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Wide field imaging biomarkers: A different perspective

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Abstract:

Wide field retinal imaging has emerged as a transformative technology over the last few decades, revolutionizing our ability to visualize the intricate landscape of the retina. By capturing expansive retinal areas, these techniques offer a panoramic view going beyond traditional imaging methods. In this review, we explore the significance of retinal imaging-based biomarkers to help diagnose ocular and systemic conditions. We discuss quantitative biomarkers, including ischemic index, nonperfusion area and more, and their application in diabetic retinopathy, central retinal vein occlusion, neurodegenerative diseases, and more. In addition, we outline qualitative biomarkers such as choroidal venous hyperpermeability and intervortex anastomoses. The role of wide field fundus autofluorescence in assessing hereditary retinal diseases is also emphasized. Standardized imaging procedures, professional collaboration, and validation across a range of clinical circumstances are necessary for the effective use of these biomarkers. They have the potential to transform disease identification, risk assessment, and customize therapy.

Keywords:

Biomarkers, qualitative biomarkers, quantitative biomarkers, retinal imaging, wide field

Introduction

The past two decades have been instrumental in the field of retinal imaging techniques and their usefulness in diagnosing ocular and systemic diseases.[1] These modalities have had a profound impact on ophthalmology and other related medical specialties. They provide clinicians with valuable insights into the structure, function, and pathological changes occurring in the patient's retina enabling better diagnosis and enhanced patient care. Retinal imaging techniques have also become faster, more precise, and capable of three dimensions because to developments in imaging software, hardware, and image processing algorithms. Research opportunities have increased as a result, and quantitative imaging biomarkers for early illness identification and therapy response evaluation have been developed. In addition, patient care has improved. It is anticipated that retinal imaging will become more and more important in healthcare as technology develops, resulting in new discoveries about the causes and treatments of a variety of ocular and systemic disorders.

Wide field imaging methods can capture the images beyond 50°, while ultrawide field (UWF) techniques can cover up to 200° of the retinal area, encompassing approximately 80% of the retinal surface. One benefit of these techniques is that they can visualize through narrow pupils. Furthermore, a lot of contemporary imaging systems enable the simultaneous acquisition of different kinds of retinal images, like fundus autofluorescence (FAF), such as blue-reflectance, infrared reflectance, or green reflectance, red-free photography, fundus photography, colour fundus stereo imaging, adaptive optics confocal scanning laser ophthalmoscopy, and fundus fluorescein angiography (FFA).

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These imaging techniques can be broadly categorized into those that show the structural characteristics of the retina and those that quantify some component of retinal function. Retinal lesions, retinal vessel size, and layer thickness are all structural characteristics. Retinal blood flow, electrical activity, and light sensitivity are just a few of the functional characteristics of the retina that can be measured by imaging techniques.[2] Based on these structural and functional characteristics, many studies have been able to describe qualitative and quantitative parameters which can serve as the biomarkers for ocular and systemic diseases.

A biomarker is a measurable trait used to indicate natural biological- or disease-related processes or to assess how the body responds to a specific treatment.[3]

Below, we will discuss the relevant biomarkers and how they can serve as the predictors of disease. Our primary objective is to highlight the significant role of biomarkers derived from the retinal imaging techniques and their role in serving as a window to ophthalmic and systemic diseases. We aim to establish a prospective approach in clinical practice that embraces these biomarkers, enabling us to explore a diverse range of diseases that may manifest through these indicators. By incorporating these biomarkers into routine clinical practice, we can expand our understanding of diseases beyond their conventional presentations. This comprehensive approach allows us to consider a broader spectrum of diseases that can be associated with specific biomarker patterns.

We will be discussing a total of four quantitative biomarkers described on UWF fluorescein angiography (UWFFA) and a couple of qualitative biomarkers described on indocyanine green angiography (ICGA) and FAF. We will conclude by discussing the limitations of wide field techniques and exploring the future scope of these modalities.

