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Prevalence and predictive factors of difficult-to-treat rheumatoid arthritis: the KURAMA cohort

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ABSTRACT

Difficult-to-treat rheumatoid arthritis (D2T RA) is a multifactorial condition in which disease activity of RA persists despite consecutive treatment with biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). To evaluate the prevalence and predictive risk factors of D2T RA in our institution, a single-center, retrospective study was conducted. Medical records of RA patients, who visited our hospital from 2011 to 2020 and had a follow-up of more than 6 months, were retrospectively reviewed. D2T RA was defined as RA with a disease activity score of 28 – erythrocyte sedimentation rate (DAS28-ESR) of 3.2 or higher at the last visit, despite the use of at least two b/tsDMARDs. A logistic regression model was used to identify risk factors. A total of 672 patients were enrolled. The mean age at disease onset was 52.1 years and females were dominant (76.3%). After a mean follow-up of 46.6 months, patients with D2T RA accounted for 7.9% of overall patients. Multivariate analysis identified high rheumatoid factor (RF) levels (≥156.4 IU/mL, odds ratio [OR]: 1.95), DAS28-ESR (OR: 1.24), and coexisting pulmonary disease (OR: 2.03) as predictive risk factors of D2T RA. In conclusion, high RF levels, high DAS28-ESR, and coexisting pulmonary disease at baseline can predict the development of D2T RA.

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Difficult-to-treat rheumatoid arthritis; disease activity; pulmonary involvement; rheumatoid arthritis; rheumatoid factor

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint damage, leading to lifelong disability if not adequately treated [1]. Over the past several decades, the landscape of RA treatment has dramatically changed [2]. A treat-to-target principle has emerged with defined therapeutic targets. If the treatment goals were not achieved within a reasonable period of time, the treatment regimens are intensified [3]. The widespread use of methotrexate (MTX) as well as the introduction of biological disease-modifying antirheumatic drugs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) have also greatly contributed to the recent advances in RA treatment [4]. Therefore, clinical remission has become a feasible therapeutic goal in many patients with RA.

On the other hand, there are still plenty of cases in which disease activity is difficult to control despite the combinatorial use of DMARDs. This is particularly evident in patients with difficult-to-treat RA (D2T RA) who experience uncontrolled disease activity, even with the use of two or more biological or targeted synthetic DMARDs (b/tsDMARDs) [5,6]. A universal definition of D2T RA has not yet been fully established, and the prevalence of D2T RA varies from study to study, ranging from 5% to 20% [5–7]. However, D2T RA has been increasingly recognized as a multifactorial condition.

Risk factors for D2T RA development can be divided into two categories: (i) factors that cause drug ineffectiveness and adverse drug reactions, such as smoking, obesity, and genetic and immunological background of patients; (ii) comorbidities and negative disease outcomes such as interstitial pneumonia and secondary fibromyalgia [6]. In addition, there are a variety of unknown factors that interactively predispose patients to develop D2T RA and influence their clinical condition. Since Japanese patients cannot tolerate high-dose MTX because of hepatotoxicity compared with patients in Western countries [8], it is necessary to clarify the prevalence and risk factors of D2T RA, particularly in Japanese patients with RA.

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In the present study, we first examined the prevalence of D2T RA in the KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) cohort. Then, we sought to identify the specific risk factors that contribute to the development of D2T RA among the clinical characteristics, lifestyle habits, and comorbidities at the time of baseline evaluation.

2. Materials and methods

2.1. Study design and patient selection

All patients who fulfill the 1987 or 2010 classification criteria for RA [9,10] in Kyoto University are registered in the KURAMA cohort study, as described previously [11,12]. The clinical and functional data are recorded at baseline and at every visit in the study. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. R0357), and written informed consent to participate in the study was obtained from all patients. The present study was conducted as a single-center, retrospective study using the KURAMA cohort database. The medical records of patients, who visited our hospital from May 2011 to May 2020 and had a follow-up of more than 6 months with valid baseline information, were retrospectively reviewed beginning with the initial visits throughout the last visits. Baseline information on the clinical characteristics, lifestyle habits, and comorbidities was obtained. During patients' follow-up, treatment changes were monitored in addition to the aforementioned clinical and functional data.

2.2. Baseline characteristics

The patients' data obtained at baseline included age, sex, height, weight, smoking history, family history of RA, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) level, swollen joint count (SJC), tender joint count (TJC), physician's global assessment of RA activity (PhGA), patient's global assessment of RA activity (PtGA), and the titers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPAs). Based on these data, DAS28-ESR, DAS28-CRP, clinical disease activity index (CDAI), and simplified disease activity index (SDAI) were calculated. The Health Assessment Questionnaire (HAQ) and modified HAQ disability index were also obtained as functional data. RF and ACPA were considered positive if the titers were more than 15 IU/mL for RF and more than 4.5 U/mL for ACPA.

2.3. Comorbidities

The data regarding comorbidities that were collected at baseline included past or current medical history of the following disorders: (1) lifestyle-related disease (hypertension, hyperlipidemia, diabetes mellitus, and any other disease such as hyperuricemia); (2) lung disease (interstitial pneumonia (IP), pulmonary tuberculosis (Tb), nontuberculous mycobacteria (NTM), chronic obstructive pulmonary disease (COPD), bronchial asthma (BA), and any other pulmonary disease such as bronchiolitis and bronchitis); (3) liver disease (current hepatitis B virus carriers, hepatitis C virus carriers, liver cirrhosis, and any other liver disease); (4) kidney disease (end stage renal disease, kidney dysfunction, and any other kidney disease); (5) heart disease (ischemic heart disease, cardiac failure, arrhythmia, and any other heart disease); (6) hematological disease; (7) gastrointestinal disease (gastroduodenal ulcer, reflux esophagitis, and any other gastrointestinal disease); (8) neurological disease (cerebrovascular disease (CVD), and any other neurological disease); (9) other autoimmune diseases (Sjogren's syndrome, polymyositis/dermatomyositis, systemic sclerosis, and any other autoimmune disease); and (10) current and past medical history of malignancies.

