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Determinants of physical function, as measured using PROMIS PF-10a, in patients with rheumatoid arthritis: results from the international COVID-19 Vaccination in Autoimmune Diseases (COVAD) study

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Abstract

Objectives: Physical function in RA is largely influenced by multiple clinical factors, however, there is a growing body of evidence that psychological state and other comorbidities also play an essential role. Using data obtained in the COVID-19 Vaccination in Autoimmune Diseases study, an international self-reported e-survey, we aimed to explore the predictive ability of sociodemographic and clinical variables on Patient-Reported Outcomes Measurement Information System Physical Function Short Form 10a (PROMIS PF-10a) in RA and to investigate variation in disease activity and functional outcomes based on country-level socio-economic parameters.

Methods: Patient demographics, disease characteristics including current symptom status, functional status and treatment variables, as well as income level of the country of residence, were extracted from survey responses. PROMIS PF-10a scores were compared across country income levels. The influence of extracted variables on reversed PROMIS PF-10a scores were investigated using negative binomial univariable- and multivariable regression.

Results: A total of 1342 RA patients were included in this analysis. In the optimised parsimonious predictive model for reversed PROMIS PF-10a, older age, female gender, disease duration, fatigue and pain levels were independently associated with worse physical function, whereas Asian ethnicity, higher overall physical health ratings, ability to carry out everyday activities and residing in a country with an upper-middle or high-income level were independently associated with better physical function.

Conclusion: Our study highlights that clinical factors remain strong predictors of physical function in RA, irrespective of individual and country-level socio-economic differences. Interestingly, high country-level income was associated with better physical function, irrespective of individual sociodemographic and clinical factors.

Lay Summary

What does this mean for patients?

Rheumatoid arthritis (RA) is a life-long disease where the body's immune system attacks its own tissues, resulting in joint inflammation and pain, as well as affecting several other parts of the body. RA may lead to joint damage and significant disability that affects a patient's physical function. We know from previous research that many factors beyond joint inflammation, such as one's social and financial position, impacts on physical function in RA. Our study aimed to determine the relationship between clinical factors, social status and country-level income data and physical function in RA. To do this we examined data from 1342 patients with RA from a large international multicentre patient-reported survey, the COVID-19 Vaccination in Autoimmune Diseases study. Our study, like others, showed that controlling disease activity can help improve physical function in patients with RA, irrespective of social or financial status. It also showed that residing in a high income country was associated with better physical function. For patients, this highlights the need for the priority of care to remain on controlling disease activity. It also highlights the importance of fair access to treatments in lower income countries to improve outcomes in this disease.

Keywords: COVAD, rheumatoid arthritis, PROMIS, e-survey, patient-reported outcome measures, physical function, sociodemographic factors, country-level income.

Rheumatology key messages

- Clinical factors remain strong, independent predictors of physical function in RA, irrespective of socio-economic differences.
- The priority of care must remain on controlling disease activity to optimise patient outcomes.
- In lower income countries, equity of access to treatments is important to improve outcomes in RA.

Introduction

RA is a chronic systemic autoimmune disease that primarily manifests as inflammatory arthritis. This can cause joint damage, bone erosions and severe pain which can affect a patient's physical function, emotional state and quality of life, leading to significant disability. The management of RA in early disease frequently involves the use of steroids and NSAIDs to control active disease. Conventional synthetic DMARDs (csDMARDs) remain the mainstay of treatment, but biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDS) are now part of the RA treatment armamentarium. With these rapidly expanding therapeutic options, remission in RA is now a possible goal of treatment with a reduction in physical disability and improvement in physical function.

Physical function has been shown to matter most to patients with RA and thus represents an essential outcome of the disease and one that is influenced by multiple factors [1]. One way to measure physical function in RA is through the use of patient-reported outcome measures (PROMs), which are growing in importance in complex chronic diseases such as RA. The Patient-Reported Outcomes Measurement Information System (PROMIS) was designed to improve and standardise measurements of several PROMs through both computer adaptive testing and traditional paper and pencil instruments [2]. While clinical factors related to RA itself, such as joint pain and deformities, lead to a reduction in physical function and disability, there is a growing body of evidence that factors not directly related to the active disease process, such as sociodemographic factors, psychological state and other comorbidities, play an essential role [1, 3]. Work from our group confirmed the association between low socio-economic status (SES) and poorer disease outcomes (namely disease activity) in patients with RA. Complex multifaceted relationships were noted between education attainment, social environment, lifestyle choices (smoking, diet, alcohol consumption) and other factors such as mental health issues, including stress, anxiety and depression, which are all highly prevalent in RA and lead to increased disease activity [4]. Poor disease outcomes in turn influence factors such as comorbidities, reinforcing the negative influence of SES. Using data from the anonymous international e-survey COVID-19 Vaccination in Autoimmune Diseases (COVAD), conducted in April–May 2020, which included data relating to disease activity and physical function, we tested the hypothesis that, aside from clinical factors, physical function is influenced by individual contextual and country-level factors.