Quantitative biomarkers

Quantitative biomarkers play a crucial role in advancing medical imaging techniques and facilitating the diagnosis, monitoring, and management of various diseases. In the context of retinal vessel imaging, these quantitative biomarkers offer valuable insights into the structural and functional characteristics of the retinal vasculature. By utilizing sophisticated imaging technologies and computational algorithms, researchers and clinicians can extract quantitative measurements from retinal images, providing objective and reproducible assessments of vascular parameters.[4-10] These quantitative biomarkers enable a deeper understanding of retinal vascular pathologies and their associations with systemic diseases. We will be discussing the following four:

A. Ischemic index
B. Nonperfusion area (NPA)
C. Leakage index and no. of microaneurysms (MA)
D. Geodesic distance.

Ischemic index

Ischemic index was described initially in patients of retinal vein occlusion on UWFFA. Using the area measurement function, the region of capillary nonperfusion visible in the arteriovenous phase image was briefly circumscribed and divided by the overall image area in pixels [Figure 1]. Leakage from the retina's blood vessels was not regarded as nonperfusion. When a color photograph of the retina was available, it was used to compare the angiography with it to identify the area of nonperfusion in eyes with significant intraretinal hemorrhage. The surrounding areas' levels of retinal perfusion were also assessed. The area of the hemorrhage was circled and divided by two to roughly represent the amount of nonperfusion if an area of hemorrhage was bordered by both perfused and nonperfused retina.[11-13]

It is a well-known fact that ischemic retina is responsible for the production of biochemical mediators. The above studies therefore concluded that retinal vein occlusion patients with higher ischemic index had significantly higher incidence of neovascularization, macular edema, and recalcitrant disease. Thomas *et al*. described ischemic index i35% as a sensitive and specific marker for the classification as an ischemic central retinal vein occlusion.[14] An attempt to correlate ischemic index and best-corrected visual acuity (BCVA) and ischemic index was made by Wang *et al*., where they found a negative correlation

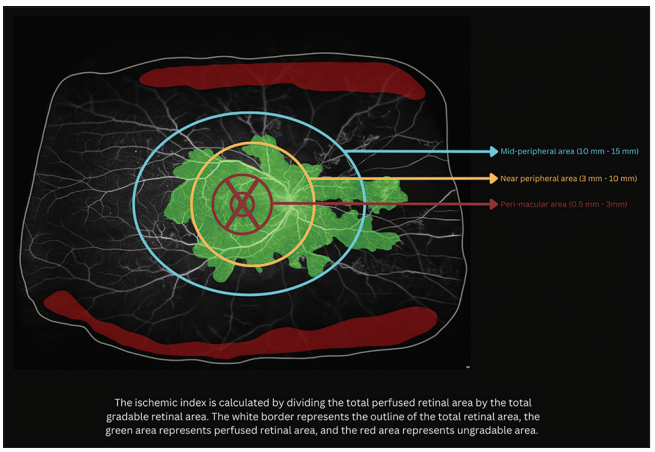

Figure 1: The ischemic index is calculated by dividing the total perfused retinal area by the total gradable retinal area and subtracting it from 1. While grading, the retinal area can be divided into different zones on an ultrawide field fluorescein angiography image namely the perimacular area (0.5–3 mm), near peripheral area (3–10 mm), and the mid-peripheral area (10–15 mm) and the index can be calculated separately for each zone. The white border represents the outline of the total retinal area, the green area represents the perfused retinal area, and the red area represents ungradable area. The remaining area is the gradable retinal area. Ischemic index in this figure is the 1-(total green area divided by the total gradable retinal area) (~0.6)

between BCVA and ischemic index in both the perimacular region and the periphery.[15]

Patel *et al*.[13] described a similar technique in diabetic macular edema patients and found that patients with a higher ischemic index required more sessions of laser photocoagulation and were more resistant to treatment. These results also correlated with vessel density on optical coherence tomography angiography (OCTA). Moreover, the ischemic index also improved on treatment with aflibercept, with significant results being observed on treatment with more frequent doses.[16-18] Similar results were found in patients with intravitreal dexamethasone implants.[19,20]

