Eleven-year alterations in hand deformities in rheumatoid arthritis by comprehensive assessment using cluster analysis and analysis of covariance

Shogo Toyama (shogot@koto.kpu-m.ac.jp)
Kyoto Furitsu Ika Daigaku https://orcid.org/0000-0002-8626-604X
Daisaku Tokunaga
Kyoto Furitsu Ika Daigaku
Shinji Tsuchida
Kyoto Furitsu Ika Daigaku
Rie Kushida
Marutamachi rehabilitation clinic
Ryo Oda
Kyoto Furitsu Ika Daigaku
Yutaka Kawahito
Kyoto Furitsu Ika Daigaku
Kenji Takahashi
Kyoto Furitsu Ika Daigaku

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Abstract

Background

Although drug therapy in rheumatoid arthritis has recently improved, treating established rheumatoid hand, consisting of three major deformities—thumb deformity, finger deformities, and ulnar drift—remains a challenge. Underlying complex pathophysiology makes it difficult to comprehensively understand these deformities, and comprehensive assessment methods require accumulated skill and long learning curves. We aimed to establish an easier composite method of understanding the pathophysiology and to elucidate alterations in deformities.

Methods

We established a rheumatoid hand cohort in 2004 and clinically evaluated 134 hands (67 patients). We repeated the evaluations in 2009 (100 hands in 52 patients) and 2015 (63 hands in 37 patients) after case exclusion. Thumb deformities, finger deformities (swan-neck and boutonnière deformity), and ulnar drift were semi-quantified and entered as parameters into a two-step cluster (cross-sectional) analysis for the data in 2004. The parameters in each cluster were plotted at each evaluation point. Two-way analysis of covariance was performed to examine whether differences existed between evaluation points and clusters for the deformity parameters.

Results

Five clusters were most appropriate to clarify each deformity: cluster 1: minimal deformity; cluster 2: type 1 thumb deformity; cluster 3: thumb deformity and severe boutonnière deformity; cluster 4: type 2 or 3 thumb deformity and severe ulnar drift; cluster 5: thumb deformity and severe swan-neck deformity. Clusters 1 and 2 had higher function than cluster 5, and cluster 3 had moderate function. Clusters 1–4 had similar disease duration, and showed different paths of deformity progression from disease onset. We considered clusters 1 and 2 as a conservative subset and clusters 3, 4, and 5 as a progressive subset. Over time, thumb deformity type altered to other types, and swan-neck deformity worsened significantly.

Conclusions

Our comprehensive assessment indicated five deformity patterns and a progressive course in rheumatoid hand. Knowledge of the characteristics of the progressive subset may allow rheumatologists to more easily determine practical interventions and functional prognosis.

Background

Rheumatoid hand, which describes the characteristic deformities in rheumatoid arthritis, is typically composed of thumb deformity, finger deformities, and ulnar drift, of varying degrees. Several studies have attempted to quantify hand function using hand space and force-time curves to evaluate hand deformity [1, 2]. Swan-neck deformity, either alone or combined with other deformities, has been reported to affect hand function more. However, it is still difficult to understand patients' overall pathophysiological conditions, such as the presence or absence, location and severity, and alterations in deformity over time, to determine the most relevant treatment.

A study of early rheumatoid arthritis patients over a 10-year period reported that approximately 50% of hands exhibited combined deformity[3]; however, the authors did not describe the severity of the deformities. Another study described the severity of deformity in a 5-year observation of established rheumatoid arthritis patients and found that overall deformities worsened with time[4]. The authors evaluated thumb deformity using the Nalebuff classification system (type 1–6)[5], finger swan-neck deformity using the Nalebuff classification (type 1–4)[6], finger boutonnière deformity using the Nalebuff classification (stage 1–3), and ulnar drift by the authors' own method[7], which quantified ulnar drift by evaluating joint parameters in an extended cohort [8].

On the basis of these findings, we hypothesized that a semi-quantitative approach using the type/stage and the ulnar drift parameters would provide a comprehensive understanding of the rheumatoid hand. This study aimed to perform a comprehensive assessment and clarify the natural course of hand deformity and function in patients with rheumatoid arthritis.

Methods

Patients

Because biological agents were first approved in our country in 2003, the data collection began in 2004 for patients with rheumatoid arthritis with any apparent hand deformity in either hand among outpatients visiting our hospital. Among 83 patients who were registered for inclusion, 67 patients (134 hands) participated in this cohort and follow-up survey. We collected repeat data in 2009 and 2015 among patients who could be followed-up. Because of loss to follow-up (n = 7), death (n = 1), clinic change (n = 6), stroke (n = 1), and surgical treatment of the hands (n = 4, hands = 4), 52 patients with 100 hands were available for reevaluation in 2009. An additional 6 patients were lost to follow-up: 6 died; 1 case developed severe dementia and was excluded from the cohort; and 9 patients (11 hands) underwent hand surgery and were excluded. In 2015, we completed a final follow-up survey of 37 patients with 63 hands (2 men and 35 women) (Fig. 1)[8].

