Frailty in seropositive rheumatoid arthritis patients of working age: a cross-sectional study

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Abstract

Objective

The prevalence of frailty has been widely researched in the elderly population. However, data about people of working age are scarce. The aim of this paper was to assess the prevalence of prefrailty and frailty in rheumatoid arthritis (RA) patients of working age, and to assess factors associated with prefrailty/frailty.

Methods

In this monocentric cross-sectional study, 100 RA patients aged 18–65 years were included. Frailty was measured with the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI) and disease activity with the Clinical Disease Activity Index (CDAI). In addition, disease duration (years), pain intensity (visual analogue scale) and employment status were also assessed.

Results

Fifty-five percent were robust, 30% prefrail and 15% were frail. Eighty-nine of the prefrail/frail individuals suffered from exhaustion. Compared to robust individuals, the prefrail/frail individuals had significantly higher median scores in disease activity [4.0 (Q_{25}–Q_{75}: 0–10) vs. 11 (Q_{25}–Q_{75}: 6–18)] and pain intensity [3.0 (Q_{25}–Q_{75}: 2.0–4.0) vs. 4.0 (Q_{25}–Q_{75}: 2.8–6.3)] and a higher rate of unemployment [31% vs. 53%]. In the multivariable analysis, higher disease activity (β=0.444; p<0.001), unemployment (β=0.243; p=0.005), higher pain intensity (β=0.186; p=0.060) and longer disease duration (β=0.181; p=0.020) were associated with a higher frailty score.

Conclusion

Frailty is common in RA patients, even those of working age. As the prevalence of frailty increases with age, it is important to take this syndrome into account in younger persons and to take action to counteract frailty.

Key words

frailty, rheumatoid arthritis, SHARE-FI

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Introduction

Rheumatoid arthritis (RA) is a systemic chronic autoimmune disease, and the most common form of chronic joint inflammation (1). The onset of this disease usually appears between the ages of 30 to 60 (2), and the disease is characterised by exhaustion, pain and physical disability, which have a higher prevalence in severe disease progression and longer disease duration (3). RA is also characterised by increased proinflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α). RA patients have reduced muscle strength, impaired physical function (4) and suffer from loss of muscle mass, which is known as rheumatoid cachexia (5). Based on the available literature, the maximum strength of the hip and the knee, for both extension as well as flexion, is approximately 75% that of the non-RA population (4).

Frailty, which was originally considered a geriatric syndrome (6), is also associated with reduced muscle strength, exhaustion and with high inflammatory markers (7, 8), contributing to perpetuation of the frailty cycle (9). There are different tools used to assess frailty (9, 10). One of them is the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI), which was developed in the SHARE study, and validated for people aged ≥50 years in primary care (11). This tool comprises assessment of muscle strength, exhaustion, loss of appetite, functional difficulties and physical activity. Dependent on cut-off values, a sex-specific frailty index is calculated, dividing individuals into robust, prefrail (an early stage of frailty) and frail.

As loss of muscle strength and muscle mass, exhaustion and increased inflammatory markers are common in RA patients, we hypothesise that frailty is also prevalent in RA patients, even those of working age. However, the prevalence of frailty in young RA patients has, to the best of our knowledge, only been examined once before (12). Furthermore, only a few studies have assessed the frailty status in the younger population. A recent study in Canada, for example, showed that the prevalence of frailty in patients with type 2 diabetes was 12.9%, and in cancer patients it reached 13.4% (13). In ambulatory patients with chronic obstructive pulmonary disease, 6.6% were considered to be frail (14). There are, however, some studies that have described the frailty prevalence in younger patients with human immunodeficiency virus infection (15, 16). In addition, the study of Althoff *et al*. (17) assessed 12% of men aged an average of 53.8 years to be frail. In contrast to the younger population, many studies have looked at the frailty status in older individuals. In very old individuals aged an average of 83.2 years living in nursing homes, frailty prevalence was shown to be 24.7%, and 61.4% were considered to be prefrail (18). One study did assess the frailty status of community-dwelling people above 65 years in Austria, and the results showed that 10.8% were frail and 40.7% were prefrail (19).