The inner surface of the eye is largely spherical, making it impossible to map it onto a flat surface without distortion, according to an intriguing study by Kim *et al*.[21] Estimating the ischemic index by UWFFA was regarded as being inaccurate in this study. With increasing distance from the center, projected periphery pictures become more distorted.[22] This is illustrated by the Mercator projection which is the distortion caused by laying the world on a flat map. A similar distortion occurs with the Optos images such that the lesions in the periphery appear larger on a flat screen than they actually are on an indirect ophthalmoscopy.[23] In order to reduce any disagreement between the measurement of nonperfused areas taken directly from Optos pictures, the ischemic index, and the real dimensions, this distortion should be addressed. Croft *et al*. accounted for this error by creating montages of Optos images taken from different gaze angles and projected them onto a three-dimensional (3D) model. They then used trigonometry to quantify the area.[24]

Non-perfusion areas

NPAs in the retina are linked to vascular blockages or closure of capillaries. Detecting small, isolated NPAs in patients with diabetic retinopathy (DR) early on are vital. NPAs are the fundamental lesions in DR, and their severity is typically assessed through indirect signs of ischemia observed in routine practice through color fundus photographs and fluorescein angiography (FFA).[25] However, this is a difficult task due to variations in overall size, shape, location, and intensity of retinal pathologies, additionally complicated by biases and variability in expertise.[4,26-29] Rasta *et al*. described NPAs as ponds surrounded by healthy capillaries in FFA images and described an automated technique to quantify NPA[26] [Figure 2]. With the advent of OCTA, Cui *et al*. described how there could be a paradigm shift to wide field swept source OCTA for the detection of NPAs.[30] It has been proved multiple times that OCTA could be as accurate or even better than UWFFA in the detection of NPAs on retinal imaging.[30-34] Different ways to improve

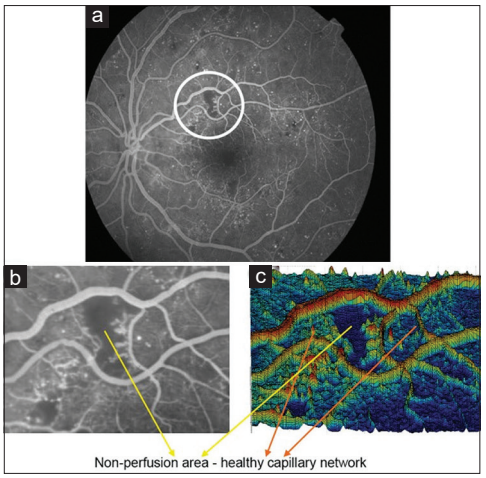

Figure 2: (a) An example fluorescein angiography (FFA) image displaying areas with inadequate blood perfusion, (b) an excerpt from the nonperfused area in the image, and (c) the three-dimensional surface representation of the non-perfusion region.[26] Adapted under the terms of the creative commons attribution license http://creativecommons.org/licenses/by-nc/4.0

retinal image quality in order for them to be analyzed have also been described by various authors.[4,27-29,35-37]

It is a well-known fact that NPA has been used to classify and prognosticate the patients of retinal vein occlusion and we have various studies testifying to the fact.[12,38,39] More recent studies have focused on how to accurately detect the NPAs by replacing percentages with the area in mm[2,32] They achieved this using a stereographic projection technique which enabled them to correct peripheral nonlinear warp (two lesions appearing to be of the same size in the image while actually being different) demonstrated in previous studies on UWFFA.[22,40,41] Similar to DR, OCTA was found to be comparable or even superior to FFA in the detection of NPA.[42]

