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Ahmad Taha Khalaf
Anhui University of Science and Technology (AUST)
Yonghong Sun
The Third Affiliated Hospital of Soochow University
Xiaoming Liu
lxm200523000@163.com

Southern University of Science and Technology Hospital

Article

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Integrative Bioinformatics and Machine Learning Identify ARG1 and S100A12 as Novel Biomarkers Associated with Innate Immune Barrier Dysfunction in Psoriasis

Ahmad Taha Khalaf[a, #], Yonghong Sun[b,#], and Xiaoming Liu[c, #*]

a. Medical College, Anhui University of Science and Technology (AUST), Huainan 232001, China.
b. Department of Nuclear Medicine, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu 213003, China
c. Department of Dermatology, Southern University of Science and Technology Hospital, Shenzhen 518055, China

* Corresponding author: liuxiaoming@sustech-hospital.cn; ta9191818@gmail.com

Co-first authors.

Abstract

Background: Psoriasis is a chronic inflammatory skin disease in which the dysfunction of the innate immune cell barrier (IICB) is implicated. However, the underlying molecular mechanisms remain incompletely elucidated. This study aimed to identify and characterize IICB-related biomarkers and their regulatory networks, thereby elucidating their roles in psoriasis pathogenesis. Methods: We obtained psoriasis-related transcriptomic datasets and a list of IICB-related genes (IICB-RGs) from public databases and the literature. We performed differential expression analysis to identify DEGs, then intersected them with IICB-RGs to identify candidate genes. We then used protein-protein interaction (PPI) network analysis, machine learning, and expression validation to identify biomarkers. We constructed a nomogram to evaluate the diagnostic probability of psoriasis. We investigated the biological functions of the biomarkers through enrichment and immune microenvironment analyses. We also predicted the upstream regulatory network and screened potential therapeutic drugs targeting the biomarkers. Results: ARG1 and S100A12 were identified as biomarkers. The diagnostic nomogram incorporating these biomarkers demonstrated excellent predictive performance. Notably, both ARG1 and S100A12 were significantly enriched in key pathways, including "Toll-like receptor signaling pathway", "cytosolic DNA-sensing pathway", and "cell cycle". Immune microenvironment analysis revealed marked dysregulation of immune cells in psoriasis and showed that both biomarkers exhibited highly similar correlation patterns with differentially infiltrated immune cell populations. Moreover, hsa-miR-27a-3p was identified as

a common regulator that targets both biomarkers. Drug prediction identified 21 drugs for ARG1 (e.g., Dequalinium) and 5 for S100A12 (e.g., Eptinezumab). Conclusion: This study identified ARG1 and S100A12 as pivotal IICB-related biomarkers in psoriasis, providing insights into their roles in dysregulated immune pathways and the skewed immune microenvironment. The constructed regulatory network and predicted therapeutic agents provide valuable resources for understanding psoriasis pathogenesis and exploring potential treatment strategies.

Keywords: Psoriasis; Innate immune cell barrier; Machine learning; Immune dysregulation.

1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by recurrent episodes of erythematous, well-demarcated plaques covered with silvery scales [1,2]. The disease is driven by excessive keratinocyte proliferation and aberrant differentiation, accompanied by a sustained inflammatory response within the epidermis and dermis [1,2]. Histopathologically, psoriasis is marked by vascular dilation in the papillary dermis, infiltration of immune cells, predominantly T lymphocytes, and a complex cytokine network that perpetuates inflammation and tissue remodeling. Beyond the skin, psoriasis is increasingly recognized as a systemic condition associated with metabolic syndrome, cardiovascular disease, and psychological burden, underscoring its broader clinical significance [3]. Current therapeutic strategies include topical agents, phototherapy, conventional systemic treatments, and biologic therapies targeting key inflammatory pathways. Although these approaches have improved disease control, a substantial proportion of patients either fail to achieve adequate responses or experience diminished efficacy over time. Safety concerns, including infection risk and potential malignancy, may also limit long-term treatment. Moreover, the marked clinical and molecular heterogeneity of psoriasis complicates patient stratification and therapeutic decision-making [4]. The absence of reliable biomarkers to predict disease course or treatment response remains a major challenge. In this context, identifying robust molecular signatures linked to disease mechanisms is essential for advancing precision medicine in psoriasis [3-5]

The innate immune cellular barrier represents the first line of host defense and plays a central role in maintaining tissue integrity and immune surveillance. It is composed primarily of neutrophils, macrophages, and dendritic cells, which coordinate rapid responses through phagocytosis, cytokine production, and antigen presentation [6]. These cells not only initiate

early immune responses but also shape downstream adaptive immunity. Increasing evidence indicates that dysregulation of this barrier contributes directly to the pathogenesis of psoriasis. Lesional skin exhibits marked alterations in innate immune cell composition and function, including enhanced neutrophil infiltration, skewing of macrophages toward a pro-inflammatory phenotype, and activation of dendritic cell subsets [7-9]. In particular, M1-polarized macrophages amplify inflammation by releasing cytokines such as tumor necrosis factor α and interleukin-23. At the same time, plasmacytoid dendritic cells promote type I interferon production, a key event in early disease initiation [9, 10]. These processes contribute to keratinocyte hyperproliferation and sustain the inflammatory cascade. Despite these advances, the molecular architecture underlying innate immune barrier dysfunction in psoriasis remains incompletely defined. The identification of key regulatory genes within this network is therefore of considerable interest, as it may reveal novel biomarkers and therapeutic targets [10-13]

In this study, we sought to systematically characterize biomarkers associated with innate immune barrier dysfunction in psoriasis by integrating transcriptomic data with curated gene sets related to innate immunity. We analyzed publicly available datasets using differential expression profiling, protein interaction network construction, and machine learning approaches to identify candidate genes of diagnostic relevance. We further evaluated these candidates through expression validation and model construction to assess their predictive performance. We conducted functional enrichment analyses and immune microenvironment profiling to explore their biological roles, and examined upstream regulatory networks and potential therapeutic targets to provide a translational context. Through this integrative framework, the present work aims to refine the molecular understanding of psoriasis and to support the development of biomarker-driven strategies for diagnosis and treatment.

2. Materials and methods

2.1 Data acquisition

We obtained psoriasis-related datasets from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). Specifically, dataset GSE30999 (platform: GPL570) included 85 lesional skin samples from psoriasis patients (psoriasis group) and 85 matched healthy control skin samples (control group). Dataset GSE6710 (platform: GPL96) contained 13 lesional skin samples from psoriasis patients (psoriasis group) and 13 control skin samples (control group). In addition, we compiled a list of 1356 innate immune cell barrier (IICB)-

related genes (IICB-RGs) from relevant literature [14]. We downloaded all data on September 4, 2025.

2.2 Discernment and related functional analyses of candidate genes

We identified differentially expressed genes (DEGs) between the psoriasis and control groups using the limma package (v 3.56.2) [15] in GSE30999 (p.adjust < 0.05, $|\log_2$ fold change (FC)| > 1). Additionally, we generated a volcano plot for DEGs using the ggplot2 package (v 3.5.1) [16] and labeled the top 10 genes showing significant up- or down-regulation, ordered by |log2FC| in descending order. In contrast, we plotted a heatmap of the labeled DEGs using the ComplexHeatmap package (v 2.16.0) [17]. We determined the intersection of DEGs and IICB-RGs using the ggvenn package (v 0.1.10) [18], identifying genes pertinent to IICB within psoriasis that we subsequently designated as candidate genes. Next, using the clusterProfiler package (v 4.15.0.003) [19], we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses (p.adjust < 0.05) on the candidate genes to elucidate the biological functions in which they participate. The enrichment results were sorted by p-adjusted values in ascending order, and the top 5 most significant GO terms from each category (biological processes [BPs], cellular components [CCs], and molecular functions [MFs]) and the top 10 KEGG terms were selected for visualization.

