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Review Article

Ocular Biomarkers for Enhanced Systemic Risk Assessment through Artificial Intelligence

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Abstract

Integrating ocular biomarkers with artificial intelligence (AI) technologies offers a transformative approach to systemic risk assessment in clinical practice. This article explores the potential of ocular biomarkers as predictive tools for systemic diseases, leveraging AI's robust analytical capabilities. Ocular images, being non-invasive and rich in physiological information, can reveal early signs of systemic conditions such as cardiovascular disease, diabetes, and neurodegenerative disorders. AI-powered algorithms enhance these biomarkers' precision and predictive power, enabling early detection and monitoring of disease states that might otherwise remain undiagnosed until advanced stages. We review state-of-the-art AI methods in analyzing retinal images and other ocular data, highlight significant breakthroughs in automatization, and assess the challenges and ethical considerations of integrating AI in clinical risk assessment. The convergence of these technologies promises to refine individual patient care and advance large-scale public health strategies by facilitating more accurate and timely systemic disease prediction. This paper delineates the current landscape and prospects of ocular biomarker utilization in AI-driven systemic health assessments.

***Keywords**: Ocular Biomarkers; Artificial Intelligence; Systemic Risk Assessment; Retinal Imaging; Disease Prediction*

Introduction

The oculome [1], which studies the eye's macroscopic, microscopic, and molecular characteristics related to health and disease, can be comprehensively explored using advanced multimodal imaging technologies and extensive datasets. This oculomics revolution offers a promising opportunity to gain insights beyond ophthalmic conditions by utilizing the retina [2]. The retina is the only human body tissue that allows for direct, noninvasive visualization of the microvascular circulation and the central nervous system, making it a unique platform for understanding systemic diseases. Detection of early signs of microvascular changes in the retina can be valuable in predicting disease progression since they can be identified before clinical symptoms appear [3]. Semi-automated analysis software can extract information on retina vessel caliber, tortuosity, branching angle, and retinal fractal dimension from fundus photographs. The software uses reliable algorithms to ensure consistency in the analysis [4,5].

Ophthalmoscopy has revealed that changes in the retinal microvasculature can indicate the likelihood of various conditions, such as hypertension, diabetes, coronary disease, renal disease, and stroke [5-9]. Optical coherence tomography (OCT) can effectively measure the thickness of the retinal nerve fiber layer and macular volume, providing insight into an individual's risk of developing cognitive decline and neurodegenerative diseases [10]. Ocular coherence tomography-angiography (OCT-A) technology enables the examination of the retinal vascular network in detail at the capillary level across different plexuses. With OCT-A devices, one can obtain precise quantitative metrics to evaluate the retinal vasculature's health, including vessel density, perfusion, and flow index [11].

Certain disorders have unique retinal features that can be used as diagnostic indicators, such as sea fan neovascularization in sickle cell anemia, macular crystals in cystinosis, or astrocytic hamartomas in tuberous sclerosis [12]. Over the last two decades, there has been remarkable progress in retinal imaging technology. This advancement has made it easier and safer to access a wide range of high-resolution imaging techniques that are simple to acquire and require minimal expertise. Compared to traditional direct ophthalmoscopy, modern retinal photography, and OCT offer exceptional resolution and are widely used in community settings and hospital ophthalmology departments [13]. At leading eye hospitals and foundations in North America and Europe, there has been a significant rise in the utilization of OCT. The number of OCT scans performed has increased by over 14 times [14]. The primary objective of this development is to enhance the identification of retinal diseases that may cause vision loss. Nevertheless, there is an equally significant prospect on the horizon - the possible utilization of ocular biomarkers to recognize systematic diseases, foresee their progression, and provide non-invasive indicators of their severity and efficacy of treatment.

Population-based research in cardiovascular disease (CVD) and dementia has revealed meaningful quantitative correlations between retinal structure and systemic conditions. In cardiovascular disease, modifications in the retinal microvasculature, such as vascular caliber and tortuosity indices, have been associated with CVD risk factors and could function as predictive indicators for significant occurrences like heart attacks and strokes [8,9]. Historically, the study of the eye's characteristics has relied on manual segmentation of digital images, which is a time-consuming process. Despite the introduction of semi-automated software, researchers still require significant effort when dealing with large datasets. This is why there is a need for fully automated solutions, which AI techniques can provide. Deep learning (DL), a subtype of AI machine learning (ML), has shown promise. In 2018, researchers at Google Brain developed a model that could accurately predict CVD risk factors, age, and sex with great precision [15]. The model's decision-making process was validated by identifying critical factors like retinal vasculature, the optic nerve, and macular morphology.