Hence, the aim of the present study was to assess the prevalence of prefrailty and frailty and the associated demographic and clinical factors in seropositive RA patients of working age.

Materials and methods

Study design

We performed a monocentric cross-sectional study at the outpatient clinic of the Second Medical Division, Kaiser Franz Josef Hospital, SMZ Süd (Austria, Vienna), from November 2015 till August 2016 (20). The primary outcome parameter of this study was the level of workability (20), which was shown to be associated with muscle strength and lower extremity function (21). As described in the study protocol, frailty status, muscle strength and inflammatory parameters were assessed as secondary parameters. All the measurements, expect for disease activity and inflammatory parameters, were performed by a study nurse. The addressed parameters were assessed by a medical doctor. The study complied with the Declaration of Helsinki (22), and ethical clearance was given by the local ethics committee of the Gemeinde-Wien (EK 15-173-0915). Written informed consent was given by all participants. The study was also registered at ClinicalTrials.gov (NCT02581852).

Participants

Participants were recruited at the outpatient clinic while waiting for their appointments (20). In the last year about 3600 patients came to the ward, 51% presented for the first time. Twenty two percent of all patients suffer from RA, 13% from osteoporosis, 9% from arthralgia. Other illnesses treated in this outpatient clinic were collagenosis, spondyloarthritis, psoriatic arthritis. Patients fulfilling the following criteria were included: 1) age ≥18 and ≤65 years; 2) RA according to the 2010 European League Against Rheumatism (EULAR) classification for seropositive RA (23); 3) sufficient knowledge of the German or English language to understand advice regarding the physical measurements, and sufficient knowledge of German, English, Serbo-Croatian or Turkish to fill in the questionnaire. Persons with the following criteria were excluded: 1) refusal or not able to sign the informed consent; 2) severe comorbidities (cancer, severe cardiovascular illness) and 3) concomitant variables affecting hand grip strength.

Measurements

- Sociodemographic data: Demographic data, including sex, age, marital status, education level and employment status, were collected.
- Frailty status – Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI): Frailty status was assessed with the *Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI)* (11). SHARE-FI is a sex-specific calculator based on the frailty criteria of Fried and colleagues, including questions concerning exhaustion, loss of appetite, functional difficulties and low physical activity (24). The fifth parameter, weakness, expressed as handgrip strength, was measured with a portable hydraulic hand dynamometer (Patterson Medical®). According to the protocol, patients were seated upright with their upper arm adducted and the elbow flexed at 90° (25). After receiving instructions, patients were asked to contract with maximum voluntary strength. Measurements were done with both hands alternating, with a 2-minute break between measurements. The maximum value was taken for analysis. Based on these five items, the discreet factor (DFactor) score (DFS) was calculated as follows (11):
  - DFS (males) = (2.280336 * exhaustion – 0.592393) * 0.3762 + (4.058274 * loss of appetite – 0.263501) * 0.3130 + (0.092326 * grip strength – 3.986646) * – 0.4653 + (3.098226 * functional difficulties – 0.365971) * 0.6146 + (1.005942 * physical activity – 1.571803) * 0.4680
  - DFS (females) = (2.077707 * exhaustion – 0.757295) * 0.4088 + (3.341539 * loss of appetite – 0.332289) * 0.3325 + (0.132827 * grip strength – 3.534515) * – 0.4910 + (2.627085 * functional difficulties – 0.461808) * 0.6012 + (0.918866 * physical activity – 1.523633) * 0.4818

  Based on the DFS, patients were divided into sex-specific categories (11):
  - Cut-off (males)
    DFS <1.211878526 robust
    DFS <3.0052612772 prefrail
    DFS <7 frail
  - Cut-off (females)
    DFS <0.3151361243 robust
    DFS <2.1301121973 prefrail
    DFS <6 frail