2.3 Determination of biomarkers

To further screen for biomarkers associated with IICB in psoriasis, we first analyzed and visualized protein-protein interactions (PPIs) using the Search Tool That Retrieves Interaction Genes (STRING) website (https://www.string-db.org) (Confidence ≥ 0.4). Subsequently, we used the Maximal Clique Centrality (MCC), Density of Maximum Neighborhood Component (DMNC), and Edge Percolated Component (EPC) algorithms in the CytoHubba plugin of Cytoscape software (v 3.10.3) [20] to compute node connectivity. We intersected the top 50 genes from the 3 algorithms using the ggvenn package (v 0.1.10), and the intersecting genes were named hub genes. We also used 3 machine-learning algorithms to identify hub genes from GSE30999. Initially, we applied support vector machine-recursive feature elimination (SVM-RFE) using the caret package (v 6.0.94) (5-fold cross-validation), with the minimum error rate as the criterion for selecting SVM-RFE characteristic genes. Simultaneously, the glmnet package (v 4.1.8) [21] was used to perform a least absolute shrinkage and selection operator (LASSO) analysis, and 5-fold cross-validation was employed to train the model. The LASSO model exhibited the lowest error rate at the minimum lambda value (lambda = lambda.min),

whereby genes with non-zero regression coefficients were identified as LASSO characteristic genes. Additionally, the XGBoost algorithm was implemented using the xgboost package (v 2.1.1.1) [22] to compute the importance scores of each hub gene (feature importance ≠ 0), thereby identifying the XGBoost-characterized genes. We generated the intersection of SVM-RFE, LASSO, and XGBoost characteristic genes using ggvenn (v 0.1.10), and nominated the overlapping genes as key genes. Moreover, we compared the expression patterns of key genes in GSE30999 and GSE6710 between the psoriasis and control groups using the Wilcoxon test ($p < 0.05$). Genes displaying marked differential expression in both sets and exhibiting a consistent trend were designated as biomarkers.

2.4 Analysis of subcellular localization

Studying biomarker localization helped provide an in-depth understanding of their biological functions. The amino acid sequences, in FASTA format, for proteins encoded by biomarkers were retrieved from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov). Subcellular localization of the biomarkers was predicted using the CELLO database (https://cello.life.nctu.edu.tw).

2.5 Development and evaluation of a nomogram

In GSE30999, we developed a nomogram to evaluate the predictive probability of biomarkers for psoriasis occurrence using the rms package (v 6.8.1) [23]. We assigned a distinct score to each biomarker, and the total score, obtained by aggregating these values, was associated with an increased risk of psoriasis development. We generated a calibration curve using the rms package (v 6.8.1) to quantify the nomogram's predictive accuracy. A slope of the calibration curve approaching 1 indicated higher accuracy of the nomogram predictions. We also evaluated calibration reliability using the Hosmer-Lemeshow (HL) test ($p > 0.05$). Additionally, the pROC package (v 1.18.5) [24] was employed to plot the receiver operating characteristic (ROC) curve of the nomogram. The Area Under the Curve (AUC) was subsequently computed to assess the model's predictive value ($AUC > 0.7$). Concurrently, decision curve analysis (DCA) was performed using the ggDCA package (v 1.1) [25] to assess the nomogram's clinical utility.

2.6 Gene set enrichment analysis (GSEA)

GSEA was conducted to elucidate the biological functions of biomarkers during psoriasis progression. The gene set "KEGG_LEGACY" of "msigdb_v2024.1.Hs.db" was extracted from the Molecular Signatures Database (MSigDB) (https://www.gsea-msigdb.org/gsea/msigdb) as

a reference gene set. In psoriasis and control groups from GSE30999, we computed Spearman correlation coefficients between each biomarker and all other genes using the psych package (v 2.4.6.26) [26]. We then ranked all genes in descending order by their correlation coefficients. We then analyzed this ranked set of genes for GSEA using the clusterProfiler package (v 4.15.0.003) (|normalized enrichment score (NES)| >1, false discovery rate (FDR) < 0.25, $p < 0.05$). We sorted the enrichment results in descending order of |NES| values, selected the top 10 pathways, and visualized them.

2.7 Immune microenvironment analysis

To characterize the role of specific immune cell subsets in psoriasis progression, we analyzed the infiltration abundance of 24 immune cell types [27] in GSE30999 using the Immune Cell Abundance Identifier (ImmuCellAI) tool (http://bioinfo.life.hust.edu.cn/ImmuCellAI). We plotted a stacked diagram to display the results. Subsequently, we used the Wilcoxon test to compare immune cell infiltration abundance between the psoriasis and control groups ($p < 0.05$). We identified immune cells with significantly different infiltration abundances as differentially infiltrated immune cells. To examine correlations among differentially infiltrated immune cells and between biomarkers and these immune cells, Spearman correlation analyses were performed using the psych package (v 2.4.6.26) ($p < 0.05$, |correlation coefficient (cor)| > 0.3).

2.8 Construction of regulatory networks and drug prediction

To investigate the regulatory effects of upstream regulatory factors on biomarkers, the miRNet database (https://www.mirnet.ca/) was used to predict microRNAs (miRNAs) that could target and regulate the biomarkers. Subsequently, the ENCORI database (https://rnasysu.com/encori/) was applied to forecast long non-coding RNAs (lncRNAs) interacting with the obtained miRNAs. Cytoscape software (v3.10.3) was used to draw an lncRNAs-miRNAs-biomarkers network diagram for visual presentation of the results. Furthermore, we identified therapeutic drug targets for biomarkers by generating predictions using the Drug-Gene Interaction Database (DGIdb) (https://dgidb.org/) and visualizing these predictions with Cytoscape (v3.10.3).

2.9 Statistical analysis

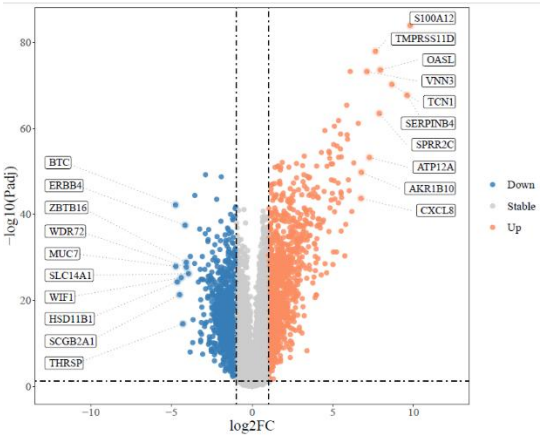
Statistical analysis was executed utilizing R (v 4.3.3). We used the Wilcoxon test to compare the 2 groups, with significance set at $p < 0.05$. Notably, **** represented $p < 0.0001$, ***

represented $p < 0.001$, ** represented $p < 0.01$, * represented $p < 0.05$, and no significance (ns) represented $p > 0.05$.

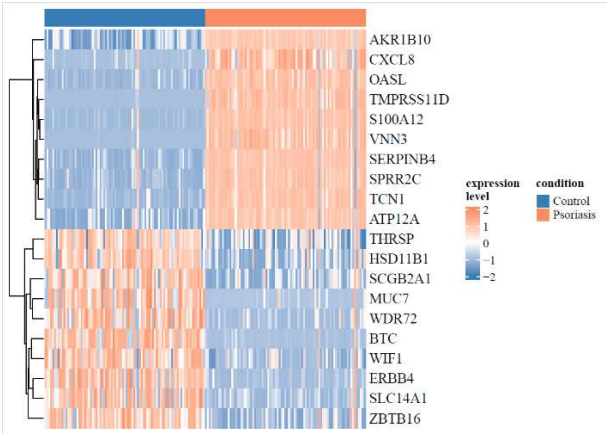
3. Results

3.1 Discovery of 200 candidate genes and investigation into their biological roles

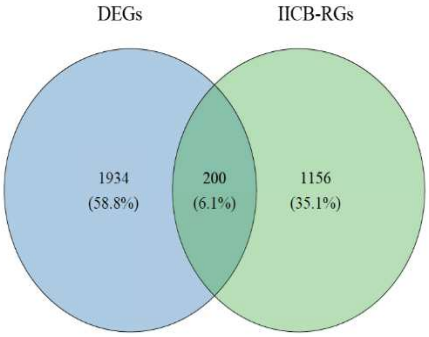
After performing differential analysis on the GSE30999 to distinguish DEGs between the psoriasis and control groups, a total of 2,134 DEGs were obtained. Specifically, compared with the control group, 963 genes were down-regulated, and 1,171 were up-regulated in the psoriasis group. We presented the results using a volcano plot and a heatmap (**Fig. 1A-B**). Taking the intersection of 2,134 DEGs and 1356 IICB-RGs yielded 200 candidate genes (**Fig. 1C**). Moreover, candidate genes were significantly enriched in 1,637 GO terms (comprising 1,509 BPs, 41 CCs, and 87 MFs) and 86 KEGG terms (p.adjust < 0.05). The top 5 of these BPs included "regulation of inflammatory response" and "positive regulation of cytokine production". The top 5 enriched CCs included "specific granule" and "cytoplasmic vesicle lumen". The top 5 of these MFs included "receptor ligand activity" and "cytokine activity". In addition, the top 10 KEGG terms included "Toll-like receptor signaling pathway", "NOD-like receptor signaling pathway", and "natural killer cell mediated cytotoxicity" (**Fig. 1D**). These findings demonstrated significant associations between candidate genes and multiple key signaling pathways, highlighting their involvement in processes such as immune responses.



