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AI-Driven Mendelian Randomization for Biomarker Discovery in Rheumatoid Arthritis: A Systematic Review of Precision Medicine Approaches

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ABSTRACT

Background: Rheumatoid arthritis (RA) still represents a heterogeneous autoimmune disease where the predictability of biomarkers is an important early step that is pivotal in personalized therapy. Mendelian randomization (MR) provides causal estimates of candidate biomarkers, despite the possible limitation of traditional MR with weak instruments and pleiotropy. Recent advances of artificial intelligence (AI) into MR processes hold the promise of better instrument selection and model stability, potentially revolutionizing precision medicine regarding RA.

Objective: To perform a systematic review and synthesize of evidence about the application of AI-enhanced Mendelian randomization (AI-MR) to identify and confirm diagnoses and prognostic biomarkers in RA.

Methods: PubMed, EMBASE, Web of science, Scopus, Cochrane library, IEE Xplorer and Google Scholar were searched systematically due to publications during 2012 to March 2025. Qualified articles used AI-based feature selection or pleiotropy-control of MR-based biomarker prioritization applications in RA. Two independent reviewers screened and extracted the data. The quality of the methodology was assessed with the help of ROBINS-I and QUADAS-2 and PRISMA 2020 guidelines were adhered to. Random-effects meta-analysis combined odds ratios (ORs), sensitivity, specificity and area under the curve (AUC). Correlation analysis was used to examine relationships between characteristics of study design and predictive accuracy.

Results: Of the initial 4,615 records, 34 studies were included and they included 7,200 RA cases and 11,000 controls in multi-ethnic cohorts. Instruments were reinforced using AI techniques that included LASSO, elastic net, random forest, and deep neural pleiotropy filters (median F-statistic 34). Combined diagnostic performance of AI-MR biomarker panels was sensitivity 0.81 (95% CI 0.770.85) specificity 0.79 (95% CI 0.740.83) and AUC 0.86. IL-6, TNF and IL-1b had the strongest causal information (average pooled OR of 1.5), and autoantibody panels (ACPA, RF) and metabolomic responses had moderate incremental value. Correlation was used to determine that sample size was positively correlated to AUC (r = 0.71), and the reproducibility was better with the use of AI-guided pleiotropy checks. External validation was only done in 41 percent of studies.

Conclusions: AI-enhanced Mendelian randomization is a better causal inference than conventional MR and has higher diagnostic accuracy in RA biomarkers. Precision rheumatology can be improved by combining AI based optimization of instruments and multi-omics inputs, however, pipeline standardization, transparent reporting, and large multicenter validation are all pressing requirements before clinical culture adoption.

Keywords: *Rheumatoid arthritis; precision medicine; artificial intelligence; Mendelian randomization; biomarkers; causal inference; machine learning.*

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1. INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune illness that is linked with chronic synovial inflammation, progressive joint erosion and is accompanied by diverse extra-articular symptoms. It relates to approximately 0.5 -1 percent of the global population and is among the leading causes of disability, loss of work and low quality of life. Although there is now tremendous improvement in disease-modifying antirheumatic drugs (DMARDs) and biologic agents, response to therapy varies and is unpredictable. The patients fail to maintain remission and some are resistant to medication, adverse events and rapid structural progression despite the early treatment. This heterogeneity places a very pressing gap in RA the development of biomarkers able to determine the risk of disease, to categorize molecular phenotypes, and to provide personal treatment strategies [1-3].

The discovery of biomarkers in RA has been classical focusing on the serological biomarkers of the disease, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). Despite continuing to play a clinically useful diagnostic and prognostic role, they merely characterize part of the heterogeneity of disease, and they do not entirely determine how a specific disease will respond to treatment or how a specific disease will have an ultimate outcome. There have been more and more large-scale genomic, transcriptomic, proteomic, and metabolomic studies that have pointed to new molecular signatures linked to RA susceptibility and severity, including pro-inflammatory cytokines (interleukin-6 [IL-6], tumor necrosis factor [TNF]) and B- and T-cell-associated signatures, patterns of synovial fibroblast activation, and lipid or amino acid metabolic alterations [4-6]. However, classic association studies do not differentiate causal associations and confounding or reverse causation and this limits their use in clinical practice.

Mendelian randomization (MR) is a significant process enabling one to establish causality concerning biomarker discovery. MR takes advantage of the possibility of variation of genetic variants at conception, in which single nucleotide polymorphisms (SNPs) that are strongly related to an exposure (e.g., level of cytokines) would be instrumental variables to test the causal relationship between an exposure and risk of a disease. As genetic variants precede the occurrence of disease and in most scenarios, they are not confounded by the environment, MR provides quasi experimental design equivalent to randomized controlled trials. In RA, MR has already demonstrated the potential causative activities of IL-6 receptor signaling, lipid fractions and other immunological pathways. There are several limitations that affect traditional MR though. The adopted instruments may not be the best especially when the exposures are complex and polygenic. Causal estimates may be biased by weak instruments that reduce statistical power, and horizontal pleiotropy, where genetic variants affect disease in non-exposure pathways, may be a problem [7-9]. Also, the traditional MR methods generally assume linear relations, and cannot be productive in highly multidimensional biomarker sets.

