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【 ORIGINAL ARTICLE 】

Scoring Model to Predict a Low Disease Activity in Elderly Rheumatoid Arthritis Patients Initially Treated with Biological Disease-modifying Antirheumatic Drugs

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Abstract:

Objective We aimed to develop a scoring model to predict a low disease activity (LDA) in elderly rheumatoid arthritis (RA) patients initially treated with biological disease-modifying antirheumatic drugs (bDMARDs).

Methods This retrospective cohort study included 82 elderly RA patients who initially received bDMARDs. The outcome was an LDA after bDMARDs initiation. We developed a predictive formula for an LDA using a multivariate analysis, the accuracy of which was assessed by the area under the curve (AUC) of the receiver operating characteristic curves; the scoring model was developed using the formula. For each factor, approximate odds ratios were scored as an integer, divided into three groups based on the distribution of these scores. In addition, the scoring model accuracy was assessed.

Results The mean age was 73.5±6.0 years old, and 86.6% were women. An LDA was achieved in 43 patients (52.4%). The predictive formula for an LDA was prepared using six factors selected for the multivariable analysis: the neutrophil-to-lymphocyte ratio (NLR), anemia, the 28-joint disease activity score with erythrocyte sedimentation rate (DAS28-ESR), serum level of matrix metalloproteinase-3 (MMP-3), diabetes mellitus (DM), and rheumatoid factor (RF). The AUC for the formula was 0.829 (95% confidence interval, 0.729-0.930). The odds ratios of the six factors were scored (DAS28-ESR and serum MMP-3=1 point, NLR, anemia, DM, and RF=2 points) and divided into three groups (≤4, 5-7, and ≥8). The high-score group (≥8) achieved a positive predictive value of 83%.

Conclusion The scoring model accurately predicted an LDA in elderly RA patients initially treated with bDMARDs.

Key words: biological disease-modifying antirheumatic drugs, elderly, rheumatoid arthritis, scoring model

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Introduction

Rheumatoid arthritis (RA) is characterized by persistent inflammatory polyarthritis of unknown etiology. RA causes cartilage degradation and joint destruction, leading to loss of the physical function and difficulties performing activities of daily living. In Japan, the prevalence of RA is 0.5%-1.0% (1).

The prevalence of elderly RA patients is consistently increasing (2, 3). Regarding treatment of elderly RA patients, biological disease-modifying antirheumatic drugs (bDMARDs) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are treatment options when first-line therapy with methotrexate (MTX) is ineffective, similar to non-elderly RA patients. In clinical practice,

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the rate of bDMARD use in elderly RA patients is lower than that in non-elderly RA patients. Data obtained from the Swiss RA registry has revealed that the rate of bDMARD use in elderly RA patients is lower than that in non-elderly RA patients (6.6% vs. 14.1%, respectively) (4). In elderly RA patients, the lower rate of bDMARD therapy may be due to the selection of drugs other than bDMARDs, owing to the risk of infection and cardiovascular disease. Furthermore, the lack of explicit clinical criteria for the initiation of bDMARDs in elderly patients with RA may present an additional influencing factor. Therefore, there may be additional elderly patients with RA who could benefit from bDMARD treatment.

A prospective cohort study reported that the 28-joint disease activity score with C-reactive protein (DAS28-CRP) and anti-citrullinated peptide antibody (ACPA) were significantly associated with sustained clinical remission in elderly patients with RA (5). However, there have been few reports on the predictors of a treatment response to bDMARDs or clinical criteria for the initiation of bDMARDs in elderly RA patients. If clinical criteria could be defined, bDMARDs would be a viable treatment option in elderly patients with RA who have not received bDMARDs despite these agents likely efficacy.

Therefore, we identified the independent predictors for a low disease activity (LDA) and developed a scoring model to predict an LDA in elderly RA patients initially treated with bDMARDs.

