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Does Including Pain, Fatigue, and Physical Function When Assessing Patients with Early Rheumatoid Arthritis Provide 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 analog 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 (PhGH) and patient (PaGH) global health] were recorded at every visit (n = 10). Pearson correlation and exploratory factor analyses (EFA), using multiple imputation (15×) and outputation (1000×), 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 using EFA with principal component extraction and oblimin rotation to determine which variables belong together.

Results. We included 379 patients. EFA 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 EFA 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 assessment, Factor 2: clinical assessment (PhGH, SJC, and TJC), and Factor 3: laboratory assessment (ESR/CRP).

Conclusion. PaGH, pain, fatigue, and physical function represent a separate aspect of the disease burden of patients with ERA, which could be further explored as a target for care apart from disease activity. [ClinicalTrials.gov: NCT01172639].

Key Indexing Terms: composite scores, disease activity, factor analysis, patient preference, patient-reported outcome measures, rheumatoid arthritis

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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 effect of RA on global health[1]. This symptom heterogeneity may hinder easy diagnosis and 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. This is why, currently, the response to treatment is determined by evaluation of composite scores, such as the Disease Activity Score in 28 joints (DAS28) or the Simplified Disease Activity Index (SDAI), which are among the most commonly used in Europe[2].

The level of disease activity in these scores is measured by clinical evaluation, patient (PaGH) and physician (PhGH) global health in relation to RA disease activity ranging from 0 to 10 or 0 to 100 on a visual analog scale (VAS), as well as laboratory variables of inflammation such as erythrocyte sedimentation rate (ESR) and

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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 between remission, and low, moderate, and high disease activity. Active disease is a predictor of damage and physical disability, and consequently, results in reduced health-related quality of life (QOL), increased costs, and mortality[3]. In line with this, a treat-to-target (T2T) of remission or at least low disease activity (LDA) is widely advocated for RA[4].

When comprehensively evaluating the effect of disease in clinical practice, physicians and patients are confronted with the difficulty of making an unambiguous distinction between aspects related to residual 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 residual problems are pain, fatigue, morning stiffness, sleep disturbances, functional disability, and impairment in mental health, work productivity, and QOL[5]. Moreover, when asked to define remission, patients identified pain, fatigue, and independence as the most important factors[6].

We hypothesized that including patient-reported outcomes (PRO) 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.

MATERIALS AND 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; ClinicalTrials.gov: NCT01172639) conducted in 13 Flemish rheumatology centers (2 academic centers, 7 general hospitals, and 4 private practices) in Belgium[7]. The study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each participating center (ref s51411), and all study participants gave their written informed consent before inclusion.

Patients with recently diagnosed RA (≤ 1 yr) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis [erosions, rheumatoid factor (RF) and/or anticitrullinated cyclic peptide (anti-CCP) positivity and baseline Disease Activity Score in 28 joints (DAS28)-CRP > 3.2) and then randomized into 4 different treatment strategies. High-risk patients were randomized to methotrexate (MTX) 15 mg weekly with a step-down glucocorticoid (GC) scheme (COBRA-Slim), or to this combination together with either sulfasalazine (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 2 subsequent treatment adaptation steps, and afterward, 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 (DAS28-CRP < 2.6)[7].

Clinical outcomes. Patients were assessed at screening and 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 case report form was filled out and routinely monitored. Clinical, patient, and laboratory variables 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 who had taken at least 1 medication dose were considered for analysis. The data were considered hierarchical because the same patients were measured at different timepoints. To deal with this type of data, exploratory factor analysis (EFA) for hierarchical data (EFA-HD) was performed. EFA-HD allows to obtain a general view of the factor structure of the variables, using data from all timepoints 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 4 steps: imputation, outputation, EFA, and a combination of the analyses by 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 center of recruitment, age, sex, 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, 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 EFA, multiple outputation (MO) was performed[12,13]. MO was used for randomly selecting 1 observation from each visit from each patient, thereby creating a subset where 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 15,000 datasets was analyzed separately using EFA.

EFA. 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 reordering the factors by maximizing Tucker factor congruence coefficient[14]. Factor matching is a step in which congruent 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 for pain, fatigue, and physical function. Tucker 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. EFA was performed per timepoint (10 visits) on the variables that are standard components of composite scores only (SJC, TJC, PaGH, PhGH, CRP, ESR) and when including 3 extra variables: pain, fatigue, and HAQ. These 10 EFA provide only information about the latent factors per timepoint, and obviously they are not useful to obtain a time-independent view of the disease status evaluation over the course of the disease process.

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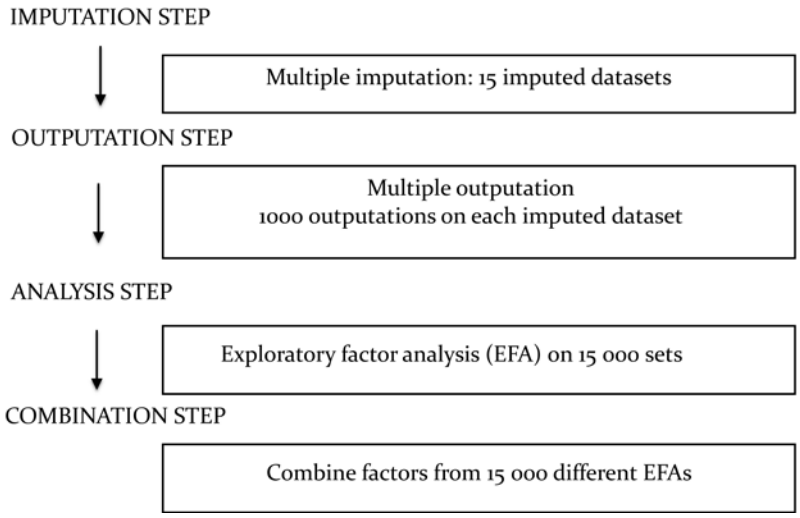

Figure 1. Flowchart of the different steps performed in exploratory factory analysis for hierarchical data.