2.4. Treatment

Treatment regimens used in the study were based on the current recommendations [4]. Briefly, once RA was diagnosed, treatment with MTX was initiated unless contraindications were identified. If the patient had any contraindications to MTX, the treatment was initiated with other conventional synthetic DMARDs (csDMARDs). If the patient had an inadequate response to csDMARDs, either one of b/tsDMARDs was added to or switched from csDMARDs. However, the economic statuses of the patients were taken into consideration, because the study was conducted in the real-world clinical setting.

2.5. Definition of D2T RA

After a minimum follow-up of 6 months, D2T RA was diagnosed based on DAS28-ESR of 3.2 or higher at the last visit, despite the use of at least 2b/tsDMARDs, including an original biological agent or a biosimilar.

2.6. Statistical analyses

All statistical analyses were performed with JMP Pro 15 (SAS Institute Inc., Cary, NC, USA) or

GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA). Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables were used. A multivariate logistic regression model was used to evaluate the factors associated with D2T RA. Receiver operating characteristics (ROC) analysis was used to determine the cut-off value. The Cochran–Armitage trend test was used to assess the trend. *p*-Values of less than .05 were considered statistically significant.

3. Results

3.1. Patients enrolled in the study

Of the 1277 RA patients who were registered in the KURAMA cohort, 334 patients were excluded because of having less than 6 months of follow-up. Patients without baseline data regarding RF and/or ACPA titers ($n = 11$), age at onset ($n = 3$), height and/or weight ($n = 6$), and comorbidities ($n = 251$) were also excluded. A total of 672 patients were enrolled in the study (Figure 1). Of the 672 patients, 233 were treatment-naïve, while 439 already received some DMARDs at baseline.

3.2. Clinical characteristics of the patients at baseline

Baseline characteristics of the 672 patients are summarized in Table 1. The mean age at disease onset was 52.1 years. About three-quarters of the patients were female, the mean body mass index (BMI) was 22.1, and 40% of the patients had a history of smoking. One-fourth of patients had a family history of RA. Positive RF and ACPA were detected in approximately 80% of patients. Median CDAI, SDAI, DAS28-ESR, and DAS28-CRP were 12.8, 13.8, 4.19, and 3.44, respectively, while median HAQ and mHAQ were 0.63 and 0.29, respectively. Other markers for disease activity are summarized in Table 1.

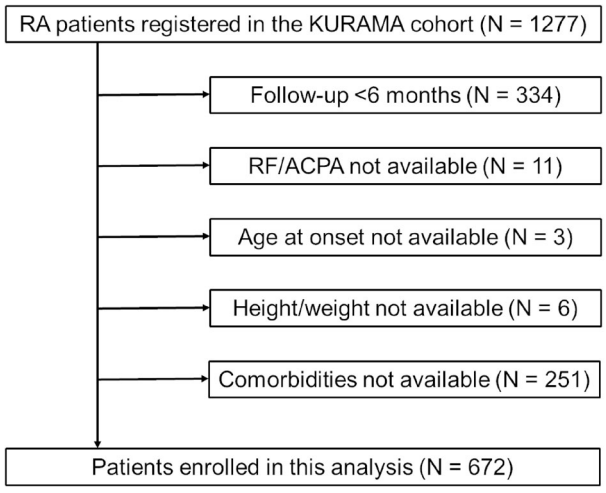

Figure 1. Patients enrolled in the study. Of 1277 rheumatoid arthritis (RA) patients who met the 1987 or 2010 classification criteria in the KURAMA cohort, patients with follow-up less than 6 months ($n = 334$), patients with rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (ACPA) not available ($n = 11$), patients with age of onset unknown ($n = 3$), patients with height and/or weight unmeasured ($n = 6$), and patients with comorbidities not available ($n = 251$) were excluded. A total of 672 RA patients were enrolled in this study.

3.3. Substantial numbers of patients fail to achieve adequate control of disease activities even after 6 months of treatment

In patients with the indicated baseline characteristics, disease activities gradually declined after 3 months ($n = 448$) and 6 months ($n = 460$) compared to baseline values (Figure 2(A)). Approximately 40% of patients achieved a state of remission and more than 60% of patients had a low disease activity (LDA) or remission based on DAS28-ESR values. However, in the last observation, after an average of 46.6 months, disease activity among all patients ($n = 672$) were comparable to disease activity at 6 months, and approximately 40% of patients had moderate or high disease activities (MDA or HDA) based on DAS28-ESR values (Figure 2(A)). By stratifying patients with MDA or HDA based on the use of b/tsDMARDs, we found that 53 patients (7.9% of overall patients) had MDA or HDA with a history of 2 or more b/tsDMARDs use, which meets the defined criteria of D2T RA (Figure 2(B)). Of note, all these patients experienced two consecutive episodes of MDA or HDA at the last and second-last visits. Additionally, when we applied CDAI to determine the prevalence of D2T RA instead of DAS28-ESR, 8.2% of patients had CDAI of 10 or higher at the last visit, despite the use of at least 2b/tsDMARDs (Figure 2(C)).

