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Profiling Algorithm of Rheumatoid Arthritis Patients Based on their Disease Specific Patient Reported Outcomes

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ABSTRACT

Rheumatoid arthritis (RA) is characterised by proliferative inflammation in the joints. The progressive process destroys anatomical structures causing pain and mechanical dysfunction. The burden of the disease extends to the psychosocial status and quality of life of patients. A modern goal-directed therapeutic strategy requires continuous monitoring of the patient's condition. Among the indicators, Patient-Reported Outcomes are of great importance in addition to objective physiological indicators. The aim of the present study is to search for and construct a higher resolution model that reflects the RA patient's perception of his/her own disease and that also meets the objective indicators. To this end, we used the Rheumatoid Arthritis Disease Activity Index – 5, the Rheumatoid Arthritis Impact of Disease, the Brief Illness Perception Questionnaire indices, and the serum level of the inflammatory biomarker C-Reactive Protein. The suitability of the physical and mental domains of the questionnaires used in the model for patient profiling and clustering was verified by statistical comparison methods with other instruments. For profiling, we chose the responses with four severity levels, for clustering we chose two PRO responses and the serum CRP high/low severity grades. These resulted in eight well-defined clusters, with the two main clusters (52 per cent) having all three factors concordant, and the six other clusters grouping contradictory responses. Patient profiles and clusters that can be constructed using the algorithmic application of validated PRO questionnaires and serum CRP level provide a more differentiated characterization of individual patients with rheumatoid arthritis.

Keywords: Rheumatoid Arthritis; Patient Reported Outcomes; Biomarker C-Reactive Protein; Profiles; Clusters

Abbreviations: ACR: American College of Rheumatologists; Brief IPQ: Brief Illness Perception Questionnaire; CRP: C-Reactive Protein, inflammatory biomarker; DAS 28: Disease Activity Index for 28 joints; EULAR: European Alliance of Associations for Rheumatology; HAQ: Health Assessment Questionnaire; OMERACT: Outcome Measurements in Rheumatoid Arthritis Clinical Trials; PRO: Patient Reported Outcome; PTGA: Patient Global Assessment; RADAI-5: Rheumatoid Arthritis Disease Activity Index-5; RAID: Rheumatoid Arthritis Impact of Disease; SF 12: Rand Short Form 12 version; S-VLA: Short Valued Life Activities Disability Questionnaire; VAS: Visual Analogue Scale

Introduction

Rheumatoid arthritis is a systemic autoimmune disease with a predominantly sterile inflammation of the connective tissue and veins of the inner lining of the joints. Uncontrolled immunological mechanisms progressively destroy the anatomical structure of the joints. This process causes severe handicaps for the affected person in many areas of social interaction (work capacity, participation), from daily activities to social activities. The burden of the disease impairs physical and mental quality of life. In addition to symptomatic anti-inflammatory and functional therapies, there is a constant effort to curb the progression of the immunological pathomechanism by inhibiting it with targeted drug interventions. This is the concept of disease-modifying therapy, whose drugs were initially sought empir-

ically, based on analogies. A deeper understanding of immunological mechanisms (mainly cellular immunological proliferation and intercellular messengers, the cytokine network) led to the development of drugs with a designed mechanism of action. The most modern form is targeted therapy using anticytokine bioproteins and small molecules that inhibit intracellular signaling [1]. After the emergence of the concept of disease-modifying therapy, therapeutic strategies have been constantly changing ("go low, go slow" practice changed to early aggressive strategy and "tight control" monitoring).