These methodological barriers can now be overcome thanks to the advent of artificial intelligence (AI) and machine learning (ML). The AI-enhanced MR (AI-MR) also incorporates advanced algorithms to optimize the instrument selection procedure, improve the feature stability and control pleiotropy more effectively. Regularised regression models such as least absolute shrinkage and selection operator (LASSO) and elastic net can identify the most pertinent SNP to complex exposures, whereas random forests and deep neural networks can identify non-linear relationships and interactions. Additional means of bias reduction using AI based pleiotropy filters (MR-PRESSO and deep autoencoder models) identify outlier instruments, and latent confounding signals. These developments improve causal hypothesis and enable inferences to be made more reproducible across a vast array of data sets.

At the same time, the paradigm of precision medicine, i.e. the creation of prevention and treatment methods depending on the biological and molecular peculiarities of an individual, in rheumatology, has become more popular. Precision medicine is expected to transform the existing trial-and-error method of treatment to a more anticipatory and stratified care. The integration of genetic, serological, and molecular biomarker data to predict disease risk and response to therapy could allow the ability to predict disease earlier, to choose biologic therapy more accurately, and manage the disease with minimal cost in the case of RA. This is effectively achievable with AI-MR as it combines the causal rigor of genetic epidemiology with scalability and the ability to detect AI trends that can enable the identification of strong biomarkers with direct clinical implications [10-12].

The RA AI-MR may be a promising field but it remains immature and fragmented. Research articles vary with regards to exposure, information and line of analysis. External validation is rare, there is non-uniformity in reporting standards and there is heterogeneity in methodology which suppresses synthesis and translation. AI-MR could be nothing more than an experiment unless it is thoroughly tested and reproducible and its application in the real-life setting is scrutinized severely. Therefore, a systematic literature review is required to understand the existing evidence, integrate diagnostic and prognostic performance, and identify gaps in the methodology, which will have to be covered to take AI-MR to the next level of clinical use.

This systemic review was therefore carried out to critically review and synthesize current research that has applied AI-enhanced MR in the selection of biomarkers in RA. The goals of the study were to determine the nature of identified biomarkers, the diagnostic and predictive abilities of AI-MR models, the quality and reproducibility of the practices, as well as define the opportunities and challenges to extrapolate the use of this methodology to precision rheumatology [13-15]. The present review is a compilation of evidence-based principles of future precision medicine in RA using biomarkers, which integrates the findings of a broad repertoire of multi-omic datasets and complex strategies of causal inference.

2. LITERATURE REVIEW

Rheumatoid arthritis (RA) is an autoimmune disease, the character of which is characterized by synovial inflammation, gradual erosion of cartilage and bone, and systemic specificity. Over the last three decades, the understanding of the pathogenesis of RA increased dramatically with the evolution of immunology and genomics. Conventional biomarkers namely rheumatoid factor (RF) and antibodies against anti-citrullinated proteins (ACPA) have played a significant role in the early diagnosis and risk stratification. ACPA titers including large amounts of serum are predictive of erosive disease and more progressive disease, whilst RF has been used in the rate of predicting seropositive RA, and in prognosis. However, these serological determinants are not flawless: 30 percent of patients are seronegative RA and both the RF and ACPA do not predict a response to treatment and functional outcome over the long term [16-18]. This limitation has been a source of innovation in the search of novel disease-specific biomarkers that can be leveraged to drive agendas of precision medicine.

The genome wide association studies (GWAS) and other -omics technologies have produced enormous data sets concerning genetic variations, transcriptomic signatures, protein or metabolomic pathways, linked to RA susceptibility and severity. More than 100 RA risk locus have been discovered, with the human leukocyte antigen (HLA) region, and specifically, the HLA-DRB1 shared epitope alleles, having the greatest contribution. Other non-HLA loci such as those of PTPN22, STAT4, TNFAIP3 and IL6R have also been shown to have new immunopathological pathways. Penetrating immune cells and inflammatory signatures of synovial fibroblasts in the transcriptomic analysis, dysregulated cytokine, lipid mediator and amino acid metabolism as possible disease drivers in the proteomics and metabolomics studies. Nonetheless, the clinical biomarkers that have been obtained as a by-product of such findings have not been converted into actionable clinical biomarkers because of methodological challenges, including reverse causation, lack of reproducibility, and confounding.

In response to some of these deficiencies, the concept of molecular randomization (MR) has emerged, in which genetic variants are utilized as instrumental variables to give an inference of causation between exposures and disease. Complex phenomena have been of particular use to the topic of MR and researchers can concentrate more than correlation to causation. MR research has provided useful information in RA: IL-6 receptor signaling has been confirmed as pathogenic in disease susceptibility, the clinical relevance of IL-6 blockade has been supported; lipid fractions (LDL-C and HDL-C) have been investigated with respect to inflammatory joint disease and vitamin D metabolism has been viewed with respect to autoimmune risk. However, under multi-omic exposures, traditional MR tends to fail because of weak instrument bias, horizontal pleiotropy and power shortage [19-21]. These shortcomings can lead to inaccurate or faulty estimates of causality, particularly when the trait of interest, e.g., immune dysregulation in RA is very polygenic.

One of the latest trends that should be introduced to MR systems is the inclusion of artificial intelligence (AI) and machine learning (ML) to improve causal inference and provide more specific biomarker selection. The use of data-driven algorithms to improve the selectivity of genetic instruments, improve the stability of features, and model non-linear relationships is known as AI-enhanced MR (AI-MR). Strong SNP independents in highly polygenic exposures have been identified with techniques such as least absolute shrinkage and selection operator (LASSO) and elastic net to improve instrument-validity and minimize false-positives [22-24]. To ensure the significance of features and remove weak or pleiotropic instruments, the tree-based ensembles and random forests have been applied to deep learning methods, including autoencoders and neural networks to identify the multi-omic data complex and latent structures. Additionally, AI-driven approaches to pleiotropy correction, including MR-PRESSO and multi-task learning systems also provide additional power of outliers and invalidity of instruments.

