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Machine Learning Applications in Immune-Mediated Inflammatory Diseases: A Pathway Towards Precision Medicine Review

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Abstract

Immune-mediated inflammatory disorders (IMIDs) like autoimmune rheumatic diseases, inflammatory bowel diseases, and multiple sclerosis are complex disorders with diverse manifestations and whimsical treatment responses. Machine learning (ML), a field of artificial intelligence (AI), has been a breakthrough in precision medicine, offering new tools to deal with high-dimensional data for better diagnosis, prognosis, and treatment planning. This review addresses the role of ML in enhancing the management of IMIDs, specifically its capacity to discover latent patterns in multi-omics, EHRs, and imaging. Evidence from supervised, unsupervised, and deep learning approaches in proteomics, immunophenotyping, and clinical datasets is integrated in this study. Major applications include ML-driven disease classification (e.g., categorization of chronic kidney disease subtypes with >97% accuracy), prediction of treatment toxicity (e.g., methotrexate-induced liver damage), and detection of digital biomarkers for subclinical atherosclerosis in systemic lupus erythematosus. Random forests and neural networks are beneficial in stratifying disease activity and forecasting long-term outcomes, with reservations regarding dataset bias, overfitting, and ethical concerns regarding data privacy. While ML holds great promise for individualized interventions, its application in clinical practice requires systematic validation, multidisciplinary collaboration, and adherence to ethical standards to counteract algorithmic bias and ensure fair care. This review stresses the potential of ML to revolutionize precision medicine in IMIDs while highlighting new challenges to practical application.

Keywords: Precision Medicine, Machine Learning, Biomarkers, Immune-Mediated Inflammatory Diseases, Artificial Intelligence.

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1. Introduction

Machine learning (ML), which is a key field of artificial intelligence (AI), is designed to derive analytical insights through experience-based learning from structured and unstructured data. The conceptual foundation of ML may be traced to Alan Turing's early hypothesis on machines that learn via experience (Turing, 1995). With every successive decade, continuous technological developments have made ML a highly influential tool for numerous scientific and clinical disciplines. Its robust capacity to detect hidden

patterns in high-dimensional data and represent complex, non-linear relationships make it a particularly valuable resource for medical research and healthcare applications (Stafford et al., 2020; MacEachern & Forkert, 2021).

In clinical medicine, ML has come to play an increasingly important part in breakthroughs in early disease detection, prognostic model-building, drug discovery, and the optimization of clinical trials. As the exponentially growing volume of patient data becomes available, ML has become a central component in the development of precision medicine strategies. This is particularly relevant to the study of immune-mediated inflammatory diseases (IMIDs)—a heterogeneous group of diseases such as autoimmune rheumatic disorders (ARDs), inflammatory bowel disease (IBD), chronic kidney disease (CKD), and multiple sclerosis (MS). These are long-standing conditions driven by immune dysregulation with mixed presentations and unpredictable treatment responses. ML thus provides a hopeful avenue to maximize disease stratification, tailor therapeutic approaches, and improve patient outcomes.

ML methods can be categorized into supervised, unsupervised, and reinforcement learning—each with unique strengths suitable for specific clinical uses (Russell et al., 2010). Supervised learning involves the acquisition of mappings between input variables and labeled outputs. It includes classification problems (e.g., disease diagnosis) and regression problems (e.g., prediction of disease activity scores), and is therefore of specific utility for biomarker discovery and prognosis.

Unsupervised learning, however, identifies latent patterns in unlabeled data, typically with clustering algorithms such as K-means, hierarchical clustering, and Gaussian mixture models. These are essential for patient subtyping and the identification of novel disease phenotypes (Orange et al., 2018; Martin-Gutierrez et al., 2021). Reinforcement learning, though less applied in clinical practice, has been demonstrated to be applied in the optimization of clinical trial design and dynamic treatment regulations (Padmanabhan et al., 2015; Ribba et al., 2020).

Deep learning, a specialized branch of ML powered by human brain-like neural networks, dominates difficult tasks like image and signal data-related tasks. Recurrent neural networks (RNNs) and convolutional neural networks (CNNs) have been instrumental to medical imaging disciplines in disease detection, prognosis, and subtype discrimination (Klang et al., 2020; Jaber et al., 2020).

The widespread adoption of electronic medical records (EMRs) and electronic health records (EHRs) in clinical workflows has provided structured patient data readily available for ML analysis. EMRs typically include visit-specific clinical measures, while EHRs extend to cumulative laboratory, imaging, and longitudinal health information from multiple care providers. These databases are rich sources for developing predictive models in personalized medicine (Landi et al., 2020).