Materials and Methods

Setting and study design

This retrospective cohort study enrolled elderly RA patients (≥65 years old) who received initial bDMARD treatment at Showa University Hospital and Showa University Koto Toyosu Hospital from November 2005 to December 2018. All patients met either the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/European League Against Rheumatism classification criteria for RA (6, 7). The eligibility criteria were patients who initially received bDMARDs as second-line treatment after csDMARD treatment was ineffective. The treatment course included infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GLM), certolizumab pegol (CZP), tocilizumab (TCZ), and abatacept (ABT). The exclusion criteria were the discontinuation of bDMARDs owing to adverse events after treatment initiation, loss to follow-up, discontinuation owing to patient request, and disease complicated by rheumatic disease, except for Sjogren's syndrome.

This study was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of the Showa University School of Pharmacy.

Measurements

The following baseline data before initial bDMARD treatment were obtained from medical records and evaluated: patient background data, including age, sex, body mass index, disease duration, smoking history, and complications such as diabetes mellitus (DM) (8) and anemia (9); drug-related data, including MTX use, MTX dosage, other csDMARD use, oral prednisolone (PSL) use, oral PSL dosage, and non-steroidal anti-inflammatory drug use; blood test data, including rheumatoid factor (RF), ACPA, serum matrix metalloproteinase-3 (MMP-3), the neutrophil-to-lymphocyte ratio (NLR), and the estimated glomerular filtration rate.

Based on the World Health Organization (WHO) classification of the elderly population, we considered the elderly population to be ≥65 years old. RF was considered to be positive for values ≥15 IU/mL and high-positive for values over 3 times the upper limit of the normal value (≥45 IU/mL) (7). ACPA was considered to be positive for values ≥4.5 IU/mL and high-positive for values over 3 times the upper limit of the normal value (≥13.5 IU/mL) (7). In addition, we used the WHO definition of anemia (hemoglobin < 12 g/dL in women and <13 g/dL in men) (10). The RA disease activity was assessed using the 28-joint disease activity score with erythrocyte sedimentation rate (DAS28-ESR) (11). At baseline, the participant's physical function was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI) (12).

Outcome

The outcome was an LDA at one year after the initiation of bDMARD therapy. LDA achievement was defined as DAS28-ESR ≤3.2 (11), while LDA non-achievement was defined as DAS28-ESR >3.2, agent discontinuation, or substitution due to ineffectiveness.

Statistical analyses

For the LDA achievement and non-achievement groups, we used Student's *t* test to compare continuous variables and the Chi-square test or Fisher's exact test to compare categorical variables. A multivariate analysis was performed using a logistic regression analysis. Significant variables ($p< 0.05$) extracted through the univariate analysis were entered into the multivariate analysis. In elderly RA patients initially treated with bDMARDs, significant independent variables contributing to an LDA were extracted using stepwise selection methods. All statistical analyses were performed using the SPSS software program, version 25 (IBM, Tokyo, Japan). P values <0.05 were considered significant.

Predictive formula for an LDA

We developed a formula for predicting an LDA using a logistic regression analysis. The analysis was performed by including three factors predictive of a treatment response to bDMARDs - DAS28-ESR (13-15), serum MMP-3 (16, 17), and RF (18, 19) - along with DM, which is highly prevalent

in elderly RA patients and is a predictor of radiographic progression (8, 20). All of these factors were added as covariates to statistically significant factors in the multivariate analysis ($p<0.05$).

Continuous variables were divided into two groups according to the upper limit of the standard value or using receiver operating characteristic (ROC) curves and Youden's index (21). The accuracy of the predictive formula for an LDA was assessed by the area under the curve (AUC) of the ROC curve.