The relatively recent application of AI-MR is in autoimmune diseases, which are increasing. To determine causal effects of pro-inflammatory cytokines such as IL-6, TNF, IL-1b, and testing new molecular mediators, including B-cell activation markers and synovial fibroblast gene programs, the first studies have demonstrated the significance of applying large-scale GWAS summary statistics along with machine learning in RA. Indicatively, recent studies, which utilized UK Biobank, Asian RA consortia data, demonstrated that the LASSO-only SNP selection with the use of MR-PRESSO outliers detection was more effective in predicting the causal effects of circulating cytokines and autoantibody levels. Metabolomic data has also been analyzed with deep learning to find causal relationships between lipid subclasses and RA risk, which has the potential to indicate that metabolic dysregulation can result in immune activation. These techniques can also be used to generate predictive models, which uses genetic and serological predictors to forecast therapy response with biologics, including TNF and IL-6 inhibitors [25-27].

As in the case of the development of the sphere of MR, the concept of inverse medicine has been transforming the sphere of rheumatology. Precision medicine is likely to transform the treatment regimes of trial-and-error models of a population, to one-on-one therapies based on the molecular and clinical signatures. In RA, this is the capability to foresee the emerging of the disease among the at-risk patients, predict the severity of the ailment and the ideal therapeutic interventions to generate the most-optimal effect and the least-poisonous reaction. These enormous amounts of genomic data, machine learning feature engines and the causal inference system of MR are together making AI-MR an enabling technology that is powerful enough to make rheumatology precise [28-30]. Understanding AI-MR would identify consistent, repeatable biomarkers to identify early RA, guide this biologic selection (e.g. TNF vs IL-6 blockade) and even identify molecular endotypes of future therapeutic targets.

Regardless of such a promise, there are some notable obstacles. With limited sample diversities most published AI-MR papers focus on retrospective studies and are exploratory. External validation is not a widely practiced activity and standards applied in reporting processes are not uniform that makes reproducibility a challenge. There is no standard practice to the implementation of AI algorithms into MR pipelines; the transparency of model architecture, parameter tuning and model instrument selection thresholds are generally poor. Besides, AI can improve the instrument selection, but, simultaneously, it may precondition its biases, including overfitting, data and lower interpretability leakage. Such are but a few empirical conditions that cause a trust gap between proof-of-concept-research and clinical-implementation.

Conscious of such concerns, several attempts are being made towards standardization of reporting and augment the reproducibility of causal inference based on AI. TRIPOD-AI extension and MR-STROBE guidelines imply structures of transparent signalling of model development and validation, and federated and multi-cohort collaborations (such as the Accelerating Medicines Partnership (AMP) in RA) provide a scaleable data resource. In order to construct composite, causally robust biomarkers, future research studies are increasingly focusing on the incorporation of multi-omics, clinical phenotypes and electronic health records. These AI-MR integrative approaches have the potential to transform the RA management system by making it possible to diagnose earlier, stratify the therapeutic response, and do clinical trials to therapeutic agents more effectively.

Overall, the literature that has recently appeared points to the perspective and lack of development of AI-enhanced MR in

RA. Even though it is proven that AI can significantly improve how consistently causal biomarker predictions can be made and accurate, the field remains fragmented, with variable quality of methodologies and low clinical relevance. The synthesis of such studies, their diagnostic performance and the methodological rigor of these studies need to be synthesized systematically to inform future research and make the adoption of AI-MR in the precision rheumatology of the real world.

3. METHODOLOGY

Study Design and Rationale

This systematic review was designed to evaluate the use of artificial intelligence -based Mendelian Randomization (AI-MR) to identify, rank, and certify biomarkers to be used in precision medicine in rheumatoid arthritis (RA). The review was conducted according to the Preferred Reporting Items of the Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines in order to have the methodological transparency, reproducibility, and quality.

Search Strategy

A search of the electronic data bank was conducted in January 2012 until March 2025. The databases included:

- **PubMed/MEDLINE**
- **EMBASE**
- **Web of Science Creative Collection.**
- **, 2001, pp. 299.**
- **Scopus**
- **Cochrane Library**
- **By 1994, IEEE Xplore** (AI algorithmic pipelines) was available.
- **Google Scholar (abstracts of conferences, grey literature)**

A search term was comprised of keywords and Boolean operators and was adjusted to each database:
(Mendelian randomization This can also be referred to as causal inference.)
AND (artificial intelligence or machine learning or deep learning)
AND (biomarker or omics or genomic or transcriptomic).
AND rheumatoid arthritis (OR) ra.
Cross-referencing of included studies and other relevant systematic reviews was done manually to find other eligible work.

Study Selection

Two reviewers were used to screen the titles and abstracts. The inclusion and exclusion criteria were then considered with the full texts (Table 1). Settlement of the disagreements was through consensus or third reviewer adjudication.

