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ORIGINAL RESEARCH

Monitoring the Time Course of Disability through a Self-Assessment Instrument "Activity Index" (IA) in RA Patients

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Abstract

Background: Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease whose etiopathogenesis is largely unknown. Available treatments, though effective, are insufficient in so far as there is no cure for a major proportion of patients. In those patients the disease becomes chronic with progressive joint damage, disability, and limitation of participation. Current treatment approaches include pain-relieving drugs and anti-inflammatory medications that slow joint damage, combined with physical therapies involving a well-balanced, highly personalized sequence of rest and exercise. As pain-relief, overall activity, mobility and participation are vital indicators of disability and response to RA treatment, regular patient feedback in this respect is key to a successful monitoring of the long-term effect of therapy. To manage such feedback, we have developed an easy-to-use self-assessment tool "Activity Index" (AI) for tablets and smartphones that enables regular assessments of RA improvement and/or deterioration in the patients' home environment. In this normative study we addressed the questions of (1) The AI sensitivity regarding the resolution of small between-patient differences; and (2) The external validity of the AI instrument when compared with "objective" laboratory and x-ray measures and the HAQ disability index.

Data material and methods: Our sample was comprised of 100 Chinese RA patients under treatment with two repeated assessments at 14-day intervals. Patients were recruited from the consecutive daily admissions at the Beijing General Hospital. As part of the recruitment, patients were documented in terms of socio-demographic characteristics and previous RA history. The repeated assessments relied on a standardized clinical protocol along with the self-rating instruments AI and HAQ (Stanford Health Assessment Questionnaire). The clinical protocol encompassed several laboratory methods in order to "objectively" quantify severity of illness and joint damage: rheumatoid factor "RF"; anti-cyclic citrullinated peptide "anti-ccp"; X-ray; and MRI. All statistical analyses were carried out by means of the Statistical Analysis Software SAS 9.3 with PROCs *FREQ, MEANS, TTEST, CORR, REG*, and *GLM* [unbalanced data].

Results: Based on a RA patient sample where 84% of study patients were treated in an outpatient nursing care setting, we validated our newly developed AI instrument for tablets and smartphones by (1) A comparison with the standard Health Assessment Questionnaire HAQ (indirect validation); and (2) Regression and correlation analyses focusing on the "objective" clinical quantity "joint damage" (external validation). The 10-item tablet/smartphone-based AI was found to measure essentially the same as the 20-item questionnaire-based HAQ, a finding that was underlined by a highly significant between-instrument correlation of $r = 0.732$ ($p < 0.0001$). In terms of external validity, the AI displayed a highly significant correlation of $r = 0.429$ ($p < 0.0001$) with the clinical quantity "Swollen Joints", thus demonstrating the instrument's efficiency in outpatient nursing care settings. By contrast, simple self-assessment scores of the form "Estimated Percentage of impairment [%]" yielded unsatisfactory results. No statistically significant clinical changes were seen over the 14-day observation period, so that the GLM approach to constructing a multivariate predictor model failed and led to inconclusive findings (model fit ≤ 0.0852).

Conclusion: Our analyses revealed the validity of the AI instrument as well as its efficiency in outpatient care settings, thus clearing the way for routine applications among patients under RA therapy. Ultimately, this monitoring approach will enable physicians to verify and optimize response to therapy in each individual patient through a more "personalized medicine". Beside assessing disease activity, the monitoring tool has the ability to assess the subjective disability for long term monitoring. The activity Index (AI) is

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easy to use and can be performed as an easy-to-use self-assessment tool for tablets and smartphones on the internet. The self-report documentation can be helpful for the treating physician during clinical visits and for long-term telemonitoring.

Keywords

Rheumatoid arthritis, Self-assessment tool, HAQ, QUALI-TOUCH activity index, Disability

Background

Rheumatoid arthritis (RA) is a devastative autoimmune disease where the patient's immune system attacks joint tissues for unknown reasons, thus causing inflammation. The course of RA is in most cases chronic with disease activity ranging from mild to severe. RA can lead to serious joint damage and disability, causing sufferers to lose the ability to work and to have a fulfilling life. The prevalence is about 0.6% in the general population worldwide with increased frequencies in older people. Across age classes, three times as many women suffer from the disease than men [1,2].

RA is not a single disease entity but characterized by etiologic heterogeneity and a broad spectrum of significant comorbidities, such as type 2 diabetes, cardiovascular diseases, and psychiatric disorders [3]. Ethnicity and socio-cultural factors seem to play a minor role as revealed by direct comparisons between Europe, the US and China [4,5].

