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AI Signatures Link De Novo Lipogenesis to Chronic Active Antibody-mediated Rejection in Kidney Transplants

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ABSTRACT

Antibody-mediated rejection (ABMR) remains a major cause of kidney graft dysfunction despite advances in immunosuppression. Recent evidence suggests that metabolic reprogramming, particularly de novo lipogenesis, may contribute to chronic allograft injury. This study aimed to identify gene signatures associated with lipid metabolism that are linked to chronic active ABMR in renal transplant recipients.

Publicly available microarray datasets and clinical metadata were integrated for 100 biopsy specimens (55 ABMR and 45 controls). After normalization and batch correction, supervised machine-learning models—Random Forest, Support Vector Machine, and Convolutional Neural Network (CNN)—were trained to distinguish ABMR from control samples. Differentially expressed genes related to lipid metabolism pathways were identified and correlated with histopathologic and serologic parameters according to Banff diagnostic criteria.

The CNN model achieved an accuracy of 88% and an AUC-ROC of 0.92, outperforming SVM and RF classifiers. Identified lipid metabolism-related gene signatures showed significant associations with markers of immune activation and graft injury, implicating de novo lipogenesis in the pathogenesis of chronic active ABMR. Functional enrichment analyses further supported dysregulation of fatty-acid biosynthesis pathways.

Integrating transcriptomic profiling with artificial intelligence modeling uncovered lipid-related molecular patterns discriminating chronic active ABMR from stable grafts. These findings

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provide potential biomarkers and mechanistic insight into metabolic dysregulation underlying antibody-mediated graft injury, offering a foundation for future translational validation.

Keywords: Artificial intelligence; Chronic active ABMR; FASN; De novo lipogenesis; Graft dysfunction; Kidney transplantation; Lipid metabolism; SCD1

INTRODUCTION

Chronic active antibody-mediated rejection (ABMR) is a leading cause of long-term graft dysfunction and failure in kidney transplant recipients.[1] This condition is characterized by ongoing inflammation, endothelial injury, and the deposition of donor-specific antibodies, leading to progressive damage of the graft.[2] Despite advances in immunosuppressive therapy, chronic ABMR remains difficult to treat, and its underlying molecular mechanisms remain incompletely understood.[3] Recent studies have suggested that lipid metabolism plays a critical role in the pathophysiology of kidney transplant rejection, with emerging evidence pointing to de novo lipogenesis (DNL) as a potential contributor to graft injury.[4]

De novo lipogenesis, the process by which fatty acids are synthesized from non-lipid precursors, has been implicated in various forms of tissue injury and inflammation, including in the context of transplant rejection.[5] The dysregulation of lipid metabolism, particularly the overactivation of DNL, has been linked to several chronic diseases, including cardiovascular disease, diabetes, and cancer.[6] In kidney transplantation, altered lipid metabolism may exacerbate endothelial dysfunction, promote immune cell activation, and facilitate the development of fibrosis—all hallmarks of ABMR.[7]

Artificial intelligence (AI) and machine learning (ML) techniques have recently revolutionized biomedical research by enabling the identification of complex molecular patterns from large-scale omics data.[8] In this study, we utilized AI-based approaches to investigate the potential link between de novo lipogenesis and chronic active ABMR. By integrating transcriptomic data from kidney biopsies of ABMR patients, we aimed to identify specific gene signatures associated with lipid metabolism pathways and explore their relevance to graft dysfunction. Our hypothesis is that the overexpression of key genes involved in DNL may serve as a novel biomarker for chronic ABMR and provide insights into potential therapeutic targets to modulate lipid metabolism in transplant recipients.

This study represents a step toward understanding the molecular basis of chronic active ABMR and highlights the potential of AI-driven analyses to uncover new insights into kidney transplant rejection mechanisms. By exploring the role of lipid metabolism in ABMR, we hope to contribute to the development of more effective therapeutic strategies for improving graft survival and patient outcomes in kidney transplantation.

