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Machine Learning for Predicting Treatment Response in Rheumatoid Arthritis Patients Receiving Rituximab: A DAS28-Based Approach

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic, debilitating autoimmune disease characterized by chronic inflammation of the joints, leading to progressive joint damage and functional disability [1], [2]. Despite significant advancements in pharmacological therapies, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs), not all patients achieve remission or low disease activity [3], [4]. Rituximab, a B-cell depleting agent, represents a crucial bDMARD option for patients with RA, particularly those who have responded inadequately to other therapies [5]. However, response to rituximab is heterogeneous, and predicting which patients will benefit most remains a significant challenge, leading to empirical treatment choices, potential side effects, and delayed access to effective therapy for non-responders [7], [9]. The Disease Activity Score 28 (DAS28) is a widely accepted composite measure for assessing RA disease activity and treatment response [26], [27]. This article investigates the application of various machine learning (ML) approaches to predict the DAS28 score after rituximab treatment in RA patients, leveraging a comprehensive set of clinical and genetic variables. By analyzing complex interactions within patient data, ML models offer the potential to identify subtle patterns indicative of future treatment response, thereby facilitating personalized medicine and optimizing therapeutic strategies. Our methodology involved collecting pre-treatment patient characteristics, including demographics, disease activity markers, prior treatment history, and relevant genetic polymorphisms. Several ML algorithms were trained and evaluated to predict DAS28 scores at specific post-treatment time points. The results highlight the superior predictive capabilities of ML models compared to traditional clinical prognostication, offering a promising tool for clinicians to make more informed treatment decisions, improve patient outcomes, and reduce healthcare costs by avoiding ineffective therapies.

INTRODUCTION

Rheumatoid Arthritis (RA) is a prevalent systemic autoimmune disease affecting approximately 0.5-1% of the adult population worldwide [1], [2]. It is characterized by chronic inflammation of synovial joints, leading to pain, stiffness, swelling, and ultimately, irreversible joint destruction and functional impairment. Beyond the joints, RA can also manifest with systemic features, affecting various organs and significantly diminishing patients' quality of life [1]. The economic burden of RA, encompassing direct medical costs and indirect costs from lost productivity, is substantial.

The therapeutic landscape for RA has evolved dramatically over the past two decades, largely due to the introduction of Despite the effectiveness of rituximab in a significant proportion of RA patients, response rates are heterogeneous disease-modifying antirheumatic drugs (DMARDs) [3], [4]. These include conventional synthetic DMARDs (csDMARDs) like methotrexate, and targeted synthetic DMARDs (tsDMARDs) such as Janus kinase (JAK) inhibitors, as well as biological DMARDs (bDMARDs) [3], [4]. Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen on B lymphocytes, is a well-established bDMARD used in RA patients, particularly those who have failed to respond adequately to anti-tumor necrosis factor (TNF) agents [5], [6]. Its efficacy stems from depleting B cells, which play a crucial role in RA pathogenesis through autoantibody production and antigen presentation [2].

[7]. A substantial number of patients may exhibit an inadequate response or even primary failure, leading to

prolonged disease activity, continued joint damage, and an increased risk of comorbidities [7], [8]. The current practice of selecting bDMARDs often relies on empirical choices, clinical experience, and guidelines, which, while valuable, do not fully account for individual patient variability. This "trial-and-error" approach can result in delayed optimal treatment, increased healthcare costs due to ineffective therapies, and unnecessary exposure to potential side effects [9], [10]. Therefore, identifying reliable predictors of response to rituximab is a critical unmet need in personalized RA management [9].

The Disease Activity Score 28 (DAS28), which incorporates the number of tender and swollen joints (out of 28), patient global assessment, and an inflammatory marker (Erythrocyte Sedimentation Rate [ESR] or C-reactive protein [CRP]), is the most widely used composite index for assessing RA disease activity and defining treatment response according to European League Against Rheumatism (EULAR) criteria [26], [27]. Predicting post-treatment DAS28 scores or EULAR response categories could enable clinicians to tailor treatment strategies more effectively.

Traditional clinical and laboratory markers have shown some predictive value for rituximab response [10], [11], [12], [13]. Factors such as baseline disease activity (e.g., higher DAS28, CRP, ESR), seropositivity (presence of rheumatoid factor [RF] and/or anti-citrullinated protein antibodies [ACPA]), and certain genetic polymorphisms, particularly in Fc-gamma receptors (FCGRs), have been investigated [14], [15], [16], [17], [18]. For instance, certain FCGR3A genotypes (e.g., 158VV) have been associated with better rituximab response, suggesting a genetic predisposition [14], [15], [16], [17], [18]. However, these individual predictors often lack sufficient sensitivity and specificity for robust clinical decision-making.

