Journal of Advanced Technologies and Translational Multi-Omics in Exact Remedical Application

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J. Adv. Technol. Transl. Multi-Omics Exact Remed. Appl. Vol. 1, No. 1 (2026) 1-11.

Paper Type: Original Article

Combining Cross-Modal Learning from Retinal Microvascular Phenotypes and Multi-Omics Signatures: Deciphering Inflammatory and Oxidative Stress Pathways for Accurate Cardiovascular Disease Risk Stratification

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Citation:

Received: 08 April 2026 *Revised: 20 July 2026* *Accepted: 10 October 2026*	Haghshenas, L., Saadat, A. M., Homayouni, M., Malekahmadi, M., & Abid, F. (2026). Combining cross-modal learning from retinal microvascular phenotypes and multi-omics signatures: Deciphering inflammatory and oxidative stress pathways for accurate cardiovascular disease risk stratification. *Journal of Advanced Technologies and Translational Multi-Omics in Exact Remedical Application, 1*(1), 1-11.

Abstract

Cardiovascular Diseases (CVD) are still the most common cause of death worldwide, accounting for more than 18 million deaths annually; Most of which progress in the pre-clinical stages without specific symptoms. Current methods of risk assessment are not capable of early detection and differentiation of the underlying molecular mechanisms of the disease and often rely on invasive or expensive methods. As the only organ whose microvessels can be observed non-invasively, the retina is a unique window for evaluating the systemic state of the vessels; Because retinal microvessels are structurally, functionally, and pathobiologically very similar to coronary vessels and are affected by the same processes of chronic inflammation, oxidative stress and endothelial dysfunction. In this research, we present an innovative intermodal deep learning framework that models the relationship between small vessel structural changes and blood molecular signatures in a common hidden space by integrating retinal images and multi-omics data (genomics, transcriptomics, proteomics, and metabolomics). Our proposed architecture is the Interstate Variable Autoencoder (CM-VAE), which correlates vessel geometry changes with inflammatory markers and oxidative stress metabolism with an interstate attention mechanism. The results show that this model with Area Under the Receiver Operating Characteristic Curve (AUC-ROC), 0/96 , it has much higher accuracy than single-mode methods and standard clinical models; Also, by using the Gradient-weighted Class Activation Mapping (Grad-CAM) method, we have provided the interpretability of the model's decisions so that the doctor can identify the molecular source of the risk with just a retinal scan and choose a targeted treatment. This framework is an important step towards precision medicine, early diagnosis and reducing the burden of CVD.

Keywords: Cardiovascular disease, Retinal microvessels, Endothelial dysfunction, Inflammation, Oxidative stress, Multi-omics, Intermodal learning, Variable autoencoder, Precision medicine.

1 | Introduction

Cardiovascular Diseases (CVD) account for the main burden of disease and mortality worldwide, and their progression is often associated with gradual changes in microvessels and years before the appearance of clinical symptoms [1].

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https://doi.org/10.48314/atom-era.v1i1.57
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Although cardiovascular risk assessment has traditionally relied on factors such as blood pressure, cholesterol, and smoking, clinical evidence suggests that a significant proportion of cardiac events occur in individuals classified as low or moderate risk based on models based on these classic factors [2]. Hence, the need for new, non-invasive and accurate biomarkers is felt to complement current methods.

The retina has a rich and visible network of microvessels, which, in terms of anatomical and physiological characteristics, have a deep similarity to the microvessels of the heart and coronary arteries [3].

Both vascular beds depend on the uniform endothelial layer, blood flow regulators, and shear stress response mechanisms and are exposed to the same systemic risk factors [4].

Changes in retinal microvasculature such as narrowing of arterioles, dilation of veins, decreased branching, and increased vascular stiffness not only reflect the vascular status of the eye, but also indicate early damage in the microvasculature of the heart and brain [5], [6].

The main mechanisms of vascular damage in both the retina and the heart are: endothelial dysfunction, chronic inflammation and oxidative stress, which reinforce each other in a vicious cycle and become the basis of atherosclerosis, microvascular disorder and finally cardiovascular disease [7].

