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ORIGINAL ARTICLE

Validity of adopting a Health Assessment Questionnaire Disability Index less than 0.5 as a target in elderly rheumatoid arthritis patients

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Abstract

Objectives The effect of age on the Health Assessment Questionnaire Disability Index (HAQ-DI) scores of rheumatoid arthritis (RA) patients and the validity of adopting HAQ-DI < 0.5 as the target for functional remission and comprehensive disease control (CDC) under a treat-to-target (T2T) treatment strategy were investigated.

Method A total of 441 RA patients with > 3-year treatment under T2T were evaluated. The relationships between the HAQ-DI score at follow-up (HAQ) and 28-joint Disease Activity Score with C-reactive protein, Sharp/van der Heijde Score, age at follow-up, and HAQ-DI at baseline were statistically evaluated with best subset regression analysis in groups separated according to age and the EULAR response. CDC status was evaluated with a chi-square test.

Results The HAQ score significantly correlated with all indices in the group ≥ 65 years old (G-O) and in the group with good or moderate EULAR responses ($p < 0.01$). No significant correlation was observed in the group < 65 years old (G-Y) or in the group with no EULAR response. The CDC ratio was not significantly different between the age groups, whereas the HAQ failure ratio was significantly greater in G-O than in G-Y ($p < 0.01$). No significant difference was found between the EULAR response groups.

Conclusions The HAQ score is influenced by age in patients > 65 years. T2T is appropriate for attaining good disease activity control but does not always lead to functional remission in these patients. The HAQ score < 0.5 is not an appropriate target for functional remission according to the CDC criteria for elderly patients.

Key Points
- *ADL in elderly RA patient aged ≥ 65 years declines corresponding to his/her aging.*
- *Functional remission for elderly RA patients is not the same as that for young RA patients.*
- *The HAQ score < 0.5 in elderly RA patient is not an appropriate target for CDC.*

Keywords Activities of daily living · Aging · Comprehensive health care · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that generally leads to discomfort or disability when performing activities of daily living (ADL) [1]. Therefore, when treating RA, rheumatologists should pay particular attention to patient ADL, as well as disease activity [2, 3]. The Health Assessment Questionnaire Disability Index (HAQ-DI) is the most popular index for assessing ADL in RA patients [4]. The HAQ score is most likely influenced by disease activity and structural damage in RA; therefore, HAQ-DI consists of a disease activity-related HAQ (ACT-HAQ) and a damage-related HAQ (DAM-HAQ) [5]. This concept is widely accepted among rheumatologists, and responses to these two subquestionnaires are commonly used for RA treatment. However, the HAQ score often generates unexpected results. Higher HAQ scores are more frequently seen in elderly

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patients even when joint deformity is minimal and disease activity is well controlled [6]. Indeed, HAQ-DI is often influenced by factors other than disease activity and joint structural damage. In the general population, HAQ-DI is influenced by several factors, such as age, subjective feelings, educational length, body mass index, and physical exercise [7]. It is clear that factors other than ACT-HAQ and DAM-HAQ affect the HAQ-DI, namely, patient senility, pain, and comorbidities [8].

A HAQ-DI score below 0.5 has been established as a functional target for RA disease control [9, 10]. However, it seems strange to indicate this index for elderly patients because aging and aging-related comorbidities adversely influence HAQ-DI. Is the HAQ score < 0.5 the right target for functional disease control in elderly RA patients? Few studies have been reported on this topic. In this study, we evaluated the effect of aging on HAQ-DI in elderly RA patients. In addition, we examined how aging affects the treat-to-target (T2T) strategy and comprehensive disease control (CDC) in daily practice. The validity of setting HAQ-DI < 0.5 as a functional target for elderly RA patients was also assessed.

Patients and methods

Patient enrollment and measurements

We treated 683 RA patients who met the American College of Rheumatology/European League Against Rheumatism classification criteria [11]. No patients with other autoimmune diseases were included. Among these, 441 patients who had been consecutively treated for > 3 years were selected for analysis in this study. All patients had been diagnosed with adult onset RA, and no idiopathic juvenile arthritis transferred patients were included. We adopted a T2T strategy as a treatment protocol in 2010 [12, 13], and all of these patients had been treated in accordance with T2T, which aims for clinical remission within 3 months after the first consultation. Patients were seen at 1-to-3-month intervals [12], at which times, we measured their Disease Activity Score in 28 joints with C-reactive protein (DAS28) [14], daily activity according to the HAQ-DI, and radiographic evaluation using the Sharp/van der Heijde Score [15] from X-ray pictures of bilateral hands and feet. The DAS28 and HAQ-DI were evaluated every visit, and the Sharp/van der Heijde Score was measured at the initial visit and every other year thereafter by a radiologist trained in Sharp/van der Heijde Score calculation.

Relationship between the HAQ-DI score and DAS28 or Sharp/van der Heijde Score and equation for these indices

The patients were separated into age groups in 10-year intervals in accordance with their average age from the initial visit until the end of follow-up: 86 patients were < 55 years old (G-1 group), 92 were 55 to 64 years old (G-2 group), 128 were 65 to 74 years old (G-3 group), and 125 were ≥ 75 years old (G-4 group). The HAQ-DI score, DAS28, Sharp/van der Heijde Score, and age at the first visit as well as the average value of these indices after the third year of follow-up were calculated for every patient. The relationships between the HAQ-DI and DAS28 and between the HAQ-DI and Sharp/van der Heijde Score at follow-up were compared for each pair of age groups. We evaluated the correlation coefficient for the approximate equation for each group, and the statistical significance for each index was evaluated from the equations.