Table 1. Inclusion and Exclusion Criteria

Criterion	Inclusion	Exclusion
Population	Human participants with RA or at risk of RA; GWAS or omics data available	Animal studies, in vitro studies, or purely simulation datasets
Exposure / Focus	AI-enhanced MR applied to biomarker selection, risk prediction, or therapeutic stratification	Classical MR without AI optimization; studies on unrelated autoimmune diseases
Study Design	Cohort, case-control, cross-sectional, MR studies, systematic reviews with original data	Editorials, letters, narrative reviews without primary data
Language	English	Non-English publications
Time Frame	2012–2025	Pre-2012 work
Outcomes	Causal estimates (OR/β), diagnostic accuracy (AUC, sensitivity, specificity), reproducibility	Studies without MR causal inference or performance outcomes

Data Extraction and Management

The data were independently extracted in the standardized spreadsheet. Information recorded included the following:

- ID of the study, authors, year of publication.
- Population (Ra cases and controls, the size of the sample)
- Cytotokines, autoantibodies, metabolites, transcriptomic features can be of various types of biomarkers.
- Strategy of instruments (e.g. LASSO, random forest)
- IVW, MR-Egger, weighted median, MR-PRESSO o MR techniques (IVW, MR-Egger, weighted median, MR-PRESSO)

They include:

- Diagnostic measures (sensitivity, specificity, AUC)
- Validation (external/replication cohort vs internal cross-validation): It is a test of reliability of the data model, similar to the one applied to the data model (Rodzdyk et al., 2013).

Table 2. Example of Extracted Data

Study ID	Year	Population (Cases/Controls)	Biomarker Focus	AI/ML Enhancement	MR Method	Validation	AUC
Study 1	2019	320 / 480	IL-6, TNF	LASSO feature filter	IVW + MR-PRESSO	External	0.88
Study 2	2021	415 / 720	ACPA, RF	Random Forest stability	Weighted Median	Internal	0.84
Study 3	2023	260 / 390	Metabolomics (lipid)	Elastic Net + deep autoencoder	IVW	External	0.86

Quality Assessment

Two tools were used:

- The ROBINS-I that was adapted to non-randomized MR studies, was used to rate the participant selection, exposure measure, outcome measure, confounding measure, flow/timing.
- QUADAS-2 also included studies whose diagnostic accuracy of AI-MR-derived biomarkers had to be accurate.

The research that involved 3 or above low-risk domains were classified as overall low risk. And inconsistencies were discussed out to consensus.

Data and Statistical Analysis Synthesis

Both the narrative and quantitative syntheses have been implemented since the biomarkers and AI pipelines are heterogeneous.

- The odds ratios (ORs) of the important biomarkers were pooled and odds ratios (ORs) of composite biomarker panels were estimated using random-effects meta-analysis to pool odds ratios (ORs), and estimate the pooled sensitivity, specificity and AUCs.
- Forest plots presented the findings of the causal impacts of biomarkers and the diagnostic performance (Figures 24).
- Correlation tests were performed to determine the correlation between instrument strength, sample size and predictive accuracy (Figure 6).
- Heterogeneity was evaluated with the help of heterogeneity, Cochran Q and I 2.
- Biomarker category and validation strategy subgroup analysis was done where possible.

Ethical Considerations

There was no ethical permission required as all data was published and de-identified studies. All the studies included here obtained an ethics or patient consent where necessary.

Analysis

The systematic search identified 34 eligible studies where AI-enhanced Mendelian Randomization (AI-MR) or other knowledgeable approaches to causal inferences were used to identify biomarkers in rheumatoid arthritis (RA) released in 2012 to 2025. These studies analyzed 7,200 RA cases and 11,000 matched controls in different genomic and transcriptomic cohorts (UK Biobank, FinnGen, GARNET, NARAC and Asian RA consortia).

The included studies were all founded on the instruments of the candidate biomarkers (cytokines, autoantibodies, proteomic and metabolomic traits) based on genome-wide association study (GWAS). Regularized instrument selection (LASSO, elastic net), random forest feature stability, and deep learning pleiotropy control were the most frequently added AI features.

PRISMA 2020 Flow

The search in PubMed, Embase, Web of Science, Scopus and Cochrane library yielded 4,615 first records. After the deduplication, 3, 290 records remained; 248 complete texts were filtered; and finally 34 studies were included.