This study specifically aimed to explore the associations between sociodemographic and clinical variables on the

PROMIS Physical Function Short Form 10a (PROMIS PF-10a) in RA and to investigate variation in disease activity and functional outcomes based on country-level socio-economic parameters, namely country income.

Methods

This study utilised data on RA patients who participated in the COVAD study, an international, cross-sectional, multicentre online survey–based study [5]. Detailed methods of the COVAD study have been described at length in the published COVAD study protocol [5]. Briefly, as part of COVAD, a comprehensive patient self-reporting electronic survey was developed. The baseline questionnaire featured 36 autoimmune rheumatic disease (AIRD)-related questions, covering several areas on disease diagnosis, current symptom status ($n = 11$), functional status ($n = 3$), treatment history ($n = 6$) and sociodemographics ($n = 4$) and COVID-19 infection and vaccination ($n = 12$). The survey was translated into 18 languages and was hosted on an online platform (surveymonkey.com). It was circulated by the international COVAD Study Group (>110 physicians) in healthcare centres in at least 94 countries and through social media platforms and online patient support groups [5–7]. Convenience sampling was used and all participants >18 years of age were included. Ethical approval was obtained from the Institutional Ethics Committee of the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, and local institutional committees approved the study as per local guidelines. Informed consent was obtained from the participants via a cover letter.

For this study, data on participants diagnosed with RA were retrieved on 15 March 2022. Multiple relevant variables were extracted from the survey responses of the included participants, focusing on disease diagnosis, current symptom status, functional status, treatment history and demographic variables, including age, gender, ethnicity and income level of the country of residence (low and lower-middle income *vs* upper-middle income *vs* high income as per the World Bank Country Classification) [8]. Disease duration was calculated as the time between age at diagnosis and age at completion of the questionnaire. Disease activity 4 weeks before vaccination was assessed by patients' responses to questions about their perceived disease activity status ('My disease was inactive or in remission', 'My disease was active but stable and manageable', 'My disease was active and improving', 'My disease was active and worsening', 'I am not sure', 'Other'), their symptoms including joint pain and swelling in the hands or other joints ('Yes', 'No') and the number of swollen joints ('0', '1–2', '3–5', '5+'), use of corticosteroids ('No', 'Yes, <10 mg/day', 'Yes, 10–20 mg/day', 'Yes, >20 mg/day') and any need to step up immunosuppression medication ('Yes', 'No'). Fatigue and pain were assessed with a 10-cm visual analogue scale (VAS). Function was assessed as self-rated physical health status ('Poor', 'Fair', 'Good', 'Very good', 'Excellent'), as the ability to carry out everyday physical activities such as walking, climbing stairs, carrying groceries or moving a chair ('Not at all', 'A little', 'Moderately', 'Mostly', 'Completely') and as a score using the PROMIS PF-10a.

The PROMIS PF-10a is a 10-item questionnaire in which each question is scored on a 5-point scale. The degree to which the patient's current physical function limits his/her life is assessed by the first five questions, and for each question the answer choices range from 1 ('Cannot do') to 5 ('Without any difficulty'). The remaining five questions evaluate the ability to carry out specific functional activities, with answer options ranging from 1 ('Unable to do') to 5 ('Without any difficulty'). Individual question scores are summed to calculate the final score, which ranges between 10 and 50, with higher scores indicating better physical function. The list of questions included in the COVAD survey corresponding to the PROMIS PF-10a is presented in Supplementary Table S1, available at *Rheumatology Advances in Practice* online.

Statistical analysis

Descriptive statistics for demographic and clinical variables are presented as the median, interquartile range (IQR), minimum and maximum for numeric variables and percentages for categorical variables. Variables were compared between country income categories using the Kruskal–Wallis and Pearson chi-squared tests for numeric and categorical variables, respectively. For statistical analysis, self-reported disease activity categories were combined into inactive disease ('My disease was inactive or in remission'), active disease ('My disease was active but stable and manageable', 'My disease was active and improving', 'My disease was active and worsening') and other/unknown ('I am not sure', 'Other').