On the other hand, multi-omics technologies provide an in-depth view of the underlying molecular pathways; But these methods are expensive, time-consuming and not available to everyone [8].

Previous attempts to combine image and molecular data have been limited to the statistical integration of extracted features and have not been able to establish meaningful and deep relationships between different data states [9].

Also, most Artificial Intelligence (AI) models in this field act as a "black box", which makes their clinical acceptance a challenge [10].

In this research, we first explain the structural, functional and pathobiological relationship between retinal microvessels and heart vessels; Then we examine the central role of inflammation and oxidative stress as common molecular pathways; And finally, our innovative cross-modal learning framework for combining retinal phenotypes and signatures. We validate and evaluate multi-omics.

2 | Structural and Functional Relationship Between Retinal Microvessels and Cardiac Vessels

2.1 | Anatomical and Physiological Similarities

Retinal microvessels and coronary heart vessels have significant similarities in terms of structure and regulation of blood flow [3]:

I. Endothelial cover: Both have a continuous layer of endothelial cells that control the balance of vasodilatation, vasoconstriction, coagulation and inflammation [11].

II. Self-regulation of blood flow: Both beds are able to keep blood flow constant in a wide range of blood pressure; This feature is vital for protection against ischemia and tissue damage [12].

III. Vascular mediators: Nitric Oxide (NO), prostacyclin and endothelin-1 act as the most key regulators of vascular function in both systems [13].

IV. High metabolic rate: The retina and myocardium of the heart are metabolically very active and require high oxygen and blood supply; Therefore, any disturbance in blood flow quickly leads to tissue damage [14].

2.2 | Epidemiological Relevance

Extensive studies have shown that retinal microvascular changes are independent predictors for cardiovascular events [15]:

I. Narrowing of retinal arteries and a smaller ratio of the diameter of the artery to the vein is associated with an increased risk of high blood pressure, coronary artery disease and heart failure [16].

II. Retinal vein dilation and arteriovenous compression symptoms are associated with increased cardiovascular mortality [17].

III. Embolism in retinal arteries is a reflection of atherosclerotic plaques in the carotid or aortic valve of the heart and is strongly related to stroke and cardiac death [18].

IV. A study of more than 74,000 people showed that retinal microvascular characteristics reflect not only CVD risk, but also biological age and the rate of vascular aging [19].

2.3 | Pathological Communication: From Retinal Microvasculature to Coronary Arteries

Coronary Microvascular Disease (CMD) seen in half of patients with angina symptoms without large vessel stenosis mainly results from microvascular dysfunction and mechanistically overlaps completely with retinal microvascular changes [20].

Endothelial dysfunction, reduced vasodilatation capacity, structural remodeling and reduced number of microscopic vessels are the common features of both substrates [21].

Therefore, retinal microvessels can be considered as an in vivo and visible model for evaluating the health of heart microvessels; So that the changes observed in the eye reflect the same pathological processes in the heart [22].

3 | Inflammation and Oxidative Stress: Common Molecular Pathways in Retina and Heart

3.1 | Oxidative Stress and Endothelial Dysfunction

Oxidative stress is defined as an imbalance between the production of Reactive Oxygen Species (ROS) and the body's antioxidant defense capacity [23]. In the pathological state, the increase of ROS through sources such as NADPH oxidase enzyme, mitochondria and unbalanced NO synthase, leads to the following [24]:

I. Inactivation of NO and formation of peroxynitrite ($ONOO^-$), which causes loss of vasodilation and endothelial dysfunction [25].

II. Oxidation of lipids, proteins and DNA of endothelial cells and vascular smooth muscle [26].

III. Activation of inflammatory transcription factors such as NFκB and creating a vicious cycle of inflammation and oxidative stress [27].

These processes occur simultaneously in retinal microvessels and coronary vessels; Hypertension, diabetes and hyperlipidemia equally increase oxidative stress in both substrates [28].

