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# The Biomarker Landscape of Ocular Ageing: Emerging Insights and Applications

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**ABSTRACT**

Ageing is a complex, multifactorial biological process characterized by progressive molecular, cellular, and functional decline across organ systems, ultimately increasing susceptibility to chronic diseases and mortality. The eye, with its transparent and easily accessible structures, offers a unique and non-invasive platform for studying systemic ageing and detecting early biological alterations. Recent advances in retinal imaging, optical coherence tomography (OCT), and artificial intelligence (AI) have heightened interest in ocular biomarkers as indicators of biological age and predictors of age-related disease risk. This systematic review synthesizes evidence on molecular, imaging-based, OCT-derived, and lens-related biomarkers of ocular ageing, highlighting their associations with systemic ageing, morbidity, and mortality. Key biomarkers include the retinal age gap, retinal microvascular alterations, OCT-derived structural parameters and the Lens age index. Collectively, these markers capture both localized manifestations of ocular ageing and broader systemic health trajectories, making them valuable candidates for early disease detection and biological risk assessment. Beyond diagnostic applications, these biomarkers may enhance personalized risk stratification, support preventive interventions, and facilitate integration with systemic ageing clocks. However, their clinical adoption faces challenges, including variability in measurement techniques, lack of standardized protocols, and limited validation across diverse populations. Addressing these barriers through harmonized methodologies, longitudinal studies, and multi-omics integration will be critical to establishing ocular biomarkers as robust and clinically reliable measures of ageing. Ultimately, their implementation could advance precision medicine, enabling earlier intervention and improved healthspan outcomes.

**Keywords:** Ocular ageing, Biomarkers, Retinal age gap, OCT, Lens age, Systemic ageing, Morbidity, Artificial intelligence, Preventive interventions, Precision medicine

## INTRODUCTION

Ageing is a universal biological process defined by a gradual decline in physiological function, increasing susceptibility to chronic diseases such as cardiovascular disease, neurodegeneration, and metabolic disorders (1). Traditional biomarkers of ageing, such as leukocyte telomere length (2) and DNA methylation-based epigenetic clocks (3), provide robust insights into biological age but often require invasive sampling and complex laboratory analyses. The eye, however, offers a non-invasive and accessible platform for studying ageing due to its rich vascular, neural, and connective tissue components, which mirror systemic physiological changes (5).

Ocular ageing manifests through well-documented structural and functional changes, including retinal nerve fiber layer (RNFL) thinning (19, 21), alterations in retinal vessel diameters (20, 24), and lens opacification (15). These changes are quantifiable using advanced imaging technologies such as fundus photography, OCT, and AI-driven analytics, which have revolutionized the identification of ocular biomarkers (6, 9, 12). Emerging evidence suggests that these biomarkers not only reflect ocular ageing but also correlate with systemic conditions, including cardiovascular disease (31), Parkinson's disease (30), and mortality risk (7, 10, 14). For instance, the **retinal age gap**, defined as the difference between chronological age and AI-estimated retinal age, has been associated with mortality and disease risk (7, 10), underscoring its potential as a clinical tool.

This systematic review aims to: (1) synthesize the current evidence on ocular ageing biomarkers, categorized into molecular, imaging-based, OCT-derived, and lens-related domains; (2) evaluate their clinical utility in predicting age-related diseases and mortality; and (3) identify challenges and future directions for their integration into clinical practice. By bridging ocular and systemic ageing research, we highlight the transformative potential of these biomarkers in precision medicine.

## METHOD

### Search Strategy

A systematic literature search was conducted across **PubMed**, **Scopus**, and **Web of Science** databases from inception to **August 2024**. Search terms included combinations of: *ocular ageing*, *retinal biomarkers*, *biological age*, *retinal vasculature*, *optical coherence tomography*, *retinal age gap*, *epigenetic ageing*, *fundus photography*, and *lens ageing*. Boolean operators (ocular OR eye) AND (biological age OR ageing biomarker) truncation symbols were used to maximize retrieval. The reference lists of included studies were hand-searched to identify additional relevant articles.

### Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

- Peer-reviewed original research or reviews published in English.
- Human studies evaluating ocular biomarkers (molecular, imaging-based, OCT-derived, or lens-related) in the context of ageing or systemic ageing outcomes.
- Studies reporting associations with chronological age, biological age, morbidity, or mortality.
- Studies utilizing imaging modalities (e.g., fundus photography, OCT) or AI-driven analyses.