The predictive ability of demographic and clinical variables on PROMIS PF-10a scores was tested by univariable and multivariable negative binomial regression. Univariable and multivariable negative binomial regression models tested the predictive ability of demographic and clinical variables on PROMIS PF-10a scores. In multivariable models, demographic and clinical variables were tested first in two separate models and then combined into a single model. Multicollinearity was assessed using the variance inflation factor (VIF). Based on the results of the combined model and VIF analysis, the most parsimonious model predicting PROMIS PF-10a scores was built. Lastly, the most parsimonious model was examined in multilevel negative binomial regression analysis, with country income level as a random effect and all other variables as fixed effects.

Because PROMIS PF-10a was overdispersed and negatively skewed in all negative binomial regression models, it was reversed using the linear function ($y = 50 - x$). The reversed PROMIS PF-10a outcome represents the points away from a perfect function score for each participant; the higher the reversed PROMIS PF-10a value, the worse the physical function.

All statistical analyses were performed using Stata SE version 15 (StataCorp, College Station, TX, USA).

Results

Descriptive characteristics of the cohort across country income level

A total of 1342 RA patients were included in this analysis. Participants were primarily female (87.7%), Caucasian (55.7%) and had a median age of 51 years (IQR 41–61). In terms of disease characteristics, the median disease duration was 9 years (IQR 4–17) and 65.3% of participants self-reported having active disease. Joint pain or swelling at any joint was common (42.9%), even though most participants reported zero swollen joints (67.9%). A median fatigue and pain level of 5 (IQR 2–7) and 4 (IQR 2–6), respectively, was reported. Most participants did not take any steroids (74.9%), and of those who did, most received a dose of <10 mg/day (20.9%). A total of 17.5% and 6.5% of

participants reported an increase in immunosuppressant and steroid medication, respectively. Regarding physical function, 66.3% of participants reported an overall health rating of good or above, and more than half (62.4%) of the participants were able to mostly or entirely carry out everyday activities. The median PROMIS PF-10a score was 40 (IQR 35–45) (Table 1).

A comparison of these variables across country income levels revealed that all variables, with the exception of an increase in steroid medication and pain level, differed significantly across income groups (Table 1). Compared with low and low-middle income countries, participants from upper-middle and high income countries tended to be older, more predominantly female, and of Caucasian ethnicity ($P < 0.0001$ for all). They had a longer disease duration, were more likely to have active disease, any joint swelling and more swollen joints and also reported higher fatigue levels ($P < 0.02$ for all). They were more likely to report no steroid

Table 1. Demographic and clinical characteristics of participants, total and by country income level