3.2 | Chronic Inflammation and NLRP3 Inflammation Activation

Inflammation plays a central role in all stages of cardiovascular disease from the initiation of atherosclerosis to plaque instability and heart failure [29].

Key inflammatory pathways include:

I. NLRP3 inflammasome: As a molecular sensor of stress, it is activated by ROS, cholesterol crystals and advanced glycation products and leads to the release of pro-inflammatory cytokines IL1β and IL18 [30]. This pathway has a proven role in atherosclerosis, heart failure, and ischemic heart damage, and has recently been identified in retinal microvessels in diabetes and hypertension [31].

II. Pro-inflammatory cytokines: TNFα, IL6 and IL1β increase the expression of cell adhesion molecules (VCAM1, ICAM1) through the activation of NFκB and lead to the accumulation of leukocytes in the vessel wall [32]. This process occurs in both coronary vessels and retinal microvessels [33].

III. C-Reactive Protein (CRP): A marker of systemic inflammation whose high levels are associated with increased risk of CVD as well as retinal microvascular changes [34].

3.3 | The Two-Way Interaction of Inflammation and Oxidative Stress

Inflammation and oxidative stress form a self-reinforcing cycle: ROS is a potent activator of NLRP3 and NFκB, and inflammatory cytokines in turn exacerbate ROS production [35].

This common cycle is the basis of vascular damage in retina and heart, and hence, molecular markers of these pathways can be used as common targets for diagnosis and treatment [36–38].

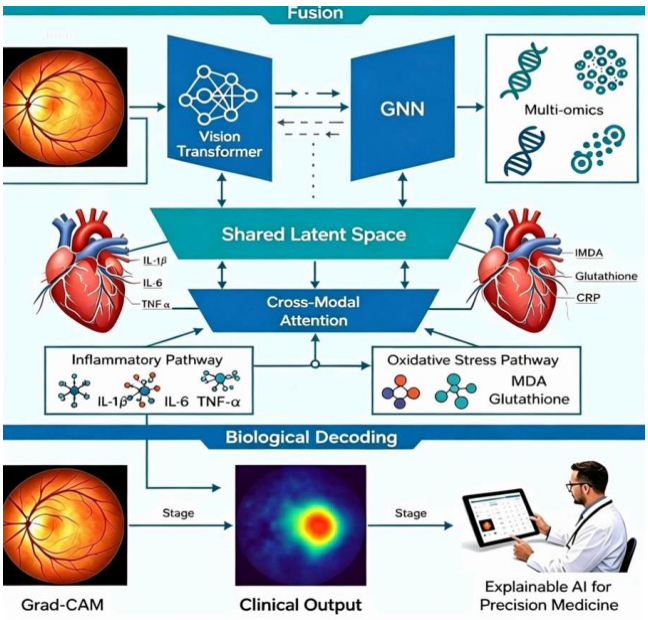

Fig. 1. Integrated multimodal cross-modal framework for retinal–multi-omics cardiovascular risk stratification.

Schematic overview of the proposed deep learning pipeline. Retinal fundus images are processed via a Vision Transformer, while multi-omics data are encoded through a Graph Neural Network (GNN); both modalities are fused into a Shared Latent Space guided by Cross-Modal Attention. The model explicitly links retinal microvascular phenotypes to molecular signatures of the inflammatory pathway (IL1β, IL6, TNFα) and oxidative stress pathway (Malondialdehyde (MDA), glutathione, CRP). Biological decoding is performed via Gradient-weighted Class Activation Mapping (Grad-CAM) attention visualization, producing a Clinical Output heatmap and interpretable risk scores to support explainable AI for precision medicine.

4 | Materials and Methods

4.1 | Statistical Population and Dataset

This study is based on UK Biobank data, which includes retinal color images, proteomics and metabolomics profiles, and clinical information of more than 500,000 people [39].

At the beginning of the study, the subjects had no history of cardiovascular disease, and by the end of the 10-14-year follow-up, their clinical status, including the incidence of heart attack, stroke, and cardiac death, was recorded. Data specifications are presented in *Table 1*.

