Remission and low disease activity matrix tools: results in real-world rheumatoid arthritis patients under anti-TNF therapy

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ACTA REUMATOL PORT. 2020;45:245-252

ABSTRACT

Background: Remission/ low disease activity (LDA) are the main treatment goals in rheumatoid arthritis (RA) patients. Two tools showing the ability to predict golimumab treatment outcomes in patients with RA were published.

Objectives: To estimate the real-world accuracy of two quantitative tools created to predict RA remission and low disease activity.

Methods: Multicenter, observational study, using data from the Rheumatic Diseases Portuguese Register (Reuma.pt), including biologic naïve RA patients who started an anti-TNF as first-line biologic and with at least 6 months of follow-up. The accuracy of two matrices tools was assessed by likelihood-ratios (LR), sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and area under the ROC curve (AUC).

Results: 674 RA patients under first-line anti-TNF (266 etanercept, 186 infliximab, 131 adalimumab, 85 golimumab, 6 certolizumab pegol) were included. The median (IQR) age was 53.4 (44.7-61.1) years and the median disease duration was 7.7 (3.7-14.6) years. The majority were female (72%). Most patients were RF and/or ACPA positive (75.5%) and had erosive disease (54.9%); 58.6% had comorbidities. At 6-months, 157 (23.3%) patients achieved remission (DAS28 ESR < 2.6) and 269 (39.9%) LDA (DAS28 ESR ≤ 3.2). Area under the curve for remission in this real-world sample was 0.756 [IC 95% (0.713-0.799)] and for LDA was 0.724 [IC 95% (0.686 -0.763)]. The highest LR (8.23) for remission state was obtained at a cut-off ≥ 67%, with high specificity (SP) (99.6%) but low sensitivity (SN) (3.2%). A better balance of SN and SP (65.6% and 73.9%, respectively) was observed for a cut-off >30%, with a LR of 2.51, PPV of 43.3% and NPV of 87.6%.

Conclusion: In this population, the accuracy of the prediction tool was good for remission and LDA. Our results corroborate the idea that these matrix tools could be helpful to select patients for anti-TNF therapy.

Keywords: Rheumatoid Arthritis; Remission; Low disease Activity; Anti-TNF therapy; Matrix tools.

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INTRODUCTION

Cost-effectiveness of rheumatoid arthritis (RA) treatment is of growing importance. Tools that could help

on the selection of RA patients who will most likely respond to biologic disease-modifying anti-rheumatic drugs (DMARDs) would be highly valued. Nowadays, remission or low disease activity (LDA) are the main treatment targets. Several independent predictors of RA remission have been described in the literature, namely baseline clinical and laboratory characteristics, along with genetic markers[1-7].

Although patients with higher disease activity at baseline, erosive disease and/or anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) positive antibodies have more often the need to start a biologic treatment in a treat-to-target approach, these patients are less likely to achieve remission or LDA than others with less aggressive disease[8-9]. This adds complexity to clinical decisions regarding which patients should start anti-TNF treatment.

Two tools that showed the ability to predict the outcomes of golimumab treatment (50mg SC once monthly for 6 months) in patients with RA were published in *2016, by Vastesaeger N. et al*.[9] These matrices analysed data from GO-MORE (an open-label, multinational, prospective study in biologic naive patients with active RA [disease activity score 28 (DAS28) - erythrocyte sedimentation rate (ESR) >3.2] despite DMARDs therapy), and are based on a combination of six baseline characteristics, namely sex, presence/absence of comorbidities, age, health assessment questionnaire (HAQ) category, ESR and tender joint count (TJC)28.

These tools may be expanded to provide practical guidance in the selection of RA candidates for anti-TNF therapy. In order to confirm their possible role in clinical practice, it is fundamental to assess its applicability in external, real-world datasets.

Therefore, in this study, we aim to estimate the accuracy of remission and LDA matrix tools, published by *Vastesaeger N. et al.*, in patients included in the Rheumatic Diseases Portuguese Register (Reuma.pt).

