Association of RETN and TNFRSF1B polymorphisms with TNF-α inhibitor response in rheumatoid arthritis patients

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Research article

Keywords: Rheumatoid arthritis, tumor necrosis factor inhibitors, single nucleotide polymorphism, pharmacogenetics

Posted Date: February 25th, 2020

DOI: https://doi.org/10.21203/rs.2.24442/v1

Abstract

Background: Despite the improvement from the introduction of tumor necrosis factor inhibitors (TNFi) in the rheumatoid arthritis (RA), TNFi therapy fails for more than 30% or results in a partial response. Thus, we aimed to explore treatment marker by examining the association of single nucleotide polymorphisms (SNPs) with response to TNFi therapy.

Method: Genes associated with RA or RA treatment were reviewed and fourteen SNPs with minor allele frequency ≥ 20% in the East Asian populations were selected and analyzed. Data were collected from 105 RA patients. Our primary endpoint was the disease activity score using 28-joint count after six months of treatment (DAS28-$_{6month}$). The secondary outcomes were the subcomponents of DAS28.

Results: A total of 88 patients were included in the final analyses. Among the 14 SNPs analyzed, one SNP showed statistical significance in DAS28-$_{6month}$: patients with the GG allele of *RETN* rs1862513 had a 4.7 times higher chance of low disease activity at 6-months than GC or CC-carriers (p = 0.033), as indicated by multivariable logistic regression analysis. Rs3397 was marginally significant in univariate analysis (p=0.059), but was significant in the multivariable model (p=0.041). The final model explained 24.5% (Nagelkerke R^2) of the variance in DAS28-$_{6month}$.

Conclusion: Our results demonstrated that, among the genes related to RA, SNPs in *RETN* and *TNFRSF1B* were associated with the response of TNFi treatment.

Background

Rheumatoid arthritis (RA) is an autoimmune disease with chronic inflammation that mainly affects the joints and can also involve other body systems such as the skin, eyes, lungs, heart and blood vessels. The pathogenesis of RA is not clear, but genetic, environmental, and autoimmunity-related factors are likely involved, which is called the “Bermuda triangle”. Genetic susceptibility has been studied in relation to environmental factors, mainly smoking and in part alcohol intake [1-4]. Indeed, a genetic component may be responsible for up to 60% of susceptibility to RA, suggesting the importance of genetics in RA [5]. On the other hand, studies on responses to treatment in relation to genetic factors are inconsistent and the results vary among different population groups.[1-3]

Tumor necrosis factor alpha (TNF-α) inhibitors (TNFi) have demonstrated efficacy in RA treatment either as monotherapy or in combination with other disease-modifying anti-rheumatic drugs. Five TNF-α inhibitors are currently available for RA therapy: etanercept, a fusion protein that was first approved by the US FDA in 1998 to treat RA, and four anti-TNF-α monoclonal antibodies (infliximab, adalimumab, golimumab and certolizumab). Despite the progress made by the introduction of TNFi, a partial response or treatment failure is observed in more than 30% of patients [6]. Therefore, it is vital to discover prognostic factors associated with TNFi response in order to avoid missing other potentially effective treatments at an early stage of disease.

Pharmacogenomics studies on TNFi show that genetic variations are important in predicting the response to treatment. Genetic variations in the *HLA-DRB1* and *TNF* regions are associated with the response to TNFi in Caucasians, but these associations have failed to reach significance in Korean patients [4-6]. Although genes or specific mutations differ among ethnic groups, biological pathways related to immune signaling and inflammation are commonly associated with the response to TNFi in Koreans [6-8]. Therefore, genes associated with RA or other autoimmune diseases could affect the therapeutic response to TNFi as they are involved in common inflammatory pathways. In the present study, we examined the association of genetic factors to the TNFi response in RA patients in Korea.

Methods

Patients

A total of 105 RA patients from two teaching hospitals who were given TNF-α inhibitors (etanercept, infliximab, adalimumab, or golimumab) from July 2017 to December 2019 were recruited. Patients' data were collected from electronic medical records and included age, sex, age at diagnosis, weight, height, concomitant drugs, comorbidities, and autoantibodies against rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACPA). Baseline data of disease activity score (DAS)-28 and its subcomponents—swollen joint score (SJC)-28, tender joint score (TJC)-28, global health (GH), and erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP) levels—were collected.