Background factor comparison analysis in accordance with age group

Clinical background data, namely sex, anti-citrullinated cyclic peptide antibodies (ACPA) at first visit, age at onset and at first visit, disease duration at first visit, concomitant glucocorticoid steroid (GCS) administration, average dosage and total dose, methotrexate (MTX) administration, and average dosage, biologic disease–modifying anti-rheumatic drug (bDMARD) administration, average rheumatoid factor, and the frailty score were collected. Frailty represents the general status decline in elderly people mainly due to muscle weakness. The frailty score was calculated as the sum of the five items used for frailty diagnosis. Monitored data such as the HAD-DI score, DAS28, and Sharp/van der Heijde Score at first visit and at follow-up as well as changes in these parameters from the first visit to follow-up were also calculated. Patients were classified into subgroups in accordance with the following criteria: patients whose (1) average age after 3 years of follow-up was < 65 years (G-1 and G-2 groups; G-Y group) and (2) average age after 3 years of follow-up was ≥ 65 years (G-3 and G-4 groups; G-O group). These parameters were compared statistically using the Mann–Whitney *U* test.

Background comparison analysis in accordance with EULAR response group

We evaluated the differences in accordance with disease activity control status. Patients were divided in accordance with the EULAR response: (1) patients who attained good or moderate EULAR responses [16] at follow-up compared with the first visit (EULAR good/moderate response group) and (2) patients whose EULAR response was evaluated as no response (EULAR no response group). Differences in the clinical background factors according to the age groups were also evaluated statistically with Mann–Whitney *U* test.

Relationship between HAQ-DI and the other indices according to age and EULAR response groups

The relationships among the HAQ-DI at follow-up, DAS28, Sharp/van der Heijde Score, age at follow-up, and HAQ-DI at baseline were statistically evaluated using best subset regression analysis for G-Y, G-O, EULAR good/moderate response group, and no response group.

Comparison of comorbidities according to age groups

The effects of comorbidities on the HAQ-DI score at follow-up were also evaluated. The patients were classified in accordance with the existence of comorbidities for each organ, and the HAQ-DI score between the positive and negative groups was compared for each organ using the Mann–Whitney *U* test. The comorbidity concurrence ratios for all organs were compared between the G-O and G-Y groups using the chi-square test.

Comprehensive disease control status comparison according to age groups

CDC status is the ultimate goal of the T2T strategy. CDC classifies remission using three indices: DAS28 < 2.6, HAQ-DI < 0.5, and change from baseline in Sharp/van der Heijde Score ≤ 0.5. The CDC status and HAQ-DI failure ratio were compared for each group using the chi-square test.

Statistical analysis software and settings

All statistical procedures were performed using StatPlus® (AnalystSoft Inc., Walnut, CA, USA). All statistical significance was set at $p < 0.01$.

Results

Overall statistics of the subjects in the study

Overall, 441 patients (337 females) were included in this study. Mean age and standard deviation at baseline were 64.5 and 13.5 years, respectively. Mean value and standard deviation at baseline were 3.13 and 1.16 for DAS28, 0.435 and 0.571 for HAQ-DI, and 53.2 and 68.1 for Sharp/van der Heijde Score, respectively. In 86.7% patients, methotrexate was administrated in their third treatment year, and mean dosage was 7.7 mg per week, whereas bDMARDs were administrated in 23.6% patients in their third treatment year. Of these, 61 patients were administered with TNF inhibitors such as infliximab, adalimumab, golimumab, and etanercept; 21 were administered with IL-6 inhibitor tocilizumab; and 22 were administered with abatacept. There was no significant difference between the G-Y and G-O groups with respect to the administration ratio of bDMARDs.