  In addition, handgrip strength was categorised as over and under the sex- and age-specific reference values (26).
  - *Knee extensor strength – isometric dynamometer*: Maximum strength of the knee extensor was assessed with an *isometric dynamometer* in a standardised procedure (27). During the test, patients sat straight, with 90° flexion in the hips. Hip and thigh were fixed, arms were crossed, and the ankle was fixed to the dynamometer. A load cell (Chatillon, Ametek Inc®) was mounted on the ankle via a length-adjustable cord. Patients were instructed to perform one maximal voluntary contraction. Strength was assessed three times for both legs, with a 2-minute break between measurements. The highest value for both legs, presented in kilogram strength (kg), was taken for the statistical analyses.
  - *Physical Performance – Short Physical Performance Battery (SPPB):* Lower extremity function was assessed with the *Short Physical Performance Battery (SPPB)*, which includes five tasks (28). A score from 0 (inability to complete the test) to 4 (highest level of performance) is obtained for gait speed, chair stands and for three balance tasks. Finally, a summary score is calculated ranging from 0 (worst performance) to 12 (best performance).
  - *Functional Disability – Health Assessment Questionnaire Disability Index (HAQ-DI):* Self-reported functional disabilities were assessed with the *Health Assessment Questionnaire Disability Index (HAQ-DI)* (29, 30). This questionnaire asks about difficulties in eight domains, with 20 questions. Activities are scored on a scale from 0 (without difficulty) to 3 (cannot be done at all). For each domain, the highest value is taken and an overall disability index between 0 (no functional disability) and 3 (severe functional disability) is calculated.
  - *Pain intensity – Visual Analogue Scale (VAS):* Pain intensity was assessed with the *Visual Analogue Scale* (VAS), a widely used unidimensional measurement instrument (31). The VAS is 10 cm long and anchored by verbal descriptors (1 = no pain, 10 = worst imaginable pain).
  - *Disease duration – years*: Disease duration was assessed using the following question: *"When was RA first diagnosed? Please indicate the exact date."* In the paper, disease duration is given in years.
  - *Disease activity – Clinical Disease Activity Index (CDAI):* Disease activity was assessed with the *Clinical Disease Activity Index* (CDAI) (32). The CDAI is a validated, widely used measurement, obtained using the formula: CDAI = SJC (28) + TJC (28) + PGA + EGA.
    SJC is the Swollen 28-Joint Count (shoulders; elbows; wrists; metacarpophalangeal joints; proximal interphalangeal joints, including thumb interphalangeal joint; knees); TJC-28 is the Tender 28-Joint Count; PGA

is the Patient's Global disease Activity self-assessment of the overall RA disease activity on a scale from 1 to 10, where 10 is maximal activity; and EGA is the Evaluator's Global disease Activity assessment of the overall RA disease activity. The following stages of disease activity are distinguished: remission (CDAI ≤2.8), low disease activity (CDAI >2.8 and ≤10), moderate disease activity (CDAI >10 and ≤22) and high disease activity (CDAI >22).

- *Inflammatory parameters*: C-reactive protein (CRP; mg/dl), tumour necrosis factor alpha (TNF-α; pg/ml) and interleukin-6 (IL-6; pg/ml) were used to obtain information about the inflammatory profile of the patients. Blood samples were taken in the morning at the Laboratory Department of SMZ Süd.
- *Drug therapy*: Used drug therapy for RA was taken from the electronic patient card. The medication was categorised into: 1. disease-modifying anti-rheumatic drugs; 2. biologicals; 3. corticosteroids; and 4. non-steroidal anti-inflammatory drugs.

