Including pain, fatigue and physical function when assessing patients with early rheumatoid arthritis provides a comprehensive picture of disease burden

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ABSTRACT

Objective: To explore the possibility of integrating patient-important outcomes like pain, fatigue and physical function into the evaluation of disease status in early rheumatoid arthritis (ERA), without compromising correct disease activity measurement.

Methods: Patients from the 2-year Care-in-early-Rheumatoid-Arthritis (CareRA) trial were included. Pain and fatigue (visual analogue scales), Health Assessment Questionnaire (HAQ), standard components of disease activity (swollen/tender joint counts (SJC/TJC), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), Physician (Ph) and Patient's (Pa) global health (GH)) were recorded at every visit (n=10). Pearson correlation and exploratory factor analyses (EFAs), using multiple imputation (15 times) and outputation (1000 times), were performed per timepoint and overall, on standard components of disease activity scores with and without pain, fatigue and HAQ. Each of the 15 000 datasets was analyzed with principal component extraction and oblimin rotation to determine which variables belong together.

Results: We included 379 patients. EFAs on standard composite score components extracted 2 factors with no substantial cross-loadings. Still, pain (0.83), fatigue (0.65) and HAQ (0.59) were strongly correlated with PaGH. When rerunning the EFAs with the inclusion of pain, fatigue and HAQ, the 2-factor model had substantial cross-loadings between factors. However, a 3-factor model was optimal, with Factor 1: Patient's assessment, Factor 2: Clinical assessment (PhGH, SJC and TJC), and Factor 3: Laboratory (ESR/CRP).

Conclusions: PaGH, pain, fatigue, and physical function represent a separate aspect of the disease burden of ERA patients, that could be further explored as a target for care apart from disease activity.

Clinical trials NCT01172639.

INTRODUCTION

The primary clinical manifestation of Rheumatoid Arthritis (RA) is inflammation of the peripheral joints resulting in swelling, stiffness and pain. However, a wider range of symptoms can be present, including functional impairment and constitutional manifestations such as fatigue as well as global health impact.(1) This symptom heterogeneity may hinder easy diagnosis but also the evaluation of changes in disease status, which may complicate the management of RA patients (beyond modulating disease activity). In RA, unlike other diseases such as hypertension or diabetes, the severity or level of disease activity cannot be evaluated by a single clinical or laboratory measurement. Which is why, currently, the response to treatment is determined by evaluation of composite scores like the disease activity score in 28 joints (DAS28) or the simplified disease activity index (SDAI) being among the most commonly used in Europe.(2)

The level of disease activity in these scores is measured via clinical evaluation, Patient (PaGH) and physician (PhGH) assessments of global health in relation to RA disease activity rating from 0-10 or 0-100 on a visual analogue scale (VAS), as well as laboratory parameters of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The clinical evaluation includes the examination of tender (TJC) and swollen joints (SJC).(1) To facilitate the use of disease activity measures, thresholds of meaning have been defined, distinguishing: remission, low, moderate and high disease activity. Active disease is a predictor of damage and physical disability, and consequently with reduced health-related quality of life, increased costs and mortality.(3) On this line, treating to a target (T2T) of remission or at least low disease activity (LDA) is widely advocated for RA.(4)

When evaluating comprehensively the impact of disease in clinical practice, physicians and patients are confronted with the difficulty to make an unambiguous distinction between aspects related to remaining disease activity requiring adaptation of pharmacological treatment and aspects requiring optimization of complementary forms of care. Unfortunately, even in patients in remission or LDA under current T2T treatment strategies, unmet needs or residual symptoms may persist and should be further explored. Among the most commonly reported remaining problems are pain, fatigue, morning stiffness, sleep disturbances, functional disability, impairment in mental health, work productivity and quality of life.(5) Moreover, when patients are asked to define remission, pain, fatigue and independence have been identified as the most important factors.(6)

We hypothesized that including patient reported outcomes could capture some of these additional aspects of the disease experience independent from traditionally measured disease components. Therefore, we explored the possibility of integrating pain, fatigue and physical function into the evaluation of disease status, in addition to the standard components of composite disease activity scores, in early RA patients treated intensively and to target.