3.4. Clinical characteristics of patients with D2T RA compared with patients with non-D2T RA

Baseline clinical characteristics of patients with D2T RA ($n = 53$) were compared with those with non-D2T RA ($n = 619$). There were no significant differences in the age of disease onset, sex, BMI, smoking history, family history of RA, or the titers of ACPA between the two groups. However, the titers of RF were significantly higher in patients with D2T RA than those with non-D2T RA (Table 1). TJCs and all clinical composite measures of disease activity including CDAI, SDAI, DAS28-ESR, and DAS28-CRP were significantly higher in the D2T RA group than in the non-D2T RA group. Higher HAQ and mHAQ in patients with D2T RA indicated that they

Table 1. A comparison of the clinical characteristics of patients with difficult-to-treat RA (D2T RA) and non-D2T RA at baseline.

	All $n = 672$	D2T RA $n = 53$	Non-D2T RA $n = 619$	p-Value
Age at onset, years, mean (SD)	52.1 (15.4)	51.7 (16.1)	52.1 (15.4)	.78
Sex, female, *n* (%)	513 (76.3)	41 (77.3)	472 (76.3)	.86
Disease duration, month, median (IQR)	60 (24–142.3)	60 (25.5–168)	60 (12–124)	.22
Body mass index, mean (SD)	22.1 (3.6)	22.2 (3.7)	22.0 (3.6)	.87
Smoker (current), *n* (%)	81 (12.1)	4 (7.5)	77 (12.4)	.38
Smoker (ever), *n* (%)	190 (28.3)	18 (34.0)	172 (27.8)	.34
Family history of RA, *n* (%)	185 (27.5)	18 (34.0)	167 (27.0)	.09
RF-positive, *n* (%)	513 (76.3)	46 (86.8)	467 (75.4)	.07
RF, median (IQR), IU/mL	40.7 (15.7–114.7)	80.4 (28.4–244.2)	38.7 (15.3–107.2)	**.002**
ACPA-positive, *n* (%)	526 (78.3)	44 (83.0)	482 (77.9)	.49
ACPA, median (IQR), U/mL	73.3 (7.5–329.0)	100.0 (16.9–454.0)	71.7 (6.9–321.0)	.14
ESR, median (IQR), mm/h	29.0 (14.0–54.0)	26.0 (19.5–59.5)	29.0 (14.0–54.0)	.26
CRP, median (IQR), mg/L	4.0 (1.0–17)	7.0 (1.0–19)	3.5 (1.0–17)	.35
Tender joints (0–28), median (IQR)	2 (0–5)	3 (1–6)	2 (0–5)	**.047**
Swollen joints (0–28), median (IQR)	2 (0–5)	4 (0–6.5)	2 (0–5)	.1
PtGA (0–100), median (IQR), mm	48.0 (21.0–66.0)	55.0 (37.0–73.0)	47.0 (20.0–65.0)	**.003**
PhGA (0–100), median (IQR), mm	28.0 (13.0–52.0)	35.0 (20.0–57.5)	28.0 (12.0–52.0)	**.08**
CDAI, median (IQR)	12.8 (6.4–21.2)	16.2 (10.9–26.1)	12.3 (6.1–20.7)	**.003**
SDAI, median (IQR)	13.8 (6.8–23.9)	18.6 (11.8–28.2)	13.6 (6.4–23.0)	**.006**
DAS28-ESR, median (IQR)	4.19 (3.07–5.21)	4.84 (3.98–5.57)	4.13 (3.00–5.13)	**.007**
DAS28-CRP, median (IQR)	3.44 (2.35–4.55)	3.96 (3.30–4.77)	3.37 (2.31–4.51)	**.009**
HAQ, median (IQR)	0.63 (0.25–1.25)	1.25 (0.63–1.88)	0.63 (0.25–1.25)	**.0002**
mHAQ, median (IQR)	0.29 (0.00–0.75)	0.75 (0.13–1.19)	0.25 (0.00–0.75)	**.0002**
Follow-up, mean (SD), months	46.6 (25.0)	53.6 (23.3)	46.0 (25.0)	**.03**
Methotrexate, *n* (%)	358 (53.3)	30 (56.6)	328 (53.0)	.67
Prednisolone, *n* (%)	178 (26.4)	19 (35.8)	159 (25.7)	.14
b/tsDMARDs, *n* (%)	227 (33.8)	21 (39.6)	206 (33.3)	.37

p-Values were calculated to compare the clinical characteristics of patients with D2T RA with those with non-D2T RA. Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables.
ACPA: anti-cyclic citrullinated peptide antibodies; b/tsDMARDs: biological or targeted synthetic DMARDs; CDAI: clinical disease activity index; CRP: C-reactive protein; DAS28: Disease Activity Score 28-joint count; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; IQR: interquartile range; mHAQ: modified health assessment questionnaire; RF: rheumatoid factor; PhGA: physician's global assessment; PtGA: patient's global assessment; SDAI: simplified disease activity index.

were functionally more impaired than those without D2T RA (Table 1). Contrary to our expectation, D2T RA patients had a significantly longer follow-up duration than non-D2T RA patients (53.6 and 46.0 months, $p = .03$). Regarding treatment profiles at baseline, there were no significant differences between the groups; however, of 233 treatment-naïve patients, 13 patients developed D2T RA, whereas 40 out of 439 treated patients developed D2T RA ($p = .13$), suggesting that treatment-naïve patients tended to develop D2T RA less likely. These results indicate that patients with D2T RA had higher disease activities as well as higher RF levels compared with those without D2T RA at baseline and that even though they were followed up for a longer duration, their RA disease activities were not successfully controlled.