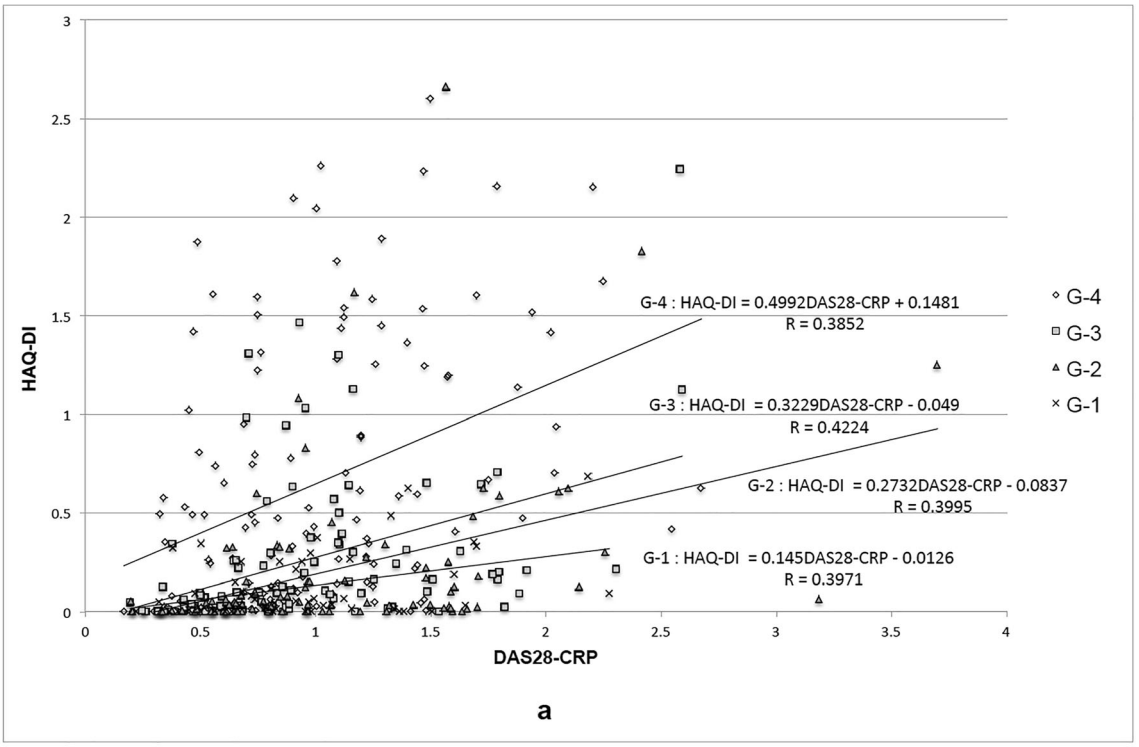
Relationship between the HAQ-DI score and DAS28 or Sharp/van der Heijde Score and equation among indices

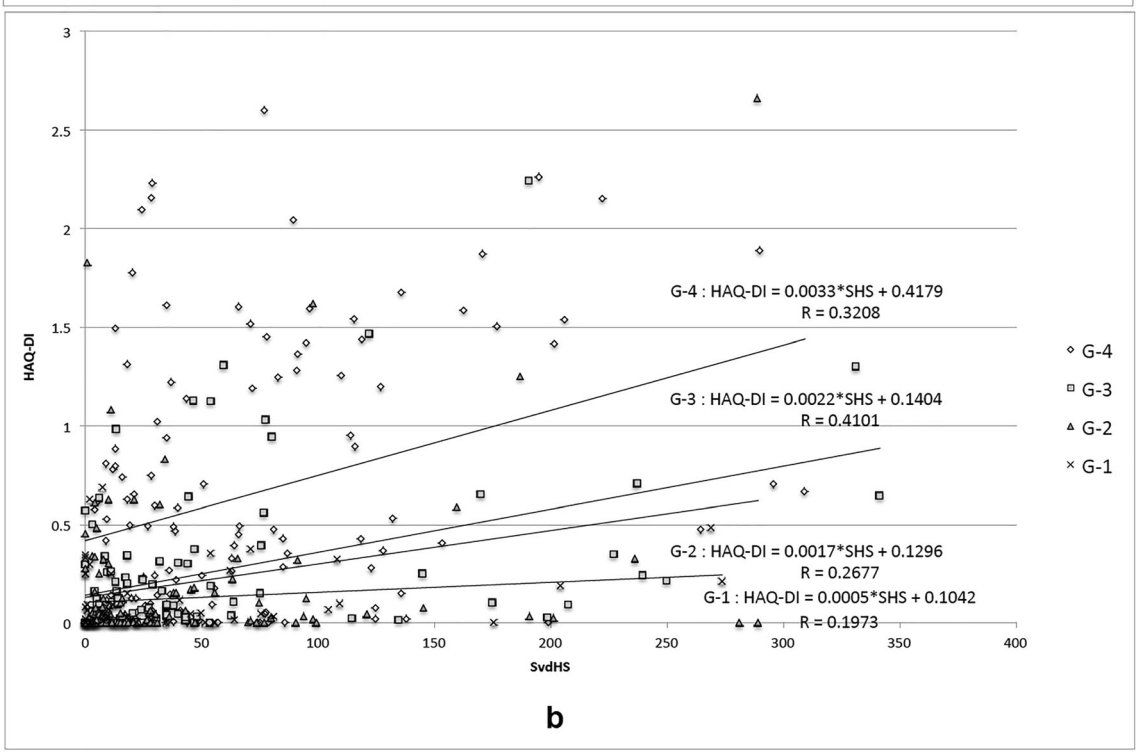
The G-1, G-2, G-3, and G-4 groups comprised 92, 86, 103, and 143 patients, of which 73.9%, 81.4%, 75.7%, and 77.7% were female, respectively. The relationship between the HAQ-DI and DAS28 is shown in Fig. 1a. Approximate equations are also shown in the figure. The HAQ-DI increased with increasing DAS28 in all groups, while the coefficients of DAS28 in the equation increased with increasing age in all groups. The coefficients of DAS28 were 0.145, 0.2732, 0.3229, and 0.4992 for the G-1, G-2, G-3, and G-4 groups, respectively. The baseline value of the HAQ-DI when the DAS28 was zero, which is expressed as a constant in the equation, was approximately zero. The constants for the equation were − 0.049, − 0.0837, and − 0.0126 for G-1, G-2, and G-3, respectively, and 0.1481 for G-4.