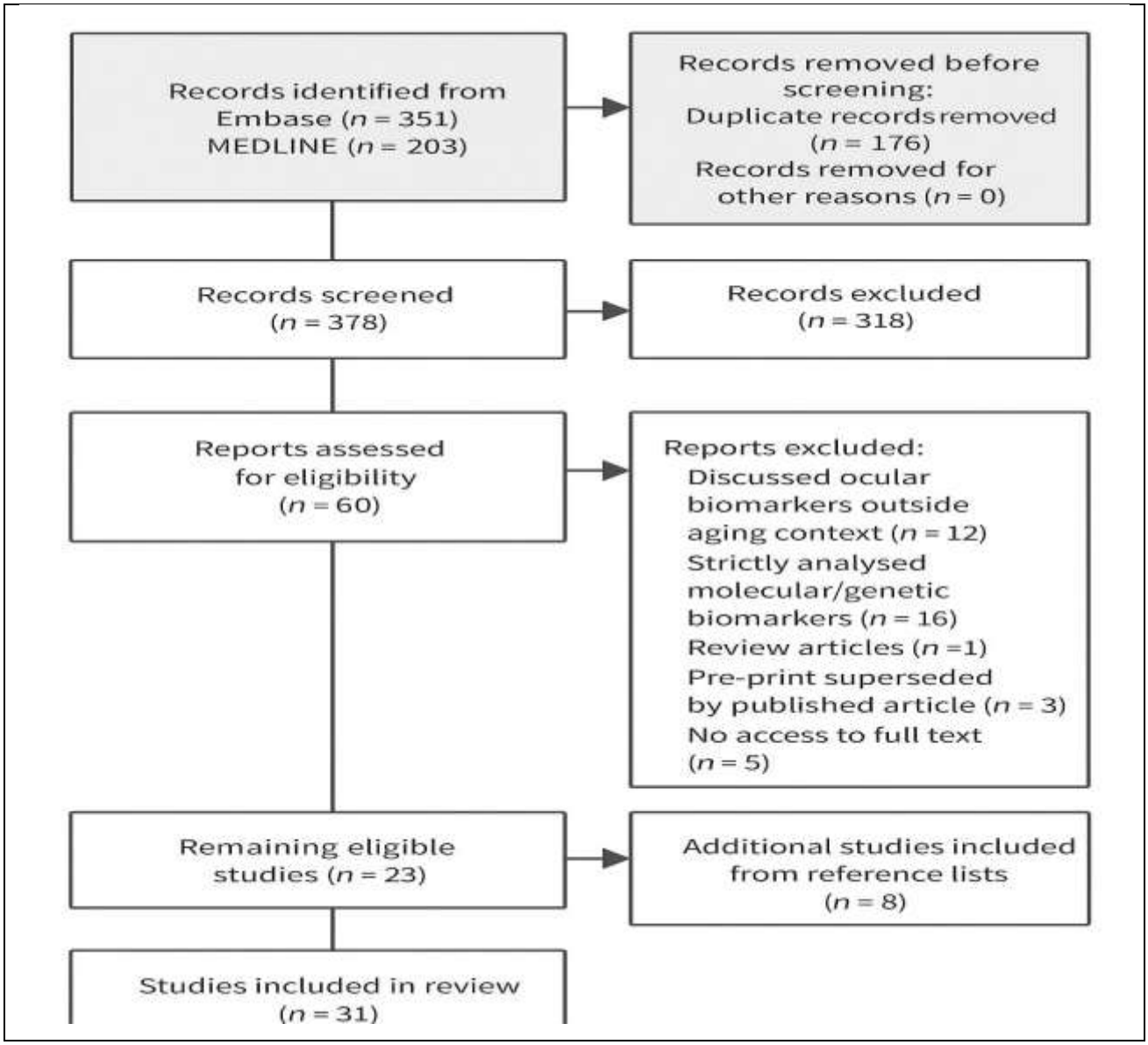
**Exclusion criteria included:**

- Animal-only studies.
- Studies focusing solely on ocular pathology (e.g., glaucoma, macular degeneration) without reference to ageing.
- Non-peer-reviewed sources or non-English publications.

### Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts, followed by full-text assessment for eligibility. Discrepancies were resolved through discussion. Data extracted included study design, population characteristics, biomarker type, measurement methods, clinical outcomes, and key findings. A total of **32 studies** were included for thematic synthesis.

**Fig. 1:- PRISMA diagram.**




**Quality Assessment**

Study quality was assessed using the **Newcastle-Ottawa Scale** for observational studies and the **Cochrane Risk of Bias Tool** for interventional studies, ensuring robustness of included evidence.