Statistical analyses

The data were tested for normality with histograms and box plots. Participant characteristics, various physical performance parameters and clinical data of the whole sample, also stratified by frailty status (robust and prefrail/frail), are presented in mean and standard deviation (SD) or median and 25th to 75th percentile (Q_{25}–Q_{75}). Categorical variables are shown in percentages. To test the differences between robust and prefrail/frail individuals, we used *t*-tests for independent samples in continuous normally distributed data, and Mann-Whitney U-tests were used in skewed data. In categorical variables, we used Chi-square tests, or Fisher's exact tests if a group was less than five. In addition, we performed Chi-square tests to explore if dichotomised disease activity (moderate and high; remission and low) was associated with the dichotomised handgrip strength (≥the reference values; <the reference values). To assess factors associated with frailty, we performed a multivariable linear regression analysis, with the SHARE-FI score as the dependent variable, and sex, age, employment status, pain intensity, disease duration and disease activity as independent variables (significant differences between robust and prefrail/frail persons are listed in Tables I-II). We did not include the inflammatory parameters (CRP, TNF-α and IL-6) in this model, as there was multicollinearity with disease activity. Due to multicollinearity with frailty status, we also excluded maximum strength of the knee extensor, physical performance and functional disability. In both cases, multicollinearity was defined as a correlation coefficient of r ≥0.700. Although sex and age were not significant in this model, they remain in the model, as frailty is a sex- and age-specific parameter (11). All the statistical analyses were performed in SPSS v. 24.0 (IBM Corp., Armonk, NY, U.S.), and a *p*-value of <0.05 was considered to be statistically significant.

Table I. Participant characteristics of the whole sample and stratified by frailty status.

	All n=100	Robust n=55	Prefrail/frail n=45	*p*-value
Sex				
Female	66.0%	58.2%	75.6%	0.068
Age (years); mean (SD)	50.9 (9.7)	49.3 (10.3)	52.0 (8.8)	0.165
Language				
German	89%	92.7%	84.4%	0.532
English	2.0%	1.8%	2.2%	
Serbo-Croatian	5.0%	1.8%	8.9%	
Turkish	4.0%	3.6%	4.4%	
Marital status				
Married, steady relationship	71.0%	74.2%	67.5%	0.674
Single, widowed, divorced	29.0%	27.8%	30.5%	
Education level				
Elementary school or no degree	18.0%	12.8%	24.4%	0.296
Secondary school	71.0%	74.5%	66.7%	
University entrance diploma or higher degree	11.0%	12.7%	8.9%	
Employment status				
Employed	59.0%	69.1%	46.6%	0.023
Unemployed	41.0%	30.9%	53.4%	

Age is presented in mean and standard deviation (SD); other parameters are shown in percentages. Differences between groups were calculated using t-tests. Differences in categorical variables were calculated using Chi-square tests or Fisher's exact tests.

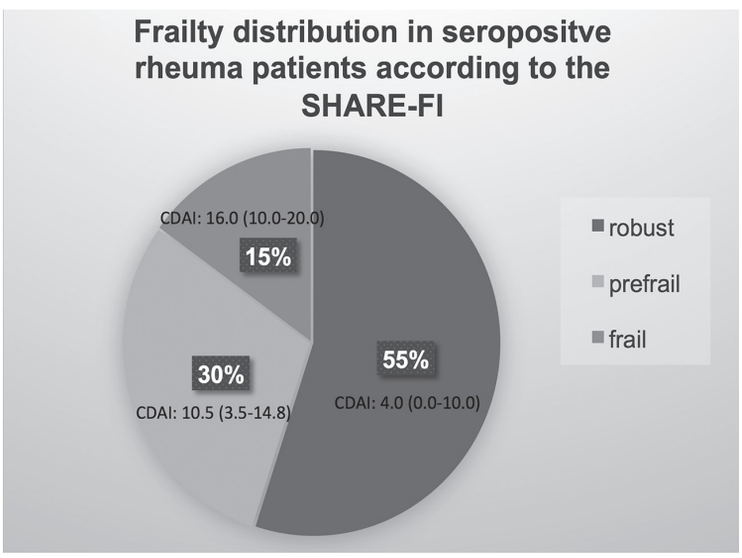

Fig. 1. Frailty distribution according to the Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe.

Table II. Physical activity and disease-describing factors of the whole sample and stratified by frailty status.