The relationship between the HAQ-DI and Sharp/van der Heijde Score is shown in Fig. 1b. The approximate equations are also shown in the figure. The HAQ score increased with increasing Sharp/van der Heijde Score in all groups. The coefficients of Sharp/van der Heijde Score in the equation increased with increasing age in all groups, similar to the relationship between the HAQ-DI and DAS28. The coefficients of Sharp/van der Heijde Score were 0.0033, 0.0022, 0.0017, and 0.0005 for G-1, G-2, G-3, and G-4, respectively. The baseline value of HAQ-DI approached 0 when Sharp/van der Heijde Score approached 0. The constant was 0.1042, 0.1296, and 0.1404 for G-1, G-2, and G-3, respectively, but was 0.4179 for G-4. The correlation coefficients of Sharp/van der Heijde Score were 0.3208, 0.4101, 0.2677, and 0.1973 and those of DAS28 were 0.3852, 0.4224, 0.3995, and 0.3971 for G-4, G-3, G-2, and G-1, respectively. The Sharp/van der Heijde Score values were smaller than the DAS28 values.

Background factor comparison analysis

The profiles of the G-O and G-Y, EULAR good/moderate response group, and no response group are shown in Table 1. There were 178 patients in the G-Y group, 263 in the G-O group, 202 in the EULAR good/moderate response group, and 239 in the EULAR no response group. There were no significant differences between any of the groups in sex distribution, average values of ACPA and





ACPA positive ratio, disease duration from onset to the first visit, DAS28 at follow-up, GCS administration dosage and length, MTX administration ratio and dosage, rheumatoid factor (RF) at follow-up, and number of comorbidities. The G-Y group had significantly lower values than the G-O for the age at onset, first visit, and follow-up, as well as in HAQ at baseline, HAQ at follow-up, frailty diagnosed ratio, frailty score at first visit, and dementia treated ratio. The EULAR good/moderate response group had significantly greater values for DAS28 at first visit, HAQ at baseline, HAQ-DI at follow-up, concomitant bDMARD administration at follow-up, and change of DAS28 than the EULAR no response group (Table 1).

◀ **Fig. 1** Scattered graph described relationship between Health Assessment Questionnaire Disability Index (HAQ-DI) and Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP) (**a**) and Sharp/van der Heijde Score (SvdHS) (**b**) at follow-up for each age group. G-1, patient average age through follow-up is less than 55; G-2, patient whose average age through follow-up is between 55 and 64; G-3, patient whose average age through follow-up is between 65 and 74; G-4, patient whose average age through follow-up is no less than 75. **a** DAS28-CRP is subtracted 0.96 from real value. Equations are approximately equation for each group. Correlation coefficients demonstrated approximately 0.4 in every equation. A common tendency that HAQ-DI increased as DAS28-CRP increases is demonstrated in every equation. In while, coefficients for DAS28-CRP are greater as age group gets older. Constant of equation for G-4 is 0.1481, what is greater than every other group's constant, for which demonstrates − 0.049, − 0.0837, and − 0.0126 Å for G-3, G-2, and G-1 respectively. That explains as basement HAQ-DI when DAS28-CRP is at basement value as 0.96. **b** Equations are approximately equation for each group. Correlation coefficients demonstrated approximately 0.2 to 0.4, as demonstrated smaller values than that of DAS28-CRP. A common tendency that HAQ-DI increased as Sharp/van der Heijde Score increases is demonstrated in every equation, while coefficients for SHS are greater as age group gets older. Constant of equation for G-4 is 0.4179, which is greater than every other groups' constant, which demonstrates 0.1404, 0.1296, and 0.1973 for G-3, G-2, and G-1 respectively

Relationship between HAQ-DI and the other indices according to age and EULAR response groups

In best subset regression analysis, the HAQ score at follow-up was set as a dependent variable, whereas HAQ at baseline, Sharp/van der Heijde Score, DAS28, and age at follow-up were set as independent variables. The correlation coefficients (*R* values) for all equations were above 0.9. This confirms that the equations had extremely strong power statistically. HAQ at baseline was the strongest factor in all groups with significant correlation. The second strongest factor was DAS28 at follow-up, and this was common in all groups. In G-O and the EULAR good/moderate response group, the third strongest factor was age at follow-up followed by Sharp/van der Heijde Score at follow-up. These factors also demonstrated statistically significant correlation, and age at follow-up was the third strong factor in the EULAR no response group, although not significant. In G-Y, age at follow-up was the weakest factor with no statistical significance (Table 2).

Comparison of comorbidities according to age groups

Compared with G-Y and G-O, psycho-neural system, skin, and cardiovascular system comorbidities were significantly more prevalent in G-O than in G-Y, while musculoskeletal system demonstrated no significant difference. In positive and negative group comparisons, the group positive for psycho-neural system, skin, and miscellaneous comorbidities had significant greater HAQ scores than the negative group (Supplemental table).

Comprehensive disease control status comparison according to age groups

The CDC ratio for G-Y, G-O, EULAR good/moderate response group, and EULAR no response group was 50.5%, 40.9%, 42.7%, and 46.5%, respectively. There was no significant difference between any of the groups. In G-O, the CDC ratio was 38.6% for the EULAR good/moderate response group and 44.3% for the EULAR no response group, with no significant difference between the two groups (Fig. 2).

