HONG KONG JOURNAL of OPHTHALMOLOGY

December 2024 Vol. 28 No. 1 ISSN 1027-8230 Online ISSN 2957-7098

香港眼科醫學院

香港眼科學刊

The Official Publication of
The College of Ophthalmologists of Hong Kong

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS

POSIFORLID®

The concept for healthy eyelids.

REICH PHARM

The Right Treatment For Blepharitis

Step 1.
Heating pad

Step 2.
Hygiene spray

Step 3.
Cleansing wipes

Step 4.
Regular lubrication

CONTENTS

香港眼科學刊

香港眼科醫學院

HONG KONG
JOURNAL OF
OPHTHALMOLOGY

The Official Publication of
the College of Ophthalmologists
of Hong Kong

December 2024

Volume 28 Number 1

ISSN 1027-8230

Editor-in-Chief
Jason CS Yam

Correspondence
The College of Ophthalmologists of Hong Kong
Room 802, 8/F, Hong Kong Academy of
Medicine Jockey Club Building
99 Wong Chuk Hang Road
Aberdeen, Hong Kong SAR, China.
Tel (852) 2761 9128
Fax (852) 2715 0089
E-mail: info@cohk.org.hk

Published by
HONG KONG ACADEMY OF MEDICINE PRESS

EDITORIAL BOARD

Information for Authors

Aims and Scope

- The *Hong Kong Journal of Ophthalmology* (HKJO) is the official publication of the College of Ophthalmologists of Hong Kong. The Journal aims to promote academic developments in ophthalmology, and to maintain continuing ophthalmological education of doctors of this specialty and other related disciplines. It is hoped that through achieving these aims, the quality of eyecare we offer to our patients can be lifted to new heights. The Journal will consider any submissions that fulfill these aims for publication.
- The Journal accepts high-quality submissions in the following categories: Original Article, Review, Perspective, Case Report, Photo Essay, Clinical Quiz, or Letter to the Editor. Editorials are by invitation only.
- The Journal is circulated to all members of the College of Ophthalmologists of Hong Kong and other professional societies and academic institutions in Hong Kong and internationally.

Journal Policies

- The HKJO adheres to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org) and the Core Practices of the Committee on Publication Ethics (COPE; https://publicationethics.org).
- Submitted manuscripts must be original works that have not been published elsewhere (in whole, in part, or as a preprint) and are not under consideration by another publication.
- To improve the quality and clarity of published articles, the Journal recommends the use of reporting guidelines in the preparation of manuscripts, such as those advocated by the EQUATOR Network (http://www.equator-network.org/), for example, CONSORT for randomized trials, or CARE for case reports.
- Any sponsor(s) of the research involved, along with grant number(s) should be provided.
- All authors must provide a statement reporting any conflicts of interest. Where none exist, please state 'The authors have no conflicts of interest to declare.' Authors may use the ICMJE Conflict of Interest form.
- For all research involving living humans (including studies involving human tissue, retrospective studies, and database studies), an appropriate research ethics committee must be consulted. A statement must be included in the manuscript that provides the name of the research ethics committee and approval number (or waiver).
- A statement on consent must also be included, indicating how patient(s)/guardian(s) provided informed consent (eg, written or verbal), or that the requirement for patient consent was waived by the review board.
- The authors shall make available the complete data on which the manuscript is based. A statement describing how the data can be accessed must be included in the manuscript. For clinical trials and other large datasets, the Journal recommends that data are deposited in a public repository and shared using a permanent identifier (such as a DOI).
- For details of the Journal policies on publication ethics, including authorship, plagiarism, and processes for handling appeals or complaints, please see the Journal website.

Submissions

- Manuscripts should be submitted through the HKJO online submission system at https://hkjo.hk/index.php/hkjo/about/submissions. Please register for an account with the system and upload files according to the instructions. All files must be submitted through the system.
- Please provide a blinded manuscript as a single file. Any identifying information (eg, references to past publications, name of an author's institution) should be masked or removed from the blinded manuscript.
- Manuscripts should be submitted in Word format (.doc or .docx).
- Manuscripts must be written in English (US spellings as per the Merriam-Webster Dictionary).
- In general, manuscripts should be prepared following the 'IMRaD' structure as recommended by the ICMJE (http://icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html).
- For each author, please provide the full name, professional qualifications, and affiliation (where the study was conducted).
- The full name, postal address, telephone and fax numbers, and email address of the corresponding author must be provided. The corresponding author, on behalf of the authors, is responsible for all contact with the Journal.
- A structured abstract of ≤250 words is required for Review Articles and Original Articles. The abstract should provide a complete summary of the article, including the aims/purpose, main methods, key results, and conclusions. Abbreviations and clinical or technical jargon should be avoided.
- Tables should be typed using the 'Insert Table' feature of MS Word, with one item of data per cell and minimal formatting. Large tables may be provided in MS Excel format. Tables should be numbered and concisely titled. Abbreviations should be defined in footnotes.
- The number of figures should be restricted to the minimum necessary to support the textual material. Figures should be .JPG format with a resolution of ≥350 dpi and should be included in the manuscript file; large image files may be submitted separately. Legends should be provided for each figure to indicate the anatomical area and pathological condition shown. All symbols and abbreviations should be defined in the legend.
- The references should be numbered in the order in which they are first cited in the text. Each reference citation should be in superscript Arabic numerals after full-stops and commas. At the end of the article, the full list of references should be presented in Vancouver style. Include the names of all authors, title of the article, abbreviated name of journal, year of publication, volume number, and inclusive pages, in that order.
- Please refer to the latest ICMJE recommendations on Manuscript Preparation for further information on references and for general guidance on style: http://icmje.org/recommendations/browse/manuscript-preparation/

Peer Review

- HKJO operates a double-blind peer-review process. Details of the peer review process can be found on the Journal website.

Copyright

- On acceptance of an article for publication in HKJO, copyright of the article is transferred to the Journal.
- The Journal has a fully Open Access policy and publishes all articles under a Creative Commons license (CC BY-NC-ND 4.0). For any use other than that permitted by this license, written permission must be obtained from the Journal.

Correspondence

- All correspondence on editorial issues should be addressed to the Editorial Office (editorial@hkjo.hk).

香 港 眼 科 醫 學 院

THE HONG KONG JOURNAL OF OPHTHALMOLOGY
BEST ORIGINAL ARTICLE AWARD

Purpose

To encourage submissions to the *Hong Kong Journal of Ophthalmology* (HKJO) by trainees and fellows of the College of Ophthalmologists of Hong Kong (COHK).

Awards and Prizes

Two awards will be given out every year. Each awardee will be given a $2000 cash prize (HK dollars), which is supported generously by the Timothy KC Liu Fund.

Eligibility

- One award is open to all fellows and members of the College; another one is limited to trainees only.
- Applicants must be a paid-up member or fellow of COHK at the time of submission.
- Trainees refer to those who have not been conferred the title 'FCOphthHK' at the time of submission.
- Only the first author of the article will be eligible for the prize. If the first author is not eligible for the award, i.e. not a member or fellow of COHK, then the order of consideration of awardee will be from the second author onwards to the last author.
- Original articles (including, but not limited to, prospective or retrospective clinical studies, observational studies, epidemiological studies, basic science studies, meta-analysis, etc) published in the HKJO during the year will automatically enter the selection process.
- Case reports (with case number <3), review articles and letters to the editor will not be eligible for this award.
- Submissions pending acceptance will not be eligible for the award.
- Entries will be based on the article as a unit, but not the author. Because of this, it is possible that one single author wins both awards, given that he/she is the first author of the two best original articles published that year (but he/she has to be a trainee in this case as one award is open for trainees only).

Selection Panel

- Editor-in-Chief
- 1 representative from The University of Hong Kong
- 1 representative from The Chinese University of Hong Kong and
- President of the College

Selection Criteria

- Originality
- Scientific merit
- Methodology
- Presentation style

Award Presentation Ceremony

The awards will be given out at the following year's conferment ceremony.

ORIGINAL ARTICLE

Prognostic factors in Chinese patients with acute non-infectious optic neuritis treated with intravenous methylprednisolone and oral prednisolone

Matthew CW Lam[1,2], Rachel WY Tsui[1,2], Jerry KH Lok[1,2,3], Noel CY Chan[2,4,5], Carmen KM Chan[1,2]
[1]*Hong Kong Eye Hospital, Hong Kong SAR, China*
[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3]*Hong Kong Ophthalmic Specialists, Hong Kong SAR, China*
[4]*Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China*
[5]*Alice Ho Miu Ling Nethersole Hospital, Hong Kong SAR, China*

Correspondence and reprint requests:
Matthew CW Lam, Hong Kong Eye Hospital, Hong Kong SAR, China. Email: matthewlam300@gmail.com

Abstract

Objectives: Non-infectious optic neuritis (ON) in Caucasians is typically associated with multiple sclerosis (MS), and steroid treatment is optional. In Chinese patients, however, ON is often atypical and more likely to be associated with neuromyelitis optica spectrum disorder (NMOSD), for which early initiation of pulse intravenous steroid treatment is recommended. We aimed to identify factors associated with visual acuity (VA) improvement after intravenous and oral steroid treatment.

Methods: We reviewed the medical records of 64 Chinese patients (64 eyes) who presented to Hong Kong Eye Hospital between 2000 and 2019 with their first episode of acute ON and received intravenous methylprednisolone and oral prednisolone.

Results: Among all cases, 45.3% were idiopathic and isolated, 25.0% were NMOSD-related, and 17.2% were MS-related. Patients with MS-related ON were younger than patients with idiopathic or NMOSD-related ON ($p<0.01$). Greater improvement in VA was associated with worse nadir VA, greater VA improvement on day 14 of steroid treatment, and NMOSD-related ON, whereas smaller improvement in VA was associated with older age and presentation before anti-aquaporin-4 testing became available.

Conclusion: Because non-infectious ON in Chinese patients is often atypical, intravenous steroid treatment is recommended (rather than optional). Treatment outcomes have improved over the past 20 years, owing to more widespread testing for anti-aquaporin-4 antibodies and more aggressive treatment of NMOSD.

Key words: Methylprednisolone; Neuromyelitis optica; Optic neuritis; Prednisolone; Steroids

Introduction

Optic neuritis (ON) in Caucasians is typically non-infectious, caused by demyelination, and associated with multiple sclerosis (MS). In the Optic Neuritis Treatment Trial (ONTT), intravenous methylprednisolone followed by oral prednisolone was found to accelerate the recovery of visual loss without altering the final visual acuity (VA). Oral steroid treatment alone (at the ONTT dose) was ineffective and increased the risk of recurrence.[1] However, neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated

disorder (MOGAD) have been increasingly recognized in patients with ON. A subsequent analysis of patients from the ONTT cohort showed that none of the serum samples was positive for anti-aquaporin-4 (AQP4) antibody and only 1.7% were positive for myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) antibody. In Chinese patients, ON is more likely to be associated with NMOSD, which requires intravenous steroid treatment. Therefore, the applicability of the ONTT protocol to the Chinese population is questionable.[2-4]

Anti-AQP4 and MOG-IgG serology tests commonly require a few days before results are available. Most cases of ON occur in seronegative patients and remain idiopathic. At the time of initial presentation, clinicians must decide whether to prescribe intravenous steroid treatment without clear information regarding the disease etiology. In our hospital, we routinely offer intravenous steroid treatment to patients with acute non-infectious ON. In this retrospective study, we aimed to identify factors associated with good visual recovery after intravenous steroid treatment.

Methods

We retrospectively reviewed the medical records of patients who presented to Hong Kong Eye Hospital between January 2000 and December 2019 with a diagnosis of ON. Inclusion criteria were age ≥12 years at presentation, Chinese ethnicity, first episode of non-infectious ON, symptom onset within 30 days of initial presentation, and completion of treatment with intravenous methylprednisolone 1 g/day for 3 days followed by oral prednisolone 1 mg/kg/day for 11 days (in accordance with the ONTT protocol). Patients with incomplete medical records, uncertain diagnosis, diagnosis other than non-infectious ON, or treatment other than the ONTT protocol were excluded.

Only one eye per patient was included in the analysis. For patients with bilateral ON, the first presenting eye was chosen. For cases with bilateral simultaneous presentation, the eye with worse nadir VA was included. In cases of simultaneous presentation where both eyes exhibited identical nadir VA, the right eye was included. VA was measured using the Snellen chart and converted to logMAR units. VA of counting fingers, hand motion, light perception, and no light perception were regarded as logMAR values of 1.8, 2.3, 2.8, and 3.0, respectively.[5] VA at different time points was retrieved from patients' records; these included nadir VA, VA at the end of the 14-day ONTT protocol, and VA at the final follow-up. Associations between VA outcomes and various factors (age at onset, etiology, presentation date, and time from symptom onset to initiation of intravenous steroid treatment) were examined.

Statistical analyses were performed using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], United States). For parametric data, differences among multiple groups were evaluated using one-way analysis of variance with Bonferroni correction. Multiple linear regression was used to identify factors associated with final VA improvement.

Results

Of the 133 patients with ON, 42 did not receive intravenous steroid treatment, 13 had a questionable diagnosis, eight had non-Chinese ethnicity, three had symptom onset >30 days prior to presentation, two received steroid treatment for other reasons before presentation, and one had incomplete data. The remaining 64 patients were included in the analysis.

The mean age of the 64 patients was 41.4±15.0 years; 71.9% were women. Most patients had unilateral ON (n=46, 71.9%), experienced ocular pain (n=28, 43.8%), and had disc swelling at presentation (n=22, 34.4%). The most common etiology was idiopathic (n=29, 45.3%), followed by NMOSD-related (n=16, 25.0%), MS-related (n=11, 17.2%), post-vaccination/post-viral (n=5, 7.8%), acute demyelinating encephalomyelitis–related (n=2, 3.1%), and MOGAD-related (n=1, 1.6%) [**Table 1**]. Among the 16 patients with NMOSD-related ON, five (31.3%) were seronegative. The mean logMAR nadir VA was 1.60±0.92 (approximate Snellen VA 20/800). The mean VA on day 14 (upon completion of the ONTT protocol) was 0.74±0.74 (approximate Snellen 20/100) and at the final visit was 0.47±0.79 (approximate Snellen 20/60). The median duration from symptom onset to presentation was 6 days (interquartile range [IQR]=2.25-10 days). The median time from presentation to initiation of steroid treatment (ONTT protocol) was 1 day (IQR=0-6 days). The median duration of follow-up was 3.26 years (IQR=1.73-6.73 years).

Comparison of the three largest subgroups (idiopathic, NMOSD-related, and MS-related ON) revealed that patients with MS-related ON were younger than patients with idiopathic ON (p=0.002) or NMOSD-related ON (p<0.001).

Patients were stratified according to presentation before or after March 2011, when our hospital began providing routine testing for anti-AQP4 antibodies. Multiple linear regression analysis showed that greater improvement in final VA was associated with worse nadir VA (β=0.532, p<0.001), greater VA improvement on day 14 of the ONTT protocol (β=0.335, p=0.007), and NMOSD-related ON (β=0.383, p=0.030), whereas smaller improvement in final VA was associated with older age (β= -0.015, p=0.003) and presentation before anti-AQP4 antibody testing became available (β= -0.738, p<0.001; adjusted R^2=0.721, p<0.001) [**Table 2**].