Current treatments, though effective, are insufficient in the sense that there is no cure for most patients. Treatment strategies include pain-relieving drugs and anti-inflammatory medications that slow joint damage, combined with physical therapies that involve a well-balanced sequence of rest and exercise. In view of better compliance, exercise programs are highly personalized and tailor-made under consideration of the patients' physical abilities, limitations, and needs; [6,7]. It has been reported that RA patients have an increased risk of experiencing functional disability with the prolongation of the course of disease [8]. A study from China revealed that there was a higher prevalence of functional disability in joint diseases compared with other diseases or traffic accidents [9].

Pain-relief, overall activity, mobility and restriction of participation are important indicators of response to RA treatment and long-term disability. Therefore, monitoring these quantities along with patient satisfaction is central to a successful therapeutic approach in the individual patient. The DAS 28 has been widely used for disease activity assessment. This is important to adapt the drug treatment and to use "the treat to target strategy" [10]. However, there is no clear consensus about a standardized disability assessment. The disability assessment can be divided in 2 categories namely an objective and subjective disability assessment. The subjective disability assessment can be captured by relevant patient reported outcomes. The disability score together with the restriction of participation is necessary to quantify a long-term effect of a successful therapy. The "Stanford Health Assessment Questionnaire" (HAQ) is a well-established self-assessment instrument that quantifies the patients' disabilities in a standardized way through the disability index "HAQ" [11,12]. Though routinely used for monitoring the time course of improvement among patients under treatment, it is not optimized as to the specifics of recovery among RA patients [13]. In addition, it does not capture the restriction of participation in daily life.

In consequence, we have developed an easy to use novel instrument called "Activity Index" (AI) that modifies and extends the HAQ in such a way that its sensitivity regarding the assessment of RA consequences (improvement and/or deterioration) is considerably improved. The AI instrument has been specifically designed as an easy-to-use self-assessment tool running on tablets and smartphones [14].

In a recent study from China it could be documented that functional disability was common in Chinese RA patients. A low quality of life and limitation of joint mobility had great impacts on functional disability [15].

In an empirical biometric study with repeated assessments on 100 patients under RA treatment we addressed the following questions: (1) Performance of the AI instrument in comparison to the standard HAQ questionnaire score; (2) Sensitivity of the AI instrument regarding the resolution of subtle between-patient differences as observed among RA patients under therapy; (3) External validity of the AI instrument regarding disability due to joint damage in comparison to "objective" laboratory measures; and (4) Comparison of the AI instrument to a self-rating of the patients disability status.

Data Material and Methods

Our sample was comprised of 100 Chinese RA patients under treatment with two repeated assessments at 14-day intervals (21 males, 79 females). Patients were recruited from the consecutive daily admissions at the Beijing General Hospital so that the full variety of between-patient differences inherent in the RA illness could be included in the study population. During recruitment, patients were documented in terms of socio-demographic characteristics and previous RA history (11 Items).

Once enrolled in the study, two repeated assessments were carried out based on a standardized clinical protocol (41 items) along with two self-rating questionnaires namely the HAQ (20 items) and the AI (10 items). Functional disability was evaluated by the HAQ disability Index. The index included 20 questions in eight activity subdimensions. Dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. The response alternative was 0, able without