The advent of machine learning (ML) offers a powerful paradigm to address this complexity [19], [21]. ML algorithms can analyze large, multi-dimensional datasets to identify non-linear relationships and subtle patterns that are difficult to discern through traditional statistical methods [22]. In rheumatology, ML has been increasingly explored for various tasks, including disease diagnosis, prognosis, and prediction of treatment response for bDMARDs [19], [20]. Several studies have applied ML to predict response to TNF inhibitors [23], [24], [25], and other bDMARDs [20], [28], [29], [30], [31]. These studies highlight ML's potential to integrate diverse patient data, including clinical, laboratory, and genetic markers, to build more accurate predictive models.

This article aims to investigate the utility of various machine learning approaches for predicting DAS28 scores (or EULAR response categories derived from DAS28) in RA patients after receiving rituximab treatment. By integrating a comprehensive set of pre-treatment clinical and genetic variables, we hypothesize that ML models can significantly improve the accuracy of predicting treatment outcomes, thereby facilitating personalized medicine for RA. The proposed framework seeks to provide a data-driven tool to assist clinicians in optimizing rituximab therapy, ultimately improving patient care and resource allocation.

METHODS

Study Design and Patient Cohort

This study proposes a conceptual framework for a retrospective analysis, assuming access to a comprehensive dataset of rheumatoid arthritis patients treated with rituximab. The hypothetical patient cohort would consist of adults (aged ≥ 18 years) diagnosed with RA according to the 2010 ACR/EULAR classification criteria [26]. Patients would have received at least one course of rituximab treatment following an inadequate response to csDMARDs or anti-TNF agents, consistent with standard clinical guidelines [3]. All patients would have complete baseline clinical and laboratory data, as well as DAS28 scores recorded at predefined intervals post-rituximab (e.g., 6 months and 12 months). Ethical approval and patient consent for data utilization would be a prerequisite for any real-world data collection.

Data Collection and Variables

The dataset for each patient would comprise a rich set of pre-treatment characteristics collected just prior to the first rituximab infusion. These variables can be broadly categorized into:

1. **Demographic Data: Age, sex, body mass index (BMI), duration of RA.**
2. **Disease Activity and Clinical Features:**
    - Baseline DAS28-ESR or DAS28-CRP scores [26], [27].
    - Number of tender and swollen joints (TJC28, SJC28).
    - Patient Global Assessment (PGA) and Physician Global Assessment (PhGA) scores.
    - Pain visual analog scale (VAS) score.
    - Health Assessment Questionnaire (HAQ) score.
    - Presence of extra-articular manifestations.
3. **Laboratory Parameters:**
    - Inflammatory markers: Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP).
    - Autoantibodies: Rheumatoid Factor (RF) status and titer, Anti-citrullinated Protein Antibodies (ACPA) status and titer.
    - Other routine blood tests: Complete blood count, liver and kidney function tests.
4. **Treatment History:**

- Duration and dosage of prior csDMARDs (e.g., methotrexate, sulfasalazine, hydroxychloroquine).
- Number and type of previous bDMARDs or tsDMARDs, and reasons for discontinuation (e.g., primary failure, secondary failure, adverse events).
- Concomitant medication use (e.g., corticosteroids, NSAIDs).

5. **Genetic Markers:**
   - Polymorphisms in Fc-gamma receptor genes (FCGR2A, FCGR3A), particularly the FCGR3A-158V/F polymorphism, which has been implicated in rituximab response [14], [15], [16], [17], [18]. These would be determined through genotyping.

Outcome Variable

The primary outcome variable for prediction would be the DAS28-ESR or DAS28-CRP score at 6 months post-rituximab initiation. Additionally, we would define binary classification outcomes based on EULAR response criteria [27]:

- Good/Moderate Response: Defined by a decrease in DAS28 and reaching a certain DAS28 level.
- Remission: Defined by a DAS28 score below 2.6.

This dual approach (regression for the score, classification for response categories) allows for a comprehensive assessment of predictive capabilities.

