Original article

Influence of Frailty on Patient Global Assessment in Rheumatoid Arthritis

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ABSTRACT

Objective: Patient Global Assessment (PtGA, range: 0-10 cm) is an important indicator of clinical outcomes, including physical function, in self-assessment of patients with rheumatoid arthritis (RA). Frailty is a concept that encompasses not only physical, but also mental, psychological, and social vulnerability. This study aimed to investigate the influence of frailty on PtGA in patients with RA.

Methods: Among 581 patients with RA who completed a questionnaire survey on frailty between June and August 2020, 559 who completed the Kihon Checklist (KCL; a 25-item questionnaire with seven domains) were included. The proportion of patients with PtGA ≤1 was compared between the frailty (KCL score ≥8), pre-frailty (KCL score 4-7), and robust (KCL score 0-3) groups. Factors associated with PtGA ≤1 were examined using multivariate logistic regression models.

Results: Of the 559 patients, 221 (39.5%) had frailty. The proportion of patients with PtGA ≤1 was significantly lower in the frailty group (33.9%) than in the robust (65.4%, P<0.001) and pre-frailty (55.7%, P<0.001) groups. Multivariate analysis revealed that frailty (vs. robust, OR: 0.37, 95% CI: 0.22-0.69), as well as disease duration and tender joint count, were factors independently associated with PtGA ≤1. When each domain of the KCL was examined, activities of daily living, physical strength, isolation, and depressive mood were factors associated with PtGA ≤1.

Conclusion: Frailty affects PtGA in patients with RA. Since frailty impacts the physical, mental, and social vulnerability aspects of PtGA, a multifaceted approach, including inflammation suppression, is needed to

improve PtGA in patients with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune inflammatory disease characterized by bone destruction and synovial inflammation. The goals of RA treatment are to prevent structural joint damage and normalize physical function by achieving and sustaining clinical remission (1). However, in recent years, the importance of subjective patient self-assessment has also been recognized in the treatment of RA. This is because the symptoms are experienced by the patients themselves and are best reflected in patient-reported outcomes (PROs) (2). PROs are now actively incorporated into the evaluation of drug efficacy. Patient Global Assessment (PtGA), a PRO, is an important indicator of clinical outcomes, including physical function (3). The most stringent remission criteria developed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) in 2011 (Boolean-based definition) include a 28 tender joint count (TJC28) of ≤1, 28 swollen joint count (SJC28) of ≤1, serum C-reactive protein (CRP) level of ≤1 mg/dl, and PtGA (0-10 cm) of ≤1 (4). A significant proportion of patients with RA do not achieve remission under the Boolean-based definition due to PtGA scores being >1, even if all other criteria are met (i.e., TJC28, SJC28, and CRP (mg/dl) all ≤1) (5). In other words, improvement of PtGA is also an important therapeutic goal in RA treatment.

Frailty is a multidimensional concept encompassing not only physical but also mental, psychological, and social vulnerability (6, 7). The prevalence of frailty increases with age (8). RA, a chronic systemic autoimmune inflammatory disease characterized by bone destruction and synovial inflammation,

64 is a cause of osteoporosis, pain, and loss of motor function, as well as frailty (9, 10). Our previous study
65 targeting RA patients (age range, 40-79 years) at urban university hospitals found that depression, physical
66 function, and disease activity are independently associated with frailty in patients with RA (11). However,
67 no study has examined the relationship between PtGA and frailty in this patient population. Accordingly,
68 the present study aimed to investigate the influence of frailty on PtGA in patients with RA using new data
69 obtained from the Tsurumai-Frailty and Locomotive Syndrome of Rheumatoid Arthritis for Globalization
70 (T-FLAG) study.
71

Materials and Methods

Patients

Data were obtained from participants of the Tsurumai-Frailty and Locomotive Syndrome of Rheumatoid Arthritis for Globalization (T-FLAG) study, a multicenter cohort study involving patients from three institutions. We conducted a questionnaire survey on frailty in 581 patients with RA between June 1 and August 31, 2020. After excluding 22 patients who did not complete the Kihon Checklist (KCL), 559 patients were included in this study. All patients met the 1987 ACR classification criteria (12) or the 2010 ACR/European League Against Rheumatism classification criteria for RA (13). This study was approved by the Ethics Committee of Nagoya University Graduate School of Medicine (2017–0271-3) and complied with the principles set forth in the Declaration of Helsinki. Informed consent was obtained by an opt-out procedure.

