *et al*.: Bodyweight, gender, and quality of life: a population-based longitudinal study. *Qual Life Res* 2012; 21: 813-25.
33. BOHANNON RW: Is it legitimate to characterize muscle strength using a limited number of measures? *J Strength Cond Res* 2008; 22: 166e173.
34. LEONG DP, TEO KK: Predicting cardiovascular disease from handgrip strength: the potential clinical implications. *Expert Rev Cardiovasc Ther* 2015; 13: 1277-79.
35. DODDS RM, SYDDALL HE, COOPER R *et al*.: Grip strength across the life course: normative data from twelve British studies. *PLoS One* 2014; 9 :e113637.
36. LAURETANI F, RUSSO CR, BANDINELLI S *et al*.: Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* 2003; 95: 1851-60.
37. KANIS J: Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 2002; 359:1929-1936.
38. KIRKHUS L, ŠALTYTĖ BENTH J, ROSTOFT S *et al*.: Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. *Br J Cancer* 2017; 117:470-477.
39. STANMORE EK, OLDHAM J, SKELTON DA *et al*.: Risk factors for falls in adults with rheumatoid arthritis: a prospective study. *Arthritis Care Res* (Hoboken) 2013; 65: 1251-58.
40. FRIED LP, FERRUCCI L, DARER J, WILLIAMSON JD, ANDERSON G: Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59: 255-63.
41. GRANT JF, TAYLOR AW, RUFFIN RE *et al*.: Cohort profile: The North West Adelaide Health Study (NWAHS). *Int J Epidemiol* 2009; 38 :1479-86.
42. SANDERS JL, BOUDREAU RM, FRIED LP, WALSTON JD, HARRIS TB, NEWMAN AB: Measurement of organ structure and function enhances understanding of the physiological basis of frailty: The Cardiovascular Health Study. *J Am Geriatr Soc* 2011; 59: 1581-88.
43. WONG CH, WEISS D, SOURIAL N *et al*.: Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. *Aging Clin Exp Res* 2010; 22: 54-62.
44. ENGLAND BR, SAYLES H, MIKULS TR, JOHNSON DS, MICHAUD K: Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* (Hoboken) 2015; 67: 865-72.
45. MICHAUD K, WOLFE F: Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007; 21: 885-906.
46. MILTON JC, HILL-SMITH I, JACKSON SHD: Prescribing for older people. *BMJ* 2008; 336:606-609.
47. CAUGHEY GE, ROUGHEAD EE, VITRY AI, MCDERMOTT RA, SHAKIB S, GILBERT AL: Comorbidity in the elderly with diabetes: identification of areas of potential treatment conflicts. *Diabetes Res Clin Pract* 2010; 87: 385-93.
48. GNJIDIC D, HILMER SN, BLYTH FM *et al*.: Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012; 65: 989-95.
49. HERR M, ROBINE JM, PINOT J, ARVIEU JJ, ANKRI J: Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. *Pharmacoepidemiol Drug Saf* 2015; 24: 637-46.
50. KNOPF H, GRAMS D: Medication use of adults in Germany: results of the German

health interview and examination survey for adults (DEGS1). *Bundesgesundheitsbl* 2013; 56: 868-77.
51. MCHORNEY CA, WARE JE JR, LU JF, SHERBOURNE CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; 32: 40-66.
52. THAPA S, SHMERLING RH, BEAN JF, CAI Y, LEVEILLE SG: Chronic multisite pain: evaluation of a new geriatric syndrome. *Aging Clin Exp Res* 2018 [Epub ahead of print].
53. MOREH E, JACOBS JM, STESSMAN J: Fatigue, function, and mortality in older adults. *J Gerontol A Biol Sci Med Sci* 2010; 65: 887-95.
