Impact of early diagnosis on functional disability in rheumatoid arthritis

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Background/Aims: To determine whether early diagnosis is beneficial for functional status of various disease durations in rheumatoid arthritis (RA) patients.

Methods: A total of 4,540 RA patients were enrolled as part of the Korean Observational Study Network for Arthritis (KORONA). We defined early diagnosis as a lag time between symptom onset and RA diagnosis of \( \leq 12 \) months, whereas patients with a longer lag time comprised the delayed diagnosis group. Demographic characteristics and outcomes were compared between early and delayed diagnosis groups. Logistic regression analyses were performed to identify the impact of early diagnosis on the development of functional disability in RA patients.

Results: A total of 2,597 patients (57.2%) were included in the early diagnosis group. The average Health Assessment Questionnaire-Disability Index (HAQ-DI) score was higher in the delayed diagnosis group (0.64 ± 0.63 vs. 0.70 ± 0.66, \( p < 0.01 \)), and the proportion of patients with no functional disability (HAQ = 0) was higher in the early diagnosis group (22.9% vs. 20.0%, \( p = 0.02 \)). In multivariable analyses, early diagnosis was independently associated with no functional disability (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.01 to 1.40). In a subgroup analysis according to disease duration, early diagnosis was associated with no functional disability in patients with disease duration < 5 years (OR, 1.37; 95% CI, 1.09 to 1.72) but not in patients with longer disease duration (for 5 to 10 years: OR, 1.07; 95% CI, 0.75 to 1.52; for \( \geq 10 \) years: OR, 0.92; 95% CI, 0.65 to 1.28).

Conclusions: Early diagnosis is associated with no functional disability, especially in patients with shorter disease duration.

Keywords: Early diagnosis; Disability; Arthritis, rheumatoid; Health assessment questionnaires
INTRODUCTION

During the past decade, early diagnosis and treatment of rheumatoid arthritis (RA) have been emphasized because a window of opportunity is believed to exist in early RA during which the disease is more responsive to treatment [1-3]. Previous studies revealed that early diagnosis and treatment prevent radiologic progression of RA and predict a greater rate of remission than does delayed treatment [4-6]. A meta-analysis of the literature showed that long-term progression of radiographic damage was significantly less frequent in patients treated with early disease-modifying anti-rheumatic drugs (DMARDs) than in patients receiving delayed treatment [6]. In addition, many studies have revealed that early intervention with DMARDs leads to a greater rate of remission than delayed intervention [7,8].

Although functional outcome is as important as disease activity and radiologic progression, only a few studies have investigated the influence of early treatment on functional outcome [8-11]. Moreover, these studies focused on patients with relatively short disease duration, between 1 to 3 years, and the effect of early diagnosis and treatment on functional outcome according to disease duration is not clear.

In this study, the aim was to determine whether early diagnosis and treatment have benefits with respect to functional status with various disease durations in patients with RA.

METHODS

Study population
All RA patients aged 18 or older who satisfied the 1987 American College of Rheumatology criteria for RA [12] and who planned to have their blood drawn for routine evaluation were asked to provide informed consent and more than 95% of patients who were requested consented to participate in Korean Observational Study Network For Arthritis (KORONA) cohort [13]. A total of 5,376 patients agreed to participate in KORONA which is one of the largest nationwide RA cohorts in Korea. Patients were recruited between September 2009 and December 2011.

We defined the date of symptom onset as the date on which the patient first recognized joint pain or swelling, and the date of diagnosis as the date on which the patient was diagnosed with RA and received treatment based on common clinical practice by a physician. We defined early diagnosis as a lag time between symptom onset and an RA diagnosis of 12 months or shorter [4]. Patients who had a longer lag time were classified as the delayed diagnosis group. All patients provided informed consent under a protocol approved by the Institutional Review Board of each site.

Functional disability and associated factors
Functional disability was measured at enrollment with the Health Assessment Questionnaire-Disability Index (HAQ-DI) validated for use in Korean patients [14]. The range of HAQ-DI scores is between 0 and 3, where 0 represents no disability and 3 indicates complete disability. In our study, we defined no functional disability as HAQ-DI = 0, since HAQ-DI in our data was strongly skewed to 0 and clinically no disability was the goal of RA treatment (Fig. 1).