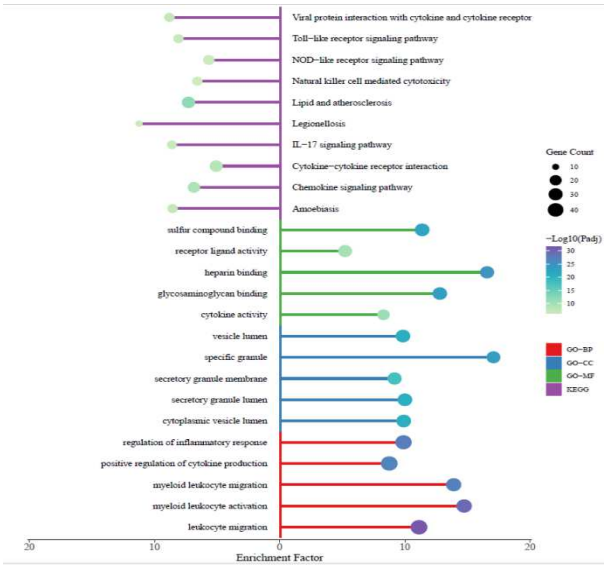
(A) Volcano plot of DEGs between psoriasis and controls.



(B) Heatmap of selected DEGs.



(C) Intersection of DEGs and IICB-related genes identifies 200 candidates.



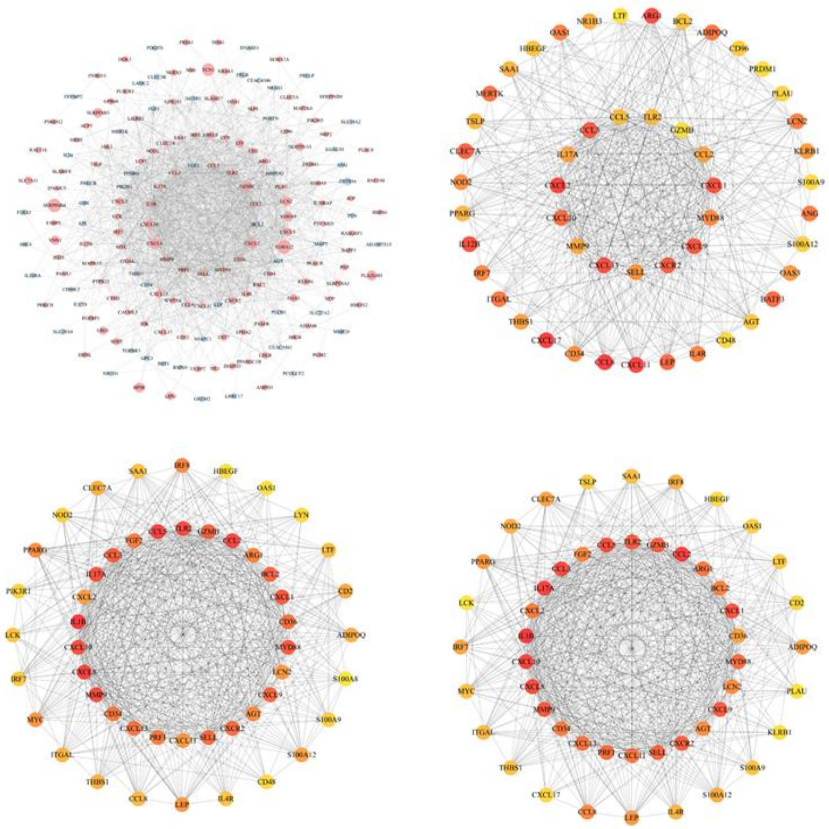
(D) GO and KEGG enrichment analysis.

Figure 1. Identification and functional analysis of candidate genes. (A) Volcano plot of DEGs between psoriasis and controls. (B) Heatmap of selected DEGs. (C) Intersection of DEGs and IICB-related genes identifies 200 candidates. (D) GO and KEGG enrichment analysis.

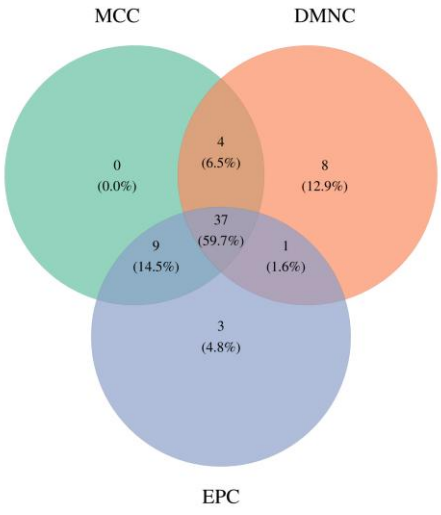
3.2 Acquisition of 2 biomarkers: ARG1 and S100A12

As shown in **Fig. 2A**, the PPI network revealed interactions among proteins encoded by 178 of the 200 candidate genes. Subsequently, 50 genes were screened out by each of the MCC, DMNC, and EPC algorithms, respectively (**Fig. 2B**). After taking the intersection of the screening results from the 3 algorithms, 37 hub genes were obtained (**Fig. 2C**). Furthermore, these 37 hub genes were incorporated into the 3 machine learning algorithms. When the number of selected features was set to 8, the SVM-RFE model achieved its maximum accuracy (0.971). The 8 genes that were selected at this stage were LCN2, ARG1, GZMB, S100A9, CXCR2, S100A12, NOD2, and CXCL13 (**Fig. 2D**). In the LASSO regression algorithm, when the lambda min was 0.0167, the model was optimal, and 5 characteristic genes were obtained, namely CXCL10, ARG1, CLEC7A, S100A12, and THBS1 (**Fig. 2E**). Additionally, 22 characteristic genes were identified using the XGBoost algorithm (**Fig. 2F**). The genes procured by the 3 algorithms were subsequently intersected to identify 2 key genes, namely ARG1 and S100A12 (**Fig. 2G**). Further analysis revealed that ARG1 and S100A12 were significantly upregulated in the psoriasis groups of GSE30999 and GSE6710 compared to the control group (**Fig. 2H**). Therefore, ARG1 and S100A12 were identified as biomarkers. Subcellular localization analysis revealed that both ARG1 and S100A12 were predominantly localized in the cytoplasm (**Fig. 2I**). This cytoplasmic localization suggested potential roles in

intracellular processes, such as signal transduction, or as cytoplasmic reservoirs for rapid immune responses.



(A) Protein–protein interaction (PPI) network of candidate genes.

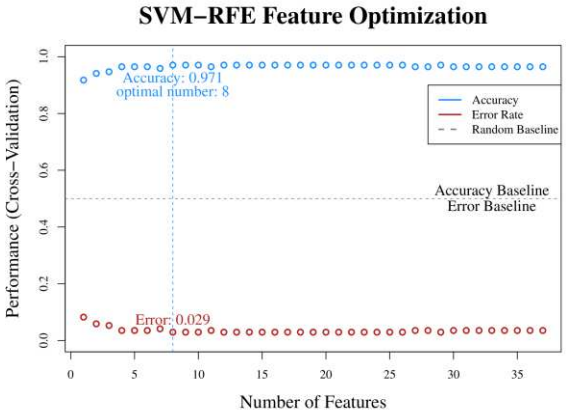


(B) Hub gene identification using MCC, DMNC, and EPC algorithms.