METHODS

STUDY DESIGN

This is a multicenter, observational study, using data from Reuma.pt, founded in 2008 by the Portuguese Society of Rheumatology[10]. We included patients registered in 12 rheumatology centres, from 2008 until 2nd January 2019.

Patients meeting the 2010 ACR/EULAR criteria for RA were included. We could only use data from the centres that accepted to participate in the study, including exclusively their registered patients who had the six baseline characteristics (sex, presence/absence of comorbidities, age, health assessment questionnaire (HAQ) category, ESR and tender joint count (TJC)28) available for analysis, otherwise we could not apply the matrix model. The study protocol was approved by the Coordinator and Scientific Board of Reuma.pt and by the Ethics Committee of Centro Hospitalar e Universitário de São João.

All the patients gave written consent for having their data registered in Reuma.pt and used for investigational purposes.

SAMPLE

Inclusion Criteria: Biologic naïve RA patients who started an anti-TNF as first-line biologic and with at least 6 months of follow-up under anti-TNF therapy.

Exclusion Criteria: patients without information on any of the six baseline characteristics (sex, presence/absence of comorbidities, age, HAQ, ESR, TJC28) were excluded from the study.

TOOLS DESCRIPTION

The Matrix has a male and female version with clinical characteristics in lines and columns and is easy to apply. Once it is selected the Matrix corresponding to the patient's gender, a probability of remission or LDA is achieved by selecting the corresponding variable in the lines and columns of the matrix. The use of this tool is similar to the one used to calculate the cardiovascular risk issued by the European Society of Cardiology, with which most clinicians are familiar.

VARIABLES

Variables included in the matrix tools: We included the 6 baseline characteristics (sex, presence/absence of comorbidities, age, HAQ category, ESR and TJC28) in which the matrices were based. The comorbidities considered were the same proposed by *Vastesaeger* N.*et al.*

Remission and low disease activity definitions and other outcome measures: Remission was defined as a DAS28-ESR <2.6 and LDA as DAS28-ESR ≤3.2. EULAR response was defined as good if DAS 28 4v improvement (0-6 months) was > 1.2 and if DAS 28 4v at 6 months was ≤ 3.2; as moderate if DAS 28 4v improvement > 0.6 and ≤ 1.2 and DAS 28 4v at 6 months ≤ 5.1 or if DAS 28 4v improvement> 1.2 and DAS 28 4v at 6 months > 3.2; as no response if DAS 28 4v im-

provement ≤ 0.6 or if DAS 28 4v improvement > 0.6 and ≤ 1.2 but with DAS 28 4v at 6 months > 5.1. American College of Rheumatology (ACR) response is defined as a percentage improvement in tender and swollen joint count (68/66) and in at least 3 of the 5 remaining ACR core measures (patient global assessment of disease activity, physician global assessment of disease activity, patient pain scale, HAQ, acute phase reactants ESR or CRP). ACR20/ ACR50/ ACR70 response represents an improvement ≥ 20%/ ≥ 50%/ ≥ 70%, respectively.

Other clinical and demographic characteristics: disease duration (defined as the time between the diagnosis and the beginning of biologic therapy), RF and ACPA positivity, presence of erosive disease, extraarticular manifestations, smoking habits, C-reactive protein (CRP), patient global assessment (PGA), swollen joint count (SJC) 28 and DAS 28 4v at baseline and at 6 months. We also assessed HAQ, ESR, TJC28 at 6 months, ∅ESR (0-6 months), ∅DAS28 4vESR, ∅HAQ, and ∅TJC28.

STATISTICAL ANALYSIS

Matrices were applied to all patients through the equation models created by *Vastesaeger N. et al.*[9] The study was performed with complete case analysis.

For each patient, we obtained an individual probability of achieving remission state at 6 months of follow-up and another individual probability of attaining LDA. As gold standard we used the actual outcome at 6 months: remission, LDA or neither.