3.5. A comparison of comorbidities in patients with D2T RA and non-D2T RA

The comorbidities associated with D2T RA compared with non-D2T RA were investigated. As shown in Table 2, both groups had comparable comorbidities. Regarding lung disease, there was no significant difference in the incidence of pulmonary diseases such as IP, Tb, NTM, COPD, and BA; however, there were more cases of 'any lung disease' in the D2T RA group ($p = .011$), where it meant a history or current medical diagnosis of at least one pulmonary disease. Similarly, 'any neurological disease' was more frequent in the D2T RA group ($p = .034$, Table 2) than non-D2T RA group. There was a trend for more cases of kidney diseases in the D2T RA group compared with non-D2T RA, but it did not reach the level of statistical significance ($p = .087$).

3.6. A comparison of treatment profiles in patients with D2T RA and non-D2T RA at the last visit

Then, treatment profiles at the last visit between the groups were compared (Table 3). Of the 53 D2T RA patients, 41 patients received an average of 6.2 mg/week of MTX, while 500 of 619 non-D2T RA patients received an average of 5.7 mg/week of MTX at the last visit. Regarding the use of glucocorticoids, 39 of the 53 D2T RA patients received an average of 4.0 mg/day of prednisolone (PSL), while 202 of 619 non-D2T RA patients received an average of 4.2 mg/day of PSL at the last observation, suggesting that more patients in the D2T RA group were receiving glucocorticoid therapy than in the non-D2T RA group ($p < .0001$). Median time from baseline to initiation of first b/tsDMARDs was similar between the groups (6 months and 7 months, respectively, $p = 0.92$); however, more patients in the D2T RA

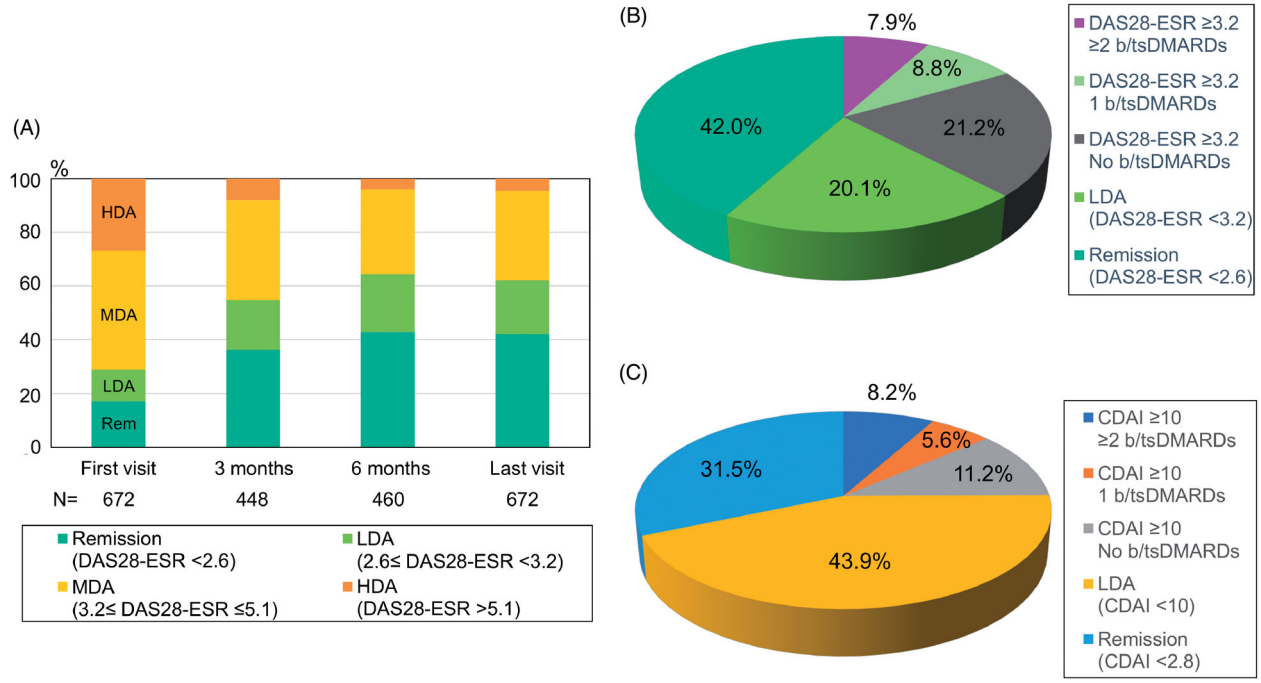

Figure 2. Substantial numbers of patients fail to achieve adequate control of RA disease activity even after 6 months of treatment. (A) Over time changes of disease activity in 672 RA patients. Disease activities at the first visit ($n = 672$), at 3 months ($n = 448$), at 6 months ($n = 460$), and at the last visit ($n = 672$) were shown. Remission, low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA) were defined by DAS28-ESR as shown in the figure. (B) At the last visit ($n = 672$), 62.1% of patients were well-controlled and in remission (42.0%) or LDA (20.1%). Among patients with moderate or high disease activities, 7.9% of patients had used 2 or more b/tsDMARDs, 8.8% of patients had used 1 b/tsDMARDs, and 21.2% of patients never used b/tsDMARDs. (C) At the last visit ($n = 672$), if disease activities were evaluated with CDAI, 31.5% of patients were in remission (CDAI $<$ 2.8) and 43.9% were in LDA (CDAI $<$ 10). Among patients with moderate or high disease activities (CDAI $\geq$ 10), 8.2% of patients had used 2 or more b/tsDMARDs, 5.6% of patients had used 1 b/tsDMARDs, and 11.2% of patients never used b/tsDMARDs. b/tsDMARDs, biological or targeted synthetic disease modifying antirheumatic drugs; CDAI: clinical disease activity index; DAS28: Disease Activity Score 28-joint count; ESR: erythrocyte sedimentation rate.

group were administered b/tsDMARDs than in the non-D2T RA group, such as golimumab ($p = .017$), tocilizumab ($p = .0001$), abatacept ($p = .025$), tofacitinib ($p = .008$), and baricitinib ($p = .0015$) at the last visits. These results indicate that D2T RA patients exhibited higher disease activities than non-D2T RA patients despite the heavier use of b/tsDMARDs.

