Supplementary Materials

A machine learning approach for prediction of CDAI remission with TNF inhibitors: a concept of precision medicine from FIRST registry

Koshiro Sonomoto[1,2], Yoshihisa Fujino[3], Hiroaki Tanaka[2], Atsushi Nagayasu[2], Shingo Nakayamada[2] and Yoshiya Tanaka[2]

1) Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Japan, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
2) The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
3) Department of Environmental Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

Corresponding author:

Prof. Yoshiya Tanaka, MD, PhD

The First Department of Internal Medicine, School of Medicine,

University of Occupational and Environmental Health, Japan

1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

Telephone: +81-93-603-1611. Fax: +81-93-691-9334

E-mail: tanaka@med.uoeh-u.ac.jp.

Figure S1 Model effectiveness comparison of four machine learning approaches using k-fold cross validation.

Box plots show the mean and 95% confidence intervals (CI) of the risk ratio determined by the ratio of positive predictive value/1 - negative predictive value of the tested machine learning approaches with k-fold cross validation (k=10). Cut-off values were determined by receiver operating characteristic curve analysis. Dotted line indicates risk ratio of 1.

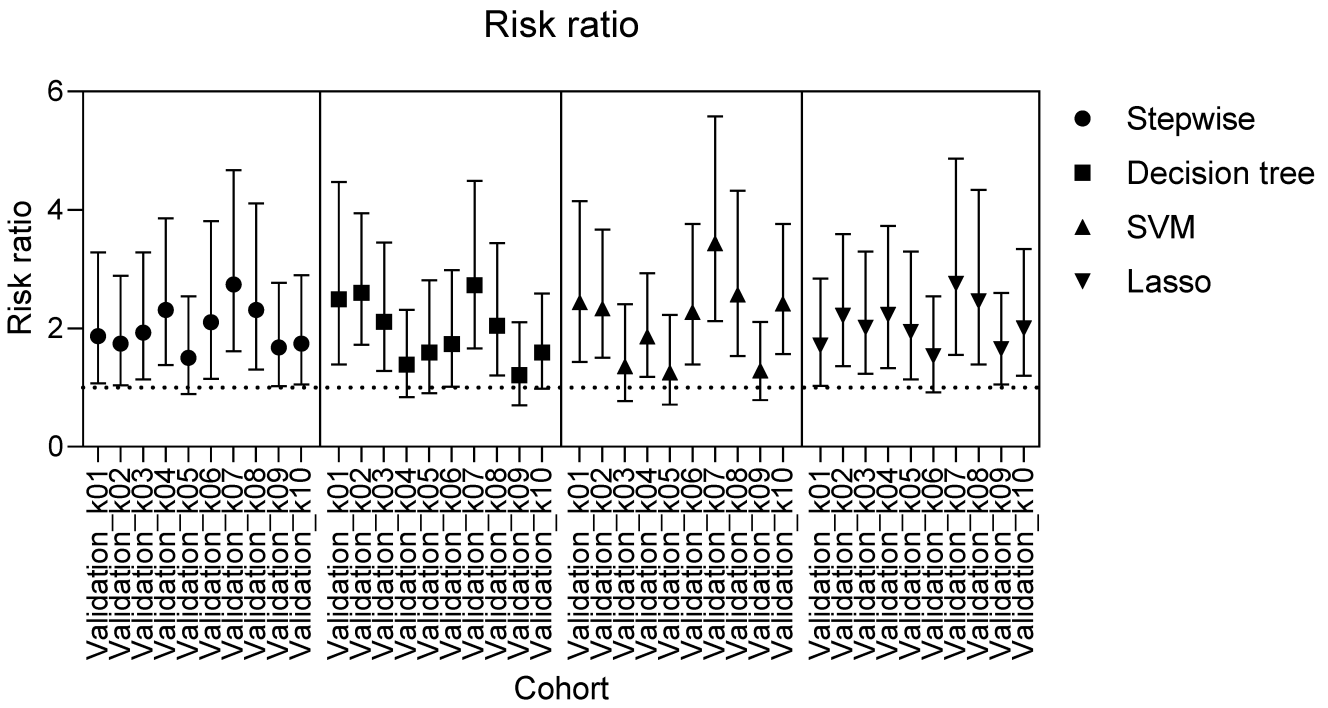
Risk ratio
6
4
2
0
Risk ratio
Validation_k01
Validation_k02
Validation_k03
Validation_k04
Validation_k05
Validation_k06
Validation_k07
Validation_k08
Validation_k09
Validation_k10
Cohort
Stepwise
Decision tree
SVM
Lasso