The accuracy of these matrix tools to predict the actual outcome was assessed using likelihood-ratios (LR), sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV) and area under the curve, with Stata® version 15.1. A better balance between SN and SP was carried out later (post-hoc analysis). Distributions were compared with Chi-square, Mann-Whitney, or Student's t-tests, as appropriate, and correlations were estimated using Spearman's correlation coefficients. All statistical tests other than diagnostic accuracy were performed using SPSS® 22.0. Accuracy estimates were obtained using Stata 15.1.

RESULTS

Six hundred and seventy-four RA patients under anti-TNF therapy as first-line biologic were included in our study. Their demographic and clinical characteristics are presented in Table I. Most patients were female (72%).

Two hundred and sixty-six were medicated with etanercept, 186 with infliximab, 131 with adalimumab, 85 with golimumab and 6 with certolizumab pegol. The median (IQR) age was 53.4 (44.7-61.1) years and the median disease duration was 7.7 (3.7-14.6) years. Most of them had RF and/or ACPA positivity (75.5%) and erosive disease (54.9%); 58.6% had comorbidities. Arterial hypertension (40.2%) and dyslipidaemia (28.4%) were the most reported comorbidities, followed by Sjögren syndrome (15.7%) and depression (12.7%).

At baseline, median (IQR) disease activity related values were: ESR 31 mm/hour (18-50), CRP 1.14 mg/dL (0.41-2.30), SJC28 7 (0-28), TJC28 10 (0-28), HAQ 1.5 (0-3). and PGA 62 (0-100). The median DAS28 ESR (IQR) was 5.57 (4.78-6.45).

At 6-months, median (IQR) disease activity related values were: ESR 19 mm/hour (10-33) mm/hour, CRP 0.4 mg/dL (0.12-1.00), SJC28 1 (0-28), TJC28 2 (0-28), HAQ 0.88 (0-3) and PGA 45 (0-100). The median (IQR) DAS28 ESR was 3.62 (2.66-4.66) (Table I).

At 6-months, 157 (23.3%) patients achieved remission and 269 (39.9%) LDA.

The median (IQR) predicted remission probability obtained in our sample was 23.3% (15.1-34.5). Moreover, 35.3% of the patients had a probability of attaining remission above or equal to 30%. Likewise, 17.7% obtained a predictive probability of remission above 40%. More than half (58.6%) had a probability of remission superior or equal to 20%. The median predictive probability LDA state was 40% (10-84%).

The AUC for the accuracy of the equations to predict remission in this real-world sample (Figure 1) was 0.756 [IC 95% (0.713-0.799)] and for LDA it was 0.724 [IC 95% (0.686 -0.763)]. SN, SP and LR are shown in (Table II). The highest LR (8.23) for remission state was obtained at a cut-off ≥ 67%, with high SP (99.6%) but low SN (3.2%). A better balance of SN and SP (65.6% and 73.9%, respectively) was observed for a cut-off >30%, with a LR of 2.51, PPV of 43.3% and NPV of 87.6% (Table II). Moreover, 20.6% attained a good EULAR response, 54.9% had a moderate response, and 24.5% did not achieve EULAR response. Concerning ACR response, although 50% did not achieve response, 27.5% achieved ACR 20 response, 14.7% ACR 50 and 7.8% ACR 70. Regarding EULAR (moderate and good response) and ACR response at 6 months, there were no differences between patients with predicted remission probabilities above or below

TABLE I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF OUR SAMPLE

Median (IQR) age (years)	53.4 (44.7-61.1)
Median disease duration	
(IQR); years	7.7 (3.7-14.6)
Sex	72% female
Erosive disease (%)	54.9%
Comorbidities (%)	58.6%
RF and/or ACPAs positivity (%)	75%
Smoking habits	Active smokers (10.4%); former smokers (N=8.6%); No smokers (54.4%); Unknown (26.6%)
Biologic therapy	Etanercept (39.5%) Infliximab (27.6%) Adalimumab (19.4%) Golimumab (12.6%) Certolizumab pegol (0.9%)
Median (IQR) ESR (mmh) (baseline / 6 months)	31 (18-50) / 19 (10-33)
Median (IQR) C-RP (mg/dL) (baseline / 6 months)	1.14 (0.41-2.30) / 0.40 (0.12-1.00)
Median (0-28) SJC28 (baseline / 6 months)	7 / 1
Median (0-28) TJC28 (baseline / 6 months)	10 / 2
Median (0-100) PGA (baseline / 6 months)	62 / 45
Median DAS28 ESR (IQR) (baseline / 6 months)	5.57 (4.78-6.45)/ 3.62 (2.66-4.66)
Median HAQ (0-3) (baseline / 6 months)	1.50 / 0.88

