PREDICTION OF 3 MONTHS MTX NON-RESPONSE (DAS28>3.2) IN EARLY RHEUMATOID ARTHRITIS

Validated prediction model to identify DMARD-naïve rheumatoid arthritis patients with high risk of insufficient response to MTX.

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RESULT

Probability of MTX non-response after 3 months of treatment: 71.7 %

Based on the following parameters:

| Parameter             | Value  |
|-----------------------|--------|
| Baseline DAS28        | 4.9 points |
| HAQ                   | 0.4 points |
| BMI                   | 22 kg/m2 |
| Erythrocyte folate    | 720 nmol/L |
| Smoking               | Yes    |

Disclaimer: Calculations alone should never dictate patient care, and are no substitute for professional judgement.
OUTCOME STRATIFICATION

Result interval 60 to 80

Based on a probability cut-off of 70% risk of insufficient response to methotrexate, calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were:

Sensitivity: 43%   Specificity: 86%   PPV: 75%   NPV: 61%

Result interval 70 to 90

Based on a probability cut-off of 80% risk of insufficient response to methotrexate, calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were:

Sensitivity: 8%   Specificity: 96%   PPV: 67%   NPV: 52%

CONDITIONAL INFORMATION

An interaction term was activated and added to the model:

Based on the provided input, a two-way interaction term between HAQ and erythrocyte folate (OR = 0.23, 95% CI 0.06 – 0.86) was automatically added to the model. This interaction term was found to significantly contribute to the model, meaning that low erythrocyte folate concentrations (<750 nmol/L) significantly predicted insufficient response when HAQ values were <0.6.

RESULT INTERPRETATION

How this model should be used:

This prediction model could assist in identification of insufficient responders at diagnosis. For patients with high probability of insufficient response to MTX, additional biologics or JAK-inhibitors could be prescribed. For those with low probabilities of insufficient response, these expensive treatments could be spared. This distinction at diagnosis could save precious time for insufficient responders, allowing earlier control of disease activity resulting in better long-term outcomes.

Model performance:

Discriminative power of the model was assessed through evaluating the area under the receiver operating characteristic curve (AUC). The AUC of the model was 0.75 (95% CI: 0.69 – 0.81), indicating that the model correctly classified patients in 75% of the cases.

Goodness-of-fit between the predicted probabilities and observed values was tested using the Hosmer-Lemeshow test. The associated P-value was 0.634, indicating good model fit.

Decisions on appropriate risk cut-offs:

Taking into consideration the “window of opportunity” for optimal treatment we consider it crucial to adequately treat insufficient MTX responders with additional bDMARDs/tsDMARDs. Therefore, our goal for this prediction model was to identify as many insufficient responders as possible, while at the same time attempting to restrict the use of bDMARDs/tsDMARDs to those patients who really need them, hence to avoid misclassification of sufficient responders. Considering this, a cut-off probability of 70% (of insufficient response) could be chosen.

At this cut-off, 75% of patients classified as insufficient responder match actual insufficient responders (PPV) and could be treated with additional bDMARDs/tsDMARDs. Additionally, at this cut-off 86% of all sufficient responders would be correctly classified as such (specificity) and could be spared additional treatment.
| Cut-off values for probabilities of Insufficient response (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-------------------------------------------------------------|----------------|----------------|---------|---------|
| 10                                                          | 1              | 0              | 49      | NA      |
| 20                                                          | 96             | 15             | 62      | 80      |
| 30                                                          | 88             | 48             | 62      | 81      |
| 40                                                          | 87             | 51             | 63      | 80      |
| 50                                                          | 73             | 71             | 71      | 73      |
| 60                                                          | 58             | 79             | 73      | 66      |
| 70                                                          | 43             | 86             | 75      | 61      |
| 80                                                          | 8              | 96             | 67      | 52      |
| 90                                                          | 1              | 100            | 1       | 51      |

Probabilities of insufficient response were calculated according to the prediction model. Model performance measures were calculated for different cut-off values (column 1). PPV = positive predictive value, NPV = negative predictive value.

*Figure 1. Model performance given different risk cut-offs for insufficient response (Gosselt et al, 2020)*

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