HAQ at follow-up failure (≥ 0.5) ratio in the CDC failure group was 50.9% for G-Y and 94.7% for G-O, with a significant difference between the two groups (Fig. 3a). There was no significant difference between the ratios for the EULAR good/moderate response and no response groups at 66.3% and 65.2% (Fig. 3b). In the G-O group, the HAQ at follow-up failure ratio for the EULAR good/moderate response and no response groups was 74.3% and 59.1%, respectively. The EULAR good/moderate response group had a greater failure ratio than the EULAR no response group, but the difference was not significant (Fig. 3c).

The HAQ score at follow-up controlled (< 0.5) ratio was 81.3% and 59.1% for G-Y and G-O, respectively. G-Y had a significantly greater HAQ score at follow-up control ratio than G-O (Fig. 4a), but no significant difference was found between the EULAR good/moderate response and no response groups, with 63.3% and 72.4%, respectively (Fig. 4b). In G-O groups, the HAQ controlled ratio at follow-up for the EULAR good/moderate response group and no response group was 38.6% and 44.3%, respectively, with no statistical difference between the two groups (Fig. 4c).

Discussion

RA is a disease that increases mortality and is characterized by a decline in ADL, concurrent comorbidities, and shortened life expectancy [17, 18]. Monitoring of the ADL for RA patients can help prevent or minimize adverse consequences and control disease activity [1, 2]. HAQ-DI is the primary index used to assess ADL. The HAQ score can show how well an RA patient maintains good health conditions and maximizes their chances of achieving normal life expectancy because predictions of mortality are similar between RA patients and persons in the normal population with the same HAQ values [19, 20].

Two well-known factors contribute to HAQ-DI: disease activity status and joint structural damage. The former contributes to ACT-HAQ and the latter to DAM-HAQ. In all related clinical trials, HAQ-DI has shown remarkable

Table 1 Clinical characteristics of each subgroups

G-O	G-Y	*p* value	Parameters	G-Egm	G-En	*p* value
263	178		Number of cases	202	239	
199 (75.7%)	138 (77.5%)	0.651	Female (%)	153 (75.7%)	184 (77.0%)	0.759
171.47 (78.0%)	124.65 (79.2%)	0.846	ACPA at first visit (average value (positive%)	213.8 (75.8%)	100.4 (80.4%)	0.183
68.90, 9.79	48.37, 9.97	0.001	Age at onset (yeas)	62.35, 13.65	58.9, 6.63	0.152
4.74, 9.22	2.69, 4.85	0.081	Disease duration at first visit (years)	3.71, 6.35	4.07, 7.14	0.522
72.82, 8.11	51.07, 9.28	0.001	Age at first visit	66.00, 12.52	62.13, 5.23	0.183
0.557, 0.622	0.256, 0.446	0.001	HAQ-DI at first visit	0.546, 0.588	0.341, 0.517	0.001
3.24, 1.19	2.95, 1.12	0.706	DAS28-CRP at first visit	3.99, 1.52	2.32, 0.36	0.001
63.34, 73.00	37.19, 56.03	0.061	SvdHS at first visit	45.75, 55.27	58.49, 75.03	0.211
62.2, 14.9	63.3, 25.4	0.872	Follow-up length (months)	41.0, 9.2	80.6, 27.4	0.001
71.11, 6.91	55.93, 8.88	0.001	Age at follow-up	69.42, 12.70	66.98, 3.47	0.214
0.548, 0.598	0.239, 0.405	0.001	HAQ-DI at follow-up	0.521, 0.555	0.339, 0.489	0.001
1.99, 0.47	2.06, 0.54	0.807	DAS28-CRP at follow-up	1.91, 0.47	2.1, 0.52	0.601
62.35, 71.91	36.69, 54.81	0.060	SvdHS at follow-up	45.09, 53.82	57.59, 74.15	0.488
52.00%	39.30%	0.325	GCS administration at follow-up (%)	51.90%	42.40%	0.586
3.08, 4.0	3.43, 3.2	0.921	GCS dosage (mg/day) and length (months)	3.49, 3.3	2.98, 4.0	0.827
88.60%	84.80%	0.911	MTX administration at follow-up (%)	89.80%	84.40%	0.846
7.41, 2.41	8.14, 2.25	0.455	MTX dosage	8.01, 2.48	7.42, 2.22	0.315
62 (23.5%)	47 (26.4%)	0.337	bDMARDs administration at follow-up (%)	71 (35.1%)	48 (20.0%)	0.008
114.2, 349.5	83.67, 147.9	0.782	RF at follow-up (U/L)	88.05, 168.3	113.1, 351.0	0.795
− 0.009	− 0.017	0.925	HAQ-DI change throughout follow-up	− 0.025	− 0.0014	0.001
− 1.25	− 0.89	0.140	DAS28-CRP change throughout follow-up	− 1.58	− 0.7	0.001
− 1.00, 6.65	− 0.47, 6.73	0.840	SvdHS change throughout follow-up	− 0.67, 7.19	− 0.88, 6.23	0.952
11:100:142	7:84:98	0.576	EULAR response (good:moderate:no)	18:184:0	0:0:240	0.001
120 (44.0%)	10 (6.0%)	0.001	Frailty diagnosed (%)	58 (28.7%)	72 (30.0%)	0.168
2.14, 2.14	0.47, 1.07	0.001	The frailty score at first visit	1.52, 1.95	1.41, 1.50	0.906
72 (26.4%)	4 (2.4%)	0.001	Dementia treated (%)	37 (18.3%)	39 (16.3%)	0.985
3.36, 2.80	2.48, 2.34	0.121	Number of comorbidities during follow-up	3.31, 2.59	2.74, 2.62	0.545