The treatment response was accessed by the DAS28-ESR at 6 months after starting TNFi treatment (DAS28-$_{6month}$). DAS28-$_{6month}$ was ≤3.2 in the low disease activity group and >3.2 of DAS28-$_{6month}$ in the moderate-to-high disease activity group [9].

Genotyping

We examined previous genetic studies associated with RA, RA treatment or other autoimmune diseases and selected statistically significant SNPs (Additional file 1). The minor allele frequency from the International HapMap Project was used to capture common SNPs present in > 20% of the East Asian (Han Chinese and Japanese) populations [10].

A total of 14 SNPs in the *MMEL1* (rs2843401, rs3890745), *RETN* (rs1862513, rs3745367, rs7408174, rs3219175), *PDZD2* (rs1532269), *TNFAIP3* (rs5029937), *TNFRSF1A* (rs767455), *TNFRSF1B* (rs3397), *CD226* (rs763361), *AFF3* (rs108655035), *PTPRC* (rs10919563), and chr.17 (rs2872507) were chosen (Supplementary table 1) and genotyped by TaqMan or SNaPshot assay. Patients' whole blood samples were collected in EDTA-tube during a regular visit and were used for subsequent DNA extraction (DNeasy Blood & Tissue Kit, Qiagen GmbH, Hilden, Germany).

Statistical analysis

Categorical variables were analyzed by chi-square test, and an independent-samples t-test was used to compare means of continuous variables between patients with DAS28-$_{6month}$≤3.2 and >3.2. Multivariable linear regression was used to predict independent risk factors associated with TNFi treatment response. Forward selection of variables was used in the regression method using the probability of R 0.05 for entry and 0.10 for removal. Regression smoothing was carried out using the loess function to validate the regression model. A receiver operating characteristic (ROC) curve was drawn to assess the predictive accuracy of the multivariable model. Statistical significance was considered at p-value of less than 0.05. Statistical analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC, USA).

Results

Among 105 patients enrolled, a total of 88 patients were included in the analyses. Seventeen patients were excluded due to the incomplete medical data. Among 88 patients included, 43 patients (48.9%) showed low disease activity (DAS28-$_{6month}$ ≤3.2). The mean age of all patients was 44 ± 13 years (range, 20–78), and 81.8% were females. Baseline characteristics of patients were not statistically different between the two groups, except for hypertension, which was more prevalent in patients with moderate-to-high disease activity (p = 0.039). The most prevalent comorbidity was hypertension (15.9%) followed by osteoporosis and hyperlipidemia (both 11.3%). Both RF and ACPA were not associated with treatment response. Methotrexate was the most common concomitant drug prescribed (87.5%), followed by hydroxychloroquine (54.5%) and leflunomide (39.7%) (Table 1).

Table 1. Patient characteristics according to the disease activity at 6 months treatment of TNF inhibitors

Characteristics, n (%)	Low disease activity	Moderate to high disease activity	p-value
Sex			0.100
Male	11 (25.6)	5 (11.1)	
Female	32 (74.4)	40 (88.9)	
Age, years	50.7 ± 13.1	55.0 ± 14.0	0.137
< 65	36 (83.7)	34 (75.6)	0.431
≥ 65	7 (16.3)	11 (24.4)	
BMI, kg/m^2	23.1 ± 3.3	22.4 ± 3.9	0.342
Duration of rheumatoid arthritis, years	8.2 ± 5.5	10.0 ± 6.9	0.171
Alcohol			0.155
Yes	7 (16.3)	4 (8.9)	
No	34 (79.1)	41 (91.1)	
Smoking			0.949
Current	5 (11.6)	5 (11.1)	
Former	2 (4.7)	2 (4.4)	
Never	35 (81.4)	38 (84.4)	
Rheumatoid factor			0.328
Positive	30 (69.8)	35 (77.8)	
Negative	13 (30.2)	9 (20.0)	
ACPA			0.609
Positive	28 (71.8)	31 (75.6)	
Negative	11 (28.2)	9 (22.0)	
Concomitant drug			
Hydroxychloroquine			0.834
Yes	24 (55.8)	24 (53.3)	
No	19 (44.2)	21 (46.7)	
Leflunomide			0.514
Yes	19 (44.2)	16 (35.6)	
No	24 (55.8)	29 (64.4)	
Methotrexate			0.522
Yes	39 (90.7)	38 (84.4)	
No	4 (9.3)	7 (15.6)	
Sulfasalazine			0.224
Yes	8 (18.6)	4 (8.9)	
No	35 (81.4)	41 (91.1)	
Tacrolimus			0.551
Yes	5 (11.6)	8 (17.8)	
No	38 (88.4)	37 (82.2)	
Comorbidity			
Diabetes			0.677
Yes	2 (4.7)	4 (8.9)	

