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Predicting clinical response in psoriatic arthritis through integrative analysis of transcriptomics and proteomics

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Abstract

Background The therapeutic response to disease-modifying antirheumatic drugs (DMARDs) remains relatively low in psoriatic arthritis (PsA), leading to delayed disease control and frequent treatment switches. Predictive biomarkers may enable personalized treatment and earlier disease control. We aimed to identify transcriptomic and proteomic markers for tofacitinib or comparator treatment outcomes and develop a prediction model to support treatment decisions in PsA patients.

Methods Baseline $CD4^+$ T-cell transcriptomics and proteomics data from 80 PsA patients in the development cohort of the TOFA-PREDICT trial were analyzed. The TOFA-PREDICT trial is a four-arm randomized trial that was designed to discover profiles of PsA patients that predict response to tofacitinib as compared with methotrexate or etanercept. Forty DMARD-naïve patients were randomized to tofacitinib or methotrexate, and 40 patients who failed DMARD-treatment were randomized to add-on tofacitinib or etanercept. Treatment response was defined as reaching minimal disease activity at 16 weeks. Feature selection was performed in the full cohort and in each treatment subgroup using XGBoost and sPLS-DA. Using different modeling strategies, prediction models were developed that combine clinical variables with transcriptomic, proteomic, or integrated multi-omics predictors. The models were cross-validated and compared using AUC-ROC and their ability to identify the most promising treatment (tofacitinib versus control) per patient.

Results Fifty percent of patients responded to treatment. Eighteen transcriptomic, ten proteomic, and two clinical predictors were selected. The integrated multi-omics model incorporating treatment–predictor interactions achieved the highest performance (AUC = 0.70 ± 0.19; variation (SD) in treatment-effects in patients 15.2% ± 14.8%). The selected proteins were significantly interconnected (p-value = 3.41E-5) and related to immune system processes.

Conclusions Integrated baseline gene and protein expression profiles combined with clinical variables can predict treatment response and identify differential treatment effects between individual patients. These findings demonstrate the potential of omics-guided personalized treatment for patients with PsA.

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Keywords Psoriatic arthritis, Transcriptomics, Proteomics, Prediction, Biomarkers

Background

Psoriatic arthritis (PsA) is a chronic and complex inflammatory disease with heterogeneous manifestations across multiple clinical domains. In patients with PsA, early initiation of effective therapy can lead to a faster treatment response, thereby improving short-term and long-term outcomes [1]. Various therapeutic options are available, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [1]. Currently, PsA treatment is guided by recommendations published and updated by four international organizations [1–4]. These recommendations are based on the severity of the disease across the clinical domains of PsA and failure of previous treatment.

Despite advances in treatment options and guidelines that have improved the management of PsA, response rates remain relatively low. For example, only 17% of patients on csDMARDs and 57% on bDMARDs achieve minimal disease activity (MDA) in PsA [5]. A delay in appropriate treatment of PsA is associated with poorer clinical outcomes, such as irreversible joint damage and reduced quality of life [6, 7]. Moreover, repeatedly adjusting therapies increases the risk of treatment side effects and increases treatment costs [8, 9]. Thus, finding factors that predict treatment response for specific therapies is an important priority in addressing the unmet need for personalized treatment in PsA patients.

A promising approach to improve current guidelines for PsA treatment, which rely only on clinical characteristics, is to incorporate predictive biomarkers [8, 10–13]. Omics technologies enable us to analyze RNA (transcriptomics), proteins (proteomics), lipids, and metabolites (metabolomics) in patient samples in great detail. These omics data can be used to search for predictive biomarkers of treatment response in PsA patients, as well as biomarkers associated with the underlying pathogenic mechanisms. Such markers may function as innovative screening tools (diagnostic or predictive biomarkers) or potential therapeutic targets [14, 15].

At present, several candidate predictive biomarkers for treatment response in PsA have been reported [10, 16–22]. Proposed biomarkers include pre-treatment levels of IL-17F [17], COMP, MMP-3 [18, 19], plasma IL-6 [18, 20], VEGF [18], pyridinoline, adiponectin, PAP, and factor VII [21]. Furthermore, several (epi)genetic and cellular biomarkers have shown predictive value for treatment response [22]. However, the clinical applicability of these biomarkers remains limited, as studies have focused on different treatments and outcome measures. Moreover, there are no reports of models that can predict the effectiveness of one specific treatment compared with another, which would be helpful in clinical decision-making.

The aim of our research was to evaluate the potential of transcriptomics, proteomics, and integrated multi-omics data to predict the effectiveness of specific treatments for individual patients with PsA. Baseline transcriptomic and proteomic data from the TOFA-PREDICT discovery cohort were analyzed [23]. Building on a recently developed prediction model based on only clinical predictors [24], this study assessed the potential of omics data to improve prediction further, thereby supporting the development of personalized treatment strategies for patients with PsA.

Methods

Study design and participants

Baseline data from the discovery cohort of the multicenter TOFA-PREDICT trial were used (EudraCT: 2017–003900-28) [23]. All patients included in this study fulfilled the Classification criteria for Psoriatic Arthritis (CASPAR) [25], had a PsA disease duration of at least eight weeks, and had active peripheral arthritis (≥ 2 swollen and ≥ 2 tender joints). The study included patients in two groups: 40 DMARD-naïve (DN) patients and 40 DMARD-failing (DF) patients. DN patients had no history of csDMARD, bDMARD, or tsDMARD use and were randomized (1:1) to tofacitinib (TOFA) or methotrexate (MTX). DF patients did not respond sufficiently to csDMARD treatment (prior use of one bDMARD, excluding etanercept (ETN), was allowed). These patients continued csDMARD background therapy and were randomized (1:1) to add-on TOFA or ETN. All patients provided written informed consent. Demographic and clinical variables were collected at baseline and/or at follow-up visits (Fig. 1A). The study was carried out in compliance with the Declaration of Helsinki and was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (MREC reference number: NL63439.041.17). Further details of the study protocol have been described previously [23].