Figure S2 Per-product performance of Lasso-generated CDAI remission predictive models

The box plots, along with their corresponding values, show the mean and 95% confidence intervals (CI) of the per-product performance of Lasso-generated clinical disease activity index (CDAI) remission predictive models. Cut-off values were determined by receiver operating characteristic curve analysis. ADA: adalimumab/adalimumab-BS, AUC: area under the curve, BS: biosimilar, CZP: certolizumab pegol, ETN: etanercept/etanercept-BS, IFX: infliximab/infliximab-BS, NPV: negative predictive value, PPV: positive predictive value, Risk ratio: PPV/(1-NPV).

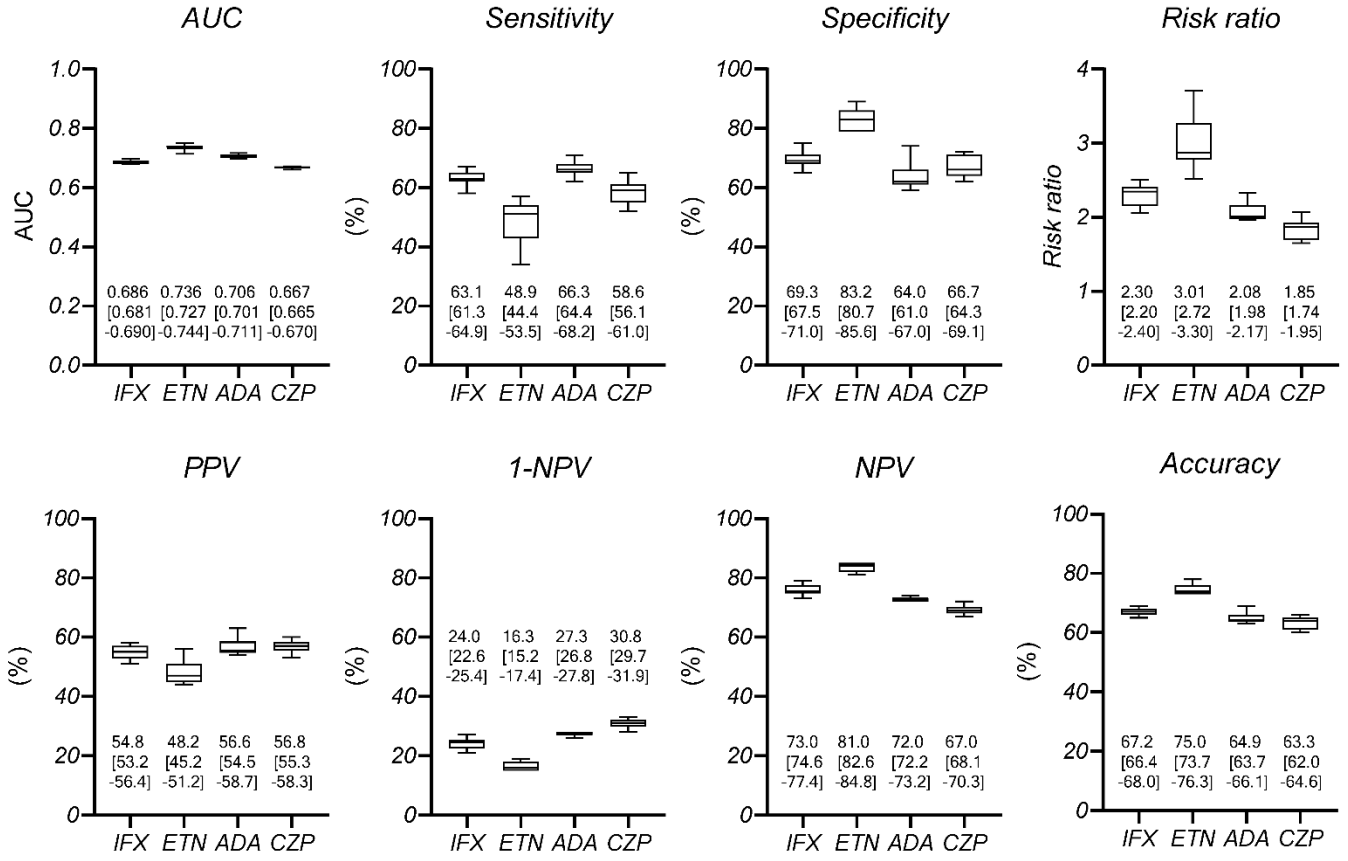
AUC
AUC
1.0
0.8
0.6
0.4
0.2
0.0
0.686 [0.681 -0.690]
0.736 [0.727 -0.744]
0.706 [0.701 -0.711]
0.667 [0.665 -0.670]
IFX ETN ADA CZP
Sensitivity
(%)
100
80
60
40
20
0
63.1 [61.3 -64.9]
48.9 [44.4 -53.5]
66.3 [64.4 -68.2]
58.6 [56.1 -61.0]
IFX ETN ADA CZP
Specificity
(%)
100
80
60
40
20
0
69.3 [67.5 -71.0]
83.2 [80.7 -85.6]
64.0 [61.0 -67.0]
66.7 [64.3 -69.1]
IFX ETN ADA CZP
Risk ratio
Risk ratio
4
3
2
1
0
2.30 [2.20 -2.40]
3.01 [2.72 -3.30]
2.08 [1.98 -2.17]
1.85 [1.74 -1.95]
IFX ETN ADA CZP