There were no major adverse effects or mortality after intravenous steroid treatment. One patient had steroid-induced central serous chorioretinopathy, another had transient ocular hypertension, and two patients had steroid-induced temporary hyperglycemia necessitating hypoglycemic agents.

Eight patients underwent plasmapheresis because of a poor response to initial steroid treatment; they were

Table 1. Clinical characteristics of 64 Chinese patients with optic neuritis by etiologies

Etiology	No. (%) of patients (n=64)	No. (%) of women (n=46)	Age at presentation, y*	Visual acuity*			Follow-up duration, y*
				Nadir	Day 14	Final	
Idiopathic	29 (45.3)	18 (62.1)	43.5±15.0	1.68±0.97	0.89±0.78	0.58±0.85	2.49
Neuromyelitis optica spectrum disorder–related	16 (25.0)	15 (93.8)	48.4±11.0	1.78±0.91	0.93±0.81	0.68±1.02	3.34
Multiple sclerosis–related	11 (17.2)	7 (63.6)	29.7±8.0	0.99±0.63	0.35±0.47	0.08±0.09	3.21
Post-vaccination/post-viral	5 (7.8)	3 (60.0)	39.1±23.1	1.64±1.15	0.46±0.58	0.25±0.25	2.86
Acute demyelinating encephalomyelitis–related	2 (3.1)	2 (100)	29.8	2.04	0.15	0.15	-
Myelin oligodendrocyte glycoprotein antibody–associated disease–related	1 (1.6)	1 (100)	30.2	1.78	0.30	0.00	-
Total	64 (100)	46 (71.9)	41.4±15.0	1.60±0.92	0.74±0.74	0.47±0.79	3.26 (1.73-6.73)

** Data are presented as mean±standard deviation or median (interquartile range)*

Table 2. Factors associated with final visual acuity improvement in multiple linear regression

Variables	β coefficient	p Value
Sex	-0.084	0.547
Age at presentation	-0.015	0.003
Presentation before March 2011	-0.738	<0.001
Time from onset to presentation	-0.029	0.087
Time from onset to treatment	0.004	0.661
Nadir visual acuity	0.532	<0.001
Visual acuity improvement on day 14	0.335	0.007
Etiology		
Idiopathic	Reference	
Post-vaccine/post-viral, acute demyelinating encephalomyelitis–related, or myelin oligodendrocyte glycoprotein antibody–associated disease–related	0.011	0.959
Multiple sclerosis–related	-0.213	0.294
Neuromyelitis optica spectrum disorder–related	0.383	0.030

eventually diagnosed with NMOSD-related ON (n=7) or acute demyelinating encephalomyelitis–related ON (n=1). All seven patients with NMOSD-related ON had nadir VA ≤20/200 at presentation (one had no light perception). After plasmapheresis, all except one patient achieved VA ≥20/30 at the final follow-up. Twelve patients were prescribed long-term maintenance immunosuppressants; they had either NMOSD-related ON (n=11) or highly steroid-responsive and steroid-dependent idiopathic ON (n=1).

Discussion

According to findings of the ONTT in 1992,[1] high-dose (1 g/day) intravenous methylprednisolone for 3 days followed by 11 days of oral prednisone resulted in better contrast sensitivity, visual field, color vision, and faster recovery; however, VA at 6 months was similar in patients with or without treatment. Oral prednisone alone did not provide additional benefit in terms of visual recovery and may even result in a higher rate of recurrent attacks. Therefore, pulse intravenous steroid treatment was considered optional, and oral prednisolone (at the ONTT dose) alone was contraindicated for patients with ON. A later study demonstrated that oral steroid treatment alone at a higher dose (ie, prednisone 1250 mg) could achieve beneficial visual outcomes, similar to the outcomes after intravenous methylprednisolone.[6] In the ONTT, 457 patients (aged 18 to 46 years) of mostly (85%) Caucasian ethnicity

were included; 92% had ocular pain and 65% exhibited retrobulbar ON without optic disc swelling. Patients with bilateral ON or evidence of systemic disease that might cause ON (other than MS) were excluded. None of the patients had anti-AQP4 antibodies, and only 1.7% had MOG-IgG antibodies.[1,3]

In Chinese patients, however, ON tends to have an atypical presentation distinct from findings in the ONTT cohort.[7,8] Ocular pain is less prevalent, as demonstrated in the present study. Although anti-AQP4 antibody seropositivity among ON cases is uncommon in Western countries, it reportedly ranges from 20% to 43.5% among Chinese patients.[4] In the present study, 25% of patients had NMOSD-related ON; they were significantly older than patients with MS-related ON. Only one patient had MOGAD-related ON. The numbers of patients with NMOSD- or MOGAD-related ON were likely underestimated because NMO and MOG serology testing only became routinely available in our center after March 2011 and April 2019, respectively.

NMOSD was considered a variant of MS but is now recognized as a distinct disease. NMOSD-related ON significantly differs from typical MS-related ON; it is characterized by a stronger predilection to women, a high incidence of bilaterality, severe visual loss, frequent involvement of the optic chiasm and a long segment of the optic nerve, and a high risk of recurrence. In the past, many cases of NMOSD-related ON were misdiagnosed as idiopathic ON. The expanding arrays of serological markers and increasing availability of anti-AQP4 antibody testing have led to improved diagnostic accuracy. Typical ON is often spontaneously resolved without treatment; however, delayed initiation of steroid treatment can be detrimental to the final visual outcome for NMOSD-related ON, which has a poor prognosis and risk of blindness.[7-11]

Similarly, MOGAD is now recognized as a distinct disorder commonly affecting children and young adults; it typically does not exhibit sex bias, unlike MS or NMOSD. Up to 50% of MOGAD-related ON is bilateral, and disc swelling is common. Patients with MOGAD-related ON are more likely to display longitudinally extensive involvement of the optic nerve and perineural enhancement on magnetic resonance imaging (MRI); they are very steroid-responsive and sometimes steroid-dependent, requiring slow tapering of oral steroid treatment and even long-term immunosuppressant therapy, especially in recurrent cases. MOGAD can be monophasic or relapsing, but there is no progressive phase. Although initial visual loss can be severe, similar to NMOSD-related ON, final visual outcomes generally are better.[9-14]

Non-infectious differential diagnoses of acute ON include demyelinating disease (with or without concurrent MS), NMOSD, and MOGAD. Historically, typical ON was diagnosed via clinical examination; MRI of the brain was performed to predict future risk of MS development. Considering the improved understanding of the radiological features of NMOSD- and MOGAD-related ON, MRI can now be used to differentiate etiologies of ON. Since the discovery of anti-AQP4 and MOG-IgG antibodies, tests of these antibodies have been recommended to guide treatment for all patients with acute ON. Cell-based assays are the preferred serological tests for anti-AQP4 and MOG-IgG antibodies. However, the turnaround time for these tests can take 1 to 2 weeks.[9,15-17] In the acute setting, where the diagnosis of ON is certain but the underlying etiology is unknown, clinicians must decide whether to initiate steroid treatment. Steroid was considered optional in ONTT, but it is important to note that almost all cases in the ONTT were idiopathic or MS-related and thus application of the ONTT findings to Chinese population is limited.

In our hospital, we routinely offer pulse intravenous steroid treatment followed by an oral taper regimen for patients with ON. We advocate early steroid treatment for Chinese patients, considering the different disease spectrum compared with Caucasians. In the present study, NMOSD-related ON was significantly associated with greater final VA improvement. This highlights its unique features: high responsiveness to and dependence on steroid treatment and presentation with more severe visual loss. VA improvement on day 14 was an important predictor of final VA improvement. In clinical settings, VA improvement on day 14 can help clinicians determine the speed of oral steroid tapering and communicate with patients to adjust expectations for visual recovery. Additionally, we identified age as an independent predictor of smaller final VA improvement, consistent with previous findings.[18] We speculate that older people have less neuroplasticity and are more likely to have vasculopathy that can predispose them to additional ischemic injury during episodes of optic nerve inflammation.

Serologic testing for anti-AQP4 antibodies was introduced to our laboratory in March 2011; it was initially performed in patients with high clinical suspicion of NMOSD but quickly became free of charge for any patient with suspected ON and is now the standard practice. Although the turnaround time is 1 to 2 weeks, anti-AQP4 antibody testing enables earlier and more accurate diagnosis of NMOSD, as well as earlier initiation of steroid and immunosuppressant treatments for NMOSD. In patients with refractory ON, plasmapheresis is effective for NMOSD- or MOGAD-related ON and can be offered more promptly when the diagnosis is made.[9,19]

All patients with NMOSD-related ON or severe or recurrent attacks of MOGAD-related ON require maintenance immunosuppressants such as azathioprine, mycophenolate mofetil, and rituximab. For the management of NMOSD, newer biologics such as eculizumab (complement activation inhibitor), tocilizumab, and satralizumab (anti-interleukin-6 antibody) have demonstrated superior efficacy. Thus, patients with NMOSD and MOGAD should be co-managed by ophthalmologists, neurologists, and rheumatologists.[20-24]

Limitations of the present study include its retrospective nature and evaluation of visual function with VA alone;

data regarding color vision, visual field, contrast sensitivity, or anatomical evaluations (eg, retinal nerve fiber layer thickness on optical coherence tomography) were either incomplete or unavailable. The proportions of patients with NMOSD-related ON and MOGAD-related ON were likely underestimated because patients who presented before the introduction of anti-AQP4 or MOG-Ig serology tests were likely to have been misdiagnosed as having idiopathic ON.

Conclusion

Because treatment outcomes differ among MS-, NMOSD-, and MOGAD-related ON, ophthalmologists should be aware of new biomarkers for ON; NMO and MOG serology testing should be conducted for all patients with ON, in addition to MRI of the brain and orbit. In the Chinese population, a considerable proportion of patients with acute ON exhibit atypical disease characteristics; therefore, pulse intravenous steroid treatment should be considered necessary (rather than optional), even before serology results are available. Over the years, VA improvement is likely the result of enhanced investigations and more aggressive treatment of NMOSD-related ON.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, CKMC was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: 621-KCKE). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

References

1. *Beck RW, Cleary PA, Anderson MM Jr, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med 1992;326:581-8.* Crossref
2. *Lai C, Tian G, Liu W, Wei W, Takahashi T, Zhang X. Clinical characteristics, therapeutic outcomes of isolated atypical optic neuritis in China. J Neurol Sci 2011;305:38-40.* Crossref
3. *Chen JJ, Tobin WO, Majed M, et al. Prevalence of myelin oligodendrocyte glycoprotein and aquaporin-4-IgG in patients in the Optic Neuritis Treatment Trial. JAMA Ophthalmol 2018;136:419-22.* Crossref
4. *Hickman SJ, Petzold A. Update on optic neuritis: an international view. Neuroophthalmology 2022;46:1-18.* Crossref
5. *Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the Freiburg visual acuity test. Invest Ophthalmol Vis Sci 2006;47:1236-40.* Crossref
6. *Morrow SA, Fraser JA, Day C, et al. Effect of treating acute optic neuritis with bioequivalent oral vs intravenous corticosteroids: a randomized clinical trial. JAMA Neurol 2018;75:690-6.* Crossref
7. *Choy BNK, Ng ALK, Lai JSM. Clinical characteristics of optic neuritis in Hong Kong population: 10-year review. Int Ophthalmol 2018;38:557-64.* Crossref
8. *Cheng AC, Chan NC, Chan CK. Acute and subacute inflammation of the optic nerve and its sheath: clinical features in Chinese patients. Hong Kong Med J 2012;18:115-22.*
9. *Gospe SM 3rd, Chen JJ, Bhatti MT. Neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein associated disorder-optic neuritis: a comprehensive review of diagnosis and treatment. Eye (Lond) 2021;35:753-68.* Crossref
10. *Stiebel-Kalish H, Hellmann MA, Mimouni M, et al. Does time equal vision in the acute treatment of a cohort of AQP4 and MOG optic neuritis? Neurol Neuroimmunol Neuroinflamm 2019;6:e572.* Crossref
11. *Bennett JL, Costello F, Chen JJ, et al. Optic neuritis and autoimmune optic neuropathies: advances in diagnosis and treatment. Lancet Neurol 2023;22:89-100.* Crossref
12. *Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018;89:127-37.* Crossref
13. *Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin oligodendrocyte glycoprotein antibody-positive optic neuritis: clinical characteristics, radiologic clues, and outcome. Am J Ophthalmol 2018;195:8-15.* Crossref
14. *Juryńczyk M, Jacob A, Fujihara K, Palace J. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. Pract Neurol 2019;19:187-95.* Crossref
15. *Sugimoto K, Mori M, Liu J, et al. The accuracy of flow cytometric cell-based assay to detect anti-myelin oligodendrocyte glycoprotein (MOG) antibodies determining the optimal method for positivity judgement. J Neuroimmunol*

2019;336:577021. Crossref
16. *Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. Neurology 2012;78:665-9*. Crossref
17. *Chen JJ, Pittock SJ, Flanagan EP, Lennon VA, Bhatti MT. Optic neuritis in the era of biomarkers. Surv Ophthalmol 2020;65:12-7*. Crossref
18. *Wang J, Zhou H, Qin L, et al. Optic neuritis in the older Chinese population: a 5-year follow-up study. J Ophthalmol 2017;2017:3458356*. Crossref
19. *Song W, Qu Y, Huang X. Plasma exchange: an effective add-on treatment of optic neuritis in neuromyelitis optica spectrum disorders. Int Ophthalmol 2019;39:2477-83*. Crossref
20. *Chen JJ, Flanagan EP, Bhatti MT, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology 2020;95:e111-e120*. Crossref
21. *Holmøy T, Høglund RA, Illes Z, Myhr KM, Torkildsen Ø. Recent progress in maintenance treatment of neuromyelitis optica spectrum disorder. J Neurol 2021;268:4522-36*. Crossref
22. *Rensel M, Zabeti A, Mealy MA, et al. Long-term efficacy and safety of inebilizumab in neuromyelitis optica spectrum disorder: analysis of aquaporin-4-immunoglobulin G-seropositive participants taking inebilizumab for ≥4 years in the N-MOmentum trial. Mult Scler 2022;28:925-32*. Crossref
23. *Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 2019;381:614-25*. Crossref
24. *Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. N Engl J Med 2019;381:2114-24*. Crossref

ORIGINAL ARTICLE

Micropulse transscleral laser therapy for glaucoma: a retrospective study

Alison YY Chan[1,2], Isabel SW Lai[1,3], Clement CY Tham[1,2,4]
[1]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2]*Hong Kong Eye Hospital, Hong Kong SAR, China*
[3]*The Hong Kong Ophthalmic Associates, Hong Kong SAR, China*
[4]*Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China*

Correspondence and reprint requests:
Dr Alison Yin Yung Chan, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong SAR, China. Email: cyy610@ha.org.hk

Abstract

Objective: To evaluate the safety and efficacy of micropulse transscleral laser therapy (MPTLT) in patients with glaucoma at a tertiary eye center in Hong Kong.
Methods: Medical records of patients who underwent MPTLT at Hong Kong Eye Hospital between 1 August 2020 and 31 July 2021 were retrospectively reviewed. Successful treatment was defined as a postoperative intraocular pressure (IOP) between 6 and 21 mmHg or a 20% reduction in IOP from baseline, without an increase in glaucoma medications (topical or oral) or additional glaucoma interventions.
Results: In total, 205 eyes underwent MPTLT either for the first time (n=100) or retreatment (n=105). The mean preoperative visual acuity was 1.6 LogMAR, and 42 (20.5%) eyes had a baseline visual acuity of light perception or worse. The mean preoperative IOP was 27.7 mmHg. All the patients were on the maximum tolerated medical therapy prior to undergoing MPTLT; the mean number of preoperative topical anti-glaucoma medications was 4.1. The mean energy administered was 116.4 J. The overall success rates were 64.9% at 1 month, 51.7% at 3 months, 42.4% at 6 months, 31.2% at 1 year, and 29.3% at 18 months. Success rates were comparable across all time points for both groups. At 18 months or the last visit before additional intervention, the mean IOP reduced 11.3% to 23.3 mmHg (p<0.001), and approximately 23% of patients had an IOP reduction of at least 20%. The mean number of topical anti-glaucoma medications required decreased 5.3% from 4.1 to 3.9 (p=0.003). The decrease was significant in eyes undergoing first-time MPTLT (p=0.004). The percentage of eyes requiring an oral carbonic anhydrase inhibitor also decreased from 72.2% to 44.9% (p<0.001). Patients who received intermediate-energy MPTLT experienced a greater reduction in the number of topical glaucoma medications and in eyes requiring oral carbonic anhydrase inhibitor (acetazolamide) than patients who received low-energy MPTLT. Of 205 eyes, 124 (60.5%) required a mean of 1.9 additional interventions per eye; the median time to the first additional intervention was 3.0 months. Overall, eight (3.9%) eyes developed complications after MPTLT.
Conclusions: MPTLT is a safe and effective treatment modality for various glaucoma subtypes, reducing IOP and the need for topical and oral anti-glaucoma medication. The optimal treatment parameters remain to be determined.