Outcome

The response to treatment was determined after 16 weeks of treatment and was defined as attaining minimal disease activity (MDA) [26]. This is a validated composite measure for PsA that evaluates skin disease (body surface area (BSA) of psoriasis), arthritis (66 swollen and 68 tender joint counts), enthesitis (Leeds Enthesitis Index,

LEI), and patient-reported outcomes (visual analog scale, VAS) for pain, patient VAS for global assessment of disease activity, and the Health Assessment Questionnaire (HAQ).

Blood sampling

At baseline, blood samples were collected in lithium heparin (Li-Hep) tubes for cell isolation and transcriptomics and in clot activator (gel) tubes for serum preparation and proteomics. For serum preparation, blood was allowed to clot for 30 min, centrifuged at 1500 × g for 10 min at room temperature, aliquoted, and stored at −80 °C until further use.

For transcriptomics, cells were isolated from Li-Hep blood via density gradient centrifugation using Ficoll-Paque Plus (400 × g for 25 min at 20 °C). After two washing steps, a portion of the peripheral blood mononuclear cells (PBMCs) was stored at −196 °C for future analysis. The remaining PBMCs were used for cell subset isolation using an autoMACS; the fractions (B cells, mDC cells and monocytes) as well as the remaining peripheral blood lymphocytes (PBL) were stored at −196 °C. For transcriptomic analysis, the PBL fraction was thawed, and $CD3^+CD4^+$ T-cells were isolated by fluorescence-activated cell sorting (FACS) using CD4 PerCP-Cy5.5 (see Supplementary Fig. 1 for the gating strategy). The $CD4^+$ T-cell fraction was lysed in RLT buffer and stored at −80 °C until further use.

mRNA sequencing

Next-generation mRNA sequencing of $CD4^+$ T cells was performed by GenomeScan B.V. (Leiden, The Netherlands). Total RNA was isolated using the MagNA Pure 96 with the Cellular RNA Large Volume Kit. The RNA quality and quantity were assessed by the Fragment Analyzer (Agilent DNF-472T33 (15 nt) HS RNA Kit). Next, the samples were prepared according to the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (NEB #E7760S/L) protocol. Briefly, mRNA was extracted from high-quality total RNA using oligo-dT magnetic beads, followed by fragmentation into 300–500 bp fragments and complementary DNA (cDNA) synthesis. Sequencing adapters were ligated to cDNA fragments, followed by PCR amplification. Paired-end sequencing was performed on the Illumina NovaSeq 6000 platform. Paired-end reads were aligned to the human reference genome (Ensembl GRCh38.p13), and the number of reads mapped to each annotated gene was quantified.

Low-count genes were filtered out to keep only genes with at least 10 reads in 20 samples. Samples with more than 40% of genes with zero counts were omitted. The raw expression counts were normalized for library size and dispersion using the DESeq2 R package (version 1.42.1) [27]. A DESeq2 object was created with sex included as a covariate in the design formula. Regularized log transformation (blind = FALSE) was applied to stabilize variance across the range of mean expression values. The resulting normalized expression matrix was used for all downstream analyses. Principal component analysis (PCA) was performed to identify potential outliers.

Serum proteomic profiling

Relative serum expression levels of 364 unique proteins were measured using the Proximity Extension Assay (PEA) technology at the Olink Analysis Facility (Uppsala, Sweden) [28]. Proteins were measured across four panels targeting inflammation, metabolism, cardiometabolic, and cardiovascular III (CVD III) proteins. Following standardized quality control procedures performed at the Olink facility, protein levels were reported as normalized protein expression (NPX) on a $\log_2$ scale. NPX values were further normalized using inter-plate controls to account for within- and across-batch variations. Proteins with more than 75% missing values were removed. Measurements below the protein-specific limit of detection (LOD) were substituted with 80% of the LOD. Missing values were imputed via the missForest R package (version 1.5) with 100 trees and a maximum of 100 iterations [29]. Each panel was imputed separately. PCA was performed to identify potential outliers.

Predictor selection

Two models were developed to predict treatment response: one using transcriptomic and clinical data and one using proteomic and clinical data. Predictor selection was performed independently for each model. All transcriptomic and proteomic-based markers were combined with 14 baseline clinical variables: sex, age, BMI, current smoking status, PsA disease duration, use of topical steroids, history of bDMARD use, presence of nail psoriasis, LEI, presence of dactylitis, BSA, Disease Activity Index for Psoriatic Arthritis (DAPSA), HAQ, and VAS for physician global assessment. A subset of omics and clinical features was selected for model development, as described in the following paragraphs.