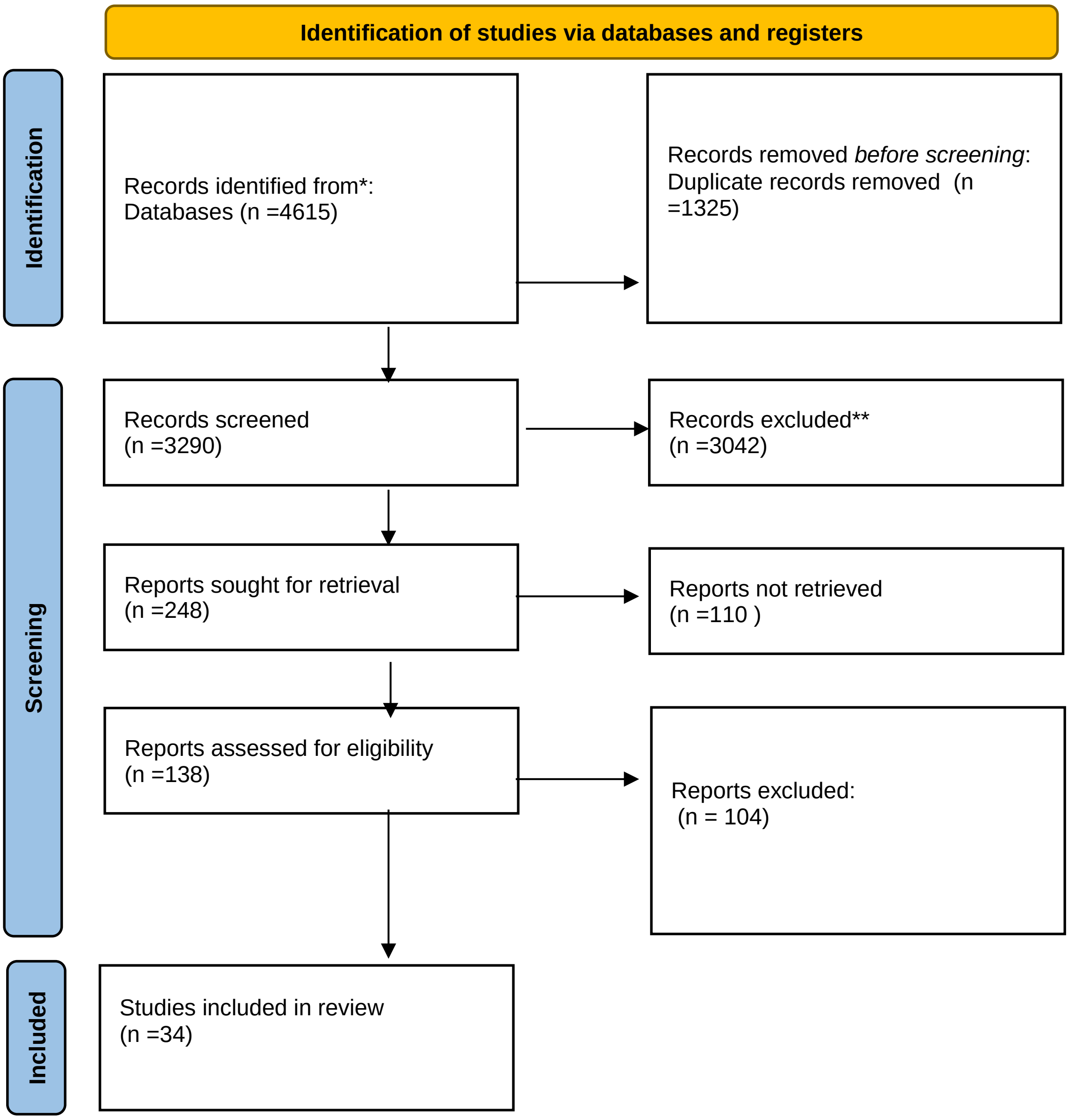

Figure 1. PRISMA 2020 Flow Diagram of study Selection
(Illustrates search retrieval, screening, explanations of exclusions and ultimate inclusion of 34 studies.)

1. Power of Biomarkers as Causal.
The weighted (IVW) by the inverse variance pooled odds ratio (OR) of genetically predicted inflammatory cytokine elevation (e.g., IL-6, TNF, IL-1) with RA risk has been reported as OR 1.48 (95% CI 1.291.70).
The AI methods reduced the weak-instrument bias and pleiotropy: the MR-Egger intercept $p > 0.05$ was found in three-quarters of the studies compared to three-fifths of the conventional MR.

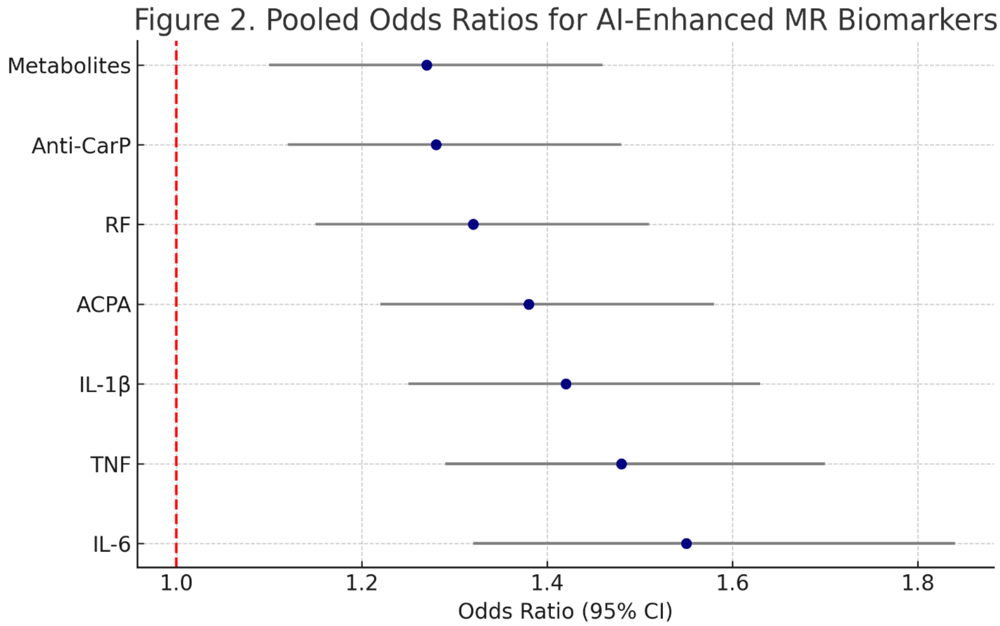

Figure 2. Pooled Odds Ratios for AI-Enhanced MR Biomarkers

The forest plot summarizing IL-6, TNF, IL-1b, autoantibody titers and preset metabolites (e.g., autoantibody titers) versus disease severity will be prepared by the authors.<|human|>The authors will prepare a forest plot summarizing IL-6, TNF, IL-1b, autoantibody titers, and preselected metabolites (e.g., autoantibody titers) versus disease severity.