METHODS

Study population

Care in early Rheumatoid Arthritis (CareRA) was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39, Clinical trials NCT01172639) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium. The study was approved by the leading Ethics Committee of the

University Hospitals Leuven after consulting the medical ethics committee of each participating centre (ref s51411), and all study participants gave their written informed consent before inclusion.

Patients with recently diagnosed RA (≤1 year) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis (erosions, rheumatoid factor (RF) and/or anti-citrullinated cyclic peptide (anti-CCP) positivity and baseline DAS28CRP>3.2) and then randomized into four different treatment strategies. High-risk patients were randomized to methotrexate (MTX) 15mg weekly with a step-down glucocorticoid (GC) scheme (COBRA-Slim) or to this combination together with either sulphasalazine (COBRA-Classic) or leflunomide (COBRA-Avant-Garde). Low-risk patients were randomized to a step-up treatment of MTX monotherapy without GC (Tight Step-Up) or to COBRA-Slim.

For patients who did not respond sufficiently to the initial medication scheme, the protocol specified two subsequent treatment adaptation steps and afterwards treatment was left at the discretion of the treating rheumatologist. Details on patient eligibility criteria, randomization process, study design and treatment intensifications have been published.(7) Overall, around 70% of the patients achieved a status of disease control after 2 years (DAS28CRP <2.6).(7)

Study assessments

Clinical outcomes

Patients were assessed at screening, baseline and then followed-up at week 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. An electronic trial record (eCRF) was filled out and was routinely monitored. Clinical, patient and laboratory

parameters were collected at every visit: SJC, TJC, PaGH -"Assuming all the ways your life is affected by your rheumatism, how did you feel on average over the past week?"-, PhGH, CRP or ESR, health assessment questionnaire (HAQ), pain and fatigue each on a VAS of 0-100.

Statistical analyses

All randomized patients having taken at least one medication dose were considered for analysis. The data were considered hierarchical because the same patients were measured at different time points. To deal with this type of data, exploratory factor analysis for hierarchical data (EFA-HD) was performed. EFA-HD allows obtaining a general view of the factor structure of the variables, using data from all time points simultaneously while also avoiding violating the assumption of independent observations. The method described by Lovik, et al. was used.(8) The EFA-HD consists of four steps: imputation, outputation, exploratory factor analysis (EFA), and combination of the analyses via congruence factor matching. A step by step flow-chart describing this methodology can be found in Figure 1.

Imputation. Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.(9) Treatment strategy, the centre of recruitment, age, gender, presence of comorbidities, RF, anti-CCP, erosions at baseline and completion of the 2 year-trial were also taken into account when applying multiple imputation. Based on Bodner (2008), the number of imputed sets was set to 15, equal to the missing data percentage.(10) Results of the 15 analyses were pooled using Rubin's rules. (11)

Outputation. To obtain samples with independent observations, which is a requirement for exploratory factor analysis, multiple outputation (MO) was performed.(12, 13) MO was used for

randomly selecting one observation from each visit from each patient, thereby creating a subset were all observations are independent of each other. To minimize loss of information, the technique was repeated 1000 times on each of the 15 multiply imputed datasets. Each of the 15000 datasets was analyzed separately using exploratory factor analysis.

Exploratory factor analysis. EFA uncovers the fact that multiple observed variables have similar patterns of responses because they are all associated with a latent, not directly observable, variable. Direct oblimin rotation was selected because the factors were correlated. Rotation in factor analysis is needed because the factor solutions are not unique (several different mathematically equivalent solutions exist), and the rotation allows us to choose the one that is the easiest to interpret. The rotated factor loadings show the association between the variable and the latent factor.

Combination of the results. The 15 000 factor analytic results were then combined after re-ordering the factors by maximizing Tucker's factor congruence coefficient.(14) Factor matching is a step in which congruent factors – factors with the same meaning in different analyses – are combined.(8) The same analysis was performed on the standard components of disease activity scores only (SJC, TJC, PaGH, PhGH, CRP, ESR) and with the addition of pain, fatigue and physical function (HAQ). We also examined the possibility to leave out PaGH as standard patient derived component of disease activity scores in exchange of pain, fatigue and physical function. Tucker's factor congruence coefficient was also used for estimating the similarity between factors that have been derived in different factor analyses to compare the final analytical results.(14)

On the 15 imputed datasets, Pearson correlations were also calculated to assess the strength of the association between all pairs of variables.