Feature selection was performed on the total cohort and on each treatment group (i.e., TOFA (DN and DF combined), MTX, and ETN) separately to find both general and treatment-specific predictors (Fig. 1B). Predictor selection was performed via two complementary multivariate techniques: eXtreme Gradient Boosting (XGBoost, *xgboost* R package version 1.7.8.1) and sparse Partial Least Squares Discriminant Analysis (sPLS-DA, *mixOmics* R package version 6.26.0) [30, 31]. XGBoost is a tree-based method that can capture non-linear patterns and complex predictor interactions, whereas sPLS-DA identifies sparse, linear-based combinations of predictors through regression. Moreover, both models handle

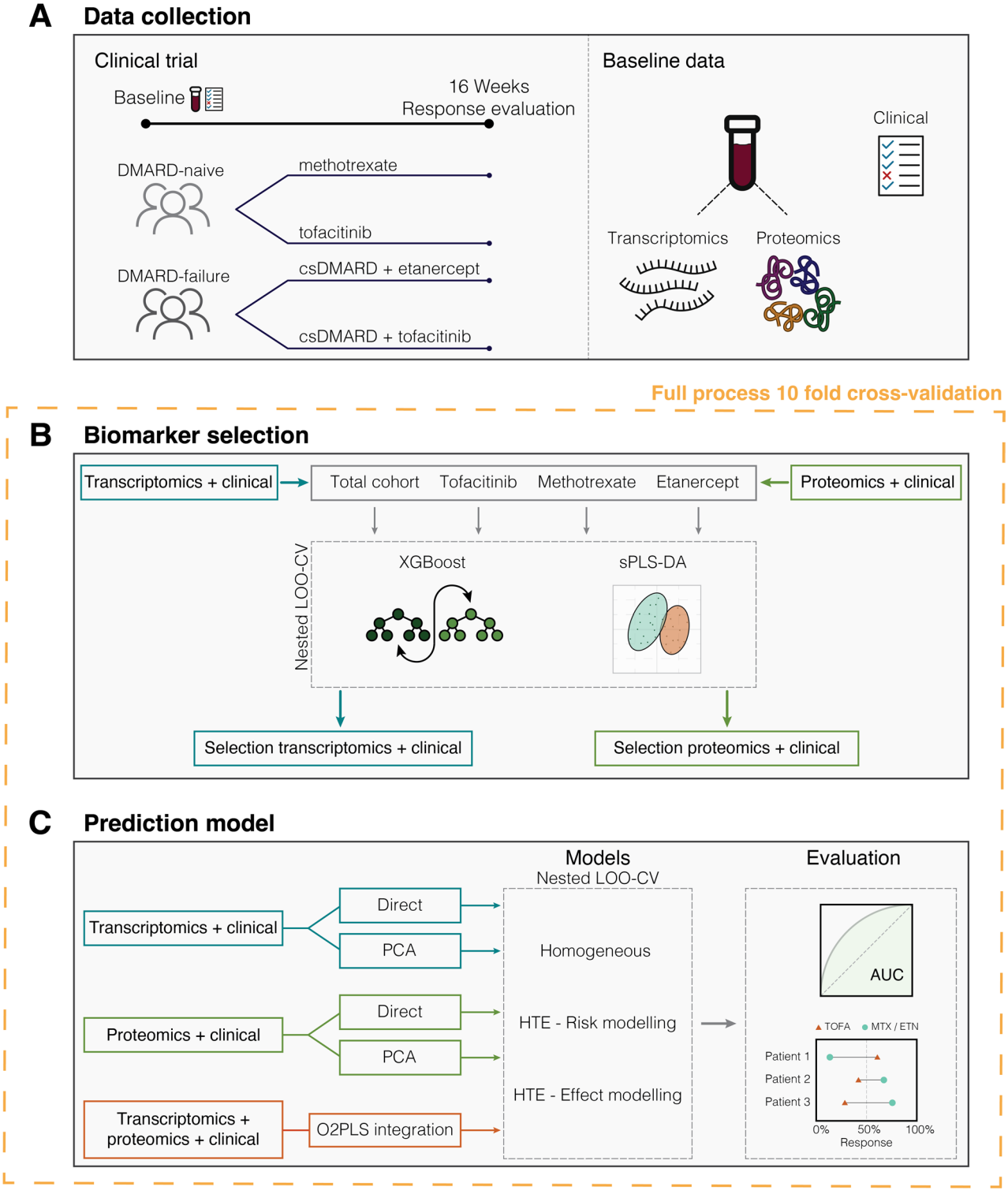

Fig. 1 Overview of the study design, data collection, and analytic workflow used to develop predictive models for treatment response in psoriatic arthritis. **A** Study design and data collection. **B** After preprocessing, feature (biomarker) selection was performed using sPLS-DA and XGBoost on the transcriptomics data combined with clinical data, and separately on the proteomics data combined with clinical data. Feature selection was performed in the total cohort and each treatment subgroup. **C** Three strategies were explored for incorporating the selected biomarkers into prediction models: (1) using the features directly, (2) applying principal component analysis (PCA) to reduce dimensionality before modeling, and (3) performing multi-omics integration using O2PLS to derive joint and specific components. After each strategy, three types of treatment effect prediction models were trained using ridge regression: a homogeneous treatment effect model (HOM), a heterogeneous treatment effect model (HTE) with risk modeling (Risk), and an HTE with effect modeling (Effect). Model performance was evaluated via ROC-AUC and the predicted differential response across treatment options (tofacitinib (TOFA) versus methotrexate (MTX) or etanercept (ETN)). The orange dashed square indicates the part embedded in the full-process 10-fold cross-validation

correlated features differently. Taking variables selected by either method reduces method-specific selection bias.