Key words: Glaucoma; Intraocular pressure; Laser therapy

Introduction

Glaucoma is a neurodegenerative eye disease characterized by progressive retinal ganglion cell loss and distinctive visual field changes. Approximately 80 million people were affected worldwide in 2020; the number is anticipated to increase to 112 million by 2040.[1] Glaucoma remains a leading cause of irreversible blindness. Although various risk factors contribute to its development, lowering intraocular pressure (IOP) is the most effective way to delay the disease's progression.

Traditionally, the treatment algorithm for glaucoma follows

a stepwise approach that comprises topical medication, laser therapy, and surgery, each with differing levels of efficacy and risks. Since the 1930s, cyclodestructive procedures have been used to coagulate or destroy the ciliary body, aiming to reduce aqueous humor production.[2] Various methods can be used for cyclodestruction, including diathermy, surgical excision, cryotherapy, ultrasound, and laser therapy (cyclophotocoagulation). To date, both transscleral and endoscopic approaches have been used for cyclophotocoagulation.[3] Transscleral diode laser cyclophotocoagulation (G-probe) used to be the primary modality for laser cyclophotocoagulation. However, it is associated with complications such as prolonged intraocular inflammation, hyphema, conjunctival burns, and cystoid macular edema, as well as higher rates of severe complications including hypotony, phthisis bulbi, malignant glaucoma, scleral perforation, and sympathetic ophthalmia.[4] Consequently, G-probe is typically a last resort for refractory glaucoma and eyes with poor visual potential.

Micropulse transscleral laser therapy (MPTLT) is a safer technique than G-probe for cyclophotocoagulation. Instead of a continuous laser transmission, MPTLT utilizes repetitive micropulses of diode laser ('on' cycles) interspersed with rest intervals ('off' cycles).[5] It is postulated that the 'off' periods promote thermal dissipation, reducing heat build-up and subsequent collateral tissue damage and adverse effects.[6] MPTLT operates through three mechanisms of action: (1) subthreshold cell damage at the pigmented ciliary epithelium level and, to a lesser extent, the non-pigmented epithelium level; (2) increased uveoscleral outflow,[7,8] and (3) a pilocarpine-like effect (ie, the contraction of ciliary muscle longitudinal fibers, increasing aqueous humor outflow via the conventional pathway).[9,10] MPTLT has demonstrated a lower incidence of complications than G-probe.[6,11] Histological examinations of autopsied eyes treated with MPTLT reveal minimal changes in the normal tissue architecture surrounding the ciliary body.[12] MPTLT's improved safety profile enables its earlier use to treat glaucoma. Its other advantages include repeatability, feasibility as an office procedure, reduced postoperative inflammation, and less need for intensive follow-up.

Methods

Medical records of patients who underwent MPTLT at Hong Kong Eye Hospital between 1 August 2020 and 31 July 2021 were retrospectively reviewed. The start date was the implementation of the revised Iridex P3 delivery device (Iridex, Mountain View [CA], USA). Data collected included patient age, sex, ethnicity, glaucoma type and severity, history of glaucoma surgery, number of MPTLT received, MPTLT parameters, visual acuity, IOP, number of topical anti-glaucoma medications taken prior to treatment/retreatment (calculated by adding the number of different medication classes), need for oral acetazolamide, incidence of complications, and need for retreatment or additional interventions. Where retreatment or additional interventions were required, the interval (in months) from the MPTLT to the first intervention and the form of intervention were noted.

All MPTLT procedures were performed at Hong Kong Eye Hospital by or under the supervision of a glaucoma specialist. Preoperatively, patients received a retrobulbar block with 2% lidocaine and 0.75% bupivacaine in a 1:1 ratio. The 810 nm laser (G6) was used with the Generation 2 MicroPulse P3 handpiece. A speculum was used to ensure adequate exposure, and topical xylocaine gel was applied to facilitate probe movement. The handpiece was moved in a continuous sliding arc motion for 15 to 20 seconds each cycle, with consistent firm pressure perpendicular to the globe. The superior and inferior hemispheres of the eye were treated while avoiding the 3 and 9 o'clock positions, any areas of scleral thinning, pigmented or hemorrhagic conjunctiva, and sites of previous glaucoma surgery. Following MPTLT, patients were prescribed topical dexamethasone plus chloramphenicol eye drops 6 times per day for 2 weeks with initial continuation of all pre-laser hypotensive therapy.

Successful treatment was defined as a postoperative IOP between 6 and 21 mmHg or a 20% reduction in IOP from baseline, without an increase in glaucoma medications (topical or oral) or additional glaucoma interventions. Patients' data were recorded until the point of treatment failure or when additional oral glaucoma medications or interventions were needed. The decision to continue or taper the use of anti-glaucoma medications subsequently was based on the postoperative IOP measured at follow-ups and the physician's discretion.

Statistical analysis was performed using SPSS (version 29.0.2.0, IBM, New York, USA). A p value of <0.05 was considered statistically significant.

Results

In total, 205 eyes underwent MPTLT either for the first time (n=100) or retreatment (n=105) [**Table 1**]. The mean patient age was 67.4 years, and the male-to-female ratio was approximately 2:1. The most common diagnosis was primary open-angle glaucoma (35.1%), followed by neovascular glaucoma (18.5%), uveitic glaucoma (10.2%), and angle-closure glaucoma (9.3%).

The mean preoperative visual acuity was 1.6 LogMAR, and 42 (20.5%) eyes had a baseline visual acuity of light perception or worse. The mean preoperative visual field index using the Humphrey visual field analyzer was 45.7%, with a baseline mean deviation of -20.0 dB and pattern standard deviation of 6.7 dB. 62 (30.2%) eyes had undergone at least one previous incisional glaucoma surgery. The mean preoperative IOP was 27.7 mmHg. All the patients were on the maximum tolerated medical therapy prior to undergoing MPTLT; the mean number of preoperative topical anti-glaucoma medications was 4.1 (range, 2-5). 148 (72.2%) eyes required an oral carbonic anhydrase inhibitor.

Table 1. Clinical characteristics of patients undergoing micropulse transscleral laser therapy (MPTLT)

	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
Age, y	67.4±15.0	67.4±15.6	67.4±14.4	0.755
Sex				<0.001
Male	136 (66.3)	55 (55)	81 (77.1)	
Female	69 (33.7)	45 (45)	24 (22.9)	
Ethnicity				0.972
Chinese	203	99	104	
Others	2	1	1	
Glaucoma				
Primary open-angle	72 (35.1)	40 (40.0)	32 (30.5)	0.153
Neovascular	38 (18.5)	16 (16.0)	22 (21.0)	0.362
Uveitis	21 (10.2)	5 (5.0)	16 (15.2)	0.016
Angle-closure	19 (9.3)	12 (12.0)	7 (6.7)	0.188
Silicone oil-related	10 (4.9)	5 (5.0)	5 (4.8)	0.937
Aphakia	8 (3.9)	4 (4.0)	4 (3.8)	0.944
Iridocorneal endothelial syndrome	7 (3.4)	3 (3.0)	4 (3.8)	0.750
Post-keratoplasty	6 (2.9)	3 (3.0)	3 (2.9)	0.952
Uveitis-glaucoma-hyphema syndrome	5 (2.4)	3 (3.0)	2 (1.9)	0.611
Red cell	4 (2.0)	2 (2.0)	2 (1.9)	0.961
Others (juvenile open-angle glaucoma, normal tension glaucoma, epithelial downgrowth, trauma, aniridia, congenital glaucoma, painful blind eye)	15 (7.3)	7 (7.0)	8 (7.6)	0.865
No. of topical intraocular pressure–lowering medications used	4.1±0.7	4.2±0.7	4.0±0.7	0.217
Use of oral carbonic anhydrase inhibitor	148 (72.2)	74 (74.0)	74 (70.5)	0.574
Preoperative intraocular pressure, mmHg	27.7±8.7	28.5±9.5	27.0±7.9	0.349
Visual acuity, LogMAR	1.6±1.0 (0.18-3.0)	1.5±1.0 (0.1-3.0)	1.7±0.9 (0.18-3.0)	0.263
Visual field index, %	45.7±34.3	53.7±30.3	38.5±36.4	0.026
Mean deviation, dB	-20.0±9.5	-17.7±8.8	-22.4±9.7	0.010
Pattern standard deviation, dB	6.7±3.7	7.7±3.7	5.9±3.5	0.011
Prior glaucoma surgery	62 (30.2)	31 (31.0)	31 (29.5)	0.818

** Data are presented as mean±standard deviation, No. (%) of patients, No. of patients, or mean ± standard deviation (range)*

Compared with patients undergoing MPTLT for the first time, a higher proportion of patients undergoing MPTLT retreatment were male (p<0.001) and had uveitic glaucoma (p=0.016) and worse visual field index (p=0.026), mean deviation (p=0.010), and pattern standard deviation (p=0.011) at baseline. The two groups were comparable in terms of other clinical characteristics.

Regarding MPTLT parameters, the mean power was 2151.6 mW for a mean duration of 173.5 s for a 31.3% duty cycle (**Table 2**). The total energy in joules (J) was calculated as power in watts (W) × total treatment duration in seconds (s) × duty cycle.[8] The mean energy administered was 116.4 J. Similar laser parameters were used for both the first-time treatment and retreatment groups. Patients were stratified by energy levels: low (<100 J, n=15), intermediate (100-<200 J, n=190), and high (≥200 J, n=0).

The overall success rates were 64.9% at 1 month, 51.7% at 3 months, 42.4% at 6 months, 31.2% at 1 year, and 29.3% at

18 months (**Table 3**). Success rates were comparable across all time points for both groups.

At 18 months or the last visit before additional intervention, the mean IOP reduced 11.3% to 23.3 mmHg (p<0.001, **Table 4**), and approximately 23% of patients had an IOP reduction of at least 20% (**Table 5**).

Overall, the mean number of topical anti-glaucoma medications required decreased 5.3% from 4.1 to 3.9 (p=0.003, **Table 6**). The decrease was significant in eyes undergoing first-time MPTLT (p=0.004) but not in eyes undergoing MPTLT retreatment (p=0.278). The percentage of eyes requiring an oral carbonic anhydrase inhibitor also decreased from 72.2% to 44.9% (p<0.001). The two groups were comparable in terms of tapering the use of oral acetazolamide.

Patients who received intermediate-energy MPTLT experienced a greater reduction in the number of topical glaucoma medications and in eyes requiring oral carbonic anhydrase inhibitor (acetazolamide) than patients who received low-energy MPTLT (**Table 7**). Nevertheless, the overall success rates were comparable between groups.

Of 205 eyes, 124 (60.5%) required a mean of 1.9 additional interventions per eye; the median time to the first additional intervention was 3.0 months (**Table 8**). The

Table 2. Micropulse transscleral laser therapy (MPTLT) parameters

	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
Power, mW	2151.6±202.5 (1500-2500)	2150.5±192.8 (1900-2500)	2154.0±212.6 (1500-2500)	0.921
Duration, s	173.5±20.0 (100-240)	172.2±15.3 (120-200)	174.7±23.6 (100-240)	0.575
Duty cycle, %	31.3	31.3	31.3	
Energy, J	116.4±14.4 (70.4-156.5)	115.7±13.1 (75.1-148.7)	117.2±15.5 (70.4-156.5)	0.223
Energy level, J				-
Low (<100)	15 (7.3)	8 (8.0)	7 (6.7)	
Intermediate (100-<200)	190 (92.7)	92 (92.0)	98 (93.3)	
High (≥200)	0	0	0	

** Data are presented as mean, mean ± standard deviation (range), or No. (%) of patients*

Table 3. Success rates at different time points after micropulse transscleral laser therapy (MPTLT)

Postoperative time point	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
1 month	133 (64.9)	64 (64.0)	69 (65.7)	0.884
3 months	106 (51.7)	51 (51.0)	55 (52.4)	0.889
6 months	87 (42.4)	42 (42.0)	45 (42.9)	0.999
12 months	64 (31.2)	33 (33.0)	31 (29.5)	0.652
18s months	60 (29.3)	28 (28.0)	32 (30.5)	0.760

** Data are presented as No. (%) of patients.*

Table 4. Intraocular pressure before and after micropulse transscleral laser therapy (MPTLT)

Intraocular pressure, mmHg	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
Preoperative	27.7±8.7 (7-64)	28.5±9.5 (11-64)	27.0±7.9 (7-52)	0.349
Postoperative 18 months	23.3±9.2 (5-58)	23.0±9.3 (9-56)	23.6±9.1 (5-58)	0.559
p Value	<0.001	<0.001	<0.001	

** Data are presented as mean ± standard deviation (range) unless otherwise indicated*

most common additional intervention was repeat MPTLT (33.1%), followed by G-probe (16.1%), MPTLT plus G-probe (16.1%), MPTLT/G-probe plus surgery (12.1%), trabeculectomy (11.3%), MPTLT plus G-probe plus selective laser trabeculoplasty (4.0%), selective laser trabeculoplasty (3.2%), insertion of a glaucoma drainage device (1.6%), and others (2.4%). Both groups were comparable in terms of the number of eyes requiring additional interventions and the number of additional interventions.