3.7. Multivariate analysis of factors associated with D2T RA

We performed univariate and multivariate analyses for identifying factors associated with D2T RA (Table 4). Variables were selected based on the clinical significance and the comparison of patients with D2T RA with those with non-D2T RA (Tables 1 and 2). With respect to RF, we did not find a significant difference in positive RF rate, but we did find a significant difference in the RF titer. Therefore, the optimal cut-off value of RF was determined by the ROC analysis to be 156.4 IU/mL (area under curve = 0.63, $p = .003$). Univariate analysis demonstrated that high RF ($\geq$156.4 IU/mL, odds ratio (OR) 2.00, 95%CI, 1.05–3.67, $p = .04$), DAS28-ESR (OR 1.26, 95%CI 1.05–1.52, $p = .02$), DAS28-CRP (OR 1.23, 95%CI 1.02–1.48, $p = .03$), HAQ (OR 1.83, 95%CI 1.32–2.53, $p = .0002$), mHAQ (OR 1.95, 95%CI 1.39–2.90, $p = .001$), any lung disease (OR 2.25, 95%CI 1.21–4.07, $p = .01$), and any neurological disease (OR 3.29, 95%CI 1.05–8.60, $p = .02$) as factors associated with D2T RA. Then, multivariate analysis showed that high RF ($\geq$156.4 IU/mL, OR 1.95, 95%CI, 1.01–3.64, $p = .04$), DAS28-ESR (OR 1.24, 95%CI 1.02–1.50, $p = .03$), and any lung disease (OR 2.03, 95%CI 1.08–3.72, $p = .03$) were identified as independent factors related to the progression to D2T RA. DAS28-CRP, CDAI, SDAI, HAQ, and mHAQ were excluded from the multivariate analysis because they were highly correlated with DAS28-ESR.

3.8. High RF levels, initial DAS28-ESR, and coexisting pulmonary disease as critical determinants of D2T RA

Based on the multivariate analysis, a total score of 3 was retrospectively given to patients at baseline for each score of high RF level ($\geq$156.4 IU/mL), MDA, or HDA on initial DAS28-ESR, and coexisting lung disease. Patients were divided into 4 groups on the basis of the score (hereafter referred to as the D2T

Table 2. Baseline comorbidities and past medical histories in patients with difficult-to-treat RA (D2T RA) compared with non-D2T RA.

	Overall $n=672$	D2T RA $n=53$	Non-D2T RA $n=619$	*p*-Value
Lifestyle-related				
HTN, *n* (%)	130 (19.3)	12 (22.6)	118 (19.1)	.59
DM, *n* (%)	57 (8.5)	6 (11.3)	51 (8.2)	.44
HL, *n* (%)	84 (12.5)	6 (11.3)	78 (12.6)	1
Any, *n* (%)	217 (32.3)	18 (34.0)	199 (32.1)	.76
Lung				
IP, *n* (%)	47 (7.0)	7 (13.2)	40 (6.5)	.085
Past Tb, *n* (%)	25 (3.7)	4 (7.5)	21 (3.0)	.13
NTM, *n* (%)	10 (1.5)	1 (1.9)	9 (1.5)	.56
COPD, *n* (%)	12 (1.8)	2 (3.8)	10 (1.6)	.24
BA, *n* (%)	27 (4.0)	4 (7.5)	23 (3.7)	.16
Any, *n* (%)	133 (19.8)	18 (34.0)	115 (18.6)	**.011**
Liver				
HBV, *n* (%)	10 (1.5)	1 (1.9)	9 (1.5)	.56
HCV, *n* (%)	8 (1.2)	1 (1.9)	7 (1.1)	.48
Liver cirrhosis, *n* (%)	4 (0.6)	0 (0)	4 (0.6)	1
Any, *n* (%)	44 (6.5)	4 (7.5)	40 (6.5)	.77
Kidney				
ESRD, *n* (%)	11 (1.6)	0 (0)	11 (1.8)	1
Any, *n* (%)	22 (3.3)	4 (7.5)	18 (2.9)	.087
Heart				
IHD, *n* (%)	25 (3.7)	2 (3.8)	23 (3.7)	1
Cardiac failure, *n* (%)	7 (1.0)	0 (0)	7 (1.1)	1
Arrythmia, *n* (%)	35 (5.2)	3 (5.7)	32 (5.2)	.75
Any, *n* (%)	75 (11.2)	7 (13.2)	68 (11.0)	.65
Hematological				
Any, *n* (%)	11 (1.6)	0 (0)	11 (1.8)	1
GI tract				
GD ulcer, *n* (%)	48 (7.1)	5 (9.4)	43 (6.9)	.42
RE, *n* (%)	17 (2.5)	2 (3.8)	15 (2.4)	.64
Any, *n* (%)	97 (14.4)	11 (20.8)	86 (13.9)	.22
Neurological				
CVD, *n* (%)	8 (1.2)	2 (3.8)	6 (1.0)	.13
Any, *n* (%)	24 (3.6)	5 (9.4)	19 (3.1)	**.034**
Other AID				
SjS, *n* (%)	19 (2.8)	2 (3.8)	17 (2.7)	.66
PM/DM, *n* (%)	4 (0.6)	1 (1.9)	3 (0.5)	.28
SSc, *n* (%)	6 (0.9)	2 (3.8)	4 (0.6)	.075
Any, *n* (%)	58 (8.6)	8 (15.1)	50 (8.1)	.12
Malignancy				
Past, *n* (%)	41 (6.1)	3 (5.7)	38 (6.1)	1
Current, *n* (%)	9 (1.3)	0 (0)	9 (1.5)	1
Any, *n* (%)	50 (7.4)	3 (5.7)	47 (7.6)	.79