XGBoost models were tuned using a hyperparameter grid search and evaluated through five times repeated five-fold cross-validation (5 × 5FCV), optimizing the area under the receiver operating characteristic curve (AUC-ROC). The most important predictors in the model (relative gain ≥ 0.75) were selected. In each subgroup analysis, the selection was capped at three predictors to prevent overfitting and to keep the total number of predictors in the final models manageable.

sPLS-DA was applied to scaled and centered data. The model parameters (number of components and number of variables per component) were optimized through 5 × 5FCV, with the Mahalanobis distance for class prediction and the AUC as the performance metric. The predictors were ranked according to their Variable Importance in Projection (VIP) scores. To ensure that at least one relevant predictor was selected in each treatment subgroup, the lowest of the four subgroup-specific maximum VIP scores was set as a global threshold. Thereafter, a maximum of three predictors were selected per subgroup.

Predictor variables selected by XGBoost or sPLS-DA from either the total cohort or treatment subgroup analyses were used to develop the prediction models. The treatment arm (as a four-level categorical variable) was used as a covariate in all the prediction models to enable treatment and disease status-specific prediction.

To predict response, three integration strategies for using the selected transcriptomic, proteomic, and clinical predictors in the prediction models were explored. First, the selected predictors were directly used in model development (see below). Second, to reduce dimensionality, PCA was applied separately to the selected transcriptomic and proteomic features. The principal components explaining at least 80% of the total variance were then used as predictors in the models. Third, since a fully integrated approach was previously found to yield superior predictions [32], we employed two-way orthogonal partial least squares (O2PLS) to statistically integrate the selected transcriptomic and proteomic markers [33]. The estimated joint and omics-specific latent components were then used as predictors in model development. Details on the fitting of the O2PLS model (*OmicsPLS* R package version 2.0.5) are described in Supplementary Information S1.

Model development

Our main objective was to develop a model that can predict individual response probabilities for treatments that are compared and, as such, identify the therapy with the highest chance of response for an individual patient. For this purpose, we evaluated three effect-modeling approaches: a so-called homogeneous treatment effect (HOM) model and two so-called heterogeneous treatment effect (HTE) models – risk modeling and effect modeling (Fig. 1C) [34]. The HOM assumes that the relative treatment effect is constant across all patients; however, the absolute size of the predicted individual treatment effect can still vary due to differences in baseline risk resulting from variations in predictor values between patients. The HTE models assume heterogeneous treatment effects across patients. In the HTE risk modeling approach (HTE-risk), it is assumed that the risk variables influence the treatment effect proportionally across all the treatments via one interaction term between the linear predictor of the HOM model and the treatment. Finally, the HTE model with effect modeling (HTE-effect) is a fully heterogeneous treatment effect model that includes interactions between all predictors and treatment. Because the HTE–effect model can lead to many coefficients and potential overfitting, an elastic net regularization step was employed to select only the most relevant predictor–treatment interactions before estimating this model. To minimize the risk of overfitting, the models were developed and evaluated with nested cross-validation (CV); leave-one-out CV (LOOCV) was used for both the inner and outer loops. All models were implemented using *nestedcv* (version 0.7.9), with λ_{1se} chosen as the penalty.

Model evaluation

To compare the performance of the models, the area under the curve (AUC) of the receiver operating characteristic curve was used. Furthermore, the models were applied to estimate, for each patient, the probability of a response to TOFA versus MTX in DN patients and to TOFA versus ETN in DF patients. A larger difference in the predicted probability between two treatments indicates a stronger preference for one of the two treatments, which is particularly important in clinical practice to help decide on the most suitable treatment option for a patient. On the other hand, if almost no variation in the difference in treatment effects is predicted, such a model will not affect clinical decision-making.

Currently, no validation dataset is available. To approximate the performance of the predictive models on a future validation dataset, the entire modeling pipeline – including predictor selection, data integration, and model development – was embedded in a full process tenfold cross-validation framework (as indicated in Fig. 1). More details on this full-process tenfold CV are described in Supplementary Information S2.

Biological exploration of selected markers

Enrichment analyses provide insights into the functional roles and biological relevance of the selected transcriptomic and proteomic markers. A protein–protein

interaction (PPI) network was constructed via STRING-db (Search Tool for the Retrieval of Interacting Genes, version 12) to visualize known and predicted physical and functional associations between proteins [35].

Results

Patients

The baseline patient characteristics of DN and DF patients were generally comparable, although, as expected, age and disease duration were slightly lower in the DN group (Table 1). MDA was achieved in 50% of all patients (DN-MTX $n = 10$; DN-TOFA $n = 10$; DF-ETN $n = 12$; DF-TOFA $n = 8$).

Clinical and demographic data were complete. mRNA sequencing was performed on 62 samples with sufficient RNA material (17 from the DN tofacitinib group and 15 from each of the other three treatment groups), resulting in gene expression data of 14,482 genes from the CD4 + T-cell subset after preprocessing. Proteomics data were measured for all patients. After preprocessing, the final dataset consisted of 350 proteins. PCA did not reveal any samples as outliers in either transcriptomics or proteomics.