With the advent of biological therapy, the achievement of complete remission (clinical, immunological, and structural) has become a realistic goal. This is reflected in the principle of "treat to target" therapy [2]. From the outset, this development has made it a mandatory methodology for clinical practice and innovative drug development to measure the course of the disease and the burden on patients as objectively and as diversely as possible. In addition to the traditional clinical indicators of inflammatory activity (as pain, joint swelling, biomarkers), instruments measuring the whole spectrum of the disease have been developed. In addition to clinical studies, the use of composite indices [3] and questionnaires that also record the burden of disease (physical, functional, and mental) perceived by patients has become a requirement in practice. Their validity and reliability required the wording of questions corresponding to the disease domains to be measured, using concepts that patients could understand [4]. In the instruments, physiological indicators are expressed in natural units, and patients' self-assessment is expressed in decimal numerical or visual analogue scales attached to questions according to domains. Patient profiles can be constructed from individual responses, and similar profiles can be sorted into sets (clusters) using epidemiological statistical techniques and artificial intelligence. The recommended core areas are mortality, the complete life impact of the disease, comprehensive pathophysiology, and a health economic aspect: social resource use. Within the core areas, a set of core domains are defined. For these, corresponding indices are identified to form the core outcome measurement set [5]. Using the definitions of profiling and clustering to characterize individual and population outcomes of rheumatoid arthritis, the Disease Activity Index for 28 joints (DAS 28) and its simplified variants are commonly used in rheumatology practice. This compact index comprises four empirically weighted indicator components: the number of tender and swollen joints in the patient, the patient's own perception of his or her disease, and the serum level of the red blood cell sedimentation or C-Reactive Protein (CRP) biomarker.

The individual profiles formed by the index can be classified into severity categories according to cut points defined on the test population. These are remission, low, medium, and high activity patient populations. The DAS 28 system also includes additional therapeutic efficacy categories according to defined index changes over a given treatment period. Patients' functional abilities are most commonly measured using the Health Assessment Questionnaire (HAQ) and its variants, developed on the basis of upper and lower limb anatomy. The exceptional effectiveness of anticytokine and signal inhibitor drugs is leading more and more patients to remission or very low activity and favorable functional status. Therefore, the remission cut points of compact indices have acquired special significance. As normative criteria for remission (with cut-offs below or above 1 unit according to the Boolean principle) and the concept of residual activity (in the border zone between remission and low disease activity) have been introduced, individual values may be close to each other and to cut-off points. In this uncertainly defined zone, the treat-to-target strategy is to enforce the intensity of therapy in some patients. On the other hand, it is encouraged to reduce the dose of the active drug in others. There is a debate about the extent to which it is advisable to consider patients' perceptions of their condition when making therapeutic decisions, as these can distort the objective picture of the disease in both directions [6,7].

Our ongoing research investigates the relationship between the personality traits of patients with rheumatoid arthritis and their self-perception. The results of our pre-screening sub-study confirmed that some patients are placed in the residual-activity category due to unfavourable self-assessment of their own condition [8]. We therefore decided to develop patient profiles and clusters based on those Patient Reported Outcome (PRO) questionnaire answers, which are developed to assess the complexity of patients' condition across multiple domains. For this purpose, we used questionnaires, mostly used in clinical studies translated, validated, and published by our team [9].

Materials and Methods

We invited 73 systematically followed patients from our rheumatoid arthritis patient registry, with a stratified selection according to gender, age, disease duration and disease-modifying therapy, to collaborate. The questionnaires were completed and submitted online in the framework of our basic research approved and authorized by the Central and Institutional Research Ethics Committees. Simultaneously recorded DAS 28 disease activity indices were available in the institutional database. We used three disease-specific and one generic questionnaire. These assessed disease activity, predominantly physical, functional, and predominantly disease perception domains. Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5): five domains, as disease activity in the last six months, pain, and general health today, morning joint stiffness yesterday, with appropriate questions [10]. Rheumatoid Arthritis Impact of Disease (RAID): seven domains and questions, as pain, functional disability, fatigue, sleep, physical and emotional well-being and coping [11], Short Valued Life Activities Disability Questionnaire (S-VLA): 14 areas with questions for basic everyday needs, cooking, housework and gardening, family and social contacts, indoor and outdoor walking, leisure activities, recreation, hobby and paid working and long-distance traveling [12], Brief Illness Perception Questionnaire (Brief IPQ): generic tool with eight domains and questions as consequences and timeline of the disease, person-

al control, treatment compliance, perceived severity, understanding and emotional response [13]. Determining the physical and mental content of the questionnaires we used the physical and mental scores of the Rand Short Form 12 version [14] and a selection of the RAID and IPQ domains (an arbitrary series of RAID 1, 2, 3, 4, 5 and IPQ 1, 5 questions/answers for physical burdens and IPQ 3, 4, 6, 7, 8 and RAID 6, 7 questions/answers for mental and emotional attitudes).