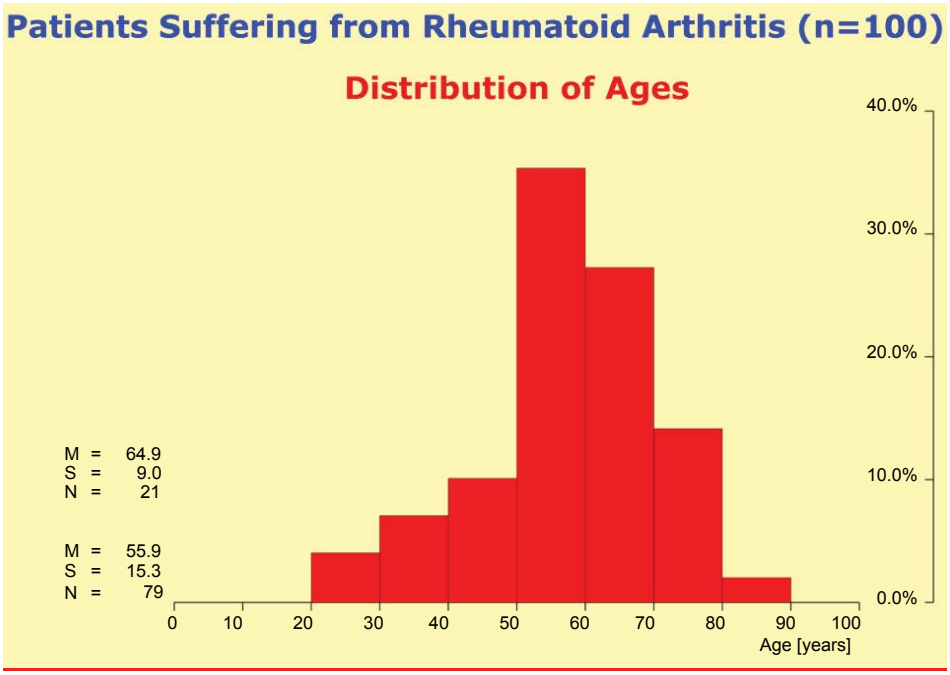

Figure 1: Age distribution for the entire sample of 100 patients suffering from rheumatoid arthritis. Even though the time duration of illness was with 10.9 versus 10.4 years very similar among males and females, significant sex-differences showed up regarding the mean age of 55.9 ± 15.3 years (females) versus 64.9 ± 9.0 years (males), thus suggesting an earlier age-of-onset for females.

活动指数调查：

1：请您评估，在**最近24小时**内出现的**最严重**的疼痛/或者不适的程度如何 ？
0（无疼痛） 到 10（极度疼痛）

无疼痛0 5 10极度疼痛

评分（ ）

2：请您评估，在**最近24小时**内出现的**平均**的疼痛/或者不适的程度如何 ？
0（无疼痛) 到 10（极度疼痛）

无疼痛0 5 10极度疼痛

评分（ ）

3：这种疼痛/或不适是否对您的睡眠质量有所影响？程度如何？
1口 **根本没**有 2口 轻度 3口 中度 4口 重度 5口 极重度

4：这种疼痛/或不适是否对您的白天工作或生**活**有所影响？程度如何？
1口 **根本没**有 2口 轻度 3口 中度 4口 重度 5口 极重度

5：这种疼痛/或不适是否对您的业余生**活**（或休闲**活**动）有所影响？程度如何？
1口 **根本没**有 2口 轻度 3口 中度 4口 重度 5口 极重度

6：这种疼痛/或不适是否对您的职业工作有所影响？程度如何？
1口 **根本没**有 2口 轻度 3口 中度 4口 重度 5口 极重度
6 口 **我没**有(职业)工作

7：您对于目前进行的**治**疗是否满意？
1口 非常满意 2口 比较满意 3口 不太满意 4口 不满意

8：请您本人评价，您的总的健康状况如何 ？
1口 不好 2 口 一般 3 口 好 4 口 很好 5 口非常好

Figure 2: Chinese Version of the Activity Index.

difficulty, 1 able with some difficulty, 2 able with much difficulty and 3 unable. The HAQ scores ranges from 0-3 with higher scores indicating more difficulty. Functional disability was defined as the HAQ score > 1 according

to previous studies [16,17]. The activity index is a short 8 items questionnaire covering the subdimensions pain, quality of life and restriction of participation in daily life focusing on household, leisure and job activities (Figure 2). The activity index is calculated by a Likert scale and has been validated in pain therapy. It can be used in an e-health format in the internet or mobile phone [14].

The clinical protocol encompassed several laboratory methods to "objectively" quantify severity of illness along with joint damage (rheumatoid factor "RF" [18], anti-cyclic citrullinated peptide "anti-ccp" [19], X-ray [20], and MRI [21]. All empirical data were stored in a SAS databank (Statistical Analysis Software, version 9.3).

Statistical analyses were carried out by means of the Statistical Analysis Software SAS 9.3 [22], while a proprietary program of the Institute for Response-Genetics, University of Zurich, was used for random sampling and the generation of postscript plots.