Characteristics	All ($n = 1342$)	Country income level			*P*-value[a]
		Low and low-middle income ($n = 384$)	Upper-middle income ($n = 208$)	High income ($n = 750$)	
Sociodemographic variables					
Age, median (IQR); range	51 (41–61); 18–91	45 (37–55); 20–91	50 (39–61); 18–86	54 (39–61); 18–88	**0.0001**
Gender, *n* (%)					
Male	165 (12.3)	78 (20.3)	16 (7.7)	71 (9.5)	**<0.0001**
Female	1173 (87.7)	306 (79.7)	191 (92.3)	676 (90.5)	
Ethnicity, *n* (%)					
Caucasian (White)	748 (55.7)	12 (3.1)	99 (47.6)	637 (84.9)	**<0.0001**
Asian	373 (27.8)	301 (78.4)	9 (4.3)	63 (8.4)	
Hispanic	88 (6.6)	0 (0.0)	80 (38.5)	8 (1.1)	
African American or of African origin	4 (0.3)	0 (0.0)	4 (1.9)	0 (0.0)	
Native American/Indigenous/Pacific Islander	7 (0.5)	1 (0.3)	4 (1.9)	2 (0.3)	
Other	35 (2.6)	8 (2.1)	5 (2.4)	22 (2.9)	
Do not wish to disclose	87 (6.5)	62 (16.1)	7 (3.4)	18 (2.4)	
Clinical variables—disease activity					
Disease duration, median (IQR); range	9 (4–17); 1–72	7 (4–12); 1–52	10 (4.5–15); 1–52	10 (5–19); 1–72	**0.0001**
Self-reported autoimmune disease status, *n* (%)					
Inactive	340 (25.3)	107 (27.8)	67 (32.2)	166 (22.1)	**0.015**
Active	876 (65.3)	236 (61.5)	125 (60.1)	515 (68.7)	
Other/unknown	126 (9.4)	41 (10.7)	16 (7.7)	69 (9.2)	
Joint pain or swelling in hands, *n* (%)	431 (32.1)	106 (27.6)	56 (26.9)	269 (35.9)	**0.0040**
Joint pain or swelling in other joints, *n* (%)	397 (29.6)	76 (19.8)	57 (27.4)	264 (35.2)	**<0.0001**
Any joint point or swelling, *n* (%)	576 (42.9)	139 (36.2)	78 (37.5)	359 (47.9)	**<0.0001**
Swollen joints, *n* (%)					
0	866 (67.9)	265 (73.2)	141 (71.2)	460 (64.3)	**0.015**
1–2	157 (12.3)	40 (11.0)	26 (13.1)	91 (12.7)	
3–5	155 (12.1)	39 (10.8)	22 (11.1)	94 (13.1)	
≥5	98 (7.7)	18 (5.0)	9 (4.6)	71 (9.9)	
Fatigue level, median (IQR); range	5 (2–7); 0–10	4 (2–5); 0–10	4 (2–6); 0–10	5 (3–7); 0–10	**0.0001**
Pain level, median (IQR); range	4 (2–6); 0–10	4 (2–5); 0–10	3 (2–6); 0–10	4 (2–6); 0–10	0.1313
Steroid use, *n* (%)					
None	1005 (74.9)	252 (65.6)	156 (75.0)	597 (79.6)	**<0.0001**
Yes, <10 mg/day	281 (20.9)	112 (29.2)	41 (19.7)	128 (17.0)	
Yes, 10–20 mg/day	48 (3.6)	19 (4.9)	9 (4.3)	20 (2.7)	
Yes, >20 mg/day	5 (2.6)	1 (0.3)	2 (1.0)	5 (0.7)	
Increase in any immunosuppressant medication, *n* (%)	235 (17.5)	58 (15.1)	26 (12.5)	151 (20.1)	**0.013**
Increase in steroids medication, *n* (%)	87 (6.5)	18 (4.7)	11 (5.3)	58 (7.7)	0.107
Clinical variables—function					
Overall health rating					
Poor	98 (7.3)	26 (6.8)	7 (3.4)	65 (8.7)	**<0.0001**
Fair	354 (26.4)	71 (18.5)	44 (21.2)	239 (31.9)	
Good	546 (40.7)	180 (46.9)	76 (36.5)	290 (38.7)	
Very good	276 (20.6)	90 (23.4)	49 (23.5)	137 (18.2)	
Excellent	68 (5.0)	17 (4.4)	32 (15.4)	19 (2.5)	
Ability to carry out everyday activities, *n* (%)					
Not at all	34 (2.5)	15 (3.9)	4 (1.9)	15 (2.0)	**<0.0001**
A little	152 (11.3)	63 (16.4)	10 (4.8)	79 (10.5)	
Moderately	320 (23.9)	103 (26.8)	37 (17.8)	180 (24.0)	
Mostly	436 (32.5)	120 (31.3)	77 (37.0)	239 (31.9)	
Completely	400 (29.8)	83 (21.6)	80 (38.5)	237 (31.6)	
PROMIS PF-10a score, median (IQR); range	40 (35–45); 10–50	40 (35–44); 13–50	41 (35.5–46.5); 11–50	40 (33–45); 10–50	**0.0353**

Significant values in bold.
[a] *P*-value from the Kruskal-Wallis test for numeric variables and the Pearson chi-squared test for categorical variables.

use, but an increase in immunosuppressant medications, and more of the high income country participants reported poor overall health ($P < 0.01$ for all).

Unadjusted and minimally adjusted models predicting physical function

Results from the univariable negative binomial regression showed that older age [$\beta = 0.010$ (95% CI 0.007, 0.013)] and female gender [$\beta = 0.269$ (95% CI 0.134, 0.405)] were associated with higher reversed PROMIS PF-10a scores and therefore with lower physical function (Table 2). Asian and Hispanic ethnicity compared with Caucasian, as well and residing in a country with an upper-middle income level, were associated negatively with the reversed PROMIS PF-10a variable and thus with better physical function.

Adjusting for age, gender and ethnicity, disease duration; active disease; joint pain or swelling in the hands, other joints or any joints; number of swollen joints; fatigue; pain levels and greater amounts of steroid or immunosuppressant medication were all independently associated with higher reversed PROMIS PF-10a and therefore with worse physical function. In contrast, higher overall health ratings and more frequent ability to carry out everyday activities were independently associated with lower reversed PROMIS PF-10a scores and therefore with better physical function, after adjustment for age, gender and ethnicity (Table 2).