ACPAs, anti-citrullinated protein antibodies; CRP, C- reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; PGA, patient global assessment; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

30% (71.4%, 77%, p= 0.833; 48.1%, 50.7%, p= 0.286, respectively) (Figure 3). Patients with a higher probability of remission achieved lower ESR values at 6 months (Spearman's rho=-0.393). Interestingly, there were differences in ∅ESR (0-6 months) between groups with distinct probabilities of achieving remission calculated through the model equation (<10%; 10-19%; 20-29%, 30-39%; 40-49%; ≥ 50%) (Table III, Figure 2).

Clinically meaningful differences in mean ∅ DAS28 ESR, mean ∅ HAQ and mean ∅ TJC28 were also observed between these groups, although without statistical significance (Figure 2). Patients in the groups with lower probability of remission had a greater absolute variation of these parameters. In fact, the improvement of these variables was more substantial in the groups with lower predicted probability of remission.

DISCUSSION

According to *Vastesaeger N. et al.*, the matrices calculate the individual remission or LDA probability for active RA patients treated with golimumab as first-line biologic, based on the combination of six baseline factor[9]. To the best of the authors' knowledge, our study represents the first attempt to test these matrix tools in an independent and real-world sample. It is also the first to extrapolate it to any other anti-TNF agent. The AUC for remission/LDA in our sample was good, meaning that the accuracy of this tool to predict remission states in real-world patients treated with golimumab and other TNF inhibitors is good.

Demographics and baseline characteristics of our cohort were quite similar to the GO-MORE sample. The proportion of patients achieving remission was also comparable in both populations (23.3% in our cohort versus 23.9% in GO-MORE), as well as for LDA (39.9% versus 37.4%, respectively)

Similar to our results, GO-MORE data revealed that patients predicted to have the lowest chance of remission, who also had the highest disease activity at baseline, had the greatest absolute change in DAS28-ESR and HAQ scores between baseline and month 6. This

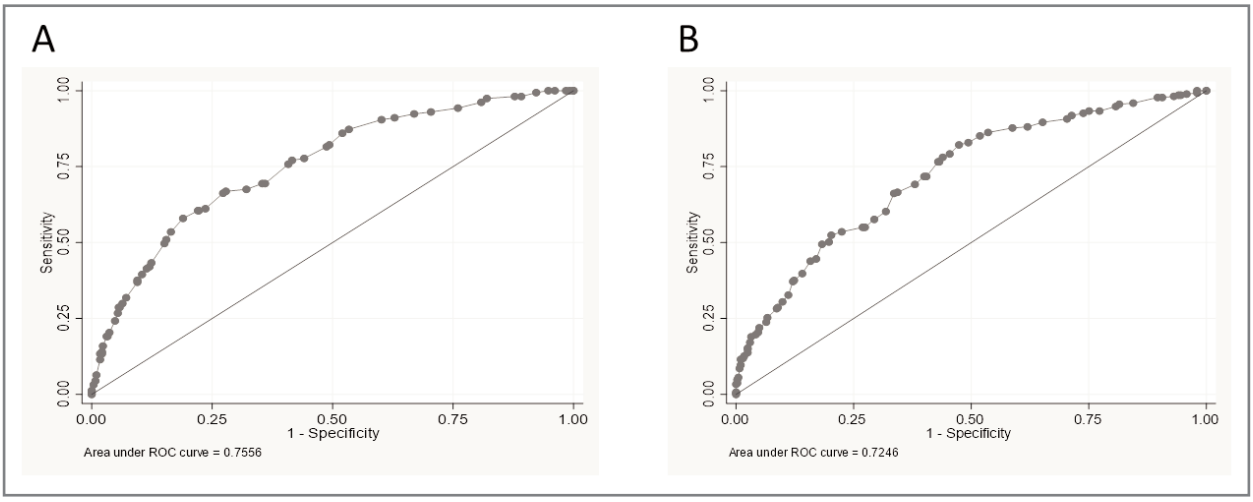

FIGURE 1. ROC curves measuring the accuracy of the equation model to predict remission (A) and low disease activity (B). ROC, receiver operating characteristic.