As to the performance of the AI instrument in comparison to the standard HAQ, we estimated the extent to which HAQ and AI disability scores corresponded to each

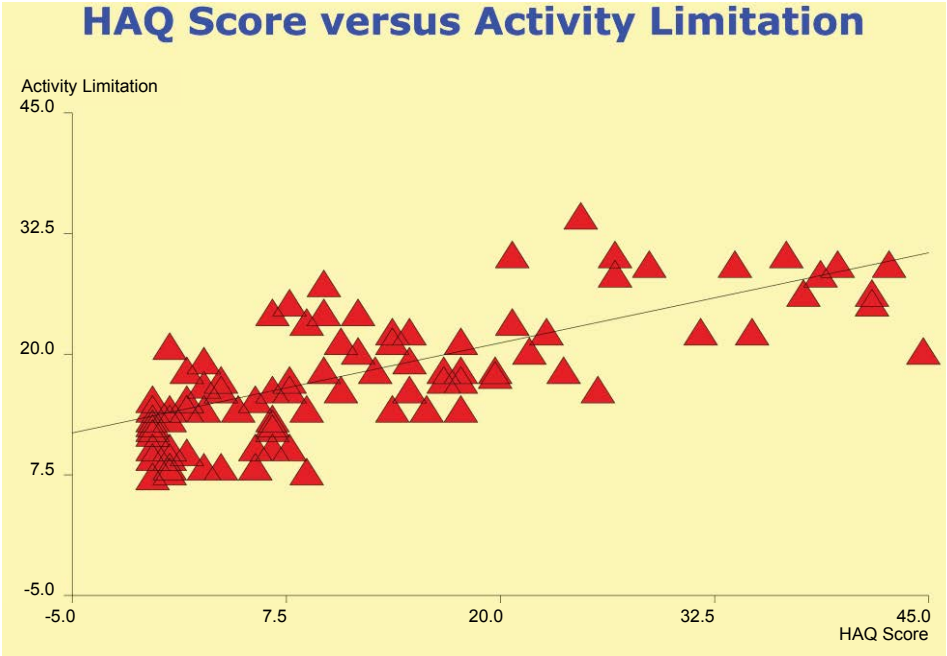

Figure 3: Scatter diagram "HAQ Score" as derived from the Stanford Health Assessment Questionnaire (HAQ) versus "Activity Limitation" as derived from the newly developed Activity Index Instrument (AI). The variation inherent in the HAQ (20 Items) is, by construction, larger than that of the AI (10 Items). Nonetheless, the 2 instruments appear to measure essentially the same as indicated by the highly significant between-instrument correlation of $r = 0.732$ ($p < 0.0001$).

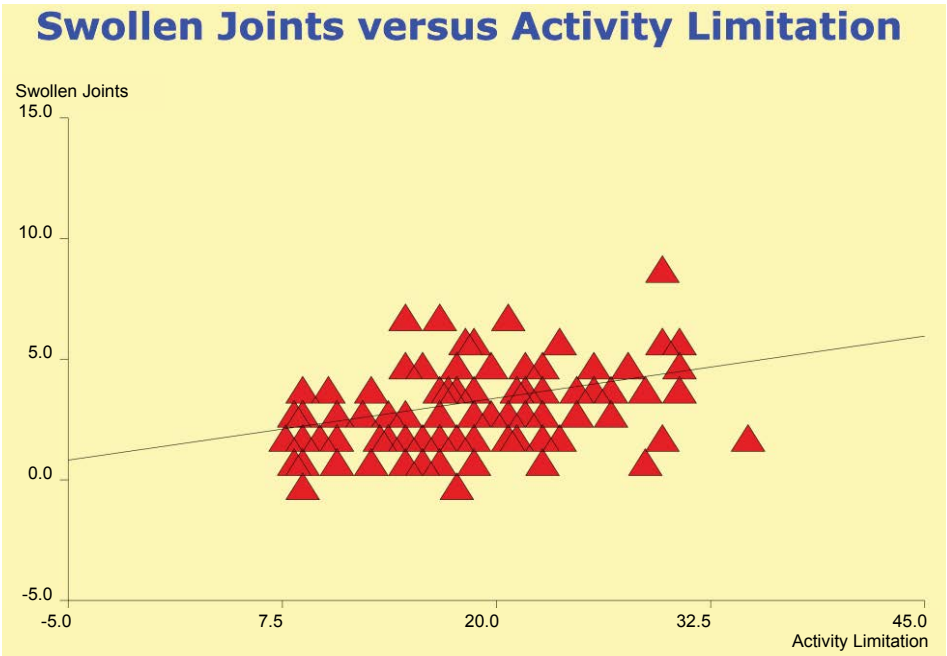

Figure 4: Scatter diagram "Swollen Joints" as derived from quantitative clinical assessments versus "Activity Limitation" as derived from the newly developed Activity Index Instrument (AI). The highly significant correlation of $r = 0.429$ ($p < 0.0001$) with "objective" laboratory quantities demonstrates the external validity of the AI instrument.

other by means of correlation and regression analyses. The sensitivity of the AI instrument regarding the resolution of subtle between-patient differences pertinent to RA patients under therapy was determined through an analysis of variance (ANOVA) along with scatter plots that detailed the empirical variations. In this context it is worth noting that "variation" is directly linked to "information": the larger the between-patient variation in terms of the variables under investigation, the better the resolution of between-patient differences.