Predictors

Transcriptomic and proteomic biomarkers (including clinical predictors) identified by XGBoost and/or sPLS-DA in the different (sub)groups as most important for predicting response are presented in Supplementary Tables 1 and 2. For the transcriptomic data, 18 mRNA markers were selected: ENSG00000272668, −180,581, −178,295, −136,830, −219,201, −078687, −287,837,

Table 1 Baseline characteristics

	Total cohort	DMARD-naïve patients		DMARD-failure patients	
	All treatments ($n = 80$)	Tofacitinib ($n = 20$)	Methotrexate ($n = 20$)	Tofacitinib + csDMARD ($n = 20$)	Etanercept + csDMARD ($n = 20$)
Demographics and medical history					
Age (years)	51.3 ± 11.5	49.2 ± 10.6	47.8 ± 10.8	54.8 ± 13.8	53.4 ± 10.0
Female	32 (40)	5 (25)	12 (60)	9 (45)	6 (30)
BMI (kg/m^2)	28.2 ± 4.9	29.1 ± 5.2	27.4 ± 5.6	29 ± 4.1	27.4 ± 4.3
Current smoking	9 (11.3)	5 (25)	2 (10)	1 (5)	1 (5)
Psoriatic arthritis duration (years)	1.3 (0.1–10)	0.1 (0.1–1.4)	0.1 (0–0.5)	11.3 (4.8–18.9)	5.5 (1.3–16.8)
Topical steroid use	5 (6)	2 (10)	1 (5)	1 (5)	1 (5)
bDMARD history	4 (5)	0 (0)	0 (0)	1 (5)	3 (15)
Disease activity					
BSA (%)	1 (1–3)	1 (1–3)	2 (1–4)	1 (0–2)	1 (1–4)
Current nail psoriasis	53 (66.3)	14 (70)	13 (65)	10 (50)	16 (80)
Current dactylitis	20 (25)	6 (30)	4 (20)	4 (20)	6 (30)
Current enthesitis	21 (26.3)	4 (20)	5 (25)	8 (40)	4 (20)
Leed Enthesitis index					
0	59 (73.8)	16 (80)	15 (75)	12 (60)	16 (80)
1	11 (13.8)	2 (10)	2 (10)	5 (25)	2 (10)
2	8 (10)	1 (5)	3 (15)	2 (10)	2 (10)
4	2 (2.5)	1 (5)	0 (0)	1 (5)	0 (0)
HAQ score	0.6 (0.4–1.1)	0.6 (0.2–1.1)	0.9 (0.3–1.5)	0.8 (0.5–1.1)	0.6 (0.4–0.9)
Tender Joint Count 68	6 (4–10)	6 (4–10)	7 (5–12)	4 (2–8)	6 (5–11)
Swollen Joint Count 66	4 (3–9)	3 (3–7)	6 (4–9)	4 (2–5)	5 (3–10)
CRP (mg/dL)	0.3 (0.1–1.1)	0.3 (0.1–1)	0.6 (0.1–1.4)	0.3 (0.2–1.1)	0.4 (0.1–0.7)
Physician global assessment (VAS 0–10)	5.1 ± 1.7	4.8 ± 1.7	5.7 ± 1.8	4.7 ± 1.5	5.2 ± 1.8
Patient global assessment (VAS 0–10)	5.1 ± 2.2	5.7 ± 1.6	5.1 ± 2.6	4.6 ± 2	5 ± 2.3
Patient pain (VAS 0–10)	5.3 ± 2.2	5.9 ± 2.1	5.5 ± 2.4	4.8 ± 2.2	5 ± 2.1
DAPSA	21.3 (17.3–29.1)	20.6 (18.6–31.9)	25.3 (17.5–35.6)	18.5 (15.2–23.9)	22.2 (19.6–32)

Data are shown as mean ± SD (normally distributed variables), median (interquartile range), or frequencies (percentages)

BMI Body mass index, *bDMARD* biological disease-modifying antirheumatic drug, *BSA* Body surface area of psoriasis, *HAQ* Health assessment questionnaire, *CRP* C-reactive protein, *VAS* Visual Analog Scale (in mm), *DAPSA* Disease Activity index for PSoriatic Arthritis

Table 2 Predictive performance across datasets and modeling approaches

	Direct			PCA		
	HOM	**HTE—Risk**	**HTE—Effect**	**HOM**	**HTE—Risk**	**HTE—Effect**
Final models						
Transcriptomics	0.92	0.97	0.85	0.92	0.96	0.92
Proteomics	0.76	0.83	*NA*	0.77	0.84	0.82
O2PLS	0.85	0.94	0.95			
Full-process CV						
Transcriptomics	0.69 ± 0.25	0.68 ± 0.25	0.69 ± 0.24	0.67 ± 0.22	0.67 ± 0.22	0.64 ± 0.23
Proteomics	0.66 ± 0.25	0.66 ± 0.23	0.62 ± 0.21	0.70 ± 0.25	0.70 ± 0.23	0.42 ± 0.15
O2PLS	0.64 ± 0.20	0.64 ± 0.20	0.70 ± 0.19			

Values are shown as AUC (area under the ROC curve). Results are shown for transcriptomics, proteomics and integrated analysis (O2PLS) across three models – HOM, HTE–Risk, and HTE–Effect model – and two approaches: direct use of selected markers in the models, and indirect use of the markers by applying PCA and using the principal components in the models. The top three rows show the AUCs for the final models, while the bottom rows show the mean ± SD AUCs from the full-process tenfold cross-validation

−101,391, −242,861, −278,661, −159,267, −180,881, −211,767, −188,277, −236,698, −274,602, −245,958, and −214,784. No clinical variables were selected. For the model using proteomic data, ten markers were selected, comprising two clinical markers, DAPSA and HAQ, and eight proteomic markers, namely, IL-6, FGF-19, APEX1, OPN, IGFBPL1, AP-N, ALDH1A1, and PSP-D.

Prediction models

We evaluated the predictive performance of all the models – HOM, HTE-risk, and HTE-effect models – and approaches (using either direct marker inclusion, PCA, or O2PLS). The results are summarized in Table 2, with detailed outputs from each model, including AUC, differences in predicted response, and odds ratios, provided in Supplementary Information 3.