Overall, eight (3.9%) eyes developed complications after MPTLT. No eyes developed macular edema, hypotony, or phthisis bulbi. Among eyes with 20/400 vision or better, none experienced permanent vision loss of >2 Snellen lines. However, six eyes with light perception to count finger vision progressed to no light perception vision. Additionally, one eye developed corneal decompensation at 1 month, necessitating endothelial keratoplasty. Another eye had a flare-up of underlying anterior uveitis and decreased visual acuity secondary to a persistent corneal epithelial defect and corneal scar formation.

Table 5. Percentage of eyes with ≥20% reduction in intraocular pressure after micropulse transscleral laser therapy (MPTLT)

Postoperative time point	% of eyes with ≥20% reduction in intraocular pressure		p Value
	Eyes undergoing first-time MPTLT (n=100)	Eyes undergoing MPTLT retreatment (n=105)	
1 month	50.0	44.8	0.486
3 months	36.0	31.4	0.555
6 months	29.0	31.4	0.762
12 months	19.0	23.8	0.496
18 months	23.0	23.8	0.999

Discussion

MPTLT is a safe and effective treatment for various types of glaucoma, significantly reducing IOP and the use of topical and systemic anti-glaucoma medications for up to 18 months. Although eyes undergoing MPTLT retreatment had worse visual field parameters at baseline, they were comparable with eyes undergoing first-time MPTLT in terms of success rate, IOP control, need for oral acetazolamide, and need for additional interventions. Intermediate-energy MPTLT was more effective than low-energy MPTLT in reducing the need for topical and systemic anti-glaucoma medications, with a comparable safety profile.

In our patients, the mean preoperative IOP was 27.7 (range, 7-64) mmHg. It is uncommon to perform MPTLT on an eye with an IOP of 7 mmHg. Before MPTLT, the patient's IOP was uncontrollable despite receiving the maximum tolerated medical therapy until he was given the highest dose of oral acetazolamide, which he was unable to wean off. The postoperative period was uneventful with no complications, and the patient was able to wean off oral acetazolamide with no need for retreatment at 18 months.

Table 6. Change in topical and systemic medication need before and after micropulse transscleral laser therapy (MPTLT)

Medication	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
No. of topical medications				
Preoperative	4.1±0.7	4.2±0.7	4.0±0.7	0.217
Postoperative 18 months	3.9±1.1	3.8±1.3	3.9±0.1	0.832
p Value	0.0030	0.0040	0.278	
% of eyes on oral acetazolamide				
Preoperative	72.2	74.0	70.5	0.574
Postoperative 18 months	44.9	46.0	43.8	0.752
p Value	<0.001	<0.001	<0.001	
Acetazolamide need				-
Reduced	91 (44.4)	43 (43.0)	48 (45.7)	
Increased	28 (13.7)	15 (15.0)	13 (12.4)	
Unchanged	41 (20.0)	21 (21.0)	20 (19.0)	
Not required throughout	45 (22.0)	21 (21.0)	24 (22.9)	

** Data are presented as mean ± standard deviation or No. (%) of patients unless otherwise indicated*

Table 7. Postoperative outcomes by energy level			
	Low energy (<100 J) [n=15]*	Intermediate energy (100-<200 J) [n=190]*	p Value
Success rate			
1 month	11 (73.3)	122 (64.2)	0.476
3 months	11 (73.3)	95 (50.0)	0.082
6 months	8 (53.3)	79 (41.6)	0.375
12 months	6 (40.0)	58 (30.5)	0.446
18 months	5 (33.3)	55 (28.9)	0.719
% of intraocular pressure reduction	13.3	11.2	
No. of topical medications used			
Preoperative	4.3±0.5	4.1±0.7	0.370
Postoperative 18 months	3.5±1.7	3.9±1.1	0.803
p Value	0.078	0.014	
% of eyes on oral acetazolamide			
Preoperative	73.3	72.1	0.919
Postoperative 18 months	60.0	42.6	0.192
p Value	0.699	<0.001	

** Data are presented as mean, mean ± standard deviation, or No. (%) of patients unless otherwise indicated*

Table 8. Need for additional interventions after micropulse transscleral laser therapy (MPTLT)				
Additional intervention	All eyes (n=205)*	Eyes undergoing first-time MPTLT (n=100)*	Eyes undergoing MPTLT retreatment (n=105)*	p Value
Eyes requiring additional interventions	124 (60.5)	59 (59.0)	65 (61.9)	0.775
No. of additional interventions	1.9±1.2 (1-8)	2.0±1.4 (1-8)	1.9±1.1 (1-5)	0.709
Time to first additional intervention, mo	3.0±4.2 (0.25-18)	3.0±4.2 (1-18)	3.0±4.1 (0.25-18)	0.714
Type of additional intervention				-
Surgical	34 (27.4)	20 (33.9)	14 (21.5)	
Non-surgical	90 (72.6)	39 (66.1)	51 (74.5)	

** Data are presented as mean ± standard deviation (range) or No. (%) of patients*

The MPTLT success rates vary from 26% to 100%, as do retreatment rates from 0% to 46%.[13] These differences can be explained by the diverse combinations of treatment parameters and heterogenous patient populations, which make direct comparisons difficult. In our patients, the overall retreatment rate was 60.5%, and the median time to retreatment was 3.0 months. This higher retreatment rate was in part due to the lower laser power used (range, 1500-2500 mW), compared with the 2000-2500 mW recommended by the manufacturer. Our cohort comprised eyes with various glaucoma subtypes such as neovascular glaucoma (18.5%) and uveitic glaucoma (10.2%), which are associated with worse prognoses[14] and higher retreatment rates than primary open-angle glaucoma.[5,13,15] Furthermore, 20.5% of eyes had a baseline visual acuity of light perception or worse and were unable to perform a Humphrey visual field analysis. The preoperative visual field mean deviation of -20.0 dB would therefore have been underestimated. There was no standardized set of indications for retreatment or additional interventions, and the decision was based on the physician's discretion at each follow-up visit, which may have contributed to the higher retreatment rate.

MPTLT is a safe procedure for both keratoplasty-naïve and post-keratoplasty eyes.[16-18] In 61 eyes with mild to advanced glaucoma treated with MPTLT, three (4.9%) eyes had corneal decompensation, and all three had previous corneal pathologies (herpetic keratitis, Fuchs' endothelial dystrophy, and bullous keratopathy).[19] In 14 eyes with refractory glaucoma treated with MPTLT, one (5%) eye

developed corneal decompensation at 3 years; the eye had a history of multiple intraocular surgeries.[20] Among our patients, one eye developed corneal decompensation 1 month after MPTLT, necessitating endothelial keratoplasty. The patient had uveitic glaucoma with a history of trabeculectomy for more than two decades. Preoperatively, there was no clinical evidence of corneal pathologies or early signs of decompensation. The MPTLT parameters were within intermediate ranges (2000 mW power, 160 seconds duration, total energy 100.2 J). Therefore, specular microscopy examination prior to treatment is advocated for patients at risk of postoperative corneal decompensation including inherited or acquired endothelial deficiencies, post-keratoplasty eyes, uveitic glaucoma, history of herpetic eye disease, and eyes with multiple previous intraocular procedures.

A laser energy level of <112 J is associated with a lower complication rate, but the treatment efficacy tends to be short-lived. In contrast, medium-energy levels (100 to <200 J) result in higher success rates and longer-lasting effects while maintaining a favorable safety profile.[21] In our patients, 93.2% of eyes received treatment within the intermediate energy range; the mean energy used was 116.4 J and the maximum energy used was 156.5 J. How higher energy levels affect treatment outcomes could be explored.

Fluence is proposed to be a more representative metric than total energy in predicting clinical outcome.[22] Fluence at the scleral surface (J/cm^2) is calculated as power in watts (W) × duty cycle (31.3%) × dwell time/area of the laser spot (for the Generation 2 (Rev 2) probe with a spot diameter of 600 μm, equivalent to an area of 0.0028 cm^2). The dwell time is the stationary pulse duration during which equal energy is deposited per unit area per unit time, which depends on the laser probe's sweep velocity. Fluence can be increased either by increasing the treatment power or decreasing the sweep velocity. When stratifying patients based on the median fluence level of 52.4 J/cm^2, total energy used is not associated with reduced IOP, but fluence is positively associated with reduced IOP.[22] Patients with fluence >52.4 J/cm^2 consistently achieve higher IOP reduction of ≥50% from baseline, despite similar total energy used. Among cohorts with the same fluence level, IOP reduction ranges from 28.5% to 49.0%, which indicates that other variables affect treatment efficacy. Nonetheless, the review study is limited by the small number of studies considered and the variation in patient inclusion criteria.

Limitations of the present study include its retrospective nature and lack of a standardized set of indications for anti-glaucoma medications, retreatment, or additional interventions. However, the sample size was large, various glaucoma subtypes were included, and the follow-up duration was up to 18 months.

Conclusion

MPTLT is a safe and effective treatment modality for various glaucoma subtypes, reducing IOP and the need for topical and oral anti-glaucoma medication. The optimal treatment parameters remain to be determined. The use of standardized laser parameters and techniques including sweep velocity and number of sweeps per hemisphere is advocated to enable systematic evaluation of dose-response relationships and comparison of results across studies.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an advisor of the journal, CCYT was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval

The study was approved by Hospital Authority Central Institutional Review Board (Reference: CIRB-2024-226-3). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

References

1. *Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology 2014;121:2081-90.* Crossref
2. *Webb TE. A review of glaucoma surgical therapy. Veterinary Ophthalmol 2020;24:34-8.* Crossref
3. *Dastiridou AI, Katsanos A, Denis P, et al. Cyclodestructive procedures in glaucoma: a review of current and emerging options. Advances Ther 2018;35:2103-27.* Crossref
4. *Fong YYY, Wong BKT, Li FCH, Young AL. A retrospective study of transcleral cyclophotocoagulation using the slow coagulation technique for the treatment of refractory glaucoma. Semin Ophthalmol 2019;34:398-402.* Crossref

5. Tan AM, Chockalingam M, Aquino MC, Lim ZI, See JL, Chew PT. Micropulse transscleral diode laser cyclophotocoagulation in the treatment of refractory glaucoma. Clin Exp Ophthalmol 2010;38:266-72. Crossref
6. Aquino MC, Barton K, Tan AM, et al. Micropulse versus continuous wave transscleral diode cyclophotocoagulation in refractory glaucoma: a randomized exploratory study. Clin Exp Ophthalmol 2015;43:40-6. Crossref
7. Barac R, Vuzitas M, Balta F. Choroidal thickness increase after micropulse transscleral cyclophotocoagulation. Rom J Ophthalmol 2018;62:144-8. Crossref
8. Abdelmassih Y, Tomey K, Khoueir Z. Micropulse transscleral cyclophotocoagulation. J Curr Glaucoma Pract 2021;15:1-7. Crossref
9. Johnstone MA, Song S, Padilla S, et al. Microscope real-time video (MRTV), high-resolution OCT (HR-OCT) & histopathology (HP) to assess how transcleral micropulse laser (TML) affects the sclera, ciliary body (CB), muscle (CM), secretory epithelium (CBSE), suprachoroidal space (SCS) & aqueous outflow system. Invest Ophthalmol Vis Sci 2019;60:2825.
10. Sanchez FG, Peirano-Bonomi JC, Grippo TM. Micropulse transscleral cyclophotocoagulation: a hypothesis for the ideal parameters. Med Hypothesis Discov Innov Ophthalmol 2018;7:94-100.
11. Abdelrahman AM, El Sayed YM. Micropulse versus continuous wave transscleral cyclophotocoagulation in refractory pediatric glaucoma. J Glaucoma 2018;27:900-5. Crossref
12. Pantcheva MB, Kahook MY, Schuman JS, Noecker RJ. Comparison of acute structural and histopathological changes in human autopsy eyes after endoscopic cyclophotocoagulation and trans-scleral cyclophotocoagulation. Br J Ophthalmol 2007;91:248-52. Crossref
13. Souissi S, Le Mer Y, Metge F, et al. An update on continuous-wave cyclophotocoagulation (CW-CPC) and micropulse transscleral laser treatment (MP-TLT) for adult and paediatric refractory glaucoma. Acta Ophthalmol 2021;99:e621-e653. Crossref
14. Kalogeropoulos D, Moussa G, Sung VC, Pappa C, Kalogeropoulos C. Neovascular glaucoma: an update. Klinische Monatsblätter Für Augenheilkunde 2022;240:305-15. Crossref
15. Tekeli O, Köse HC. Outcomes of micropulse transscleral cyclophotocoagulation in primary open-angle glaucoma, pseudoexfoliation glaucoma, and secondary glaucoma. Eur J Ophthalmol 2020;31:1113-21. Crossref
16. Lee JH, Vu V, Lazcano-Gomez G, et al. Clinical outcomes of micropulse transscleral cyclophotocoagulation in patients with a history of keratoplasty. J Ophthalmol 2020:1-6. Crossref
17. Zemba M, Dumitrescu OM, Stamate AC, Barac IR, Tataru CP, Branisteanu DC. Micropulse transscleral cyclophotocoagulation for glaucoma after penetrating keratoplasty. Diagnostics 2022;12:1143. Crossref
18. Subramaniam K, Price MO, Feng MT, Price FW. Micropulse transscleral cyclophotocoagulation in keratoplasty eyes. Cornea 2019;38:542-5. Crossref
19. Basto RC, Almeida J, Roque JN, et al. Clinical outcomes of micropulse transscleral cyclophotocoagulation: 2 years of experience in Portuguese eyes. J Curr Glaucoma Pract 2023;17:30-6. Crossref
20. Thanapaisal S, Sriphon P, Suparattanagool P, Thawongklang S. Long-term efficacy and safety of micropulse transscleral cyclophotocoagulation in the treatment of refractory glaucoma. J Med Assoc Thailand 2022;105:855-60. Crossref
21. Sanchez FG, Peirano-Bonomi JC, Brossard Barbosa N, Khoueir Z, Grippo TM. Update on micropulse transscleral cyclophotocoagulation. J Glaucoma 2020;29:598-603. Crossref
22. Grippo TM, Sanchez FG, Stauffer J, Marcellino G. MicroPulse transscleral laser therapy: fluence may explain variability in clinical outcomes: a literature review and analysis. Clin Ophthalmol 2021;15:2411-9. Crossref

REVIEW ARTICLE

Artificial intelligence and external photographs in ophthalmology: a systematic review

Kenneth Ka Hei Lai[1,2*], *Carmen Sze Ching Lo*[3*], *Han Wang*[1], *Xiaoyan Hu*[1], *Fatema Mohamed Ali Abdulla Aljufairi*[1,4], *Jake Uy Sebastian*[1,5], *Chi Pui Pang*[1], *Kelvin Kam Lung Chong*[1,2,6]

[1]*Department of Ophthalmology and Visual Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2]*Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China*
[3]*Department of Ophthalmology, Department of the Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*
[4]*Department of Ophthalmology, Salmaniya Medical Complex, Government Hospitals, Bahrain*
[5]*Department of Ophthalmology, Vicente Sotto Memorial Medical Center, Cebu City, Philippines*
[6]*Hong Kong Eye Hospital, Hong Kong SAR, China*

**Contributed equally*

Correspondence and reprint requests:
Dr Kelvin Kam Lung Chong, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China. Email: chongkamlung@cuhk.edu.hk

Abstract

We systematically reviewed the literature regarding the use of artificial intelligence trained with external photographs, defined as unprocessed clinical images taken from cameras and slit-lamps, for measurement of eyelid/periorbital parameters and detection and classification of multiple ophthalmic diseases including blepharoptosis, thyroid eye disease, eyelid tumors, keratitis, trachoma, pterygium, diabetic retinopathy, cataract, strabismus, and other oculofacial disorders.