In columns, mean value and standard deviation are shown separated with "," except of case numbers. In case number columns, case number and percentage of each group in parenthesis are shown

G-O patient group in which patient's average age at follow-up were no less than 65 years old, *G-Y* patient group in which patient's average age at follow-up were less than 65 years old, *G-Egm* patient group in which patient' response of DAS28 at follow-up met good or moderate in EULAR response criteria, *G-En* patient group in which patient' response of DAS28 at follow-up met no in EULAR response criteria, *ACPA* anti-citrullinated cyclic antibodies, *HAQ-DI* Health Assessment Questionnaire Disability Index, *DAS28-CRP* 28-joints disease activity index with C-reactive protein, *SvdHS* Sharp/van der Heijde Score, *GCS* glucocorticoid steroid, *MTX* methotrexate, *bDMARDs* biologic disease modifying anti-rheumatic drugs, *RF* rheumatoid factor

reductions after drug intervention; however, it never reaches zero [21–23]. RA leads to joint destruction, which exacerbates HAQ-DI in the long term. However, even in trials studying early stage RA patients, HAQ-DI reduction could not reach zero for all elderly patients [3]. Even after early RA patients have achieved clinical remission, we often observe persistent disabilities that increase HAQ-DI remnants for elderly patients. These results suggest that aging can also increase the HAQ-DI in RA patients.

ADL in humans naturally declines with aging. There are several indices for the measurement of ADL related to aging, such as the Clinical Frail Scale and Locomotive Syndrome Risk Test [24, 25]. These tests are convenient for assessing functional decline during aging [26, 27], but they are not widely used in RA treatment. The HAQ-DI is considered the standard index for ADL in RA treatment, and if the relationship between the HAQ-DI and aging is clarified in detail, this index is expected to be the most convenient assessment tool.

In this study, we attempted to clarify the effect of aging on the HAQ-DI and how aging relates to the other indices commonly used in RA treatment. To fulfill the purpose, we classified the patients in four classes based on their age for statistical analysis. Secondly, we conducted best subset regression analysis for HAQ-DI at follow-up with other clinical indices, such as age, to evaluate which factor is statistically predominant. Finally, influence on CDC was evaluated by determining

Table 2 Results of best subset regression analyses of HAQ-DI at follow-up and the other parameters for G-Y, G-O, G-Egm, and G-En

Group	HAQ@BL	DAS28@FU	SvdHS@FU	Age@FU	*R* value
G-Y	*< 1.0 × 10^{-12}*	*1.430 × 10^{-3}*	7.076 × 10^{-1}	9.043 × 10^{-1}	0.9812
G-O	*< 1.0 × 10^{-12}*	*1.400 × 10^{-4}*	*2.700 × 10^{-3}*	*1.500 × 10^{-4}*	0.9861
G-Egm	*< 1.0 × 10^{-12}*	*1.000 × 10^{-4}*	*3.251 × 10^{-2}*	*3.820 × 10^{-3}*	0.9849
G-En	*< 1.0 × 10^{-12}*	*2.040 × 10–3*	7.939 × 10^{-1}	4.034 × 10^{-1}	0.9870

In columns except *R* values, *p* value is shown. Italicized values demonstrate significance less than 1%

HAQ-DI Health Assessment Questionnaire Disability Index, *DAS28-CRP* 28-joints disease activity index with C-reactive protein, *SvdHS* Sharp/van der Heijde Score, *G-Y* patient group in which patient's average age at follow-up were less than 65 years old, *G-O* patient group in which patient's average age at follow-up were no less than 65 years old, *G-Egm* patient group in which patient' response of DAS28 at follow-up met good or moderate in EULAR response criteria, *G-En* patient group in which patient' response of DAS28 at follow-up met no in EULAR response criteria, *@BL* at first visit, *@FU* at follow-up, *R value* regression coefficient

whether the HAQ score < 0.5 was appropriate for elderly patients. This study may be the first report to evaluate the effect of aging on clinical indices that are usually used while monitoring RA patients under targeted treatment protocol such as T2T with real world data. In accordance with this purpose, we examined patient data obtained after the third treatment year because the type of data collected should be identical and should not be influenced by quick protocol changes in RA treatment using the T2T strategy and the consequent rapid changes in index values [2, 28, 29]. T2T is a targeted treatment method that aims to achieve clinical remission within 3 to 6 months; hence, the data for the first treatment year would not have been suitable for our purpose. We concluded that data from the third year and later would be more appropriate after reviewing the novel data from the PREMIER Trial [19] and from our previous study on comprehensive disease remission (CDR) [30]. We found that the values of the three indices for CDR, namely the DAS28, yearly progress of Sharp/van der Heijde Score, and HAQ-DI, stabilize after the third treatment year. Thus, statistical consistency was guaranteed.