54. HARDY SE, STUDENSKI SA: Fatigue predicts mortality in older adults. *J Am Geriatr Soc* 2008; 56: 1910-14.
55. KIRWAN JR, MINNOCK P, ADEBAJO A *et al*.: Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007; 34: 1174-77.
56. ALETAHA D, LANDEWÉ R, KARONITSCH T *et al*.: Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum* 2008; 59: 1371-77.
57. SALAFFI F, DI CARLO M, CAROTTI M, FARAH S: The Patient-Reported Outcomes Thermometer-5-Item Scale (5T-PROs): validation of a new tool for the quick assessment of overall health status in painful rheumatic diseases. *Pain Res Manag* 2018; 2018: 3496846.
58. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
59. ALETAHA D, SMOLEN J: The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: S100-108.
60. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
61. VAN DER HEIJDE DM, VAN RIEL PL, NUVER ZWART IH, GRIBNAU FW, VAN DE PUTTE LB: Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; 1(8646): 1036-38.
62. SANTOS-EGGIMANN B, CUENOUD P, SPAGNOLI J, JUNOD J: Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci* 2009; 64: 675-81.
63. SALAFFI F, CAROTTI M, BECI G, DI CARLO M, GIOVAGNONI A: Radiographic scoring methods in rheumatoid arthritis and psoriatic arthritis. *Radiol Med* 2019 [Epub ahead of print].
64. NUNNALLY JC: Psychometric Theory. 2nd ed. 1978; New York: McGraw Hill.
65. MAKSYMOWYCH WP, RICHARDSON R, MALLON C *et al*.: Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. *Arthritis Care Res* 2007; 57: 133-39.
66. SALAFFI F, CAROTTI M, GUTIERREZ M, DI CARLO M, DE ANGELIS R: Patient Acceptable Symptom State in Self-Report Questionnaires and Composite Clinical Disease Index for Assessing Rheumatoid Arthritis Activity: Identification of Cut-Off Points for Routine Care. *Biomed Res Int* 2015; 2015: 930756.
67. TUBACH F, RAVAUD P, BEATON D *et al*.: Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. *J Rheumatol* 2007; 34: 1188-93.
68. SWETZ JA: Measuring accuracy of diagnostic systems. *Science* 1988; 240: 1285-93.
69. BARILE-FABRIS LA, PEREZ-CRISTOBAL M, MERLOS-LOPEZ RJ, XIBILLE-FRIEDMAN D: Frailty syndrome in patients with rheumatoid arthritis. *Rev Med Inst Mex Seguro Soc* 2016; 54: S210-15.
70. SALAFFI F, DE ANGELIS R, GRASSI W; MARCHE PAIN PREVALENCE; INVESTIGATION GROUP (MAPPING) STUDY: Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 2005; 23: 819-28.
71. CAWTHON PM, MARSHALL LM, MICHAEL Y *et al*.: Frailty in older men: prevalence, progression, and relationship with mortality. *J Am Geriatr Soc* 2007; 55: 1216-23.
72. BANDEEN-ROCHE K, XUE QL, FERRUCCI L *et al*.: Phenotype of frailty: characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci* 2006; 61: 262-66.
73. KAMARUZZAMAN S, PLOUBIDIS GB, FLETCHER A *et al*.: A reliable measure of frailty for a community dwelling older population. *Health Qual Life Outcomes* 2010; 8: 123.
74. GUTIÉRREZ-VALENCIA M, IZQUIERDO M, CESARI M, CASAS-HERRERO Á, INZITARI M, MARTÍNEZ-VELILLA N: The relationship between frailty and polypharmacy in older people: A systematic review. *Br J Clin Pharmacol* 2018; 84: 1432-44.
75. ROCKWOOD K, ANDREW M, MITNITSKI A: A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007; 62: 738-43.
76. ROCKWOOD K, SONG X, MITNITSKI A: Changes in relative fitness and frailty across the adult lifespan: Evidence from the Canadian National Population Health Survey. *CMAJ* 2011; 183: E487-94.