Leakage index and no. of microaneurysms

The presence of MA has been an important marker for the diagnosis and grading of severity of DR, and UWF imaging has only abetted the same. However, quantitative assessment of these had been a manual process carried out by trained human graders. Ehlers *et al*. described an automated algorithm-based technique to quantify MA and detect leakage by dewarping the UWFFA images and obtaining a stereographic 3D projection and two-dimensional mapping of the same which were then processed by the algorithm.[24,43] Tanchon *et al*. also carried out a similar study in 32 eyes of diabetic patients and quantified leakage and ischemia using an automated algorithm. They then developed a "leakage index" similar to the ischemic index where leakage was evaluated to a proportion of activity.[44] Similar to other markers, the number of MA and the leakage index improved with anti-vascular endothelial growth factor treatment. Babiuch *et al*. carried out a couple of studies where they demonstrated

a decrease in panretinal MA count and leakage index with treatment. They expressed pan retinal leakage index as a percentage, obtained by dividing the area of leakage by the total analysable retinal area. In addition to this, they calculated the zonal leakage indices of three zones, a three disc diameters (DD) posterior zone, a 6 DD boundary centered at fovea and a 9 DD boundary centered at fovea, all of which demonstrated consistently decreasing levels with treatment.[45,46]

Geodesic distance

Geodesic distance, which is defined as the distance between two vertices, is the length in terms of the number of edges of the shortest path between the vertices.[47] It was used in previous studies in obtaining 3D images of the aorta and in predicting the cognitive decline in Alzheimer's disease.[48,49] In ophthalmology, it has been used in pupil localization and automated segmentation of retinal layers.[25,50] It was identified as a promising biomarker in UWF imaging by Sevgi *et al*. They utilized an existing tool (Morpholib Image J) to generate geodesic distance maps centered on the optic disc using vessel masks. Geodesic distance referred to the shortest path with in extracted vessel masks from the optic disc center to the specific point of interest. The mean and maximum geodesic distance was also defined. The mean geodesic distance was significantly higher in normal eyes compared to eyes with DR[51] [Figure 3].

The same author also demonstrated a decreased geodesic distance, in addition to other parameters in eyes with sickle cell retinopathy.[52] Further studies need to be carried out to demonstrate change with treatment.

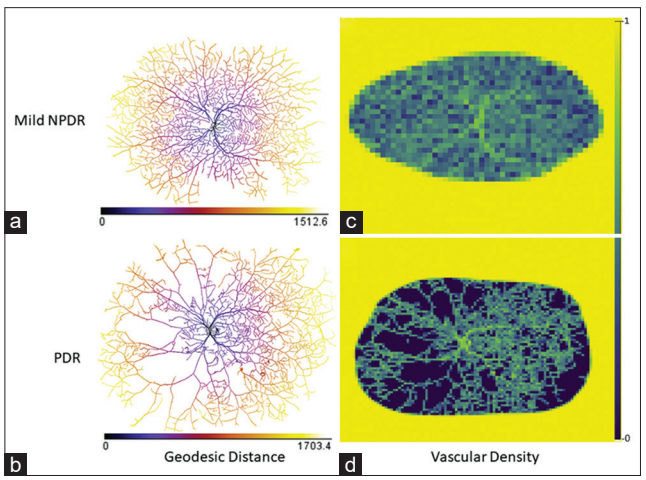

Figure 3: Examples of eyes with nonproliferative diabetic retinopathy (NPDR) (a and c) and proliferative diabetic retinopathy (PDR) (c and d) were analysed using geodesic distance maps and localized vessel density maps. The optic disc center served as the reference point for geodesic distance maps, indicating distance variations through a color spectrum (a and b). In localized vessel density maps for NPDR and PDR eyes, purple marked areas with zero vessel density, as per the color scale, while yellow regions were excluded based on expert-defined regions of interest.[51] Adapted under the terms of the creative commons attribution license http://creativecommons.org/licenses/by-nc/4.0/. PDR = Proliferative diabetic retinopathy, NPDR = Nonproliferative diabetic retinopathy