TABLE II. SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES AND LIKELIHOOD RATIO FOR DIFFERENT PREDICTED PROBABILITY CUT-OFFS FOR REMISSION AND LDA

Cut-off	SN	SP	PPV	NPV	LR
For remission					
20%	85.4%	49.5%	33.9%	91.8%	1.7
30%	65.6%	73.9%	43.3%	87.6%	2.5
40%	41.4%	88.6%	52.9%	83.1%	3.6
50%	24.2%	95.2%	60.3%	80.5%	5.0
67%	3.2%	99.6%	71.4%	77.2%	8.2
For low disease activity					
20%	95.5%	18.5%	43.9%	86.4%	1.2
30%	86.3%	46.4%	51.7%	83.6%	1.6
40%	69.1%	61.9%	54.7%	75.1%	1.8
50%	49.4%	81.7%	64.3%	70.9%	2.7
77%	4.8%	99.8%	92.9%	61.2%	19.6

SN: sensitivity, SP: specificity, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood-ratio.

suggests that patients who are least likely to attain remission improve the most.

Our study has some limitations. It is an observational study in which the choice of the most appropriate therapy for each patient and its successive adjustments were not previously predefined. Moreover, we also do not access therapeutic compliance. Although, the Reuma.pt and GO-MORE samples seem similar and it would be interesting to test different populations, they still represent independent samples that differ in the way that our population is treated with different anti-TNFs and the GO-MORE population is only with golimumab. In addition, we did not have access to the data of patients registered at Reuma.pt from those rheumatology centres that did not accept the invitation to participate in the study, being totally impossible to inform about any differences between the latter and our sample. Thus, we cannot totally exclude the possibility of a selection bias in our Reuma.pt sample.

Moreover, although AUC in the ROC analysis of the prediction models was relatively high, not all factors that may affect response were included in the model.