No	41 (95.3)	41 (91.1)	
Dyslipidemia			0.316
Yes	3 (7.0)	7 (15.6)	
No	40 (93.0)	38 (84.4)	
Hypertension			0.039
Yes	3 (7.0)	40 (93.0)	
No	11 (24.4)	34 (75.6)	
Osteoporosis			0.739
Yes	4 (9.3)	6 (13.3)	
No	39 (90.7)	39 (86.7)	
Vitamin D deficiency			1.000
Yes	3 (7.0)	4 (8.9)	
No	40 (93.0)	41 (91.1)	

ACPA: Anticyclic citrullinated peptide antibody; BMI: body mass index; DAS28: disease activity score 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

To determine the possible influence of disease status of patients on their response to TNFi, baseline DAS28 and its subcomponents were examined. Baseline DAS28 was significantly lower in the low disease activity group than in the moderate-to-high disease activity group (p = 0.034) (Table 2).

Table 2. Baseline DAS28 and its subcomponents according to the disease activity at 6 months treatment of TNF inhibitors

	Low disease activity	Moderate to high disease activity	p-value
DAS28	5.5 ± 1.2	6.0 ± 1.1	0.034
Total joint count 28	9.1 ± 8.2	12.0 ± 7.1	0.077
Swollen joint count 28	6.8 ± 7.5	7.7 ± 5.1	0.499
Global health	58.6 ± 19.6	59.2 ± 17.1	0.875
ESR	47.7 ± 28.7	53.0 ± 27.0	0.371
CRP	2.5 ± 3.9	2.1 ± 2.1	0.484

DAS28: disease activity score 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; count

Among the 14 SNPs genotyped, GG-carriers of rs1862513 were more likely to show low disease activity at 6-months of TNFi treatment than GC or CC-carriers (p = 0.020). Marginal significance was revealed for Rs3397, with higher disease activity in CC-carriers than in patients with the T allele (p = 0.059). Other 12 SNPs did not reach statistical significance in terms of DAS28-$_{6month}$ (Table 3).

Table 3. Genotype association with the disease activity at 6 months treatment of TNF inhibitors

Gene, rs number	Low disease activity	Moderate to high disease activity	p-value
RETN rs1862513			0.020
GG	11 (25.6)	3 (6.7)	
GC, CC	32 (74.4)	42 (93.3)	
RETN rs3219175			0.673
AA	3 (7.0)	2 (4.4)	
AG, GG	40 (93.0)	43 (95.6)	
RETN rs3745367			0.391
GG	15 (34.9)	20 (44.4)	
GA, AA	28 (65.1)	25 (55.6)	
RETN rs7408174			1.000
CC	1 (2.3)	2 (4.4)	
CT, TT	42 (97.7)	43 (95.6)	
TNFAIP3 rs5029937			0.574
GG	37 (86.0)	36 (80.0)	
GT	6 (14.0)	9 (20.0)	
PDZD2 rs1532269			0.198
CC	14 (32.6)	21 (46.7)	
CG, GG	29 (67.4)	24 (53.3)	
MMEL1 rs3890745			0.654
TT	16 (37.2)	14 (31.1)	
TC, CC	27 (62.8)	31 (68.9)	
MMEL1 rs2843401			0.505
TT	13 (30.2)	17 (37.8)	
TC, CC	30 (69.8)	28 (62.2)	
TNFRSF1A rs767455			0.328
TT	30 (69.8)	36 (80.0)	
TC, CC	13 (30.2)	9 (20.0)	
TNFRSF1B rs3397			0.059
CC	16 (37.2)	26 (57.8)	
CT, TT	27 (62.8)	19 (42.2)	
CD226 rs763361			0.658
CC	17 (39.5)	15 (33.3)	
CT, TT	26 (60.5)	30 (66.7)	
AFF3 rs10865035			0.464
AA	9 (20.9)	13 (28.9)	
AG, GG	34 (79.1)	32 (71.1)	
PTPRC rs10919563			0.505
GG	30 (69.8)	28 (62.2)	
GA,AA	13 (30.2)	17 (37.8)	
Chr.17 rs2872507			0.831
GG	26 (60.5)	26 (57.8)	