Within the mental/emotional domains we compiled the IPQ 3, 4, 7 and the RAID 7 answers for positive mental attitudes e. g. coping and the IPQ 6, 8 and RAID 4, 6 answers for negative mental attitudes e.g., anxiety and emotional response. The internal consistency of the control-confirmation question combinations was found to be equivalent to that of the baseline questionnaires (Cronbach's alpha indices for the selection of 7 physical domains 0,9351, for the 7 mental domains 0,7614, for the selected negative mental attitude domains 0,7774, for the selected positive ones 0,4843, while the original Hungarian RAID Cronbach's alpha is 0,9488 and IPQ Cronbach's alpha is 0,7446). We emphasize that patients completed only the original, validated RAID, IPQ and Rand SF 12 questionnaires, answering the original domain-matched questions in a context verbalized and defined by the developers on numerical rating scales. The RAID and IPQ domain selections were used only in the statistics. Patients scored their responses in 0-10 numeric rating scores, four severity grades for S-VLA and 2 to 6 grades for Short Form 12. Scores were grouped according to the quartiles of questionnaire respondents (25-25%) and patients were classified according to severity based on cut-off and median scores of the quartiles. Patient profiles were developed according to each severity category of the respective tool and displayed as automated textual descriptors, like a school report or qualification.

These were checked by comparative statistical analysis and correlations were used to select the best clustering indicators, which were associated with individual CRP values of the respective patients as an objective biomarker. The validity of the clusters was compared using epidemiological statistical methods (Spearman correlation, chi-squared test, positive and negative predictive value), The individual personal composition of the clusters was compared by identifying each patient (anonymised). The method provides the possibility to assess physical and mental components within the individual patient profile. Only validated questionnaires were used in the development of the patient profile. The check-confirm question combinations were not implemented in the profiling and clustering.

Results/Observations

Individual patient profiles were constructed using four severity grades of their RADAI-5, RAID, VLA and IPQ scores. The RADAI-5 score cutoffs and severity categories are similar to the concurrent DAS 28 index scores according to the developers' publication and with the cutoffs and activity categories in our cohort (correlation coefficient 0.7256, p<0.00001). As a biomarker of inflammatory activity, the patients' concurrent serum CRP levels were chosen. We aimed to determine the differentiating value of PRO indicators measured by questionnaires and CRP as an objective indicator, and the meaningfulness of these data series as a measure of inflammatory phenotypes and mental stress. This is presented by the correlation coefficients and Chi squared values between the baseline questionnaires and control instruments (Table 1). The control instruments are dominated by physical and mental domains, respectively. The strength of correlations shows the differential power of the baseline questionnaires. There is a good separation between the constructs measuring predominantly physical burdens of inflammatory origin (RADAI-5 and RAID), those measuring compensated functional limitations (VLA) and the patient-indicators provided by the IPQ, which predominantly reflects mental challenges. A marked contrast is highlighted by the weak correlations of CRP biomarker values with physical and mental workload. This indicates that a proportion of patients' self-assessment is demonstrably different from the current objective status of their disease. In the light of these findings, the basic questionnaires were examined in terms of cluster formation. Table 2 shows the correlations between the indicators and questionnaires that make up the potential cluster formation profile. There is a strong correlation between the CRP value and the RADAI-5, but a weaker correlation between the RAID and the CRP. There is a very strong relationship between RADAI-5 and RAID constructs.

Table 1: Correlations of profiling questionnaires and control instruments.

