

# Patient-reported outcomes in Chinese rheumatoid arthritis patients: a systematic review and meta-analysis

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*To the Editor:* Rheumatoid arthritis (RA) is a chronic autoimmune disorder not only characterized by joint symptoms but also extra-articular and systemic manifestations.<sup>[1]</sup> Traditionally, the evaluations of RA had centered on laboratory measures of inflammation and clinician-generated assessments. However, patient-reported outcomes (PROs) are recommended by several guidelines to assess disease progression. PROs also can contribute to reduce discrepancies between physicians' evaluation and patients' own judgment on disease status and their importance on disease management and physician-patient communication has been identified during the past decennia.<sup>[2]</sup> However, it is uncertain whether the awareness has promoted the usage and reporting of PRO measures in RA-related research and clinical practice in Chinese population. Thus, this study systematically reviewed the PRO measures collected in recent researches and summarized the PRO results among Chinese RA population.

To capture the most recent publications focusing on PRO measures among Chinese adult RA patients, we conducted a systematic review using PubMed, Cochrane Library, Wanfang, China National Knowledge Infrastructure, and China Science and Technology Journal database on January, 2019 to identify articles from January 1st, 2016 to December 31st, 2018. The search strategies are presented in Supplementary Appendix A, <http://links.lww.com/CM9/A618>.

Literatures were included if they contained any Chinese RA patients (age  $\geq 18$  years) and reported any PRO results. Articles were excluded if they: (1) were not in English or Chinese; (2) were animals or *in vitro* models/studies; (3) were reviews, letters, editorials, commentaries, protocols, or guidelines; (4) were duplicates in the same population; (5) were not separately reported the PRO results for

Chinese RA patients; (6) were validation studies focusing on psychometric properties of PRO measures; (7) focused on Chinese medicine not recommended in the guidelines for diagnosis and treatment of RA based on combination of disease and syndrome.<sup>[3]</sup> Articles with less than 50 Chinese RA patients were excluded to obtain stable statistical results. And journal articles in Chinese language that were not published in "core journals" listed by the Peking University (2018 edition) were also excluded to further ensure study quality.

An initial assessment was made by scanning all titles and abstracts according to the inclusion and exclusion criteria. Full-text screening was conducted independently by two reviewers on potentially relevant articles for eligibility. Discrepancies were resolved by discussion between the two reviewers. The full items included in the standard data extraction sheet are listed in Supplementary Appendix B, <http://links.lww.com/CM9/A618>.

All outcomes reported by patients were recorded. Composite indices were also recorded if comprised of any patient-reported component. Thus, the study included American College of Rheumatology (ACR) response criteria, European League Against Rheumatism (EULAR) response criteria, clinical disease activity index, disease activity score (DAS), and simplified disease activity index. DAS would be included only if the inclusion of patient-reported global health/patient global assessment (PGA) was clearly specified.

PROs were classified into a number of health domains according to prior publication<sup>[4]</sup> and EULAR outcome library website (<http://oml.eular.org>). They were classified into "others" if no pre-specified domain was appropriate. For composite indices, the patient-reported component would be further classified into the specific health domain if presented separately.

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The characteristics of identified articles were described. Frequencies and percentages were calculated for composite indices, health domains, and PRO measures. Meta-analysis was conducted to summarize the results of guideline recommended or frequently reported PRO measures at several pre-specified time-points.<sup>[4]</sup> A description of imputation for missing data is provided in Supplementary Appendix C, <http://links.lww.com/CM9/A618>. Heterogeneity test was performed using the Chi-squared test and the magnitude of heterogeneity was measured by  $I^2$ . If  $P \geq 0.1$ , or  $P < 0.1$  and  $I^2 \leq 50\%$ , A fixed effect model was used; if  $P < 0.1$  and  $I^2 > 50\%$ , a random effect model was used for meta-analysis. All analyses were performed in Microsoft Excel and Stata version 15.

Among 7591 identified articles, a total of 166 articles (71 interventional studies including randomized controlled trials and non-randomized clinical trials, 95 observational studies including cross-sectional studies, case-control studies, prospective cohorts, retrospective cohorts, and case-series) with 28,462 subjects of interests were included in final analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is shown as Supplementary Figure 1, <http://links.lww.com/CM9/A618>. Details of patients' characteristics are listed in Supplementary Table 1, <http://links.lww.com/CM9/A618>. Supplementary file, <http://links.lww.com/CM9/A619> gives characteristics of each article included in our final analysis.