At each evaluation, we evaluated patients' hand deformity and functional assessments. Drug therapies were prescribed by the 2nd, 3rd, and 6th authors in accordance with globally-used treatment guidelines (the guidelines/recommendations suggested by the European League Against Rheumatism [EULAR] and the American College of Rheumatology [ACR] changed several times during the follow-up period).

Deformity evaluation

Thumb deformity, all four digits' swan-neck deformity or boutonnière deformity, and ulnar drift were assessed according to the Nalebuff classification of thumb deformity (type 1–6)[5]; the Nalebuff classification of swan-neck deformity (Type 1–4) and boutonnière deformity (stage 1–3) for the fingers[6, 7]; and ulnar drift (total score 0–8). The ulnar drift total score was calculated by adding scores for the four parameters for the metacarpophalangeal joints (deviation, subluxation, reduction, and bone destruction), and the score ranged from 0 to 2 for each parameter. The severity of ulnar drift was evaluated according to the sum of each parameter's score, and scores increased with worsening of the ulnar drift[8]. Hand deformities were evaluated by the 1st, 2nd, and 3rd authors, who are surgeons specializing in the rheumatoid hand.

Functional evaluation

Patient-rated subjective indicators that evaluate unilateral hand function are better for polyarticular diseases such as rheumatoid arthritis. Therefore, the authors adopted the Kapandji index as a measure of function at the start of the cohort[9]. The Kapandji index evaluates finger extension (20 points), finger flexion (20 points), and thumb opposition (10 points), with a maximum of 50 points. The Kapandji index evaluates unilateral hand function within minutes independent of impact from the elbow and shoulder joint. As in a previous study, we chose this functional evaluation method [10]. The 5th author, who is an occupational therapist and a specialist in hand therapy, independently conducted the functional evaluation (Kapandji index).

Data management and comprehensive assessment

The outcomes of the clinical evaluations were managed by a hand surgeon who was not an author in this study, and by the 4th author, independently.

A comprehensive understanding of the rheumatoid hand regarding the characteristic deformities was derived from the cluster analysis according to the described clinical parameters. The numerical values for thumb deformity (0–6) were entered as nominal variables because, to our knowledge, no studies have compared function between each deformity type. Finger deformities exist independently from the index to little finger with varying severity, and the presence of swan-neck deformity or boutonnière deformity also varies; therefore, several parameters should be considered and entered into the analysis (which finger, type of deformity, and severity). Because the thumb has the most important functional role in both rheumatoid hands and normal hands[11, 12], we considered that the evaluated parameters should be minimized to weight the impact from thumb deformity in the cluster analysis. Therefore, the score for finger deformity according to the Nalebuff classification (swan-neck deformity: 0–4, boutonnière deformity: 0–3) were totaled separately from the swan-neck deformity score and the boutonnière deformity score from the index to the little finger. We entered the values for only these two scores as ordinal variables.

Ulnar drift score was an ordinal variable and was entered directly into the analysis[8]. We performed two-step cluster analysis using a log likelihood ratio because one of the parameters was a nominal variable to the results evaluated in 2004. The number of clusters was determined according to silhouette measures of cohesion and separation and predictors of importance. The characteristics of each cluster were determined according to the distributions of the entered parameters.

Alterations in the parameters over time

To identify alterations over time for each cluster assigned as of 2004, the means of the parameters were plotted for 2004, 2009, and 2015 for each cluster. Because the disease duration impacts the degree of deformity, duration was used as a covariate in the analysis. Moreover, to examine whether differences existed between clusters and evaluation points, we conducted a two-way between-subject analysis of covariance (ANCOVA), with clusters and evaluation points as the independent variables and swan-neck deformity score, the boutonnière deformity score, and ulnar drift score as the dependent variables. For multiple comparisons, the post-hoc Bonferroni's test was used. Similarly, another ANCOVA was conducted with Kapandji index as the dependent variable to examine whether any differences were present regarding function.

Results

Patients' demographics and drug therapy

The patients' demographics are shown in Supplementary Table 1. Drug therapy was performed in accordance with the treatment guidelines/recommendations of the European League Against Rheumatism and the American College of Rheumatology, which changed several times during the follow-up period. Therefore, disease activity generally improved over time, despite the fact that patients aged. The number of cases treated with biological agents was 3 in 2004, 7 in 2009, and 13 in 2015.