p-Values were calculated to compare patients with D2T RA with those with non-D2T RA, and were determined using Fisher's exact test.
AID: autoimmune disease; BA: bronchial asthma; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; DM: diabetes mellitus; ESRD: end stage renal disease; GD: gastroduodenal; GI: gastrointestinal; HBV: hepatitis B virus; HCV: hepatitis C virus; HL: hyperlipidemia; HTN: hypertension; IHD: ischemic heart disease; IP: interstitial pneumonia; NTM: nontuberculous mycobacteria; PM/DM: polymyositis/dermatomyositis; RE: reflux esophagitis; SjS: Sjogren's syndrome; SSc: systemic sclerosis; Tb: tuberculosis.

Table 3. Treatment profiles in patients with difficult-to-treat RA (D2T RA) compared with non-D2T RA at the last visit.

	Overall $n=672$	D2T RA $n=53$	Non-D2T RA $n=619$	*p*-Value
MTX				
Use, *n* (%)	541 (80.5)	41 (77.4)	500 (80.8)	.59
Dose (mg/week)	5.8	6.2	5.7	.97
PSL				
Use, *n* (%)	241 (35.9)	39 (73.6)	202 (32.6)	<.0001
Dose (mg/day)	4.2	4	4.2	.67
Anti-TNF				
ADA, *n* (%)	29 (4.3)	4 (7.5)	25 (4.0)	.28
CZP, *n* (%)	15 (2.2)	3 (5.6)	12 (1.9)	.11
ETN, *n* (%)	24 (3.6)	3 (5.6)	21 (3.4)	.43
GLM, *n* (%)	44 (6.5)	8 (15.1)	36 (5.8)	.017
IFX, *n* (%)	40 (6.0)	1 (7.5)	39 (6.3)	.36
Anti-IL-6				
SAR, *n* (%)	8 (1.2)	1 (7.5)	7 (1.1)	.48
TCZ, *n* (%)	77 (11.5)	16 (30.2)	61 (9.9)	.0001
CTLA4-Ig				
ABT, *n* (%)	64 (9.5)	10 (18.9)	54 (8.7)	.025
tsDMARDs				
TOF, *n* (%)	6 (0.9)	3 (5.6)	3 (0.5)	.008
BAR, *n* (%)	13 (1.9)	4 (7.5)	9 (1.5)	.015
PEF, *n* (%)	1 (0.1)	0 (0)	1 (0.2)	1

p-Values were calculated to compare the clinical characteristics of patients with D2T RA with those with non-D2T RA. Mann–Whitney test for continuous variables and Fisher's exact test for categorical variables.
ABT: abatacept; ADA: adalimumab; BAR: baricitinib; b/tsDMARDs: biological or targeted synthetic DMARDs; CTLA4-Ig: cytotoxic T-lymphocyte antigen 4-immunoglobulin; CZP: certolizumab pegol; ETN: etanercept; GLM: golimumab; IFX: infliximab; MTX: methotrexate; PSL: prednisolone; SAR: sarilumab; TCZ: tocilizumab; TNF: tumor necrosis factor; TOF: tofacitinib; PEF: peficitinib.

RA score), and disease activities at the last visit were examined with scores of 0–3. The D2T RA score was found to inversely correlate with the remission rates. As the D2T RA score increased, the remission rate decreased from 60% of score 0 ($n=132$) to 20% of score 3 ($n=23$) (Figure 3(A)), the mean CDAI scores increased from 0.4 of score 0 to 12.4 of score 3 (Figure 3(B)), and the rate of D2T RA increased from 2% of score 0 to 22% of score 3 (Figure 3(C)). When the D2T RA score was applied to treatment-naïve patients at baseline ($n=233$), the score was positively correlated with the development of D2T RA (Figure 3(D)). These results confirmed that the above-mentioned three factors were critical contributors to D2T RA development and that the combinational score of the three factors (the D2T RA score) efficiently predicts patients' progression to D2T RA.

4. Discussion

This study demonstrated that patients with D2T RA accounted for 7.9% of overall patients with RA in real-world clinical practice. Additionally, D2T RA was found to be prevalent among patients with relatively high disease activity, high RF titers, and coexisting pulmonary disease at baseline. The difference in disease activities at the last visits between patients with D2T RA and those with non-D2T RA was not attributable to concomitant MTX use. Patients with D2T RA were less likely to discontinue PSL than those with non-D2T RA. These results indicate that in routine clinical practice, a significant proportion of patients remains symptomatic and may require specific management strategies.

The prevalence of D2T RA varies by its definition and has generally been estimated to be between 5% and 20% [5–7,13]. In this study, D2T RA prevalence was found to be approximately 8% (Figure 2(B,C)). Of a total of 943 patients, including those who were excluded from the study due to lack of baseline information, 84 patients (8.9%) met the defined criteria of D2T RA at the last visits. Therefore, the

Table 4. Multivariate analysis of factors associated with difficult-to-treat RA.