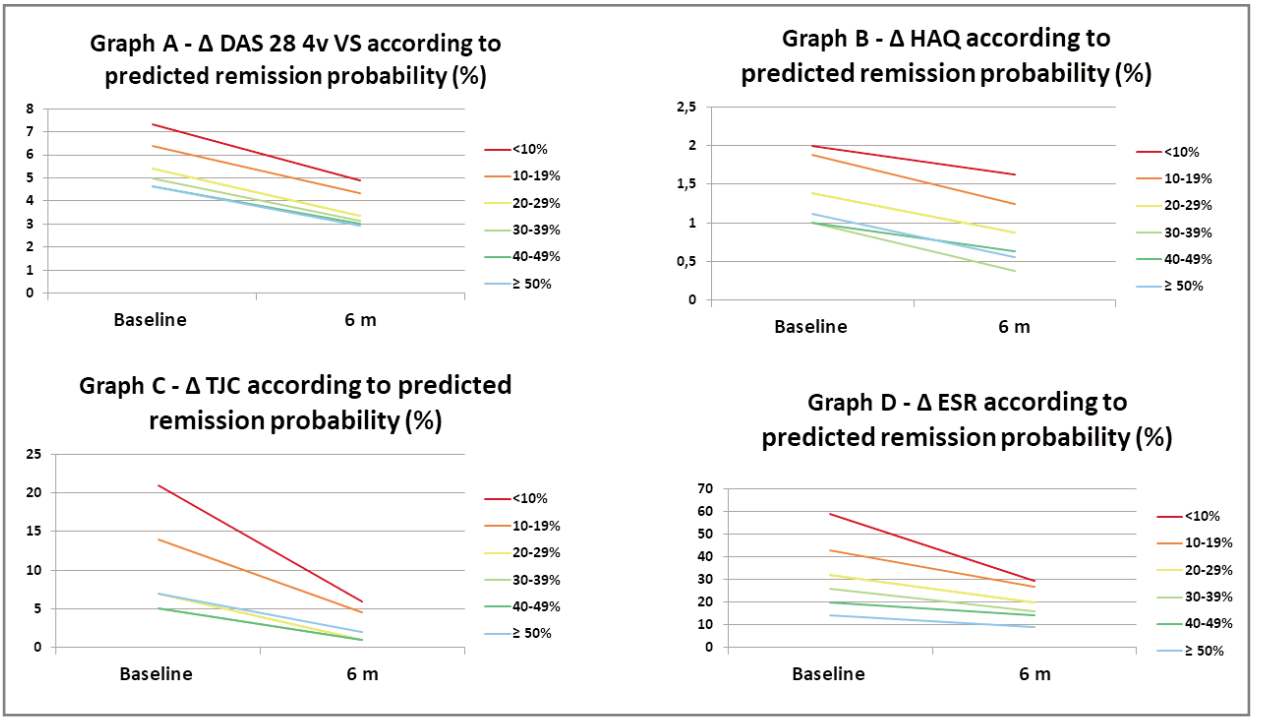

FIGURE 2. Relationship between predicted remission rate and ΔDAS-28 ESR 4v (Graph A), ΔHAQ (Graph B), ΔTJC28 (Graph C) and Δ ESR (Graph D)
DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; TJC, tender joint count.

TABLE III. DISEASE ACTIVITY RELATED VALUES COMPARISON BETWEEN PATIENTS IN DIFFERENT GROUPS ACCORDING TO THE PROBABILITY OF REMISSION CALCULATED BY EQUATION MODEL

Probability of remission state at 6 months	Total patients	Remission at 6 months (N)	No remission at 6 months (N)	Mean Δ DAS 28 4v VS (SD)	Mean Δ HAQ (SD)	Mean Δ TJC 28 (SD)	Median ∅ESR (min-max)
<10%	52	2	50	2.40 (0.99)	0.23 (0.72)	17 (13.17)	23 (-25 to 94)
10-19%	195	17	178	1.50 (1.11)	0.34 (0.63)	9.04 (8.68)	10 (-53 to 60)
20-29%	143	29	114	1.97 (1.03)	0.36 (0.51)	6.75 (6.70)	8.5 (-22 to 61)
30-39%	111	37	74	1.84 (0.95)	0.32 (0.69)	7.0 (5.59)	7.5 (-13 to 38)
40-49%	56	25	31	1.32 (1.44)	0.06 (0.42)	4.5 (3.66)	2.5 (-15 to 16)
≥ 50%	117	47	70	1.58 (1.30)	0.250 (0.696)	10 (9.84)	5.5 (-11 to 34)

DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; SD, standard deviation; TJC, tender joint count.

For example, patient expectations about the effectiveness of treatment are associated with remission, and this factor was not considered for analysis[11]. In addition, SJC28 is a more objective variable than TJC28, but it was not used in the model. Furthermore, it would be important to capture different outcomes, such as patient and physician-reported outcomes, other variables, namely amplitude of improvement, and better characterized comorbidities. Indeed, comorbidities play an important role as they contribute to disability, need for healthcare and, ultimately, mortality[12]. The comorbidities are not well defined in these tools once they all were given the same weight, independently of their severity. Some of them are quite common in the RA