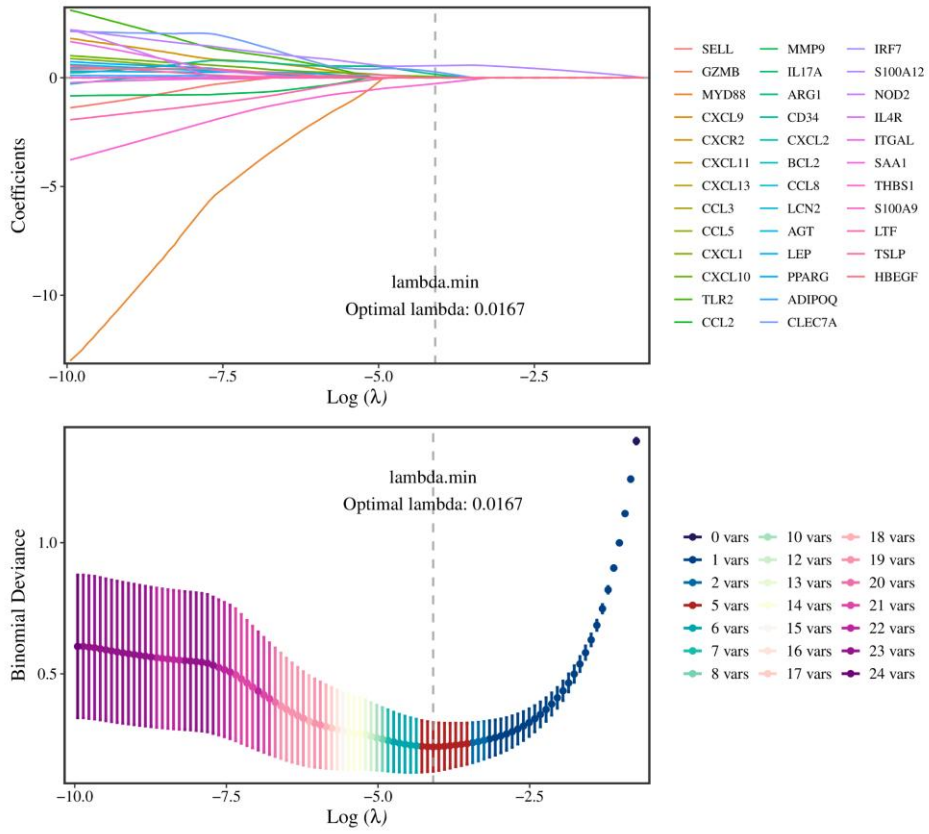
(C) Integrated hub gene network visualization.

(D) Expanded interaction network of hub genes.

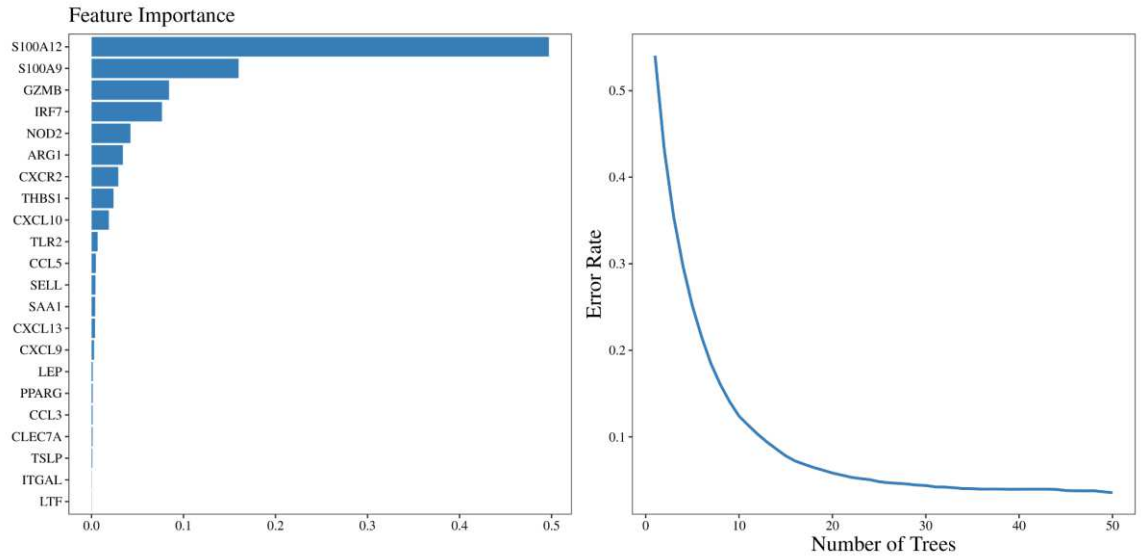
(E) Venn diagram showing overlap among MCC, DMNC, and EPC methods.



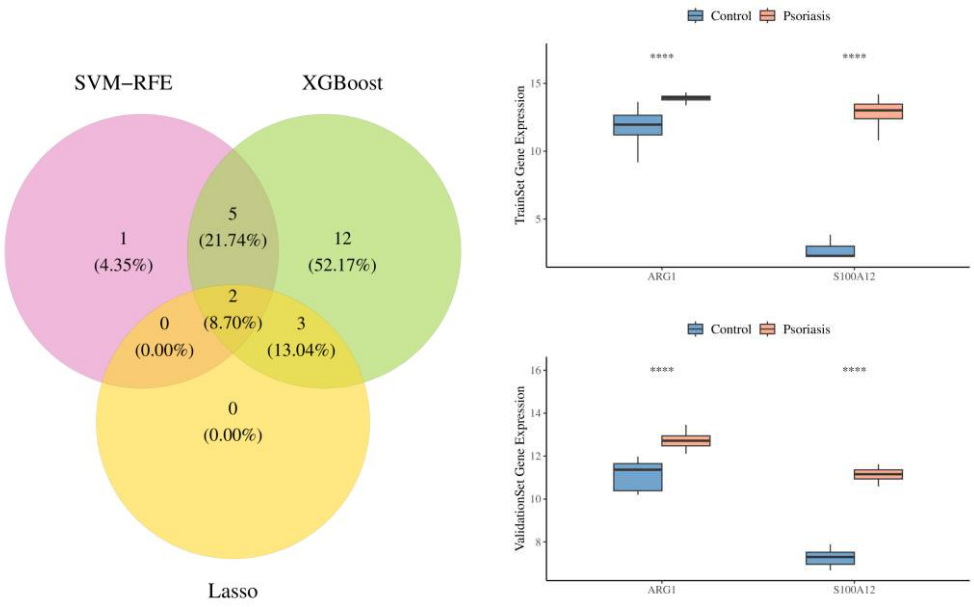
(F) SVM-RFE feature optimization showing optimal feature number.

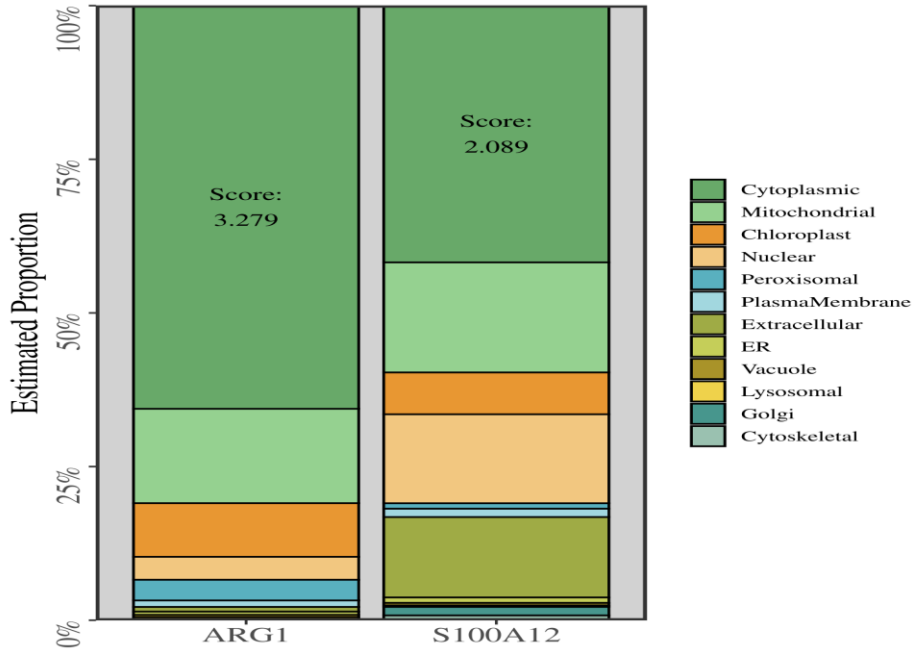


(G) LASSO regression analysis for feature selection.