We attempted to evaluate the influence of aging in patients with good or moderate EULAR responses to determine the effect of tight disease control under T2T and the feasibility of T2T for elderly patients. Many of the patients in the G-O group attained good or moderate EULAR responses; however, HAQ-DI remained high even in the EULAR good/moderate response group. These results suggest that T2T, which is often aimed at clinical remission, is feasible for elderly RA patients. Some reports have suggested that the clinical target should be set to low disease activity for elderly patients [31, 32]; however, this is not supported by our results. On the other hand, a numeric target below 0.5 for HAQ-DI is often impossible to attain with elderly patients because of their age.

Our analysis suggested that aging was a strong candidate that could influence the HAQ-DI score of RA patients. The first reference HAQ score is recognized as a very strong predictor of future HAQ scores, even if the patient is in an early RA stage or if the disease activity is high. In our study, the HAQ score at baseline was the most dominant factor associated with the HAQ score. This indicates that a patient's background, such as education level, exercise habits, psychological status, and perhaps lifestyle diseases, before treatment is the most important factor that will influence ADL [6, 8, 18]. However, age was found to be a significant factor in the G-O group. Increasing age is a major factor associated with increasing total HAQ scores and all eight of its components, just as gender is a strong factor associated with the total HAQ and subdimension scores [33].

The results of this study showed no effects of aging on the HAQ-DI scores of patients in the G-Y group. These results indicate that aging only affects the HAQ-DI score for patients > 65 years old. We assumed the HAQ score for patients < 65 years in groups other than the G-Y group was 0 because of the lack of an effect from aging on the scores of these

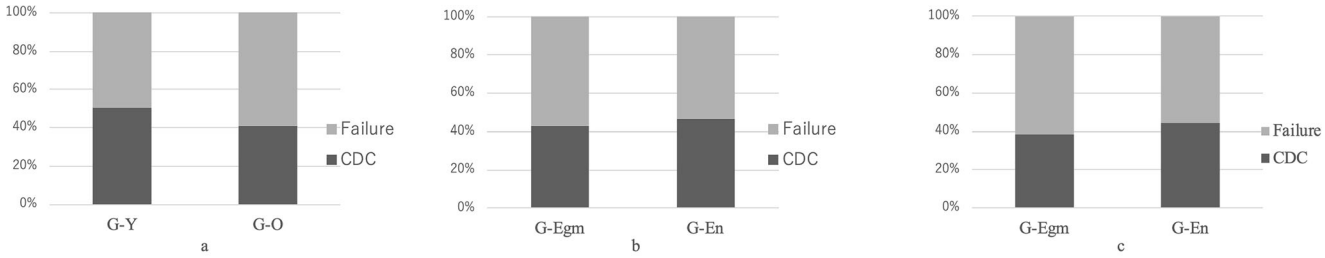


Fig. 2 Comprehensive disease control (CDC) ratio for each group. G-Y, a patient groups whose age was < 65; G-O, a patient group whose age was ≥ 65; G-Egm, a patient groups whose EULAR response was good or moderate; G-En, a patient group whose EULAR response was no response. **a** CDC ratio for G-Y and G-O. CDC ratio is greater in G-Y, but no statistical significance demonstrated. **b** CDC ratio for G-Egm and G-En. There is no significant difference. **c** CDC ratio for G-Egm and G-En in G-O. There is no significant difference

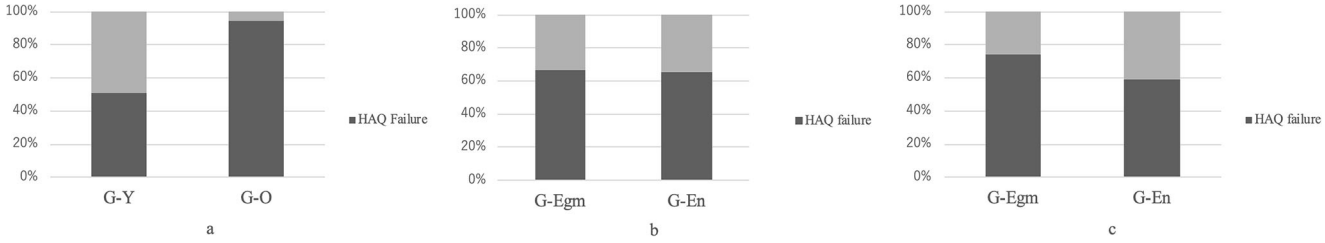


Fig. 3 HAQ-DI failure ratio in CDC Failure group for each group. G-Y, a patient groups whose age was < 65; G-O, a patient group whose age was ≥ 65; G-Egm, a patient groups whose EULAR response was good or moderate; G-En, a patient group whose EULAR response was no response. **a** HAQ-DI failure ratio of G-Y and G-O. G-O demonstrated significantly greater failure ratio than G-Y ($p < 0.01$). **b** HAQ-DI failure ratio of G-Egm and G-En. No statistical difference demonstrated. **c** HAQ-DI failure ratio of G-Egm and G-En in G-O group. G-Egm shows greater HAQ-DI failure ratio; however, no significant difference was demonstrated

younger patients. This assumption worked as expected. Sokka and her colleagues advocated that HAQ scores increase exponentially for patients in their late 60s or older [7, 34], which supported our general findings.