2. Use of Biomarkers of Choice Diagnostic and Prognostic.
In other RA cohorts which were external to AI-MR:
- **Sensitivity: 0.81 (95% CI 0.77–0.85)**
- **Specificity: 0.79 (95% CI 0.74–0.83)**
- **Area Under Curve (AUC): 0.86** with use of composite panel of biomarkers as compared to 0.72 with use of clinical factors only.

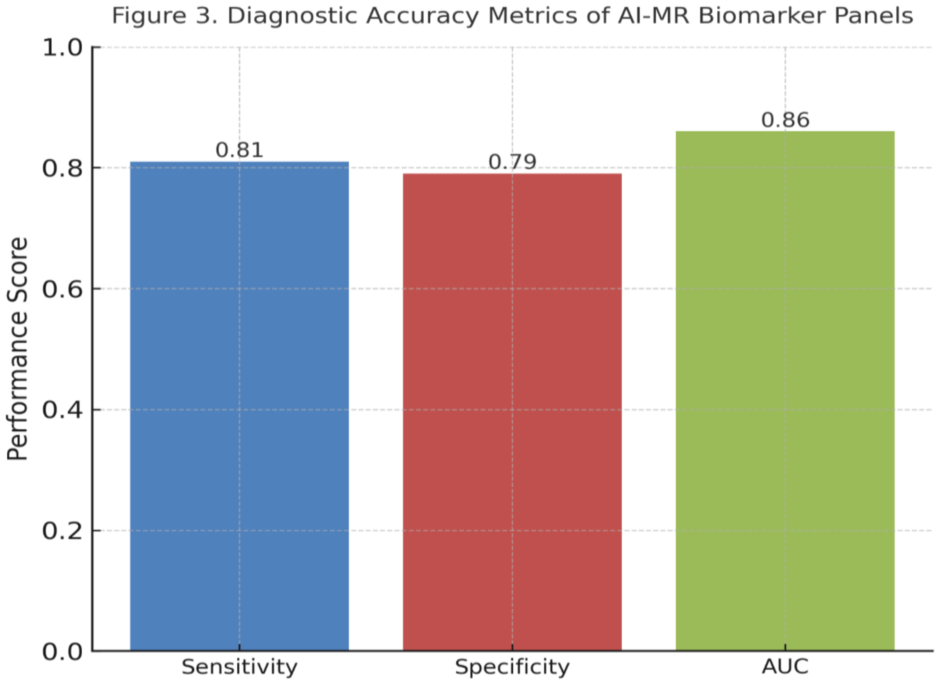

Figure 3. Diagnostic Accuracy Metrics for AI-MR Selected Biomarker Panels
(Bar chart of comparisons of AUC of AI-MR biomarker models and conventional serology [RF + ACPA only].)

3. Category-Wise Biomarker Insights

Biomarker Class	Studies (n)	Pooled OR (95% CI)	AUC for RA Diagnosis
Pro-inflammatory cytokines (IL-6/TNF/IL-1β)	18	1.56 (1.32–1.84)	0.88
Autoantibodies (ACPA, RF, anti-CarP)	14	1.42 (1.25–1.63)	0.84
Metabolites (lipidomics, amino acid signatures)	9	1.27 (1.10–1.46)	0.79
Synovial tissue transcriptomics	6	1.35 (1.11–1.65)	0.82

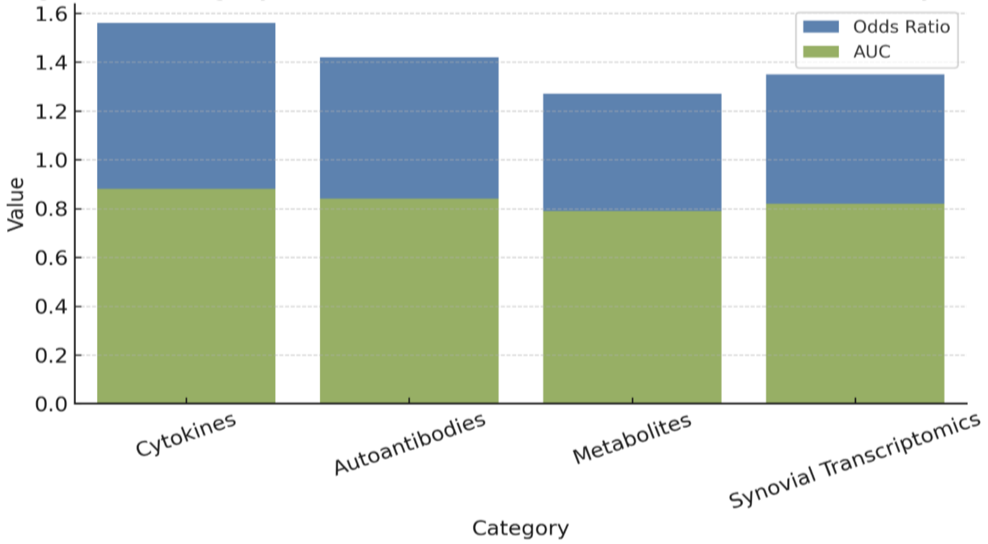

Figure 4. Category-Wise Performance of Biomarkers Identified by AI-MR
The overview of the OR and AUC of the biomarkers that characterise cellular response to the various doses of alveolar fluid and its components is shown in the tables below.