(H) Random forest feature importance and error rate analysis.





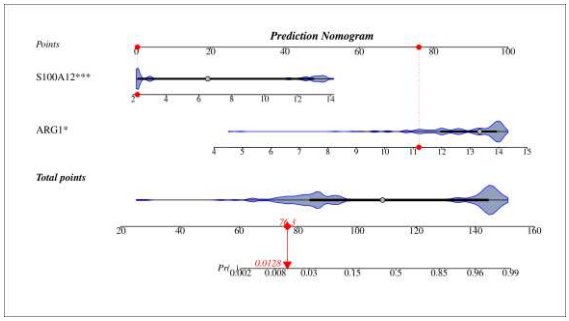
(I) Expression validation of key genes (ARG1 and S100A12) and subcellular localization analysis.

Figure 2. Identification and validation of hub genes and machine learning-based feature selection.
(A) Protein–protein interaction (PPI) network of candidate genes.
(B) Hub gene identification using MCC, DMNC, and EPC algorithms.
(C) Integrated hub gene network visualization.
(D) Expanded interaction network of hub genes.
(E) Venn diagram showing overlap among MCC, DMNC, and EPC methods.
(F) SVM-RFE feature optimization showing optimal feature number.
(G) LASSO regression analysis for feature selection.
(H) Random forest feature importance and error rate analysis.
(I) Expression validation of key genes (ARG1 and S100A12) and subcellular localization analysis.

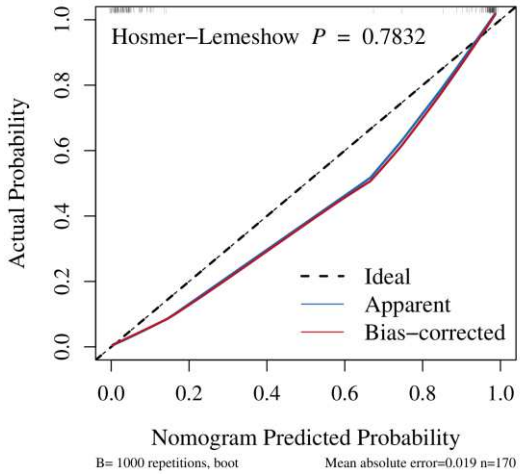
3.3 The nomogram performed favorably in diagnosing psoriasis

To further assess the diagnostic utility of ARG1 and S100A12, a predictive nomogram was developed. The nomogram revealed that a total score of 76.3 corresponded to a psoriasis probability of 0.0128. Elevated total points from ARG1 and S100A12 were associated with an increased probability of psoriasis (**Fig. 3A**). In addition, the nomogram model demonstrated a

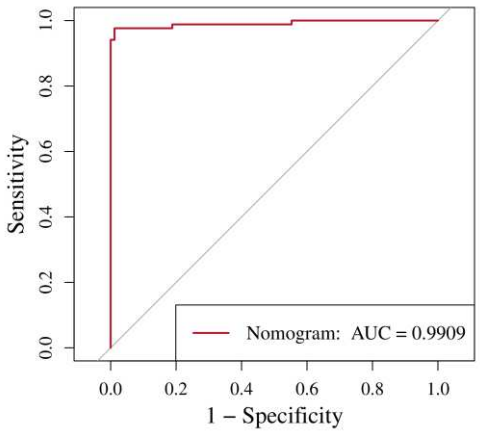
low diagnostic error rate (HL test: p = 0.7832), as substantiated by the calibration curve depicted in **Fig. 3B**. The ROC curve revealed that the nomogram showed excellent diagnostic value (AUC = 0.9909) (**Fig. 3C**). The DCA curves confirmed that the nomogram had great clinical utility (**Fig. 3D**). To sum up, a well-constructed nomogram was developed, and the calibration, ROC, and DCA curves demonstrated their favorable predictive performance.



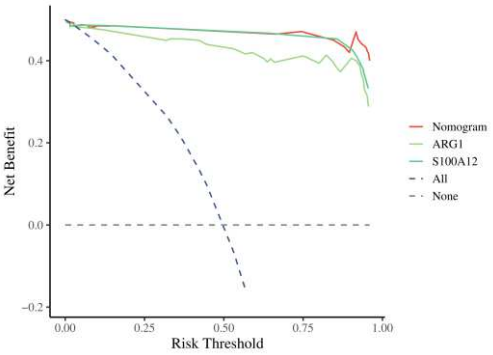
(A) Nomogram based on key genes (ARG1 and S100A12) for predicting psoriasis risk.



(B) Calibration curve demonstrating agreement between predicted and observed probabilities (Hosmer–Lemeshow P = 0.7832).



(C) Receiver operating characteristic (ROC) curve showing diagnostic performance (AUC = 0.9909).



(D) Decision curve analysis evaluating clinical utility of the nomogram compared with individual genes and default strategies.

Figure 3. Construction and validation of the diagnostic nomogram model.

3.4 Shared and distinct functional enrichment of ARG1 and S100A12

Further exploration of the biomarkers' biological functions was conducted. The GSEA revealed that ARG1 was significantly enriched in 65 pathways, including "non homologous end joining" (**Fig. 4A**). In contrast, S100A12 was enriched in 75 pathways, such as "P53 signaling pathway" (**Fig. 4B**). Interestingly, both biomarkers showed prominent and shared enrichments in key processes such as the "Toll-like receptor signaling pathway", "ribosome", "proteasome", "NOD-like receptor signaling pathway", "cytosolic DNA sensing pathway", "RIG-I-like receptor signaling pathway", "pyrimidine metabolism", "DNA replication", and "cell cycle".

This overlap indicated their cooperative involvement in fundamental immune-sensing mechanisms and cell-proliferation-related functions.

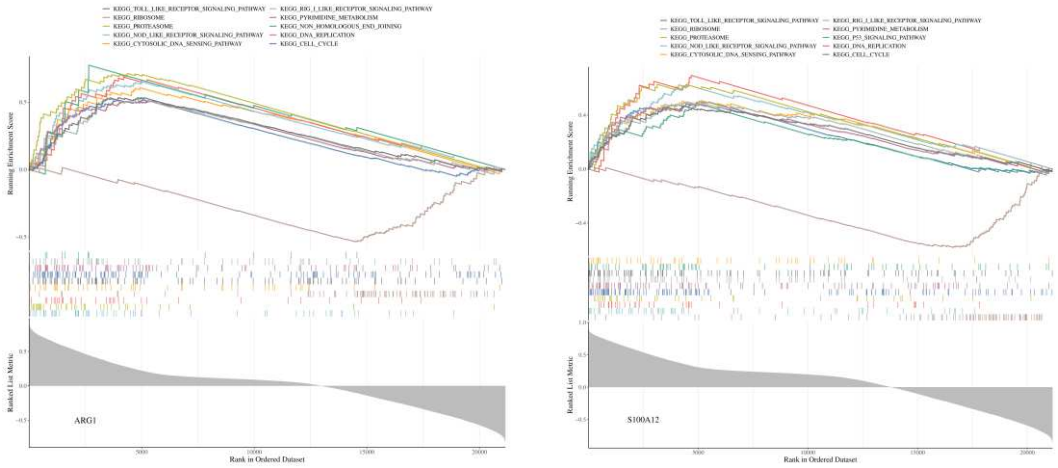
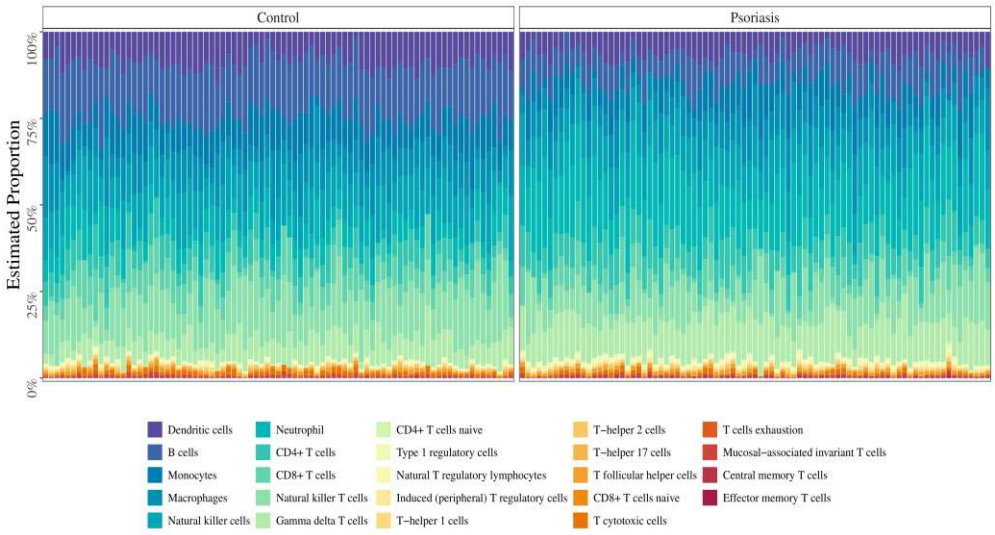


Figure 4. Functional enrichment and immune infiltration analysis. (A) Gene set enrichment analysis (GSEA) of ARG1 showing enrichment of immune-related pathways, including Toll-like receptor and NOD-like receptor signaling.