Qualitative biomarkers

Qualitative biomarkers on retinal imaging offer a powerful means of visually assessing and interpreting the characteristics of the retinal vasculature. Instead of relying solely on quantitative measurements, qualitative biomarkers provide important subjective information about the presence or absence of specific features, patterns, or abnormalities in retinal images. These biomarkers are evaluated by skilled clinicians or trained experts who visually analyze the images and identify visual cues that may indicate the presence of certain diseases or conditions. Qualitative biomarkers in retinal imaging can provide valuable diagnostic information, aid in disease classification, and help guide treatment decisions. We will discuss the following:

A. Choroidal venous hyperpermeability/intervortex anastomoses
B. Potential biomarkers on FAF.

Choroidal venous hyperpermeability/intervortex anastomoses

The involvement of the posterior pole in pachychoroid diseases has been well established.[53] However, with UWF imaging, it has been possible to demonstrate involvement of the periphery in the disease spectrum. Verma *et al*. in a study on 55 eyes evaluated the normal peripheral extent of choroidal vasculature using UWF ICGA images. They estimated the normal extent of choroidal vasculature to be 893.2 mm^2.[54] Studies were also done to compare the vascular patterns in patients with pachychoroid disease with normal patients. Bacci *et al*. analyzed the parameters such as choroidal venous hyperpermeability, asymmetric drainage of the choroidal venous system, and intervortex anastomoses in eyes with pachychoroid disease. Pachychoroid eyes demonstrated greater variability in choroidal drainage across quadrants, with all eyes showing evidence of choroidal venous hyperpermeability, and most of them showing evidence of intervortex anastomoses, most prominent in the temporal quadrant, which also corresponded to higher choroidal thicknesses[55] [Figures 4 and 5].

Similar findings of asymmetric drainage and venous hyperpermeability were found in a study by Hiroe and Kishi[56] They characterized central serous chorioretinopathy as a disease of "vortex vein occlusion."

Wide field fundus fundus autofluorescence findings in hereditary retinal diseases

Wide field FAF has proven to be a useful tool in the evaluation of retinal abnormalities in patients with hereditary retinal disease. While the term dystrophy is attributed to hereditary retinal diseases, the term degeneration encompasses both hereditary and acquired diseases which lead to progressive loss