Demographics of each cluster

The demographics of each cluster regarding the patients' background characteristics in 2004 are shown in Table 2. The cluster numbers were not automatically assigned by the statistical software but were rearranged and assigned in the order of mildest degree of deformity. Regarding age, cluster 4 was significantly younger; disease duration was significantly longer in cluster 5; and regarding the Kapandji index, cluster 4 scored lower, although not significantly, and cluster 5 scored significantly lower. In our cohort, there was no type 5 thumb deformity at any evaluation point. In 2004, when cluster analysis was performed, cluster 1 had no thumb deformity in all 49 hands. In cluster 2, 45 hands had type 1 thumb deformity, and one hand had type 4 thumb deformity. In cluster 3, 10 hands had type 1 thumb deformity, and 4 hands had type 6 thumb deformity. In cluster 4, five hands had type 2 deformity, and three hands had type 3 thumb deformity. In cluster 5, two hands had no thumb deformity, eight hands had type 1 thumb deformity, one hand had type 2 thumb deformity, and six hands had type 6 thumb deformity.

Significant differences in scores between clusters were seen in all of the swan-neck and boutonnière deformity and ulnar drift hands (Table 2). The swan-neck and boutonnière deformity scores were higher in certain clusters, while the ulnar drift scores increased moderately even in clusters that were not significantly different. According to these findings, the characteristics of each cluster were as follows: cluster 1: minimal finger deformities and ulnar drift without thumb deformity; cluster 2: type 1 thumb deformity and minimal finger deformities with ulnar drift; cluster 3: type 1 or 6 thumb deformity and severe boutonnière deformity with ulnar drift; cluster 4: type 2 or 3 thumb deformity with severe ulnar drift; and cluster 5: various types of thumb deformity and severe swan-neck deformity with ulnar drift.

Deformity alterations in each cluster over time

Alterations in thumb deformity are shown in Figure 2. Of the thumbs without deformity in cluster 1, 75.7% (28/37) at 5 years and 26.3% (5/19) at 10 years retained *no deformity*, excluding excluded cases. Alterations to type 1, 2, and 3 were observed from the original status. In the other clusters, type 1 to type 2 alterations were often observed. In one case, there was an alteration from type 2 to type 3.

Plots of the swan-neck deformity score, boutonnière deformity score, and ulnar drift score are shown in Figure 3A–C. In the ANCOVA results, for the swan-neck deformity score, there was no interaction between the two factors, clusters and evaluation points, and multiple comparisons were performed because there was a significant main effect on cluster ($F = 101.638$, $p < 0.001$) and the evaluation point ($F = 13.827$, $p < 0.001$). Cluster 5 was significantly different from all other clusters in the comparisons, and there were also significant differences between 2004 and 2015 and between 2009 and 2015. For the boutonnière deformity score, there was no interaction between the two factors, clusters and evaluation points, and there was a significant main effect with cluster ($F = 14.607$, $p < 0.001$); however, the effect regarding the evaluation point ($F = 0.457$, $p = 0.633$) was not significant. In multiple comparisons, cluster 3 was significantly different compared with all other clusters, and there was also a significant difference between clusters 1 and 5. For the ulnar drift score, there was no interaction between the two factors, clusters and evaluation points, and there was a significant main effect with cluster ($F = 10.927$, $p < 0.001$), but the effect regarding the evaluation point ($F = 0.970$, $p < 0.380$) was not significant.

In multiple comparisons, cluster 4 was significantly different between clusters, compared with all other clusters, and there was also a significant difference between clusters 1 and 2. These results can be rephrased as follows: cluster 1 involved hands that were originally less deformed, but which developed thumb deformity and swan-neck deformity over time. Cluster 2 was the second least deformed hand after cluster 1, but there was a subset of cluster 2 with a progression of mainly type 1 thumb deformity to other types of hands, with swan-neck deformity and ulnar deviation over time. Cluster 3 had a subset with thumb deformity similar to cluster 2, but with a high degree of boutonnière deformity. Cluster 4 had a subset with type 2 and 3 thumb deformities and a high degree of ulnar drift, and because these hands were already highly deformed, they showed little progression over time. Cluster 5 had the most severe thumb deformity (type 6) and a high degree of swan-neck deformity in half of the hands.

Functional alterations in each cluster over time

Alterations in Kapandji index over time are shown in Figure 3D. The ANCOVA analysis showed no interaction between the two factors, clusters and evaluation points, with a significant main effect on cluster (F = 10.707, p = 0.001) but not on evaluation point (F = 1.348, p = 0.273). In multiple comparisons, clusters 1 and 2 were significantly different compared with clusters 4 and 5.

Discussion

In this study, rheumatoid hands were divided into groups by cluster analysis using parameters related to representative deformities, and alterations in deformity and function over time were compared with covariates of disease duration. Although there have been reports on the incidence of hand deformities in rheumatoid arthritis within 10 years from its onset and comparisons of grip strength by existing hand deformity[2, 3], comprehensive assessment of rheumatoid hand, including thumb deformity, and their alterations over time are not reported, to the best of our knowledge.