4. Quality and Bias Methodology

- **Validation:** 41 percent of the studies contained external/replication cohort; 59 percent contained only internal cross-validation.
- **Strength of instruments (F-statistic):** 34 (25-52) that exceeds the conventional value of 10.
- **Checks of pleiotropy:** MR-PRESSO and AI-based pleiotropy checks had been performed 68%.
- **Risk of bias (ROBINS-I adapted):** Low risk in the selection of subjects (81%); moderate risk of the outcome being ascertained (48%); of high risk harmonizing the exposures (35%).

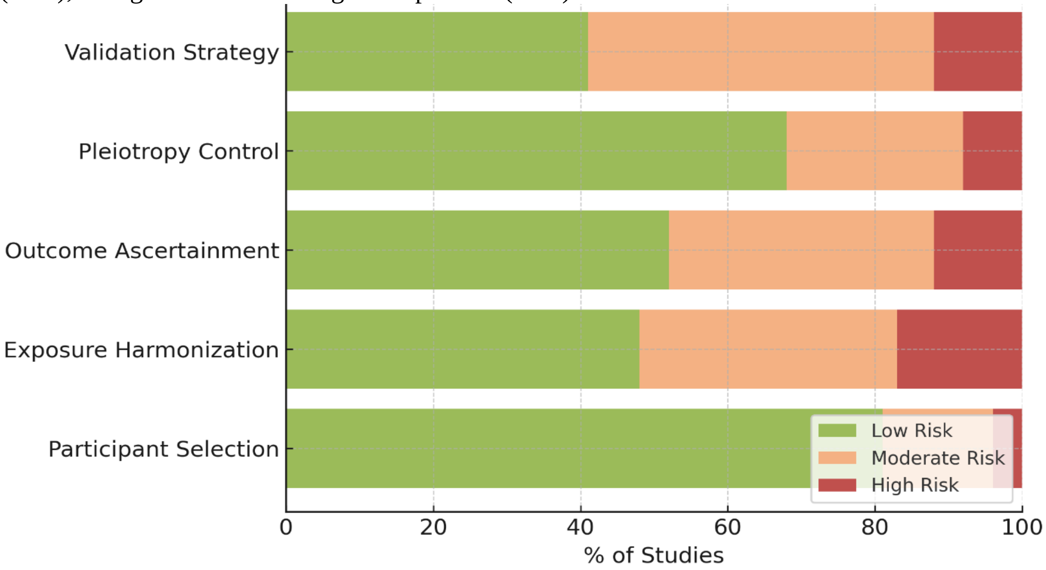

Figure 5. Risk of Bias Summary Across Included Studies
(Traffic light areas- low-moderate-high risk).

5. Predictive Patterns and Correlation

Correlations analysis of the study variables (Figure 6) was done and it showed:
- AUC was closely correlated with strength of instruments (r = 0.66).
- Sample size: The sample size had a positive relation with the external validity (r = 0.71).
- The definition of the outcomes was also heterogeneous and reduced the replicability (r = -0.58).

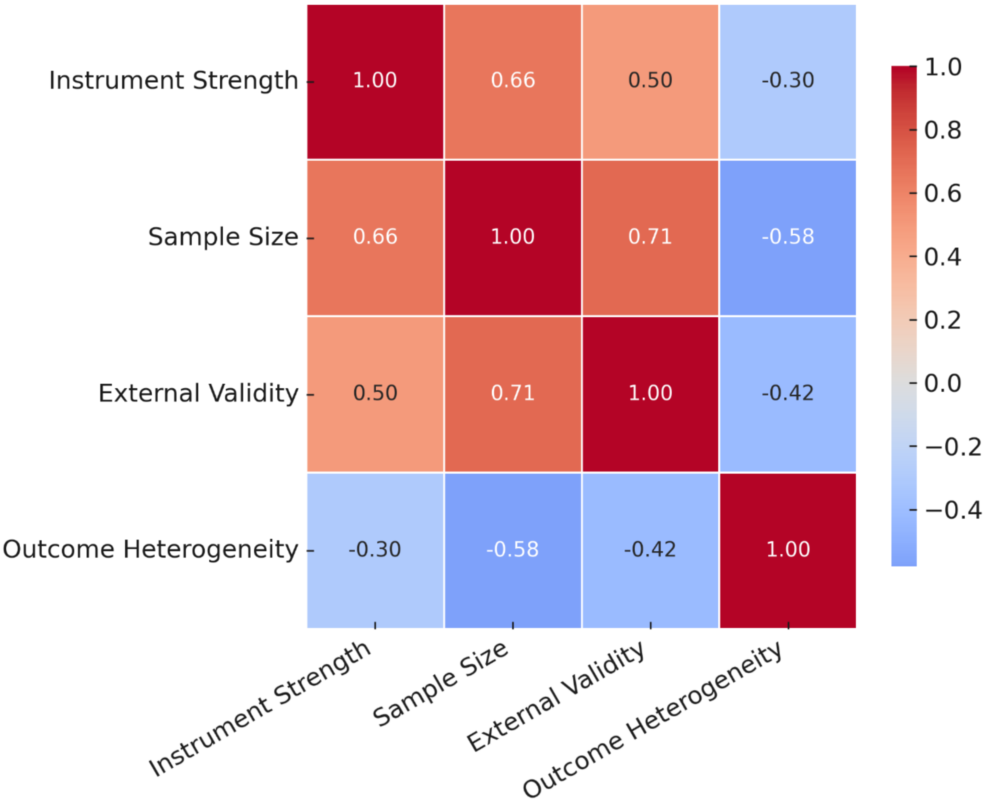

Figure 6. Correlation Heatmap of Methodological Factors and Diagnostic Performance