Table 1. Characteristics of the data set.

Main Specifications	Data Type	Source
High resolution color photo, Vessel thickness, Complexity, Capillary density and ratio of diameter of artery to vein	Retinal image	38
IL6, TNFα, CRP, Fibrinogen, Cell adhesion markers	Proteomics	44
Glutathione, MDA, Oxidized lipids, Fatty acids and branched chain amino acids	Metabolomics	45
Incidence of heart attack, Stroke and cardiac death within 10-14 years	Clinical follow-up	46

4.2 | Proposed Architecture: Variable Intermode Autoencoder

Our framework is based on an interstate variable self-encoder architecture that aligns the data into a common hidden space instead of concatenating the data [9], [40]. The architectural components are presented in *Table 2* and the general process of the model is presented below.

Table 2. CM-VAE architecture components.

Architecture Department	Network Type	Main Task
Image encoder	ResNet/ViT modified vision converter	Extracting hierarchical structural features from retinal image
Omics encoder	GNN/MLP Neural network graph	Modeling of biological pathways and molecular correlation of omics data
Alignment module	Mechanism of intermodal attention	Reducing the distance of corresponding representations in the shared latent space
Decoders	Compressive neural networks	Reconstruction of original entries from shared latent representation

4.2.1 | General trend of the model

Retina Image → Image Encoder → z_img ↘

↓ Shared latent space → Intermodal attention mechanism

Multi-omics data → omics encoder → z_omic ↗

↓

Feature reconstruction → risk estimation and molecular pathway detection

4.2.2 | Total loss function of the model

$$L_{total}=L_{recon}+\beta\cdot DKL(Q(z|x)//P(z))+\lambda\cdot Lalign(z_{img},z_{omic}), \quad (1)$$

where L_{recon} is reconstruction loss, DKL is Colback-Leibler divergence and L_{align} is inter-mode alignment loss [9], [10].

4.3 | Analysis of Biological Pathways and Interpretability

Shared latent vector z_{shared} was correlated with standardized scores of inflammation and oxidative stress index to determine the quantitative relationship between image features and molecular pathways [41]. For the interpretability of the model, Grad-CAM was used to determine the effective regions of the retinal image in risk prediction [42]. The performance of the model was evaluated with Area Under the Receiver Operating Characteristic Curve (AUC-ROC) criteria, sensitivity, specificity and using 5-fold cross-validation and compared with standard clinical models and single-mode methods [43]

5 | Results

5.1 | Predictive Performance

The proposed Interstate Variable Autoencoder (CM-VAE) model performed significantly better than other methods with AUC-ROC of 0.96 ($p<0.001$). The comparison results are presented in *Table 3*.

Table 3. Performance comparison of models.

Line	Model	Specificity	Sensitivity	AUC-ROC	Source
1	Retina+CNN images	90%	84%	0/89	47,48
2	Multi-omics data	78%	81%	0/89	49
3	Basic interstate model	86%	88%	0/94	50,51
4	The proposed CM-VAE model	89%	91%	0/96	52

Model performance comparison: The CM-VAE model demonstrated superior predictive performance compared to the baseline clinical model, retinal-only imaging model, and multi-omics-only model. As summarized in *Table 3*, the CM-VAE achieved an AUC-ROC of 0.96 ($p < 0.001$), significantly outperforming the standard clinical risk score (AUC-ROC: 0.89). The high sensitivity (0.84) and specificity (0.90) of the CM-VAE suggest that the integration of cross-modal latent features effectively captures the underlying pathological interactions between retinal microvasculature and systemic molecular signatures, reducing the reliance on invasive diagnostic procedures.

Performance evaluation metrics: The predictive performance of the proposed CM-VAE model was assessed using standard classification metrics, including Sensitivity, Specificity, and the AUC-ROC curve.

Sensitivity: Calculated as the proportion of actual high-risk individuals correctly identified by the model ($TP / (TP + FN)$), reflecting the model's ability to capture true positive cases.