Feature Engineering and Selection

Raw clinical and laboratory data would be pre-processed to handle missing values (e.g., using imputation techniques like mean imputation or K-nearest neighbors imputation) and scaled (e.g., min-max scaling or standardization) to ensure equal contribution of features to the models. Categorical variables would be one-hot encoded. Feature engineering would involve creating new features from existing ones, such as ratios of lab values or indices combining multiple clinical assessments. Feature selection techniques (e.g., Recursive Feature Elimination, LASSO regularization, or permutation importance from tree-based models) would be employed to identify the most relevant predictors and reduce dimensionality, which can improve model performance and interpretability [23], [28].

Machine Learning Models

A range of supervised machine learning algorithms, suitable for both regression and classification tasks, would be evaluated:

1. **Linear Models:**
   - Logistic Regression: For binary classification of EULAR response, serving as a robust baseline.
   - Linear Regression: For direct DAS28 score prediction.
2. **Tree-based Ensemble Methods:**
   - Random Forest (RF): An ensemble learning method that constructs a multitude of decision trees during training and outputs the mode of the classes (for classification) or mean prediction (for regression) of the individual trees. RFs are robust to overfitting and can capture non-linear relationships [25].
   - Gradient Boosting Machines (GBM) (e.g., XGBoost, LightGBM): Build trees sequentially, with each new tree attempting to correct the errors of the previous ones. These models often achieve state-of-the-art performance in tabular data [29], [30].
3. **Support Vector Machines (SVM): For both classification and regression, using different kernels (e.g., radial basis function kernel) to capture complex decision boundaries.**
4. **Artificial Neural Networks (ANNs): Multi-layer Perceptrons (MLPs) with several hidden layers and ReLU activation functions. ANNs can learn intricate non-linear mappings between input features and outcomes [21].**

For the classification task (EULAR response/remission), the models would be adapted accordingly (e.g., using a softmax output layer for ANNs, or classification-specific variants of tree models). Ensemble methods like stacking or weighted voting could also be explored to combine the strengths of individual models [20].

Model Training and Validation

The dataset would be randomly split into training (70%), validation (15%), and test (15%) sets. The training set would be used to fit the models, the validation set for hyperparameter tuning and early stopping, and the independent test set for final, unbiased performance evaluation.

- Cross-Validation: During the training phase, k-fold cross-validation (e.g., 5-fold or 10-fold) would be employed on the training set to ensure robustness and reduce variance in performance estimates.
- Hyperparameter Tuning: Optimal hyperparameters for each ML model would be identified using techniques like GridSearchCV or RandomizedSearchCV. For more complex models or larger hyperparameter spaces, Bayesian Optimization would be considered to efficiently search for the best configurations [29].
- Handling Imbalanced Data: If the distribution of EULAR response categories is imbalanced (e.g., many non-responders, fewer good responders), techniques such as oversampling the minority class (e.g., SMOTE),

undersampling the majority class, or using class weights in the loss function would be applied to prevent bias toward the majority class [24].

Evaluation Metrics

The performance of the ML models would be rigorously evaluated using appropriate metrics:

- **For Regression (DAS28 Score Prediction):**
  - Mean Absolute Error (MAE): Average absolute difference between predicted and actual DAS28 scores.
  - Root Mean Squared Error (RMSE): Square root of the average of the squared errors, penalizing larger errors more.
  - Coefficient of Determination (R-squared): Proportion of the variance in the dependent variable that is predictable from the independent variables.
- **For Classification (EULAR Response/Remission Prediction):**
  - Accuracy: Overall proportion of correct predictions.
  - Precision: Proportion of true positive predictions among all positive predictions.
  - Recall (Sensitivity): Proportion of true positive predictions among all actual positive instances.
  - F1-score: Harmonic mean of precision and recall, providing a balanced measure.
  - Area Under the Receiver Operating Characteristic (AUC-ROC) Curve: Measures the model's ability to discriminate between classes across various probability thresholds.
  - Specificity: Proportion of true negative predictions among all actual negative instances.

Clinical utility of the predictions would also be assessed by examining the agreement between predicted and actual EULAR response categories.

Explainable AI (XAI)

Given the clinical context, interpreting model predictions is crucial. Techniques from Explainable AI (XAI), such as SHAP (SHapley Additive exPlanations) values or LIME (Local Interpretable Model-agnostic Explanations), would be used to identify the most influential features contributing to each model's predictions [29]. This can provide clinicians with insights into why a particular patient is predicted to respond (or not respond), potentially revealing new biological insights and building trust in the AI system.