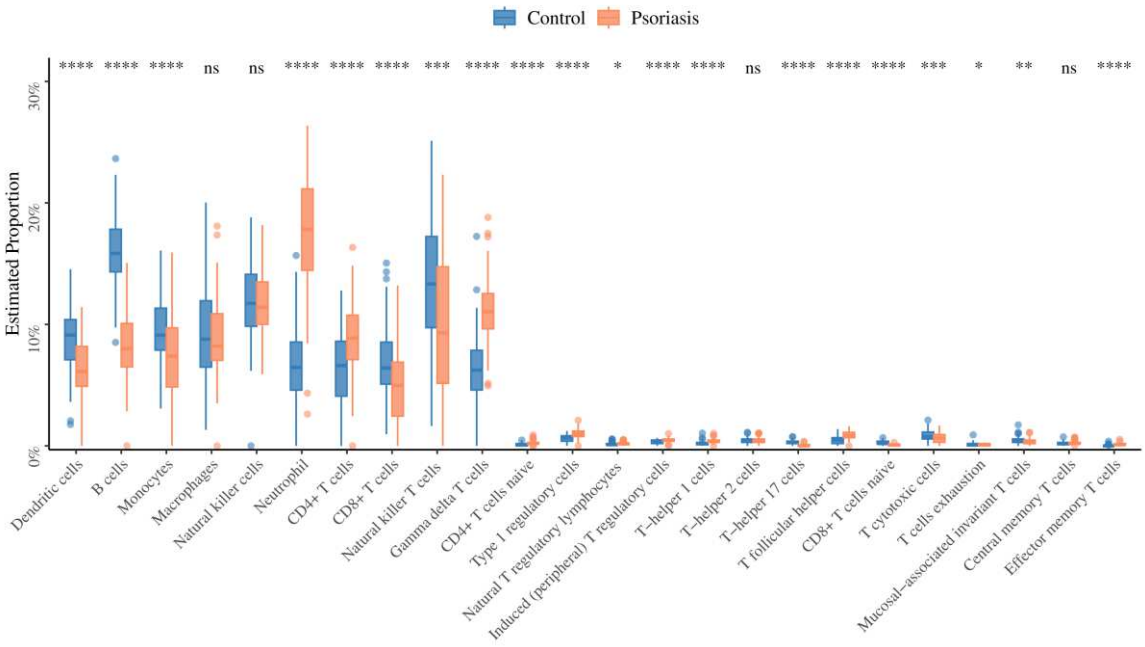


(B) GSEA of S100A12 indicating involvement in inflammatory and immune signaling pathways.

3.5 Characterization of the psoriatic immune microenvironment and coordinated biomarker associations

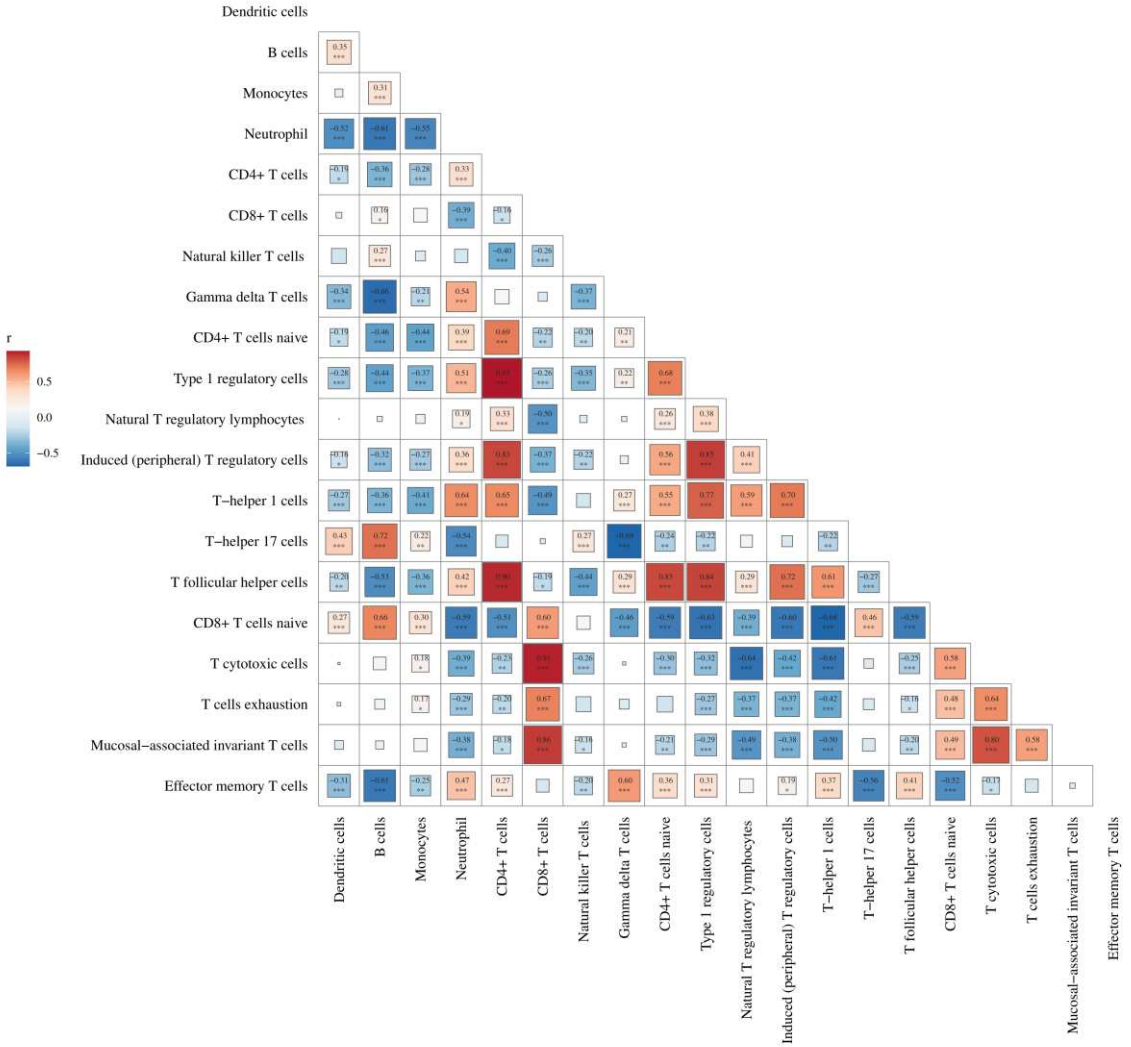
This study further analyzed the immune microenvironment of psoriasis. **Fig. 4C** visualized the immune infiltration profiles of 24 immune cell types in the psoriasis and control groups from

GSE30999. Marked disparities in infiltration levels of 20 immune cell types were noted between the psoriasis and control groups ($p < 0.05$). For instance, compared with the control group, immune cells, such as neutrophils, in the psoriasis group exhibited greater abundance of infiltration. In comparison, cells such as B cells had lower infiltration abundance (Fig. 4D). Further, there was a strong negative correlation between B cells and gamma delta T cells (γδ T cells) (cor = -0.65, p = 2.67e-22). In contrast, an intense positive correlation was observed between T cytotoxic cells and $CD8^+$ T cells (cor = 0.91, p = 1.68e-66) (**Fig. 4E**). A remarkable concordance was also observed in the correlation patterns of ARG1 and S100A12 with differentially infiltrated immune cells. Both biomarkers displayed concerted strong negative correlations with B cells, T helper 17 cells, and naive $CD8^+$ T cells. They observed strong positive correlations with populations, including γδ T cells and neutrophils (Fig. 4F). These findings implied that ARG1 and S100A12 may co-regulate or respond to the skewed immune cell composition in psoriasis, particularly the expansion of innate immune cells and the suppression of certain adaptive immune cells.