In addition to the comparison with the standard HAQ (indirect validation), the AI disability scores were externally validated by means of regression and correlation analyses based on the clinical quantity "joint damage" which was assessed by X-rays and "objective" laboratory measures of disease activity. Finally, using a generalized linear model (GLM) we aimed to construct a multivariate predictor model and related classifiers from the patients' repeated assessments in order to determine the extent to which a suitable combination of variables measured at entry into study can predict later outcome.

The study was approved by the local ethics committees and written informed consent was obtained from all participants. There are no conflicts of interest.

Results

When recruiting our study population from the continuous daily hospital admissions at the Beijing General Hospital the first 100 eligible RA patients were 79 females and 21 males, so that the female to male ratio deviated to some extent from the ratio of 3:1 as predicted by worldwide, ethnicity-independent prevalence data. Female patients were with a mean age of 55.9 ± 15.3 years significantly younger than male patients with a mean age of 64.9 ± 9.0 years ($p = 0.01$). Additionally, female patients exhibited a more severe form of the illness ($p = 0.01$). By contrast, no statistically significant sex differences showed up regarding the time duration of illness (10.9 versus 10.4 years), thus suggesting an earlier age-of-onset among females. The age distribution for the sample is given in Figure 1.

Of these study patients, 84% were treated in an outpatient nursing care setting, thus being an ideal target population for testing our newly developed self-assessment tool that monitors pain-relief, overall activity and disability in the patients' home environment. Ultimately, this monitoring approach will enable the doctors in charge to verify and optimize response to therapy in each individual patient and to monitor the long-term outcome of disability and participation.

In the next step, we determined the extent to which the patients' scores derived through the "Stanford Health Assessment Questionnaire" (HAQ) correspond with the scores derived through the newly developed "Activity Index Instrument" (AI). The variation inherent in the HAQ (20 Items) is, by construction, larger than that of the AI (10 Items). This is a critical point since larger variation typically means better resolution regarding the resolution of subtle between-patient differences. Contrary to expectations, the two instruments turned out to measure essentially the same as indicated by the highly significant between-instrument correlation of $r = 0.732$ ($p < 0.0001$). The Scatter diagram "HAQ Scores" versus "AI Scores" illustrates this finding in an intuitive way (Figure 3).

To externally validate the AI through "objectively" assessable laboratory quantities we have carried out a re-