	All	Robust n=55	Prefrail/frail n=45	*p*-value
Frailty component				
Exhaustion (yes)	60.0%	36.4%	88.9%	<0.001
Loss of appetite (yes)	8.0%	3.6%	4.4%	0.015
Functional difficulties (yes)	30.0%	3.6%	62.2%	<0.001
Handgrip strength (kg); mean (SD)	32.3 (15.0)	39.3 (13.7)	23.8 (11.9)	<0.001
≥ the reference value (yes)*	33.7%	51.9%	11.4%	<0.001
Low physical activity				
> Once a week (yes)	49.0%	63.6%	31.1%	<0.001
Once a week (yes)	21.0%	25.5%	15.6%	
1–3 times a month (yes)	9.0%	3.6%	15.6%	
Hardly or never (yes)	21.0%	7.3%	37.8%	
Knee extensor strength (kg); mean (SD)	38.8 (17.0)	47.5 (16.1)	28.2 (11.3)	<0.001
Physical performance (SPPB score); mean (SD)	10.8 (1.9)	11.7 (0.7)	9.8 (2.4)	<0.001
Functional disability (HAQ-DI score); median (Q_{25}–Q_{75})	0.5 (0.0–1.0)	0.1 (0.0–1.3)	1 (0.0–2.9)	<0.001
Pain intensity (VAS scale); median (Q_{25}–Q_{75})	3.0 (2.0–5.0)	3.0 (2.0–4.0)	4.0 (2.8–6.3)	0.001
Disease duration (years); median (Q_{25}–Q_{75})	6.0 (3.0–11.08)	4.0 (2.5–10.0)	7.0 (4.0–16.5)	0.027
Disease activity (CDAI points); median (Q_{25}–Q_{75})¥	8.0 (9.0–13.0)	4.0 (0.0–10.0)	11.0 (6.0–18.0)	<0.001
Remission	29.9%	40.4%	17.8%	0.008
Low	34.2%	38.5%	28.9%	
Moderate	27.8%	17.3%	40.0%	
High	8.1%	3.8%	13.3%	
Inflammatory parameters				
CRP (mg/dl); median (Q_{25}–Q_{75})	3.2 (1.1–6.7)	2.0 (0.9–4.4)	4.8 (2.2–9.7)	0.002
TNF-α (pg/ml); median (Q_{25}–Q_{75})	1.6 (0.6–2.4)	1.3 (0.4–2.3)	2.0 (1.2–2.9)	0.036
IL-6 (pg/ml); median (Q_{25}–Q_{75})	3.9 (2.0–7.9)	2.8 (1.8–6.0)	5.7 (2.6–16.8)	0.007
Drug therapy				
Disease-modifying anti-rheumatic drugs (yes)	80.0%	85.5%	73.3%	0.209
Biologicals (yes)	44.0%	43.6%	44.4%	1.000
Corticosteroids (yes)	17.0%	14.5%	20.0%	0.594
Non-steroidal anti-inflammatory (yes)	15.0%	16.4%	13.3%	0.673

Data are presented in mean and standard deviation (SD) or median and 25th to 75th percentile (Q_{25}–Q_{75}), or percentages. Differences between groups were calculated using *t*-tests or Mann-Whitney U-tests, if data were skewed. Differences in categorical variables were calculated using Chi-square tests or Fisher's exact tests.
*According to the sex- and age-specific reference values of Bohannon *et al*. (26)

Results

A total of 140 RA patients fulfilled the inclusion criteria and were asked to participate in the study. As 14 (1.0%) patients were not interested in taking part, 6 (4.3%) did not have time, 4 (2.9%) had language problems and 17 (12.1%) did not complete the measurements, 100 patients were included. Sixty-six percent of the study participants were female and had a mean average age of 50.5 (SD: 9.7) years, with a median of 53 years (Table I). The majority of the study participants completed the questionnaire in the German language, were married or lived in a steady relationship, had finished secondary school, and 59% stated that they were working at the moment.