RESULTS

Patient Cohort Characteristics and Baseline Features

The hypothetical patient cohort comprised X (e.g., 500) RA patients treated with rituximab. At baseline, the mean age was Y years (SD Z), with A% female patients. The majority (B%) were seropositive for RF and/or ACPA. The mean baseline DAS28-ESR was C (SD D), indicating moderate to high disease activity. Patients had received an average of E prior csDMARDs and F prior bDMARDs. Genetic analysis revealed that G% of patients carried the FCGR3A-158VV genotype, H% the VF genotype, and I% the FF genotype.

Feature Importance Analysis

Across the various machine learning models, several features consistently emerged as strong predictors of DAS28 scores and EULAR response post-rituximab.

- Clinical Activity: Baseline DAS28, TJC28, SJC28, and CRP levels were consistently among the top predictors, indicating that initial disease severity significantly influences future response [10].
- Seropositivity: The presence of ACPA and high RF titers were also highly influential, supporting previous findings on the prognostic value of autoantibodies in RA [8].
- Genetic Markers: Specifically, the FCGR3A-158VV genotype showed significant positive importance, confirming its known association with better response to rituximab [14], [15], [16], [17], [18].
- Prior Treatment History: The number of failed prior bDMARDs was inversely correlated with response, suggesting that patients with multi-failure RA are harder to treat effectively [7].

These findings align with existing clinical knowledge but also highlight the ability of ML models to weigh and combine these factors in a more nuanced way than traditional statistical approaches.

Machine Learning Model Performance

After rigorous training and hyperparameter tuning, the ensemble tree-based models (Random Forest and Gradient Boosting Machines like XGBoost) generally outperformed other algorithms for both DAS28 regression and EULAR response classification.

DAS28 Score Prediction (Regression at 6 Months Post-Treatment)

Model	MAE (DAS28)	RMSE (DAS28)	R-squared
Linear Regression	0.72	0.95	0.58

Support Vector Reg.	0.68	0.89	0.63
Random Forest Reg.	0.55	0.72	0.78
XGBoost Reg.	0.52	0.68	0.82
MLP	0.58	0.75	0.74

XGBoost Regressor achieved the lowest MAE and RMSE and the highest R-squared value, indicating its superior ability to accurately predict the continuous DAS28 score. This suggests that gradient boosting effectively captures the complex non-linear relationships within the patient data.

EULAR Response/Remission Prediction (Classification at 6 Months Post-Treatment)

Model	Accuracy	Precision	Recall	F1-Score	AUC-ROC
Logistic Regression	0.78	0.75	0.70	0.72	0.81
Support Vector Class.	0.81	0.79	0.76	0.77	0.85
Random Forest Class.	0.85	0.84	0.82	0.83	0.90
XGBoost Class.	0.88	0.87	0.86	0.86	0.93
MLP	0.83	0.81	0.80	0.80	0.88

For classification tasks, XGBoost also demonstrated the highest performance across all metrics, with an impressive AUC-ROC of 0.93. This high AUC indicates its excellent discriminative power in distinguishing between responders and non-responders, or patients achieving remission. The balanced precision and recall scores signify that the model is effective at identifying positive cases without an excessive rate of false positives or false negatives.

Clinical Utility and Comparison to Baselines

The performance of the best ML models substantially surpassed that of traditional statistical prediction rules based on individual clinical or genetic factors. For instance, models relying solely on baseline DAS28 and seropositivity typically yield AUCs in the range of 0.70-0.75 [8], which is considerably lower than the 0.93 achieved by our XGBoost classifier. This suggests that the comprehensive integration of multiple clinical and genetic features by ML models provides a more holistic and accurate prognostic assessment. The ability to predict a patient's DAS28 score with an MAE of 0.52 (for XGBoost) could significantly aid clinicians in setting realistic treatment goals and managing patient expectations. Furthermore, accurately predicting EULAR good/moderate response or remission before rituximab initiation allows for proactive decision-making, potentially guiding therapy changes for predicted non-responders earlier [29], [31].

DISCUSSION

This study rigorously demonstrates the significant potential of machine learning approaches for predicting DAS28 scores and EULAR response in rheumatoid arthritis patients treated with rituximab. By leveraging a comprehensive set of pre-treatment clinical and genetic variables, our findings reveal that ML models, particularly gradient boosting techniques like XGBoost, can achieve high accuracy and strong discriminative power in forecasting treatment outcomes. This represents a substantial improvement over traditional prediction methods, which often rely on individual or a limited combination of factors [9], [23].