Scoring model to predict an LDA

A scoring model was developed using the predictive formula for an LDA in clinical application. The odds ratios (ORs) for other factors were derived by the smallest ORs among the factors, approximated to the nearest integer (22). For each factor, approximate ORs were scored as an integer. For each patient, the scores were calculated as the sum of the scores of each factor. The patients were divided into three groups based on the distribution of their scores. The accuracy of the scoring model was assessed by the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results

Patient characteristics

Overall, 111 elderly RA patients initially treated with bDMARDs were enrolled in this study. We excluded 29 patients who experienced adverse events (n=19), were lost to follow-up (n=5), discontinued treatment by request (n=4), or presented with disease complicated by rheumatic disease, except for Sjogren's syndrome (n=1). We ultimately evaluated 82 elderly RA patients.

The patient baseline characteristics are shown in Table 1. The mean age was 73.5±6.0 years old, and the mean disease duration was 6.6±9.9 years. In total, 71 (86.6%) were women. The mean DAS28-ESR was 5.3±1.3. RF was negative in 9 (11.5%), positive in 12 (15.4%), and high-positive in 57 (73.1%). ACPA was negative in 8 (15.7%), positive in 2 (3.9%), and high-positive in 41 (80.4%). The frequency of concomitant MTX use was 60 (73.2%), with a mean dosage of 8.2±2.6 mg/week. The frequency of concomitant oral PSL use was 48 (58.5%), with a mean dosage of 4.9±2.6 mg/day. The frequency of bDMARD treatment was as follows: IFX, 16 (19.5%); ETN, 9 (11.0%); ADA, 10 (12.2%); GLM, 10 (12.2%); CZP, 6 (7.3%); TCZ, 12 (14.6%); and ABT, 19 (23.2%).

Outcome

One year after initiating treatment with bDMARDs, an LDA was achieved in 43 (52.4%) patients.

The univariate analysis

In the LDA achievement group, the DAS28-ESR (4.9±1.3 vs. 5.7±1.0, p=0.001), serum MMP-3 level [243.7±259.2 vs. 397.0±304.5 (ng/mL), p=0.017], NLR (3.8±1.7 vs. 6.0±4.2, p=0.006), and anemia proportion (51.2% vs. 79.5%, p=0.008) were significantly lower than those observed in the LDA non-achievement group (Table 1).

The multivariate analysis

Table 2 shows the ORs and 95% confidence interval (CI) for each factor. In the logistic regression analysis, the NLR and anemia were independent significant predictors of an LDA in elderly RA patients initially treated with bDMARDs.

Predictive formula for an LDA

The predictive formula for an LDA was prepared using the six factors selected by the logistic regression analysis: the NLR, anemia, the DAS28-ESR, serum MMP-3, DM, and RF. The probability of achieving an LDA was represented by the following formula:

$$Logit\ (p)=1.172+(-0.521)\times DAS28\text{-}ESR+(-0.923)\times serum\ MMP\text{-}3+(-1.061)\times NLR+(-1.066)\times anemia+(-1.205)\times DM+1.215\times RF$$

The ROC curves showed that the AUCs of the predictive formula using 2 factors (i.e., NLR and anemia) and that using 6 factors were 0.722 (95% CI, 0.604-0.840) and 0.829 (95% CI, 0.729-0.930), respectively (Fig. 1).

Scoring model to predict an LDA

The integer scores assigned from the ORs of the six factors were as follows: 1 point for the DAS28-ESR and serum MMP-3; 2 points for the NLR, anemia, DM, and RF (Table 3).

The sum of the scores of six factors, ranging from 0 to 10, was calculated for all patients (Table 3). A plot of observed and predicted outcome against scores was obtained for 82 patients. Table 4 shows the number and rate of patients in the LDA achievement and non-achievement groups for each score. The patients were divided into three groups: low-score group (≤4 points; n=18), middle-score group (5-7 points; n=32), and high-score group (≥8 points; n=23). After the initiation of bDMARD treatment, the LDA achievement rate was 11% in the low-score group, 53% in the middle-score group, and 83% in the high-score group (Fig. 2).