According to the SHARE-FI score, 15% of the included patients were frail, 30% were prefrail and 55% were robust (Fig. 1). There was no significant difference in frailty prevalence between people aged ≤50 years (50%) and people aged 50–65 years (36.8%) (p=0.199). Among all the participants, almost two-thirds suffered from exhaustion and one-third had functional disabilities, recorded by problems in climbing more than one flight of stairs and walking 100 m (Table II). In addition, half of the participants stated that they did physical activity less than once a week, and 66.3% had handgrip values under the sex- and age-specific reference values. Maximum strength of the knee extensor came to 38.8 (SD: 17.0) kg, with a significant difference between prefrail/frail and robust persons. Furthermore, prefrail/frail individuals had a significantly lower physical performance score and a higher HAQ-DI score (Table II). Pain intensity was also higher in persons categorised as prefrail/frail.

There was also a significant difference in all the clinical parameters, including disease duration and disease activity (Table II). Moderate or high disease activity was more common in prefrail/frail individuals compared to robust individuals. Further analyses showed that these persons were not more likely to have handgrip strength lower than the reference values when compared to persons in remission or with low disease activity (moderate or high disease activity and higher than the reference value: 41%; remission or low disease activity and lower than the reference value: 59%; p=0.365). Again, there was a significant difference in inflammatory parameters, as shown in Table II. However, no difference in the drug therapy between robust and prefrail/frail persons could be detected.

In the multivariable analysis, unemployment (β=0.243; p=0.005), higher pain intensity (β=0.186; p=0.060), longer disease duration (β=0.181; p=0.020) and higher disease activity (β=0.444; p<0.001) were associated with a higher frailty score (Table III). These parameters explained 49.7% of the variability of the frailty index (R^2=0.497). Among these parameters, disease activity was the variable most strongly associated with the frailty index (highest standardised beta value).

Discussion

Our findings demonstrate that frailty is present in 15% of RA patients younger than 65 years. Even more alarming is that an additional 30% are found to be prefrail. The prevalence of frailty is in line with the results of the study of Andrews *et al*. (12), who assessed the frailty prevalence in younger RA patients with a mean age of 58.0 (SD 10.8) years. However, the percentage of

Table III. Variables associated with the frailty score.

	R^2; *p*-value	Included independent variable	Standardised β-value	*p*-value
SHARE-FI	0.497 *p*<0.001	Age (years)	0.023	0.787
		Sex (female)	0.095	0.208
		Employment status (unemployed)	0.243	0.005
		Pain intensity (VAS scale)	0.186	0.060
		Disease duration (years)	0.181	0.020
		Disease activity (CDAI points)	0.444	<0.001

Results are based on the multivariable linear regression analysis, including sex, age, employment status, pain intensity, disease duration and disease activity as independent variables. Inflammatory parameters, maximum strength of the knee extensor, physical performance and functional disability were not included, due to multicollinearity.

prefrail patients, at 69%, is much higher in their sample. A possible reason for this might be that the participants in the study of Andrews *et al*. (12) had a longer disease duration of 19.2 (SD: 10.6) years and a lower handgrip strength of 17.4 (SD: 9.3) kg. Another possible reason might be the different methods of assessing frailty status: Anderson *et al*. (12) measured frailty with the Fried phenotype, and in the present study we used the SHARE-FI score.

Comparing these numbers to the prevalence in community-dwelling people above 65 years in Austria (frail: 10.8%; prefrail: 40.7%) (19), and compared to the prevalence of frailty in geriatric individuals living in nursing homes (frail: 24.7%; prefrail: 61.4%) (18), these numbers for RA patients are worrying. Furthermore, these numbers are even higher than those in Canadian cancer patients (13) and stable chronic obstructive pulmonary disease patients (14). As our results show that people with higher disease activity and longer disease duration are more likely to be frail than robust, and as exhaustion, loss of appetite, functional difficulties, low physical activity and handgrip strength are typical for RA patients, there is a high probability that the frailty score might "relabel" people with higher disease activity as frail. Nonetheless, as frailty is a geriatric syndrome that increases with age (24), we can expect an even higher prevalence in elderly RA patients. Thus, the present data indicate that, especially in this patient group, it is important to take frailty into account and to think about strategies to counteract frailty.