Check-control constructions. Profiling questionnaires	Rand Short Form 12 version physical score	Rand Short Form 12 version mental score	RAID/IPQ Selected physical burden domains	RAID/IPQ Selected mental challenge domains.	IPQ/RAID Selected negative mental domains	IPQ/RAID Selected positive mental domains
CRP	0,3711 p<0,01	0,2907 p<0,05	0,4749 p<0,001	0,3318 p<0,01	0,3780 p<0,01	0,2645 p<0,05
RADAI-5	0,7287 p<0,0001	0,4882 p<0,001	0,7887 p<0,0001	0,5490 p<0,001	0,6278 p<0,001	0,4235 p<0,001
RAID	0,6842 p<0,001	0,4899 p<0,001	0,9569 p<0,00001	0,7204 p<0,0001	0,8123 p<0,00001	0,5938 p<0,001

VLA	0,6408 p<0,001	0,5474 p<0,001	0,6573 p<0,001	0,5031 p<0,001	0,4997 p<0,001	0,4496 p<0,001
IPQ	0,6118 p<0,001	0,6802 p<0,001	0,7237 p<0,0001	0,9061 p<0,00001	0,8435 p<0,00001	0,7734 p<0,0001

Table 2: Correlations of questionnaires for selecting multi-facet cluster formation.

Chi square 2x2 and 4x4 boxes Spearman correlation	**CRP**	**RADAI-5**	**RAID**	**VLA**	**IPQ**
CRP	-	15,0 p<0,001 27,6 p<0,05	16,9 p<0,001 26,8 p<0,01	7,2 p<0,01 25,8 p<0,01	2,4 n. s. 12,2 n. s.
RADAI-5	0,5741 p<0,001	-	23,4 p<0,00001 47,2 p<0,00001	18,8 p<0,00001 31,7 p<0,001	13,3 p<0,001 24,9 p<0,01
RAID	0,4806 p<0,001	0,7253 p<0,0001	-	11,8 p<0,001 19,9 p<0,05	23,0 p<0,00001 9,9 p<0,01
VLA	0,4652 p<0,001	0,5663 p<0,001	0,5334 p<0,001	-	23,4 p<0,00001 31,5 p<0,001
IPQ	0,2999 p<0,05	0,6022 p<0,01	0,6317 p<0,001	0,6531 p<0,001	-

The indicators of functional capacity decline (VLA questionnaire) were evenly correlated with the RADAI-5, RAID and IPQ questionnaires and showed a weaker correlation with CRP levels, considering the IPQ tool is dominated by mental workload. On the basis of the correlations of the potential cluster forming tools, we tested them by the homogeneity of some cluster models. We compared the person composition of the cluster defined with the chosen cluster-forming items with the composition of the four main profile formers and the clusters formed with only RAID and IPQ questionnaires but without CRP. We found that the positive predictive value of the chosen cluster representation was 60%, compared to both comparators, but without the CRP values, the positive predictive value between clusters trained using only patient self-assessment was 90 % and the negative predictive value was 9.5 %. In turn, the positive and negative likelihood indices indicate that the inclusion of the objective biomarker CRP changes the person composition of the clusters. The data is shown in Table 2. suggest forming clusters that treat equally different profiles based on the complementary information provided by the CRP biomarker, RAID and IPQ questionnaires. We concluded that for the purpose of cluster analysis, the four severity grades are difficult to treat with conventional statistical methods. Finally, the RAID, IPQ questionnaires and the CRP biomarker with two severity grades (below and above median scores, CRP below and above 10 mg/l) were chosen as the clustering levels. We defined eight clusters with three components: dominantly physical, dominantly disease perception attitude and inflammatory biomarker. The personal composition of the clusters is presented in a hierarchical dendrogram (Figure 1). Overall, 51 % of patients were concordant for all three and 49 % were discordant regarding one or two levels of the clustering algorithm. 43% of patients reported high mental burden, however 12% with totally inactive inflammation.