## RESULT

### 1. Molecular and Epigenetic Biomarkers

Molecular biomarkers of ageing, such as **telomere length** and **DNA methylation patterns**, have been extensively studied in systemic contexts (2, 3). In ocular ageing, leukocyte telomere length correlates with retinal microvascular function, suggesting a link between ocular and systemic ageing (22, 26). For example, Shokr et al. (22) demonstrated that shorter telomere length is associated with altered retinal vessel calibers in individuals with low cardiovascular risk, indicating potential as a biomarker for early ageing detection. Similarly, Martens et al. (26) found correlations between retinal microcirculation and telomere length in a general population, reinforcing the eye's role as a systemic ageing indicator.

Epigenetic clocks, based on DNA methylation patterns, are robust predictors of biological age (3). While direct application to ocular tissues is limited, emerging studies suggest that retinal imaging may indirectly reflect epigenetic ageing signatures (9). Ahadi et al. (9) used longitudinal fundus imaging to develop a retinal ageing clock, identifying genome-wide associations that align with systemic epigenetic markers, paving the way for non-invasive epigenetic assessments.

## 2. Imaging-Based Biomarkers

### *Retinal Age Gap*

The **retinal age gap**, derived from AI analysis of fundus photographs, has emerged as a powerful biomarker. Zhu et al. (7) found that a larger retinal age gap (i.e., retinal age exceeding chronological age) predicts increased mortality risk, with hazard ratios comparable to systemic biomarkers. Similarly, Abreu-Gonzalez et al. (8) reported that retinal age correlates with diabetic retinopathy severity, suggesting its utility in grading disease progression. The retinal age gap also predicts neurodegenerative conditions, such as Parkinson's disease (30), and cardiovascular events (31), highlighting its broad clinical relevance.

### *AI-Driven Fundus Imaging*

AI algorithms applied to fundus photography have revolutionized biological age estimation. Nusinovici et al. (10) demonstrated that retinal photograph-based deep learning models stratify morbidity and mortality risk with high accuracy. Wang et al. (11) advanced this field by developing a multimodal image Transformer system that integrates fundus images with other imaging modalities, achieving precise biological age predictions and identifying disease risk. These models leverage features such as retinal vessel tortuosity, drusen presence, and pigmentary changes, which are hallmarks of ocular ageing (28).

### *Retinal Microvascular Complexity*

Retinal vasculature undergoes age-related remodeling, including vessel narrowing and increased tortuosity (20, 24, 25). Leung et al. (20) and Wong et al. (24) established early associations between retinal vessel diameters, age, and blood pressure, laying the groundwork for microvascular biomarkers. More recently, Popovic et al. (17) identified **retinal microvascular complexity** as a novel biomarker of biological age, with fractal dimension analysis revealing age-related declines in vascular network intricacy. These findings suggest that microvascular metrics could enhance systemic ageing assessments.

## 3. OCT-Derived Biomarkers

Optical coherence tomography (OCT) provides high-resolution imaging of retinal layers, enabling precise quantification of age-related structural changes. Alamouti and Funk (21) reported progressive retinal thinning with age, particularly in the macular region, while Patel et al. (19) documented RNFL loss as a hallmark of ocular ageing. These structural changes are quantifiable and reproducible, making OCT a cornerstone of ocular biomarker research.

AI-augmented OCT analysis has further enhanced predictive capabilities. Shigueoka et al. (12) and Chueh et al. (13) developed deep learning models to predict chronological age from macular OCT scans, achieving high accuracy across diverse populations. Notably, Chen et al. (14) demonstrated that OCT-derived age estimates predict mortality risk, with neural network models identifying subtle retinal features imperceptible to human observers. These advancements underscore OCT's potential as a non-invasive tool for systemic ageing assessment.

**Table: - 1: Ocular Biomarkers in Biological Ageing: Molecular, Imaging and Systemic Integration**

| Category | Biomarker | Method/Approach | Key Findings / Relevance | References |
|---|---|---|---|---|
| **Molecular & Epigenetic Biomarkers** | Telomere Length | Leukocyte telomere measurement | Shorter telomeres correlate with altered retinal vessel calibers and microcirculation; reflects systemic ageing | 22, 26 |
| | DNA Methylation / Epigenetic Clocks | Epigenetic profiling; longitudinal fundus imaging | Retinal ageing clock aligns with systemic epigenetic markers; potential non-invasive ageing assessment | 3, 9 |
| **Imaging-Based Biomarkers** | Retinal Age Gap | AI analysis of fundus photos | Larger retinal age gap predicts mortality, diabetic retinopathy severity, neurodegenerative and cardiovascular risk | 7, 8, 30, 31 |
| | AI-Driven Fundus Imaging | Deep learning, multimodal image transformers | Stratifies morbidity/mortality risk; identifies retinal features like vessel tortuosity, drusen, pigment changes | 10, 11, 28 |
| | Retinal Microvascular Complexity | Fractal dimension analysis of retinal vasculature | Age-related decline in microvascular network intricacy; complements systemic ageing assessment | 17, 20, 24, 25 |
| **OCT-Derived Biomarkers** | Retinal Layer Thickness | OCT imaging | Macular thinning and RNFL loss as hallmark features of ocular ageing | 19, 21 |
| | AI-Augmented OCT Analysis | Deep learning on OCT scans | Predicts chronological age | 12, 13, 14 |