GA, AA	17 (39.5)	19 (42.2)

We performed multivariable logistic regression analysis to determine the independent factors including both genetic and non-genetic variables. Hypertension, baseline DAS28, rs1862513, and rs3397 (all $p < 0.1$ in univariate analysis), sex, age, and body mass index were also included. The model explained 24.5% (Nagelkerke R^2) of the variance in DAS28-$_{6month}$ and correctly classified 67.0% of the cases. C-allele carriers of rs1862513 were 4.67-times more likely to exhibit moderate-to-high disease activity than GG carriers. CC carriers of rs3397 were 2.66-times more likely to exhibit moderate-to-high disease activity than T-allele carriers (Table 4).

Table 4: Multivariable binary logistic model for moderate to high disease activity at 6 months treatment of TNF inhibitors

	OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Female	2.75 (0.87-8.73)	0.086		
Age ≥ 65	1.66 (0.58-4.79)	0.345		
BMI	0.94 (0.84-1.06)	0.339		
Hypertension	4.31 (1.11-16.74)	0.035	3.65 (0.85-15.63)	0.082
Baseline DAS28	1.53 (1.02-2.29)	0.039	1.45 (0.94-2.23)	0.091
Rs1862513 CC, CG (reference = G G)	4.81 (1.24-18.69)	0.023	4.67 (1.14-19.19)	0.033
Rs3397 CC (reference = CT, TT)	2.31 (0.98-5.43)	0.055	2.66 (1.04-6.82)	0.041

*Adjusted for sex, age, BMI, hypertension, baseline DAS28, rs1862513 and rs3397.

OR: odds ratio, CI: confidence interval, BMI: body mass index, DAS28: disease activity score 28

A calibration plot of the actual response to TNFi treatment versus probabilities of response estimated by the multivariable model was drawn with loess function to validate the regression model. The fitted loess lines indicated excellent calibration, and variability was minor within the range of predicted probability where the majority of patients were in (Figure 1).

To assess the predictive accuracy of TNFi response, a ROC curve based on the multivariable model was drawn. The area under the ROC curve for detecting the response to TNFi was 0.77 (95% CI, 0.67-0.87) (Figure 2).

Discussion

This study aimed to investigate the possible association between genetic variation and response to TNFi treatment. Among the candidate gene polymorphisms examined, two SNPs, rs1862513 and rs3397, were associated with the response to TNFi in our RA patients. Worse treatment outcome was seen in patients with the C allele of rs1862513 and CC carriers of rs3397.

Rs1862513 is located in the promoter region of the *RETN* gene, which has been investigated by many groups. Previous studies of resistin (RETN) dealt with obesity and insulin resistance in diabetes.[11-13] Resistin modulates the release and effect of various chemokines and cytokines, and is a key component associated with metabolic and inflammatory diseases.[14] It is estimated that up to 70% of the variation in circulating resistin levels can be explained by genetic factors, although the mechanism and functional implications of this genetic control are still unknown.[15] In the Framingham Offspring Study, rs1862513 was associated with resistin levels but with high heterogeneity across studies.[16] The C allele was associated with higher resistin levels in a meta-analysis that was mainly driven by the Japanese study.[17] We speculate that the C– allele carriers of rs1862513 have higher resistin levels, which could worsen the outcome following TNFi treatment because an increased level of resistin is linked to enhanced inflammatory and disease activity in RA patients.[18]