Among the final models, the transcriptomics HTE-risk model with the direct approach achieved the highest AUC of 0.97. When the final model performances were compared with the results from the full-process tenfold CV analysis, a decrease in the AUC was observed across all the datasets and modeling approaches as expected (Table 2). The AUC of the transcriptomics HTE–risk model (direct approach) decreased to 0.68 ± 0.25. The highest AUC after the full-process CV was observed for the multi-omics (O2PLS) HTE-effect model: AUC = 0.70 ± 0.19.

Each model was used to calculate the predicted probabilities of response for each patient for both TOFA and the alternative treatment (MTX for DN patients and ETN for DF patients). The absolute difference between these two predicted probabilities was then computed per patient to show the estimated treatment benefit according to the models. The largest absolute differences in the predicted response between TOFA and the alternative treatment were observed in the transcriptomics and proteomics HTE-effect models with the PCA approach, and in the O2PLS HTE-effect model: 15.7% ± 10.9, 12.8% ± 9.1, and 25.9% ± 23.1, respectively (see models 6, 12, and 15 in Supplementary Information 3). After the full-process CV, these absolute differences in predicted response remained large (20.9% ± 18.7, 10.6% ± 8.0, and 15.2% ± 14.8, respectively).

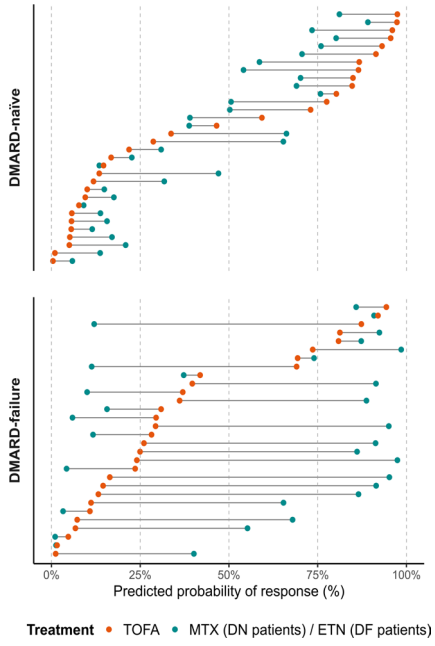

Fig. 2 Results from the O2PLS HTE – effect model. Predicted response probabilities for tofacitinib (TOFA) compared with methotrexate (MTX) in DMARD-naïve (DN) patients, and TOFA compared with etanercept (ETN) in DMARD-failure (DF) patients. Each line represents an individual patient, with dots indicating the predicted response probabilities under each treatment option. More variation in these individualised treatment effects indicates a higher potential for impacting decision-making for an individual patient

Taken together, the results indicate that the O2PLS HTE-effect model provides a good balance between predictive performance and clinical relevance. Using this model, 68% of patients had an absolute difference greater than 10% between the predicted probability of response to TOFA and the alternative treatment, as shown in Fig. 2 (55% ± 9 after full-process CV; see model

15 in Supplementary Information 3). This indicates that, for most patients, the model identified one treatment option with at least a 10% higher predicted probability of response, suggesting potential clinical relevance for treatment selection. A detailed description of the multi-omics integration process and the fitted O2PLS model is available in Supplementary Information S1.

Functional enrichment

The protein–protein interaction network was significantly enriched, with a PPI enrichment p-value of 3.41e-05 (Supplementary Fig. 2 A). One cluster of proteins was found in which five selected proteins (ALDH1A1, AP-N, FGF-19, IL-6, and OPN) were directly or indirectly linked to proteins annotated to immunoglobulin complexes and proteins involved in immune system processes (Supplementary Fig. 2B). Furthermore, three selected proteins (AP-N, IL-6, and OPN) are associated with pro-inflammatory pathways that are involved in both COVID-19 and rheumatoid arthritis.

Discussion

In this study, we investigated the potential of transcriptomic and proteomic markers for predicting treatment response in PsA patients. To the best of our knowledge, our results are the first to demonstrate the use of omics and multi-omics in a model for predicting treatment response in PsA. Three model architectures – HOM, HTE-risk, and HTE-effect – were evaluated across three data integration strategies: direct input of selected markers, initial dimensionality reduction via PCA, and multi-omics integration via O2PLS.

The highest apparent performance was observed for the HTE–risk transcriptomic model with the direct approach (AUC 0.97). However, after embedding the entire process – from feature selection through modeling – in a full-process tenfold CV, performance dropped across all methods. After this stringent validation, the O2PLS HTE-effect model showed the best balance between predictive performance (AUC = 0.70 ± 0.19) and the ability to discriminate between treatment options. In general, HTE–effect models, in combination with PCA or based on integrated omics (O2PLS), generated the largest differences in predicted response probabilities between treatment options. Therefore, HTE-effect models align best with the goal of treatment selection rather than risk stratification alone.

Notably, after feature selection, only two baseline clinical variables, DAPSA and HAQ, were retained in the proteomics model, whereas none were selected in the transcriptomic model. In the methotrexate subgroup, DAPSA rather than HAQ was selected, suggesting that baseline inflammatory disease activity may be more informative for methotrexate responsiveness than functional impairment. Furthermore, integrating transcriptomics and proteomics to capture both shared and data-specific variation and incorporating the integrated omics data with clinical variables in the models yielded more stable predictions. These findings suggest that omics markers capture heterogeneity that is not reflected by routine clinical parameters. As such, omics data might better reflect the complex molecular nature of treatment response in a heterogeneous disease such as PsA.