Kihon Checklist

The KCL is a screening tool used to identify older people who are at high risk of requiring nursing care in the future (14, 15). This simple, self-reporting yes/no survey consists of 25 questions, each scored as 0 or 1 point. The KCL is divided into the following seven domains: activities of daily living (questions 1-5), physical strength (questions 6-10), nutrition (questions 11-12), oral function (questions 13-15), isolation (questions 16-17), cognitive function (questions 18-20), and depressive mood (questions 21-25).

Total KCL scores range from 0 to 25 points, with 8, 4-7, and 0-3 points defining ‘frailty,’ ‘pre-frailty,’ and ‘robust,’ respectively. (15, 16).

Data collection

The following demographic and clinical data were collected from clinical records: age, sex, body mass index (BMI), disease duration, SJC and TJC, serum C-reactive protein (CRP) levels, PtGA, use of MTX, targeted disease-modifying antirheumatic drugs (DMARDs), and/or glucocorticoids, KCL score, and Health Assessment Questionnaire-Disability Index (HAQ-DI) score. With regard to PtGA, patients were asked to rate the question, “Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today (in Japanese)?” (4), on a visual analog scale with anchors of 0 cm (very well) and 10 cm (very poor).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as percentage. Differences in demographic and clinical data, including PtGA, among the frailty, pre-frailty, and robust groups were analyzed by the chi-squared test for categorial variables and one-way analysis of variance (ANOVA) for continuous variables. The significance of individual differences in PtGA was evaluated with the Bonferroni test, if one way ANOVA yielded significant differences. The

proportion of patients with PtGA ≤1, one of the ACR/EULAR remission criteria (4), was compared between the three groups using the chi-squared test. Trends in the proportion of patients with PtGA ≤1 according to scores of each domain of the KCL were assessed by the Cochran-Armitage trend test. Factors associated with PtGA ≤1 were assessed using univariate and multivariate logistic regression models with frailty and scores of each KCL domain as experimental variables, and age, sex, BMI, disease duration, SJC, TJC, serum CRP levels, and use of methotrexate, tDMARDs and/or glucocorticoids as a priori variables according to previous studies (17, 18). In addition, sensitivity analysis was performed to assess the potential confounding effect of age by dividing patients into two groups: <65 years and ≥65 years. Statistical analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (19). $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Demographic and clinical characteristics of all patients included in this study are shown in Table 1. Data on BMI, CRP, and HAQ-DI were available for 543, 554, and 557 patients, respectively, and other data were available for all patients. Of all patients, 221 (39.5%) had frailty as defined by a KCL score ≥8. Patients with frailty were more likely to be older, had a longer disease duration, had a higher TJC, SJC, CRP, and HAQ-DI score, and had a lower rate of methotrexate use and higher rate of glucocorticoid use, compared to those without frailty.

Proportion of patients with PtGA ≤1

One way ANOVA revealed significant differences in PtGA among the robust (1.1 ± 1.6), pre-frailty (1.9 ± 2.2), and frailty (2.9 ± 2.5) groups (P<0.001) (Figure 1a). The Bonferroni test revealed significant differences in PtGA between the robust and pre-frailty groups (P<0.01), the robust and frailty groups (P<0.001), and the pre-frailty and frailty groups (P<0.001). The proportion of patients with PtGA ≤1 was significantly lower in the frailty group (33.9%) than in the robust (65.4%, P<0.001) and pre-frailty (55.7%, P<0.001) groups (Figure 1b). The Cochran-Armitage trend test revealed that the proportion of patients with PtGA ≤1 tended to decrease with increasing scores for activities of daily living (P<0.001), physical strength (P<0.001), nutrition (P=0.007), isolation (P=0.003), and depressive mood domains (P<0.001). No

significant trend was observed in the proportion of patients with PtGA ≤1 according to the scores of oral function and cognitive function.