PPV
(%)
100
80
60
40
20
0
54.8 [53.2 -56.4]
48.2 [45.2 -51.2]
56.6 [54.5 -58.7]
56.8 [55.3 -58.3]
IFX ETN ADA CZP
1-NPV
(%)
100
80
60
40
20
0
24.0 [22.6 -25.4]
16.3 [15.2 -17.4]
27.3 [26.8 -27.8]
30.8 [29.7 -31.9]
IFX ETN ADA CZP
NPV
(%)
100
80
60
40
20
0
73.0 [74.6 -77.4]
81.0 [82.6 -84.8]
72.0 [72.2 -73.2]
67.0 [68.1 -70.3]
IFX ETN ADA CZP
Accuracy
(%)
100
80
60
40
20
0
67.2 [66.4 -68.0]
75.0 [73.7 -76.3]
64.9 [63.7 -66.1]
63.3 [62.0 -64.6]
IFX ETN ADA CZP

Figure S3 Performance summary of Lasso-generated CDAI remission predictive models in the sub-cohort post-abatacept subcohort

The box plots, along with their corresponding values, show the mean and 95% confidence intervals (CI) of performance for Lasso-generated clinical disease activity index (CDAI) remission predictive models, which include 10 models generated using the k-fold cross-validation method. The models were developed in the cohort after November 2010, following the launch of abatacept. Cutoff values were determined by receiver operating characteristic curve analysis. AUC: area under the curve, NPV: negative predictive value, PPV: positive predictive value, Risk ratio: PPV/(1-NPV).