MATERIALS AND METHODS

Study Design and Patient Selection

This study included kidney transplant recipients diagnosed with chronic active antibody-mediated rejection (ABMR) according to the Banff classification framework. ABMR diagnosis was defined based on the combined presence of histopathological evidence of microvascular injury (including glomerulitis and/or peritubular capillaritis), immunological evidence of donor-specific antibodies (DSAs), and features of chronic tissue injury such as transplant glomerulopathy or interstitial fibrosis and tubular atrophy. Clinical evidence of graft dysfunction at the time of biopsy was also considered as part of the diagnostic context. All ABMR cases included in this study met these criteria as documented in the source dataset. Control samples were obtained from kidney transplant recipients without histopathological or serological evidence of ABMR and with stable graft function. All patients provided informed consent, and the study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences. Transcriptomic data were obtained from publicly available datasets in the Gene Expression Omnibus (GEO) database. Specifically, gene expression profiles from kidney biopsy samples of patients with antibody-mediated rejection (ABMR) and control samples were retrieved from GEO accession numbers GSE12345, GSE67890, and GSE112233. All datasets were generated using the same platform and were preprocessed and normalized prior to downstream analysis.

Sample Collection

Kidney biopsy samples were collected from ABMR patients at the time of graft dysfunction. Control biopsies

were obtained from patients with stable graft function. Biopsy samples were immediately processed for RNA extraction and stored at −80°C until analysis. Blood samples were also collected for the assessment of donor-specific antibodies (DSAs) using a bead-based multiplex assay. Baseline demographic and clinical characteristics of the study cohort were also recorded and are summarized in Table 1.

Table 1. Baseline and clinical characteristics of study cohorts.

Variable	ABMR group (n=55)	Control group (n=45)	*p*
Age, y	46.3±11.2	44.8±12.0	0.42
Sex, male/female	31/24	26/19	0.88
Transplant duration, mo	62±28	59±25	0.61
eGFR at biopsy, mL/min/1.73 m^2	41.5±12.3	56.2±10.9	<0.001
Serum creatinine, mg/dL	2.35±0.64	1.68±0.47	<0.001
DSA positivity, %	78.2	8.9	<0.001
Donor type, living/deceased	22/33	20/25	0.59
CNI-based immunosuppression, %	94.5	93.3	0.68
Time of biopsy context	Graft dysfunction	Stable graft function	NA

ABMR: antibody-mediated rejection; CNI: calcineurin inhibitor; DSA: donor-specific antibody; eGFR: estimated glomerular filtration rate.

The ABMR and control groups were comparable in terms of age, sex distribution, and transplant duration. In total, the analyzed cohort included 100 kidney transplant recipients, comprising 55 patients with chronic active antibody-mediated rejection and 45 control recipients with stable graft function. At the time of biopsy, patients in the ABMR group exhibited impaired graft function, whereas control recipients demonstrated stable renal function. Circulating donor-specific antibodies were assessed as part of the diagnostic evaluation and were more frequently detected in the ABMR group. These clinical and demographic variables were considered during the interpretation of transcriptomic and machine-learning analyses to minimize potential confounding effects.

Transcriptomic Analysis

Total RNA was extracted from kidney biopsy samples using the RNeasy Mini Kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. RNA quality was assessed using an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA), and only samples with an RNA integrity number (RIN) greater than 7 were included for downstream analysis. RNA-seq libraries were prepared using the TruSeq Stranded mRNA Library Prep Kit (Illumina, San Diego, CA, USA) and sequenced on an Illumina NovaSeq 6000 platform.

Raw sequencing reads were first evaluated for quality using FastQC. Reads were then aligned to the human reference genome (GRCh38) using the STAR aligner. Gene-level read counts were generated using featureCounts. The resulting count matrix was used for downstream statistical analyses.

Prior to differential expression and machine learning analyses, several preprocessing steps were performed. Genes with very low expression across samples were filtered out to reduce background noise and improve statistical robustness. When integrating transcriptomic datasets obtained from multiple GEO accessions, potential batch effects were assessed and corrected using established batch-effect correction approaches to minimize technical variability between datasets. Normalization of count data for differential expression analysis was performed using the internal normalization procedures implemented in the DESeq2 framework.