Factors associated with PtGA ≤1

Of all patients included in this study, 278 (49.7%) had PtGA ≤1. Odds ratios (ORs) for PtGA ≤1 were calculated using logistic regression analyses, with frailty as an experimental variable (Table 2) or scores of each KCL domain as experimental variables (Table 3). Multivariate analysis revealed that frailty (vs. robust, OR: 0.37, 95% CI: 0.22-0.69), as well as disease duration (OR: 0.97, 95% CI: 0.95-0.99) and tender joint count (OR: 0.57, 95% CI: 0.49-0.67), were factors independently associated with PtGA ≤1, whereas pre-frailty had no significant association with PtGA ≤1 (Table 2). Frailty was independently associated with PtGA ≤1 in both patients aged <65 years (n=196) (vs. robust, OR: 0.36, 95% CI: 0.15-0.88) and those aged ≥65 years (n=363) (vs. robust, OR: 0.41, 95% CI: 0.21-0.81) (Supplementary Table 1). After adjusting for age, sex, BMI, disease duration, SJC, TJC, and serum CRP levels, activities of daily living (OR: 0.78, 95% CI: 0.67-0.90), physical strength (OR: 0.68, 95% CI: 0.58-0.80), isolation (OR: 0.79, 95% CI: 0.50-0.97), and depressive mood (OR: 0.79, 95% CI: 0.69-0.90) were significantly associated with PtGA ≤1 (Table 3).

Discussion

This study demonstrated that frailty is associated with PtGA in patients with RA. The proportion of patients with PtGA ≤1 was roughly 30% lower in the frailty group than in the robust group. Multivariate analysis revealed that frailty is negatively associated with the achievement of PtGA ≤1 independently of signs of joint inflammation. Although causality cannot be proven due to the cross-sectional design, PtGA appears to be partially driven by frailty. The present findings provide important new insights into further research to improve PtGA scores in patients with RA.

PtGA is a crucial component of validated disease activity scores and remission criteria in patients with RA, such as the ACR/EULAR remission criteria (i.e., PtGA ≤1) (4). PtGA is reportedly driven by signs of joint inflammation, including SJC, TJC, and serum inflammation markers (20). Based on multivariate analysis, TJC, but not SJC and CRP, was identified as a factor independently associated with PtGA ≤1. This might be explained by TJC being more dependent on a patient's perception of disease activity than SJC (21). A previous study reported that PtGA was higher in patients with established RA than in those with early RA (22). A similar difference was observed between the two groups, even in the sub-population of patients with no visible inflammation (TJC, SJC, and CRP all ≤1). These findings are consistent with disease duration being another factor independently associated with PtGA ≤1.

Other than inflammation (i.e., TJC, SJC28, and CRP), a variety of factors have been reported to affect PtGA, including sex, pain, and disease activity (3, 23). In patients with RA suffering from joint

deformities, the HAQ-DI, a measure of physical function, has been reported to correlate with PtGA (24). Previous studies reported that frailty is significantly associated with higher disease activity in patients with RA (11, 25, 26). The present study focused on the influence of frailty on PtGA, a major limiting factor in achieving clinical remission, and is the first to show that such an association exists in RA patients. We also found that frailty affected PtGA independently of signs of joint inflammation. PtGA in patients with joint inflammation can be improved by reinforcement with immunosuppressive treatment, but PtGA driven primarily by factors not related to joint inflammation may not. Appropriate adjuvant measures for frailty may be necessary in patients who do not achieve PtGA ≤1, even in the absence of signs of significant joint inflammation. Frailty is a multifaceted concept that encompasses not only physical but also mental and social vulnerability (27). Previous studies reported that depression and health-related QOL were significantly associated with frailty in patients with RA (11, 25, 26) as well as in the general population (6). In the present study, activities of daily living, physical strength, isolation, and depressive mood were the domains of frailty associated with PtGA ≤1. In other words, PtGA is affected by not only physical frailty but also mental/social frailty, suggesting the need for a multifaceted approach that also aims to improve depression. The rate of frailty has been known to increase with age (8). Therefore, age should also be taken into account when considering the effects of frailty. In the present study, sub-analyses revealed that frailty was associated with PtGA both in younger and older patients. Given the concern for adverse events related to immunosuppressant use, it is important to determine whether the cause of high PtGA is inflammation or