Deep learning algorithms are particularly well-adapted to medical imaging modalities such as MRI, CT, X-ray, and ultrasound due to their capacity to process rich visual data. Applications are to cancer diagnosis and staging, neurologic disease detection, and automation of radiologic workflow (Lakhani et al., 2018; Liu et al., 2019). In radiology, ML has enabled significant advances like computer-aided image segmentation, multi-modal image registration, computer-aided detection, functional brain mapping with fMRI, image-based clinical decision support systems for retrieval, and interpretation of radiology reports with natural language processing (Wang & Summers, 2012).

Perhaps most critical of all applications of ML in IMIDs is biomarker discovery—applying molecular data to characterize disease subtypes and predict clinical outcomes. As opposed to traditional symptom-based evaluation, ML software is able to process high-dimensional omics data (e.g., proteomics, metabolomics, RNA-sequencing) to establish disease endotypes and classify patients with similar clinical profiles (Teruel et al., 2017; Imhann et al., 2019).

Diagnostic biomarkers should be optimal, low-cost, minimally invasive, and amenable to routine analysis, allowing early detection in at-risk groups. Prognostic biomarkers, which predict outcomes like progression of disease or risk of recurrence, are likely to require more advanced analysis of biological fluids like blood, urine, cerebrospinal fluid, and even exhaled air (Glazyrin et al., 2020; Sola Martínez et al., 2020; Toscano & Patti, 2021).

Digital biomarkers, based either on EHRs or imaging data, also promise improved diagnostic accuracy. Imaging-based biomarkers, though powerful, are hampered by high operational costs and the need for large datasets to secure valid ML predictions (Ciurtin et al., 2019; Liu et al., 2019). For the sake of predicting treatment response and identifying risk factors for treatment resistance, ML has been applied to explore immunological, genetic, and phenotypic data (Bek et al., 2016; Waddington et al., 2020). These tools are gradually building a future where individualized treatment plans are derived based on

predictive analytics to deliver more precise interventions. This review highlighted the clinical applications of various ML techniques in the prediction, diagnosis, and prognosis of autoimmune rheumatic disorders, inflammatory bowel disease, autoimmune chronic kidney disease, and multiple sclerosis, and ML applications for patient stratification and treatment selection.

2. Machine Learning to Improve Prognosis, Diagnosis, and Prediction for Immune-Mediated Inflammatory Diseases

Machine learning (ML) has emerged as a paradigm-changing technology in the biomedical field, among others, due to its capacity to handle high-dimensional data and learn latent patterns not possible to attain by conventional statistical methods. Compared to conventional analytic approaches, which rely on a priori hypotheses and collapse with complex interactions between variables, ML can detect nonlinear patterns and choose the right biomarkers from vast data sets, for example, those derived from omics technologies (Seyed Tabib et al., 2020). For example, variable importance in random forest algorithms may be measured with metrics like the "mean decrease in Gini," which gives an indication of how much a feature contributes towards enhancing the accuracy of the classification by the model.

ML-based feature selection has also been very useful in diseases with well-delineated genetic contributions, such as some cancers (Henry & Hayes, 2012). However, the discovery of biomarkers in IMIDs, which are diseases featuring complex interactions between genetics and environment, is a more difficult task. Nevertheless, promising applications of ML to the diagnosis and prognosis of these diseases have been demonstrated in recent research.

3. Diagnostic Applications of ML in IMIDs

ML has been applied effectively to distinguish between IMIDs and other diseases by analyzing proteomic, immunophenotypic, and clinical data. Glazyrin et al. (2020), for example, employed K-nearest neighbour algorithms in plasma proteomics data to distinguish CKD subtypes with more than 97% classification efficiency. While conventional statistical techniques could not classify disease subtypes, ML models distinguished diabetic nephropathy from glomerulonephritis. However, attempts to reproduce these findings through urine samples were hindered by limited sample

quantities and the concern of overfitting. The proposed two-phase diagnostic pipeline—urine-screening followed by subtype classification on plasma—is focused on opportunities for employing ML to reduce such invasive tests as biopsies.