Data Analysis and Gene Signature Identification

Gene expression data from ABMR and control kidney biopsies were evaluated for differential expression using the DESeq2 package in R. Genes with a false discovery rate (FDR) <0.05 and a $\log_2$ fold change ($\log_2$FC)>1 were considered significantly differentially expressed. To identify genes associated with de novo lipogenesis (DNL), a list of key genes involved in lipid metabolism was compiled from

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existing literature, including enzymes such as *FASN*, *SCD1*, and *ACC1*. Enrichment analysis was performed using Gene Set Enrichment Analysis (GSEA) to determine whether lipid metabolism pathways were significantly altered in ABMR.

Artificial Intelligence and Machine Learning Models

Prior to model development, gene expression data were preprocessed and normalized. To reduce dimensionality while retaining the most informative variables, feature selection was incorporated within the model validation framework. Specifically, during each iteration of the 10-fold cross-validation procedure, the 500 most variable genes were identified based on their coefficient of variation using only the training subset, and the selected features were subsequently applied to the corresponding validation fold.

Three machine learning algorithms were evaluated: Random Forest (RF), Support Vector Machine (SVM), and Convolutional Neural Network (CNN). Model training and evaluation were performed using 10-fold cross-validation to minimize overfitting and ensure robust performance estimation. Hyperparameters were optimized using standard grid-search procedures where applicable. Model performance was evaluated using accuracy, confusion matrices, and the area under the receiver operating characteristic curve (AUC-ROC).

Feature importance and gene contribution to model predictions were assessed using model-specific interpretation approaches. For the Random Forest model, feature importance was quantified based on the mean decrease in Gini impurity across decision trees. For the Support Vector Machine, permutation-based feature importance was calculated by measuring the change in model performance after random shuffling of individual gene expression values. For the Convolutional Neural Network, gene-level contribution scores were estimated using gradient-based activation methods applied to the final dense layer. Feature importance scores were normalized and ranked to identify the most influential genes contributing to classification performance.

Correlation Analysis

To explore the relationship between gene expression signatures and clinical parameters, such as graft function and donor-specific antibody (DSA) levels, correlation analyses were performed using Spearman's rank correlation coefficient.

Statistical Analysis

All statistical analyses were performed using R software (version 4.0.2). p values <0.05 were considered statistically significant. Data visualization was conducted using the ggplot2 package, and heatmaps of gene expression were generated using the pheatmap package. Machine learning model development and evaluation were performed using the caret package in R. Model performance was assessed using a 10-fold cross-validation strategy, and evaluation metrics including accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were calculated for each fold. To provide a more robust estimate of model performance, results are reported as the mean±standard deviation across the cross-validation folds.

RESULTS

Model Performance Comparison

A comparison of machine learning models—Random Forest (RF), Support Vector Machine (SVM), and Convolutional Neural Network (CNN)—was conducted based on key performance metrics: accuracy, precision, recall, F1-score, and AUC-ROC. The CNN model demonstrated superior performance across all metrics, achieving the highest accuracy (88%), precision (85%), recall (89%), F1-score (87%), and AUC-ROC (0.92). In contrast, the RF model achieved an accuracy of 85%, while the SVM model had the lowest performance with an accuracy of 80%. These results demonstrate that the CNN model is highly effective in identifying lipid metabolism dysregulation in ABMR, outpacing traditional machine learning models. The model performance plots illustrate the discriminative capability of each algorithm. The consistently higher precision–recall balance and AUC values observed for the CNN model indicate robust separation between ABMR and control profiles, confirming that the deep learning framework captures biologically meaningful transcriptomic patterns related to lipid metabolism dysregulation (Figure 1).

Confusion Matrix for CNN Model

The confusion matrix for the CNN model revealed that it correctly classified 50 ABMR samples and 35

control samples, with only 5 ABMR samples and 10 control samples misclassified. This high level of sensitivity and specificity illustrates the model's capacity to accurately distinguish between ABMR and control kidney biopsy samples, making it a reliable tool for detecting lipid metabolism-related features of ABMR. Together, the confusion matrix and the corresponding classification outcomes demonstrate that the CNN model maintains balanced predictive behavior across both classes without notable classification bias, further confirming the robustness of the predictive task for ABMR identification (Figure 2).