Sensitivity analysis

A sensitivity analysis of EFA per visit without MO was also performed. In the sensitivity analysis, EFA was performed per time point (10 visits) on the variables that are standard components of composite scores only (SJC, TJC, PaGH, PhGH, CRP, ESR) and when including three extra variables: pain, fatigue and HAQ. These ten EFAs provide only information about the latent factors per time point, and obviously they are not useful to obtain a time-independent view of the disease status evaluation over the course of the disease process.

All analyses were performed with R (version 3.5.3) and SAS 9.4.

RESULTS

In total, 379 patients with a mean (SD) age of 53.9 (13.0), 77% positive to RF or anti-CCP and 69% women, were included in CareRA of which 289 were stratified to high-risk and 90 to low-risk. The different EFAs based on the standard components of disease activity measurement instruments supported the traditional approach of composite scores extracting two factors with no substantial cross-loadings (<0.3) of the same variable on more than one factor (Table 1). This 2-factor model explained about 80% of the variance of the construct representing "disease activity" in the sense of the biological inflammatory process in peripheral joints. Still, pain (0.83), fatigue (0.65) and HAQ (0.59) were strongly correlated with PaGH (Table 2). When rerunning the EFAs including also these variables, the 2-factor model had substantial cross-loadings (≥0.3), meaning that the same variable was loading on more than one factor with variables also changing the

factors in which they had primarily loaded (data not shown due to high number -1000- analyses). However, when a third factor clearly emerged, the so-called Patient's assessment factor, a straightforward interpretation was obtained. This first factor, extracted via principal component analysis, explained most of the variance. It included PaGH and the three new variables (pain, fatigue, HAQ), all being patient reported outcomes, so we designated it the Patient factor. Factor 2 contained SJC, TJC and PhGh, all being evaluated by the clinician, which we designated as the Clinical factor, and Factor 3 with CRP and ESR which we referred to as the Laboratory factor, for obvious reasons (Table 3). The three factors explained about 76% of the variance of the broader concept of "disease activity" which could also be called "disease burden" alluding to all the ways in which the disease process affects the patient. While it is impossible to directly compare the factor analyses, the Tucker's congruence coefficient showed that the laboratory (0.99) and clinical assessment (0.87) factors were invariant -measure the same- for the six variables included in traditional disease activity composite scores.

The sensitivity analysis of EFAs per visit with the extended set of variables also showed high cross-loadings in the 2-factor model (Table 4). Again, if a 3-factor model emerged, there were no substantial cross-loadings over time (Supplementary Table 1). The cross-loadings were probably due to the lack of a simple factor structure in the 2-factor model with the extended set of variables. The 2-factor model, with only the standard components of composite disease activity scores, had no substantial cross-loadings over time (Supplementary Table 2).

We investigated the possibility to leave PaGH out of the model to evaluate to what extent this would decrease the explained variation in disease burden. Leaving out PaGH however

destabilized the factor structure as HAQ was loading on both the Clinical and Patient factor (Supplemental Table 3).

DISCUSSION

By including relevant PROs to the standard measurements included in composite scores for evaluating disease activity in RA, a better understanding of the disease burden in terms of Patient's perceptions was obtained in this study. A 3-factor model including the new factor “patient perception” on top of “clinical assessment” and “laboratory assessment” gave the best representation of the disease status based on the extended set of variables. Because the original two factors remain in this 3-factor model, additional information is gained without losing the well-established Clinical and Laboratory factors.

Evaluating all the variables included in composite scores contributes to a more comprehensive evaluation than the classical question at an outpatient visit "how are you". The PaGH is put forward as a crucial component of composite disease activity scores, as it gives voice to the Patient, but it is also not unambiguous nor all-encompassing in this respect. However, there has been much debate about its interpretation and reliability.(15) Adding to this controversy is the inconsistent phrasing of the question referring to this outcome, either all-encompassing global health or more specific disease activity related aspects.(15) It could be argued that "Patient Global(PG)", "Patient Global Health(PaGH)" or "Patient Global Assessment (PGA) of disease activity" are not interchangeable. In CareRA, the question asked to patients alluded to the broad definition of patients' "global assessment".