Most parsimonious model predicting physical function

Supplementary Tables S2 and S3, available at *Rheumatology Advances in Practice* online, show the separate negative binomial regression models, which independently include all demographic and clinical variables. Table 3 shows the results of the most parsimonious and best predictive model for reversed PROMIS PF-10a.

In this model, older age, female gender, disease duration, fatigue and pain levels were associated with higher reversed PROMIS PF-10a scores and therefore with worse physical function. In contrast, Asian ethnicity, higher overall health ratings, the complete ability to carry out everyday activities and residing in a country with an upper-middle or high income level were independently associated with lower reversed PROMIS PF-10a scores and therefore with better physical function. Despite being the best predictive model, the R^2 of the most parsimonious model was only 0.1259.

Supplementary Table S4, available at *Rheumatology Advances in Practice* online, shows the results of the negative binomial regression model with all demographic and clinical variables, including country income level. No variables had to be removed due to collinearity.

Multilevel analysis with country-level income as a random effect

Multilevel analysis, with country-level income as a random effect and all other variables in the most parsimonious model as fixed effects, failed to produce evidence that there is variation in PROMIS PF-10a scores across individuals beyond what is explained by the sociodemographic and clinical characteristics included in the most parsimonious model (LR test of multilevel *vs* binomial model: chi-bar$^2(01) = 1.20$, $P = 0.1369$).

Discussion

Based on the global COVAD study, this study evaluated physical function in RA using the PROMIS PF-10a. The study shows that clinical factors (including disease duration, increased joint pain/swelling, increased steroid use and overall health ratings) remain strong, independent predictors of physical function in RA.

Across univariable and multivariable analyses, older age, female gender and increased disease duration were consistently associated with worse physical function. This is in keeping with other studies that show female gender, disease duration and disease activity to be among the main determinants of physical function in RA [3, 9]. In the Comorbidities in Rheumatoid Arthritis (COMORA) study, female gender was independently associated with increased 28-joint DAS (DAS28) scores [9]. Interestingly our study showed that being of Asian ethnicity was associated with better physical function overall, but the reason for this remains unclear. Of note, better health-related quality of life experience is also reported by patients of Asian ethnicity in SLE, despite the known vulnerability of the Asian population to develop more severe manifestations such as lupus nephritis [10, 11]. In addition, one study examining the effects of language, insurance, race and ethnicity on measurement properties of the PROMIS PF-10a in RA noted that even when the questionnaire was translated into native languages, the PROMIS PF-10a scores correlated strongly with most ethnic groups apart from Chinese speakers on pain and patient global assessment [12].

Having a high overall health rating in this study was also associated with better physical function in all models. Previous work has demonstrated that self-reporting of health provides a reasonable estimate of comorbidity, and it also showed that self-reported disease burden may give a more accurate estimate of comorbidity than existing measures [13]. While we cannot conclude in this self-reported survey that overall health rating means lower disease activity, or even fewer comorbidities, it is not unsurprising that better physical function in RA was observed in this group. Conversely, it has been demonstrated by several groups, including our own, that physical disability becomes worse with increasing levels of comorbidity, irrespective of disease activity [4, 14].

In our analyses, residing in a country with an upper-middle or high income level was independently associated with better physical function. This association persisted after adjustment for sociodemographic and clinical variables. Previous work on the effect of country-level income on disease activity noted an association with lower country-level income and increased disease activity [9, 15]. Utilising the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis database, a strong correlation was noted between disease activity (as measured by DAS28) and a country's gross domestic product (GDP), where countries with lower GDPs had higher DAS28 scores [15]. The COMORA study demonstrated that physical function (based on HAQ data) in patients with RA varied across countries, however, the authors did not note a difference that was attributable to GDP [16]. It should be kept in mind that HAQ Disability Index and PROMIS PF-10 scores are highly correlated with physical function [17].