The *TNFRSF1B* gene encodes tumor necrosis factor receptor superfamily 1B, which is one of the two receptors that TNF-α binds to and further activates NF-κB, triggering inflammatory pathways.[19] Genetic polymorphisms in TNFRSF1B have been studied mostly in patients with Crohn's disease or tuberculosis. Although the outcomes of these studies were different from that of our study, the CT and TT alleles of rs3397 were associated with lower expression of *TNFRSF1B* and increased susceptibility to *Mycobaterium avium* subsp *paratuberculosis* infection in Crohn's disease patients following TNFi treatment.[20] But, in a systematic review of the TNFi response in patients with inflammatory bowel diseases, rs3397 was a nonsignificant SNP, suggesting that the data on its effect on TNFi response are inconclusive.[21] Also, studies on the role of rs3397 in susceptibility to tuberculosis yielded inconsistent results.[22-24] In one study in RA patients, an rs3397 variant was associated with a risk of RA but this study failed to provide evidence regarding the role of rs3397 in the response to TNFi.[25] Thus, most studies of rs3397 showed contradictory and inconclusive results across different populations. From our results, we speculate that the C allele triggers a strong inflammatory response via the TNF-α pathway, which might be related to a weaker response to TNFi treatment. This could be a meaningful evidence for future treatments considering rs3397 in relation to TNFi response in Korean RA patients.

Hypertension was significantly associated with TNFi response in univariate analysis. Since the pathophysiology of increased blood pressure is multifactorial, blood pressure control in inflammatory autoimmune disorders is largely related to chronic inflammation and an immune-mediated mechanism. There is a direct association between inflammation and hypertension, although the underlying mechanism remains undetermined .[26, 27] The prevalence of hypertension is high in RA patients and its control is worse than in the general population.[28] In a similar manner, our patients with hypertension had a higher risk of worse outcome following TNFi treatment than patients without hypertension. However, hypertension did not remain a significant factor in the multivariable regression model after

adjusting for demographic and genetic factors. This indicates that more studies with different patient populations are needed to ascertain the association of hypertension with TNFi response in RA patients.

Conclusion

Our findings suggest that *RETN* rs1862513 and *TNFRSF1B* rs3397 are associated with TNFi treatment response in RA patients. As RA is a genetically and biologically heterogeneous disease, more than one SNP might be needed as a prediction factor for TNFi treatment. Despite this complexity, our regression model demonstrated good prediction as shown from the calibration plot and the ROC curve. We believe that our findings can contribute to prediction of the response to TNFi treatment in RA patients.

Abbreviations

CRP: c-reactive protein

DAS28: disease activity score using 28-joint count

ESR: erythrocyte sedimentation rate

GH: global health

RA: rheumatoid arthritis

RETN: resistin

RF: rheumatoid factor

SJC: swollen joint score

SNP: single nucleotide polymorphism

TJC: tender joint score

TNFi: tumor necrosis factor inhibitors

TNFRSF1B: TNF receptor superfamily member 1B

Declarations

Ethics Approval and Consent to Participate: This study was approved by the ethics committees (Ajou University Hospital: AJIRB-BMR-OBS-17-153 and Chungbuk National University Hospital: 2017-06-011-004) and patients gave their written informed consent. The study was conducted according to the principles of the Declaration of Helsinki (2013).

Consent for publication: Not applicable

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author, who has the ORCID identifier 0000-0002-9535-7314, on reasonable request.

Competing interest: The authors declare that they have no competing interests.

Funding: This work was supported by the Basic Science Research Program through National Research Foundation (NRF) funded by the Korea government (MSIP; Ministry of Science, ICT & Future Planning) (NRF-2017R1C1B5016202) and the Medical Research Center Program (2017R1A5A2015541) of the NRF funded by the Korean government (MSIP). The funding sources did not have a role in the design, conduct, and analysis of the study.

Authors' contributions

Nga Thi Trinh: Methodology, Formal analysis, Writing – Original Draft, Hyun Jeong Kim: Conceptualization, Methodology, Validation, Writing – Original Draft, Woorim Kim: Formal analysis, Investigation, Sang Oh Kang: Resources, Data curation, Kyung Hyun Min: Resources, Data curation Ha Rim Yeon: Resources, Data curation, Joo Hee Kim: Conceptualization, In Ah Choi: Resources, Data curation, Ju Yang Jung: Conceptualization, Hyoun Ah Kim: Supervision, Visualization, Writing – Review & Editing, Kyung Eun Lee: Writing – Review & Editing, Supervision, Project administration, Funding acquisition