The PaGH has been found to be influenced by factors not strictly related to disease activity such as pain, fatigue, and physical function.(16) Pain was indeed strongly correlated to PaGH (0.83) in our cohort, similar as in other cohorts (0.86).(17) PaGH, as an overarching evaluation of wellbeing by the patient, was more strongly correlated with pain, fatigue and HAQ respectively than these patient-reported outcomes were among each other, pairwise. This could indicate that PaGH, containing an objective judgement but also a personal and psychosocial appraisal, might act like a glue holding other patient reported variables in place within the model, possibly explaining the destabilizing effect of leaving out PaGH. Moreover, pain, fatigue and functional independence have been identified as the most critical factors when patients were asked to define remission.(6) A clear understanding of what PaGH is measuring is key for accurate interpretation of the composite scores, including this outcome, appreciating its value but also its limitations.

By considering this as a separate factor along with other patient-important aspects such as pain, fatigue and physical function, we could demonstrate that PaGH indeed represents a different latent concept than the other two latent factors in our three-factor model, clinical evaluation and laboratory tests. The first latent factor was referring to what we could call the Patient's perception of "disease burden" alluding to all the ways in which the disease process affects the patient’s perceived functioning and health and the latter two more directly to "disease activity" in the sense of the biological inflammatory process in peripheral joints.

While the 2-factor EFA focusses on aspects of "disease activity" the 3-factor EFA covers the more global "disease burden". A direct comparison of the 2- and 3-factor EFAs is not possible, but both analyses showed very clear factor structures with no relevant cross-loadings and very high

primary-loadings. From a statistical perspective, both factor analytic models were satisfactory. Moreover, the 3-factor remained optimal when EFAs were performed per visit.

Based on the 3-factor analysis, a broader perspective of the patients' self-evaluation could be taken into account, including patient-important outcomes like pain, fatigue and physical function, while preserving the validity of the existing scale. This was demonstrated with the congruence coefficient, which indicates near-perfect congruence for the laboratory factor (0.99) and good congruence for the clinical factor (0.87). These factors thus have the same meaning in the 3-factor model as they do in the 2-factor and thus the information measured by these variables remains the same.

In turn, the 3-factor model could result in a more adequate estimation of the remaining disease burden, despite optimal control of disease activity, by evaluating the patient-important outcomes separately from the laboratory factor and the clinical factor and providing an opportunity for more appropriate personalized treatment according to Patient's needs. Complementary care options other than drug adaptations could be suggested to patients whose disease burden does not seem to be directly related to disease activity, for instance when the Patient-derived factor is clearly incongruent with the clinical as well as the laboratory factor. A more tailored or perhaps even dual-target might be needed for addressing the complete disease burden, making a distinction between aspects directly related to inflammatory disease activity and impact of disease not directly related to disease activity.(18)

CONCLUSION

By including patient-relevant outcomes such as pain, fatigue and physical function besides PaGH to the standard components of disease activity scores, a more patient-centered estimation of the disease burden could be obtained and should be further explored as a target for care, in view of the further development of a more holistic care strategy without compromising accurate disease activity measurement needed for pharmacological targeting.

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Contributors

PV, RW, AB, SP, AL, DDC made substantial contributions to the conception or design of the study. AL and SP performed the statistical analysis. The manuscript was written by SP, PV, RW, AB, AL and DDC and subsequently revised critically by all the remaining coauthors. All authors were involved in data interpretation and approved the final version to be submitted for publication.

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Data availability statement: The authors commit to making the relevant anonymized patient data available for a specified purpose approved by the institution and the principal investigator of the CareRA study and with a signed data access agreement.

Patient involvement: The pragmatic CareRA protocol was strongly inspired by daily interactions of the investigators with RA patients in daily clinical practice. Patients were not formally involved in setting the research question or the outcome measures, nor were they invited to comment on study design or the interpretation of the results of this manuscript. However, results of this research will be disseminated to study participants, all stakeholders and the general public in collaboration with patient organizations and the Belgian patient partners program (trained patients who educate physicians, medical students and other health care professionals in collaboration with a rheumatologist).