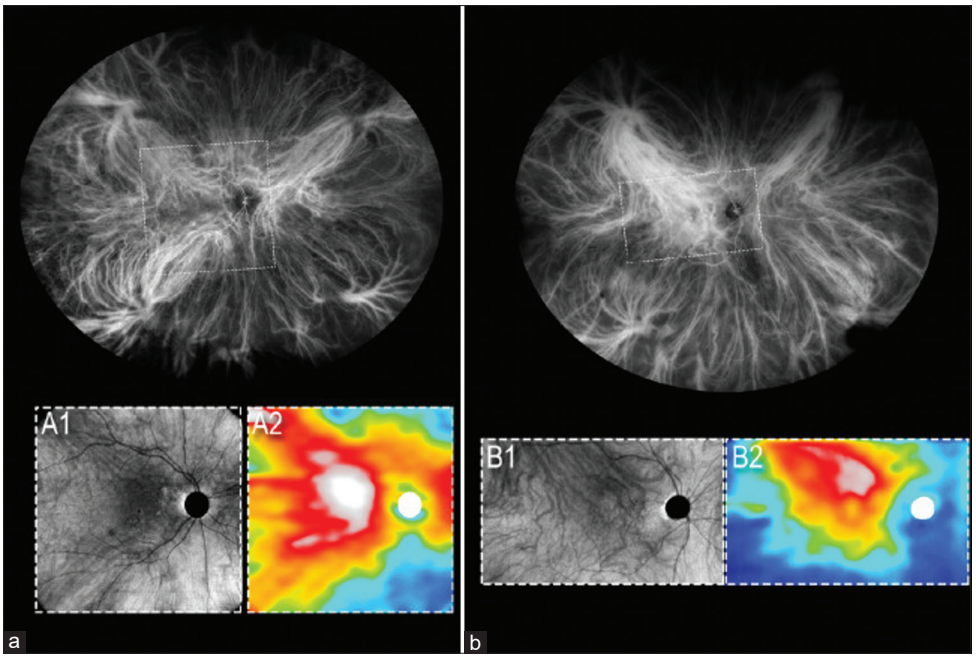

Figure 4: In the ultrawide field indocyanine green angiography images of two patients with central serous chorioretinopathy, irregular choroidal venous drainage patterns were observed. One patient had a smaller inferonasal vortex vein system, leading to imbalanced drainage (a). In the other patient, small inferior vortex vein systems caused asymmetrical macular drainage (b). En-face swept source optical coherence tomography scans and choroidal thickness maps (warmer colours correspond to increased thickness and areas of increased drainage) confirmed these findings (A1, A2, B1, B2), emphasizing the significance of understanding these vascular variations for accurate diagnosis and treatment planning.[55] Adapted under the terms of the creative commons attribution license http://creativecommons.org/licenses/by-nc/4.0

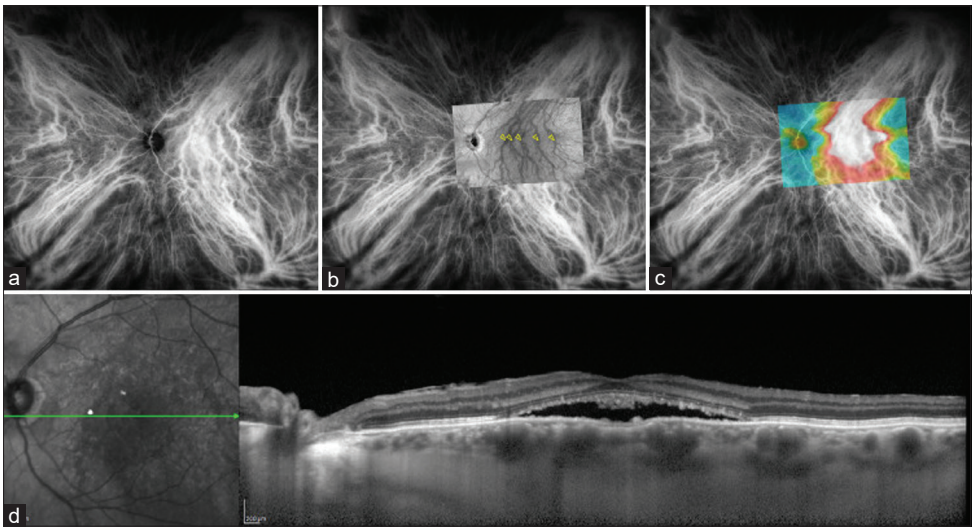

Figure 5: In the left eye of a 60-year-old man with complex central serous chorioretinopathy, ultrawide field indocyanine green angiography and swept-source optical coherence tomography (SS-OCT) images revealed significant findings. Intervortex venous anastomoses between superotemporal and inferotemporal vortex vein systems were observed (a) in the SS-OCT en face projection, highlighted by yellow open arrowheads (b). The corresponding choroidal thickness map demonstrated these anastomoses in the macular region with maximal choroidal thickness (c). Additionally, a spectral-domain optical coherence tomography B-scan passing through the fovea displayed a subfoveal neurosensory detachment and enlarged choroidal veins occupying the full-thickness choroid (d).[55] Adapted under the terms of the creative commons attribution License http://creativecommons.org/licenses/by-nc/4.0

of retinal function.[57] UWF fundus imaging has been instrumental in providing additional information about the involvement of the retinal periphery in these disorders. Peripheral retinal involvement in patients with rod predominant diseases reflects as an area of decreased FAF in retinitis pigmentosa patients in a study by Furutani *et al.*, and this patchy area tends to spare the nasal retina.[58,59] This area also correlated with visual field defect and increased with the age and duration of disease[41,60] [Figure 6]. Another disease in which wide field FAF has been useful is choroideremia, in which imaging was used to identify peripheral fundus changes in female carriers, which included patchy retinal pigment epithelium (RPE) pigmentation and pigmentary

granularity. This was also confirmed by histopathological and immunofluorescence studies.[61,62] Cone rod dystrophies, which is a disease which predominantly involves the central fundus, was better evaluated by wide field FAF imaging as the area of decreased FAF correlated with the visual field defect.[63]