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Figures

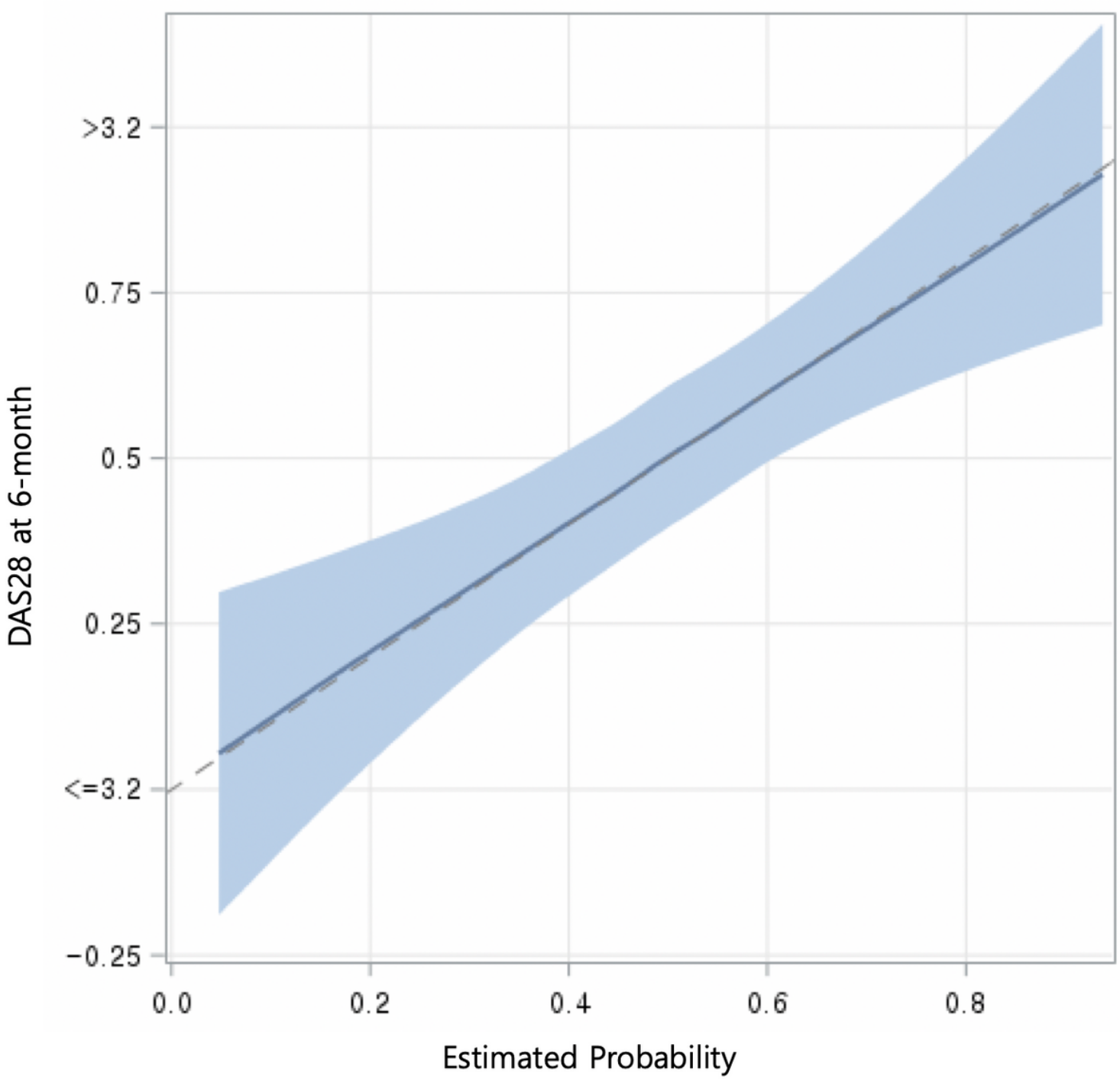

Figure 1

Calibration plot of the actual DAS28 at 6-months versus the model estimated probabilities of DAS28 at 6-months of TNF-α inhibitor treatment. The dotted 45 degree line represents perfect calibration such that the model estimated probability equals the actual proportion of patients with moderate-to-high disease activity at 6-months. The bold line is a nonparametric loess smooth of the points; this estimates the actual local proportion of patients with moderate-to-high disease activity. The shaded region is a 95% confidence interval of the loess smoother.