Similarly, immunophenotyping data from juvenile idiopathic arthritis (JIA) patients have been explored with random forest models with excellent diagnostic accuracy (AUC = 0.90) (Van Nieuwenhove et al., 2019). Interestingly, even though invariant natural killer T (iNKT) cells were identified as the most crucial variables, their exclusion had little effect on model performance, suggesting a more complex biological interaction than could be deduced from variable importance rankings alone. Functional MRI data have also been used for ML-based diagnosis of neuropsychiatric systemic lupus erythematosus (SLE), where support vector machines achieved moderate diagnostic accuracy (AUC = 0.75), although small sample sizes constrained more generalizability (Simos et al., 2019).

Electronic health records (EHR) and electronic medical records (EMR) are another useful data source for ML-driven diagnosis. Jorge et al. (2019) applied natural language processing and rule-based methods to identify SLE cases from EHRs with excellent diagnostic performance (AUC = 0.909). Similarly, Murray et al. (2018) applied ensemble learning methods (e.g., AdaBoost) to an imbalanced dataset and obtained reliable outcomes (AUC = 0.94). These studies demonstrate the potential of scalable ML systems to aid in diagnosing complex autoimmune diseases using everyday clinical data.

Other than diagnosis, ML has also been used to detect complications and treatment-related risks. Lin et al. (2015) applied logistic regression to EMR data to predict methotrexate-induced liver toxicity in rheumatoid arthritis (RA) patients with a positive predictive value of 0.756. Another example is the FIND FH algorithm, which used random forest classifiers to detect familial hypercholesterolemia from health-care databases, with 77–87% expert validation rates (Myers et al., 2019).

ML is being more commonly applied to stratify disease activity and predict long-term outcomes in IMIDs. For example, Kegerreis et al. (2019) employed supervised learning techniques to predict whole blood gene expression data to label SLE patients as having active or inactive disease based on the SLE Disease Activity Index (SLEDAI). Random forest models could achieve 83% accuracy based on raw gene expression data, although robustness was compromised across validation sets, pointing out the problem of standardization. Hoi et al. (2021) extended this study by categorizing high disease activity

(SLEDAI-2K ≥10) with 10 prevalent clinical and demographic variables on 5,680 patient visits. The best multinomial logistic regression model had 88.6% accuracy, suggesting a cost-effective alternative for the early detection of high-risk SLE patients.

Regarding long-term prognosis, Ceccarelli et al. (2017) used a recurrent neural network (RNN) to predict chronic damage in SLE from longitudinal clinical and laboratory data. The model, trained on over five visits per patient and tested by 8-fold cross-validation, achieved an AUC of 0.77. This study demonstrates the utility of time-series ML models for predicting progressive disease outcomes. The same method has been applied in multiple sclerosis (MS), where ML models forecasted the development of MS relapsing-remitting to secondary progressive MS with an accuracy of approximately 85% at different times in the future (Seccia et al., 2020). Regardless of imbalanced data—the common case in disease models of progressive type—the research highlights the value of ML prognosis in therapeutic decision and monitoring of the disease.

ML has also been shown to hold great promise in cardiovascular risk detection, particularly among patients with inflammatory diseases. Sánchez-Cabo et al. (2020) derived an elastic net regression model from routine clinical variables that outperformed traditional risk scores for the prediction of subclinical atherosclerosis. More recently, Coelewij et al. (2021) demonstrated that serum metabolomics data could be used to predict SLE patients with subclinical atherosclerosis using logistic regression, where VLDL and leucine were among the top features.

Whereas predictive accuracy is enhanced by ML models, utility to a large extent depends on input data quality, quantity, and relevance. For instance, whereas boosted survival trees fared better than other methods for cirrhosis development prediction in hepatitis C, polygenic risk scores still outcompeted ML models for coronary artery disease prediction in independent data sets (Konerman et al., 2019; Gola et al., 2020). These findings justify the need for meticulous data integration and rigorous model validation in ML research.

4. Translating Models to Practice

While machine learning (ML) models have achieved outstanding performance in research settings, translating these models into daily clinical practice remains a key challenge. Such a chasm—often referred to as the "AI Chasm"—highlights the gap between model creation

and real-world clinical deployment, where the ultimate objective is improving patient outcomes (Keane & Topol, 2018).

Evaluation of ML models is typically done based on a range of performance metrics, such as accuracy, area under the curve (AUC), precision, sensitivity, and specificity, that reflect model performance under controlled conditions. Such statistical metrics do not directly equate to clinical utility and could be difficult for clinicians to interpret without technical expertise (Saito & Rehmsmeier, 2015; Shah et al., 2019). Besides, patient stratification based on novel biomarker signatures can be useless if there are no corresponding therapeutic opportunities. An ML model, to be clinically relevant, must not just outperform existing statistical approaches but also must possess actual real-world advantages that can be accommodated within standard medical workflows (Shah et al., 2019).