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Figure 1: Flow chart of the different steps performed in exploratory factory analysis for hierarchical data

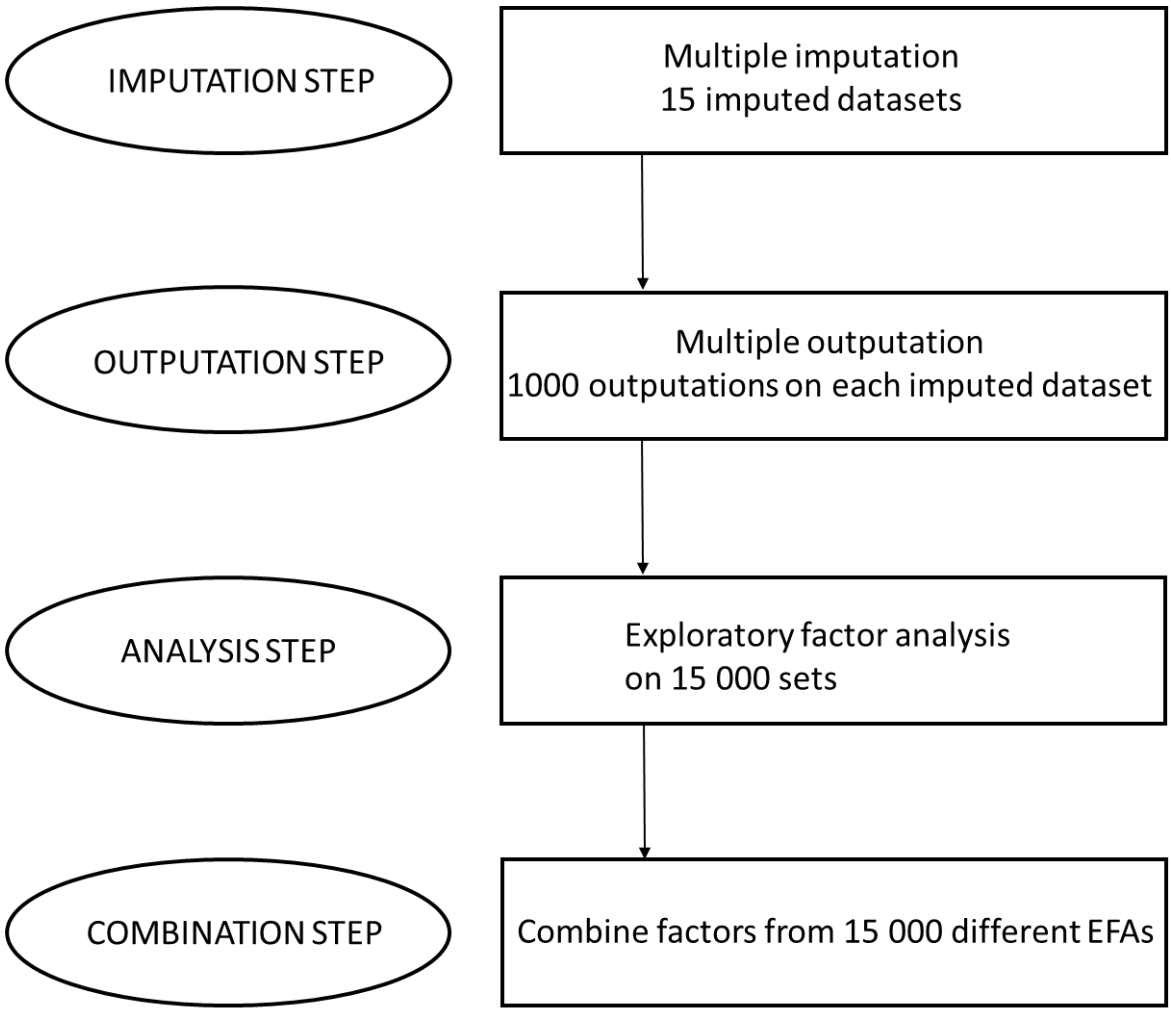

Table 1: Exploratory factor analysis extracting 2-factor model with composite scores variables

F1: Clinical	**F2: Laboratory**
PaGH: 0.72	CRP: 0.88
SJC28: 0.82	ESR: 0.77
TJC28: 0.87	
PhGH: 0.90	

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained.