Clusters 1–4 of the five clusters had similar disease duration but wide variation in deformities, meaning that the period of time hand joints became symptomatic from the onset of RA was the same in clusters 1–4, but cumulative damage to the joints differed between the clusters. Cumulative disease activity in RA has been shown to affect the prognosis of the joint[13]; therefore, differences in the degree of deformity between clusters indicate a difference in outcomes with long-term drug therapy from the onset. Generally, it is impossible to know the exact relationship between differences between clusters and disease activity because it is not possible to know the progressive disease activity of patients since their disease onset. However, in any case, a large difference in hand phenotypes emerged in the approximately 17-years of patients’ disease duration. The hand clusters in this study revealed a typical pattern of deformity progression, and we identified a subset in which only mild and few deformities developed, which is good news, clinically. Conversely, type 2 and 3 thumb deformities are a factor to consider treating aggressively, as these types are often considered to be a subset of strong functional impairment complicated by severe ulnar drift.

The remaining cluster (cluster 5) had the least functioning hands, with severe thumb deformity combined with severe swan-neck deformity and with a longer disease duration than the other clusters. In this study, we did not reclassify hands in 2009 and 2015 classified by the parameters in 2004, using methods such as discriminant analysis for moves between clusters that could be followed in 2009 or 2015. Therefore, it is unclear whether hands moved between clusters over time. However, significant swan-neck deformity scores in the hands in cluster 5 indicate that swan-neck deformity exists in all fingers. Therefore, we believe it is reasonable to assume that cluster 5 developed swan-neck deformity early in disease duration versus the possibility of progression to swan-neck deformity from other clusters. Hands with swan-neck deformities had the least function in previous reports,[1, 2, 14], and our results were similar. In addition, approximately half of the patients this group also have type 6 thumb deformity (mutilans deformity) [15], which also significantly affects hand function. Therefore, because the treatment of type 6 thumb deformity and severe swan-neck deformity is still "challenging work", it seems reasonable to treat while the joint destruction is milder. Further research to investigate the limitations of surgical treatment are warranted.

Regarding alterations in deformity over time, swan-neck deformity progressed over time, whereas boutonnière deformity and ulnar drift did not progress significantly. However, the results of the longitudinal plots show a decrease in boutonnière deformity scores and an increase in ulnar drift scores for some clusters. Regarding the boutonnière deformity score, cases with severe deformity dropping out of the study, rather than showing improvement in deformity, caused the score improvement, which does not mean that deformity improves over time. In contrast, regarding the ulnar drift score, groups were clearly divided into progressive and non-progressive deformities. Ulnar drift has been reported to increase over time[3], and function is also reported to worsen with time[16]. In our study, only 63 hands were available in 2015, suggesting the possibility of a type II error. In addition, regarding function, there was no significant difference between the assessment scores over time; in fact, some groups showed a slight increase in mean scores. Overall, however, the deformity parameters deteriorated, suggesting that factors other than deformity may have influenced the results. During the 11-year observation period, C-reactive protein concentration and erythrocyte sedimentation rates) improved. The number of biologics used in this study increased from 3 (4.5%) in 2004, to 7 (13.5%) in 2009, and to 13 (35.1%) in 2015. The effect of biologics on improving hand function has been widely reported[17], and their increased use might also have improved the scores in the present study.

Regarding thumb deformities, the Nalebuff classification divided thumbs into six types by the initially affected joint and its appearance[15, 18], and type change over time was not considered. Additionally, to our knowledge, no studies have compared hand function by type, and none have quantified the impact of deformity type on hand function. Our results showed that type 1 is the primary phenotype in thumb deformity, and type 2 and 4 are secondary lesions of type 1. Seven of our type 2 cases changed from type 1, which may be explained by initial flexion contracture of the metacarpophalangeal joint with secondary carpometacarpal joint involvement. In contrast, change to type 3, which initially involves the carpometacarpal joint, occurred mainly in thumbs without deformity, except for one case. Therefore, type 3 is also a primary phenotype, as is type 1. We observed no patients in whom thumb deformity altered to type 6, in this study, but it is well known that type 6 is the final form of joint destruction, known as “mutilans”. The underlying mechanisms influencing these phenotype differences are still unknown, but our results may raise controversy regarding the underlying pathological mechanism of thumb deformities.

Quantifying finger deformities, specifically swan-neck deformity and boutonnière deformity, was challenging in this study. Anatomically, the index to little fingers have different roles. The index and middle fingers are mainly used in extension for reach behaviors, in contrast to the ring and little fingers, which work in flexion while grasping. Therefore, the affected finger should be considered when interpreting our results. A previous study evaluated each affected finger separately[19], but the authors did not evaluate the proximal interphalangeal joint and did not describe the finger deformity phenotypes. Another study reported the results of a stratified analysis by finger among patients who underwent surgery with silicone arthroplasty. The authors reported that the ring and little fingers had larger extension lags[20], but the authors did not describe hand function. A study evaluating finger deformity separately showed an almost even distribution for the characteristic finger deformities from the index to little fingers[4]. However, to our knowledge, no patient-rated subjective indicator evaluating hand function assesses fingers separately; therefore, the absence of weighting impact on function difference by each finger would have minimal impact on the results.