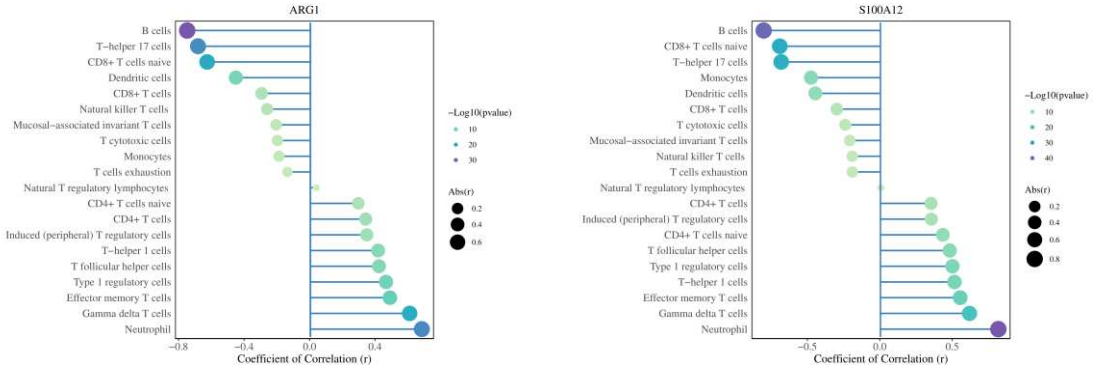


(C) Immune cell infiltration landscape comparing control and psoriasis groups.

(D) Differential analysis of immune cell proportions between groups.



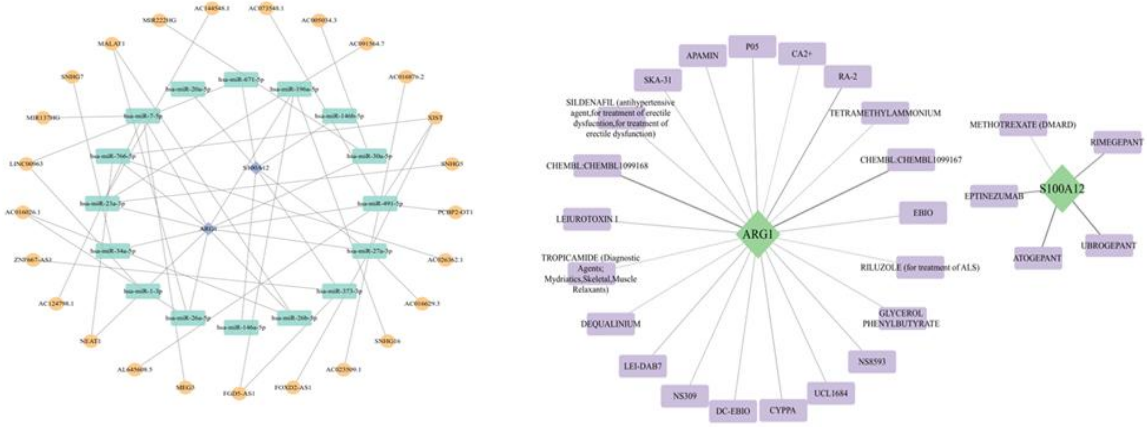
(E) Correlation heatmap showing relationships among infiltrating immune cells.



(F) Correlation analysis between key genes (ARG1 and S100A12) and immune cell infiltration levels.

3.6 Exploration of the regulatory network and drug prediction for biomarkers

The constructed lncRNAs-miRNAs-biomarkers network revealed 16 miRNAs predicted to target either ARG1 or S100A12. Among these, hsa-miR-27a-3p was identified as a common regulator that targets both biomarkers. Furthermore, 25 lncRNAs, including XIST and MALAT1, were retrieved as putative upstream regulators targeting these miRNAs (**Fig. 5A**). Subsequently, 21 drugs targeting ARG1, such as Leiurotoxin I and Dequalinium, were predicted using the DGIdb database. In contrast, only 5 drugs were predicted to target S100A12: Methotrexate (a DMARD), Rimegepant, Eptinezumab, Atogepant, and Ubrogepant (Fig. 5B). These findings revealed potential regulatory mechanisms and therapeutic targets for biomarkers, providing crucial insights for subsequent functional validation and therapeutic development.



(A) (B)

Figure 5. Regulatory network and drug–gene interaction analysis. (A) ceRNA network showing interactions among lncRNAs, miRNAs, and key genes (ARG1 and S100A12). The network highlights potential regulatory axes involving multiple non-coding RNAs such as MALAT1, NEAT1, and XIST. (B) Drug–gene interaction network illustrating potential therapeutic compounds targeting ARG1 and S100A12, including methotrexate and other small molecules. filecite turn4file1

4. Discussion

Psoriasis is increasingly understood as a disorder in which epidermal pathology is tightly coupled to a distorted immune landscape, and growing evidence places the innate immune cell barrier at the center of this process. Dysfunction of this barrier does not simply accompany

inflammation; rather, it helps establish and sustain the chronic inflammatory circuitry that defines psoriatic lesions. In the present study, by integrating large-scale psoriasis transcriptomic datasets with a curated set of innate immune cell barrier-related genes, we identified ARG1 and S100A12 as the two most robust biomarkers associated with this axis [28-30]. Both genes were consistently upregulated across two independent datasets, showed strong diagnostic performance when combined in a nomogram, converged on innate immune sensing and proliferation-related pathways, and displayed highly coordinated associations with the psoriatic immune microenvironment. Taken together, these findings support the view that ARG1 and S100A12 are not passive markers of inflammation but may represent key nodes linking innate immune activation, metabolic adaptation, and tissue remodeling in psoriasis [28-30].

Among the two biomarkers, ARG1 is particularly interesting because it sits at the intersection of immune regulation and cellular metabolism. Arginase 1 catalyzes the hydrolysis of L-arginine to ornithine and urea, thereby competing with nitric oxide synthase for substrate availability. In immunobiology, this has important consequences: arginine depletion can suppress T-cell proliferation and function, while increased ornithine availability can support polyamine synthesis and cellular growth. ARG1 has been widely studied in macrophage biology, myeloid-derived suppressor cell function, and immune-metabolic reprogramming in chronic inflammatory disease and cancer, where it is commonly linked to local immunosuppression and altered effector responses. Recent work has also implicated ARG1 in inflammatory skin diseases, including psoriasis, where it appears to regulate pathogenic T-cell responses and myeloid activation [30-35].

First, ARG1 emerged here not merely as a differentially expressed gene, but as a highly ranked hub gene retained across topological network analysis and three independent machine-learning algorithms [34]. This supports its stability as a psoriasis-associated signal and reduces the chance that its selection reflects dataset-specific noise. Second, the functional profile associated with ARG1 in our analysis suggests that its role in psoriasis may extend beyond immune suppression. In addition to enrichment in innate immune pathways, ARG1 was linked to DNA replication, cell cycle programs, and repair-related pathways [33-35, 36]. This raises the possibility that ARG1 contributes to the hyperproliferative component of psoriasis, perhaps by enhancing polyamine metabolism downstream of ornithine production. Such a mechanism would fit well with the well-known excessive growth and aberrant differentiation of keratinocytes in psoriatic skin. From this perspective, ARG1 may contribute to psoriasis

through a dual mechanism: on the one hand, it modifies the local immune milieu by restricting arginine availability and altering lymphocyte fitness; on the other hand, it may support tissue-level proliferative responses that drive plaque formation [37, 38].