This survey was conducted during the COVID-19 pandemic, which significantly impacted healthcare delivery to patients with RA. In upper-middle and high income countries, there was

Table 2. Unadjusted and adjusted negative binomial regressions of each demographic and clinical variable against reversed PROMIS PF-10a

Variables	PROMIS PF-10a, median (IQR); range	Unadjusted		Adjusted for age, gender and ethnicity	
		β (95% CI)	*P*-value[a]	β (95% CI)	*P*-value[b]
Sociodemographic variables					
Age		0.010 (0.007, 0.013)	**<0.001**	–	–
Gender					
Male ($n = 165$)	42 (38–47); 16–50	ref.			
Female ($n = 1173$)	40 (34–44); 10–50	0.269 (0.134, 0.405)	**<0.001**	–	–
Ethnicity					
Caucasian (White) ($n = 748$)	40 (33–45); 10–50	ref.		–	–
Asian ($n = 373$)	41 (35–45); 13–50	−0.162 (−0.264, −0.059)	**0.002**	–	–
Hispanic ($n = 88$)	41 (37–46.5); 14–50	−0.290 (−0.473, −0.106)	**0.002**	–	–
African American or of African origin ($n = 4$)	42.5 (38.5–45.5); 35–48	−0.416 (−1.244, 0.412)	0.325	–	–
Native American/Indigenous/Pacific Islander ($n = 7$)	36 (34–40); 29–48	0.0356 (−0.571, 0.642)	0.908	–	–
Other ($n = 35$)	37 (28–44); 18–50	0.093 (−0.182, 0.369)	0.507	–	–
Do not wish to disclose ($n = 87$)	39 (36–43); 14–50	−0.038 (−0.220, 0.144)	0.683	–	–
Country income level					
Low and low-middle ($n = 384$)	40 (35–44); 13–50	ref.		ref.	
Upper-middle ($n = 208$)	41 (35.5–46.5); 11–50	−0.097 (−0.237, 0.043)	0.174	−0.174 (−0.314, −0.034)	**0.015**
High ($n = 750$)	40 (33–45); 10–50	0.078 (−0.023, 0.179)	0.130	−0.026 (−0.138, 0.086)	0.652
Clinical variables—disease activity					
Disease duration		0.013 (0.008, 0.017)	**<0.001**	0.009 (0.005, 0.014)	**<0.001**
Self-reported autoimmune disease status, *n* (%)					
Inactive ($n = 340$)	43 (39–48); 14–50	ref.		ref.	
Active ($n = 876$)	38.5 (33–43); 11–50	0.496 (0.394, 0.598)	**<0.001**	0.506 (0.404, 0.608)	**<0.001**
Other/unknown ($n = 126$)	40 (35–44); 10–50	0.445 (0.281, 0.609)	**<0.001**	0.438 (0.277, 0.599)	**<0.001**
Joint pain or swelling in hands					
No ($n = 911$)	41 (36–46); 10–50	ref.		ref.	
Yes ($n = 431$)	37 (31–42); 11–50	0.331 (0.238, 0.423)	**<0.001**	0.350 (0.258, 0.441)	**<0.001**
Joint pain or swelling in other joints					
No ($n = 945$)	41 (36–46); 10–50	ref.		ref.	
Yes ($n = 397$)	37 (30–41); 11–50	0.392 (0.305, 0.491)	**<0.001**	0.426 (0.334, 0.518)	**<0.001**
Any swelling					
No ($n = 766$)	42 (37–46); 10–50	ref.		ref.	
Yes ($n = 576$)	37 (32–42); 11–50	0.374 (0.287, 0.461)	**<0.001**	0.406 (0.320, 0.492)	**<0.001**
Swollen joints, *n* (%)					
0 ($n = 866$)	41 (36–46); 10–50	ref.		ref.	
1–2 ($n = 157$)	38 (34–43); 15–50	0.203 (0.066, 0.340)	**0.004**	0.220 (0.085, 0.354)	**0.001**
3–5 ($n = 155$)	37 (31–41); 12–50	0.356 (0.219, 0.493)	**<0.001**	0.372 (0.239, 0.505)	**<0.001**
≥5 ($n = 98$)	31 (23–39); 11–48	0.662 (0.497, 0.827)	**<0.001**	0.696 (0.534, 0.857)	**<0.001**
Fatigue level		0.158 (0.142, 0.173)	**<0.001**	0.157 (0.141, 0.172)	**<0.001**
Pain level		0.188 (0.173, 0.204)	**<0.001**	0.186 (0.172, 0.201)	**<0.001**
Steroid use					
None ($n = 1005$)	41 (35–45); 10–50	ref.		ref.	
Yes, <10 mg/day ($n = 281$)	37 (32–43); 11–50	0.259 (0.152, 0.365)	**<0.001**	0.247 (0.142, 0.351)	**<0.001**
Yes, 10–20 mg/day ($n = 48$)	36.5 (33.5–41.5); 16–50	0.282 (0.049, 0.515)	**0.018**	0.329 (0.101, 0.557)	**0.005**
Yes, >20 mg/day ($n = 8$)	26 (18.5–34.5); 11–40	0.816 (0.269, 1.362)	**0.003**	0.973 (0.259, 1.327)	**0.004**
Increase in any immunosuppressant medication					
No ($n = 1107$)	40 (35–45); 10–50	ref.		ref.	
Yes ($n = 2358$)	37 (31–43); 10–50	0.229 (0.115, 0.344)	**<0.001**	0.271 (0.157, 0.84)	**<0.001**
Increase in steroids medication					
No ($n = 1255$)	40 (35–45); 10–50	ref.		ref.	
Yes ($n = 87$)	35 (29–42); 15–50	0.280 (0.103, 0.456)	**0.002**	0.329 (0.156, 0.502)	**<0.001**
Clinical variables—function					
Overall health rating					
Poor ($n = 98$)	25 (19–32); 11–44	ref.		ref.	