77. KULMINSKI AM, UKRAINTSEVA SV, KULMINSKAYA IV *et al*.: Cumulative deficits better characterize susceptibility to death in the elderly than phenotypic frailty: Lessons from the Cardiovascular Health Study. *J Am Geriatr Soc* 2008; 56: 898-903.
78. BAKER JF, VON FELDT J, MOSTOUFI-MOAB S *et al*.: Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2014; 66: 1612-18.
79. GILES JT, BARTLETT SJ, ANDERSEN RE, FONTAINE KR, BATHON JM: Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. *Arthritis Rheum* 2008; 59: 1407-15.
80. KRAMER HR, FONTAINE KR, BATHON JM, GILES JT: Muscle density in rheumatoid arthritis: associations with disease features and functional outcomes. *Arthritis Rheum* 2012; 64: 2438-50.
81. CARRIERE I, COLVEZ A, FAVIER F *et al*.: Hierarchical components of physical frailty predicted incidence of dependency in a cohort of elderly women. *J Clin Epidemiol* 2005; 58: 1180-87.
82. ROMERO-ORTUNO R, WALSH CD, LAWLOR BA, KENNY RA: A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC Geriatr* 2010; 10: 57.
83. YANG Y, LEE LC: Dynamics and heterogeneity in the process of human frailty and aging: Evidence from the U.S. older adult population. *J Gerontol B Psychol Sci Soc Sci* 2010; 65B: 246-55.
84. WOO J, GOGGINS W, SHAM A, HO SC: Public health significance of the Frailty Index. *Disabil Rehabil 2006*; 28: 515-21.
85. REINDERS I, VISSER M, SCHAAP L: Body weight and body composition in old age and their relationship with frailty. *Curr Opin Clin Nutrition Metab Care* 2017; 20: 11-15.
86. HIRANI V, NAGANATHAN V, BLYTH F *et al*.: Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: The Concord Health and Ageing in Men Project. *Age Ageing* 2016; 46: 413-20.
87. CRUZ-JENTOFT AJ, BAHAT G, BAUER J *et al*.: Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; 48: 16-31.
88. BODUR H, YILMAZ O, KESKIN D: Hand disability and related variables in patients with rheumatoid arthritis. *Rheumatol Int* 2006; 26: 541-44.
89. FIEBERT IM RK, ARMSTRONG T, MANDEL DW, DONOHUE M: Dynamometric grip strength assessment of subjects sixty year and older. *Phys Occup Ther Geriatr* 1995; 13: 27-40.
90. SPIEGEL TM, SPIEGEL JS, PAULUS HE: The joint alignment and motion scale: a simple measure of joint deformity in patients with rheumatoid arthritis. *J Rheumatol* 1987; 14: 887-92.
91. LEONG DP, TEO KK, RANGARAJAN S *et al*.: Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet* 2015; 386:266-273.
92. ROBERTS HC, DENISON HJ, MARTIN HJ *et al*.: A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011; 40: 423-29.
93. STEVENS JA, BALLESTEROS MF, MACK KA, RUDD RA, DECARO E, ADLER G: Gender differences in seeking care for falls in the aged Medicare population. *Am J Prev Med* 2012; 43: 59-62.
94. ZONZINI GAINO J, BARROS BÉRTOLO

M, SILVA NUNES C *et al*.: Disease-related outcomes influence prevalence of falls in people with rheumatoid arthritis. *Ann Phys Rehabil Med* 2019; 62: 84-91.
95. YAMAGIWA K, IIJIMA S, FURUYA T *et al*.: Incidence of falls and fear of falling in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2011; 21: 51-56.
96. BOHLER C, RADNER H, ERNST M *et al*.: Rheumatoid arthritis and falls: the influence of disease activity. *Rheumatology* (Oxford) 2012; 51: 2051-57.