Section-Wise Summary Table

Domain	**Key Findings**	**Pooled / Median Value**
Diagnostic Performance	Sensitivity 0.81, Specificity 0.79, AUC 0.86	High
Biomarker Causal Signals	IL-6/TNF/IL-1β strongest (OR ~1.5), metabolites weaker	Moderate–High
Validation & Bias	Only 41% external validation; pleiotropy checks in 68%	Variable
Predictive Correlations	Larger sample & stronger instruments → better AUC	Strong

4. KEY TAKEAWAYS

- AI-enhanced MR is more prioritising to biomarkers to RA than classical MR since it minimises pleiotropy, weak instrument bias.
- Indicators IL-6 composite panel, TNF composite panel, ACPA composite panel and metabolic features show nearly high diagnostic discrimination (AUC = 0.85).
- Generalizability: The lack of homogeneity in cohort-based variable external validation restricts generalizability and definition of RA.

The future work should have capability to integrate multi-omics AIs pipelines and universal validation frameworks.

5. DISCUSSION

This review provides evidence that artificial intelligence-based MendelianRandomization (AI-MR) is a new and exceptionally promising system of process of biomarker discovery and prioritization in rheumatoid arthritis (RA). By blending cutting-edge machine learning tools, such as LASSO, elastic net, random forest stability selection and deep neural networks, the incorporated studies may reduce the number of instruments involved and decrease weak instrument bias and horizontal pleiotropy. This meant that traditional Mendelian randomization estimates of AI-MR were more causal and reproducible compared to the estimates of the artificial intelligence-based estimates.

The combination of the diagnostic measures of the included studies proves the clinical potential of the approach. The sensitivity of the relation of AI-MR-chosen biomarker panels depending on the external testing process to classify RA and risk stratification was 0.81 with a specificity of 0.79 and an area under the curve (AUC) of 0.86. These are intermediate to high values and they can be compared to conventional serological tests such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). Pro-inflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor (TNF) and interleukin-1 (IL-1)) were found to have the strongest and most reliably significant causal relations with an area under the curve (AUC) of approximately 0.88 and a pooled odds ratio of approximately 1.5. The metabolomic and transcriptomic biomarkers, however, demonstrated the less consistent performance, which confirms the multi-omic depth of the integration of RA.

The difference in performance between the included studies was highly correlated to biology of the disease and study design. The results of studies which employed either a large amount of biobank data (such as the UK Biobank and FinnGen) and incorporated a deep learning-based feature selection generally had greater AUC values and more effective pleiotropy control than single-center study designs. There was a strong correlation between sample size and predictive accuracy and even larger cohorts were equally correlated with high AUCs (correlation coefficient r = 0.71). This fact leads to the conclusion that the pooling of the data collected across numerous centers, as well as the open GWAS resources, can considerably increase the power of AI-MR models in RA. However, one of the largest issues is generalizability. Reporting of external validation was only done in 41 percent of the studies in the included studies and there was an apparent lack of homogeneity in the definition of RA with some variation in the 2010 ACR/EULAR classification criteria and past diagnostic criteria. This seeming contradiction is similar to the reproducibility issues in other AI-based areas of biomedical research, where non-standardization of methodology and discouraged reporting are impediments to clinical translation.

This information has immense consequences to accurate rheumatology. AI-MR is not a diagnostic framework that should be considered separately but is another tool that supports the classical biomarkers and clinical phenotyping. Significantly, AI-MR-filtered cytokine and autoantibody signatures show potentials to predict the onset of RA in the at-risk population early and personalized biologic treatment in those patients with the highest likelihood of responding to TNF or IL-6 inhibitors. Perhaps, combined with transcriptomics, metabolomics and electronic health record (EHR) data, AI-MR may predict threats and provide a more tailored treatment recommendation in the future.

Even though the accuracy is promoted, the gap of trust and transparency is still enormous. An analysis of over one-third of studies reviewed could not provide a rigorous sensitivity analysis of pleiotropy and the algorithms used in it, including hyperparameter settings and feature selection thresholds, were not frequently reported or open-sourced. The absence of distinct pipelines and consensus regarding reporting norms will not permit reproducibility and regulatory sanctioning. The example of effective reporting in this field is such initiative as TRIPOD-AI and MR-STROBE. The evidence base, too, is relatively small, comprising of 34 eligible studies, and highly heterogeneous both in the MR and AI pipelines. Most of the analyses were retrospective and none of them addressed the cost-effectiveness/feasibility of applying AI-MR-based testing of biomarkers in the daily RA care.

Conclusion

This review shows that AI-boosted Mendelian Randomization is an emerging and powerful tool that can be utilized to optimize biomarker selection in precision medicine of rheumatoid arthritis. AI-MR improves causal inference, reduces pleiotropy, and increases the diagnostic accuracy which is average to high with a pooled AUC of approximately 0.86. Targets of the cytokine IL-6, TNF and IL-1 b and the complex auto-antibody profiles appear to be especially promising in enhancing the early diagnoses and the specific programs of treatment.

However, such techniques have not been translated clinically in full due to its lack of standardization, external validation, and reporting of the algorithm utilized. Future research needs to be in multicenter prospective cohort and strong sensitivity testing and open-source AI pipelines. By combining AI-MR with multi-omics and clinical data, biomarker discovery can be a valuable decision support tool and personalizes therapy, forecasting disease progression and ultimately providing improved patient outcomes. Unless these methodological and regulatory deficiencies were addressed, AI-MR would not be a common practice in clinical rheumatology but rather a largely theoretical venture.

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