Abalem *et al*. demonstrated that patients with Stargardt's disease have areas of hyper autofluorescence in the periphery on wide field imaging and these areas not only corresponded to visual field defects on perimetry and electroretinograms (ERG) abnormalities, but these patients also had a poorer outcome as compared to those with only macular involvement. Zhao *et al*. described peripheral congenital hypertrophy of the RPE type lesions in Stargardt's disease, had markedly decreased visual acuity, large central scotomas, abnormal full field ERG, and widespread involvement of the peripheral retina on wide field photography and FAF.[64,65] In a unique study by Fujimoto *et al*. carried out on 46 eyes of patients with Stickler's syndrome, patients with the disease showed hyperautofluorescent and hypoautofluorescent areas, and this preceded the development of the characteristic radial paravascular retinal degenerations observable by fundoscopy or conventional fundus imaging.[66] Eyes with predominantly hypoautofluorescent areas were more likely to have visual field defects. Other diseases in which wide field FAF enabled better visualization and prognostication were multiple evanescent white dot syndromes and Vogt-Koyanagi-Harada disease.[67,68]

Limitations of Quantitative/Qualitative Analysis of Wide Field Images

Wide field imaging does come with its own set of limitations. These machines have high costs and therefore limiting their accessibility, especially in resource-limited settings. These techniques also come with the challenge of needing skilled photographers for imaging as the images can have artifacts. These artifacts then become a deterrent in the accurate assessment of biomarkers from these images. Even a minor artifact can cause inaccurate numerical values for the assessed parameters at a microscopic level. It is important to keep in mind the calibration of each image taken by the software while analyzing them as they can be variable. Like other ophthalmic imaging techniques, image quality can be limited by the presence of media opacities such as corneal opacities and cataract. As mentioned above, it is important to account for the projection error on Optos and OCTA images as peripheral lesions may appear larger than they actually are. It is also important to not solely rely on these retinal images for the diagnosis of retinal lesions as the absence of true colors in these images can lead to diagnostic errors, and therefore, a thorough clinical examination is irreplaceable.

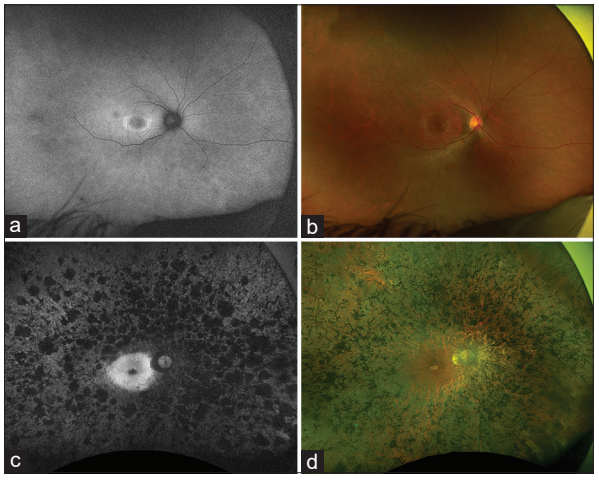

Figure 6: Image shows fundus autofluorescence (FAF) of two different patients, one with early retinitis pigmentosa (RP) (a), corresponding color photo (b), and another one with FAF of late stage RP (c), and corresponding color photo (d)

Future and Challenges

The utilization of biomarkers in retinal imaging holds great promise for future. With ongoing advancements in imaging modalities, such as OCTA and adaptive optics imaging, we can expect the development of novel biomarkers that provide even greater insights into retinal vascular dynamics and microstructural changes.