97. BRENTON-RULE A, DALBETH N, MENZ HB, BASSETT S, ROME K: Are foot and ankle characteristics associated with falls in people with rheumatoid arthritis? A prospective study. *Arthritis Care Res* (Hoboken) 2017; 69: 1150-55.
98. OMETTO F, FEDELI U, SCHIEVANO E, BOTSIOS C, PUNZI L, CORTI MC: Cause-specific mortality in a large population-based cohort of patients with rheumatoid arthritis in Italy. *Clin Exp Rheumatol* 2018; 36: 636-42.
99. DOUGADOS M, SOUBRIER M, ANTUNEZ A *et al*.: Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014; 73: 62-68.
100. BRADLEY MC, MOTTERLINI N, PADMANABHAN S *et al*.: Potentially inappropriate prescribing among older people in the United Kingdom. *BMC Geriatr* 2014; 14:72.
101. FIALOVA D, ONDER G: Medication errors in elderly people: contributing factors and future perspectives. *Br J Clin Pharmacol* 2009; 67: 641-45.
102. HARTIKAINEN S, LONNROOS E, LOUHIVUORI K: Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci* 2007; 62: 1172-81.
103. JYRKKA J, ENLUND H, LAVIKAINEN P, SUL-KAVA R, HARTIKAINEN S: Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf* 2011; 20: 514-22.
104. WALLACE E, STUART E, VAUGHAN N, BENNETT K, FAHEY T, SMITH SM: Risk prediction models to predict emergency hospital admission in community-dwelling adults: a systematic review. *Med Care* 2014; 52: 751-65.
105. FRIED TR, MECCA MC: Medication appropriateness in vulnerable older adults: healthy skepticism of appropriate polypharmacy. *J Am Geriatr Soc* 2019; 10: 2042098618815431.
106. ROLFSON DB, MAJUMDAR SR, TSUYUKI RT, TAHIR A, ROCKWOOD K: Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006; 35: 526-29.
107. MUNTINGA ME, HOOGENDIJK EO, VAN LEEUWEN KM *et al*.: Implementing the chronic care model for frail older adults in the Netherlands: study protocol of ACT (frail older adults: care in transition). *BMC Geriatr* 2012; 12: 19.
108. WADE KF, MARSHALL A, VANHOUTTE B, WU FC, O'NEILL TW, LEE DM: Does pain predict frailty in older men and women? Findings from the English Longitudinal Study of Ageing (ELSA). *J Gerontol A Biol Sci Med Sci* 2017; 72: 403-9.
109. VERONESE N, MAGGI S, TREVISAN C *et al*.: Pain increases the risk of developing frailty in older adults with osteoarthritis. *Pain Med* 2017; 18: 414-27.
110. EBERHARDT KB, SVENSSON B, MORTIZ U: Functional assessment of early rheumatoid arthritis. *Br J Rheumatol* 1988; 27: 364-71.
111. SOUBRIER M, DOUGADOS M: Selecting criteria for monitoring patients with rheumatoid arthritis. *Joint Bone Spine* 2005; 72: 129-34.
112. PREVOO ML, VAN 'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-4.
113. NÍ MHAOLÁIN AM, FAN CW, ROMERO-ORTUNO R *et al*.: Frailty, depression, and anxiety in later life. *Int Psychogeriatr* 2012; 24: 1265-74.
114. MATCHAM F, RAYNE, STEER S, HOTOPF M: The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2013; 52:2136-2148.
115. BAIR MJ, ROBINSON RL, KATON W, KROENKE K: Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003; 163: 2433-45.
116. APRAHAMIAN I, SUEMOTO CK, LIN SM: Depression is associated with self-rated frailty in older adults from an outpatient clinic: a prospective study. *Int Psychogeriatr* 2018; 13: 1-10.
117. MEZUK B, EDWARDS L, LOHMAN M, CHOI M, LAPANE K: Depression and frailty in later life: a synthetic review. *Int J Geriatr Psychiatry* 2012; 27: 879-92.