	Univariate		Multivariate	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age at onset	1.00 (0.98–1.02)	.84		
Sex (Male/Female)	0.94 (0.46–1.78)	.86		
Body mass index	1.01 (0.93–1.09)	.83		
Smoking (current)	1.74 (0.69–5.88)	.27		
Smoking (ever)	1.34 (0.72–2.39)	.35		
Family history of RA	1.39 (0.75–2.49)	.28		
RF ≥ 156.4 IU/mL	2.00 (1.05–3.67)	.04	1.95 (1.01–3.64)	.04
ACPA-positive	1.39 (0.69–3.10)	.37		
ESR	1.00 (0.99–1.01)	.40		
CRP	0.96 (0.83–1.08)	.57		
DAS28-ESR	1.26 (1.05–1.52)	.02	1.24 (1.02–1.50)	.03
DAS28-CRP	1.23 (1.02–1.48)	.03		
CDAI	1.24 (1.03–1.49)	.03		
SDAI	1.24 (1.04–1.51)	.03		
HAQ	1.83 (1.32–2.53)	.0002		
mHAQ	1.95 (1.30–2.90)	.001		
Any lifestyle disease	1.09 (0.59–1.94)	.79		
Any lung disease	2.25 (1.21–4.07)	.01	2.03 (1.08–3.72)	.03
Any liver disease	1.18 (0.34–3.09)	.76		
Any kidney disease	2.73 (0.77–7.65)	.08		
Any heart disease	1.23 (0.49–2.68)	.62		
Any hematological disease	1.05 (0.45–2.23)	.99		
Any GI tract disease	1.62 (0.77–3.17)	.18		
Any neurological disease	3.29 (1.05–8.60)	.02	2.85 (0.89–7.70)	.08
Any AID	2.02 (0.85–4.32)	.09		
Any malignancy	0.73 (0.17–2.09)	.61		

p-Values were determined by univariate or multivariate logistic regression analysis.
ACPA: anti-cyclic citrullinated peptide antibodies; AID: autoimmune disease; CI: confidence interval; CRP: C-reactive protein; DAS28: Disease Activity Score 28-joint count; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; HAQ: health assessment questionnaire; mHAQ: modified health assessment questionnaire; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor.

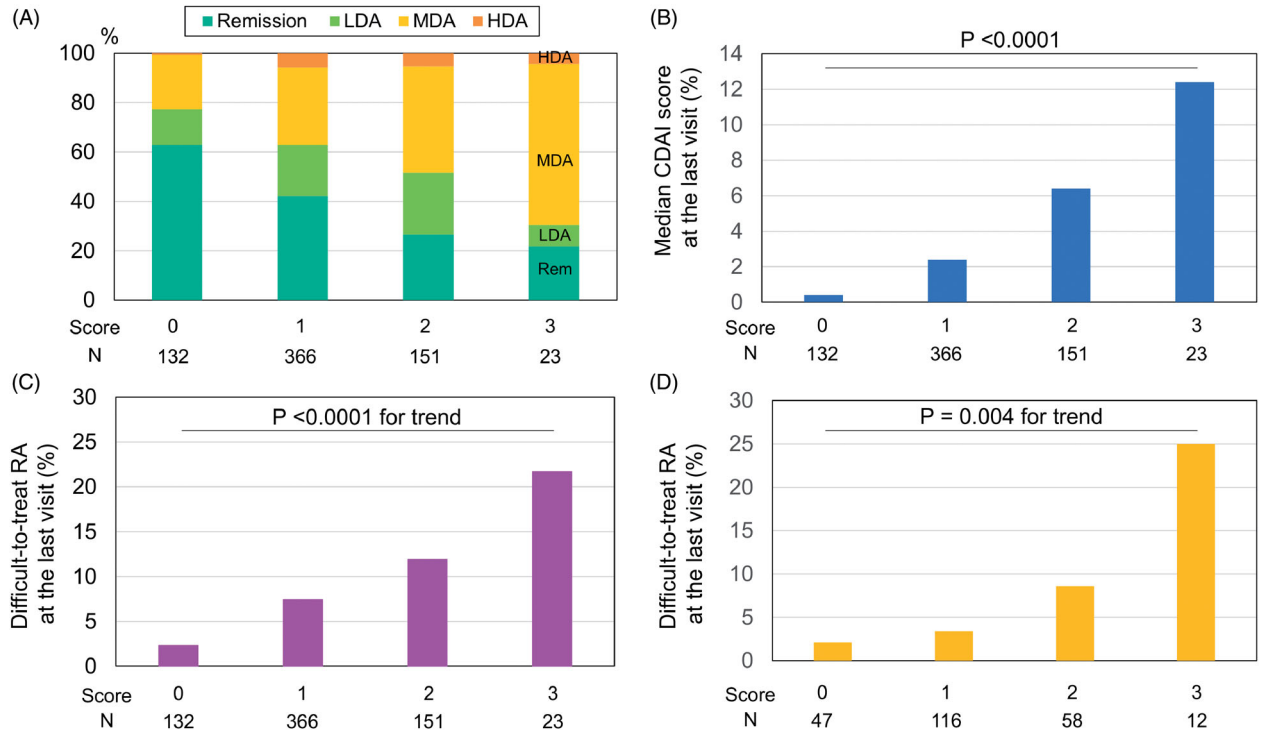

Figure 3. High RF level, baseline DAS28-ESR, and coexisting pulmonary disease as critical determinants of difficult-to-treat rheumatoid arthritis. (A) Disease activity at the last visit sorted by the difficult-to-treat rheumatoid arthritis (D2T RA) score at the first visit. The D2T RA score is based on: (1) moderate or high disease activity defined by DAS28-ESR; (2) coexisting pulmonary disease; and (3) high titer of rheumatoid factor (≥156.4 IU/mL). Remission, low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA) were defined by DAS28-ESR as shown in the Figure 2. (B) The median CDAI scores at the last visit sorted by the D2T RA score that was measured at the first visit. Mann-Whitney test was used. (C) The incidence of D2T RA at the last visit sorted by the D2T RA score that was measured at the first visit. Cochran–Armitage trend test was used to access the trend. (D) The incidence of D2T RA at the last visit among treatment-naïve patients ($n = 233$) sorted by the D2T RA score measured at baseline. Cochran-Armitage trend test was used to access the trend. CDAI, clinical disease activity index; DAS28, Disease Activity Score 28-joint count; ESR, erythrocyte sedimentation rate.