From a clinical perspective, prediction models are valuable only if they can meaningfully distinguish between treatment options at the individual patient level. Predicted probabilities of response were calculated using the models for each patient for both TOFA and the alternative treatment, and the absolute difference between these two probabilities was calculated as a measure of potential clinical impact. The HTE-effect models, and particularly the O2PLS approach, demonstrated the greatest potential for supporting treatment selection. Using this HTE-effect O2PLS model, 68% of patients had an absolute difference greater than 10% between the predicted probability of response to TOFA and to the alternative treatment. This means that for more than two-thirds of patients the model identified one treatment associated with at least a 10% higher predicted probability of response.

In the DN group, 37.5% of patients were predicted to have more than a 10% higher probability of response to TOFA than to MTX, whereas 25% were predicted to favor MTX by more than 10%. Similarly, in the DF group, 23% had at least a 10% higher predicted probability of response to TOFA compared with ETN, while 50% were predicted to favor ETN by more than 10%. Although a cross-validated AUC of approximately 0.70 is considered moderate, such individualized treatment contrasts could still provide clinical value by reducing the time to effective treatment through prioritization of treatment options, especially when no clear preference otherwise exists.

Several of the selected proteins have direct mechanistic links to PsA pathobiology and to the modes of action of the studied therapies. IL-6 is a pro-inflammatory cytokine that is associated with PsA severity and the transition from psoriasis to PsA [18, 19, 36–38]. Furthermore, MTX is known to lower serum IL-6 levels, making IL-6 a relevant marker of treatment response [39]. Upregulated levels of osteopontin (OPN, involved in inflammation, bone remodeling, and immune regulation) in synovial fluid are also associated with PsA [40]. There is no definitive evidence that OPN can predict PsA outcomes; however, elevated OPN levels have been associated with poorer response to treatments such as MTX in rheumatoid arthritis patients [41, 42]. Finally, PSP-D was found to be significantly upregulated in lesional psoriatic skin [43, 44]; links to PsA have not been established.

Among the selected transcripts are two genes that point to T-cell receptor segments: *TRAJ37* and *TRBJ2-3*. A variety of T-cell receptor gene segments have been proposed to be overrepresented in psoriasis [45]. Several long non-coding RNAs (lncRNAs) and pseudogenes were also selected. While these have no clear function or association with PsA, they could still play a role in the pathogenesis of PsA through regulatory effects on genes involved in inflammation and on microRNAs [46].

Network analysis revealed biological coherence of the selected markers. The protein–protein interaction network was significantly enriched (PPI enrichment p = 3.41e-05), with a cluster connecting multiple proteins to nodes annotated to immunoglobulin complexes, which are associated with autoimmune and inflammatory processes. This finding is consistent with previous research showing that immunoglobulin genes are upregulated in PsA skin lesions [47]. Furthermore, several proteins in the cluster are involved in immune system processes.

A key strength of our study is the robust internal validation approach and validation of the overall selection and modeling approach to increase reproducibility. Additionally, regularization techniques were used to reduce the risk of overfitting. Limiting the number of selected features and exploring models that provide treatment-specific predictions further improves feasibility for clinical application. Both feature selection methods identified partially overlapping biomarker sets, which may reflect the correlated structure of high-dimensional omics data. Because these methods rely on different modeling principles, they may select alternative but similarly predictive features.

Several limitations of this study should be acknowledged. Despite extensive internal validation, there remains a risk of overfitting due to the limited sample size and the absence of an external validation cohort. Subgroup sample sizes were limited, and feature selection in the treatment subgroups may be less stable. In addition, the ethnic background of the patients was not included in the analysis, which may limit the generalizability of the findings. A relatively large proportion of the samples (23%) were of insufficient quality for RNA sequencing, and several selected transcriptomic markers are unannotated, which limits biological interpretation despite their predictive value. Finally, transcriptomic profiling was performed using bulk RNA sequencing, which captures the average gene expression across $CD4^+$ T cells but does not resolve cell-to-cell heterogeneity. Consequently, signals from subpopulations may have been diluted. Nevertheless, compared with single-cell methods, bulk technologies offer greater stability at lower cost and are currently more feasible for clinical translation [48]. Future studies could extend this work by profiling other immune cell subsets or using larger proteomic platforms to see if those provide complementary predictive information.

Furthermore, the clinical applicability of prediction models based on biomarkers requires careful consideration. Although our findings show potential for clinical impact, independent validation in external cohorts is required, followed by prospective impact studies to determine whether model-based treatment selection improves patient outcomes. From a feasibility perspective, the relatively limited number of selected biomarkers supports the potential development of a targeted biomarker panel, which could facilitate implementation in clinical practice.

Conclusions

By integrating baseline $CD4^+$ T-cell transcriptomics with serum proteomics, the O2PLS HTE–effect model achieved the most robust performance after full-process cross-validation. The model showed promise for supporting treatment selection by predicting notable (≥ 10%) patient-specific differences in the probability of achieving MDA between tofacitinib, methotrexate, and etanercept. If these results are confirmed in independent cohorts, multi-omics guided treatment selection has the potential to enable more personalized treatment plans and shorten the time to clinical response in patients with PsA.