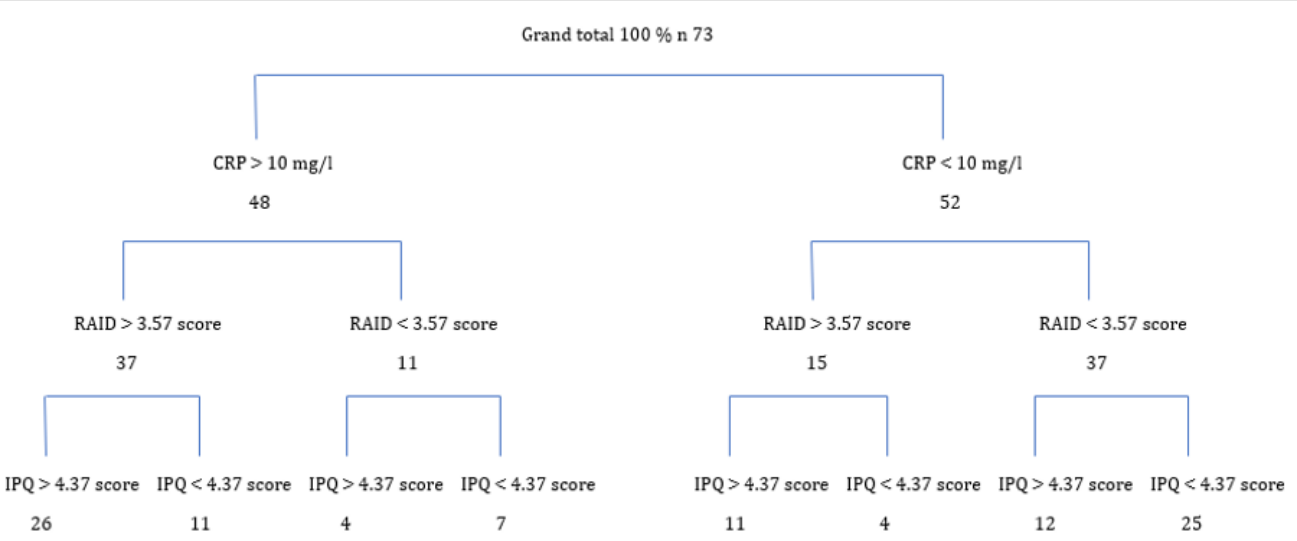

Figure 1: Hierarchical dendrogram of patient clusters.

Discussion

Rheumatoid arthritis has a complex impact on all major aspects of patients' lives. This is experienced heterogeneously by patients and expressed by weighting their responses to questions targeting each aspect (Patient Reported Outcomes). The aim of our research is to investigate how patients' perceived burden of disease is related to their current level of an objective biomarker of inflammation. Our findings from validated Hungarian PRO questionnaires completed by known, reliable patients are consistent with other reported experiences from the original questionnaires. The developers of the RADAI-5 questionnaire have found that the test-population score averages, cut points and categories (remission, low, moderate, and high activity) closely parallel similar measures of the DAS 28 compact index [15]. Similar findings have been made in a study validating the RADAI-5 instrument based on the strong correlations observed with additional domains (pain, fatigue, function, and quality of life) [16]. We found the same in our own study and therefore used the RADAI-5 questionnaire as a reliable disease activity instrument. The RAID questionnaire was developed as an instrument to reflect the complex face and burden of rheumatoid arthritis [11]. Its validation has demonstrated that its cut-offs correspond to the DAS 28 cut points, activity, and therapy assessment categories. This study supports our finding that RAID, as a PRO, is suitable for measuring the physical burden of rheumatoid arthritis [17]. The main developer of the OMERACT (Outcome Measurements in Rheumatoid Arthritis Clinical Trials) core domain criteria accepted that the RAID domain scores correctly reflect core domains and are suitable for representing the subjective burden of patients with rheumatoid arthritis [18].