Key words: *Artificial intelligence; Face; Ophthalmology*

Introduction

Artificial intelligence (AI) is a type of machine learning that applies complex algorithms to analyze large amounts of data.[1,2] AI has demonstrated good performance in the management of diabetic retinopathy, glaucoma, age-related macular degeneration, and myopia.[3-6] Fundus photography and optical coherence tomography are commonly used in the field of AI ophthalmology. Facial images have been used in AI for facial recognition, emotion recognition, and medical diagnoses (eg, Down syndrome, fetal alcohol syndrome, and other genetic disorders).[7-10] In recent years, AI has been used to analyze external photographs, defined as unprocessed clinical images taken from cameras and slit-lamps, for multiple ophthalmic diseases.

Reliable screening tools can facilitate timely diagnoses and prompt treatment, thereby reducing morbidity and health burden. Technological advances enable the use external photographs in AI.[11,12] Facial images can readily be acquired using cameras, making them cost-effective and convenient screening tools for multiple ophthalmic diseases such as thyroid eye disease (TED) and eyelid tumors, especially among patients with poor access to healthcare services. Ophthalmology is one of the highest-demand healthcare fields; the use of AI and external photographs has great potential to revolutionize ophthalmology services by shortening waiting time, enhancing disease management, and improving patient outcomes.[13] We systematically reviewed the literature regarding clinical applications of AI and external photographs in the field of ophthalmology.

Methods

The PubMed, Scopus, Web of Science, and IEEE databases was systematically searched on 27 April 2023 using key words: 'artificial intelligence' OR 'machine learning' OR 'neural network' OR 'deep learning' and a combination of 'facial landmarking' OR 'external photo' OR 'face photo' OR 'eyelid' OR 'anterior segment photograph' OR 'anterior segment image' OR 'anterior segment photo'

OR 'pterygium'. The PRISMA guidelines were followed without language restrictions. The quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2.

Inclusion criteria were (1) clinical trials, prospective and retrospective cohort studies, comparative studies, validation, or evaluation studies, and epidemiologic studies; (2) studies involving facial images or external photographs in AI for detecting ophthalmic conditions; and (3) original articles. Exclusion criteria were (1) studies for which the full text was unavailable; (2) studies reporting the use of AI for non-ophthalmic conditions; (3) studies involving images taken from optical coherence tomography (OCT), fundus photography, or oculus keratography; and (4) review articles without original data.

Two reviewers independently searched the literature and screened the abstracts of identified studies. Disagreements were resolved by discussion with four senior reviewers. The two reviewers then independently assessed the full text of eligible studies, and data were extracted and cross-validated. In cases of unresolved disagreement, a thorough discussion involving all reviewers was conducted until a consensus was reached. The study selection process based on the PRISMA flowchart[14] is shown in the **Figure**. A customized form was used to record year of publication, study population, types of ophthalmic conditions, number and focal region of external photographs, number of test sets, types of deep neural network, and key findings. The risk of bias was assessed by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2.

Results

In total, 48 studies were included in the systematic review (**Table 1**). Among the 48 studies, 14 exhibited low risk for all four risk of bias parameters and eight displayed low risk for all three applicability concerns parameters (**Table 2**).

Measurement of eyelid/periorbital parameters

The eyelid is usually assessed during evaluation of other ophthalmic disorders. The eyelid position is measured by placing an opaque ruler in front of the patient's eye.[15] Moriyama et al[16] used an AI system trained with two-dimensional facial images to parameterize the fine structures of the eyes including the position of the iris, degree of eyelid opening, and the shape, complexity, and texture of the eyelid. The system also estimated the movement parameters of the eyelids and iris. This model failed to match well only five out of 577 images. Thomas et al[17] compared manual and AI-automated measurements of the vertical palpebral aperture and reported good agreement between the two methods (Pearson correlation coefficient=0.87); 94% of measurements were within two standard deviations of the mean. Van Brummen et al[18] used AI to assess eight periorbital measurements including marginal reflex distance (MRD) 1 and 2, medial and lateral canthal heights, medial and lateral brow heights, and medial and lateral intercanthal distances.

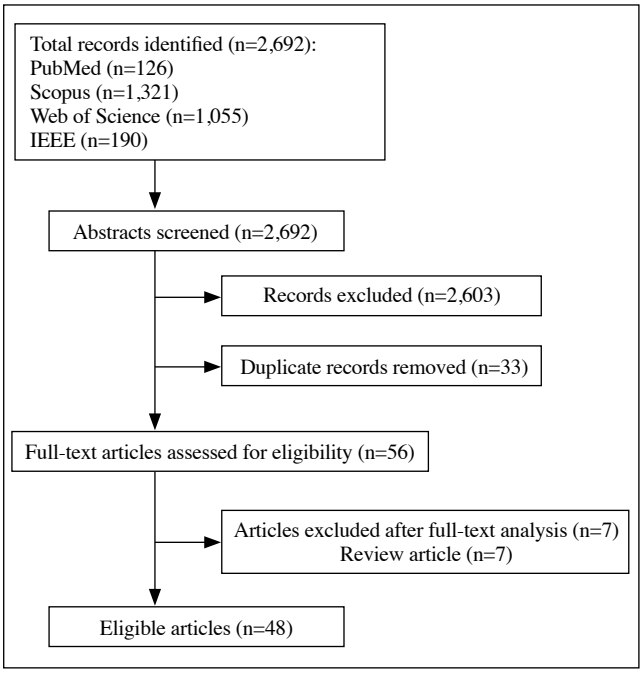


Figure. Flowchart showing the literature search process.

The performance of AI closely agreed with that of human graders; the mean absolute differences were 0.5 mm for MRD 1 and 2 and lateral and medial canthal heights, 1.5 to 2 mm for lateral and medial brow heights, and 2 to 4 mm for medial and lateral intercanthal distances. Chen et al[19] described the first smartphone-based AI-assisted image-processing algorithm for measurements of MRD 1 and 2 and levator function; the respective Pearson correlation coefficients between the smartphone-based AI and gold standard AI-assisted software were 0.91, 0.84, and 0.73. Cao et al[20] compared AI and manual segmentations of eyelid features on two-dimensional digital photographs; the Dice coefficients for eyelid and corneal segmentation between the two methods were 0.922 and 0.973, respectively. Zhu et al[21] used an automated algorithm to measure eyelid position based on nine parameters and reported 91% accuracy. Manual measurement of eyelid parameters can be time-consuming, subjective, and unrepeatable. AI-assisted eyelid assessments may enhance efficiency and repeatability in busy clinical settings.

Blepharoptosis

Blepharoptosis refers to the drooping of inferior displacement of the upper eyelid obstructing the visual axis. Hung et al[22] used an AI system to identify blepharoptosis in clinical photographs and achieved 92% sensitivity and 88% specificity. Tabuchi et al[23] developed a smartphone application that used AI to automatically detect blepharoptosis in facial images; the accuracy was 83% and the area under the curve (AUC) was 0.9. Hung et al[24] used an AI model to identify referable blepharoptosis using facial images; the model performed better than a non-ophthalmic physician. Lou et al[25] used AI to automatically measure eyelid morphological properties before and after blepharoptosis surgery and then compared the results with

those of manual measurements. The interclass correlation coefficient between the two methods for measurement of MRD 1 and 2 ranged from 0.93 to 0.97. Bahçeci Şimşek et al[26] analyzed surgical outcomes after upper eyelid surgery (blepharoplasty and Müller's muscle-conjunctival resection) using AI facial landmark detection based on palpebral distance, eye-opening area, and average brow height. Qu et al[27] used AI-based facial images to assess blepharoplasty outcomes in terms of lower eyelid skin wrinkles, eyelid lacrimal sulci, skin gloss, and aesthetic scores. Sun et al[28] used fully automatic postoperative appearance prediction based on facial images and reported an overall performance of 86% in predicting postoperative appearance after blepharoptosis surgery. AI based on facial images can detect blepharoptosis and predict postoperative appearance after upper eyelid surgery.

Thyroid eye disease

TED is an autoimmune inflammatory disease that occurs in up to 40% of patients with Graves' disease; it is the most common orbital disorder in adults.[29] Prompt diagnosis and treatment are essential because mild disease can progress to sight-threatening conditions such as exposure keratopathy and dysthyroid optic neuropathy.[30] Yoo et al[31] used a deep learning model to predict postoperative appearance (after orbital decompression) in patients with TED using external ocular images. Subjective quality assessment by three ophthalmologists showed promising results; AI can be a supportive tool for prediction of postoperative images and decision making. Moon et al[32] used a machine learning system to detect TED and predict the clinical activity score (CAS) using external photographs. The system achieved 88% sensitivity and 87% specificity for TED detection and predicted the CAS within one point of the reference in up to 85% of patients. Karlin et al[33] used AI to detect TED and differentiate severity using external photographs and reported 85% accuracy, with higher recall for active cases. Huang et al[34] used an AI network to detect TED based on nine eye positions; the network displayed an average AUC exceeding 0.85. Shao et al[35] used a deep learning system to automatically measure eyelid morphology in TED patients and reported strong agreement between automatic and manual measurements. The use of AI systems to detect and evaluate TED may enable timely diagnosis and management.

Eyelid tumors

Eyelid tumors constitute 5% to 10% of all skin tumors, and timely diagnosis is important to minimize both morbidity and mortality.[36] Typically, an eyelid tumor is detected during eyelid examination, and histopathological examination is required to confirm the diagnosis. Adamopoulos et al[37] used an AI system to identify eyelid basal cell carcinoma using external photographs and reported a maximum accuracy of 100%. Li et al[38] used AI to distinguish malignant and benign eyelid tumors based on external photographs and reported a maximum accuracy of 81.8%. Hui et al[39] used an AI system to differentiate malignant from benign eyelid tumors using facial images and exhibited a maximum accuracy of 81%; malignant tumor images comprised basal cell carcinoma (49%), sebaceous adenocarcinoma (26%), squamous cell carcinoma (10%), and melanoma (7%). Lee et al[40] used an AI network to differentiate malignant from benign/no eyelid lesions; the mean AUCs of the two convolutional neural network (CNN) models were 0.91 and 0.95. Patients with eyelid tumors may benefit from AI that uses facial images to identify high-risk lesions for early referral.

Keratitis

Keratitis is a major cause of visual impairment and can rapidly progress to corneal perforation and vision loss if left undiagnosed; early detection and management can halt disease progression and improve visual outcomes.[41] Infectious keratitis can be classified as bacterial, fungal, parasitic, and viral; identification of the causative agent is important for clinical management.[41] Xu et al[42] first described an AI system for keratitis diagnosis based on slit-lamp images solely and reported 80% accuracy, which was significantly higher than the 49.27%±11.5% by human ophthalmologists. Ji et al[43] developed a multi-attribute AI network based on anterior segment images and reported an average diagnostic accuracy of 84.89% and a maximum accuracy of 89.51%. Kuo et al[44] compared the performance of various deep learning algorithms in diagnosing bacterial keratitis using external eye photographs; the diagnostic accuracies of all models (69%-72%) were comparable to those of ophthalmologists (66%-74%), with the EfficientNet B3 exhibiting the best average AUC (74% sensitivity, 64% specificity, and 77% positive and 61% negative predictive values). Natarajan et al[45] used an AI system to detect viral keratitis based on slit-lamp images and reported a maximum accuracy of 72%. Hung et al[46] used an AI system based on slit-lamp images to differentiate bacterial from fungal keratitis and reported a maximum accuracy of 80.0% (79.6% to 95.9% for bacterial keratitis and 26.3% to 65.8% for fungal keratitis). Redd et al[47] developed a corneal photograph-based AI model to differentiate bacterial from fungal corneal ulcers; the best-performing model achieved a maximum AUC of 0.83, compared with 0.42 to 0.79 by human experts. Zhang et al[48] used a deep learning system and reported a maximum diagnostic accuracy of 77.08% for infectious keratitis (70.27% for bacterial keratitis, 77.71% for fungal keratitis, 83.81% for *Acanthamoeba* keratitis, and 79.31% for herpes simplex keratitis). Hu et al[49] evaluated six deep learning algorithms based on slit-lamp images and reported a maximum accuracy of 0.735 and a maximum AUC of 0.85 (0.87 for viral keratitis, 0.87 for fungal keratitis, and 0.64 for bacterial keratitis). Kogachi et al[50] used CNNs to differentiate culture-positive from culture-negative infectious keratitis based on corneal photographs; the CNNs failed to detect morphological differences between culture-positive and culture-negative statuses on external photographs. Loo et al[51] used AI to identify biomarkers of infectious keratitis using external photographs and reported good accuracy (Dice coefficient 0.62-0.95); these biomarkers were strongly correlated (0.84) with best-corrected visual acuity (BCVA).[52] AI can facilitate diagnosing infectious keratitis and identifying the causative pathogen based on external photographs.