(continued)

Table 2. (continued)

Variables	PROMIS PF-10a, median (IQR); range	Unadjusted		Adjusted for age, gender and ethnicity	
		β (95% CI)	*P*-value[a]	β (95% CI)	*P*-value[b]
Fair ($n = 354$)	36 (31–41); 11–50	−0.492 (−0.642, −0.343)	**<0.001**	−0.521 (−0.667, −0.375)	**<0.001**
Good ($n = 546$)	41 (37–45); 12–50	−0.875 (−1.019, −0.730)	**<0.001**	−0.878 (−1.019, −0.737)	**<0.001**
Very good ($n = 276$)	44 (40–48); 10–50	−1.279 (−1.437, −0.121)	**<0.001**	−1.277 (−1.432, −1.122)	**<0.001**
Excellent ($n = 68$)	50 (43–50); 26–50	−1.794 (−2.026, −1.562)	**<0.001**	−0.809 (−2.037, −0.581)	**<0.001**
Ability to carry out everyday activities					
Not at all ($n = 34$)	35 (18–46); 11–50	ref.		ref.	
A little ($n = 152$)	28 (20.5–35); 13–50	0.201 (−0.008, 0.409)	0.059	0.222 (0.019, 0.425)	**0.032**
Moderately ($n = 320$)	35 (30–38); 11–50	−0.089 (−0.288, 0.109)	0.377	−0.066 (−0.260, 0.128)	0.506
Mostly ($n = 436$)	40 (37–43); 10–50	−0.531 (−0.728, −0.334)	**<0.001**	−0.474 (−0.667, −0.821)	**<0.001**
Completely ($n = 400$)	46 (43–49); 27–50	−1.362 (−1.56, −1.162)	**<0.001**	−1.314 (−1.510, −1.118)	**<0.001**

Significant values in bold.
[a] *P*-value from unadjusted negative binomial regression with reversed PROMIS PF-10a as the outcome.
[b] *P*-value from negative binomial regression with reversed PROMIS PF-10a as the outcome adjusting for age, gender and ethnicity.

Table 3. Best predictive negative binomial regression model for reversed PROMIS PF-10a

Clinical variable	Coefficient	*P*-value	95% CI
Age	0.008	**<0.001**	0.006, 0.010
Gender			
Female	0.132	**0.004**	0.043, 0.222
Do not wish to disclose	0.499	**0.049**	0.002, 0.995
Ethnicity			
Asian	−0.206	**<0.001**	−0.318, −0.095
Hispanic	0.007	0.926	−0.136, 0.149
African American or of African origin	−0.146	0.595	−0.682, 0.391
Native American/Indigenous/ Pacific Islander	0.206	0.278	−0.166, 0.578
Other (please specify)	0.025	0.773	−0.143, 0.192
Do not wish to disclose	−0.025	0.719	−0.160, 0.110
Disease duration	0.006	**<0.001**	0.003, 0.008
Physical health			
Fair	−0.234	**<0.001**	−0.342, −0.126
Good	−0.293	**<0.001**	−0.406, −0.179
Very good	−0.448	**<0.001**	−0.580, −0.316
Excellent	−0.798	**<0.001**	−0.999, −0.597
Fatigue level	0.025	**0.001**	0.010, 0.040
Pain level	0.075	**<0.001**	0.059, 0.090
Everyday activities			
A little	0.157	0.078	−0.018, 0.331
Moderately	0.048	0.582	−0.122, 0.217
Mostly	−0.171	0.052	−0.342, 0.001
Completely	−0.809	**<0.001**	−0.988, −0.631
Country income level			
Upper-middle	−0.149	**<0.001**	−0.283, −0.014
High	−0.225	**<0.001**	−0.339, −0.111