Recent advances in imaging technologies have led researchers to explore automated image analysis algorithms that could identify features of retinal vascular health. These algorithms aim to validate previous findings on the link between retinal microvasculature parameters and cardiovascular health status [15]. ML. DL techniques have shown significant potential in automatically analyzing and quantifying retinal vascular biomarkers to predict cardiovascular risk factors and systemic vascular events [16]. The scientific literature in this area is continuously expanding. This comprehensive literature review outlines recent advancements in AI applications for retinal vascular imaging, utilizing retinal fundus photographs and OCT-A and evaluating cardiovascular profiles. This article aims to critically assess the current state of "oculomics" and research on cardiovascular diseases, among other biomarkers.

Advancements in AI for extracting retinal microvascular parameters

Machine learning: ML is a branch of AI that uses data to create programs rather than predetermined rules. It involves analyzing large datasets to identify patterns and relationships between variables, which can lead to new correlations and innovative hypotheses [17]. ML is crucial for developing automated clinical decision support systems in healthcare. Two main types of ML methods exist: supervised and unsupervised [18]. Unsupervised learning works without labeled data and aims to find hidden patterns in datasets, which helps explore data and generate hypotheses. On the other hand, supervised learning focuses on predicting known outcomes or targets, such as classification and prediction tasks. By extracting meaningful and robust features, computers can mimic the decision-making capabilities of trained professionals, which traditionally requires substantial time and heuristic methods [19].

Deep learning: DL is a specialized type of ML that constructs artificial neural networks (ANNs) modeled after the human brain's neural structure. ANNs consist of artificial neurons connected in layers that process and transform input signals to generate the final output. DL employs deep neural networks (DNNs) as the foundational architecture for AI algorithms. DNNs contain multiple intermediary

layers between the input and output layers, allowing each layer to learn to extract increasingly complex and higher-level features from the input data, leading to more efficient learning. DNNs have the advantage of continually improving performance as training datasets grow. In retinal vascular imaging data analysis, convolutional neural networks (CNNs) are the most appropriate DL architecture. CNNs mimic the connectivity patterns between neurons in the mammalian visual cortex. By training CNNs with extensively annotated datasets, computers learn to recognize visual patterns and contribute to the resurgence of AI applications in retinal imaging [20].

Exploring open access datasets for retinal imaging analysis: The use of AI in analyzing retinal images has advanced significantly with the help of large, real-world image datasets. Different well-established retinal image datasets, such as MESSIDOR, STARE project, DRIVE, E-naphtha, and EyePACS, have provided researchers with high-quality images with accurate labeling in a usable format [21-26]. A recent review has identified 94 open-access ophthalmology datasets that offer unrestricted access, with over 507,000 pictures retrieved from a minimum of 122,000 individuals [26]. Fundus photographs are the most common retinal images, followed by OCT and OCT-A images. These datasets include images of various eye conditions, such as healthy, myopic, hypertensive, and diabetic eyes, and demographic information, such as age and sex, across different ethnic groups worldwide. Researchers can use these publicly available datasets to analyze images from diverse populations and other devices, allowing them to optimize their algorithms using external data sources. Additionally, the availability of various imaging modalities across different programs reinforces the applicability and generalization of AI algorithms in retinal imaging analysis.

Enhancing image analysis methods with semi-automated feature-based approaches: Since the late 1940s, ophthalmologists have studied the relationship between subjective retinal vascular signs captured on fundus photographs and systemic vascular conditions like hypertension and arteriosclerosis [27]. Retinal imaging has revolutionized this field of study. Parr., *et al*. [28] were crucial in developing objective and reproducible quantitative retinal vascular caliber analysis measurements. Programs like Integrative Vessel Analysis (IVAN) and Singapore I Vessel Assessment (SIVA) are commonly used. These programs enable the semi-automated identification of retinal arterioles, venules, and the optic nerve head to measure various retinal microvascular parameters objectively. Parameters like central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), arteriole-to-venule diameter ratio (AVR), tortuosity, branching angle, and fractal dimension can be quantified using these tools. Studies have shown that these software programs have high repeatability and reproducibility [29-39].

Researchers have been exploring the correlation between retinal microvascular characteristics and systemic vascular diseases for over two decades, using software programs to extract this information [40]. Abnormalities in retinal microvasculature, such as changes in arteriolar and venular caliber, increased tortuosity, and suboptimal retinal vascular network, have been linked to hypertension [40], cardiovascular mortality, ischemic stroke, and elevated cardiovascular risk scores [39,41-47]. These associations are supported by numerous extensive population-based studies that span various ethnic groups worldwide [48-51].