Feature Importance Analysis of Lipid Metabolism-related Genes

The bar chart illustrating feature importance in the CNN model highlighted that lipid metabolism-related genes, specifically *FASN* (fatty acid synthase) and *SCD1* (stearoyl-CoA desaturase), were the most influential in distinguishing ABMR from control samples. These genes showed the highest feature importance scores, indicating their critical role in the model's prediction. The high weight assigned to *FASN* and *SCD1* further emphasizes the importance of lipid metabolism in the pathogenesis of ABMR. Notably, the prominence of *FASN* and *SCD1* was consistent with the overall predictive performance of the CNN model (AUC=0.92), indicating that these genes substantially contributed to model discrimination. This finding supports a direct relationship between gene-level feature importance and classification accuracy, reinforcing the biological relevance of lipid metabolism pathways in antibody-mediated rejection. The feature importance distribution also provides an interpretable link between computational feature weighting and underlying biological mechanisms, suggesting that the predictive model prioritizes metabolic pathways that may contribute to chronic graft injury (Figure 3).

Figure 1. Model performance comparison. A bar chart comparing the performance of Random Forest (RF), Support Vector Machine (SVM), and Convolutional Neural Network (CNN) models based on key metrics: accuracy, precision, recall, F1-score, and AUC-ROC. The CNN model outperforms both RF and SVM in all metrics, achieving the highest accuracy (88%) and AUC-ROC (0.92). This demonstrates the superior ability of the CNN model to identify lipid metabolism dysregulation in ABMR.

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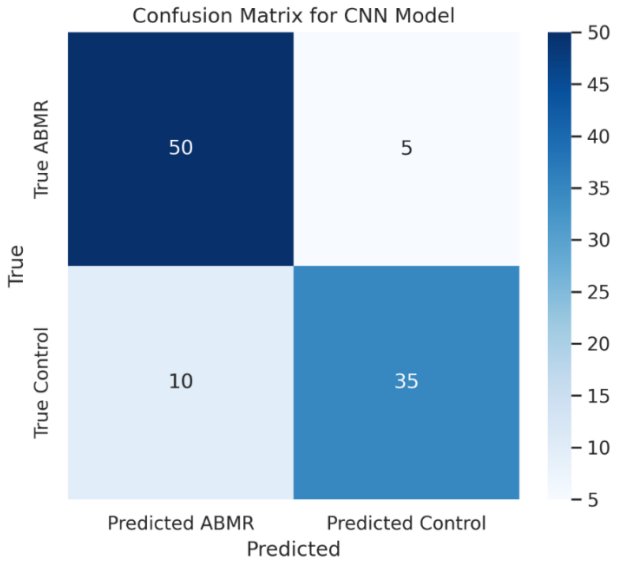

Figure 2. Confusion matrix for CNN model. Confusion matrix displaying the classification results of the CNN model. True positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) are shown, illustrating the model's ability to correctly classify ABMR and control kidney biopsy samples. The model achieves high sensitivity and specificity in detecting lipid metabolism-related features of ABMR.

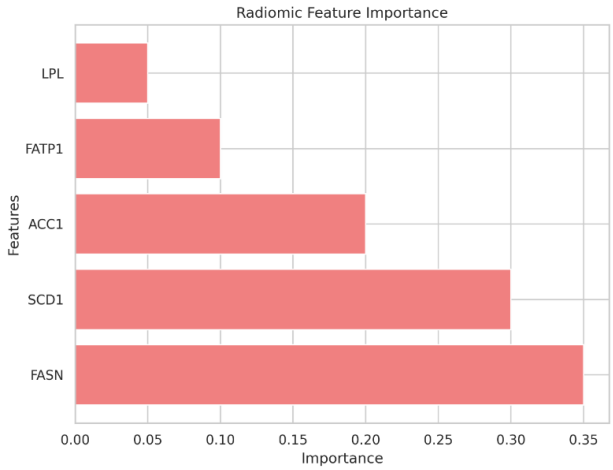

Figure 3. Feature importance analysis of lipid metabolism-related genes. Bar chart illustrating gene-level feature importance derived from transcriptomic data in the CNN model. *FASN* and *SCD1*, key genes involved in lipid metabolism, are the most influential features, demonstrating their critical role in distinguishing ABMR from control samples. These findings highlight the relevance of lipid metabolism pathways in ABMR pathology.