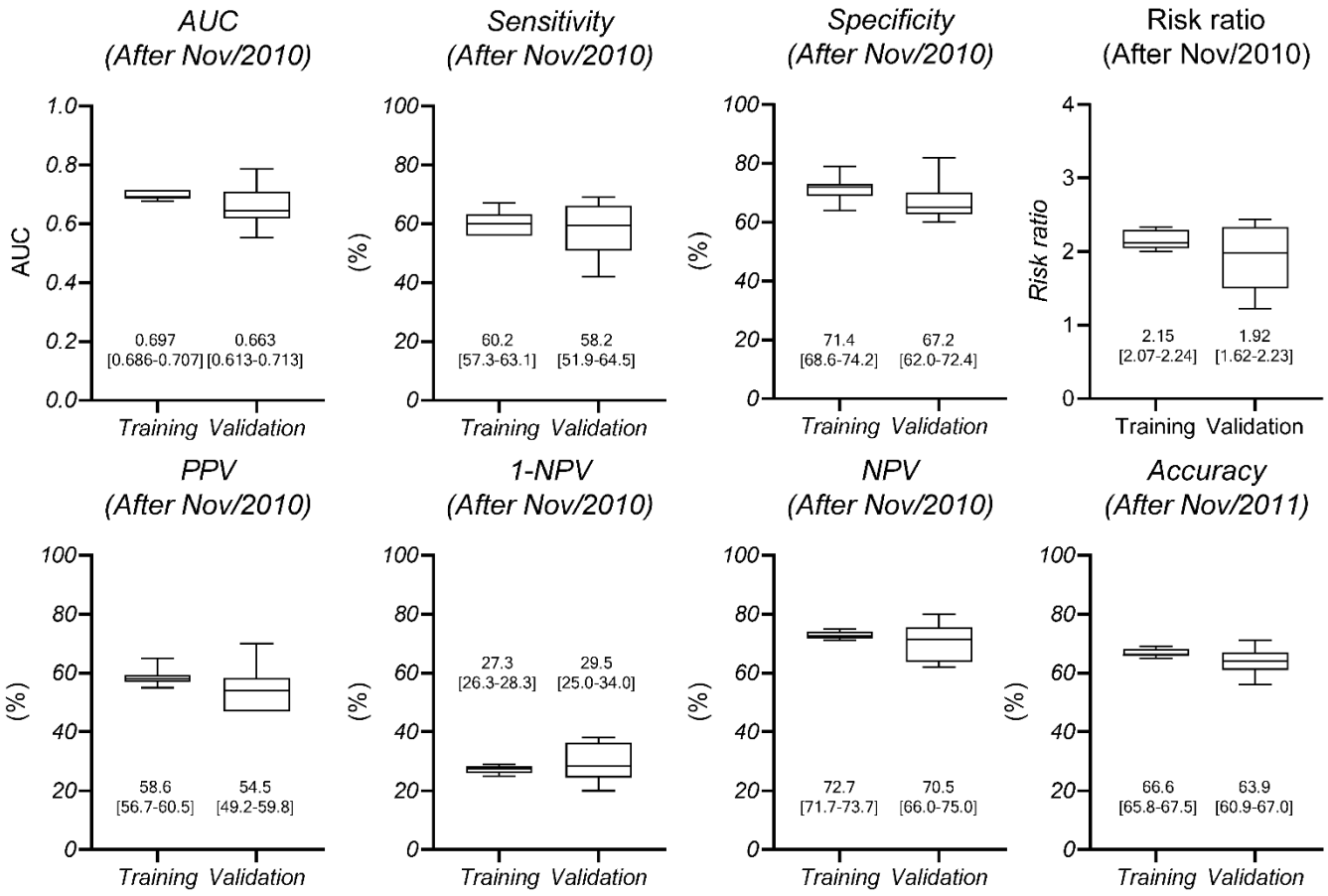
AUC
(After Nov/2010)
AUC
1.0
0.8
0.6
0.4
0.2
0.0
0.697
[0.686-0.707]
0.663
[0.613-0.713]
Training
Validation
Sensitivity
(After Nov/2010)
(%)
100
80
60
40
20
0
60.2
[57.3-63.1]
58.2
[51.9-64.5]
Training
Validation
Specificity
(After Nov/2010)
(%)
100
80
60
40
20
0
71.4
[68.6-74.2]
67.2
[62.0-72.4]
Training
Validation
Risk ratio
(After Nov/2010)
Risk ratio
4
3
2
1
0
2.15
[2.07-2.24]
1.92
[1.62-2.23]
Training
Validation
PPV
(After Nov/2010)
(%)
100
80
60
40
20
0
58.6
[56.7-60.5]
54.5
[49.2-59.8]
Training
Validation
1-NPV
(After Nov/2010)
(%)
100
80
60
40
20
0
27.3
[26.3-28.3]
29.5
[25.0-34.0]
Training
Validation
NPV
(After Nov/2010)
(%)
100
80
60
40
20
0
72.7
[71.7-73.7]
70.5
[66.0-75.0]
Training
Validation
Accuracy
(After Nov/2011)
(%)
100
80
60
40
20
0
66.6
[65.8-67.5]
63.9
[60.9-67.0]
Training
Validation