In this study, the swan-neck deformity scores and boutonnière deformity scores were treated equally and entered into the cluster analysis. Several studies have shown that swan-neck deformity indicates more severe disability than boutonnière deformity[1, 2, 14]. This suggests that scores from swan-neck deformity should be weighted; however, our previous study showed that both deformities contribute equally to hand function. Therefore, we used the same quantification method, in this study.

Our results suggest several paths of hand deformity progression after the onset of RA (Fig. 4). Because this study was not a follow-up study from the onset, we cannot indicate the proportions of the conservative and progressive subsets (Fig. 4). However, in the clusters in this study, many of the hands fit into the conservative subset, indicating milder deformities, which is fortunate for the patients, clinically. Of course, it should not be forgotten that type 1 thumb deformity also involves strong functional deficits as it progresses [10], and, therefore, requires early treatment. Minimal swan-neck or boutonnière deformity is considered to constitute the conservative subset, whereas multiple deformities constitute the progressive subset. Initially, it is difficult to determine the subset, but more attention should be paid to swan-neck deformity as this deformity progressed in our 11-year observation after the paradigm shift in drug therapy. Type 2 and 3 thumb deformities may also be an indicator of the progressive subset, complicated by severe ulnar drift. Similarly, type 6 thumb deformity is a clear indicator of progression and is a target for treatment because this deformity causes severe clinical functional impairment.

This study has several limitations. First, because our cohort was not followed from the onset of RA, we are unable to show how deformities developed in each subset. If we were able to show the proportion of occurrence and which deformities occurred first, we might have been able to provide a better indication of treatment. Second, the cluster analysis assigned hands to each cluster group retrospectively. Therefore, our clusters are explanatory research and cannot necessarily be applied to new single hands; additional studies are needed. Third, the results of this study could have been more meaningful if it was clear which type of thumb deformity was more disabling. A further comparison of thumb deformity in another cohort is warranted. Fourth, we used the Kapandji index as a functional evaluation. This index is usually used as a functional mobility measure and reflects functional impairment. Therefore, using an index that reflects unilateral disability, such as the Michigan Hand Outcomes Questionnaire[21], the results of this study could be more reflective of disability in the rheumatoid hand. Unfortunately, we were unable to adopt these patient-reported outcome measures at the beginning of the study.

Conclusions

Our comprehensive assessment of rheumatoid hand characteristics could be a useful tool for both rheumatologists and physicians unfamiliar with patients with impaired activities of daily living.

Abbreviations

rheumatoid arthritis: RA

analysis of covariance: ANCOVA

Declarations

Ethics approval and consent to participate

This study received full ethical approval from the institutional review board of Kyoto Prefectural University of Medicine (approval number: ERB-C-351), and the study was performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication

All patients provided oral and written informed consent at each evaluation point.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

TS, the first author, contributed to gathering, analyzing, and interpreting the data, and writing the manuscript. OR, TD, and KY contributed to the clinical evaluation and data interpretation. KR contributed independently to the functional assessments and clinical evaluations as an occupational therapist. TS contributed to the data analysis. TK contributed to the design of this study.

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Tables

Due to technical limitations, Tables 1 and 2are provided in the Supplementary Files section.