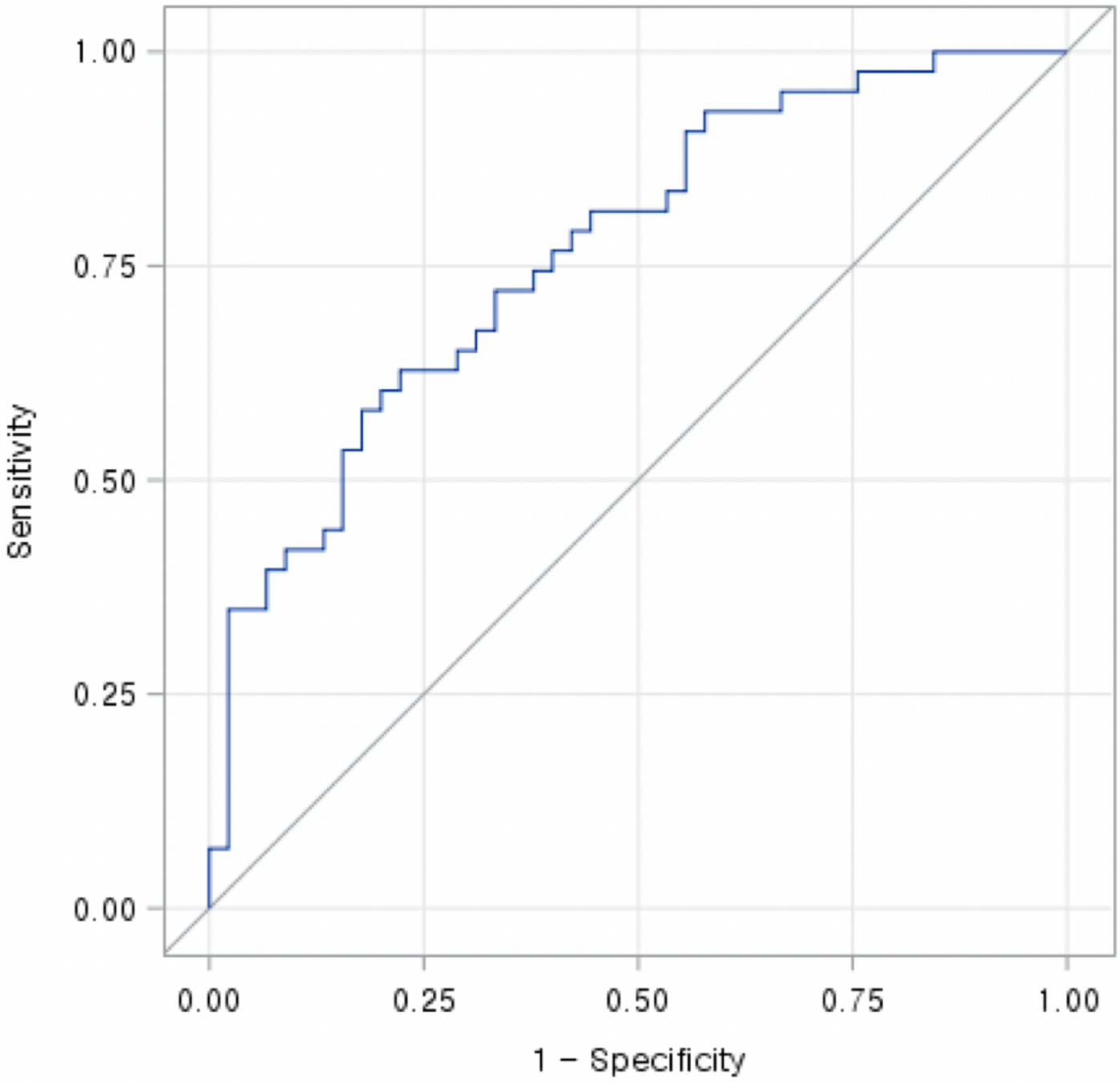

Figure 2

Area under the DAS28 curve for moderate-to-high disease activity related to TNF-α inhibitor treatment. AUC of DAS28 is 0.77 (95% CI, 0.67-0.87, P value < 0.0001).

Supplementary Files

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