In addition, the integration of artificial intelligence (AI) and machine learning algorithms in the analysis of retinal biomarkers has the potential to further enhance accuracy, efficiency, and clinical applicability. Some of these applications have been described above where different algorithms for the segmentation of retinal images have been used for the diagnosis, disease severity classification, and detection of peripheral lesions on wide field imaging. DR is one of the most widely studied areas. Yang *et al*. have summarized the applications of AI and deep learning algorithms in UWF imaging.[69] They described two types of preprocessing methods utilized in UWF imaging-the augmented and the histogram equalization method. A combination of the two is also used. However, these are limited by the requirement of high-quality UWF images which are difficult to acquire and the limited database. Nevertheless, it holds promise to significantly impact ophthalmic care, even in the remotest of areas.

These wide field imaging techniques also play an important role in providing intraoperative assistance. Starting from the preoperative evaluation where they help provide the precise localization of pathology and help surgeons strategize their surgical approach, for example, in retinal detachment, retinal tears, and proliferative vitreoretinopathy. Wide angle viewing systems are the invaluable tools in retinal surgeries, providing surgeons with an expansive and

detailed view of the posterior segment. These systems, like the BIOM® 5, enhance visualization of the retinal periphery, critical for procedures such as retinal detachment repair, DR treatment, and macular surgeries. By offering a broader perspective, wide angle systems aid surgical planning, guide precise maneuvers, and facilitate complete pathology assessment. The advanced optics and real-time imaging empower surgeons to achieve the better outcomes in complex cases, improving surgical accuracy and patient outcomes. Postsurgery, wide field imaging is essential to monitor the patient's progress and adequately address all the areas of concern.

However, it is crucial to acknowledge certain limitations and challenges associated with retinal biomarkers. Variations in imaging protocols, image quality, and interpretation can introduce potential biases and affect the reproducibility of results. Standardization and consensus on imaging protocols, data analysis techniques, and biomarker validation are essential to ensure robust and reliable biomarker utilization across different clinical settings and research studies.

Moving forward, interdisciplinary collaborations between ophthalmologists, imaging specialists, data scientists, and clinicians from various medical disciplines will be crucial for advancing the field of retinal biomarkers. By working together, we can further refine and validate existing biomarkers, discover new biomarkers, and establish comprehensive frameworks for their clinical implementation. In addition, longitudinal studies and large-scale multicenter trials are needed to evaluate the long-term prognostic value of retinal biomarkers and their potential role in guiding therapeutic interventions and assessing treatment responses.

In conclusion, biomarkers in wide field retinal imaging have revolutionized our understanding of retinal vascular health and its implications in systemic diseases. Through their integration into routine clinical practice, these biomarkers have the potential to enhance early disease detection, risk stratification, and personalized treatment strategies. As we continue to unlock the full potential of retinal biomarkers, we are poised to witness transformative advancements that will ultimately improve patient outcomes and shape the future of retinal care.

Literature Search

The methodology employed for this review article involved an extensive search and analysis of the existing literature available on PubMed. A comprehensive search strategy was developed to identify the relevant articles focusing on biomarkers in retinal imaging. The PubMed database was systematically queried using appropriate keywords, including "retinal biomarkers," "retinal imaging," "quantitative biomarkers," and related terms. The search was limited to the articles published in the English language. Initially, a comprehensive review of titles and abstracts was carried out to identify the articles that might be relevant. Following that, the entire content of the selected articles was acquired and scrutinized to determine their suitability for inclusion in the review. Approximately 230 articles from PubMed were meticulously reviewed, with a specific focus on publications after 2010. A few articles preceding this timeframe were retained for the historical context. After meticulous screening to exclude redundant information and biomarkers specific to singular ocular conditions, 64 articles were selected for in-depth analysis. This curated selection encompasses various study designs, comprising original research articles, review papers, and meta-analyses. The selected articles provided insights into the various aspects of biomarkers in retinal imaging, including their clinical applications, diagnostic value, prognostic significance, and emerging technologies. The extracted information from these articles was synthesized and organized to present a comprehensive overview of the current state of knowledge regarding biomarkers in retinal imaging and their applications.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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