Figure S4 Clinical application of Lasso predictive model

b/tsDMARDs: biologic/targeted synthetic disease-modifying antirheumatic drugs, CDAI: clinical disease activity index, CTLA4Ig: cytotoxic T-lymphocyte-associated protein 4 immunoglobulin, IL-6Ri: interleukin-6 receptor inhibitor, JAKi: Janus kinase inhibitor, MTX: methotrexate, MOA: mechanism of action, TNFi: tumor necrosis factor inhibitor.

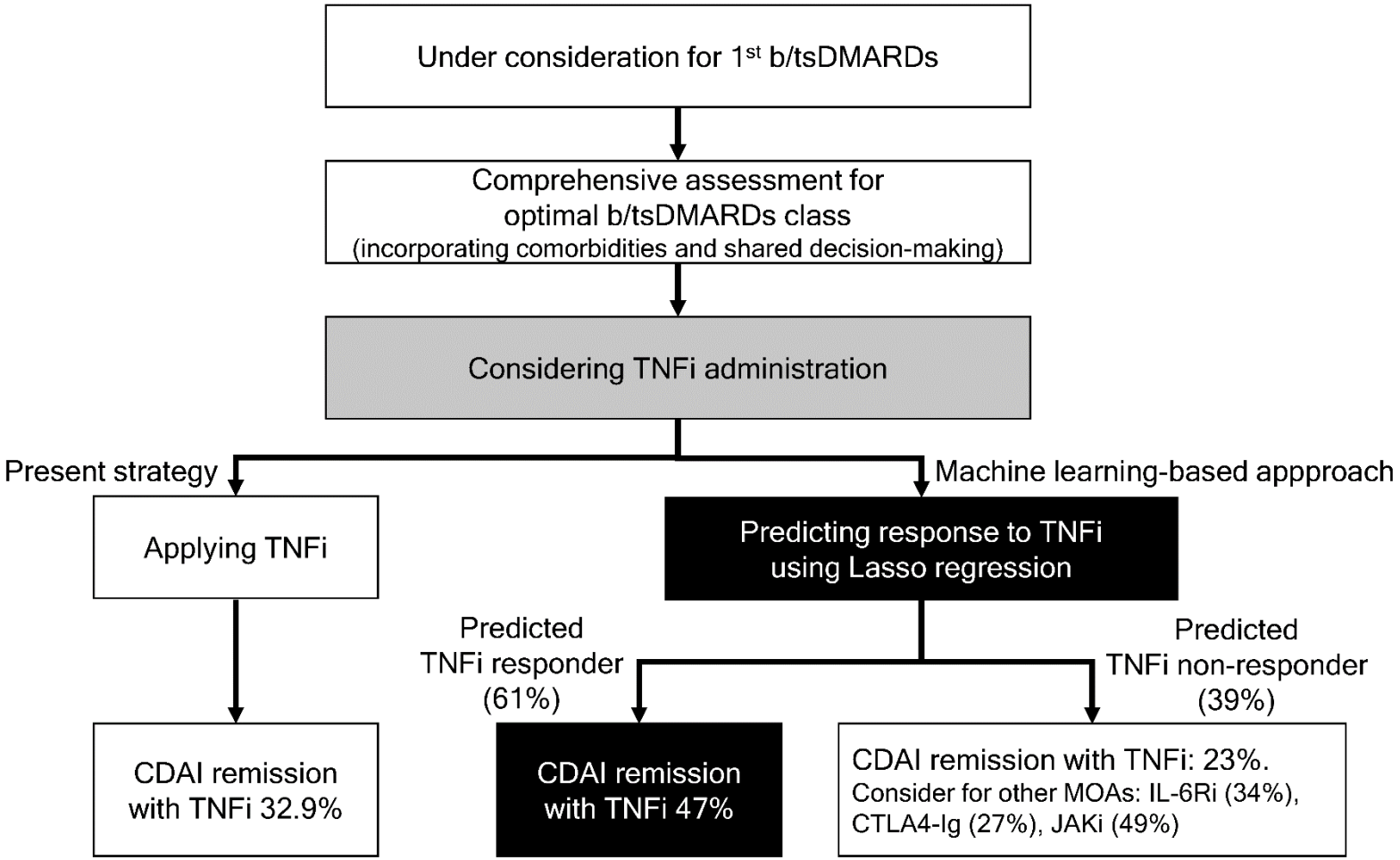
Under consideration for 1st b/tsDMARDs
Comprehensive assessment for optimal b/tsDMARDs class (incorporating comorbidities and shared decision-making)
Considering TNFi administration
Present strategy
Machine learning-based appproach
Applying TNFi
Predicting response to TNFi using Lasso regression
Predicted TNFi responder (61%)
Predicted TNFi non-responder (39%)
CDAI remission with TNFi 32.9%
CDAI remission with TNFi 47%
CDAI remission with TNFi: 23%.
Consider for other MOAs: IL-6Ri (34%), CTLA4-Ig (27%), JAKi (49%)