Table 5 shows the accuracy of the scoring model. The high-score group (≥8) achieved a sensitivity of 50%, specificity of 89%, PPV of 83%, and NPV of 62%.

Discussion

In this study, we revealed that the NLR and anemia were independent predictors of an LDA in elderly RA patients initially treated with bDMARDs. Furthermore, we developed a scoring model to predict an LDA that included the following six factors: the NLR, anemia, the DAS28-ESR, serum MMP-3, DM, and RF. The developed scoring model divided the patients into three groups. The high-score group (≥8)

Table 1. Comparison of Baseline Characteristics between LDA Achievement and LDA Non-achievement (n=82).

Variable	Total	LDA achievement	LDA non-achievement	p value
	n=82	n=43	n=39	
Age, (years), mean±SD	73.5±6.0	73.4±6.2	73.6±5.9	0.857
Women, n (%)	71 (86.6)	37 (86.0)	34 (87.2)	0.880
Disease duration, (years), mean±SD	6.6±9.9	5.5±7.8	7.7±11.7	0.308
BMI, (kg/m^2), mean±SD	21.8±4.0	21.6±3.4	22.0±4.7	0.682
DAS28-ESR, mean±SD	5.3±1.3	4.9±1.3	5.7±1.0	0.001**
HAQ, mean±SD	0.9±0.7	0.8±0.7	0.9±0.7	0.819
RF†, (IU/mL), mean±SD	170.3±282.1	206.1±351.9	132.6±179.4	0.252
RF component, n (%)				0.079
RF negative	9 (11.5)	4 (10.0)	5 (13.1)	
RF low-positive	12 (15.4)	3 (7.5)	9 (23.7)	
RF high-positive	57 (73.1)	33 (82.5)	24 (63.2)	
ACPA‡, (U/mL), mean±SD	391.9±501.2	406.4±549.0	369.3±429.3	0.799
ACPA component, n (%)				0.364
ACPA negative	8 (15.7)	3 (9.6)	5 (25.0)	
ACPA low-positive	2 (3.9)	2 (6.5)	0 (0.0)	
ACPA high-positive	41 (80.4)	26 (83.9)	15 (75.0)	
Serum MMP-3, (ng/mL), mean±SD	316.6±290.2	243.7±259.2	397.0±304.5	0.017*
NLR, mean±SD	4.8±3.3	3.8±1.7	6.0±4.2	0.006**
eGFR, (mL/min/1.73m^2), mean±SD	70.7±25.8	70.0±26.8	71.4±25.2	0.809
Smoking history, n (%)	19 (23.2)	12 (27.9)	7 (17.9)	0.286
DM, n (%)	19 (23.2)	7 (16.3)	12 (30.8)	0.120
Anemia§, n (%)	52 (65.0)	21 (51.2)	31 (79.5)	0.008**
MTX use, n (%)	60 (73.2)	29 (67.4)	31 (79.5)	0.219
MTX dosage, (mg/week), mean±SD	8.2±2.6	8.1±2.5	8.2±2.7	0.934
Other csDMARDs use, n (%)	28 (34.1)	15 (34.9)	13 (33.3)	0.882
Oral PSL use, n (%)	48 (58.5)	25 (58.1)	23 (59.0)	0.939
Oral PSL dosage, (mg/day), mean±SD	4.9±2.6	4.8±2.5	5.1±2.6	0.641
NSAIDs use, n (%)	54 (65.9)	26 (60.5)	28 (71.8)	0.280

*p<0.05, **p<0.01.

†LDA achievement: 40 patients, LDA non-achievement: 38 patients.

‡LDA achievement: 31 patients, LDA non-achievement: 20 patients.

§LDA achievement: 41 patients, LDA non-achievement: 39 patients.