In order to find the factors associated with no functional disability (HAQ-DI = 0), the demographic characteristics and clinical information were collected by detailed interviews and medical records, and disease activity was obtained by rheumatologists or well-trained health professionals at enrollment [15-17]. Since there were many patients with longer disease durations, to re-
duce the recall bias about remote information including date of symptom onset and RA diagnosis, well-trained interviewer circumstantially asked patients about this information, accompanied by chart review in available patients.

Information on bone erosion at diagnosis was collected by rheumatologists or radiologists by determining whether bone erosion was present on hand and wrist radiographs using the radiographic image or description of bone erosion on medical chart of patients when they were diagnosed. Comorbidities were composed of prevalent diseases among RA patients including cardiovascular disease, hypertension, gastrointestinal disease, hepatitis, diabetes mellitus, thyroid disease, pulmonary disease, and malignancy.

**Statistical analysis**
In addition to demographic characteristics, clinical information, and disease activity, we compared the HAQ-DI score and the proportion of patients with no functional disability between early and delayed diagnosis groups, using the chi-square test and Student t test. Multivariable logistic regression analysis was performed to identify the impact of early diagnosis on no functional disability, adjusting for variables such as age, sex, disease duration, education, absence of bone erosion, rheumatoid factor (RF) positivity, hemoglobin, disease activity score employing 28 joint-erythrocyte sedimentation rate (DAS28-ESR) and no comorbidity that were known to be associated with functional disability in previous studies [15-17] or significant in the crude analysis. The significance level was set at \( p < 0.05 \).

Three separate logistic regression models were performed, according to disease duration, to analyze the impact of early diagnosis on functional disability of disease course. The disease durations tested, which defined as the duration between date of diagnosis and enrollment, were less than 5, 5 to 10, and \( \geq 10 \) years. For three separate logistic regression models, \( p \) value adjusted for multiple comparisons (\( p < 0.0167 \) corrected for three analysis) by the Bonferroni method was considered to be statistically significant. Statistical analyses were performed using SAS software version 9.2 (SAS, Cary, NC, USA).

**RESULTS**

**Demographic and clinical features**
A total of 2,597 patients (57.2%) were included in the early diagnosis group and 1,943 patients (42.8%) in the delayed diagnosis group. The demographic and clinical characteristics of the patients are listed in Table 1.

The mean delay before diagnosis was 3.5 ± 3.7 months in the early diagnosis group and 48.7 ± 62.8 months in the delayed diagnosis group. The early diagnosis group was younger (52.8 ± 12.1 years vs. 54.5 ± 12.2 years, \( p < 0.01 \)) and its mean disease duration was longer than that of the delayed diagnosis group (8.3 ± 7.7 years vs. 7.5 ± 7.3 years, \( p < 0.01 \)). The early diagnosis group also had a higher educational level than the delayed diagnosis group (59.5% vs. 53.8% with high school or higher, \( p < 0.01 \)).

In terms of functional disability, the average HAQ-DI score was higher in the delayed diagnosis group (0.64 ± 0.63 vs. 0.70 ± 0.66, \( p < 0.01 \)), the mean difference between two groups was 0.06, standard error 0.02, and 95% confidence interval (CI) was 0.021 and 0.097. The proportion of patients with no functional disability was higher in the early diagnosis group (22.9% vs. 20.0%, \( p = 0.02 \)), especially in those with disease duration less than 5 years (29.7% vs. 23.8%, \( p < 0.01 \)) (Fig. 2).

**Impact of early diagnosis on no functional disability**
Early diagnosis was associated with no functional disability (odds ratio [OR], 1.19; 95% CI, 1.03 to 1.37) in crude analysis. In addition, several of the variables listed in Table 2 were also significantly associated with no functional disability.