Table S1 Simulation of the efficacy of Vastesaeger's DAS-remission predictive model on the study population

Study population			Vastesaeger's model efficacy on the study population							
Remission criteria	Data available (N)	Remission rate (%)	Cut-off of remission probability assigned for the simulation	Predicted TNFi responder (%)	Sensitivity (%)	Specificity (%)	PPV (%)	1-NPV (%)	NPV (%)	Risk ratio [95% CI]
DAS28-ESR	1239	40.0	67%	1.8	3.0	99.1	68.2	39.5	60.5	1.73 [1.29-2.31]
			50%	11.5	20.2	94.2	69.9	36.1	63.9	1.94 [1.69-2.21]
			40%	19.5	32.3	89.0	66.1	33.7	66.3	1.96 [1.73-2.22]
			30%	35.3	51.6	75.6	58.6	29.9	70.1	1.96 [1.72-2.23]
			20%	59.2	74.6	51.0	50.4	25.0	75.0	2.02 [1.71-2.39]
			ROC (25%)	46.2	63.5	65.4	55.1	27.1	72.9	2.03 [1.76-2.35]
CDAI	1216	35.5	67%	1.8	2.8	98.7	54.5	35.2	64.8	1.55 [1.05-2.29]
			50%	11.4	16.0	91.1	49.6	33.7	66.3	1.47 [1.22-1.78]
			40%	19.7	25.2	83.4	45.6	33.1	66.9	1.38 [1.17-1.63]
			30%	35.4	43.1	68.9	43.3	31.3	68.7	1.38 [1.19-1.61]
			20%	59.2	67.8	45.5	40.7	28.0	72.0	1.45 [1.23-1.71]
			ROC (21%)	55.6	65.3	49.7	41.7	27.8	72.2	1.50 [1.28-1.77]

Remission probability for each patient in the study population was calculated based on the model by Vastesaeger N et. al. (8). Each row indicates the estimation power of different cut-off values for remission probability. CDAI: clinical disease activity index, DAS28: disease activity score 28, PPV: positive predictive value, NPV: negative predictive value, Risk ratio: PPV/(1-NPV), ROC: revised cut-off value for Vastesaeger's model by receiver operating characteristic curve using the study population, TNFi: tumor necrosis factor inhibitor.