Recently, validation of the RAID against the components of the DAS 28 index and several other instruments e.g., Helplessness Index for coping has been repeated. The correlations found were in line with previous validation and support our results [19]. RAID data sets from rheumatoid arthritis were compared with RAID data sets from other arthritis patients using a large German database. The authors concluded that RAID can be used as a generic tool to measure the typical disease burden in these patients [20]. It is generally accepted that the clinical picture of rheumatoid arthritis includes negative mental components such as anxiety and depression. Few generic disease-perception instruments have been used (seven questionnaires with 18-70 domains), so little experience is available. The Brief Illness Perception Questionnaire was chosen because it contains questions to measure the dominance of negative attitudes and the domains of positive approach (coping, resilience), according to validation evaluations. An epidemiological statistical analysis of our scores demonstrated that the IPQ indicates mental distress independent of disease-specific perceptions. One explanation for the weak correlation between the biomarker CRP and PROs, in particular IPQ, may be that some patients with low levels of pathological inflammation perceive their own condition as more severe. Supposedly they are projecting their previous experience of being exposed to significant mental stress. A key question for PRO research on rheumatoid arthritis is how objectively it reflects patients' expectations. Several studies highlight the contradictions between PROs and objective indicators. One study analyzing the first 5 years of early rheumatoid arthritis found that one third of patients report intolerable pain after 2 to 5 years, consistent with patient-rated health, function and joint tenderness, but with low laboratory indicators [21]. A similar discrepancy was observed in a group

of patients followed for nine years, in which 29 percent of patients reported adverse pain and fatigue, with indicators of low activity and good functional parameters [22].

In a patient group followed for three years, 1055 patients were grouped into clusters using a five-factor hierarchical method (pain, self-perception, fatigue, sleep disturbance, and quality of life). The clusters were assessed for anxiety and the physical and mental components of the Rand Short Form 36 questionnaire, with a total of 18 variables assessed. PRO scores showed an inverse correlation with the number of inflamed joints [23]. In another study patients treated with conventional, targeted, and biological therapies were assessed with the RAID questionnaire to determine the proportion of patients with unmet expectations. They were assessed using the same methods as our study. The distribution of RAID responses was consistent with our recorded values. Seventeen percent of patients were in remission and in acceptable state, 13% reported low disease burden, 37% moderate disease burden and 35% significant disease burden. RAID scores were compared with measures of nine selected PRO domains (6 physical and 3 mental) and treatment satisfaction. Thirty-five per cent of patients reported unmet expectations [24]. Another working group compared RAID scores with DAS 28 scores and found similar distributions [25]. The Rheumatoid Arthritis Medication Study followed 1127 patients with early rheumatoid arthritis for a year. At the start of the follow-up, two groups were stratified according to their self-assessment of whether their condition was satisfactory.

The satisfaction group was 52% of patients, with necessarily more favourable scores at the start and end of follow-up compared with the non-satisfaction group. The outcome of those satisfied with their condition was examined. Both objective and subjective indicators were followed, comparing the number of active joints with the PRO indicator scores. The scores were categorised as „high", „moderate" and „low" according to median and interquartile ranges. In this way, six clusters were formed. Evaluating changes over one year, it was found that those with initially high PRO scores perceived worse outcomes [26]. Studies examining the objective value of Patient Reported Outcomes prompted a group of leading experts to review the criteria for rheumatoid arthritis remission status, specifically the PRO component of the Patient Global Assessment (PtGA) [27]. As a result, the American College of Rheumatologists (ACR) and the European Alliance of Associations for Rheumatology (EULAR) have revised the Boolean remission threshold for PtGA scale from 1 cm VAS to 2 cm. This reduces the risk that some higher PtGA values will show excess activity [28].

Conclusion

The rheumatoid arthritis patient profiles and clusters that can be constructed using the algorithmic application of validated PRO questionnaires provide a more differentiated characterization of individual patients with rheumatoid arthritis than the composite indexes and functional status measures used in daily practice. This may be of importance not only in the detailed mapping of unmet physical needs but also in identifying patients with more pronounced mental handicaps. This patient group may also be a possible category of "difficult to treat" rheumatoid arthritis patients, i.e., criterion 2.e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life" [29]. The algorithm of the described method can be developed into a computer program and calculator. The four severity grades can be analyzed in more detail with the Latent Profile Analysis and Latent Class Analysis programs. We intend to use the patient profiles and sets in further personality research.

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