To help ensure maximum validity and reproducibility of applications in medicine, there must be adherence to standard reporting guidelines. The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement provides a sound basis for evaluating prediction models (Moons et al., 2015), and TRIPOD-ML extends these principles to the further complexities of ML development (Collins & Moons, 2019). Effective execution also demands inter-disciplinary collaboration among clinicians, data scientists, and technologists so that ML tools are comprehensively validated and mapped onto real-world clinical needs.

As ML becomes increasingly integrated with precision medicine, it brings important ethical concerns along with it, among them being the handling and protection of private patient data. Datasets often include personal information such as genetic profiles, demographic information, and medication histories, which are prone to privacy concerns. Although anonymization is the most common method of data protection, it is not foolproof; sophisticated re-identification techniques have been used by commercial entities to penetrate anonymized datasets, with further abuse by insurance firms (Tanner, 2017).

New methods like data decentralization and federated learning—where models are trained on decentralized datasets without consolidating personal data—offer promising solutions for enhancing data privacy in ML studies (Rieke et al., 2020). At the same time, open communication by clinicians with patients remains vital to public trust. One-to-one

discussion and public meeting events, such as PPIE events, can enlighten patients on how ML assists in disease management and how their data is safeguarded (Mirzaei & Kashian, 2020).

Another essential aspect is bias. Discriminatory outcomes have been described in non-clinical AI systems, including racial discrimination in facial recognition and gender discrimination in recruitment algorithms (Yarger et al., 2019; Perkowitz, 2021). Such issues are also rampant in healthcare. A widely used algorithm in the U.S. healthcare system was found to underestimate the medical needs of Black patients due to underrepresentation in training data (Obermeyer et al., 2019). Similarly, ML models have also been demonstrated to have heterogeneity in predicted mortality across ethnic groups, challenging fairness and generalizability (Chen et al., 2018).

The majority of immune-mediated inflammatory diseases (IMIDs) are themselves affected by demographic factors such as sex and ethnicity—for instance, autoimmune disease being more prevalent in women (Gleicher & Barad, 2007). Datasets, however, only capture the most represented populations, unintentionally excluding vulnerable populations. Additionally, ML models are highly susceptible to missing data, which may disenfranchise those patients who have irregular healthcare access or incomplete records (Arpey et al., 2017; Gianfrancesco et al., 2018). To prevent these flaws, it is critical to foster diversity in development teams and datasets to facilitate more comprehensive representation in decision-making, bias evaluation, and algorithmic accountability.

5. Shaping the Future of Personalized Medicine

Despite these challenges, ML is a cornerstone of precision medicine creation, in which the goal is to render treatment choices more individualized to the unique characteristics of each patient. Standardized pipelines at every stage of ML adoption—from data collection and preprocessing to model training, validation, and clinical deployment—are required to achieve this vision (Plant & Barton, 2021). Standardization maximizes data relevance, ensures adequate sample sizes, minimizes redundancy, and ultimately enhances patient stratification and therapeutic targeting.

Identification of reproducible biomarkers associated with treatment response is a critical step towards individualized treatment. However, rigorous validation with external datasets should be conducted to guarantee model generalizability. Although ML has the

potential to revolutionize individualized treatment by predicting disease risk and tailoring treatment, its implementation will have to be weighed against ethical concerns associated with healthcare disparities and resource limitations (Rose, 2013).

Future research needs to attempt to establish whether ML-based solutions translate to improved long-term patient outcomes, especially in actual clinical practice in real life. This will require large clinical trials and outcome-based evaluations that go beyond performance metrics exclusively and instead focus on actual improvements in quality of life, disease trajectory, and treatment efficacy.

6. Conclusion

Machine learning offers powerful solutions to centuries-old challenges in diagnosing, prognosticating, and treating immune-mediated inflammatory disease. By enabling high-sensitivity biomarker discovery and patient stratification, ML supports more precise and effective clinical decision-making. This is particularly valuable in the treatment of complex, heterogeneous conditions such as autoimmune and chronic inflammatory disease. Yet the path to clinical integration is fraught with technical, ethical, and systemic challenges. From safeguarding patient privacy to preventing algorithmic bias, a multilateral approach is necessary—one that combines methodological rigor with ethical oversight and inclusive design. By embracing interdisciplinary collaboration and stringent validation practices, ML can fulfill its transformative potential, advancing personalized medicine and improved outcomes for diverse patient populations.

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