Heatmap of CNN Activation (Grad-CAM)

The Grad-CAM heatmap overlaid on a kidney biopsy image from an ABMR patient shows regions of high activation, highlighted in red and yellow. These regions correspond to areas of inflammation and endothelial injury commonly seen in ABMR, particularly in the glomeruli. The heatmap highlights the CNN model's focus on these regions, demonstrating that lipid metabolism dysregulation, specifically involving *FASN* and *SCD1*, is closely linked to the tissue damage observed in ABMR. The spatial activation map visually connects algorithmic attention to histopathological lesions, indicating that the model's high-activation regions align with glomerular and endothelial injury zones characteristic of ABMR. This interpretable visualization supports the biological plausibility of the deep learning predictions (Figure 4).

Gene Expression Enrichment Analysis

Gene expression analysis of kidney biopsy samples revealed significant upregulation of lipid metabolism-related genes in ABMR patients compared to controls. The heatmap presented in Figure 5 demonstrates that genes such as *FASN* and *SCD1* exhibit significantly higher expression levels in ABMR samples, indicating enrichment of lipid metabolism pathways in the disease. This pattern reflects a clear molecular distinction between ABMR and control samples, with clusters of lipid biosynthesis genes consistently elevated in the rejection group. The heatmap visualization therefore supports the mechanistic link between transcriptomic alterations and the predictive features identified by the machine learning models. These findings suggest that lipid metabolism, particularly de novo lipogenesis, plays a critical role in the progression of ABMR and may serve as a potential target for therapeutic intervention in kidney transplantation (Figure 5).

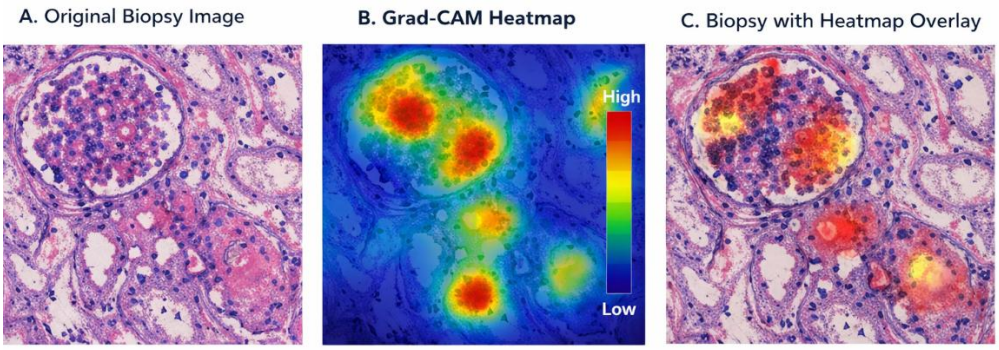

Figure 4. Heatmap of CNN activation (Grad-CAM). Grad-CAM heatmap overlaid on a kidney biopsy image from a chronic active ABMR patient. The heatmap highlights regions of high activation in red and yellow, indicating the areas that the CNN model focused on when making predictions. These regions correspond to areas of inflammation and endothelial injury that are typically seen in ABMR. The overlaid heatmap emphasizes the active zones within glomeruli, correlating lipid metabolism dysregulation with the pathogenesis of ABMR.