Figures

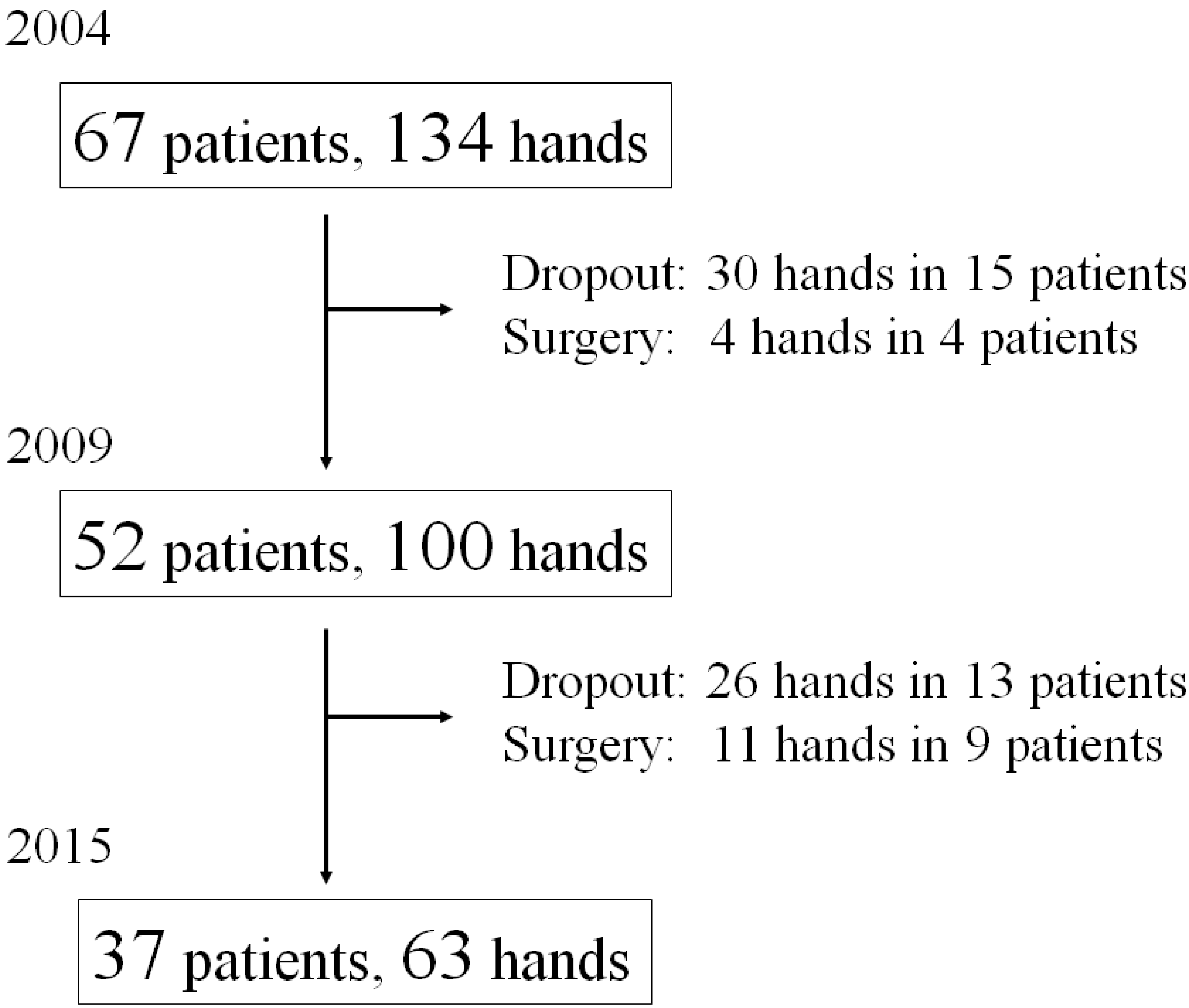
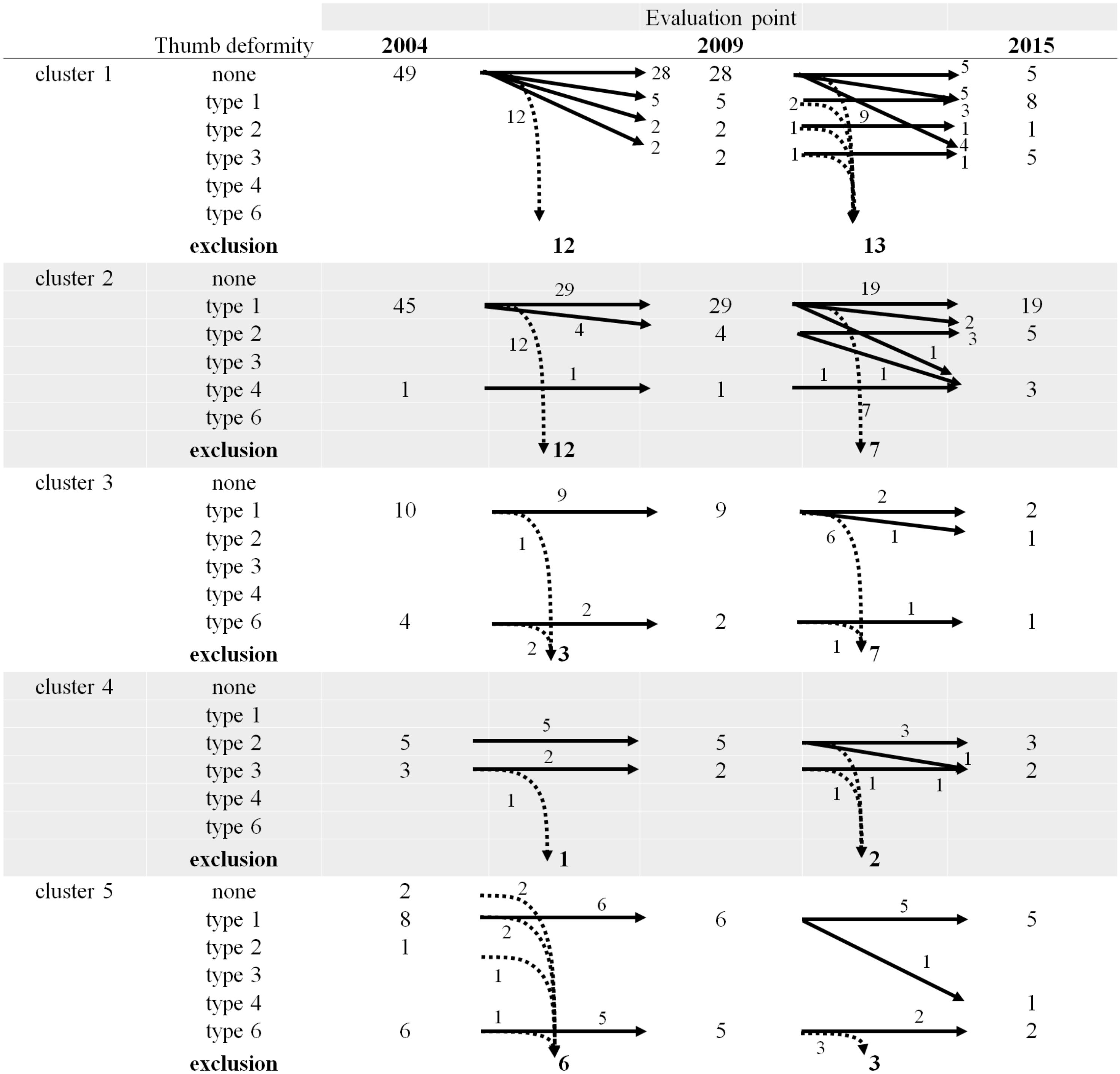