prevalence could be similar, roughly around 5–20% if the same definition was applied. In the literature, a variety of terms are used to describe D2T RA, such as treatment-refractory RA, multidrug-resistant RA, or persistent RA, complicating the situation [5]. Very recently, the European League Against Rheumatism (EULAR) Task Force has proposed the first set of definition and treatment recommendations for D2T RA [5,14]. These efforts could facilitate the optimization of effective treatment strategies for D2T RA.

The task force also conducted an international survey of the characteristics of D2T RA and demonstrated that comorbidities and extra-articular manifestations play key roles in the pathogenic mechanisms of D2T RA [5]. Comorbidities that were referred in the survey included cardiovascular disease, infection, malignancy, diabetes mellitus, osteoporosis, pain syndrome, lung disease, kidney disease, depression, obesity, gastrointestinal disease, osteoarthritis, and others [5]. Although our study did not cover all of these comorbid conditions, as exemplified by the fact that the incidence of cardiovascular events is considerably different between Japanese and Western populations [15], it is unlikely that Japanese and Western populations would share the same comorbidities that predispose to D2T RA incidence. In our study, coexisting pulmonary disease was found to be a key factor for D2T RA incidence. Of the 53 patients with D2T RA, 18 patients had some form of pulmonary involvement at baseline (Table 2). These patients may have had a limited choice of drugs to manage RA. In fact, only 10 out of 18 patients with pulmonary involvement (55.6%) had concomitant use of MTX. These results confirmed that comorbid pulmonary diseases represent a significant challenge in the treatment of RA and patients with pulmonary involvement may need specific management strategies that are currently not included in the RA treatment recommendations [4].

Moreover, neurological diseases were found to be associated with D2T RA based on univariate analysis, but not by multivariate analysis (Table 4). However, the prevalence of neurological diseases among RA patients was low, and only 5 out of 53 patients with D2T RA had some neurological diseases that included past cerebrovascular disease, polyneuropathy, epilepsy, and others. This patient population had persistent disease activities mainly because of the lack of improvement in PtGA. Since the international survey conducted by the EULAR task force did not include neurological disease as potential interfering comorbidities [5], further validation through a large-scale study is warranted.

In the present study, initial DAS28-ESR was identified as a critical risk factor for D2T RA (Table 4), and patients with MDA or HDA at baseline had a higher likelihood of developing D2T RA than those with LDA or remission (Figure 3). Several previous studies reported that patients with higher disease activity at baseline are more likely to have persistent disease activity, or less likely to achieve drug-free remission than those with lower disease activity at baseline [16–18]. A combination of MTX with bDMARDs can suppress radiographic progression if the treatment was initiated at an early stage of the disease course of RA in patients with HDA at baseline [17–19]. Therefore, b/tsDMARDs should be added to csDMARDs early after diagnosis in such patients if they are not contraindicated.

The presence of RF, especially at high levels, is one of the poor prognostic factors for joint damage in RA [4]. Factors that contribute to poor prognosis include MDA or HDA even with the use of csDMARDs, high ESR and/or CRP, high SJC, the presence of RF and/or ACPA, the presence of early erosions, and failure of two or more csDMARDs [4]. These prognostic factors provide a strong rationale for adding b/tsDMARDs to treat patients with inadequate response to MTX [4]. In general, a high titer of RF correlates with higher disease activity of RA [20,21] and also predicts extra-articular complications, such as pulmonary involvement [22,23]. High baseline RF titers were identified as a critical factor for patients' progression to D2T RA. Therefore, all of the risk factors identified by the multivariate analysis in this report may be associated with high RF levels. Patients with these risk factors require more careful, but aggressive treatment strategies. Recently, it has been reported that high baseline RF titers were associated with better response to abatacept [24–26] and tocilizumab [27,28]. These agents might be suitable for this population of patients with high-risk factors.

The strength of the study is that baseline characteristics and comorbidities were investigated in detail in a relatively large number of patients, whereas the study has several limitations. First, the study design was a retrospective, single-center study. Second, approximately one-third of patients were excluded from the analysis because of a lack of valid baseline information. Third, patients who had already been treated at the initial visit to our hospital were mixed with those with untreated patients in this study population. Ideally, this study should be conducted only on treatment-naïve patients. However, 65.3% of the patients enrolled in this study had already been treated with some DMARDs at the first visits. Fourth, RA patients could develop several comorbidities during the disease course. The

study took only baseline comorbidities into account because the study aimed to identify baseline factors associated with D2T RA A. Additionally, the study did not consider the use of csDMARDs but focused on the number of b/tsDMARDs in the definition of D2T RA. Lastly, the study was conducted in a real-world clinical setting. Therefore, the study included patients who needed b/tsDMARDs but had limited access to the drugs due to economic reasons, which could have influenced the prevalence of D2T RA.

Despite these limitations, the study demonstrated that D2T RA represents a significant proportion of patients with RA and that high baseline RF levels and high disease activity as well as coexisting pulmonary disease influence the progression to D2T RA. Further validation of these risk factors through conducting studies with a larger number of patients and optimization of treatment strategies for these patients are needed.

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