189 frailty in order to improve PtGA and provide appropriate treatment in RA patients regardless of age.

190 Notably, patients with frailty had a significantly lower rate of MTX use and a higher rate of
191 glucocorticoid use compared to those without frailty. These differences in treatment are possibly due to the
192 higher age of patients with frailty. Indeed, patients aged ≥65 years were more likely to have a lower rate of
193 MTX use and a higher rate of glucocorticoid use compared to those aged <65 years (Supplementary Table
194 1). Similar differences were observed in a previous study (28). Elderly patients may have less tolerance to
195 MTX due to comorbidities such as renal dysfunction. MTX use was associated with PtGA in univariate
196 analysis but not in multivariate analysis. Accordingly, it is unlikely that the differences in treatment have
197 affected our main finding that frailty is associated with PtGA.

198 An important goal of therapeutic interventions for frailty is to improve PtGA. Exercise
199 interventions have been reported to prevent frailty by improving gait, muscle strength, physical motor
200 functions, and activities of daily living (29). While exercise therapy has also been reported to be effective
201 in treating psychological frailty (30), few high-quality intervention studies have been conducted on social
202 frailty. This suggests that a multifaceted approach to prevent frailty may ultimately improve PtGA in
203 patients with RA.

204 There are several limitations in this study. First, as this was a cross-sectional study that analyzed
205 frailty status and PtGA at the time of the questionnaire survey, causality between frailty and PtGA cannot
206 be proven in a strict sense. However, based on a previous longitudinal study reporting the impact of frailty

on changes in physical function (18), PtGA may be partially driven by frailty. In addition, the present study did not demonstrate the effect of therapeutic interventions for frailty to improve PtGA. A longitudinal study will be necessary to address these issues in the future. Second, there was no information on medical history, history of surgery, comorbidities, complications, nutrition, or exercise habits. Since these factors may affect frailty, physical function, and disease activity in RA patients, future studies which include these factors are warranted.

In conclusion, PtGA is affected by not only physical frailty but also mental/social frailty. In order to improve PtGA in patients with RA, mental, psychological, and social care will be necessary in addition to controlling inflammation and improving physical function.

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Disclosure statement

The authors declare no conflicts of interest.

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Graphical Abstract Text

Frailty affects Patient Global Assessment (PtGA) in patients with rheumatoid arthritis (RA). Since frailty impacts the physical, mental, and social vulnerability aspects of PtGA, a multifaceted approach, including inflammation suppression, is needed to improve PtGA in patients with RA.