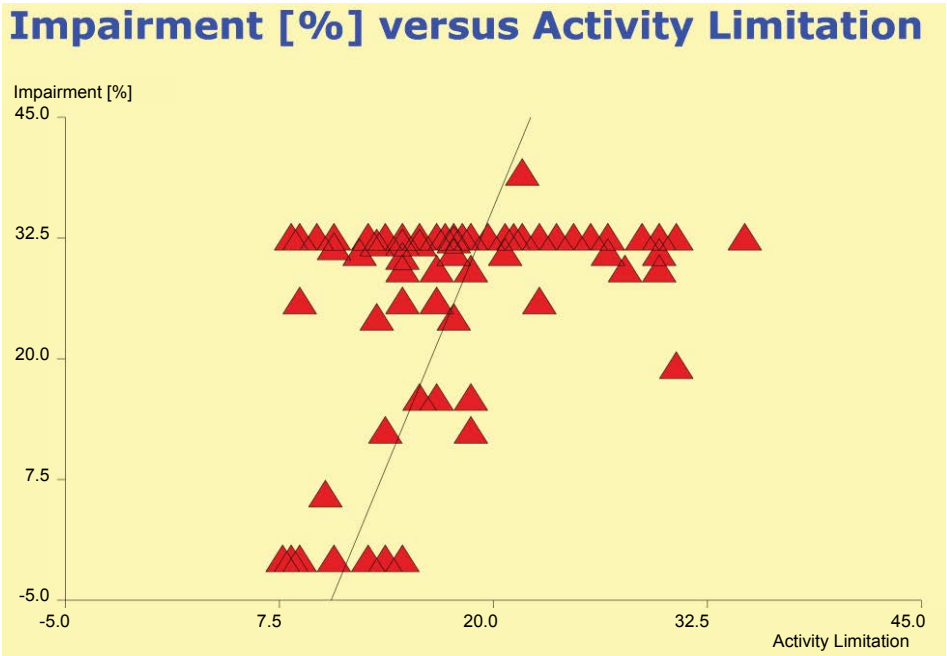

Figure 5: In contrast to the newly developed Activity Index Instrument (AI), a simple self-assessment Score of the form "Estimated Percentage of impairment [%]" yields unsatisfactory results: A majority of patients place themselves rather indifferently somewhere around 32.5% as shown by the above scatter diagram "Impairment [%]" versus "Activity Limitation".

gression analysis (linear regression) to estimate and detail the relationship between "AI scores" on the one hand and "Swollen Joints" on the other. We found that "AI scores" (independent variable) predicted "Swollen Joints" (dependent variable) surprisingly well (Figure 4). The respective correlation was with $r = 0.429$ highly significant ($p < 0.0001$), thus underlining the validity of the AI instrument as well as its efficiency in an outpatient care setting estimating disease activity and hence activity limitation.

By contrast, self-assessment scores of the form "Estimated Percentage of impairment [%]" yielded unsatisfactory results. In fact, most patients rated themselves rather indifferently as suffering from an impairment somewhere around 32.5% (on a scale of 100%) as shown in the scatter diagram "Impairment [%]" versus "AI score" (Figure 5). On the other hand, this scatter diagram also revealed the sensitivity of the AI instrument regarding the resolution of subtle between-patient differences that are typical for RA patients under therapy. Resolution of these subtle differences may be critically important for prediction models regarding response to therapy and quantification of disability and limitation of participation.

Over the observation period of 14 days, we did not see much improvement or deterioration in the clinical RA picture of the patients under investigation. In fact, none of the quantitative dimensions included in the study exhibited changes that reached statistical significance in the analysis of variance. This result might have been expected, given the average illness duration of more than 10 years, and the fact that response to therapy among RA patients is often slow and occurs only in small steps. As there was no direct intervention between the 2-week observation period a direct consequence of this general lack of clinical change (improvement or deterioration), our GLM approach to constructing a multivariate predictor model of response to therapy failed and led to inconclusive results (model fit ≤ 0.0852). However, it demonstrates that disability and activity limitation does not change fast. Similarly, it was not possible to construct the respective classifiers.

As reliable predictor models of response to RA therapies would be of great practical value for a successful and personalized treatment approach to RA patients, we are planning a new "efficacy" study with repeated assessments over 4 weeks where disease activity together with activity limitation and participation will be studied. These data will allow us to broach anew the issue of RA predictor models.

Discussion

It is extremely important to start an effective RA treatment as soon as possible. With this "treat to target therapy" a permanent disability of these patients can be reduced. This key message could be proofed in a RA registry which monitored RA patients over the time course of 20 years. It could be documented that patients should be treated within the first 6 months after first symptoms [23]. Other factors such as obesity and illiteracy can contribute to the progression of disability in RA patients [24,25]. The most important factor which influences poor patient reported outcomes such as the HAQ and the AI is high disease activity [26]. In elderly RA patients' pain and depression are modifiable factors which are associated with disease activity and are therefore related to disability [16]. However, it is still unclear which assessment instruments should be used for long-term monitoring of RA patients. There are several instruments to assess disease activity such as the DAS 28, the clinical disease activity index and the Rapid 3. Disability in RA is usually measured by the HAQ disability index although this instrument has some limitations. In addition, there is a missing instrument to measure activity and participation limitation. In an Indian study the DAS 28, the HAQ and the Rapid 3 were compared with the clinical disease activity index. This study also included RA patients with illiteracy [11]. These authors could document that the clinical disease activity index was useful to make a reasonable clinical decision. However, it is important to capture relevant parameters to predict long-term disability in RA patients. In another study the authors could document that measuring pain, fatigue and joint stiffness at baseline have only a limited value to predict long-term disability of RA patients [27]. There is an increasing body of evidence to study the effect of disability in the different setting of daily life such as paid and unpaid work, leisure, quality of life and participation. Some Mexican authors could show a different impact on these different dimensions of daily life [28]. 25% of RA patients had a permanent work disability after 10 years of treatment with disease modifying drugs. Under this perspective it seems extremely important to monitor long-term disability beside disease activity. Another study could show that differences of quality of life exist between paid and unpaid work. (homework) [29]. In our study we could document that the activity index AI showed similar results like the HAQ disability index. However, the AI is much easier to perform for patients and depicts relevant dimensions of paid and unpaid work and participation limitation. Hence it gives more valuable information about the consequences of RA as a disease. It also measures pain and quality of life and it exists an electronic format for tablets and smartphones. As with disease activity these tools can be used for long term monitoring of in- and outpatients [30-32].