| | | | | |
|---|---|---|---|---|
| | | | and mortality risk; detects subtle features invisible to human observers | |
| **Lens-Related Biomarkers** | LensAge Index | Deep learning on slit-lamp images | Quantifies lens ageing; predicts ocular disease and systemic outcomes; non-invasive and accessible | 15 |
| **Systemic Integration / Multisystem Ageing** | Combined Ocular & Systemic Metrics | Integration of retinal, lens, vascular, and molecular markers | Enhances holistic biological age assessment; retinal age gap correlates with arterial stiffness and cardiovascular risk | 16, 28, 29, 31 |

**4. Lens-Related Biomarkers**

The lens undergoes age-related changes, including opacification and loss of elasticity, which contribute to presbyopia and cataract formation. The **LensAge index**, introduced by Li et al. (15), leverages deep learning to quantify lens ageing from slit-lamp images. This index predicts not only ocular disease risk (e.g., cataracts) but also systemic outcomes, such as mortality and age-related disease incidence. The LensAge index's non-invasive nature and accessibility make it a promising candidate for self-monitoring and population-level screening.

**5. Systemic Integration and Multisystem Ageing**

Ageing is heterogeneous across organ systems, as demonstrated by Sayer et al. (16) and Tian et al. (29). Ocular biomarkers, while powerful, must be integrated with systemic indicators to capture the full spectrum of biological ageing. For example, retinal age gap correlates with arterial stiffness and cardiovascular disease (31), while macular drusen in midlife may indicate accelerated biological ageing (28). These findings suggest that ocular biomarkers complement systemic clocks, such as telomere length and epigenetic markers, to provide a holistic view of ageing.

## DISCUSSION

### Clinical Utility of Ocular Ageing Biomarkers

Ocular biomarkers offer several advantages: they are **non-invasive**, **cost-effective**, and leverage widely available imaging technologies. The **retinal age gap** stands out for its predictive power across diverse outcomes, including mortality (7), diabetic retinopathy (8), Parkinson's disease (30), and cardiovascular events (31). OCT-derived metrics, particularly when enhanced by AI, provide high-resolution insights into retinal structure, enabling early detection of age-related changes (12, 14). The **LensAge index** extends this utility to anterior segment assessment, offering a complementary approach for systemic ageing monitoring (15).

### Challenges and Limitations

Despite their promise, several challenges hinder clinical adoption:

- **Standardization**: Variability in imaging protocols, AI algorithms, and biomarker definitions limits cross-study comparability. For instance, retinal age gap calculations differ across studies due to variations in training datasets and deep learning architectures (7, 10).
- **Validation**: Most studies are conducted in specific populations, with limited representation of diverse ethnicities or socioeconomic groups. Longitudinal, multi-ethnic cohorts are needed to confirm generalizability.
- **Integration**: Ocular biomarkers must be combined with systemic clocks (e.g., epigenetic, proteomic) to enhance predictive accuracy. Current studies rarely integrate multimodal data, limiting their clinical scope (29).
- **Accessibility**: While fundus photography and OCT are widely available in high-income settings, their use in low-resource environments remains limited, posing challenges for global implementation.

### Future Directions

The future of ocular ageing biomarkers lies in **multimodal integration** and **personalized medicine**. Combining retinal age gap, OCT-derived metrics, and LensAge with systemic biomarkers (e.g., telomere length, DNA methylation) could create comprehensive ageing clocks. Advances in AI, particularly multimodal Transformer systems (11), may enable real-time, point-of-care biological age estimation. Additionally, standardized protocols and global validation studies are critical to translate these biomarkers into routine clinical practice. Collaborative efforts, such as large-scale biobanks and international consortia, could accelerate these developments.

## CONCLUSION

The biomarker landscape of ocular ageing is a rapidly evolving field with transformative potential for clinical practice. Retinal age gap, OCT-derived structural metrics, and lens-related indices, such as LensAge, offer non-invasive, accessible tools for assessing biological age and predicting age-related diseases and mortality. These biomarkers bridge ocular and systemic ageing, providing a unique perspective on multisystem decline. However, challenges in standardization, validation, and integration with systemic markers must be addressed to unlock their full potential. By advancing multimodal approaches and leveraging AI-driven analytics, ocular ageing biomarkers could revolutionize precision geriatric medicine, enabling earlier diagnosis, targeted prevention, and improved health outcomes.

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