After adjusting for variables that were significant in crude analysis, early diagnosis (OR, 1.19; 95% CI, 1.01 to 1.40) remained associated with no functional disability. In addition, male gender (OR, 2.88; 95% CI, 2.29 to 3.63), disease duration less than 5 years (OR, 1.42; 95% CI, 1.16 to 1.75), higher level of education (OR, 1.70; 95% CI, 1.39 to 2.17), absence of bone erosion at diagnosis (OR, 1.42; 95% CI, 1.20 to 1.68), RF positivity (OR, 1.49; 95% CI, 1.13 to 1.98), and lack of comorbidity (OR, 1.30; 95% CI, 1.09 to 1.54) were associated with no functional disability. The age (OR, 0.98; 95% CI, 0.97 to 0.99) and DAS28-ESR (OR, 0.45; 95% CI, 0.42 to 0.49) were negatively associated with no functional disability.
Impact of early diagnosis on no functional disability according to disease duration

We also performed a subgroup analysis to analyze the influence of early diagnosis on no functional disability according to disease duration (Table 3). Early diagnosis was associated with no functional disability in patients with disease duration less than 5 years (OR, 1.37; 95% CI, 1.09 to 1.72) but not in patients with longer disease duration (for 5 to 10 years: OR, 1.07; 95% CI, 0.75 to 1.52; for ≥10 years: OR, 0.92; 95% CI, 0.65 to 1.28).

In addition, no functional disability was affected by several variables along with the disease course. RF positivity (OR, 1.66; 95% CI, 1.16 to 2.38) was associated with no functional disability only where disease duration was less than 5 years. On the other hands, absence of bone erosion at diagnosis (OR, 1.73; 95% CI, 1.23 to 2.43 for ≥10 years) was associated with no functional disability only where disease duration was less than 5 years.
years) was associated with no functional disability where disease duration exceeded 10 years. Male gender (for < 5 years: OR, 2.69; 95% CI, 1.96 to 3.70; for 5 to 10 years: OR, 3.29; 95% CI, 2.03 to 5.32; for ≥ 10 years: OR, 3.00; 95% CI, 1.86 to 4.85) and DAS28-ESR (for < 5 years: OR, 0.46; 95% CI, 0.41 to 0.51; for 5 to 10 years: OR, 0.41; 95% CI, 0.34 to 0.48; for ≥ 10 years: OR, 0.47; 95% CI, 0.40 to 0.55) were consistently associated with no functional disability irrespective of disease duration.

**DISCUSSION**

In this study, the early diagnosis group showed lower HAQ-DI score, and a higher proportion of patients with no functional disability compared with delayed diagnosis group, though the differences were not large. We found that early diagnosis was independently associated with no functional disability after adjusting for various factors. In particular, early diagnosis was associated with no functional disability in patients with disease duration of less than 5 years, whereas no benefit of early diagno-

![Figure 2. Proportion of patients with no functional disability (Health Assessment Questionnaire-Disability Index [HAQ-DI] score = 0) in each group according to disease duration. \( ^a p < 0.05 \), chi-square test.](image)

| Table 2. Associated factors for no functional disability (HAQ-DI = 0) |
|--------------------------|--------------------------|--------------------------|
| **Factor**               | **Crude OR (95% CI)**    | **Multivariable OR (95% CI)** |
| Age, yr                  | 0.97 (0.96–0.97)\(^a\)   | 0.98 (0.97–0.99)\(^a\)    |
| Male sex                 | 3.42 (2.87–4.07)\(^a\)   | 2.88 (2.29–3.63)\(^a\)    |
| Early diagnosis          | 1.19 (1.03–1.37)\(^a\)   | 1.19 (1.01–1.40)\(^a\)    |
| Disease duration, yr     |                          |                          |
| < 5                      | 2.34 (1.06–2.79)\(^a\)   | 1.42 (1.16–1.75)\(^a\)    |
| ≥ 5 and < 10             | 1.80 (1.46–2.22)\(^a\)   | 1.25 (0.99–1.59)          |
| ≥ 10                     | 1                        | 1                        |
| Education                |                          |                          |
| Middle school or less    | 1                        | 1                        |
| High school or more      | 2.50 (2.14–2.93)\(^a\)   | 1.70 (1.39–2.07)\(^a\)    |
| Absence of bone erosion at diagnosis | 1.94 (1.68–2.24)\(^a\) | 1.42 (1.20–1.68)\(^a\)    |
| RF positivity            | 1.07 (0.84–1.36)         | 1.49 (1.13–1.98)\(^a\)    |
| Hemoglobin               | 1.36 (1.28–1.43)\(^a\)   | 0.85 (0.80–1.02)          |
| DAS28-ESR                | 0.43 (0.40–0.46)\(^a\)   | 0.45 (0.42–0.49)\(^a\)    |
| No comorbidity           | 1.62 (1.41–1.87)\(^a\)   | 1.30 (1.09–1.54)\(^a\)    |