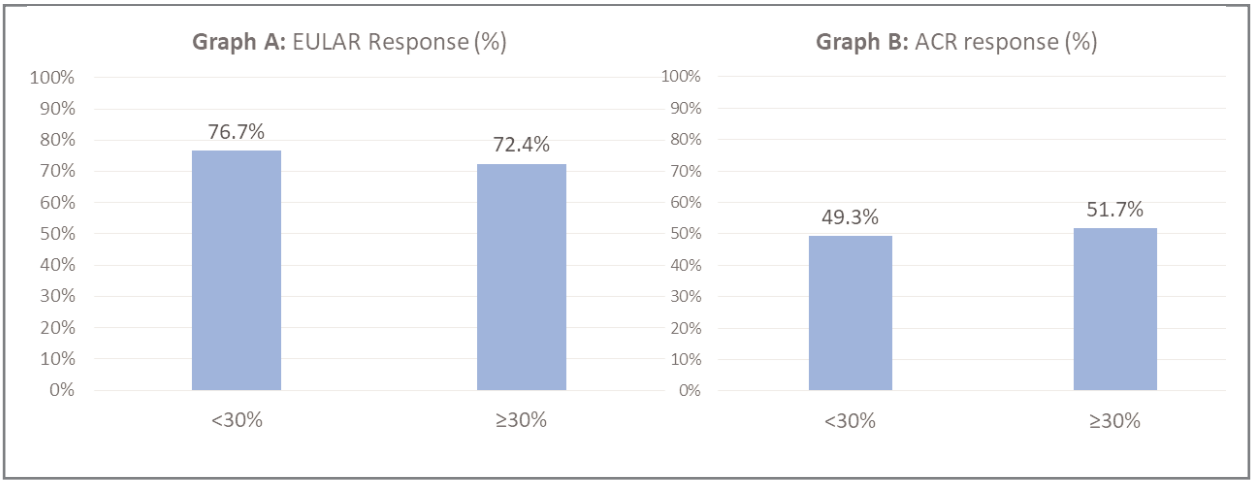

FIGURE 3. Proportion of EULAR (moderate and good) response (Graph A) and ACR 20, 50 and 70 response (Graph B) in patients with predictive remission value < and ≥ 30%
ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

population, and these matrix tools do not discriminate between them. In this context, a standardized approach to assess comorbidities is of the utmost importance, such as a comorbidity index[12]. However, the demonstrated accuracy of this tool for the treat to target strategy with a TNF antagonist can inform the rheumatologist and the patient about the choice of treatment after an inadequate response to methotrexate.

Another point is that patients who had the worst predicted values for remission were also those who improved the most. In line with this, the proportion of EULAR/ ACR response was similar between the group of patients with predicted remission probability < 30% and those with predicted remission probability ≥ 30%. Patients with higher baseline disease activity scores are least likely to achieve the (strict) remission definition at 6 months, as this may be a too short follow-up period for this type of patients. On the other hand, those with lower disease activity scores more easily achieve remission thresholds, even though the change in absolute terms is smaller. Patients with higher disease activity at baseline may never achieve the strict remission, persisting with moderate disease activity over time despite a clinically important improvement. This should be taken into account when setting the therapeutic goal for an individual patient.

Thus, these tools are not aimed at identifying patients who improve the most with treatment intervention, as they assess disease states and not a response to treatment. Although this information can be important to assess treatment efficacy, maybe clinical response tools would be more useful estimating those who would benefit most from biologic treatment.

Even so, these tools appear to be quite efficient to predict remission states. If physicians can transmit to patients what their estimated probability of attaining remission is, we hypothesize that expectations management may improve, contributing to better outcomes. We believe that this tool ensures a more structured patient information about their treatment outcomes, contributing for a shared decision between the rheumatologist and the patient during the prescription of biological agents, improving patient satisfaction and confidence.

CONCLUSION

Our results suggest that the matrix tools proposed by *Vastesaeger N et al.* could be helpful to predict the probability of RA patients attaining remission/LDA when treated with TNF antagonists, in daily clinical practice.

KEY MESSAGES

The matrix tools proposed by *Vastesaeger N et al* can be helpful to predict the probability of RA patients attaining remission/LDA when treated with TNF antagonists in daily clinical practice;

These matrix tools do not adequately identify patients who have the most substantial decrease in disease activity after treatment with TNF antagonists;

Patients with highest disease activity scores at baseline improve the most with TNF antagonists, but are less likely to attain remission at 6 months.

ACKNOWLEDGEMENTS

The authors thank Vastesaeger N for gently providing the formulas.

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