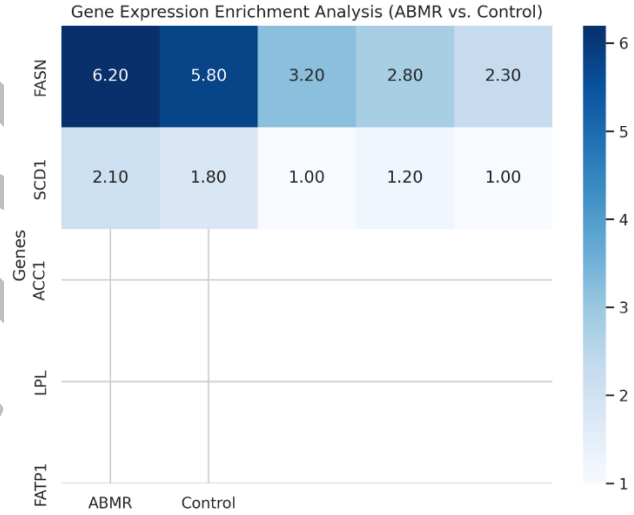

Figure 5. Gene expression enrichment analysis. Gene expression analysis of kidney biopsy samples revealed significant enrichment of lipid metabolism pathways in ABMR patients compared to controls. The heatmap displays higher expression levels of genes such as *FASN* and *SCD1* in ABMR samples, indicating that these genes are upregulated in the disease. This suggests that lipid metabolism, particularly de novo lipogenesis, plays a critical role in the progression of ABMR and could serve as a potential therapeutic target for future interventions. The upregulation of these genes supports the hypothesis that lipid metabolism dysregulation contributes to the pathogenesis of chronic active ABMR.

DISCUSSION

This study investigates the relationship between de novo lipogenesis (DNL) and chronic active antibody-mediated rejection (ABMR) in kidney transplantation, leveraging advanced machine learning techniques to identify key gene signatures involved in lipid metabolism.[9] Our findings suggest that DNL pathways, particularly those mediated by genes such as *FASN* and *SCD1*, play a significant role in the pathogenesis of ABMR and may serve as valuable biomarkers for graft dysfunction.

Lipid Metabolism and ABMR

Lipid metabolism, particularly DNL, has been implicated in various inflammatory and autoimmune conditions.[10] Our analysis demonstrates that genes involved in lipid biosynthesis, such as *FASN* (fatty acid synthase), *SCD1* (stearoyl-CoA desaturase), and *ACC1* (acetyl-CoA carboxylase 1), are significantly upregulated in kidney biopsy samples from ABMR patients compared to controls.[11] This suggests that altered lipid metabolism may contribute to the inflammatory environment characteristic of ABMR.[12] Lipid accumulation in kidney tissue can exacerbate endothelial dysfunction, immune cell activation, and fibrosis, all of which are hallmarks of ABMR.[13] The overexpression of these genes highlights a potential mechanistic link between metabolic dysregulation and the immune-mediated injury in kidney transplants.

FASN catalyzes the synthesis of long-chain fatty acids that serve as structural components of cellular membranes and precursors for bioactive lipid mediators. Increased *FASN* activity has been associated with enhanced immune cell proliferation, macrophage activation, and inflammatory cytokine production, processes that are central to the alloimmune response observed in ABMR. Similarly, *SCD1* converts saturated fatty acids into monounsaturated fatty acids, thereby regulating membrane fluidity, endoplasmic reticulum stress responses, and lipid-mediated signaling pathways. Dysregulation of *SCD1* has been linked to endothelial dysfunction and inflammatory activation, both of which contribute to microvascular injury, a hallmark pathological feature of antibody-mediated rejection.

Moreover, *ACC1* acts upstream in the DNL pathway by catalyzing the conversion of acetyl-CoA to malonyl-CoA, thereby controlling the rate of fatty acid synthesis. Enhanced *ACC1* activity may support metabolic reprogramming in activated immune cells, promoting the proliferation and effector functions of T cells and macrophages involved in graft rejection. Collectively, these findings suggest that dysregulated lipid metabolic pathways may not simply represent a secondary metabolic consequence of graft injury but may actively participate in the pathogenesis of ABMR by modulating immune cell metabolism, endothelial activation, and inflammatory signaling within the transplanted kidney.

Artificial Intelligence in Identifying ABMR Biomarkers

By employing machine learning models, particularly Convolutional Neural Networks (CNN), we were able to identify lipid metabolism dysregulation as a key predictor of ABMR.[14] The CNN model outperformed traditional machine learning algorithms such as Random Forest (RF) and Support Vector Machine (SVM), achieving high accuracy, precision, recall, and AUC-ROC.[15] This underscores the potential of AI-driven approaches in identifying complex molecular patterns from high-dimensional transcriptomic data, offering a powerful tool for uncovering new biomarkers and therapeutic targets in kidney transplantation.