Multivariable OR was adjusted for age, sex, disease duration, education, absence of bone erosion, RF positivity, hemoglobin, DAS28-ESR, and no comorbidity.

HAQ-DI, Health Assessment Questionnaire-Disability Index; OR, odds ratio; CI, confidence interval; RF, rheumatoid factor; DAS28-ESR, disease activity score employing 28 joint-erythrocyte sedimentation rate.

\(^a p < 0.05\).
sis was observed in patients with disease duration more than 5 years. However, male gender and lower disease activity were consistently associated with no functional disability. In addition, absence of bone erosion at diagnosis was an independent factor for no functional disability where disease duration was longer than 10 years.

There have been several studies which assessed factors affecting functional outcome in RA patients [15-17]. They reported that several variables including age, gender, education, disease duration, disease activity, radiographic progression, and comorbidity were associated with functional disability; these results were comparable with our study. On the other hand, in our study, positive RF showed results opposite to those of previous study that reported positive RF was a predictor of worse functional disability [15]. Since positive RF is one of the criteria in RA classification [12,18], patients with positive RF tend to be diagnosed earlier and have greater possibility of receiving intensive treatment. Therefore, we assumed that positive RF could be associated with no functional disability when adjusting for variables including early diagnosis. However, further study for RF and functional status is needed to lead a conclusive result.

In our study, the mean difference of HAQ-DI score between early and delayed diagnosis group was 0.06; it is a relatively small difference, and does not exceed the minimally important difference (MID) for HAQ-DI from previous studies [19-23]. Considering that the mean HAQ-DI scores from previous studies were up to twice than ours, the MID of our study would be expected to be smaller than theirs. However, this difference of 0.06 might be clinically insignificant and thus additional study of MID in patients with similar baseline HAQ-DI is required.

Concerning the early diagnosis, a few previous studies have investigated the impact of early diagnosis on functional disability (Table 4) [8-11]. Two reported better outcomes for patients diagnosed early [8,10], whereas others found similar outcomes between the early diagnosis and delayed diagnosis groups [9,11]. The patients examined in those studies were early RA patients who had never received DMARDs, and the numbers of patients investigated ranged from 40 to 608. Two of these studies defined early diagnosis as a delay of less than 3 months from symptoms to diagnosis of RA [8,10]. The others classified patients into an early and a delayed treatment group according to the time between first visit and referral or referral and the start DMARDs [9,11]. The former pair of studies noted that HAQ scores improved more in the early diagnosis group and more patients in the early

### Table 3. Associated factors for no functional disability (HAQ-DI = 0) according to disease duration

| Factor                        | Disease duration, yr, OR (95% CI) |
|-------------------------------|----------------------------------|
|                               | < 5 (n = 2,052)                  | 5 ≤ and < 10 (n = 1,013) | ≥ 10 (n = 1,475) |
| Age                           | 0.98 (0.97–0.99)                 | 0.98 (0.97–1.00)        | 0.98 (0.96–0.99) |
| Male sex                      | 2.69 (1.96–3.70)                 | 3.29 (2.63–5.32)        | 3.06 (1.86–4.85) |
| Early diagnosis               | 1.37 (1.09–1.72)                 | 1.07 (0.75–1.52)        | 0.92 (0.65–1.28) |
| Education                     |                                  |                      |
| Middle school or less         | 1                                | 1                      | 1                      |
| High school or more           | 1.93 (1.45–2.57)                 | 1.44 (1.04–2.21)       | 1.50 (1.02–2.21) |
| Absence of bone erosion at diagnosis | 1.25 (0.99–1.58)             | 1.50 (1.06–2.11)       | 1.73 (1.23–2.43) |
| RF positivity                 | 1.66 (1.16–2.38)                 | 1.68 (0.84–3.39)       | 0.97 (0.54–1.74) |
| Hemoglobin                    | 0.94 (0.85–1.03)                 | 0.97 (0.85–1.11)       | 0.99 (0.86–1.13) |
| DAS28-ESR                     | 0.46 (0.41–0.51)                 | 0.41 (0.34–0.48)       | 0.47 (0.40–0.55) |
| No comorbidity                | 1.23 (0.98–1.56)                 | 1.40 (0.97–2.01)       | 1.36 (0.97–1.92) |