SD: standard deviation, LDA: low disease activity, BMI: body mass index, DAS28-ESR: the 28-joint disease activity score with erythrocyte sedimentation rate, HAQ-DI: health assessment questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibody, serum MMP-3: serum matrix metalloproteinase-3, NLR: neutrophil-to-lymphocyte ratio, eGFR: estimated glomerular filtration rate, DM: diabetes mellitus, MTX: methotrexate, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, PSL: prednisolone, NSAIDs: non-steroidal anti-inflammatory agent

Table 2. Multivariate Analysis of Predictive Factors for LDA in Elderly RA Patients Initially Treated with bDMARDs (n=82).

Variable	β	Odds ratios	95% CI	p value
NLR	-0.316	0.729	0.566-0.939	0.014
Anemia	-1.133	0.322	0.108-0.962	0.042

Logistic regression model with backward selection, including DAS28-ESR, serum MMP-3, NLR, and anemia.

RA: rheumatoid arthritis, LDA: low disease activity, bDMARDs: biological disease-modifying antirheumatic drugs, NLR: neutrophil-to-lymphocyte ratio

achieved a PPV of 83%. We showed that the developed scoring model accurately predicted an LDA in elderly RA patients initially treated with bDMARDs. This model is suggested to reflect clinical criteria for the initiation of bDMARDs in elderly RA patients who would be able to benefit from bDMARDs. There have been few reports on predictors of a treatment response to bDMARDs or clinical criteria for the initiation of bDMARDs in elderly RA patients. Therefore, the developed scoring model has high clinical application value.

Data obtained from the Swiss RA registry show that the rate of bDMARD use in elderly RA patients is about half of that in non-elderly RA patients (4). This relatively low rate of bDMARD therapy in elderly RA patients may be attrib-

uted to the selection of drugs other than bDMARDs, owing to the risk of infection and multiple comorbidities. Furthermore, the disease activity in elderly RA patients is higher than that in non-elderly RA patients (23), which this leads to further deterioration of the physical and cognitive function and depression (24, 25) and makes treatment more difficult. Therefore, it is important to predict the treatment response after the initiation of bDMARD therapy in elderly patients with RA. The developed scoring model can reliably predict an LDA in these patients, and using this model, it may be possible to actively initiate bDMARDs in elderly RA patients. As a result, more elderly RA patients would be able to achieve good control of their disease activity.

To our knowledge, this is the first study to show that the NLR and anemia are independent predictors of an LDA in elderly RA patients initially treated with bDMARDs. The NLR is reportedly a useful predictor of the efficacy of anti-tumor necrosis factor (TNF)-α agents in patients with RA 45.3±11.1 years old (26). However, no study has focused on useful predictors in elderly patients with RA. This is the first study to show that the NLR is a useful LDA predictor in elderly patients with RA.

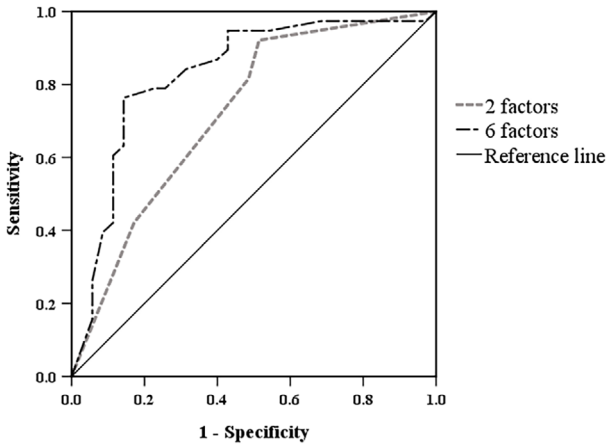


Figure 1. Receiver operating characteristic curves. Two factors (NLR and anemia) and six factors (DAS28-ESR, serum MMP-3, NLR, anemia, DM, and RF) were compared. The areas under the curve of the receiver operating characteristic curves for 2 and 6 factors were 0.722 and 0.829, respectively. NLR: neutrophil-to-lymphocyte ratio, DAS28-ESR: 28-joint disease activity score with erythrocyte sedimentation rate, serum MMP-3: serum matrix metalloproteinase-3, DM: diabetes mellitus, RF: rheumatoid factor