The immune-correlation analysis further strengthens this interpretation. ARG1 showed negative correlations with B cells, Th17 cells, and naive CD8+ T cells, while showing positive correlations with neutrophils and γδ T cells. At first glance, the inverse correlation with Th17 cells may seem counterintuitive given the established centrality of the IL-23/IL-17 axis in psoriasis [39, 40]. However, this pattern may reflect microenvironmental compartmentalization rather than contradiction. A high-ARG1 state may represent a lesion dominated by myeloid and innate inflammatory activity in which local arginine depletion restrains the expansion or persistence of selected adaptive subsets, even as the broader inflammatory network continues to favor psoriasis progression. In other words, ARG1 may help shape a skewed immune milieu characterized by excessive innate activation and selective adaptive suppression rather than uniform amplification of all inflammatory cell types. This interpretation is consistent with recent work showing that arginine metabolism can profoundly influence T-cell fitness and effector function under inflammatory conditions [34, 42].

S100A12, in contrast, is more readily recognizable as a classic inflammatory amplifier [43]. Neutrophils and monocytes/macrophages predominantly produce a member of the S100 calcium-binding protein family, S100A12, which acts as a damage-associated molecular pattern molecule [44]. It can engage receptors such as RAGE and TLR4, thereby triggering downstream inflammatory signaling, cytokine release, and leukocyte recruitment [45]. Dysregulated S100A12 expression has been documented in several immune-mediated disorders, including atopic dermatitis, systemic sclerosis, and other chronic inflammatory diseases, where it is commonly associated with disease activity and tissue injury [47-50]. In psoriasis, elevated S100A12 has been reported in lesional tissue and the circulation, with higher levels correlating with inflammatory burden and clinical severity [51-53]. The present study supports these observations and places S100A12 within a more integrated mechanistic framework.

Like ARG1, S100A12 was consistently upregulated across datasets and selected by all three machine-learning approaches, indicating that its relevance is not incidental. Its GSEA profile linked it to the p53 signaling pathway and to multiple immune-sensing pathways. This is

notable because p53-associated stress signaling may reflect the adaptation of keratinocytes and infiltrating immune cells to persistent inflammatory and oxidative stress [54]. S100A12 may therefore serve not only as an extracellular inflammatory alarm signal but also as a marker of the cellular stress state that accompanies chronic plaque inflammation. More importantly, S100A12 shared with ARG1 a striking enrichment in Toll-like receptor, NOD-like receptor, cytosolic DNA sensing, and RIG-I-like receptor signaling [55]. This overlap is one of the most informative findings of the study. It suggests that the two biomarkers converge on a core innate immune module that integrates extracellular danger sensing, intracellular pattern recognition, and downstream inflammatory transcriptional programs [54].

This convergence allows a biologically plausible model to be proposed. In psoriatic lesions, S100A12 may function as an upstream inflammatory initiator and amplifier. Released from activated neutrophils and myeloid cells, it can engage danger-sensing receptors and intensify innate immune signaling. This would favor production of cytokines such as IL-1β, IL-6, and TNF-α and contribute to recruitment of additional innate immune cells. ARG1, in parallel, may act as a metabolic and immunoregulatory effector, helping to stabilize this inflammatory state [54-56]. By remodeling local arginine metabolism, ARG1 may suppress selected adaptive immune compartments while providing metabolic support for proliferative and reparative processes in keratinocytes and innate immune cells. In this framework, S100A12 drives signal amplification, whereas ARG1 helps enforce metabolic conditions that sustain the altered inflammatory niche. Their coordinated upregulation would therefore be expected to reinforce both chronic inflammation and epidermal hyperplasia [54-57].

The immune infiltration analysis supports this hypothesis. Among the 24 immune cell populations examined, 20 differed significantly between psoriasis and control skin, highlighting the breadth of immune remodeling in psoriasis. Notably, neutrophil counts increased, a hallmark of active psoriatic inflammation. The positive association of both biomarkers with neutrophils is biologically coherent, especially for S100A12, given its established myeloid origin [58,59]. Their shared positive correlation with γδ T cells is also relevant, as these cells are increasingly recognized as rapid responders that produce pro-inflammatory cytokines that bridge innate and adaptive immunity. By contrast, negative correlations with B cells and certain T-cell subsets suggest that lesions with high ARG1 and S100A12 expression may be biased toward a highly activated innate immune state rather than a balanced inflammatory infiltrate [58, 59]. This coordinated pattern is one of the stronger

pieces of evidence from the present study, because it implies that ARG1 and S100A12 are linked not just to psoriasis broadly, but to a specific immune architecture within the disease.

Regulatory network analysis offers another layer of interest. The identification of hsa-miR-27a-3p as a shared upstream miRNA suggests that these two biomarkers may be co-regulated, at least in part, by common post-transcriptional mechanisms [60]. Likewise, the prediction of lncRNAs such as XIST and MALAT1 points to the possibility of higher-order regulation of non-coding RNAs [61]. These observations remain predictive and biologically plausible and warrant follow-up, particularly given the increasing role of non-coding RNAs in inflammatory skin disease and immune-cell programming. The drug interaction analysis is also provocative. The prediction of agents targeting ARG1 and the identification of methotrexate among compounds linked to S100A12-related networks may provide a useful starting point for therapeutic exploration. These findings should not be overinterpreted, but they do suggest that the ARG1–S100A12 axis may be amenable to translational approaches [62, 63].

This study has several strengths. It used two independent psoriasis datasets, combining differential expressions with network topology and machine learning. It moved beyond biomarker screening to include immune infiltration, pathway analysis, regulatory prediction, and drug-gene interaction mapping. Even so, several limitations should be acknowledged. First, all major conclusions are derived from retrospective transcriptomic data and computational inference. Although cross-dataset consistency strengthens confidence, it does not replace mechanistic validation. Second, the datasets represent bulk tissue expression, which limits cellular resolution and may obscure compartment-specific effects. Third, the inferred regulatory networks and drug interactions remain hypothetical until tested experimentally. Finally, the excellent diagnostic performance of the nomogram, while encouraging, may be inflated by the structure of the training dataset and will require external validation in independent clinical cohorts.

5. Conclusion

This study identifies ARG1 and S100A12 as two closely linked biomarkers associated with psoriasis by integrating transcriptomic profiling, network analysis, and multiple machine-learning approaches. From an initial pool of differentially expressed genes, a stepwise filtering strategy led to the consistent selection of these two genes across independent algorithms and datasets. This convergence across methods supports the stability of the findings and reduces the likelihood of random selection. Both biomarkers demonstrated clear upregulation in

psoriasis and showed strong diagnostic performance when incorporated into a nomogram, with high accuracy and good agreement between predicted and observed outcomes. Functional enrichment analysis indicated that ARG1 and S100A12 converge on key innate immune pathways, including Toll-like receptor and NOD-like receptor signaling, supporting their involvement in inflammatory signaling processes central to psoriasis. The immune infiltration analysis adds an important layer of interpretation. The positive associations of both genes with neutrophils and γδ T cells, along with their negative correlations with B cells and selected T cell subsets, suggest a shift toward an innate-dominant immune environment. These findings are consistent with the known roles of S100A12 as a pro-inflammatory mediator and ARG1 as a regulator of immune metabolism and cellular responses. The data support a coordinated model in which S100A12 contributes to inflammatory signal amplification, while ARG1 modulates the metabolic and cellular context that sustains these responses. The predicted regulatory network, including shared miRNAs such as hsa-miR-27a-3p and lncRNAs such as XIST and MALAT1, suggests that both biomarkers may be subject to common upstream control. The identification of potential drug–gene interactions further indicates possible avenues for therapeutic exploration, although these predictions require experimental confirmation. However, regulatory relationships and drug interactions remain theoretical and need functional validation. The diagnostic performance of the nomogram should also be tested in independent clinical cohorts to confirm its reliability. Future work should focus on experimental validation of ARG1 and S100A12 in relevant cellular and animal models to determine their functional roles. Approaches such as gene perturbation studies can clarify whether these genes act as drivers or markers of disease processes. Single-cell and spatial transcriptomic analyses would help define their cell-specific expression patterns and interactions within the tissue microenvironment. Further investigation of the identified non-coding RNA regulators may provide insight into upstream mechanisms controlling these biomarkers. In parallel, testing the predicted drug interactions in preclinical systems may help assess their therapeutic potential. Integrating additional data types, including proteomic and metabolomic profiles, could also improve understanding of how immune signaling and metabolic regulation intersect in psoriasis.

CRediT authorship contribution statement

Ahmad Taha Khalaf: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Yonghong Sun: Writing – review & editing, Software, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

Xiaoming Liu: Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition.

Declaration of Competing Interests

None.

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