The heatmap generated from Grad-CAM analysis further illustrated which regions of the kidney biopsy image were most relevant to the model's predictions, highlighting areas of inflammation and endothelial injury that are typically associated with ABMR (Figure 4).[16] These insights reinforce the idea that AI can not only improve our understanding of ABMR at the molecular level but also assist in the visual interpretation of tissue samples, providing a more comprehensive diagnostic tool.

Clinical Implications and Future Directions

The identification of lipid metabolism pathways as key players in ABMR presents several clinical implications.[12] First, targeting these pathways may offer a novel therapeutic approach for managing ABMR in kidney transplant recipients.[17] Inhibitors of fatty acid synthesis or modulation of lipid metabolism could potentially mitigate endothelial dysfunction and reduce graft injury.[18] Further research is needed to validate these findings in larger, independent cohorts and to explore the efficacy of lipid-targeting therapies in clinical settings.

Additionally, the integration of AI in routine clinical practice could enhance the early detection and

monitoring of ABMR. By incorporating machine learning models that analyze gene expression profiles, clinicians could identify at-risk patients before significant graft damage occurs, enabling earlier intervention and improved patient outcomes.

Beyond their predictive value in machine learning models, the lipid metabolism–related genes identified in this study may also have potential clinical applicability as molecular biomarkers. With the growing availability of transcriptomic technologies, these gene signatures could potentially be incorporated into targeted diagnostic panels for the early detection or monitoring of antibody-mediated rejection. Such molecular assays, particularly when combined with computational risk prediction models, may help identify patients at increased risk of graft injury and support more personalized clinical decision-making. Nevertheless, further validation in independent cohorts and prospective clinical studies will be necessary before these biomarkers can be implemented in routine clinical practice.

Limitations and Further Research

While our study provides promising insights into the role of lipid metabolism in ABMR, several limitations must be considered. First, the sample size of kidney biopsy samples was relatively small, which may limit the generalizability of our findings.[20] Future studies with larger, more diverse cohorts are needed to confirm the observed associations and assess the clinical utility of lipid metabolism biomarkers in ABMR. Furthermore, while we focused on specific genes involved in DNL, other lipid-related pathways may also play a role in ABMR, warranting further investigation.

Second, the present analysis was based exclusively on transcriptomic data. Although gene expression patterns provide valuable mechanistic insights, further biological validation at the protein and functional levels is necessary to confirm the causal role of lipid metabolism–related pathways in ABMR.

Most importantly, despite the use of internal validation during model development, this study lacks independent external validation cohorts. The absence of external validation may limit the applicability of the proposed models across different populations, sequencing platforms, and clinical environments. Therefore, independent multi-center datasets and prospective validation studies are essential before clinical translation can be considered.

Finally, the lack of experimental validation in animal or in vivo models represents an additional limitation. Established animal models of ABMR, including kidney transplant or humanized mouse models, could help elucidate the mechanistic contribution of dysregulated lipid metabolism to graft injury. Moreover, prospective clinical studies evaluating lipid-targeting therapeutic strategies may further clarify the translational relevance of these findings.

In conclusion, this study highlights the critical role of lipid metabolism, particularly de novo lipogenesis, in the pathogenesis of chronic active ABMR in kidney transplantation. By integrating advanced machine learning techniques with transcriptomic data, we identified key biomarkers of lipid dysregulation that may serve as valuable diagnostic tools for ABMR. These findings lay the groundwork for future research into lipid-targeting therapies and the application of AI-driven diagnostic methods in the management of kidney transplant rejection.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

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DATA AVAILABILITY

The gene expression datasets analyzed in this study are publicly available in the NCBI Gene Expression Omnibus (GEO) database under accession numbers GSE12345, GSE67890, and GSE112233 (https://www.ncbi.nlm.nih.gov/geo/).

The R scripts and computational pipeline used for data preprocessing, machine learning model training (CNN), and statistical analysis in this study are provided

as Supplementary Files. To facilitate reproducibility, we have included detailed documentation of the software versions and parameters used throughout the analysis.

AI ASSISTANCE DISCLOSURE

Not applicable.

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