In the pathophysiology of RA, neutrophils are the first immune cells to reach the synovium (27), causing joint damage via the production of reactive oxygen species and protease (28, 29). Neutrophils play a role in the persistence of inflammation and the progression of joint damage. Notably, the lymphocyte count in patients with RA tends to be lower than that in healthy subjects (30, 31). In addition, a previous study reported that the NLR is positively correlated with the disease activity in RA patients (30). Therefore, our findings suggest that a high NLR reflecting localized joint inflammation can cause a high disease activity, affecting LDA achievement.

Anemia in RA is prototypical of anemia of chronic disease (ACD) (9). The pathogenesis of ACD is related to inflammatory cytokines, such as interleukin-6 and TNF-α. These inflammatory cytokines reduce serum erythropoietin levels and serum iron levels induced by hepcidin production (32-34). Therefore, anemia with RA is considered to reflect chronic inflammation, related to inflammatory cytokines. A previous study reported that patients with high baseline TNF levels demonstrate a lower clinical response to IFX (35). Therefore, anemia with RA was considered to reduce the therapeutic effect of bDMARDs through chronic inflammation involving inflammatory cytokines, thus affecting the LDA achievement.

The ROC curves showed that the AUC of the predictive formula for an LDA including six factors (the NLR, anemia, the DAS28-ESR, serum MMP-3, DM, and RF) was higher than that of the formula including statistically significant factors (the NLR and anemia) in the multivariate analysis

Table 3. Logistic Regression Analyses of the Predictive Formula for LDA and Score.

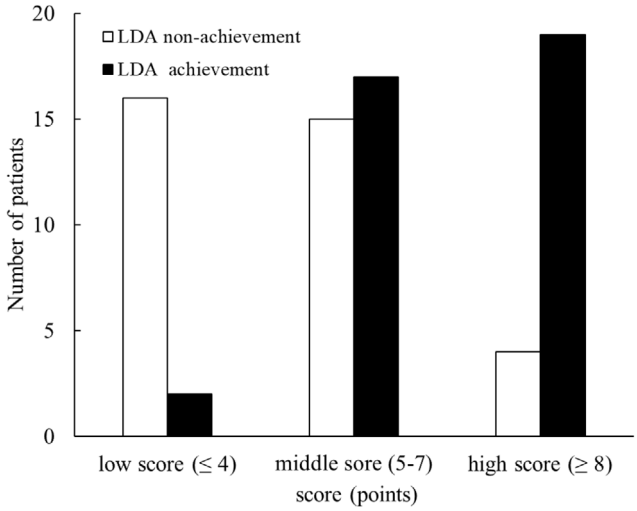
Variable	Category	β	Odds ratios	95% CI	p value	Score†
DAS28-ESR	<5.2 vs. ≥5.2	-0.521	0.594	0.182-1.943	0.389	1
Serum MMP-3 (ng/mL)	<300 vs. ≥300	-0.923	0.397	0.114-1.390	0.149	1
NLR	<5.5 vs. ≥5.5	-1.061	0.346	0.096-1.253	0.106	2
Anemia	(-) vs. (+)	-1.066	0.344	0.097-1.221	0.099	2
DM	(-) vs. (+)	-1.205	0.300	0.071-1.206	0.102	2
RF (IU/mL)	<45 vs. ≥45	1.215	3.370	0.917-12.377	0.067	2
Constant		1.172	3.229		0.123	

Logit (p)=1.172+ (-0.521) ×DAS28-ESR+ (-0.923) ×Serum MMP-3+ (-1.061) ×NLR+ (-1.066) ×Anemia+ (-1.205) ×DM+1.215×RF

Logistic regression model with backward selection, including DAS28-ESR, serum MMP-3, NLR, anemia, DM, and RF.