Figure 1

Flow diagram of this study. Patient registration in our hand cohort. The hands contralateral to the surgery side and patients who remained in the study were included in the cohort.



The numbers indicate the number of cases. The solid line shows the cases that changed between the evaluation points, and the dotted line shows the cases that dropped out between the evaluation points.

Figure 2

Thumb alterations in this study. This figure shows the progression of thumb deformity over time. Several specific patterns of deformity progression can be seen.

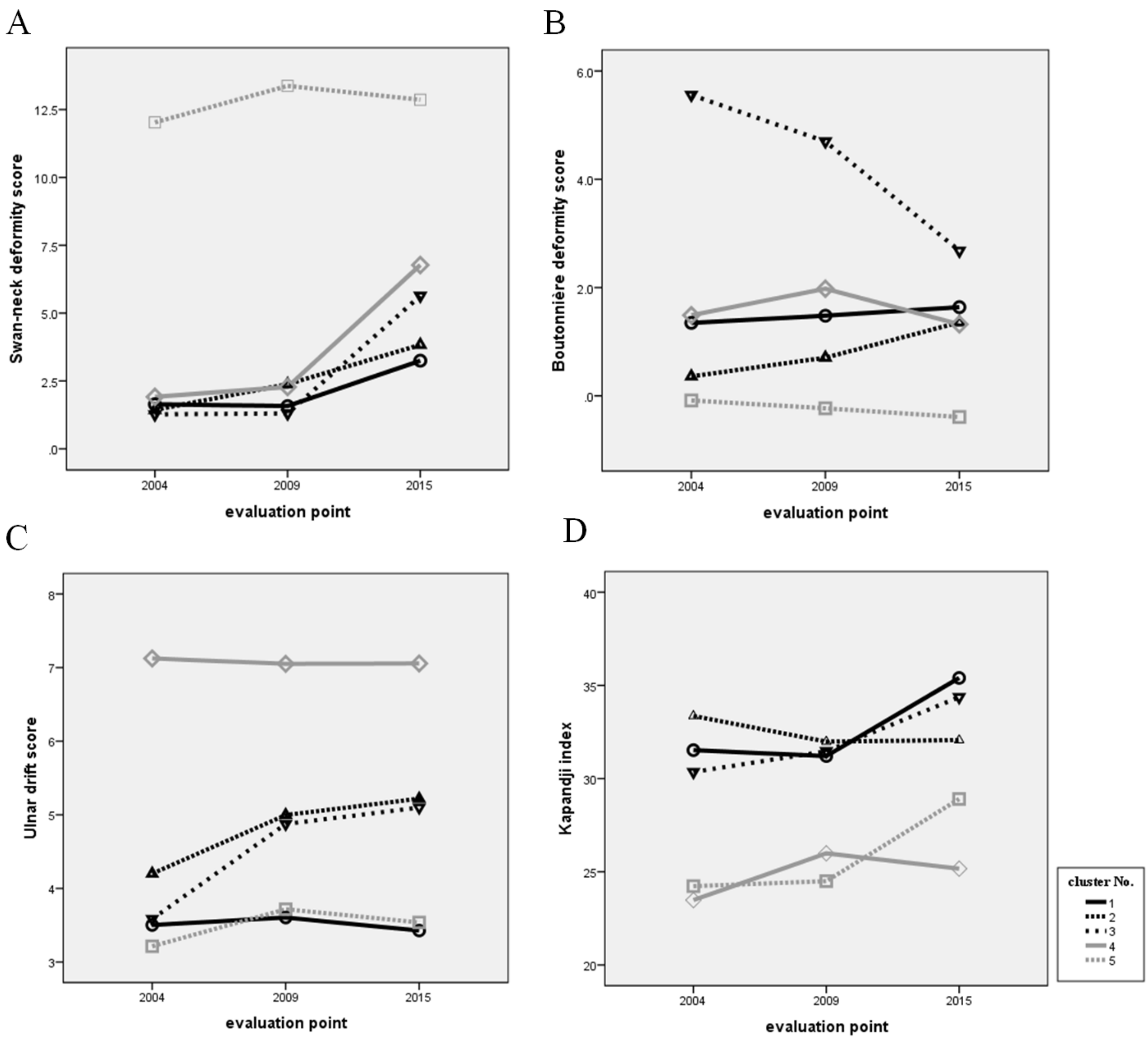


Figure 3

Trajectory plots. The trajectory plots show progression of deformities over time and the differences between the clusters (A-C). Functional impairment did not worsen during the 11 years of the study (D).