Table 1. Summary of studies included in the systematic review

Study	Study aims	Outcome measures	Sample size	Origin of images	Algorithm/ architecture
Measurement of eyelid/periorbital parameters					
Moriyama et al,[16] 2006	To propose a system for detailed analysis of the eye region	Accuracy by comparing positions of model points for upper and lower eyelids, as well as iris center	577 images	-	Generative eye region model
Thomas et al,[17] 2020	To determine whether OpenFace (AI) can extract clinically useful measurements from images before and after ptosis correction	Agreement in interpupillary distance to vertical palpebral aperture ratio between AI and clinicians: Bland-Altman plots	32 patients	-	-
Van Brummen et al,[18] 2021	To develop an AI tool for standardized objective assessment of eyelid and periorbital soft tissue position	Accuracy of segmentation: Dice coefficient; agreement between graders: Bland-Altman plots, mean absolute difference, ICC	418 images (retrospective), 42 images (prospective); training/ validation size: 397 (80%/20%); test size: 21	United States	-
Chen et al,[19] 2021	To propose the first smartphone-based AI-assisted image processing algorithm for measurements of MRD 1 and 2 and levator function	Pearson correlation coefficients: agreement between model and gold standard in terms of ICC, mean absolute error, and limits of agreement	822 eyes in 411 participants; training size: 72%; validation size: 18%; test size: 10%	Taiwan	-
Cao et al,[20] 2021	To propose a deep learning approach for automatic and objective evaluation of morphologic eyelid features using two-dimensional digital photographs, and to assess agreement between automatic and manual measurements	Accuracy of model: Dice coefficient; agreement between manual and automatic MRDs: Spearman correlation coefficient, intraclass correlation coefficient, Bland-Altman plots	406 eyes in 203 normal participants; automatic morphologic measurement of eyelids: 203; automatic eyelid and cornea identification network: training size: 872; validation size: 220; test size: 276	China	-
Zhu et al,[21] 2022	To develop an automated algorithm for measuring ophthalmic parameters to facilitate diagnosis of ptosis, eyelid retraction, and other eye pathologies	Object detection: recall, precision, accuracy, IoU; parameter measurement results: recall, precision, accuracy, IoU	8,200 images; training size: 75%; validation size: 10%; test size: 15%	China	-
Blepharoptosis					
Hung et al,[22] 2021	To develop an algorithm for accurate identification of blepharoptosis from clinical photographs	Accuracy, sensitivity, specificity, PPV, NPV, F1 score, AUC	500 images; training size: 136 normal, 177 blepharoptosis; validation size: 34 normal, 45 blepharoptosis; test size: 18 normal, 24 blepharoptosis	Taiwan	-
Tabuchi et al,[23] 2022	To assess AI performance in automated classification of images taken using a tablet for individuals with blepharoptosis and with normal eyelid	Accuracy, sensitivity, specificity, AUC	1276 images of 606 participants (624 from 347 blepharoptosis cases, 652 from 367 normal participants)	Japan	-
Hung et al,[24] 2022	To develop an AI model that accurately and automatically identifies referable blepharoptosis, then compare its performance with that of non-ophthalmic physicians	Accuracy, sensitivity, specificity, AUC	782 images; training size: 587; validation size: 145; test size: 25 ptotic eyes, 25 healthy eyes	-	-
Lou et al,[25] 2021	To propose a novel deep learning image analysis method that automatically measures eyelid morphological properties before and after blepharoptosis surgery	Agreement between manual and automated measurements of MRD 1 and 2: ICCs; automated model reliability: ICCs	135 ptotic eyes in 103 patients; training size: 4.138 eyes in 2069 volunteers; test size: 135 eyes in 103 patients	China	-
Bahçeci Şimşek et al,[26] 2021	To evaluate postoperative changes using a computer vision algorithm for anterior full-face photographs of patients who underwent upper eyelid blepharoplasty surgery with or without Müller's muscle-conjunctival resection	Postoperative change in right eye palpebral distance and left eye palpebral distance; postoperative change in right eye-opening area, left eye-opening area ratio	55 patients	Turkey	-

Table 1. (cont'd)

Study	Study aims	Outcome measures	Sample size	Origin of images	Algorithm/ architecture
Qu et al,[27] 2022	To explore the impact of a multichannel CNN-based eye model on eye plastic surgical repair and aesthetic effects	Reconstruction effects: similarity (overlapping volume), efficiency (required time); surgical results: ocular score, aesthetic score; complication rates	64 patients	China	-
Sun et al,[28] 2022	To automatically predict postoperative appearance after blepharoptosis surgery	Overall prediction performance: eye overlap ratio; local prediction performance: lid contour analysis by midpupil lid distances, absolute error between predicted and actual MRD1; agreement with clinicians: 5-point satisfaction scale, 10-point similarity survey	970 pairs of images of 450 eyes in 362 patients; training/validation size: 895; test size: 75	China	-
Thyroid eye disease					
Yoo et al,[31] 2020	To present a deep learning model for realistic prediction of postoperative appearance after orbital decompression surgery	Performance comparison between adversarial network models: similarity to postoperative images, image quality; TED O classification performance: accuracy, sensitivity, specificity, AUC; subjective quality assessment by ophthalmologists	109 pairs of pre- and post-operative images; training size: 76 pairs; validation size: 76 pairs and 500 synthesized pairs; test size: 33 pairs	-	-
Moon et al,[32] 2022	To develop a machine learning system that mimics an expert's CAS assessment using digital facial images, then evaluate its accuracy for predicting the CAS and diagnosing active TED	Diagnostic performance in identifying active TED: sensitivity, specificity, AUC; diagnostic performance in CAS prediction	1020 patients; training size: 920; test size: 100	Korea	-
Karlin et al,[33] 2022	To describe a deep learning classifier that identifies TED based on facial images	Accuracy, sensitivity, specificity	Training size: 1994 images; test size: 344 images	United States	-
Huang et al,[34] 2022	To establish an intelligent system for TED diagnosis based on facial images	Model ability to conduct binary classification (yes/no): AUC, sensitivity, specificity; accuracy of eye location, corneal and scleral segmentation: IoU	21 840 images of 3120 eyes in 1560 patients; training size: 70%; validation size: 10%; test size: 20%	China	-
Shao et al,[35] 2023	To propose a deep learning approach that automatically measures eyelid morphology in patients with TED	Accuracy of model: Dice coefficients, IoU; measurement agreement between automatic and manual measurements of MRDs: Bland-Altman plots, intraclass correlation coefficients	74 TED, 74 healthy eyes; training size: 18 000 facial images for eye detection, 3452 eye images for eye segmentation; validation size: 3000 facial images for eye detection, 272 eye images for eye segmentation; test size: 9000 and 148 facial images for eye detection, 148 eye images for eye segmentation	China	-
Eyelid tumors					
Adamopoulos et al,[37] 2021	To develop an intelligent system for pattern recognition, identification, and classification of eyelid basal cell carcinoma	Performance: accuracy score on classification	65 images of basal cell carcinoma, 78 images of healthy individuals; training size: 70%; validation size: 30%	Greece	-
Li et al,[38] 2022	To develop an AI system that automatically locates eyelid tumors and distinguishes between malignant and benign eyelid tumors	Diagnostic performance: accuracy, sensitivity, specificity, AUC; agreement with clinicians: unweighted Cohen's kappa coefficients	1533 images; training size: 883; validation size: 168; internal test size: 197; external test size: 285	China	-

Table 1. (cont'd)

Study	Study aims	Outcome measures	Sample size	Origin of images	Algorithm/ architecture
Hui et al,[39] 2022	To develop a deep learning image analysis system for the automatic identification of benign and malignant eyelid tumors	Accuracy, sensitivity, specificity, AUC	309 images of 229 patients; development size: 309; validation size: 36	China	-
Lee et al,[40] 2023	To evaluate deep learning model performance, compared with that of human ophthalmologists, in differentiating eyelid lesions using clinical eyelid photographs	Diagnostic performance: accuracy, sensitivity, specificity, PPV, NPV, AUC	4954 images of 928 patients; training size: 4475; test size: 134	Korea	-
Keratitis					
Xu et al,[42] 2021	To propose a sequential-level deep model that effectively discriminates infectious corneal disease via classification of clinical images	Diagnostic performance: accuracy	2284 images of 867 patients; training size: 1922; test size: 362	China	-
Ji et al,[43] 2022	To propose a multi-task recognition method for automatic diagnosis of keratitis	Diagnostic performance: accuracy, precision, recall, specificity, F1 score	954 images; training size: 668; test size: 286	China	-
Kuo et al,[44] 2021	To compare the performances of various deep learning algorithms for diagnosing bacterial keratitis using external eye photographs	Diagnostic performance: sensitivity, specificity, PPV, NPV, AUC	1512 images of 1512 patients; 5 datasets of 185-186 images of bacteria keratitis and 116-117 images of non-bacterial keratitis; training size: 4 datasets; validation size: 1 dataset	Taiwan	-
Natarajan et al,[45] 2022	To use and study the application of AI-based deep learning algorithms for diagnosing viral keratitis	Diagnostic performance: sensitivity, specificity, AUC	307 images of 285 eyes; training size: 267; test size: 40	India	-
Hung et al,[46] 2021	To develop a deep learning model for identifying bacterial keratitis and fungal keratitis using slit-lamp images	Diagnostic performance: accuracy, AUC	1330 images of 580 patients; training size: 904; validation size: 212; test size: 214	Taiwan	-
Redd et al,[47] 2022	To develop computer vision models for image-based differentiation of bacterial and fungal corneal ulcers, then compare their performances with those of human experts	AUC	980 images of 980 patients; training size: 396; validation size: 50; test size: 100, 80	India	-
Zhang et al,[48] 2022	To construct a deep learning auxiliary diagnostic model for early diagnosis of infectious keratitis	Diagnostic performance: accuracy, AUC	4830 images; training size: 4347; test size: 483; external validation size: 200 images	China	-
Hu et al,[49] 2023	To propose a deep learning system based on slit-lamp images for automatic screening and diagnosis of infectious keratitis	Accuracy, recall, specificity, AUC	2757 images of 744 patients; training size: 1925; validation size: 301; test size: 531	China	VGG-16, ResNet34, Inception-v4, DenseNet121, ViT-Base, EfficientNetV2-M
Kogachi et al,[50] 2023	To determine whether CNNs can detect morphological differences between images of microbiologically positive and negative corneal ulcers	AUC	1970 images of 886 patients; training size: 1590; validation size: 200; test size: 211	India	-
Loo et al,[51] 2021	To propose a fully automatic deep learning algorithm for segmentation of ocular structures and microbial keratitis biomarkers on slit-lamp photography images	Performance: Dice similarity coefficient, Hausdorff distance	133 eyes; training size: 95; validation size: 19; test size: 19	United States, India	-
Loo et al,[52] 2021	To assess the clinical applicability of automatic image analysis in microbial keratitis by evaluating the relationship between BCVA and biomarker measurements on slit-lamp photographs	Performance of automatic segmentation measurement; correlation between measurements and BCVA	76 patients	United States, India	-

Table 1. (cont'd)

Study	Study aims	Outcome measures	Sample size	Origin of images	Algorithm/ architecture
Trachoma					
Kim et al,[55] 2019	To test an automated algorithm in evaluating eyelid photographs for clinical signs of trachoma	Performance: accuracy, sensitivity, specificity; agreement between automated algorithm and expert graders: Cohen's kappa coefficients	1656 images; validation size: 100	Niger, Ethiopia	CNN with 3 stage convolutional layers, fully connected layers, and 2 hidden layers
Socia et al,[56] 2022	To evaluate the plausibility of an AI model for augmenting and replacing human image graders in the evaluation and diagnosis of TF	Diagnostic performance: sensitivity, specificity, PPV; agreement with clinicians: Cohen's kappa coefficient	2299 images; training/validation size: 44 TF; test size: 12 TF; external cohort: 1546; training/ validation size: 421 TF; test size: 106 TF	Tanzania	ResNet101, VGG-16
Pterygium					
Lopez et al,[60] 2019	To present a deep learning method for automatic classification of pterygium and non-pterygium images	Performance: AUC, sensitivity, specificity	3017 images (325 pterygium, 2692 non-pterygium)	Brazil	CNN
Zulkifley et al,[61] 2019	To propose a deep learning approach for automatic detection and localization of pterygium-infected tissues based on color images	Performance: accuracy, sensitivity, specificity	120 images (60 pterygium, 60 normal); training size: 80%; test size: 20%	Australia	Pterygium-Net based on CNN
Zhu et al,[62] 2022	To propose a two-category model and a segmentation model that assist with pterygium diagnosis based on anterior segment images	Performance: sensitivity, specificity, AUC, kappa value; comparison of model performance: mean IoU, IoU, mean average precision, and pixel accuracy	1034 images (517 pterygium, 517 normal); training size: 734 (367 pterygium); test size: 300 (150 pterygium)	China	AlexNet, VGG-16, ResNet18, ResNet50, PSPNet
Wan et al,[63] 2022	To propose a deep learning system for diagnosing and measuring the pathological progress of pterygium with anterior segment images	Performance: Dice coefficient, kappa consistency coefficient	489 images (245 pterygium, 244 normal); training size: 250; test size: 239	China	U-Net++
Fang et al,[64] 2022	To evaluate the performance of deep learning algorithms based on color anterior segment photographs from slit-lamp and hand-held cameras for detecting the presence and extent of pterygium	Detection: AUC, sensitivity, specificity	3132 images of 2932 eyes (1566 pterygium, 1566 non-pterygium); training size: 2503; internal test set size: 629; external test set size: 6311	Singapore	CNN with VGG-16, multilayer perceptron
Hung et al,[65] 2022	To evaluate the efficacy of a deep learning system based on slit-lamp photographs in pterygium grading and recurrence prediction	Grading: sensitivity, specificity, F1 score, accuracy; prediction: sensitivity, specificity, PPV, NPV	237 images of 237 eyes (176 pterygium, 61 non-pterygium); training size: 189 images; testing size: 48 images	Taiwan	DL network with U-Net, multilayer perceptron
Jais et al,[66] 2021	To propose a machine learning model for changes in BCVA after pterygium surgery according to morphological characteristics	Performance: accuracy, sensitivity, specificity	93 images; training size: 90%; test size: 10%	Malaysia	Support Vector Machine, Naive Bayes Classifier, decision tree, logistic regression
Liu et al,[67] 2023	To determine accuracy of a fusion training AI model in pterygium screening and detection using a smartphone	Detection: accuracy; segmentation: F1 score, sensitivity, specificity, AUC	20 987 slit-lamp images; 1094 smartphone images; training size: 15 456; validation size: 3080; test size: 6625	China	RFRC (Faster RCNN based on ResNet101), SRU-Net (U-Net based on SE-ResNet50)
Diabetic retinopathy					
Babenko et al,[68] 2022	To propose a deep learning model trained on external photographs of eyes for the detection of diabetic retinopathy, diabetic macular edema, and poor blood glucose control	Superiority of deep learning model predictions compared with baseline model predictions: AUC, DeLong method; sensitivity, specificity, PPV, NPV	Development size: training set 126 066 patients, tuning set 19 766 patients; validation size (4 sets): 27 415, 5058, 10 402, 6266 patients	United States	Inception-v3

Table 1. (cont'd)

Study	Study aims	Outcome measures	Sample size	Origin of images	Algorithm/ architecture
Cataract					
Kiuchi et al,[70] 2022	To develop an AI system for preoperative safety management in cataract surgery based on facial recognition, laterality confirmation, and intraocular lens parameter verification	Accuracy and authentication rate of facial recognition on the first attempt; cumulative authentication rate after repeated attempts; false rejection rate, false acceptance rate	171 patients (162 patients in facial recognition test)	Japan	ISG-539
Strabismus					
Huang et al,[71] 2021	To provide an automatic strabismus screening method for people in remote areas with limited access to healthcare	Positional similarity estimates of normal and strabismus images (ratio)	60 images (30 strabismus, 30 normal)	Korea	-
Other oculofacial disorders					
Schulz et al,[72] 2023	To determine the feasibility, validity, reliability of clinically meaningful eyelid measurements automatically extracted from videos of individuals with oculofacial disorders	Feasibility, validity, reliability	77 facial nerve palsy, 33 ptosis, 33 TED, 65 controls; 7101 training images	-	Custom program VALID (video analysis of eyelids) based on U-Net
Greene et al,[73] 2019	To compare the sensitivity of a clinician-based tool (eFACE) to a well-established facial palsy intervention (eyelid weight placement) with the sensitivity of an automated facial measurement algorithm (Emotrics)	Palpebral fissure distance reduction	53 patients	United States	Emotrics

Abbreviations: AI=artificial intelligence, AUC=area under the curve, BCVA=best-corrected visual acuity, CAS=clinical activity score, CNN=convolutional neural networks, ICC=intraclass correlation coefficient, IoU=intersection over union, MRD=margin reflex distance, NPV=negative predictive value, PPV=positive predictive value, TED=thyroid eye disease, TF=trachomatous inflammation – follicular

Trachoma

Trachoma is an infection by ocular strains of *Chlamydia trachomatis*, which is readily treatable with azithromycin.[53,54] Clinical signs of trachoma often guide treatment decisions.[54] Kim et al[55] developed a CNN-based automated algorithm based on external eye images to assess clinical signs of trachoma: trachomatous inflammation–follicular (TF) and trachomatous inflammation–intense (TI). Maximum accuracy was 0.70 for TF and 0.85 for TI; agreements between AI and expert graders were κ=0.44 and κ=0.69 for TF and TI, respectively.[55] Socia et al[56] used an AI model to detect TF using external eye images and reported a maximum sensitivity of 95% and positive predictive value of 50% to 70%; the model reduced the burden of skilled image graders by 66% to 75%. AI can assist with clinical assessment of trachoma, reducing the burden on skilled image graders.