One underlying reason for the high prevalence of prefrailty and frailty could be the high amount of people suffering from exhaustion, which is a common phenomenon in RA patients (33-35). According to the available literature, exhaustion has been reported in 40–80% of RA patients (33), and has been shown to have a multifactorial cause (34). Mentioned reasons are pain, physical inactivity, depression and sleep disturbance (36). Apart from the high prevalence of exhaustion, functional difficulties and low handgrip strength were also very common in our sample. Furthermore, we expected an association between disease activity and handgrip strength, but this was refuted by the data. Nonetheless, the non-association is in line with the available literature, which describes only a limited association (37). A further study, made up of patients with a disease duration of at most two years, saw a stronger association, and these participants even reached normal handgrip strength when the disease was in remission (38). Apart from handgrip strength, the maximum strength of the knee extensor was unexpectedly high. Compared to a sample without illnesses that affect the musculoskeletal system, with a mean age of 67.8 (SD: 4.8) years, knee extensor strength, measured with the same procedure as used in this study, came to 35.9 (SD: 11.6) kg (39). This average value is 2.9 kg lower than the value measured in our study. As muscle strength declines with increasing age (40, 41), we have to take the difference in age into account. Nevertheless, the values in our RA patients were higher than expected.

Besides physical inactivity (42), the chronically high inflammatory markers might play a role in the physiological process, leading to the high prevalence of prefrailty and frailty. In this context, it ought to be mentioned that Cooney and colleagues (43) identified the excessive production of proinflammatory cytokines as being responsible for cachexia in RA patients. In addition, in older persons, studies have shown that high inflammatory markers are associated with lower muscle mass and lower muscle strength, and are also related to self-reported functional disabilities (44, 45). These inflammatory markers, and the glucocorticoid treatment, might lead to reduced myocyte protein synthesis and increased protein degradation (46, 47). As we saw a significant difference between people who were assessed as prefrail/frail and the robust individuals, we assume that inflammatory markers and cytokines, in combination with the low level of physical activity, might contribute to the high prevalence of frailty in our data set.

Interventions to prevent or reduce frailty include physical training, nutritional interventions and medication to lower inflammation (9). For RA patients, the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) have recommended a combination of endurance, strength and flexibility exercises (2, 48). Apart from the general effects of physical training (*e.g*. cardiovascular, musculoskeletal effects, effects on bones and overall function), the training also has specific health benefits in RA patients; for example, it positively influences the rheumatoid cachexia (43). Exercise also decreases functional disabilities and improves functional capacity and joint count. This positive impact has been shown to be clinically relevant (49). However, to date, no direct association between diet and RA has been proven (50, 51). Considering that cardiovascular diseases are common in this population (52), and considering that 24% subjectively report food as having an influence on their RA symptoms (53), it is recommended that national nutritional guidelines are followed (52). For the prevention of frailty, energy and protein intake are of special relevance (54, 55).

The major strength of this study was that frailty status was assessed, for the first time, in RA patients of working age. In addition, we also collected data about the inflammatory profile and the strength of the lower extremities of the patients. The major limitation was that no data of a matched control group were available. Additionally, the SHARE-FI has only been validated for persons aged ≥50 years. Consequently, further research is needed to validate the use of the SHARE-FI in RA patients, especially in patients aged <50 years. As exhaustion plays a role, and is very common in RA patients, the frailty prevalence might be overestimated. Secondly, the relatively small sample size is another limitation, making a generalisation difficult. Therefore, further studies should assess the frailty status in a larger population. Apart from this, the SHARE-FI mainly assesses physical frailty, with only limited consideration of the biopsychosocial concept.

Taken together, frailty and prefrailty are common in RA patients of working age and are more prevalent than would be expected. As the prevalence of frailty increases with age, the present data indicate that it is important to take frailty into account, even in younger persons, and to take action to counteract frailty.

A very interesting aspect for further research would be to assess the frailty status in an extended sample size and to investigate if the frailty score is lower in RA patients who have entered into permanent remission after early treatment, whereby they did not develop any joint damage, compared to age- and sex-matched patients who have been treated less aggressively.

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