†The total scores are 0-10 points.

LDA: low disease activity, DAS28-ESR: 28-joint disease activity score with erythrocyte sedimentation rate, Serum MMP-3: serum matrix metalloproteinase-3, NLR: neutrophil-to-lymphocyte ratio, DM: diabetes mellitus, RF: rheumatoid factor



LDA non-achievement (%)	89	47	17
LDA achievement (%)	11	53	83

Figure 2. **Rate of LDA achievement divided into three groups based on the score. LDA: low disease activity**

Table 4. **Rate of LDA Achievement at One Year after the Initiation of bDMARD Therapy for Each Score between LDA Achievement or LDA Non-achievement.** †

Score	LDA achievement (n=38)	LDA non-achievement (n=35)
0	0 (0)	0 (0)
1	1 (50)	1 (50)
2	0 (0)	7 (100)
3	0 (0)	1 (100)
4	1 (12)	7 (88)
5	4 (33)	8 (67)
6	5 (45)	6 (55)
7	8 (89)	1 (11)
8	9 (82)	2 (18)
9	4 (100)	0 (0)
10	6 (75)	2 (25)

†Values are the number (%) of patients with a given score (n=73, 9 missing data).

LDA: low disease activity, bDMARDs: biological disease-modifying antirheumatic drugs

(AUC: 0.829 vs. 0.722, respectively). This suggested that the predictive formula using six factors can more accurately predict an LDA. The scoring model was developed using the predictive formula for an LDA and divided into three groups for clinical application. The high-score group (≥8) achieved a PPV of 83% and specificity of 89%. These results suggest that the high-score group (≥8) of the developed scoring model can accurately predict elderly RA patients who can achieve an LDA.

Several limitations associated with the present study warrant mention. First, the present study lacked specific data on ACPA. The logistic regression analysis could not include ACPA, which has been reported to be associated with sustained clinical remission in elderly RA patients. If a logistic regression analysis including ACPA could be performed, a scoring model with greater accuracy might have been developed. Second, we defined the outcome as an LDA at one year after the initiation of bDMARD therapy. This study aimed to develop a scoring model as a clinical criterion for the initiation of bDMARDs in elderly RA patients who might benefit from bDMARDs in the long term. Further research is needed to validate the short-term benefits of bDMARDs at one, three, and six months, which are the time points recommended in the "Treat to Target" strategy (36). Third, the developed scoring model has not been externally validated. Further research is needed to confirm the external validity of the developed scoring model. Fourth, the six factors that were included as components of the developed scoring model (i.e., NLR, anemia, DAS28-ESR, serum MMP-3, DM, and RF) may be applied to non-elderly RA patients treated with initial bDMARDs. However, this study aimed to develop a scoring model that could reliably predict an LDA in elderly RA patients initially treated with bDMARDs. Therefore, whether or not it can reliably predict an LDA in non-elderly RA patients is unclear; the model needs to be studied further to validate its applicability to non-elderly RA patients initially treated with bDMARDs.

In conclusion, our results suggest that the developed scoring model accurately predicted an LDA in elderly RA patients initially treated with bDMARDs. The developed scoring model will be useful for determining the appropriate bDMARD treatment in elderly patients with RA who can benefit from these agents. Elderly RA patients in the high-score group (≥8) can start taking bDMARDs, leading to a good control of disease activity. Further research is needed to validate the short-term benefits of developed scoring model.

Table 5. The Accuracy of the Scoring Model to Predict LDA in Elderly RA Patients Initially Treated with bDMARDs.

Score	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥0	100	0	52	0
≥5	95	46	65	89
≥8	50	89	83	62

RA: rheumatoid arthritis, LDA: low disease activity, bDMARDs: biological disease-modifying antirheumatic drugs

The authors state that they have no Conflict of Interest (COI).

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