Pterygium

Pterygium, a common fibrovascular degeneration disease, is characterized by a wing-shaped conjunctival tissue growth that extends over the adjacent cornea.[57] It is readily treatable with surgery, and its recurrence risk is closely related to the size of the pterygium; thus, early identification and grading of pterygium are essential.[58,59] Lopez et al[60] developed a deep learning model for pterygium identification using external eye photographs in two color formats: RGB (ie, red, green, and blue) and grayscale. The model classified images as pterygium or non-pterygium with an AUC of 99.4%. Similarly, Zulkifley et al[61] constructed a deep learning model based on color photographs of the eye to detect pterygium, with 95% sensitivity and 98% sensitivity; the model simultaneously localized pterygium tissues with 81% accuracy. Zhu et al[62] developed a two-category and segmentation-based model of pterygium using anterior segment photographs; the model had 99.0% diagnostic accuracy, 98.7% sensitivity, and 99.3% specificity. In addition, the model can be used to stratify pterygium severity and risk. Wan et al[63] used deep learning techniques to measure pterygium severity in terms of the width of corneal invasion by pterygium and reported Dice coefficients of 0.902 to 0.962 and a kappa coefficient of 0.918. Fang et al[64] developed a deep learning algorithm based on color anterior segment photographs taken from slit-lamp and hand-held cameras to detect referable pterygium and reported AUCs of 98.5% to 99.5%. Hung et al[65] applied deep learning on slit-lamp photographs for pterygium grading and recurrence risk prediction and reported 86.7% to 91.7% accuracy for grading and 81.8% specificity and 66.7% sensitivity for prediction. Jais et al[66]

Table 2. Risk of bias assessment of included studies

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Measurement of eyelid/periorbital parameters							
Moriyama et al,[16] 2006	Low	Low	Unclear	Unclear	Low	Low	Unclear
Thomas et al,[17] 2020	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Van Brummen et al,[18] 2021	Low	Low	High	Low	Unclear	Low	High
Chen et al,[19] 2021	Low	Low	Low	Low	Unclear	Low	Low
Cao et al,[20] 2021	Low	Low	Low	Low	High	Low	Low
Zhu et al,[21] 2022	Unclear	Low	Low	Low	Unclear	Low	Low
Blepharoptosis							
Hung et al,[22] 2021	Low	Low	Low	Low	High	Low	Low
Tabuchi et al,[23] 2022	Unclear	Low	Low	Low	High	Low	Low
Hung et al,[24] 2022	Low	Low	Low	Low	Unclear	Low	Low
Lou et al,[25] 2021	Low	Low	Low	Low	Unclear	Unclear	Low
Bahçeci Şimşek et al,[26] 2021	Low	Low	Low	Low	Low	Low	Low
Qu et al,[27] 2022	Low	Low	Unclear	Unclear	Unclear	Low	High
Sun et al,[28] 2022	Unclear	Unclear	High	Low	High	High	High
Thyroid eye disease							
Yoo et al,[31] 2020	Unclear	Low	Unclear	Low	Unclear	Low	Unclear
Moon et al,[32] 2022	Low	Low	Low	Unclear	Low	Low	Low
Karlin et al,[33] 2022	Low	Low	Low	High	Unclear	Low	Low
Huang et al,[34] 2022	Low	Low	Low	Low	Low	Unclear	Low
Shao et al,[35] 2023	Low	Low	Low	Low	Low	Low	Low
Eyelid tumors							
Adamopoulos et al,[37] 2021	Unclear	Low	High	High	Unclear	Low	Unclear
Li et al,[38] 2022	Low	Low	Low	High	High	Unclear	Low
Hui et al,[39] 2022	Low	Low	Low	High	High	Low	Low
Lee et al,[40] 2023	Low	Low	Low	Low	Unclear	Low	Low
Keratitis							
Xu et al,[42] 2021	Low	Low	Low	High	Unclear	Low	Low
Ji et al,[43] 2022	Low	Low	Low	Low	Unclear	Low	Low
Kuo et al,[44] 2021	Low	Low	High	High	Unclear	Low	Unclear
Natarajan et al,[45] 2022	Low	Low	Low	Low	Unclear	Low	Low
Hung et al,[46] 2021	Unclear	Low	Low	Low	Unclear	Unclear	Low
Redd et al,[47] 2022	Unclear	Low	Low	Unclear	Unclear	Low	Unclear
Zhang et al,[48] 2022	Unclear	Low	Low	Unclear	Unclear	Low	Low
Hu et al,[49] 2023	Low	Low	Low	Low	Unclear	Unclear	Low
Kogachi et al,[50] 2023	Low	Low	Unclear	Low	Unclear	Low	Unclear
Loo et al,[51] 2021	Low	Low	Unclear	Unclear	Low	Low	Low
Loo et al,[52] 2021	Low	Low	Low	Unclear	Low	Low	Low

Table 2. (cont'd)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Trachoma							
Kim et al,[55] 2019	Low	Low	Low	Low	Low	Low	Low
Socia et al,[56] 2022	Unclear	Low	Low	Unclear	Unclear	Low	Low
Pterygium							
Lopez et al,[60] 2019	Unclear	Unclear	Low	Low	High	High	Low
Zulkifley et al,[61] 2019	Unclear	Low	Low	Unclear	High	Low	Low
Zhu et al,[62] 2022	Unclear	Low	Low	Unclear	Unclear	Low	Low
Wan et al,[63] 2022	Unclear	Low	Low	Unclear	Unclear	Low	Low
Fang et al,[64] 2022	Low	Low	Low	Low	Low	Low	Low
Hung et al,[65] 2022	Unclear	Low	Low	Low	Low	Unclear	Low
Jais et al,[66] 2021	Unclear	Low	High	Unclear	Unclear	Low	High
Liu et al,[67] 2023	Unclear	Low	Low	Low	Low	Low	Low
Diabetic retinopathy							
Babenko et al,[68] 2022	Unclear	High	Low	Low	Unclear	High	Low
Cataract							
Kiuchi et al,[70] 2022	High	Low	Unclear	Unclear	High	Unclear	Unclear
Strabismus							
Huang et al,[71] 2021	Unclear	Low	High	High	Unclear	Low	High
Other oculofacial disorders							
Schulz et al,[72] 2023	Low	Low	High	High	High	Low	High
Greene et al,[73] 2019	Low	Low	High	Low	Unclear	Low	Unclear

evaluated the performance of four machine learning models in postoperative classification of changes in BCVA according to pterygium characteristics on external photographs; the best-performing model (ie, Support Vector Machine) achieved 94.4% accuracy, 100% specificity, and 92.1% sensitivity. Liu et al[67] trained an AI fusion model using slit-lamp and smartphone images to detect and grade pterygium and reported 92.38% accuracy (AUC=0.94) with smartphone-based images and 94.29% accuracy (AUC=0.96) with slit-lamp images. These findings support the use of AI systems based on camera and slit-lamp-based images for pterygium screening and severity grading.

Diabetic retinopathy

Diabetic retinopathy screening usually requires a fundus examination or fundus photographs. Babenko et al[68] used an AI system that assessed pupil size, conjunctival vessel caliber, and tortuosity based on external photographs of the eyes to detect diabetic retinopathy, diabetic macular edema, and poor blood glucose control; its predictive performance was better than that of logistic regression models based on demographic and medical history data. Predictions could be generalized to patients in various diabetic retinopathy screening programs. Their AI model achieved superior prediction, compared with the baseline model.

Cataract

In ophthalmic surgery, common types of surgical confusion include implantation of the wrong intraocular lens, operation on the wrong eye, treatment of the wrong patient, and performance of the wrong procedure.[69] Kiuchi et al[70] developed an AI system for preoperative safety management in cataract surgery, utilizing external photographs to confirm patient identity. Authentication rates during initial and subsequent attempts were 92.0% and 96.3%, respectively. When combined with laterality confirmation and intraocular lens parameter verification by AI, the false rejection rate and false acceptance rate were both 0%. Implementation of AI in ophthalmic surgery can improve preoperative safety management and reduce preventable instances of surgical confusion.

Strabismus

Strabismus is a condition in which the eyes are not properly aligned with each other; this misalignment can cause double vision, loss of stereopsis, and suppression. Huang et al[71] trained an AI system with frontal facial images to calculate the distances from the pupil center to the medial and lateral canthi and measure deviation in the positional similarity of the two eyes for strabismus screening. The results were promising that the system could serve as a strabismus screening tool for patients living in remote areas.

Other oculofacial disorders

Schulz et al[72] measured eyelid parameters (MRD 1 and 2, blink lagophthalmos, and ocular surface area exposure) on facial videos in patients with facial nerve palsy or TED and reported good reliability and validity. Greene et al[73] used an automated facial measurement algorithm (Emotrics) for eyelid parameters in patients with unilateral facial palsy who received an eyelid weight; the agreement between measurements using the clinician-graded facial function scale (eFACE) and Emotrics measurements was good.

Discussion

This systematic review showed that AI using external photographs exhibits high accuracy in measuring periorbital parameters and in detecting a wide range of ophthalmic diseases such as TED, blepharoptosis, eyelid tumors, keratitis, trachoma, pterygium, strabismus, and diabetic retinopathy. AI can grade the severity of diseases such as TED, trachoma, and pterygium and can differentiate various eyelid tumor and keratitis types based on external photographs. Overall, external photographs provide a rich source of information for AI algorithms, which can be applied to a wide range of ophthalmic conditions.

AI has an increasing role in ophthalmology, mainly due to advances in multimodal imaging. Deep learning systems can identify vision-threatening diabetic retinopathy and age-related macular degeneration using fundus photographs and OCT images, thereby preventing treatment delays.[74,75] Diagnosing retinopathy of prematurity is challenging for ophthalmology trainees; AI can distinguish the disease using fundus photographs, thereby improving diagnostic accuracy and avoiding treatment delays.[76] AI can predict disease severity and determine disease progression in glaucoma through analyses of the visual field and the optic nerve structure's retinal nerve fiber on OCT or fundus photographs.[77,78] In recent years, external photographs have been increasingly used in ophthalmology; external photographs have great potential to serve as reliable screening tools, thereby reducing waiting time, enhancing management, and improving outcomes.

Deep-learning models mimic the diagnostic approaches of ophthalmologists, and classifiers can associate features of ophthalmic diseases at periorbital landmarks within image datasets for disease diagnosis. For example, eyelid signs are the most common presenting sign in TED. AI can detect these signs using external photographs based on eyelid parameters that correspond to areas emphasized by ophthalmologists. Although TED diagnosis is usually confirmed through clinical examination, a survey study in the United Kingdom revealed that the initial diagnosis of TED was incorrect in 58% of patients, and 25% of patients had a 1-year delay in diagnosis.[79] Deep learning systems reported thus far have demonstrated promising performance in identifying new cases of TED, enabling the prioritization of early-onset and urgent-care cases.

AI screening tools can reduce social inequality by facilitating access to healthcare services. Patients with low socioeconomic status and low health literacy may have difficulties accessing healthcare services. The use of AI in disease detection and severity grading may help prioritize patients who need early eye care to attend specialty clinics, especially those living in rural regions. A reliable screening tool enables timely detection and reduces morbidity, especially in cases of TED and eyelid tumors as well as other sight-threatening but readily treatable conditions such as keratitis, trachoma, and pterygium. Initial screening of photographs taken by smartphone can be conducted without sophisticated equipment, thereby enhancing convenience and accessibility of healthcare services. Additionally, AI can enhance the personalization of treatment plans. For example, patients undergoing blepharoptosis correction may receive AI prediction of their postoperative appearance; this can be an adjunctive tool for preoperative assessment in clinical settings. Taken together, deep learning systems offer a positive outlook regarding widespread clinical application of AI.

Despite encouraging results in the use of AI to detect ophthalmic conditions based on external photographs, several challenges must be addressed before its implementation in real-world settings. Major foreseeable issues include standardization, validation, applicability, and ethical concerns.[80] Standardization remains the greatest challenge because external photographs are highly operator-dependent and easily affected by lighting conditions[35]; this is compounded by the subjectivity of image quality and the technical demands of AI programs. Standardized protocols for photograph capture and analysis, as well as objective thresholds for quality control, should be established to reduce inter-operator variability and ensure consistency.[81-83] Further training of models with images of variable quality such as those captured at different angles and under different lighting conditions is recommended.[28,33] Furthermore, most studies have targeted Asian populations, and there is a lack of studies targeting Black or Hispanic populations. This may decrease generalizability in terms of applicability and feasibility within these populations. Large-scale multi-country collaborations are needed to ensure that AI algorithms are reliable across diverse settings in real-world environments.[23,24,38,40,47,64] Furthermore, ethical issues related to the use of facial photographs are expected. Compared with OCT and fundus photographs, external photographs are more recognizable and identifiable, leading

to privacy concerns. Strict compliance with regulations on data collection, storage, and use transparency is essential.

To enhance clinical relevance of AI models as screening tools, training AI models with larger numbers of early-stage lesions can improve their sensitivity to more subtle disease processes.[32,40] Incorporation of clinical information (such as chief complaints and medical histories) into AI models may better mimic the clinical-reasoning process during identification and classification of ophthalmic diseases.[34,39,67] To expand the use of AI beyond clinical settings, incorporation of smartphones and cameras as less-specialized initial screening tools is suggested.[39,65,67] The fusion training model that combines high-quality slit-lamp images with external photographs enables high-accuracy detection and grading for initial screening by smartphone.[67] Future research may focus on the use of AI in community settings and beyond.