Multivariable OR was adjusted for age, sex, education, absence of bone erosion, RF positivity, hemoglobin, DAS28-ESR, and no comorbidity.

HAQ-DI, Health Assessment Questionnaire-Disability Index; OR, odds ratio; CI, confidence interval; RF, rheumatoid factor; DAS28-ESR, disease activity score employing 28 joint-erythrocyte sedimentation rate.

*p < 0.0167 (Bonferroni adjustment).
## Table 4. Impact of early diagnosis on functional outcome in previous studies

| Study                | Country | Early diagnosis | Definition | Number | Delayed diagnosis | Definition | Number | Follow-up period | Conclusion |
|----------------------|---------|----------------|------------|--------|------------------|------------|--------|-----------------|------------|
| Lard et al. (2001) [9] | Netherlands | Immediate DMARDs treatment | Definition | 97 | Usual treatment | Number | 109 | 2 yr | HAQ showed modest improvement in both groups. |
| Nell et al. (2004) [10] | Austria | Symptom onset to diagnosis < 3 months | Definition | 20 | Symptom onset to diagnosis ≥ 9 months | Number | 20 | 36 mon | Very early RA group had greater improvement at 3 months that was maintained through 3 years. |
| Descalzo et al. (2012) [11] | Spain | Referral within 15 days and immediate treatment | Definition | 447 | Usual treatment without specific protocol | Number | 161 | 2 yr | HAQ score was not statistically difference between groups. |
| Gremese et al. (2013) [8] | Italy | Symptom onset to diagnosis < 3 months | Definition | 105 | Symptom onset to diagnosis ≥ 3 months | Number | 376 | 12 mon | More very early RA patients achieved an HAQ < 0.5 at the 1-year follow-up despite similar HAQ values at baseline. |
| Present study | Korea | Symptom onset to diagnosis ≤ 12 months | Definition | 2,597 | Symptom onset to diagnosis > 12 months | Number | 1,943 | Cross-sectional study | Early diagnosis is associated with no functional disability, especially in patients with shorter disease duration. |

DMARD, disease-modifying antirheumatic drug; HAQ, health assessment questionnaire; RA, rheumatoid arthritis.
data. We think we can draw a conclusive result when we analyze repetitive data using follow-up outcomes in future study using the prospective KORONA cohort. Third, since many of our patients had long disease durations, there may have been recall bias for symptom onset and date of diagnosis. The distinction between early and delayed diagnosis may therefore be more reliable in the case of patients with recent disease onset, but less reliable in the case of patients with disease of longer duration because of recall bias. This could have reduced the differences of functional disability between the early and delayed diagnosis groups among the patients with longer disease duration.

Despite the above limitations, our data show that early diagnosis is associated with no functional disability as well as other variables. A prospective cohort study of patients with relatively short disease durations of less than 5 years would allow the confirmation of the impact of early diagnosis on functional disability in the cases of longer disease durations.

In conclusion, early diagnosis was associated with no functional disability, especially in patients with shorter disease duration. On the other hand, absence of bone erosion at diagnosis was an independent factor for no functional disability where disease duration was longer than 10 years. Male gender and lower disease activity were consistently associated with no functional disability. Additional studies will be required to confirm these findings in the cases of longer disease durations. In addition, the difference of HAQ-DI score between early and delayed diagnosis group in this study was small; therefore, further study using patient population with various HAQ-DI distribution is needed to draw conclusive results.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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