316 Table 1. Baseline characteristics of patients

	Total	Robust KCL score 0-3	Pre-frailty KCL score 4-7	Frailty KCL score ≥8	
	(n=559)	(n=153)	(n=185)	(n=221)	P value
Age, years	67 ± 13	63 ± 13	66 ± 13	70 ± 13	<0.001
Female, %	73.0	69.9	73.0	75.1	0.541
Body mass index[a]	22.0 ± 4.0	22.0 ± 3.8	22.1 ± 4.2	21.8 ± 4.0	0.828
Disease duration, years	11 ± 10	10 ± 8	10 ± 9	13 ± 10	0.004
SJC, 0-28 scale	0.7 ± 2.0	0.4 ± 1.6	0.6 ± 1.5	0.9 ± 2.6	0.035
TJC, 0-28 scale	2.1 ± 4.0	1.3 ± 2.9	1.6 ± 2.9	3.1 ± 5.0	<0.001
CRP, mg/dl[b]	0.42 ± 1.08	0.24 ± 0.53	0.34 ± 0.71	0.62 ± 1.51	0.002
PtGA, cm	2.1 ± 2.3	1.1 ± 1.6	1.9 ± 2.2	2.9 ± 2.5	<0.001
PhGA, cm	1.7 ± 2.0	0.9 ± 1.4	1.5 ± 1.9	2.4 ± 2.2	<0.001
DAS28-CRP	2.21 ± 1.05	1.84 ± 0.78	2.12 ± 0.94	2.55 ± 1.19	<0.001
Use of methotrexate, %	61.4	73.2	61.1	53.4	<0.001

Use of targeted DMARDs, %	38.5	34.6	36.2	43.0	0.197
Use of glucocorticoids, %	30.6	27.5	25.4	37.1	0.024
KCL	6.9 ± 4.7	1.9 ± 1.0	5.3 ± 1.1	11.7 ± 3.3	<0.001
HAQ-DI[c]	0.48 ± 0.66	0.11 ± 0.22	0.24 ± 0.39	0.92 ± 0.78	<0.001

317 SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; PtGA: Patient Global
318 Assessment; PhGA: Physical Global Assessment; DAS28: 28-joint disease activity score, DMARDs:
319 disease-modifying antirheumatic drugs; KCL: Kihon Checklist; HAQ-DI: Health Assessment
320 Questionnaire Disability Index.
321 Data are shown as mean ± SD or percentage.
322 [a]Data were obtained from 543 patients.
323 [b]Data were obtained from 546 patients.
324 [c]Data were obtained from 557 patients.

Table 2. Factors associated with Patient Global Assessment (PtGA) ≤1

			Odds ratio (95% confidence interval)	
	PtGA ≤1 (n=278)	PtGA >1 (n=281)	Univariate	Multivariate
Age, years	66 ± 13	67 ± 13	0.99 (0.96-1.01)[a]	1.01 (0.99-1.03)[a]
Female, %	73.0	73.0	1.01 (0.69-1.46)	1.04 (0.64-1.68)
Body mass index	21.9 ± 4.2	22.1 ± 3.9	0.99 (0.95-1.03)[a]	0.99 (0.94-1.05)[a]
Disease duration, years	10 ± 9	12 ± 10	**0.98 (0.96-0.99)[a]**	**0.97 (0.95-0.99)[a]**
SJC, 0-28 scale	0.3 ± 1.2	1.1 ± 2.6	**0.73 (0.63-0.85)[a]**	0.86 (0.74-1.01)[a]
TJC, 0-28 scale	0.6 ± 1.2	3.6 ± 5.0	**0.57 (0.50-0.66)[a]**	**0.57 (0.49-0.67)[a]**
CRP, mg/dl	0.29 ± 0.73	0.56 ± 1.33	**0.73 (0.58-0.92)[a]**	0.90 (0.68-1.18)[a]
Use of methotrexate, %	65.8	56.9	**1.46 (1.03-2.05)**	1.16 (0.75-1.80)
Use of tDMARDs, %	34.9	42.0	0.74 (0.53-1.04)	1.02 (0.66-1.57)
Use of glucocorticoids, %	27.0	34.2	0.71 (0.50-1.02)	0.92 (0.59-1.45)
Frailty status				
Robust, %	36.0	18.9	1.00 (reference)	1.00 (reference)
Pre-frailty, %	37.1	29.2	0.67 (0.43-1.04)	0.72 (0.43-1.20)
Frailty, %	27.0	52.0	**0.27 (0.18-0.42)**	**0.37 (0.22-0.69)**

SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs.

Data are shown as mean ± SD or percentage.

Values in bold indicate statistical significance ($P<0.05$).

[a]OR for a 1-unit increase in each item.