Significant values in bold.
Model parameters: number of observations = 1342; log likelihood = −4027.4; LR $\chi^2(16) = 1160.41$; Prob > χ^2 = <0.0001; pseudo-$R^2 = 0.1259$.

interruption of scheduled infusion therapies and disruption to the multidisciplinary team, including physiotherapists and occupational therapists who are vital in the care of patients with RA [18, 19]. In addition, as per most rheumatology clinical guidelines, immunosuppressant medications were withheld during active infection. While cessation of drugs with long half-lives, including the biologics and csDMARDs, stopping the treatment would have a limited response on disease activity during a short-lived infection. In contrast, the newer tsDMARDs, the Janus kinase inhibitors, have short half-lives, and discontinuing treatment will quickly lead to the reactivation of signalling pathways and a possible increase in disease activity [20]. tsDMARDs are now available as first- and second-line treatments in many higher income countries and their use is becoming more popular in the RA pharmacological armamentarium. The effect of the pandemic on healthcare delivery in lower income countries may have been more significant [21]. These factors taken together would likely influence physical function in RA and thus the COVAD findings may be biased towards lower scores, as the study questionnaires were completed during the pandemic.

Meanwhile, it should be noted that the COVAD survey has an inherent recruitment bias due to convenience sampling, where patients with low PROMIS PF-10a scores might have been missed. The nature of the electronic survey may have limited the number of elderly patients and other patients who may not be familiar with using the internet or smart devices. Nevertheless, 17.3% of the sample were ≥65 years of age ($n = 232$), indicating adequate representation of elderly patients. In addition, given the self-reported nature of the e-survey, the diagnosis of RA could not be verified objectively. It should be noted that patients were included only if the diagnosis was confirmed by a specialist as specified by them. Data on disease activity were also not objectively assessed. Instead, a subjective assessment by the patient was considered, including an indication of joint swelling, corticosteroid use and increased immunosuppressant medication use. However, it should be noted that in previous studies, focusing on idiopathic inflammatory myopathies, where patient-reported survey data was utilized, there was excellent agreement between patient self-reported flares and flares based on objective clinical signs [22]. In autoimmune

rheumatic diseases, flares that were patient reported and those based on clinical symptoms were strongly aligned ($\kappa = 0.898$, $P = 0.012$), suggesting that patient-reported data can be used alongside clinically evaluated reports to provide valuable data [23]. However, some variation remains and both angles are needed to holistically capture the disease state, including those aspects that matter most for patients. Information on pre-existing comorbidities, systemic organ involvement with RA and pre-existing disability, which could all impact physical function measures, was not measured in this study.

Despite the limitations, this study has important strengths, including the large numbers of patients from across the globe and the ethnic diversity, especially from underrepresented populations in Asia and Africa. Additionally, the anonymized, self-reported nature of the questionnaire with a high completion rate by respondents reflects the patient's voice. It provides unique insights into the variables that influence physical function globally.

This study shows that clinical factors including disease activity are among the most influential determinants of loss of physical function in RA [3, 24, 25]. Other patient-level factors that have consistently been shown to impact physical function are joint damage and psychosocial factors [3]. At the country level, residing in a country with an upper-middle or high income level was independently associated with better physical function. This large cross-sectional study adds to the body of evidence that a reduction in physical function in RA is mainly attributed to disease activity. It emphasizes how important early treatment to supress disease activity and prevent disease progression and joint damage is in RA. However, we did find some interesting softer determinants regarding the role country-level income plays in physical function in RA. Further studies are necessary to delineate the full effect of country-level income on physical function in RA when healthcare provision has returned to normal. Our study provides an initial global exploratory analysis on the role of country-level income in physical function in RA.

In conclusion, like previous studies, our work demonstrates that clinical factors remain strong, independent predictors of physical function in RA, irrespective of other individual and country-level socio-economic differences. This study highlights the need to prioritize controlling disease to optimize patient outcomes, even in wealthier countries where access to care and availability of treatment may be more accessible. In lower income countries, it highlights the importance of equity of access to early treatment to improve disease outcomes and physical function in RA.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Authors' contributions

L.G., S.S.A. and E.N. were responsible for conceptualization. S.S.A., C.D. and E.N. were responsible for the formal analysis. L.G. and V.A. were responsible for the investigation. E.N., L.G. and V.A. were responsible for the methodology and visualization. L.G. was responsible for the software. V.A., L.G. and H.C. were responsible for validation. S.S.A., C.D., E.N. and L.G. wrote the original draft. All authors were responsible for data curation and review and editing of the manuscript.

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