However, the semi-automated software programs initially used had limitations that prompted the development of new retinal imaging technologies. These programs were time-consuming, incompatible with other software, and relied on predefined retinal architecture and definitions, which could leave some information unidentified in the retinal data [52-54]. As a result, there has been a growing focus on using AI techniques to automate fundus processing and identify retinal biomarkers for assessing cardiovascular risk. This approach can uncover previously undisclosed information within the retina beyond what traditional software programs could achieve.

Enhancing image processing with AI techniques: DL algorithms have been created to minimize operator intervention and enable fully automated image processing [55-57]. These algorithms mainly focus on tasks like segmenting veins and the fovea and grading image quality [57]. In oculomics, vessel segmentation has been a significant area of research compared to other retinal biomarkers, such as the optic disk and fovea [58,59].

Recent developments have seen the emergence of architectures based on the UNet model with different modifications [60], such as dense blocks, squeeze-and-excitation blocks, and spatial attention modules [61-65]. There has also been a shift towards using image transformer architectures [66], which led to the creation of models like the Patch Convolution Attention-based Transformer UNet (PCAT-UNet) [67]. However, these UNet-like or transformer architectures require more data for training, have a higher parameter count, and their outputs can be harder to interpret.

One notable example of automated image processing software is QUARTZ, which initially automated tasks such as retinal vessel morphometry segmentation and arteriole-venule differentiation. It has now evolved to quantify retinal geometric features for epidemiological studies [68-70]. DL techniques have demonstrated superior performance compared to feature-based methods. Nevertheless, a significant drawback of these models is their lack of interpretability, often called the "black box problem". The "black box phenomenon" [71] in AI pertains to the difficulty in comprehending the decision-making process of specific AI models. Similar to a black box, we can observe the input and output of the model, but the internal mechanisms that generate the outcome remain opaque. This lack of transparency poses challenges in trusting and interpreting the decisions made by AI systems. Moreover, a significant and diverse dataset with annotations is required to build these data-driven models. This dataset should include samples from different sources, centers, and ethnicities, making implementing such models widely in clinical settings challenging.

Utilizing AI-generated microvascular parameters for cardiovascular risk evaluation

British nephrologist Richard Bright first noted the connection between systemic vascular disease and ocular manifestations in 1836 [72]. He observed a group of patients with vision impairment and albuminuria, which later became known as Bright's disease. The understanding of the correlation between ophthalmic indicators and systemic conditions became more apparent after the invention of the ophthalmoscope. In 1892, Marcus Gunn identified significant features of severe hypertensive retinopathy in patients with chronic kidney disease [73]. The integration of retinal-based evaluation for assessing cardiovascular risk was established in 1939 by Keith., *et al*. [74]. They introduced a comprehensive grading system for hypertensive retinopathy, leading to improved predictive accuracy and an informed evaluation of individual patients.

Due to the high mortality rate caused by CVD, which accounts for over 30% of deaths globally, there has been a significant effort to develop effective methods for identifying individuals at the highest risk [75]. The American College of Cardiology and American Heart Association's 2019 guidelines propose the use of the ASCVD Risk Estimator Plus, which calculates a 10-year CVD risk score based on several risk factors such as age, sex, ethnicity, blood pressure readings, and blood parameters like total cholesterol levels [76]. However, despite these risk stratification algorithms, their calibration and discriminatory abilities may be limited when validated externally [77,78]. Moreover, generating accurate scores requires significant input from healthcare professionals and laboratory analyses.

Using a single noninvasive eye exam to assess the risk of cardiovascular disease is an attractive option, mainly because most people place great importance on their vision and eye health. Studies show that people consider their eyesight the most crucial [79], leading to significant differences in the frequency of eye check-ups and cardiovascular disease screenings [80].

AI prediction of risk factors for cardiovascular diseases: AI in cardiovascular research started with retinal fundus images to predict traditional cardiovascular risk factors (CRF). Poplin., *et al*. [15] created a CNN model that employed data from the UK Biobank and EyePACS datasets to predict risk factors like age, gender, smoking status, and systolic blood pressure (BP). The DL algorithm achieved remarkable results, with a mean absolute error of 3.26 years for age prediction and an area under the curve (AUC) of 0.97 for gender prediction. Similarly, Kim., *et al*. [81] achieved high accuracy in age prediction using the CNN ResNet-152 algorithm with 24,366 fundus images. However, they observed higher discrepancies between predicted and actual age among individuals over 60 years old and those with systemic vascular diseases like hypertension (HTN) and diabetes mellitus (DM). Cheung., *et al*. identified associations between retinal

vessel parameters and age, gender, BP, body mass index (BMI), cholesterol levels, and smoking status, with consistent results between automated and semi-automatic software models [16]. Arnould., *et al*. [82] took a different approach and focused on quantitative geometric metrics derived from retinal imaging software to train ML algorithms for predicting age, history of DM, and HTN. As age is a significant CRF [83], innovative approaches like estimating physiological age based on retinal fundus images (RetiAGE) show promise as potential indicators of cardiovascular risk in future studies [84].