The effect of aging is more evident when disease activity is well controlled. We excluded patients who had no response on the EULAR response criteria to diminish the effect of disease activity on the increase in the HAQ-DI scores in the EULAR good/moderate response group. Our results for the EULAR good/moderate response group showed a significant aging effect on the HAQ scores. These results suggest that the effect of disease activity on the HAQ score is so strong that it is statistically evident even after T2T is successfully fulfilled.

However, the effect of aging was not evident for disease activity control. Both the G-O and G-Y groups showed no significant differences in the DAS28. This finding suggests that aging does not influence disease activity control. Therefore, physicians should not hesitate to use T2T to achieve clinical remission, even in elderly patients. Although issues such as bioavailability, drug compliance, comorbidities, and dementia may be present in elderly individuals, we should use rapid protocol changes when needed to treat older RA patients because senile patients tend to respond quickly to drugs in general.

These facts have been previously pointed out and described by Vita et al. [35]. However, the researchers had analyzed data for 1741 subjects to investigate the effects of aging and health risks and reported that aging and health risks increased the risk for future disabilities. The researchers also stated that RA and osteoarthritis could increase the risk of future disabilities. However, their report was published before T2T was announced and implemented. Our study analyzed the relationship between disabilities and aging with disease activity and joint destruction under a T2T treatment strategy. We found that even for RA patients who had been treated under T2T at an early stage, the influence of age was inevitable, and the effect of aging on HAQ-DI became more evident for patients > 75 years old. The mean age of the population in many developed countries has been increasing, which means that many RA patients may be older because the life expectancy for RA patients has been increasing [36–39].

The influence of aging on CDC is clearly demonstrated in this study. There was no difference in the CDC ratio between the patients older or younger than 65 years old, but elderly patients had greater HAQ-DI failure ratios than younger patients among the CDC failure cases. Even with good disease activity control, aging prevents CDC attainment due to HAQ failure with the present criteria. Because the influence of aging is evident after age 65, setting the criteria of CDC for functional remission to the HAQ score < 0.5 is not appropriate for patients ≥ 65 years old. We cannot provide a specific cutoff value for the functional remission. However, one candidate criteria for functional decline is frailty, which reflects the physical status of elderly individuals [40, 41]. However, there have been few reports concerning frailty in RA patient [42]. Thus, further study is necessary.

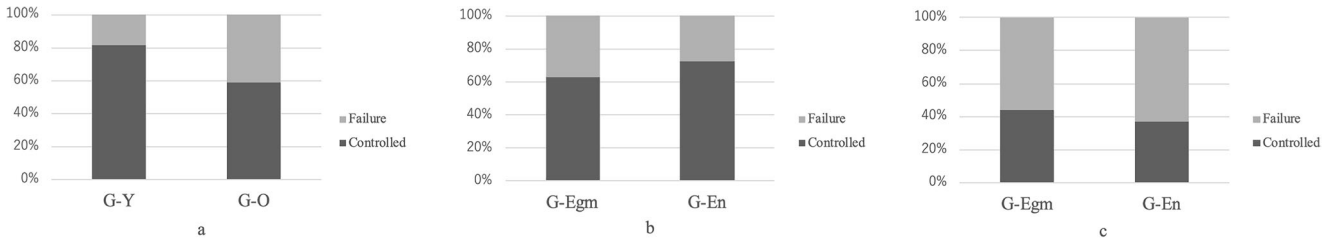


Fig. 4 HAQ-DI controlled (< 0.5) ratio for each group. G-Y, a patient groups whose age was < 65; G-O, a patient group whose age was ≥ 65; G-Egm, a patient groups whose EULAR response was good or moderate; G-En, a patient group whose EULAR response was no response. **a** HAQ-DI controlled ratio for G-Y and G-O. G-Y demonstrated significant greater HAQ-DI controlled ratio than G-O ($p < 0.01$). **b** HAQ-DI controlled ratio for G-Egm and G-En. G-En shows greater HAQ-DI controlled ratio than G-Egm, however, no significant difference demonstrated. **c** HAQ-DI controlled ratio for G-Egm and G-En in G-O group. No statistically significant difference was demonstrated

Certain limitations should be considered when interpreting our results. The effects of other factors, such as sex, disease duration, mixing with other drugs (such as corticosteroids), depression, and ethnic differences, remain unclear. However, in our study, there were no significant differences in sex or corticosteroid usage between the groups. Disease duration was longer in the G-O group than in the G-Y group because older patients naturally tend to have longer medical histories. The effect of ethnic differences also remains unclear because all of our patients were Japanese. Two other concerns are that the sample size was relatively small and that this study was conducted at a single institution, both factors that may have introduced selection bias. Consequently, there is a risk that our results may not be reproducible, so studies conducted at other institutions are necessary to confirm our results.

In conclusion, elderly patients tend to have higher HAQ scores due to aging even after disease activity is controlled. Therefore, it is important to consider patient age because it is unwise to obstinately pursue HAQ scores < 0.5 for RA patients ≥ 65 years old. AGED-HAQ should be subtracted from the real HAQ-DI to obtain a better estimate of the HAQ score from disease activity and joint deformity.

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Compliance with ethical standards

This study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of Japan under the Declaration of Helsinki. The Ethics Committee of the institution approved the protocol and consent forms (approval number: YH-RA-201803). Patients and their families were informed that personal information would be anonymous and used only for analysis before they signed the consent forms.

Disclosures None.

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