331 Table 3. Associations between scores of each Kihon Checklist domain and Patient Global Assessment ≤1

	Odds ratio (95% confidence interval)	
Domains	Unadjusted	Adjusted[a]
Activities of daily living	**0.76 (0.68-0.86)**	**0.78 (0.67-0.90)**
Physical strength	**0.63 (0.56-0.71)**	**0.68 (0.58-0.80)**
Nutrition	**0.66 (0.48-0.90)**	0.92 (0.62-1.36)
Oral function	0.75 (0.25-2.23)	1.23 (0.28-5.46)
Isolation	**0.67 (0.51-0.87)**	**0.79 (0.50-0.97)**
Cognitive function	0.82 (0.66-1.01)	0.84 (0.65-1.10)
Depressive mood	**0.73 (0.65-0.82)**	**0.79 (0.69-0.90)**

332 Data are shown as odds ratio for a 1-point increase in each domain.

333 Values in bold indicate statistical significance ($P<0.05$).

334 [a]Odds ratio adjusted for age, sex, body mass index, disease duration, swollen joint count, tender joint

335 count, serum C-reactive protein levels, and use of methotrexate, targeted disease-modifying antirheumatic

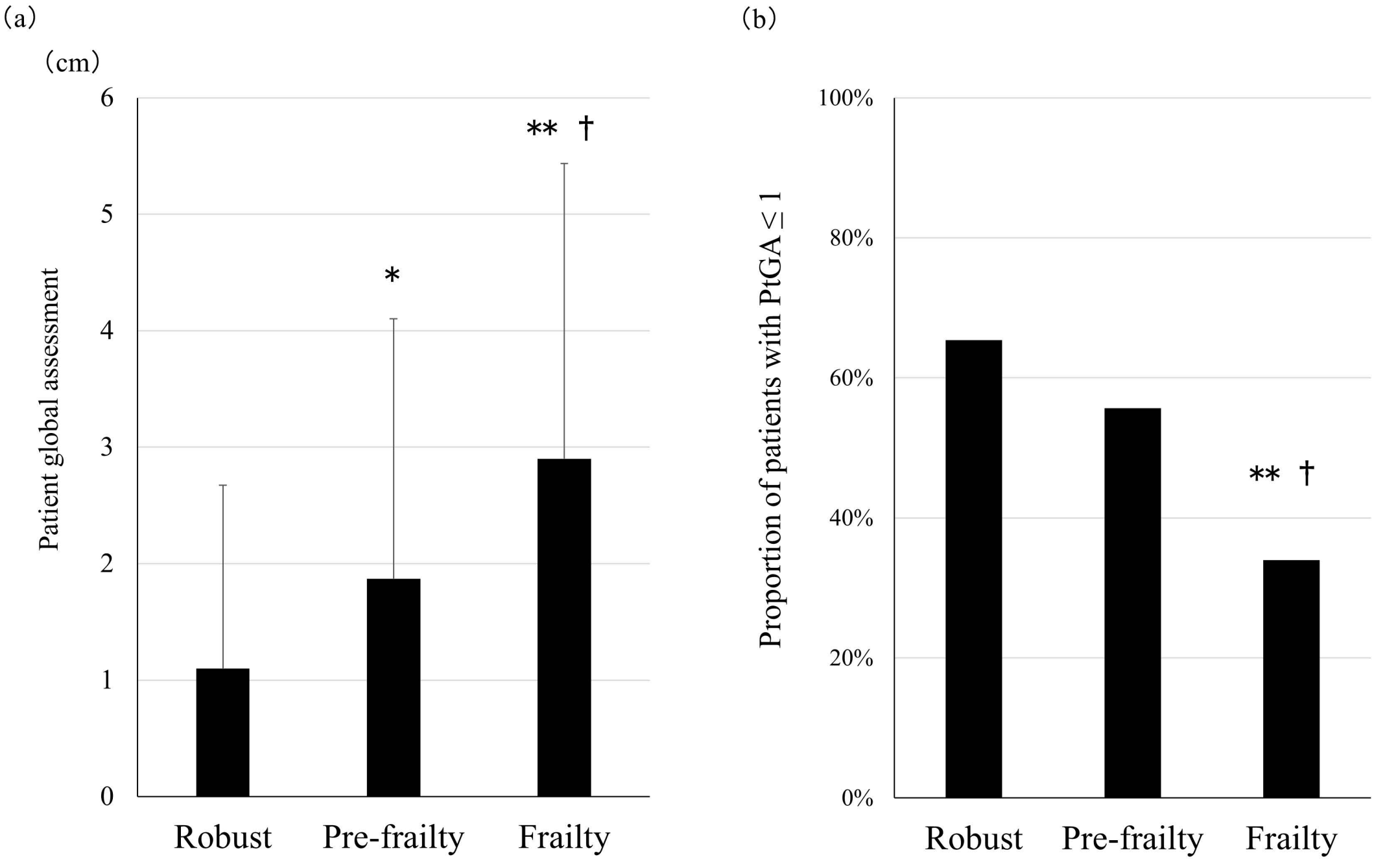
336 drugs, and/or glucocorticoids

Figure legends

Figure 1. (a) Patient Global Assessment (PtGA, 0-10 cm scale) and (b) proportion of patients with PtGA ≤1 stratified by frailty. *P<0.01 vs. robust, **P<0.001 vs. robust, †P<0.001 vs. pre-frailty.

Title of the supplementary table

Supplementary Table 1. Factors associated with Patient Global Assessment ≤1 by age


(a)
(cm)
Patient global assessment
6
5
4
3
2
1
0
*
** †
Robust
Pre-frailty
Frailty
(b)