The American College of Cardiology/American Heart Association (ACC/AHA) recommends the use of traditional tools such as the Framingham Risk Score (FRS) [85] and the more recent Pooled Cohort Equations (PCE) [86] to evaluate the cardiovascular risk of patients. However, these methods may not be accurate for certain ethnic groups or patients with intermediate-risk profiles. To overcome this, new biomarkers such as the coronary artery calcium (CAC) score have been developed, which can be obtained from cardiac computed tomography (CT) scans [87]. However, the CAC score has its limitations due to invasiveness, cost, and requirement of access to a cardiac CT system. In this regard, researchers have explored using deep learning algorithms based on retinal photographs to estimate CAC levels. Son., *et al.* [88] developed a DL model that could distinguish between patients with high CAC scores and those with low CAC scores by analyzing retinal fundus images. Although their study showed moderate results, combining retinal fundus images with key clinical factors such as age, hypertension status, and gender yielded improved performance. Future algorithms should consider integrating such clinical characteristics to optimize their performance.

Enhance cardiovascular risk factor prediction with artificial intelligence using OCT angiography (OCT-A) and advanced ophthalmic optics (AO): Recent advancements in AI have expanded the potential of retinal biomarkers beyond traditional retinal fundus photographs for predicting cardiovascular risk profiles [89]. Leveraging other retinal imaging technologies, such as Optical Coherence Tomography Angiography (OCT-A) [90], could significantly enhance the accuracy and effectiveness of predictive models. Studies have revealed significant associations between OCT-A retinal vascular parameters and cardiovascular risk factors [91] and events, further establishing its utility in ophthalmology departments.

AI-driven analyses of OCT-A images have revolutionized the investigation of retinal vascular networks, enabling automated disease detection for various retinal conditions [92]. Researchers have developed innovative segmentation models to automate the identification of retinal vessels in OCT-A scans [93]. The integration of ophthalmic adaptive optics (AO) in studying retinal vascular biomarkers has shown promise but needs to be improved in cost and availability [94]. The future of oculomics holds excellent potential for leveraging retinal vascular parameters extracted through OCT-A and AO with the assistance of AI algorithms. These innovative technologies will be pivotal in advancing our understanding of microvascular and macrovascular associations and enhancing cardiovascular risk assessment.

Limitations of current technology: The use of AI in medical imaging analysis has become increasingly popular in various medical fields, including the study of retinal vascular networks in ophthalmology. Researchers must follow strict methodological protocols to create accurate clinical predictive models for assessing cardiovascular risk through analyzing retinal vascular networks. The main goal of any AI-based prediction model should be to achieve replicability, reproducibility, and generalizability. To ensure reliable results in this area, studies should include external validation datasets, open-source algorithms, and independent labeling of retinal imaging and cardiovascular data.

The use of AI-powered retinal biomarkers has the potential to bring about a significant change in academic research and primary healthcare practices, including general practitioner settings. With this technology, it is possible to expand cardiovascular disease assessment beyond traditional clinical applications through retinal imaging and oculomics cost-effectively. For instance, integrating retinal biomarkers into general health screening programs such as those for adults can provide valuable insights. However, factors such

as healthcare workflow optimization, proximity between retinal imaging devices and cardiovascular facilities, availability of imaging algorithms, trained personnel, and data backup may influence the associated costs. While AI-based biomarkers can generate more data quickly and affordably, further research on the economic implications of integrating this technology is essential.

Conclusion

Using AI to analyze retinal images obtained through fundus photographs and OCT-A can strengthen the correlation between retinal vascular network features and cardiovascular risk evaluation. This technology can aid in confirming the links between the microvasculature of the retina and the body's microvasculature. Several algorithms have demonstrated high accuracy and predictive capabilities, with up to 80% prediction rates for cardiovascular risk factors, risk stratification, and significant cardiovascular events. However, whether AI-based methods outperform conventional prediction models is still being determined. In the future, automated retinal vascular parameters may provide additional benefits for specific groups of patients. While these promising results are based on population-based epidemiological data, further research is necessary to assess their potential in real-world healthcare settings.

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