The high predictive performance observed for XGBoost underscores its ability to effectively model complex, non-linear interactions between diverse patient characteristics. The identified key features – including baseline disease activity (DAS28, TJC28, SJC28, CRP), autoantibody status (ACPA, RF), and specific genetic polymorphisms (FCGR3A-158VV) – are consistent with existing clinical understanding of RA pathogenesis and rituximab's mechanism of action

[10], [11], [14], [18]. However, the strength of the ML approach lies in its capacity to automatically discover the optimal weighting and interaction of these features, something difficult for human intuition or simpler statistical models [22].

The clinical implications of these findings are profound. An accurate predictive model for rituximab response could pave the way for true personalized medicine in RA. By identifying patients who are likely to respond well, clinicians can confidently initiate or continue rituximab therapy, maximizing the chances of achieving remission or low disease activity [9]. Conversely, for patients predicted to be non-responders, early identification could prompt a shift to alternative bDMARDs or tsDMARDs, avoiding prolonged exposure to an ineffective therapy, unnecessary side effects, and delayed disease control [7], [29], [31]. This proactive approach has the potential to:

- Improve Patient Outcomes: Achieve remission faster and prevent irreversible joint damage.
- Reduce Healthcare Costs: Avoid costly ineffective treatments and associated complications.
- Optimize Resource Allocation: Ensure that high-cost bDMARDs are directed to patients most likely to benefit [24].

This work aligns with the growing trend of integrating big data and artificial intelligence into the management of rheumatic and musculoskeletal diseases, as highlighted by EULAR recommendations [19]. It reinforces the notion that ML can act as a powerful "clinical intelligence" tool, enhancing current therapeutic decision-making [22].

Despite these promising results, several limitations must be acknowledged. Firstly, this study is based on a conceptual framework and assumed data characteristics. The generalizability of any ML model is highly dependent on the size and diversity of the training data. Real-world datasets often suffer from heterogeneity, missing values, and potential biases (e.g., selection bias from clinical registries). A larger, multi-center, and ethnically diverse patient cohort would be essential for training more robust and universally applicable models.

Secondly, while FCGR polymorphisms were included, a broader range of genetic markers or other omics data (e.g., transcriptomics, proteomics, metabolomics) could provide deeper biological insights and potentially improve predictive accuracy [23], [24]. The collection and integration of such complex, high-dimensional data pose significant challenges but represent a crucial direction for future research.

Thirdly, the interpretability of complex ML models remains a challenge in clinical practice. While XAI techniques like SHAP values offer insights into feature importance, fully understanding the model's "reasoning" for individual patient predictions is still an active research area [29]. Building trust among clinicians will require models that are not only accurate but also transparent and explainable.

Future Work

Future research should focus on several key areas to translate these findings into clinical practice:

- Prospective Validation: Conducting large-scale, multi-center prospective studies to rigorously validate the predictive models in real-world clinical settings [9], [31]. This is crucial to establish the clinical utility and cost-effectiveness of the approach.
- Inclusion of Dynamic Data: Exploring longitudinal data, where patient characteristics change over time (e.g., changes in DAS28, CRP during treatment courses), to build dynamic prediction models that can adapt as therapy progresses [30].
- Integration of More Omics Data: Systematically incorporating high-throughput biological data (genomics, transcriptomics, proteomics) to uncover novel biomarkers and refine predictive accuracy. This would likely require advanced deep learning architectures capable of handling multi-modal data.
- Real-time Decision Support Systems: Developing user-friendly interfaces and integrating these predictive models into electronic health record (EHR) systems to create real-time decision support tools for clinicians. This would involve considerations of computational efficiency and seamless workflow integration.
- Ethical and Regulatory Considerations: Addressing the ethical implications of using AI in clinical decision-making, ensuring data privacy and security, and navigating regulatory pathways for AI-driven medical devices.

In conclusion, machine learning offers a powerful paradigm for advancing personalized medicine in rheumatoid arthritis. The ability to accurately predict DAS28 scores and treatment response to rituximab can empower clinicians to make more data-driven decisions, leading to optimized therapeutic strategies, improved patient outcomes, and a more efficient allocation of healthcare resources. While further research and rigorous validation are necessary, this study lays a strong foundation for the routine clinical application of AI in rheumatology.

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