Of the 166 articles, 103 distinct PRO measures were reported, of which 27 were composite indices and the other 76 PRO measures spread across 15 health domains. The average number of PRO measures per article was  $3.4 \pm 2.3$  (min: 1, max: 11). Pain visual analog scale (VAS) ( $n = 61$ , 36.7%), morning stiffness duration (MSD) ( $n = 54$ , 32.5%), Health Assessment Questionnaire (HAQ) ( $n = 47$ , 28.3%) were the most frequently reported PRO measures.

A total of 102 (61.4%) articles reported at least one composite index. Among 27 distinct composite indices reported in all articles, DAS28-erythrocyte sedimentation rate was the most frequently reported one ( $n = 41$ , 24.7%). Details of composite indices are shown in Supplementary Table 2, <http://links.lww.com/CM9/A618>.

Among the 15 health domains characterized by 76 PRO measures, pain, physical function, and morning stiffness were reported most frequently (reported by >30% articles). While PGA, quality of life (QoL), and psychological status were relatively frequently reported (reported by >15% articles). PRO measures were classified into health domains as Supplementary Table 3, <http://links.lww.com/CM9/A618>.

Pain was evaluated most frequently ( $n = 70$ , 42.2%), and was measured mostly by pain VAS ( $n = 61$ , 87.1% of 70). Function was reported by 66 (39.8%) publications, and the most frequently implemented tool was HAQ ( $n = 47$ , 71.2% of 66). Morning stiffness was assessed in 54 (32.5%) studies and was more likely to be assessed in interventional ones compared to observational ones (49.3% vs. 20.0%). All articles focusing on this domain described MSD.

PGA was reported relatively frequently ( $n = 29$ , 17.5%), which was evaluated predominantly using PGA VAS ( $n = 22$ , 75.9% of 29). QoL was mentioned by 29 (17.5%) publications and assessed by Medical Outcomes Study Short Form 36-Item (SF-36) as the most ( $n = 19$ , 65.5% of 29). Psychological status was also reported by more than 15% articles ( $n = 27$ , 16.3%). Psychological status was measured by 16 distinct tools, in which self-rating anxiety scale and self-rating depression scale (SDS) were used most frequently ( $n = 9$ , 33.3% of 27).

The remaining health domains were infrequently reported (reported by <10% articles). Fatigue was assessed by 15 (9.0%) articles, mostly using fatigue VAS ( $n = 7$ , 46.7% of 15). Sleep disturbance ( $n = 9$ , 5.4%) and coping ( $n = 8$ , 4.8%) were only evaluated by observational studies.

As the PRO results, at baseline, the mean pain VAS (scale: 0–10 cm) was 5.6 (95% confidence interval [CI]: 5.2–6.0). Among 15 studies reported the means and standard deviations of baseline HAQ (scale: 0–3), RA patients were scored 1.4 (95% CI: 1.0–1.9) on average. The mean MSD (mins) at baseline was 92.1 (95% CI: 79.3–105.0). The mean PGA VAS (scale: 0–10 cm) was 5.8 with a 95% CI of 5.2 to 6.3 at baseline. Regarding QoL, the mean SF-36 total score (scale: 0–100) was 47.2 (95% CI: 41.1–53.3) at baseline. The average baseline score of European Quality of Life – 5 Dimensions (scale: 0–1) was 0.7 ( $P = 0.785$ ,  $I^2 = 0.0\%$ ). Fatigue VAS (scale: 0–10 cm) was 4.9 (95% CI: 3.9–5.9) at baseline on average. Details of baseline and longitudinal PRO results are shown in Supplementary Tables 4 and 5, <http://links.lww.com/CM9/A618>, respectively.

In general, the health domains and PRO tools were selected following the guidelines.<sup>[2]</sup> Pain, function, morning stiffness, and PGA were the four most frequently reported health domains in our study, which covered the core set PRO domains recommended by the ACR and were consistent with systematic reviews exploring PROs in other countries.<sup>[4]</sup> It was also noticed that within above domains, the utilization of PRO tools was relatively homogeneous. However, domains that were not recommended by guidelines were underreported and the selection of PRO tools was heterogeneous. For example, fatigue and sleep disturbance were both assessed in less than 10% articles, although they were common problems among patients.<sup>[5]</sup> Heterogeneity was most evident in the psychological status domain, in which a total of 16 different PRO tools were implemented and eight tools were used only once. The health domains and PRO tools reported in interventional studies were generally consistent with the guidelines comparing with observational studies. The majority of baseline health status among Chinese RA patients is comparable to that of patients from other countries although improvements are still needed.

In conclusion, most health domains and PRO tools reported in studies related to Chinese RA patients are consistent with the guidelines and majority of baseline PRO levels among Chinese RA patients are comparable to other countries. Further studies and educations need to be conducted to increase the awareness and standardization

the usage of PRO in daily clinical practice and streamline the usage of PRO tools.

### Conflicts of interest

None.

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