Table S2 Per-product efficacy of Vastesaeger's model in predicting CDAI remission in the study population

Study population			Vastesaeger's model efficacy on the study population						
Product	N	CDAI Remission rate (%)	Predicted TNFi responder (%)	Sensitivity (%)	Specificity (%)	PPV (%)	1-NPV (%)	NPV (%)	Risk ratio [95% CI]
IFX/IFX-BS	373	33.0	58.7	65.9	44.8	37.0	27.3	72.7	1.36 [0.99-1.85]
ETN/ETN-BS	193	23.8	31.6	47.8	73.5	36.1	18.2	81.8	1.98 [1.21-3.25]
ADA/ADA-BS	360	40.6	63.9	74.0	43.0	47.0	29.2	70.8	1.61 [1.19-2.17]
CZP	267	41.6	56.2	59.5	46.2	44.0	38.5	61.5	1.14 [0.85-1.53]

ADA: adalimumab, BS: biosimilar, CDAI: clinical disease activity index, CI: confidence interval, CZP: certolizumab pegol, ETN: etanercept, IFX: infliximab, NPV: negative predictive value, PPV: positive predictive value, Risk ratio: PPV/(1-NPV), TNFi: tumor necrosis factor inhibitor.

Table S3 Variables included for statistical modeling

Variable	Missing rate
Female	0.0%
Age	0.0%
Smoking	0.0%
BMI	0.1%
eGFR	0.0%
RA duration	0.0%
Steinbrocker stage	0.0%
Morning stiffness	0.1%
Tender joint count (28)	0.0%
Swollen joint count (28)	0.0%
Evaluator's global assessment	25.2%
Patient's global assessment	0.1%
Patient's assessment, pain	18.5%
HAQ	13.3%
RF, positive	0.0%
ACPA, positive	20.3%
ESR	0.0%
CRP	0.0%
MMP-3	2.5%
Methotrexate dose	0.0%
Concomitant GC	0.0%
GC dose, PSL equivalent	0.0%
Concomitant csDMARDs	0.0%
White blood cell count	0.1%
Lymphocytes	0.1%
Neutrophils	0.1%
Albumin	0.1%
HbA1c	10.6%
IgG	0.2%
IgA	1.0%
IgM	1.0%
CH50	0.8%
C3	2.0%
C4	2.1%
KL-6	6.0%
Antinuclear antibody	1.2%
anti dsDNA antibody	5.6%
anti SS-A antibody, positive	2.9%
Polymyalgia rheumatica	0.0%
Interstitial lung disease	0.0%
Coexisting lung diseases	0.0%
NTM	0.0%
Pneumonia	0.0%
Malignancy	0.0%
Fracture	0.0%
Pneumocystis pneumonia	0.0%
Interstitial lung disease	0.0%
Tuberculous	0.0%

ACPA: anti-citrullinated peptide antibody, BMI: body mass index, csDMARDs: conventional synthetic disease modifying anti rheumatic drug, eGFR: estimated glomerular filtration rate, GC: glucocorticoid, HAQ: health assessment questionnaire, MMP-3: matrix metalloproteinase 3, NTM: nontuberculous mycobacteria disease, RA: rheumatoid arthritis, RF: rheumatoid factor.

Table S4 Performance of Lasso-generated CDAI remission predictive models on Calendar cohort

Cohort	N	Remission rate (%)	Predicted TNFi responder (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	1-NPV (%)	Risk ratio [95% CI]
Training cohort										
Training_Calendar	901	37.0	42.5	0.695	62.2	69.0	54.0	75.7	24.3	2.22 [1.86-2.65]
Validation cohort										
Validation_Calendar	103	47.5	49.5	0.667	61.2	61.1	58.8	63.5	36.5	1.61 [1.05-2.46]

The results indicate the performance of the CDAI remission predictive model generated using the training cohort (Training_Calendar: including patients before September 2019), on both the training and validation cohorts (after October 2019). Cut-off values were determined through receiver operating characteristic curve analysis. AUC: area under the curve, CI: confidence interval, NPV: negative predictive value, PPV: positive predictive value, Risk ratio: PPV/(1-NPV), TNFi: tumor necrosis factor inhibitor.