Conclusion

Our analyses revealed the validity of the AI instrument as well as its efficiency in outpatient care settings, thus clearing the way for routine applications among RA patients to monitor short and long-term disability and limitation of participation. Ultimately, this monitoring approach can be used as e-health tool and will enable

doctors in charge to verify and optimize response to therapy in each individual patient through a more "personalized medicine". It also helps to build long term registries to monitor disability and participation limitation and to measure the effect of novel therapeutic agents.

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Conflict of Interest

The trade mark QUALITOUCH is owned by Medcap Gmbh and Prof. Dr. R. Theiler.

References

1. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, et al. (2011) The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum 63: 633-639.
2. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, et al. (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 73: 492-509.
3. Ruscitti P, Ursini F, Cipriani P, Ciccia F, Liakouli V, et al. (2017) Prevalence of type 2 diabetes and impaired fasting glucose in patients affected by rheumatoid arthritis: Results from a cross-sectional study. Medicine (Baltimore) 96: e7896.
4. Liu D, Yuan N, Yu G, Song G, Chen Y (2017) Can rheumatoid arthritis ever cease to exist: a review of various therapeutic modalities to maintain drug-free remission? Am J Transl Res 9: 3758-3775.
5. Reed GW, Collier DH, Koenig AS, Saunders KC, Pappas DA, et al. (2017) Clinical and demographic factors associated with change and maintenance of disease severity in a large registry of patients with rheumatoid arthritis. Arthritis Res Ther 19: 81.
6. Alemao E, Johal S, Al MJ, Rutten-van Mölken M (2018) Cost-Effectiveness Analysis of Abatacept Compared with Adalimumab on Background Methotrexate in Biologic-Naive Adult Patients with Rheumatoid Arthritis and Poor Prognosis. Value Health 21: 193-202.
7. Einarsson JT, Willim M, Ernestam S, Saxne T, Geborek P, et al. (2018) Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a Nationwide Study in Sweden. Rheumatology (Oxford).
8. Johnsson PM, Eberhardt K (2009) Hand deformities are important signs of disease severity in patients with early rheumatoid arthritis. Rheumatology (Oxford) 48: 1398-1401.
9. Li ZG (2009) Facing the challenge of low recognition and high disability in rheumatoid arthritis. Zhonghua Yi Xue Za Zhi 89: 1873-1875.
10. Kavanaugh A, van Vollenhoven RF, Fleischmann R, Emery P, Sainsbury I, et al. (2018) Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis. Ann Rheum Dis 77: 289-292.
11. Kumar BS, Suneetha P, Mohan A, Kumar DP, Sarma KVS (2017) Comparison of Disease Activity Score in 28 joints with ESR (DAS28), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire Disability Index (HAQ-DI) & Routine Assessment of Patient Index Data with 3 measures (RAPID3) for assessing disease activity in patients with rheumatoid arthritis at initial presentation. Indian J Med Res 146: S57-S62.
12. Bruce B, Fries JF (2005) The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 23: S14-S18.
13. Wolfe F, Pincus T, Fries JF (2001) Usefulness of the HAQ in the clinic. Ann Rheum Dis 60: 811.
14. Kirrstetter AR, Brenig C, Gengenbacher M, Meier B, Ott A, et al. (2017) Experience in measuring the quality of treatment in interventional pain therapy: The Activity Index on a touchscreen PC. Schmerz 31: 131-138.
15. Ji J, Zhang L, Zhang Q, Yin R, Fu T, et al. (2017) Functional disability associated with disease and quality-of-life parameters in Chinese patients with rheumatoid arthritis. Health Qual Life Outcomes 15: 89.
16. Karpouzas GA, Draper T, Moran R, Hernandez E, Nicassio P, et al. (2017) Trends in Functional Disability and Determinants of Clinically Meaningful Change Over Time in Hispanic Patients with Rheumatoid Arthritis in the US. Arthritis Care Res (Hoboken) 69: 294-298.
17. Kronisch C, McLernon DJ, Dale J, Paterson C, Ralston SH, et al. (2016) Brief Report: Predicting Functional Disability: One-Year Results from the Scottish Early Rheumatoid Arthritis Inception Cohort. Arthritis Rheumatol 68: 1596-1602.
18. Schwedler C, Häupl T, Kalus U, Blanchard V, Burmester GR, et al. (2018) Hypogalactosylation of immunoglobulin G in rheumatoid arthritis: relationship to HLA-DRB1 shared epitope, anticitrullinated protein antibodies, rheumatoid factor, and correlation with inflammatory activity. Arthritis Res Ther 20: 44.
19. Lee YH, Bae SC, Song GG (2015) Diagnostic accuracy of anti-MCV and anti-CCP antibodies in rheumatoid arthritis: A meta-analysis. Z Rheumatol 74: 911-918.
20. Ørnbjerg LM, Østergaard M, Jensen T, Hørslev-Petersen K, Stengaard-Pedersen K, et al. (2017) Hand bone loss in early rheumatoid arthritis during a methotrexate-based treat-to-target strategy with or without adalimumab-a substudy of the optimized treatment algorithm in early RA (OPERA) trial. Clin Rheumatol 36: 781-789.
21. Schrepf A, Kaplan CM, Ichesco E, Larkin T, Harte SE, et al. (2018) A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. Nat Commun 9: 2243.
22. Mayo C, Conners S, Warren C, Miller R, Court L, et al. (2013) Demonstration of a software design and statistical analysis methodology with application to patient outcomes data sets. Med Phys 40: 111718.
23. Gwinnutt JM, Symmons DPM, MacGregor AJ, Chipping JR, Marshall T, et al. (2017) Twenty-Year Outcome and Association Between Early Treatment and Mortality and Disability in an Inception Cohort of Patients with Rheumatoid Arthritis: Results from the Norfolk Arthritis Register. Arthritis Rheumatol 69: 1566-1575.
24. Baker JF, England BR, Mikuls TR, Sayles H, Cannon GW, et al. (2018) Obesity, Weight Loss, and Progression of Disability in Rheumatoid Arthritis. Arthritis Care Res (Hoboken).
25. Hammad M, Eissa M, Dawa GA (2018) Factors contribut-