F: factor, PaGH: Patient's global health assessment, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

Table 2: Pearson correlations of all measured variables after combining 15 000 datasets

	CRP	ESR	SJC28	TJC28	PhGH	PaGH	Fatigue	Pain	HAQ
CRP	1								
ESR	**0.464**	1							
SJC28	0.292	**0.319**	1						
TJC28	0.247	0.271	**0.756**	1					
PhGH	0.228	0.293	**0.680**	**0.679**	1				
PaGH	0.204	0.231	**0.403**	**0.470**	**0.564**	1			
Fatigue	0.144	0.145	0.236	**0.312**	**0.385**	**0.650**	1		
Pain	0.193	0.219	**0.394**	**0.465**	**0.570**	**0.834**	**0.632**	1	
HAQ	0.209	0.263	**0.407**	**0.464**	**0.492**	**0.588**	**0.430**	**0.572**	1

Moderate (0.3-0.7) and strong (>0.7) correlations in **bold**

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PaGH: Patient's global health assessment, PhGH: physician's global health assessment, HAQ: health assessment questionnaire

Table 3: Exploratory factor analysis extracting 3-factor model with extended set of variables

F1: Patient	**F2: Clinical**	**F3: Laboratory**
Fatigue: 0.90	SJC28: 0.92	CRP: 0.87
Pain: 0.86	TJC28: 0.89	ESR: 0.78
HAQ: 0.57	PhGH: 0.76	
PaGH: 0.87		

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained.

F: factor, PaGH: Patient's global health assessment, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

Table 4: Exploratory factor analysis **per time point** extracting a 2-factor model with extended set of variables

Timepoint	**Week 0**		**Week 8**		**Week 16**		**Week 28**		**Week 40**	
Variables	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment
CRP	-0.11	0.74	0.02	0.84	-0.03	0.70	0.01	0.80	-0.07	0.72
ESR	-0.05	0.71	-0.01	0.85	-0.06	0.55	0.04	0.76	-0.01	0.74
SJC28	0.07	0.80	0.60	0.11	-0.07	0.87	0.64	-0.23	0.41	0.19
TJC28	0.14	0.73	0.74	-0.04	0.13	0.70	0.79	-0.25	0.60	0.07
PaGH	0.90	0.04	0.87	-0.03	0.93	-0.01	0.82	0.20	0.85	0.09
Fatigue	0.85	-0.14	0.65	-0.01	0.81	-0.12	0.57	0.27	0.74	-0.04
PhGH	**0.48**	**0.50**	0.79	0.04	**0.36**	**0.60**	**0.78**	**-0.86**	0.60	0.26
Pain	0.94	-0.04	0.83	0.01	0.91	0.02	0.79	0.23	0.85	0.08
HAQ	0.62	0.26	0.74	-0.06	0.62	0.26	0.64	0.20	**0.54**	**0.32**
Timepoint	**Week 52**		**Week 65**		**Week 78**		**Week 91**		**Week 104**	
Variables	Clinical	Laboratory	Clinical	Laboratory	Clinical	Laboratory	Clinical	Laboratory	Clinical	Laboratory

	assessment	assessment	assessment	assessment	assessment	assessment	assessment	assessment	assessment	assessment
CRP	-0.05	0.69	-0.01	0.84	-0.04	0.45	**0.34**	**0.52**	-0.05	0.65
ESR	-0.13	0.66	0.02	0.83	-0.19	0.55	0.05	0.54	-0.14	0.59
SJC28	0.10	0.72	**0.61**	**0.98**	0.15	0.70	0.11	0.40	0.07	0.74
TJC28	**0.39**	**0.46**	0.72	0.07	**0.34**	**0.54**	0.22	0.46	0.19	0.64
PaGH	0.90	0.03	0.84	-0.07	0.88	-0.01	0.86	0.06	**0.87**	**0.34**
Fatigue	0.83	-0.18	0.75	-0.12	0.82	-0.17	0.75	0.01	0.86	-0.15
PhGH	**0.46**	**0.41**	0.70	0.02	**0.45**	**0.55**	0.44	0.28	**0.39**	**0.49**
Pain	0.92	-0.10	0.84	-0.08	0.89	-0.02	**0.83**	**0.87**	0.85	0.07
HAQ	0.65	0.15	0.72	0.09	0.62	0.18	0.66	0.14	0.69	0.05

Factor loadings presented (correlation between the observed score and the latent score). Substantial cross-loadings (>0.3) have been highlighted in bold. The factor order is by % of variance explained.

PaGH: patient's global health assessment, HAQ: health assessment questionnaire, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment