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Clinical science

# Development of prediction models to select older RA patients with comorbidities for treatment with chronic low-dose glucocorticoids

**Linda Hartman [1,2,*], José A. P. da Silva [3,4], Frank Buttgereit [5], Maurizio Cutolo[6], Daniela Opris-Belinski[7], Zoltan Szekanecz [8], Pavol Masaryk[9], Marieke J. H. Voshaar[10], Martijn W. Heymans[2], Willem F. Lems[1], Désirée M. F. M. van der Heijde [11], Maarten Boers[2]**

[1]Amsterdam Rheumatology and Immunology Center, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, The Netherlands
[2]Department of Epidemiology and Data Science, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, The Netherlands
[3]Reumatologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[4]Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[5]Department of Rheumatology and Clinical Immunology, Charité – University Medicine Berlin, Berlin, Germany
[6]Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy
[7]Department of Rheumatology, Carol Davila University, Bucharest, Romania
[8]Department of Rheumatology, Institute of Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary
[9]National Institute for the Rheumatic Diseases, Piešťany, Slovakia
[10]Tools Patient Empowerment, Amsterdam, The Netherlands
[11]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

*Correspondence to: Linda Hartman, Department of Rheumatology, Amsterdam UMC, location VUMC, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: l.hartman@amsterdamumc.nl

## Abstract

**Objective:** To develop prediction models for individual patient harm and benefit outcomes in elderly patients with RA and comorbidities treated with chronic low-dose glucocorticoid therapy or placebo.

**Methods:** In the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) study, 451 RA patients ≥65 years of age were randomized to 2 years 5 mg/day prednisolone or placebo. Eight prediction models were developed from the dataset in a stepwise procedure based on prior knowledge. The first set of four models disregarded study treatment and examined general predictive factors. The second set of four models was similar but examined the additional role of low-dose prednisolone. In each set, two models focused on harm [the occurrence of one or more adverse events of special interest (AESIs) and the number of AESIs per year) and two on benefit (early clinical response/disease activity and a lack of joint damage progression). Linear and logistic multivariable regression methods with backward selection were used to develop the models. The final models were assessed and internally validated with bootstrapping techniques.

**Results:** A few variables were slightly predictive for one of the outcomes in the models, but none were of immediate clinical value. The quality of the prediction models was sufficient and the performance was low to moderate (explained variance 12–15%, area under the curve 0.67–0.69).

**Conclusion:** Baseline factors are not helpful in selecting elderly RA patients for treatment with low-dose prednisolone given their low power to predict the chance of benefit or harm.

**Trial registration:** https://clinicaltrials.gov; NCT02585258.

**Keywords:** RA, prediction models, glucocorticoids, disease activity, joint damage progression, adverse events of special interest

**Rheumatology key messages**

- Low-dose prednisolone has strong effects on benefit and harm in RA patients ≥65 years of age.
- Other variables are of little clinical relevance to predict benefit or harm in RA patients.

## Introduction

RA is a systemic, inflammatory disease primarily located in the joints, resulting in pain, joint damage, functional disability and reduced quality of life. Treatment of RA is essential to prevent these outcomes, but the treatment itself may also result in adverse events (AEs) and comorbidity [1].

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Current RA treatment strategies are mostly treat to target [2] and consist of conventional DMARDs (cDMARDs), biologic DMARDs (bDMARDs), NSAIDs and glucocorticoids (GCs), such as prednisolone, in different doses and combinations [1]. Ideally, treatment strategies are tailored for individual patients, taking into account the respective estimates of the probabilities of risks and benefits [3]. With this knowledge, rheumatologists could be more efficient in selecting the most appropriate treatment and also in preventing and timely caring of AEs, thus reducing the disease burden for individuals and society [3].

RA treatment strategies are increasingly targeted on individual patients [4], but this remains difficult [5] because of the lack of individualized treatment guidelines [6, 7] and prediction models [3, 8, 9]. Currently, no prediction models for daily clinical practice are available [10]. In previous studies, a variety of predictive factors for benefit of antirheumatic drugs was found. However, most factors have a low predictive value [8] and they have not always been combined in a prediction model.

In the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) study, low-dose prednisolone (5 mg/day) given in addition to background treatment was proven more effective than placebo in reducing disease activity [11, 12] and damage progression [13] in a high-risk elderly RA trial population [14]. The co-primary outcome harm, which was expressed as the occurrence of at least one predefined AE of special interest (AESI), was higher for the prednisolone group [14].

Further information is needed to obtain more knowledge about individualized treatment strategies and the use of prediction models in clinical practice. Therefore, the aim of this study was to develop internally validated prediction models from the GLORIA study dataset to determine individual harm and benefit outcomes for elderly RA patients with comorbidities treated with chronic low-dose GCs.

## Methods

### Study design and population

The prediction models for harm and benefit outcomes were developed from the dataset of the 2-year, pragmatic, multicentre, investigator-initiated, double-blind, placebo-controlled, randomized GLORIA study. The GLORIA study was approved by the medical ethical committee of VU University Medical Center and all patients provided written informed consent. The study was executed according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

The study population consisted of 451 patients with RA [15, 16] with a 28-joint DAS (DAS28) $\geq$2.60 and age $\geq$65 years. Patients were recruited from 28 hospitals in seven European countries between June 2016 and December 2018. Patients were randomized to receive 5 mg/day prednisolone or matching placebo. All co-medications, except for oral GCs, were allowed. Details about the study have been reported previously [14, 17].

Models with an outcome at 2 years were developed in the dataset of the modified intention-to-treat population ($n = 444$). This comprised patients who took at least one capsule of study medication and had at least a baseline and follow-up assessment. Models with an outcome at 3 months were developed in the dataset of the per-protocol population ($n = 304$). This comprised patients from the above population who had complete data, $\geq$80% adherence, no modification of antirheumatic treatment and no protocol violations in the first 3 months of the study.

### Outcomes

Eight prediction models were developed (Fig. 1). The first set of four models disregarded study treatment and examined general predictive factors. The second set of four models was similar but examined the additional role of treatment (low-dose prednisolone). For each set of four models there are two for harm (occurrence of one or more AESIs after 2 years and the number of AESIs per year) and two for benefit [early response of disease activity (EULAR good response [18] or a 50% improvement in the ACR score [19] after 3 months and a lack of joint damage progression after 2 years (i.e. less than one progression over 2 years)]. Joint damage progression was measured with the Sharp–van der Heijde score [20]. AESIs included serious adverse events (SAEs) according to the GCP definition and the following ('other AESI'): any AE (except worsening of disease) leading to discontinuation; myocardial infarction, cerebrovascular or peripheral arterial vascular event; newly occurring hypertension, diabetes, infection, cataract or glaucoma requiring treatment or symptomatic bone fracture.

AESIs were recorded during study visits and adjudicated without knowledge of treatment allocation. The number of AESIs per year was calculated by dividing the total number of AESIs during the study by the study duration.

### Predictors

At baseline, several clinical measurements were performed and questionnaires regarding health and quality of life were collected. These variables were used as possible predictors. In preparation, to limit excessive statistical testing and false-positive results, 38 possible predictors were grouped into five predictor sets based on prior knowledge and first examined per set. The sets were termed, for example, 'personal' (e.g. age, gender) and 'disease' (e.g. disease activity, damage) (full list in Supplementary Data S1, available at *Rheumatology* online). These sets were applied in all models.

Two stratification factors applied in the study (start/switch antirheumatic drugs at baseline and prior use of GCs) were also assessed as possible predictors. Treatment centre was the third stratification factor, but this factor was not included for several reasons. First, there was large variability in the number of patients per centre. Second, it was not a significant random factor in the main analysis of the GLORIA study due to the small cluster effect. Finally, prediction models with a random factor quickly become too complex and hard to interpret.

### Missing data

Missing value analysis was used to examine the amount and patterns of missing data in the possible predictors and outcomes. Based on this analysis, we assumed that data were missing at random. Missing data were imputed with Bayesian single stochastic regression imputation (predictive mean matching) [21] for each of the first four models. We decided to include a maximum of 25 variables in the imputation model, i.e. the outcome measure, all variables with missing data and the variables with the highest correlation to the variables with missing data. These five variables were DAS28,

**Main prediction models**

| **Models 1-4**<br>**disregarding study treatment**<br>Outcome = a + b*factor | **to predict outcome:** | **Models 5-8**<br>**including study treatment**<br>Outcome = a + $b_1$*treatment + $b_2$*factor + $b_3$*treatment*factor |
|---|---|---|
| 1. | which patients have ≥1 AESI after two years | 5. |
| 2. | the number of AESIs per year | 6. |
| 3. | which patients have an early response | 7. |
| 4. | which patients have less than 1 point damage progression over two years | 8. |

**Exploratory prediction models**

| **Models 1-4**<br>**disregarding study treatment** | **to predict outcome:** | **Models 5-8**<br>**including study treatment** |
|---|---|---|
| 1. | which patients have ≥1 AE after two years | 5. |
| 2. | the number of AEs per year | 6. |
| 3. | which patients have ≥1 infection after 2 years | 7. |
| 4. | the number of infections after 2 years | 8. |

**Post-hoc prediction models**

Repeat all analyses with the adaptation of the following outliers:

- One outlier in the outcome AESI rate (52.1) was adjusted to the second highest value (19.2)
- Two outliers (111 and 154%) in the variable medication adherence measured with pill count were adjusted to 110%

Repeat all analyses with BMI as a categorical (low: <18.5, normal: 18.5-25.0, high: ≥25.0) instead of a continuous scale.

**Figure 1.** Overview of main, exploratory and post hoc prediction models

gender, count of active comorbidities, history of RA surgery and adherence measured with pill count. For the prediction model with the outcome 'early response' we used the DAS28 values that were imputed with single stochastic imputation by chained equations in the main GLORIA analysis [14].

## Statistical analyses

Linear and logistic multivariable regression models were used to develop the models. The strategy to develop models 1–4 (disregarding treatment) was as follows: starting with the first model (occurrence of one or more AESIs), the variables in the

first predictor set ('personal') were tested for significance ($P < 0.05$); this was repeated for the other predictor sets. Variables found significant in a set were further tested together for significance ($P < 0.05$) to build the final model. These steps were repeated for models 2–4. We chose backward selection as the most practical method given the large number of possible predictors.

The strategy to develop models 5–8 (including the effect of treatment) was as follows: starting with the first model (model 5; the occurrence of one or more AESIs including study treatment), interaction terms were made with all variables of the first predictor set ('personal') that were significant in model 1. Then, backward selection with these main effects (including the main effect of treatment) and interactions was run again and significant effects were retained ($P < 0.05$ for main effects, $P < 0.10$ for interactions; in case of significant interaction, their main effects always remained in the model regardless of significance). The procedure was repeated for the other predictor sets. Variables and interactions found significant in a set were further tested for significance to build the final model. These steps were repeated for the other models. All prediction factors were measured at baseline, unless indicated otherwise.

The strategy for the third ('comorbidities') and fourth ('medication') predictor set was slightly different. The variables 'count of active comorbidities' and 'Rheumatic Disease Comorbidity Index (RDCI)' in the 'comorbidities' predictor set were probably highly correlated. Therefore the tests for significance of the variables in the 'comorbidities' predictor set were done for all variables of the predictor set plus the variable 'count of active comorbidities' but excluding the variable 'RDCI', and then again for all variables of the predictor set plus the variable 'RDCI' but excluding the variable 'count of active comorbidities'. The same strategy was applied to the 'medication' predictor set and the variables 'medication adherence, measured with pill count' and 'medication adherence, measured with MMAS-8 questionnaire'. We compared the *P*-values of the variables in the differently composed predictor sets and studied if there were differences in the significance of the variables. Based on this information, we decided which of the collinear variables of the predictor sets 'comorbidities' and 'medication' to use. The required sample size for the models was calculated with the 'psampsize' package [22] in R (R Foundation for Statistical Computing, Vienna, Austria).

### Exploratory analyses

As exploratory analyses, eight prediction models with AEs or infection as outcome were developed (Fig. 1). Again, the first four models disregarded treatment allocation to examine general predictive factors. The second set of four models was similar but examined the additional role of study treatment. For each set of four models there were two for harm in general (occurrence of one or more AEs after 2 years and the number of AEs after 2 years) and two for infections (occurrence of one or more infections after 2 years and the number of infections after 2 years).

### Post hoc analyses

As post hoc analysis (Fig. 1), the outlier in the outcome AESI rate (52.1) was adjusted to the second highest value (19.2) because 52.1 was an unrealistically high value due to a patient with a few AESIs while the study participation was only 1 week. The two outliers (111% and 154%) in 'medication adherence measured with pill count' were adjusted to 110% [23].

To increase insight, we also performed analyses stratified for treatment in models where interaction terms proved significant (Supplementary Data S3, available at *Rheumatology* online).

### Performance of models

The performance of the final models was assessed with explained variance (Nagelkerke's $R^2$), calibration (Hosmer–Lemeshow test, $P \geq 0.05$ indicates a good model fit) and the amount of discrimination [concordance index (C-index); area under the receiver operating characteristics (AUC ROC) curve] for the models with a dichotomous outcome. For the models with a continuous outcome, the $R^2$ was calculated to assess the quality of the models.

### Internal validation

The final models were internally validated with the 'validate' function in R [24]. Each model was bootstrapped 250 times [25] and backward selection was used to run the models. The bootstrap-corrected C-index (AUC), bootstrap-corrected explained variance ($R^2$) and calibration slope (shrinkage factor) were reported to indicate the extent of optimism of each model.

SPSS version 26 was used to impute missing data, perform the model exercise and test the quality of the models. R version 4.0.3 was used to calculate the sample size and to internally validate the models.

## Results

In total, 444 of 451 randomized patients were included in the analyses because 2 patients never started study medication and 5 patients discontinued before the first follow-up. About two-thirds of the patients completed the 2-year trial. Reasons for discontinuation were 'other' reasons [including coronavirus disease 2019 (COVID-19)-related access issues and unwillingness to continue the trial, 20%], AEs (14%) and lack of efficacy of the study medication (4%) [14].

Data on predictors were quite complete except for anti-CCP status (13% missing; Table 1). For outcome, many patients had missing values for joint damage progression (42%), as this was measured only at baseline and 2 years.

The required sample size was 438 patients if the model contained 20 variables, $R^2$ was set at 0.3 and the shrinkage factor was set at 0.8 [22].

A few variables were found to be predictive for the outcome in one of the models regardless of treatment, and likewise in models that included effect of treatment, with partial overlap (Table 2, Fig. 2). The results of the post hoc analyses for the models with a benefit outcome and the models to predict occurrence of an AESI did not differ from the original analyses. For the models to predict the number of AESIs per year, only the results of the post hoc analyses were shown, because these results were seen as more reliable than the results including the extremely high outliers. The interpretation and the relationship with the outcome of the predictors in all final models (Table 2) are presented in Fig. 2 (see also Supplementary Data S2, available at *Rheumatology* online).

### Performance of models

The performance of the models was sufficient (Table 3). For example, for the model with the outcome having one or more AESI including treatment interaction, 12% of the variance was explained by the predictive variables in the model. The

**Table 1.** Outcomes and possible baseline predictors including the percentages of missing values for the intention-to-treat population ($n = 444$), split for study treatment

| Outcomes | Prednisolone ($n = 221$) | Missing, % | Placebo ($n = 223$) | Missing, % |
|---|---|---|---|---|
| Occurrence of one or more AESI after 2 years, *n* (%) | 131 (59) | 0 | 108 (48) | 0 |
| Number of AESIs per year, median (IQR), range | 0.5 (1.1), 0–10.9 | 0 | 0.0 (1.0), 0–19.2 | 0 |
| Early response of disease activity after 3 months[a], *n* (%) | 69 (44) | 0 | 31 (30) | 0 |
| Lack of joint damage progression after 2 years, *n* (%) | 102 (46) | 40 | 86 (39) | 44 |
| Predictors | | | | |
| Personal factors | | | | |
| Age, years, mean (SD), range | 73 (5), 65–87 | 0 | 73 (5), 65–88 | 0 |
| Female, *n* (%) | 158 (72) | 0 | 154 (69) | 0 |
| Education level[b], *n* (%) | | 1 | | 1 |
| Lower | 170 (77) | | 186 (83) | |
| Higher | 49 (22) | | 35 (16) | |
| Smoking, *n* (%) | 32 (15) | 1 | 29 (13) | 0 |
| Alcohol use, *n* (%) | 100 (45) | 1 | 98 (44) | 0 |
| BMI, mean (SD), range | 27.2 (4.5), 19.1–41.9 | 3 | 27.2 (4.5), 18.2–44.1 | 2 |
| Blood pressure, mmHg, mean (SD), range | 99 (12), 68–141 | <1 | 98 (11), 73–142 | <1 |
| Disease factors | | | | |
| DAS28, mean (SD), range | 4.43 (1.04), 1.87–7.43 | 0 | 4.61 (1.06), 2.05–7.71 | 0 |
| Disease duration, years, mean (SD), range | 11 (10), 0–45 | <1 | 10 (10), 0–52 | 1 |
| RF positive, *n* (%) | 146 (66) | 1 | 149 (67) | 4 |
| Anti-CCP positive, *n* (%) | 118 (53) | 13 | 133 (60) | 12 |
| Joint damage ≥0.5, *n* (%) | 173(78) | 10 | 177(79) | 8 |
| Joint damage score, | 20 (35), 0–196 | 10 | 17 (33), 0–276 | 8 |
| Arthritis helplessness index (range 5-25)[c], mean (SD), range | 15 (3), 8–25 | 2 | 15 (3), 5–24 | <1 |
| RAID score (range 0–10)[c], mean (SD), range | 4.6 (2.1), 0.2–9.0 | 1 | 4.9 (2.3), 0–10 | 1 |
| Comorbidities | | | | |
| Presence of one or more active comorbidity, *n* (%) | 208 (94) | 0 | 208 (93) | 0 |
| Presence of one or more active specific GC-related comorbidity, *n* (%) | 105 (48) | 0 | 119 (53) | 0 |
| Number of active comorbidities, mean (SD), range | 4.2 (2.9), 0–14 | 0 | 3.9 (3.0), 0–15 | 0 |
| RDCI (range 0–9)[c], mean (SD), range | 1.9 (1.4), 0–6 | 0 | 1.9 (1.5), 0–7 | 0 |
| Occurrence of one or more prior comorbidity, *n* (%) | 144 (65) | 0 | 140 (63) | 0 |
| Occurrence of one or more prior specific GC-related comorbidity, *n* (%) | 48 (22) | 0 | 42 (19) | 0 |
| Number of previous comorbidities, mean (SD), range | 2.2 (2.4), 0–11 | 0 | 2.0 (2.5), 0–14 | 0 |
| Occurrence of one or more prior comorbidity related to infections, *n* (%) | 29 (13) | 0 | 27 (12) | 0 |
| Number of current medications for comorbidities, mean (SD), range | 2.6 (2.6), 0–10 | 0 | 2.9 (2.9), 0–16 | 0 |
| History of joint surgery for RA, *n* (%) | 44 (20) | 0 | 31 (14) | 0 |
| Number of patient symptoms (range 0–53), mean (SD), range | 8.0 (5.7), 0–28 | 2 | 7.8 (6.7), 0–40 | 3 |
| Medication | | | | |
| Number of concomitant medications, mean (SD), range | 5.6 (3.7), 0–16 | 0 | 5.8 (4.0), 0–19 | 0 |
| Previous use of DMARDs, *n* (%) | 63 (29) | 0 | 67 (30) | 0 |
| Previous use of biologics, *n* (%) | 17 (8) | 0 | 28 (13) | 0 |
| Current use of biologics, *n* (%) | 38 (17) | 0 | 34 (15) | 0 |
| Medication adherence (%; measured with pill count) at 3 months, mean (SD), range | 89 (20), 0–103 | 0 | 89 (22), 0–110 | 0 |
| Medication adherence (measured with MMAS-8 questionnaire) at 3 months[d](range 0–8), mean (SD), range | 7.2 (1.0), 3.8–8.0 | 2 | 7.2 (1.1), 1.0–8.0 | 1 |
| Start/switch antirheumatic drugs (stratification factor), *n* (%) | 24 (11) | 0 | 24 (11) | 0 |
| Prior use of GCs (stratification factor), *n* (%) | 104 (47) | 0 | 103 (46) | 0 |
| Health and daily functioning | | | | |
| Difficulty in daily functioning (HAQ; range 0–3)[c], mean (SD), range | 1.27 (0.68), 0–2.75 | 1 | 1.15 (0.72), 0–2.75 | <1 |
| Utility (quality of life index value; range –0.45–1)[d], mean (SD), range | 0.66 (0.21), −0.21–1 | 2 | 0.69 (0.18), −0.16–1 | 1 |
| VAS about health (range 0–100)[d], mean (SD), range | 61 (19), 5–100 | 1 | 63 (19), 3–100 | 1 |
| | 38 (8), 22–58 | 2 | 39 (8), 17–59 | 1 |

(continued)

**Table 1.** (continued)

| Outcomes | Prednisolone ($n = 221$) | Missing, % | Placebo ($n = 223$) | Missing, % |
|---|---|---|---|---|
| SF-36 physical component summary score (range 0–100)[d], mean (SD), range | 48 (10), 24–68 | 2 | 49 (10), 20–68 | 1 |
| SF-36 mental component summary score (range 0–100)[d], mean (SD), range | | | | |

[a] The outcome early response of disease activity after 3 months was calculated for the per-protocol population ($n = 304$); prednisolone, $n = 156$; placebo, $n = 148$.
[b] Lower education level is defined as primary or secondary school, higher education level is defined as higher education (non-university and university).
[c] A higher score means a worse outcome.
[d] A higher score means a better outcome.
IQR: interquartile range; RAID: rheumatoid arthritis impact of disease; MMAS-8: 8-item Morisky Medication Adherence; EQ-5D: European Quality of Life 5-Dimensions questionnaire; VAS: visual analogue scale; SF-36: 36-item Short Form Health Survey.

**Table 2.** Predictors included in the final prediction models, including and excluding the effect of study treatment and interactions

| Variable[a] | OR/β[b] | 95% CI (OR/β) | *P*-value |
|---|---|---|---|
| **AESI yes/no** | | | |
| Number of previous comorbidities/conditions[c] | 1.17 | 1.08, 1.28 | <0.001 |
| BMI[d] | 0.95 | 0.91, 0.99 | 0.027 |
| Number of concomitant medications[e] | 1.06 | 1.00, 1.11 | 0.044 |
| Joint damage[f] | 1.67 | 1.01, 2.76 | 0.045 |
| **AESI yes/no + treatment effect[g]** | | | |
| Study treatment | 104.59[f] | 3.05, 3584 | 0.010 |
| Number of previous comorbidities/conditions[c] | 1.19 | 1.09, 1.30 | <0.001 |
| Joint damage[h] | 3.25 | 1.50, 7.02 | 0.003 |
| Joint damage[h] * study treatment | 0.31 | 0.11, 0.89 | 0.029 |
| No prior treatment with biologics | 0.95 | 0.45, 2.36 | 0.946 |
| No prior treatment with biologics * study treatment | 0.19 | 0.03, 1.05 | 0.056 |
| **AESI rate** | | | |
| Medication adherence (pill count) at 3 months[i] | −0.03 | −0.04, −0.03 | <0.001 |
| No start/switch antirheumatic treatment | −0.87 | −1.47, −0.27 | 0.005 |
| **AESI rate + treatment effect[g]** | | | |
| Study treatment | −3.78 | −6.50, −1.06 | 0.007 |
| Medication adherence (pill count) at 3 months[i] | −0.04 | −0.06, −0.03 | <0.001 |
| Medication adherence (pill count) at 3 months[i] * study treatment | 0.02 | 0.00, 0.04 | 0.014 |
| No start/switch antirheumatic treatment | −1.30 | −2.16, −0.45 | 0.003 |
| No start/switch antirheumatic treatment * study treatment | 0.98 | −0.22, 2.18 | 0.109 |
| **Early response** | | | |
| Number of concomitant medications[e] | 0.89 | 0.83, 0.95 | 0.001 |
| Difficulty in daily functioning (HAQ) score[j] | 0.50 | 0.30, 0.82 | 0.006 |
| Utility (quality of life score, EQ-5D)[k] | 0.11 | 0.02, 0.62 | 0.013 |
| **Early response + treatment effect[g]** | | | |
| Study treatment | 3.19 | 1.88, 5.40 | <0.001 |
| Number of concomitant medications[e] | 0.90 | 0.84, 0.97 | 0.005 |
| Difficulty in daily functioning (HAQ) score[j] | 0.66 | 0.45, 0.97 | 0.034 |
| **No damage progression** | | | |
| Joint damage score[l] | 0.98 | 0.97, 0.99 | <0.001 |
| Prior occurrence of comorbidities/conditions related to glucocorticoid use | 2.87 | 1.43, 5.76 | 0.003 |
| Utility (quality of life score, EQ-5D)[k] | 0.14 | 0.03, 0.56 | 0.006 |
| Medication adherence (pill count) at 3 months[i] | 0.98 | 0.97, 1.00 | 0.030 |
| **No damage progression + treatment effect[g]** | | | |
| Study treatment | 1.74 | 1.09, 2.79 | 0.020 |
| Joint damage score[l] | 0.98 | 0.97, 0.99 | <0.001 |

[a] All variables are measured at baseline, unless indicated otherwise.
[b] The OR is presented for the logistic models (all outcomes except AESI rate) and the $\beta$ is presented for linear models (outcome AESI rate).
[c] Number of previous comorbidities/conditions: OR refers to a change of one extra previous comorbidity/condition.
[d] BMI: OR refers to a change of one point in BMI.
[e] Number of concomitant medications: OR refers to a change of one extra previous concomitant medication.
[f] OR is probably artificially inflated by the small number of observations of patients who had no joint damage, zero previous comorbidities and were previously treated with biologics.
[g] The models including the variables that were found to be predictive in the models with interaction with study treatment stratified for prednisolone and placebo (without interaction terms) can be found in Supplementary Data S3, available at *Rheumatology* online.
[h] Joint damage: OR refers to joint damage (>0.5 point) at baseline.
[i] Medication adherence (pill count) at 3 months: OR refers to 1% more medication adherence (measured with pill count) after 3 months of study treatment.
[j] Difficulty in daily functioning (HAQ) score: OR refers to a change of one point in HAQ score (range 0–3).
[k] Utility (quality of life score, EQ-5D): OR refers to a change of one point in utility score (range −0.446–1).
[l] Joint damage score: OR refers to a change of one point in joint damage score (range 0–448).
OR: odds ratio; EQ-5D: EQ-5D: European Quality of Life 5-Dimensions questionnaire.

AUC was 0.67, which means that the ability to discriminate between patients with and without an AESI was poor.

## Internal validation

The models were internally validated and the performance of the models was reasonable (Table 4). For example, for the model to predict which patients have one or more AESI after 2 years (including treatment interaction), the C-index was 0.64. This means that in 64% of the patients the prediction rule discriminates well between a prednisolone and placebo patient to develop an AESI. The explained variance ($R^2$) was 0.09, which means that 9% of the variance in the outcome can be explained by the predictive factors in the model. The calibration slope (shrinkage factor) was 0.87, indicating that overoptimism is expected if you apply the prediction rule in a new RA population with the same characteristics.

## Exploratory analyses

In the exploratory analyses, for the model with the AE rate as an outcome, a change of antirheumatic treatment at

**A**

| To predict: / Baseline predictive factor: | Harm | |
|---|---|---|
| | ≥1 AESI | # AESIs |
| More prior comorbidities | | |
| Higher BMI | ? | |
| More medication | | |
| More joint damage | | |
| More adherence | | |
| No change of antirheumatic treatment at baseline | | |

**B**

| To predict: / Baseline predictive factor: | Harm | | | |
|---|---|---|---|---|
| | ≥1 AESI | Prednisolone effect | # AESIs | Prednisolone effect |
| More prior comorbidities | | | | |
| Higher BMI | ? | | | |
| More medication | | | | |
| More joint damage | | **Neutralized*** | | |
| More adherence** | | | | |
| No change of antirheumatic treatment at baseline | | | | **Neutralized*** |
| No prior treatment with biologicals | | | | |

**C**

| To predict: / Baseline predictive factor: | Benefit | |
|---|---|---|
| | Early response | No damage progression |
| More medications | | |
| More joint damage | | |
| More adherence | | ? |
| More disability (HAQ) | | |
| Better QoL (EQ-5D) | ? | |
| Prior occurrence of GC-related comorbidity | | |

**Figure 2.** Interpretation of predictors in the harm and benefit models disregarding and examining the effect of study treatment (i.e. low-dose prednisolone). For the benefit model, only the model disregarding the effect of study treatment is shown (panel C), because no effect of study treatment was found. **(A)** Baseline predictive factors for harm, disregarding the effect of prednisolone (red: an increase in harm; green: a decrease in harm; white: the variable is not included in the model; ?: a counterintuitive relationship). **(B)** Baseline predictive factors for the harm prediction model and the interaction with prednisolone, with the addition of the variables that were found to be predictive in the models disregarding the effect of prednisolone (red: an increase in harm; green: a decrease in harm; white: the variable is not included in the model; ?: a counterintuitive relationship). **(C)** Baseline predictive factors for the benefit prediction model, disregarding the effect of prednisolone (red: less benefit; green: more benefit; white: the variable is not included in the model; ?: a counterintuitive relationship). Full colour figure is available at *Rheumatology* online. *Neutralized means that the addition of prednisolone to the model counteracted the adverse effect of the baseline predictive factor. In other words, more joint damage is associated with an increased likelihood of at least one AESI, but this increase is gone after the addition of prednisolone to the model. Similarly, no change of antirheumatic treatment at baseline is associated with a greater number of AESIs, but this increase is gone after the addition of prednisolone to the model. **More adherence was associated with a lower number of AESIs; the addition of prednisolone to the model partially counteracted this effect. EQ-5D: European Quality of Life 5-Dimensions questionnaire

baseline appeared to be predictive (Supplementary Data S4, available at *Rheumatology* online). Serious infections were rare, with 35 patients reporting a serious infection, thus we did not develop a model with serious infection as an outcome.

## Discussion

In the many models studied in the GLORIA study dataset, apart from study treatment, we found only a few variables to be predictive for the outcome. The relationship of these factors with the outcomes were weak, sometimes counterintuitive and thus

**Table 3.** Quality of the prediction models disregarding and including the interaction with treatment

| Prediction model | Nagelkerke's $R^{2a}$ | Hosmer–Lemeshow test[a] | AUC ROC[a] | $R^2$ |
|---|---|---|---|---|
| AESI yes/no | 0.07 | 0.98 | 0.59 | – |
| + treatment effect | 0.12 | 0.96 | 0.67 | – |
| AESI rate | – | – | – | 0.16 |
| + treatment effect | – | – | – | 0.15 |
| Early response | 0.09 | 0.54 | 0.65 | – |
| + treatment effect | 0.14 | 0.87 | 0.69 | |
| Damage progression | 0.04 | 0.46 | 0.57 | – |
| + treatment effect | 0.13 | 0.43 | 0.69 | – |

[a] Nagelkerke's $R^2$, Hosmer–Lemeshow test and the AUC ROC could only be calculated for the prediction models with a dichotomous outcome.

**Table 4.** Internal validation of the prediction models

| Prediction model | C-index[a] | $R^2$ | Shrinkage factor[a] |
|---|---|---|---|
| AESI yes/no | 0.62 | 0.06 | 0.83 |
| + treatment effect | 0.64 | 0.09 | 0.87 |
| AESI rate | – | 0.11 | – |
| + treatment effect | – | 0.08 | – |
| Early response | 0.62 | 0.06 | 0.88 |
| + treatment effect | 0.68 | 0.12 | 0.93 |
| Damage progression | 0.73 | 0.16 | 0.92 |
| + treatment effect | 0.68 | 0.12 | 0.97 |

[a] The C-index and shrinkage factor could only be calculated for the prediction models with a dichotomous outcome.

of little clinical relevance. In other words, we were unable to build a useful model to identify patients at greater risk of benefit or harm of low-dose prednisolone treatment.