All analyses were performed with R (version 3.5.3; R Foundation for Statistical Computing) and SAS 9.4 (SAS Institute Inc.).

RESULTS

In total, 379 patients were included in CareRA [mean (SD) age of 53.9 (13.0) yrs, 77% RF- or anti-CCP–positive, 69% women), of which 289 were stratified to high risk and 90 to low risk[7]. The different EFA, based on the standard components of disease activity measurement instruments, supported the traditional approach of composite scores extracting 2 factors with no substantial cross-loadings (< 0.3) of the same variable on > 1 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 EFA including these variables, the 2-factor model had substantial cross-loadings (≥ 0.3), meaning that the same variable was loading on > 1 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 patient assessment factor, a straightforward interpretation was obtained. This first factor, extracted by principal component analysis, explained most of the variance. It included PaGH and the 3 new variables (pain, fatigue, HAQ), all being PRO, 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. Last, factor 3 included CRP and ESR, which we referred to as the Laboratory factor (Table 3). The 3 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 congruence coefficient showed that the laboratory (0.99) and clinical assessment (0.87) factors were invariant (measure the same) for the 6 variables included in traditional disease activity composite scores.

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

Variables	Factor 1: Clinical	Factor 2: Laboratory
PhGH	0.90	
TJC28	0.87	
SJC28	0.82	
PaGh	0.72	
CRP		0.88
ESR		0.77

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (< 0.3) and not presented. The factor order is by % of variance explained. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PaGH: patient global health assessment; PhGH: physician global health assessment; SJC28: 28 swollen joint count; TJC28: 28 tender joint count.

The sensitivity analysis of EFA per visit with the extended set of variables also showed high cross-loadings in the 2-factor model (Supplementary Table 1). Again, if a 3-factor model emerged, there were no substantial cross-loadings over time (Supplementary Table 2, available with the online version of this article). 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 3).

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 factors (Supplementary Table 4, available with the online version of this article).

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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; HAQ: Health Assessment Questionnaire; PaGH: patient global health; PhGH: physician global health; SJC28: 28 swollen joint count; TJC28: 28 tender joint count.

Table 3. Exploratory factor analysis extracting a 3-factor model with an extended set of variables.

Variables	Factor 1: Patient	Factor 2: Clinical	Factor 3: Laboratory
Fatigue	0.90		
PaGH	0.87		
Pain	0.86		
HAQ	0.57		
SJC28		0.92	
TJC28		0.89	
PhGH		0.76	
CRP			0.87
ESR			0.78

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (< 0.3) and not presented. The factor order is by % of variance explained. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PaGH: patient global health assessment; PhGH: physician global health assessment; SJC28: 28 swollen joint count; TJC28: 28 tender joint count.

DISCUSSION

By including relevant PRO to the standard measurements included in composite scores for evaluating disease activity in RA, a better understanding of the disease burden in terms of patients' 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 2 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 classic question, "How are you?" at an outpatient visit. 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 assessment (PGA), PaGH, or patient global assessment of disease activity (PtGA) are not interchangeable. In CareRA, the question asked to patients alluded to the broad definition of PGA.

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 well-being by the patient, was more strongly correlated with pain, fatigue, and HAQ, than these PRO were among each other, pairwise. This could indicate that PaGH, containing an objective judgment 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 it out. 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, and when including PaGH, it is important to appreciate its value while also recognizing its limitations.

By considering PaGH as a separate factor, along with other patient-important aspects such as pain, fatigue, and physical function, we demonstrated in our study that PaGH indeed represents a different latent concept than the other 2 latent factors (clinical evaluation and laboratory tests) in our 3-factor model. The first latent factor refers to the patient's perception of disease burden, specifically to all the ways in which the disease process affects the patient's perceived functioning and health; the latter two refer more directly to disease activity in the sense of the biological inflammatory process in peripheral joints.

Whereas the 2-factor EFA focuses on aspects of disease activity, the 3-factor EFA covers the more global disease burden. A direct comparison of the 2- and 3-factor EFA 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

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satisfactory. Moreover, the 3-factor remained optimal when EFA 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 such as 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 model, and thus the information measured 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 and clinical factors, and providing an opportunity for more appropriate personalized treatment according to patients' 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 factors. A more tailored or perhaps even dual-target approach might be needed for addressing the complete disease burden, making a distinction between aspects directly related to inflammatory disease activity and effects of disease not directly related to disease activity[18].

In conclusion, by including patient-important 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 further developing of a more holistic care strategy without compromising accurate disease activity measurement needed for pharmacological targeting.

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DATA AVAILABILITY

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. 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 healthcare professionals in collaboration with a rheumatologist).

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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