Abbreviations

AUC-ROC	Area under the receiver operating characteristic curve
bDMARDs	Biologic disease-modifying antirheumatic drugs
BSA	Body surface area
CASPAR	Classification criteria for psoriatic arthritis
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
DAPSA	Disease Activity Index for Psoriatic Arthritis
DMARDs	Disease-modifying antirheumatic drugs
DN	DMARD-naïve
DF	DMARD-failing
ETN	Etanercept
FACS	Fluorescence-activated cell sorting
HAQ	Health Assessment Questionnaire
HOM	Homogeneous treatment effect
HTE	Heterogeneous treatment effect
LEI	Leeds Enthesitis Index
LOD	Limit of detection
LOOCV	Leave-one-out cross-validation
MDA	Minimal disease activity
MTX	Methotrexate
NPX	Normalized protein expression
NSAIDs	Nonsteroidal anti-inflammatory drugs
O2PLS	Two-way orthogonal partial least squares
PBL	Peripheral blood lymphocyte
PBMCs	Peripheral blood mononuclear cells
PCA	Principal component analysis
PPI	Protein–protein interaction
PsA	Psoriatic arthritis
sPLS-DA	Sparse Partial Least Squares Discriminant Analysis
TOFA	Tofacitinib
tsDMARDs	Targeted synthetic disease-modifying antirheumatic drugs
VAS	Visual analog scale
VIP	Variable Importance in Projection
XGBoost	EXtreme Gradient Boosting

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-026-03788-9.

Supplementary Material 1. Figure S1. Flow cytometry gating strategy. Gates were predefined and applied uniformly to all samples, based on unstimulated fluorescence minus one (FMO) healthy controls. Supplementary Information S1O2PLS is a method to integrate two (omics) datasets. The variation in the two datasets is decomposed into three parts: joint variation between the datasets, orthogonal variation that is specific to each dataset, and noise. The O2PLS model was fitted to the selected transcriptomic and proteomic markers via the OmicsPLS package (version 2.0.5) in R.(33) Before the O2PLS model was fitted, the transcriptomic and proteomic datasets were centered. The number of latent components in the joint and omicsspecific (orthogonal) parts was chosen based on a scree plot. The final model consists of five joint components, two transcriptomic-specific components, and one protein-specific component. The proportions of explained variance in the joint, orthogonal, and noise components for transcriptomics were 38.9%, 36.6%, and 24.6%, respectively. For the proteomics data, the proportions of explained variance in the joint, orthogonal, and noise components were 80.4%, 11.1%, and 8.5%, respectively. The latent joint and orthogonal components of the final model, together with the selected clinical variables, were used as predictors in the prediction models. The loadings of the final model indicate the importance of each variable on each joint and omics-specific component, as visualized in Figures S1-1 and S1-2. Furthermore, a boxplot is provided (Figure S1-3) to show differences in scores for each (joint and omics-specific) component between responders and non-responders. Figure S1-1. O2PLS transcriptomics loadings. The loadings of five joint components are shown from left to right on row one and two. The loadings of the two orthogonal components are shown on the third row. Figure S1-2. O2PLS proteomics loadings. The loadings of five joint components and one orthogonal component are shown from left to right and top to bottom for the proteomics data. Figure S1-3. Boxplots comparing component scores between responders (MDA = 0) and nonresponders (MDA =1). Figures (A) and (B) show the scores for the joint and, respectively, orthogonal components of the transcriptomics data. Figures (C) and (D) show the scores for the joint and, respectively, orthogonal components of the proteomics data. Two-sample t-test pvalues are shown above each panel. Supplementary Information S2Full process 10-fold cross-validation.To approximate the performance of the predictive models in a validation dataset, the entire modeling pipeline – including predictor selection, data integration, and model development – was embedded in a 10-fold crossvalidation framework. The process embedded in this full-process CV is indicated in Figure 1. All the settings of the selection methods (XGBoost and sPLS-DA) and prediction models were kept the same in the 10FCV. The O2PLS method was performed with five joint components, two RNA-specific components, and one proteinspecific component. If the set of selected predictors in a certain CV round was not large enough (i.e. < 8 predictors selected), the number of components was selected based on a cross-validation within the O2PLS package (crossval_o2m). The reported mean AUCs were averaged over 10 rounds of CV. The AUCs of the HTE–effect models specifically were averaged over all rounds in which at least one interaction was selected. Table S1. Selected transcriptomic markers. Table S2. Selected proteomic and clinical markers. Figure S2. Protein-protein interaction (PPI) network of selected proteins and protein-coding genes (n = 15). (A) The PPI network shows selected proteins in blue and proteins of selected protein-coding genes in red, together with neighbours in the first and second shells (white). The network is significantly enriched, PPI enrichment p-value = 3.41E-5. The lines represent evidence of interaction. (B) Functional enrichments in the PPI network. Five proteins are involved in immune system processes. Six proteins have immunoglobulin domains. Four proteins have associations with immunopathological damage of rheumatoid arthritis (RA). Lastly, four proteins are involved in proinflammatory pathways that are shared by COVID-19 and rheumatoid arthritis. ANPEP: AP-N. SPP1: OPN.

Supplementary Material 2.

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Authors' contributions

Conceptualization and design of the work: M.L.M.B., P.M.J.W., S.C.M., S.B. Methodology: M.L.M.B., P.M.J.W., S.B. Data analysis and writing original draft: M.L.M.B. Data acquisition: J.S., A.N., H.E.V., S.C.M., L.G.S., A.H., S.A.V. All authors read, substantially reviewed, and approved the final manuscript.

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Data availability

The datasets underlying this article are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All patients provided written informed consent. The study was carried out in compliance with the Declaration of Helsinki and was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (MREC reference number: NL63439.041.17).

Consent for publication

Not applicable.

Competing interests

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