Previous literature is scarce, with only a few previous studies with data of limited quality and generalizability. Variables to predict the occurrence or number of AESIs have not been examined in other studies as far as we know. A few studies found that the infection risk increased after GC [26, 27] or biologic treatment [26, 28]. These findings are in line with our finding that low-dose prednisolone increased the number of infections and that prior biologic treatment was slightly predictive for this outcome. Current bDMARD treatment was not found to be predictive, probably caused by the small number of patients treated. In previous studies [27, 29, 30], Rheumatoid Arthritis Observation of Biologic Therapy risk score [26] and serious infections (with variable definitions) were strongly associated with increasing age, comorbidities, higher GC dosages and prior serious infections. We did not specifically ask about prior serious infections in the medical history, so these are most likely underreported. Nevertheless, it is likely that such a history will increase the risk of subsequent infections in our population.

Our observation that difficulties in daily functioning show a slightly lower chance of early response is in line with previous findings with anti-TNF therapy [31] or sustained remission [32]. In previous studies, a variety of other variables were found to predict treatment response. These variables include the presence of comorbidities [33], male [34, 35] or female [36] gender, older age [34], higher tender [34] or swollen [32] joint counts, lower number of erosions [32], RF [34] or anti-CCP [34] positivity, obesity [37, 38], smoking [39], shorter disease duration [36], methotrexate treatment [31], prior DMARD use [36] and lower baseline disease activity [36, 40]. We also assessed most of these variables, but they were not predictive for early response in our dataset.

The predictive power of the baseline joint damage score on damage progression has been confirmed by other studies [41–44]. Previous studies found a variety of predictive variables for damage progression. Disease duration [43], anti-CCP [8, 39, 41, 42, 45] or RF [43–47] positivity, smoking [39] and female gender [8, 45] were found as predictors in previous studies, but not in our study. In addition, patient global assessment of health [43], erosions [39, 46], ESR [39, 41, 43, 45–47], CRP [39, 44], anti-CCP2 positivity [48], elevated MMP-3 levels [42], citrullinated fibrinogen positivity [48], high anti-mutated citrullinated vimentin titres [48], multibiomarker disease activity scores [49] and DRB1*04 genes [46] were found as predictors. Our models did not include these variables, as some were already part of the DAS28 measurement and the others were not determined.

Reasons for differences between our study and previous studies regarding predictive factors could be the higher mean age (73 years compared with 50–55 years in most studies), and consequently more comorbidities and frailty, a longer disease duration and heterogeneity in antirheumatic treatment between studies. Frailty was indirectly captured by prior comorbidities and questionnaires about health and daily functioning. The absence of age itself as a predictor is best explained by the limited spread since all patients were ≥65 years of age.

## Performance of the models

The performance of the models including the effect of study treatment was sufficient, with explained variances ranging from 12 to 15% and AUC values around 0.68. A possible explanation for the moderate performance is the limited number of predictors in all models. As in most studies, the explained variance was low. This means that the predictive factors only explain a small part of the variance between patients.

A few other studies have examined the performance of their prediction models in an RA population. In two studies, models to predict damage progression were developed with an AUC of 0.77 [10] and 0.87 [42], somewhat better than the 0.69 in our study. However, in two other models the AUC was worse: 0.60 [48] and 0.61 [49]. Guillemin *et al.* [43] developed a model with an explained variance of 77%, which was high compared with the explained variance of 13% in our model. This might mean that we missed some variables that are predictive for joint damage. However, three of the five predictors in that study were also assessed as predictors in our model. An additional explanation might be the overall low rate of damage progression, limiting the power to detect associations.

Regarding early response, the AUC was 0.62 in a model to predict treatment response [40] and 0.66 in a model to predict remission [32] compared with 0.69 in our model. For the model with occurrence or number of AESIs as the outcome, no performance measurements from other studies are available.

The limitations of most previous studies are that the quality of the prediction models was not assessed and that the models were not internally or externally validated.

## Strengths and limitations

A unique characteristic of our study is that the prediction models apply specifically to an elderly RA population, while previous studies targeted their models on younger patients. Another strength is that we assessed a high number of possible predictors in a pre-planned way to limit the amount of

statistical testing. Moreover, we did not focus on one outcome, but developed models with four different outcomes that are all relevant for RA patients. In addition, the pragmatic design of the trial with permission to use all antirheumatic medication leads to a situation that is similar to clinical practice and thus high generalizability of the findings. A final strength of our study is that we performed an internal validation with bootstrapping techniques to correct for optimism.

The most important limitation is of course the moderate performance of the models, with variables that are of questionable clinical relevance. Another limitation is that we had missing data at the end of the study, mainly in the outcome joint damage progression, because of premature discontinuation and missed assessments due to COVID-19. This was addressed through imputation. A final limitation is that we were unable to test the generalizability of our models by external validation. We only internally validated our models with bootstrapping techniques. This method is not as good as external validation, but internal validation is seen as a good alternative [50].

## Conclusion

We previously reported that low-dose prednisolone has strong effects in RA patients ≥65 years of age, with a favourable balance of benefit and harm. In the current study we found little or no evidence to suggest that other factors are important to predict risks and benefits of such treatment in elderly RA patients.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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