Proportion of patients with PtGA ≤ 1
100%
80%
60%
40%
20%
0%
** †
Robust
Pre-frailty
Frailty

Supplementary Table 1. Factors associated with Patient Global Assessment ≤1 by age

	Age <65 years		Age ≥65 years	
	n=196	Multivariate OR (95% CI)	n=363	Multivariate OR (95% CI)
Age, years	52 ± 10	1.02 (0.98-1.06)[a]	75 ± 6	0.99 (0.94-1.03)[a]
Female, %	76.0	0.47 (0.18-1.20)	71.3	1.43 (0.79-2.60)
Body mass index	22.3 ± 4.4	1.02 (0.93-1.12)[a]	21.8 ± 3.8	0.95 (0.88-1.03)[a]
Disease duration, years	8 ± 7	**0.94 (0.89-0.99)[a]**	13 ± 10	0.98 (0.95-1.01)[a]
SJC, 0-28 scale	0.8 ± 2.1	0.83 (0.66-1.04)[a]	0.6 ± 2.0	0.85 (0.67-1.07)[a]
TJC, 0-28 scale	2.1 ± 3.5	**0.55 (0.43-0.71)[a]**	2.1 ± 4.2	**0.56 (0.45-0.68)[a]**
CRP, mg/dl	0.36 ± 1.04	0.88 (0.57-1.36)[a]	0.46 ± 1.11	0.86 (0.58-1.27)[a]
Use of methotrexate, %	67.9	0.75 (0.34-1.67)	57.9	1.47 (0.85-2.56)
Use of tDMARDs, %	45.9	0.94 (0.44-2.00)	34.4	1.20 (0.69-2.10)
Use of glucocorticoids, %	28.6	0.81 (0.36-1.80)	31.7	1.01 (0.57-1.78)
Frailty status				
Robust, %	35.7	1.00 (reference)	22.9	1.00 (reference)
Pre-frailty, %	33.7	**0.41 (0.18-0.95)**	32.8	1.01 (0.53-2.10)
Frailty, %	30.6	**0.36 (0.15-0.88)**	44.4	**0.41 (0.21-0.81)**

OR: odds ratio; CI: confidence interval; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs.

Data are shown as mean ± SD or percentage.

Values in bold indicate statistical significance ($P<0.05$).

[a]OR for a 1-unit increase in each item.