ing to disability in rheumatoid arthritis patients: An Egyptian multicenter study. Reumatol Clin.

26. Bae SC, Cho SK, Won S, Lee HS, Lee SH, et al. (2018) Factors associated with quality of life and functional disability among rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs for at least 6 months. Int J Rheum Dis 21: 1001-1009.

27. Twigg S, Hensor EMA, Emery P, Tennant A, Morgan AW, et al. (2017) Patient-reported Outcomes as Predictors of Change in Disease Activity and Disability in Early Rheumatoid Arthritis: Results from the Yorkshire Early Arthritis Register. J Rheumatol 44: 1331-1340.

28. Vazquez-Villegas ML, Gamez-Nava JI, Celis A, Sanchez-Mosco D, de la Cerda-Trujillo LF, et al. (2017) Prognostic Factors for Permanent Work Disability in Patients with Rheumatoid Arthritis Who Received Combination Therapy of Conventional Synthetic Disease-Modifying Antirheumatic Drugs: A Retrospective Cohort Study. J Clin Rheumatol 23: 376-382.

29. Anno S, Sugioka Y, Inui K, Tada M, Okano T, et al. (2018) Evaluation of work disability in Japanese patients with rheumatoid arthritis: from the TOMORROW study. Clin Rheumatol 37: 1763-1771.

30. Walker UA, Mueller RB, Jaeger VK, Theiler R, Forster A, et al. (2017) Disease activity dynamics in rheumatoid arthritis: patients' self-assessment of disease activity via WebApp. Rheumatology (Oxford) 56: 1707-1712.

31. Theiler R, Alon E, Brugger S, Ljutow A, Mietzsch T, et al. (2007) Evaluation of a standardized internet-based and telephone-based patient monitoring system for pain therapy with transdermal fentanyl. Clin J Pain 23: 804-811.

32. Theiler R, Widler C (2008) Standardized telephone interviews to monitor pain. Pilot study to determine feasibility. Schmerz 22: 75-81.