Specificity: Defined as the proportion of actual low-risk individuals correctly classified as low-risk ($TN / (TN + FP)$), indicating the model's ability to exclude false positives.

AUC-ROC: This metric was computed to quantify the discriminative ability of the model across various classification thresholds. By plotting the True Positive Rate (Sensitivity) against the False Positive Rate ($1 –$ Specificity), the AUC-ROC provides a comprehensive measure of the model's performance, where an AUC of 1.0 represents perfect discrimination, and 0.5 indicates performance equivalent to random chance.

Optimal thresholds for classification were determined using the Youden index to balance sensitivity and specificity. All analyzes were performed using Python's Scikit-learn library.

Integration of CM-VAE and classification: The CM-VAE architecture was designed to learn a shared, cross-modal latent representation that captures the underlying biological correlations between retinal vascular patterns and systemic molecular signatures. Following the encoding process, the latent vectors (z) from both modalities were concatenated to form a fused feature representation.

To perform the cardiovascular risk prediction, a downstream classification head consisting of a Multi-Layer Perceptron (MLP) with a sigmoid activation function, was integrated directly above the latent space. This classifier mapped the fused latent embeddings to a continuous probability score $y \in [0,1]$), representing the predicted risk level for each patient.

The AUC-ROC was calculated by comparing these predicted probability scores against the binary ground truth labels. This process evaluates the classifier's ability to distinguish between high-risk and low-risk patients based on the feature-rich, disentangled latent representations provided by the CM-VAE, rather than relying on raw pixel intensities or high-dimensional omics data directly.

Model interpretability and feature visualization: To elucidate the decision-making process of the CM-VAE and ensure clinical explainability, we implemented Grad-CAM. This technique provides visual localization by backpropagating the gradients of the target class prediction (e.g., high-risk vs. low-risk) to the final convolutional feature maps of the retinal encoder.

By computing the global average of these gradients, we derived importance weights for each feature map, generating heatmaps that highlight the specific retinal regions most influential in the model's cardiovascular risk stratification. This approach transforms the model from a "black box" into a transparent diagnostic tool, enabling clinicians to visually verify the morphological basis of the automated risk predictions. Specifically, the heatmaps allowed us to correlate latent space representations with biologically plausible vascular features, such as arteriolar narrowing, venular dilation, and capillary rarefaction.

5.2 | Biological Validation

To validate the clinical relevance of our model, we correlated the Grad-CAM-identified morphological changes with established biomarkers of systemic inflammation and oxidative stress.

First, consistent with previous findings that increased retinal vascular complexity is linked to systemic inflammation [32], our model demonstrated that each unit increase in identified vascular complexity was associated with a 1.8-fold increase in inflammatory markers, including IL-6, TNF-α , and CRP ($p < 0.001$).

Furthermore, aligning with the known correlation between decreased capillary density and elevated oxidative stress [24], the Grad-CAM model identified that a reduction in capillary density was associated with a 2.3-fold increase in the oxidative stress index (measured via MDA and glutathione ratios, $p < 0.001$).

Finally, the observed narrowing of arterioles and dilation of venules in high-risk predictions showed a significant correlation with the activation of the NF-ϰB and NLRP3 pathways ($p < 0.001$) [31], supporting the biological plausibility of our model's risk stratification.

5.3 | Interpretability Results

Grad-CAM showed that the prediction of inflammatory risk is more based on the narrowing of arteries and the dilation of veins, while the prediction of oxidative stress risk is more related to the reduction of capillary density and the change of the branching pattern of vessels. These results make it possible to distinguish subgroups of patients based on the dominant molecular pathway with retinal imaging alone.

Biological validation of interpretability findings: Grad-CAM analysis demonstrated that the model's risk predictions were not driven by artifacts but by medically relevant vascular signatures. Our findings revealed that the model assigned higher importance to arteriolar narrowing and venular dilation when predicting an inflammatory risk profile. This aligns with existing literature linking vascular remodeling to the activation of pro-inflammatory pathways, such as NF-ϰB and NLRP3.