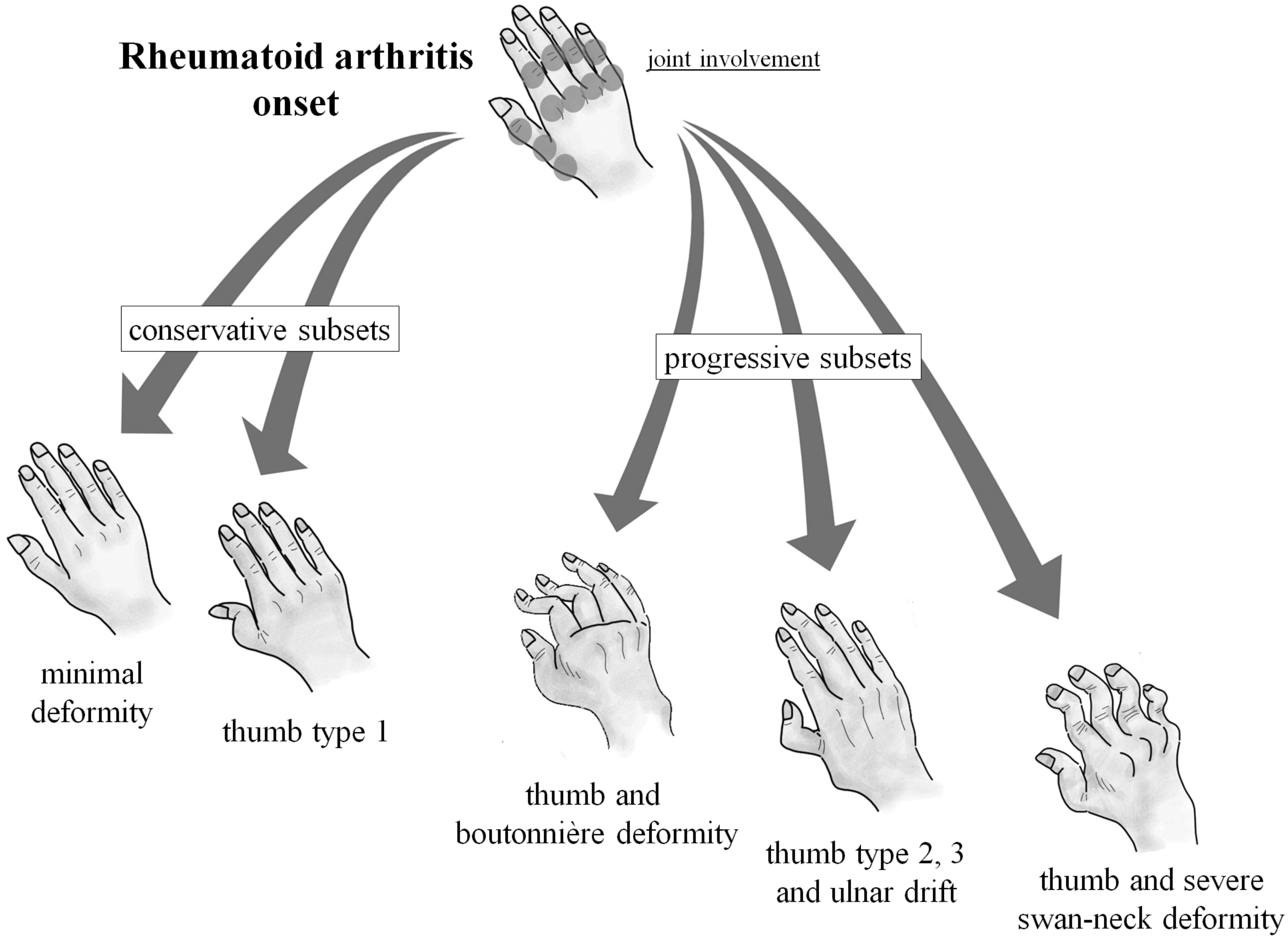


Figure 4

The paths of rheumatoid hand development. From the onset of rheumatoid arthritis, patterns appeared in hand deformity development. There were two subsets: a conservative subset with only type 1 thumb deformities, at most, and a progressive subset that developed significant deformities. Multiple finger deformities, including swan-neck deformities, and type 2 and 3 thumb deformities could be a useful indicator.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1r2.tif
- table2r2.tif
- suppleTab1.tif