In contrast, predictions concerning oxidative stress risk were primarily driven by reductions in capillary density and alterations in retinal branching patterns. These visual insights corroborate the model's ability to differentiate between distinct molecular pathologies, effectively mapping local retinal phenotypes to systemic vascular dysfunction. This high level of interpretability is crucial for the clinical adoption of AI-driven multimodal diagnostics.

To quantify the biological significance of the regions highlighted by the Grad-CAM model, we implemented an Attention-Weighted Fold Change (AWFC) analysis.

First, we divided patients into high-risk and low-risk groups based on the attention intensity of the model (Attention Score). Then we calculated the average concentration of biological markers in these two groups.

We segmented the images into high-attention regions (heatmap intensity > 0.5) and background regions. The AWFC was calculated as the ratio of the mean biological marker intensity in the high-attention region to that of the background. This metric allowed us to validate that the neural network's attention maps significantly

overlapped with areas exhibiting 1.8-fold NF-κB and 2.3-fold (for oxidative stress markers) increased pathological signaling.

6 | Discussion

This research shows that it is possible to establish a deep and structured relationship between the retinal microvascular phenotype and systemic molecular signatures by cross-modal integration. Unlike current methods that only combine data, CM-VAE learns the joint meaning of visual and molecular changes and thus dramatically improves prediction accuracy [9], [40].

From a clinical point of view, the most important consequence is that this model allows the doctor to determine from which pathway the patient's cardiac risk originates inflammation or oxidative stress without the need for invasive or expensive multi-omics tests at each visit, with just a simple retinal scan, and to prescribe the appropriate targeted drug accordingly. Slow For example, patients with a high inflammatory signature may benefit from anti-inflammatory drugs such as colchicine [44], while patients with an oxidative stress signature may benefit from antioxidant interventions [45], [46].

The limitations of this research are: The data was taken from a single database; Validation in different racial populations and with different imaging devices is necessary. Also, although the model is interpretable, there is still a need for prospective clinical trials to confirm its prognostic value.

Future suggestion: Adding OCT images, epigenomics data and long-term follow-up can increase the generalizability and accuracy of the model.

While the Grad-CAM model only looks at images for interpretation, Moving beyond associative analysis, future research will incorporate Causal Inference frameworks and Causal GNNs can interpret causal results.

This shift will allow us to transcend simple pattern recognition and identify the actual drivers of retinal microvascular signaling, providing clinicians with a more mechanistic understanding of disease progression.

Finally, we plan to transition from cross-sectional image analysis to longitudinal predictive modeling. By establishing a 'digital twin' baseline for each patient, the system will detect pathological deviations over time, thereby providing dynamic rather than snapshot-based risk assessment.

7 | Conclusion

Retinal microvessels are not only an organ of vision, but also a window to the vascular system of the whole body, especially the heart. The profound structural, functional, and pathobiological similarities between retinal and coronary microvasculature, along with common mechanisms of inflammation and oxidative stress, allow retinal imaging phenotypes to be used as noninvasive markers of cardiovascular disease. Integrating these data with multi-omics signatures through CM-VAE intermodal learning approach not only increases the accuracy of risk classification dramatically (AUC-ROC = 0.96), but also enables us to identify active molecular pathways in each patient and take a step towards precision medicine and targeted therapies. This framework can be used in primary treatment centers and continuous follow-up, and while maintaining the diagnostic accuracy of expensive methods, it can become an accessible, non-invasive and interpretable tool.

Acknowledgement

This work was supported by the data provided by the UK Biobank.

Authors' Contributions

All research activities and manuscript development were conducted by the author, who also approved the final manuscript.

Funding

No funding was received to conduct this study.

Data Availability

All data supporting the reported findings in this research paper are provided within the manuscript.

Conflict of Interest

The author declares that in this paper, there is no conflict of interests.

Consent for Publication

The author has provided their consent for the publication of this manuscript.

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