Overall, AI has demonstrated promising performance in the detection and classification of various ophthalmic conditions based on external photographs; it can serve as an inexpensive and convenient tool for patients to access healthcare services. Further studies are needed to confirm the role of deep learning methods in improving diagnostic accuracy and clinical applicability.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an advisor or editor of the journal, CPP and KKLC were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

References

1. *Shen Y, Xiao T, Yi S, Chen D, Wang X, Li H. Person re-identification with deep Kronecker-product matching and group-shuffling random walk. IEEE Trans Pattern Anal Mach Intell 2021;43:1649-65.* Crossref
2. *Huang Z, Yu Y, Xu J, Ni F, Le X. PF-Net: point fractal network for 3D point cloud completion. In: Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition; 2020: 7662-70.* Crossref
3. *Gargeya R, Leng T. Automated identification of diabetic retinopathy using deep learning. Ophthalmology 2017;124:962-9.* Crossref
4. *Yousefi S, Elze T, Pasquale LR, et al. Monitoring glaucomatous functional loss using an artificial intelligence-enabled dashboard. Ophthalmology 2020;127:1170-8.* Crossref
5. *Schmidt-Erfurth U, Vogl WD, Jampol LM, Bogunović H. Application of automated quantification of fluid volumes to anti-VEGF therapy of neovascular age-related macular degeneration. Ophthalmology 2020;127:1211-9.* Crossref
6. *Du R, Xie S, Fang Y, et al. Deep learning approach for automated detection of myopic maculopathy and pathologic myopia in fundus images. Ophthalmol Retina 2021;5:1235-44.* Crossref
7. *Roomaney I, Nyirenda C, Chetty M. Facial imaging to screen for fetal alcohol spectrum disorder: a scoping review. Alcohol Clin Exp Res 2022;46:1166-80.* Crossref
8. *Dias R, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. Genome Med 2019;11:70.* Crossref
9. *Qin B, Liang L, Wu J, Quan Q, Wang Z, Li D. Automatic identification of Down syndrome using facial images with deep convolutional neural network. Diagnostics (Basel) 2020;10:487.* Crossref
10. *Mukhiddinov M, Djuraev O, Akhmedov F, Mukhamadiyev A, Cho J. Masked face emotion recognition based on facial landmarks and deep learning approaches for visually impaired people. Sensors (Basel) 2023;23:1080.* Crossref
11. *Debnath T, Reza MM, Rahman A, Beheshti A, Band SS, Alinejad-Rokny H. Four-layer ConvNet to facial emotion recognition with minimal epochs and the significance of data diversity. Sci Rep 2022;12:6991.* Crossref
12. *Kizilgul M, Karakis R, Dogan N, et al. Real-time detection of acromegaly from facial images with artificial intelligence. Eur J Endocrinol 2023;188:lvad005.* Crossref
13. *Goetz RK, Hughes FE, Duignan ES, et al. A template for reducing ophthalmology outpatient waiting times: community ophthalmic care. Ir J Med Sci 2018;187:237-41.* Crossref
14. *Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.* Crossref
15. *Starck WJ, Griffin JE Jr, Epker BN. Objective evaluation of the eyelids and eyebrows after blepharoplasty. J Oral Maxillofac Surg 1996;54:297-303.* Crossref
16. *Moriyama T, Kanade T, Xiao J, Cohn JF. Meticulously detailed eye region model and its application to analysis of facial images. IEEE Trans Pattern Anal Mach Intell 2006;28:738-52.* Crossref
17. *Thomas PBM, Gunasekera CD, Kang S, Baltrusaitis T. An artificial intelligence approach to the assessment of abnormal lid position. Plast Reconstr Surg Glob Open 2020;8:e3089.* Crossref
18. *Van Brummen A, Owen JP, Spaide T, et al. PeriorbitAI: artificial intelligence automation of eyelid and periorbital measurements. Am J Ophthalmol 2021;230:285-96.* Crossref
19. *Chen HC, Tzeng SS, Hsiao YC, Chen RF, Hung EC, Lee OK. Smartphone-based artificial intelligence-assisted prediction*

for eyelid measurements: algorithm development and observational validation study. JMIR Mhealth Uhealth 2021;9:e32444. Crossref
20. *Cao J, Lou L, You K, et al. A novel automatic morphologic analysis of eyelids based on deep learning methods. Curr Eye Res 2021;46:1495-502.* Crossref
21. *Zhu X, Song X, Min X, et al. Calculation of ophthalmic diagnostic parameters on a single eye image based on deep neural network. Multimed Tools Appl 2022;81:2311-31.* Crossref
22. *Hung JY, Perera C, Chen KW, et al. A deep learning approach to identify blepharoptosis by convolutional neural networks. Int J Med Inform 2021;148:104402.* Crossref
23. *Tabuchi H, Nagasato D, Masumoto H, et al. Developing an iOS application that uses machine learning for the automated diagnosis of blepharoptosis. Graefes Arch Clin Exp Ophthalmol 2022;260:1329-35.* Crossref
24. *Hung JY, Chen KW, Perera C, et al. An outperforming artificial intelligence model to identify referable blepharoptosis for general practitioners. J Pers Med 2022;12:283.* Crossref
25. *Lou L, Cao J, Wang Y, et al. Deep learning-based image analysis for automated measurement of eyelid morphology before and after blepharoptosis surgery. Ann Med 2021;53:2278-85.* Crossref
26. *Bahçeci Şimşek İ, Şirolu C. Analysis of surgical outcome after upper eyelid surgery by computer vision algorithm using face and facial landmark detection. Graefes Arch Clin Exp Ophthalmol 2021;259:3119-25.* Crossref
27. *Qu Y, Lin B, Li S, et al. Effect of multichannel convolutional neural network-based model on the repair and aesthetic effect of eye plastic surgery patients. Comput Math Methods Med 2022;2022:5315146.* Crossref
28. *Sun Y, Huang X, Zhang Q, et al. A fully automatic postoperative appearance prediction system for blepharoptosis surgery with image-based deep learning. Ophthalmol Sci 2022;2:100169.* Crossref
29. *Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. N Engl J Med 1993;329:1468-75.* Crossref
30. *Bartalena L, Kahaly GJ, Baldeschi L, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol 2021;185:G43-G67.* Crossref
31. *Yoo TK, Choi JY, Kim HK. A generative adversarial network approach to predicting postoperative appearance after orbital decompression surgery for thyroid eye disease. Comput Biol Med 2020;118:103628.* Crossref
32. *Moon JH, Shin K, Lee GM, et al. Machine learning-assisted system using digital facial images to predict the clinical activity score in thyroid-associated orbitopathy. Sci Rep 2022;12:22085.* Crossref
33. *Karlin J, Gai L, LaPierre N, et al. Ensemble neural network model for detecting thyroid eye disease using external photographs. Br J Ophthalmol 2023;107:1722-9.* Crossref
34. *Huang X, Ju L, Li J, et al. An intelligent diagnostic system for thyroid-associated ophthalmopathy based on facial images. Front Med (Lausanne) 2022;9:920716.* Crossref
35. *Shao J, Huang X, Gao T, et al. Deep learning-based image analysis of eyelid morphology in thyroid-associated ophthalmopathy. Quant Imaging Med Surg 2023;13:1592-604.* Crossref
36. *Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. A retrospective study of 5504 cases and review of literature. Am J Dermatopathol 2009;31:256-62.* Crossref
37. *Adamopoulos A, Chatzopoulos EG, Anastassopoulos G, Detorakis E. Eyelid basal cell carcinoma classification using shallow and deep learning artificial neural networks. Evol Syst (Berl) 2021;12:583-90.* Crossref
38. *Li Z, Qiang W, Chen H, et al. Artificial intelligence to detect malignant eyelid tumors from photographic images. NPJ Digit Med 2022;5:23.* Crossref
39. *Hui S, Dong L, Zhang K, Nie Z. Noninvasive identification of benign and malignant eyelid tumors using clinical images via deep learning system. J Big Data 2022;9:84.* Crossref
40. *Lee MJ, Yang MK, Khwarg SI, et al. Differentiating malignant and benign eyelid lesions using deep learning. Sci Rep 2023;13:4103.* Crossref
41. *Austin A, Lietman T, Rose-Nussbaumer J. Update on the management of infectious keratitis. Ophthalmology 2017;124:1678-89.* Crossref
42. *Xu Y, Kong M, Xie W, et al. Deep sequential feature learning in clinical image classification of infectious keratitis. Engineering 2021;7:1002-10.* Crossref
43. *Ji Q, Jiang Y, Qu L, Yang Q, Zhang H. An image diagnosis algorithm for keratitis based on deep learning. Neural Process Lett 2022;54:2007-24.* Crossref
44. *Kuo MT, Hsu BW, Lin YS, et al. Comparisons of deep learning algorithms for diagnosing bacterial keratitis via external eye photographs. Sci Rep 2021;11:24227.* Crossref
45. *Natarajan R, Matai HD, Raman S, et al. Advances in the diagnosis of herpes simplex stromal necrotising keratitis: a feasibility study on deep learning approach. Indian J Ophthalmol 2022;70:3279-83.* Crossref
46. *Hung N, Shih AK, Lin C, et al. Using slit-lamp images for deep learning-based identification of bacterial and fungal keratitis: model development and validation with different convolutional neural networks. Diagnostics (Basel) 2021;11:1246.* Crossref
47. *Redd TK, Prajna NV, Srinivasan M, et al. Image-based differentiation of bacterial and fungal keratitis using deep convolutional neural networks. Ophthalmol Sci 2022;2:100119.* Crossref
48. *Zhang Z, Wang H, Wang S, et al. Deep learning-based classification of infectious keratitis on slit-lamp images. Ther Adv Chronic Dis 2022;13:20406223221136071.* Crossref
49. *Hu S, Sun Y, Li J, et al. Automatic diagnosis of infectious keratitis based on slit lamp images analysis. J Pers Med 2023;13:519.* Crossref
50. *Kogachi K, Lalitha P, Prajna NV, et al. Deep convolutional neural networks detect no morphological differences between culture-positive and culture-negative infectious keratitis images. Transl Vis Sci Technol 2023;12:12.* Crossref
51. *Loo J, Kriegel MF, Tuohy MM, et al. Open-source automatic segmentation of ocular structures and biomarkers of microbial keratitis on slit-lamp photography images using deep learning. IEEE J Biomed Health Inform 2021;25:88-99.* Crossref
52. *Loo J, Woodward MA, Prajna V, et al. Open-source automatic biomarker measurement on slit-lamp photography to estimate visual acuity in microbial keratitis. Transl Vis Sci Technol 2021;10:2.* Crossref
53. *Burton MJ, Mabey DC. The global burden of trachoma: a review. PLoS Negl Trop Dis 2009;3:e460.* Crossref
54. *World Health Organization. Trachoma control. A guide for programme managers. Accessed 19 February 2024. Available from: http://apps.who.int/iris/bitstream/10665/43405/1/9241546905_eng.pdf.*
55. *Kim MC, Okada K, Ryner AM, et al. Sensitivity and specificity of computer vision classification of eyelid photographs for programmatic trachoma assessment. PLoS One 2019;14:e0210463.* Crossref
56. *Socia D, Brady CJ, West SK, Cockrell RC. Detection of trachoma using machine learning approaches. PLoS Negl*

Trop Dis 2022;16:e0010943. Crossref
57. *Chu WK, Choi HL, Bhat AK, Jhanji V. Pterygium: new insights. Eye (Lond) 2020;34:1047-50*. Crossref
58. *Nejima R, Masuda A, Minami K, Mori Y, Hasegawa Y, Miyata K. Topographic changes after excision surgery of primary pterygia and the effect of pterygium size on topographic restoration. Eye Contact Lens 2015;41:58-63*. Crossref
59. *Aidenloo NS, Motarjemizadeh Q, Heidarpanah M. Risk factors for pterygium recurrence after limbal-conjunctival autografting: a retrospective, single-centre investigation. Jpn J Ophthalmol 2018;62:349-56*. Crossref
60. *López YP, Aguilera LR. Automatic classification of pterygium-non pterygium images using deep learning. In: VipIMAGE 2019: 391-400*. Crossref
61. *Zulkifley MA, Abdani SR, Zulkifley NH. Pterygium-Net: a deep learning approach to pterygium detection and localization. Multimed Tools Appl 2019;78:34563-84*. Crossref
62. *Zhu S, Fang X, Qian Y, et al. Pterygium screening and lesion area segmentation based on deep learning. J Healthc Eng 2022;2022:3942110*. Crossref
63. *Wan C, Shao Y, Wang C, Jing J, Yang W. A novel system for measuring pterygium's progress using deep learning. Front Med (Lausanne) 2022;9:819971*. Crossref
64. *Fang X, Deshmukh M, Chee ML, et al. Deep learning algorithms for automatic detection of pterygium using anterior segment photographs from slit-lamp and hand-held cameras. Br J Ophthalmol 2022;106:1642-7*. Crossref
65. *Hung KH, Lin C, Roan J, et al. Application of a deep learning system in pterygium grading and further prediction of recurrence with slit lamp photographs. Diagnostics (Basel) 2022;12:888*. Crossref
66. *Jais FN, Che Azemin MZ, Hilmi MR, Mohd Tamrin MI, Kamal KM. Postsurgery classification of best-corrected visual acuity changes based on pterygium characteristics using the machine learning technique. ScientificWorldJournal 2021;2021:6211006*. Crossref
67. *Liu Y, Xu C, Wang S, et al. Accurate detection and grading of pterygium through smartphone by a fusion training model. Br J Ophthalmol 2023;108:336-42*. Crossref
68. *Babenko B, Mitani A, Traynis I, et al. Detection of signs of disease in external photographs of the eyes via deep learning. Nat Biomed Eng 2022;6:1370-83*. Crossref
69. *Parikh R, Palmer V, Kumar A, Simon JW. Surgical confusions in ophthalmology: description, analysis, and prevention of errors from 2006 through 2017. Ophthalmology 2020;127:296-302*. Crossref
70. *Kiuchi G, Tanabe M, Nagata K, Ishitobi N, Tabuchi H, Oshika T. Deep learning-based system for preoperative safety management in cataract surgery. J Clin Med 2022;11:5397*. Crossref
71. *Huang X, Lee SJ, Kim CZ, Choi SH. An automatic screening method for strabismus detection based on image processing. PLoS One 2021;16:e0255643*. Crossref
72. *Schulz CB, Clarke H, Makuloluwe S, Thomas PB, Kang S. Automated extraction of clinical measures from videos of oculofacial disorders using machine learning: feasibility, validity and reliability. Eye (Lond) 2023;37:2810-6*. Crossref
73. *Greene JJ, Tavares J, Guarin DL, Hadlock T. Clinician and automated assessments of facial function following eyelid weight placement. JAMA Facial Plast Surg 2019;21:387-92*. Crossref
74. *Bellemo V, Lim ZW, Lim G, et al. Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. Lancet Digit Health 2019;1:e35-e44*. Crossref
75. *Dong L, Yang Q, Zhang RH, Wei WB. Artificial intelligence for the detection of age-related macular degeneration in color fundus photographs: a systematic review and meta-analysis. EClinicalMedicine 2021;35:100875*. Crossref
76. *Scruggs BA, Chan RVP, Kalpathy-Cramer J, Chiang MF, Campbell JP. Artificial intelligence in retinopathy of prematurity diagnosis. Transl Vis Sci Technol 2020;9:5*. Crossref
77. *Bojikian KD, Lee CS, Lee AY. Finding glaucoma in color fundus photographs using deep learning. JAMA Ophthalmol 2019;137:1361-2*. Crossref
78. *Zheng C, Johnson TV, Garg A, Boland MV. Artificial intelligence in glaucoma. Curr Opin Ophthalmol 2019;30:97-103*. Crossref
79. *Lim NC, Sundar G, Amrith S, Lee KO. Thyroid eye disease: a Southeast Asian experience. Br J Ophthalmol 2015;99:512-8*. Crossref
80. *He M, Li Z, Liu C, Shi D, Tan Z. Deployment of artificial intelligence in real-world practice: opportunity and challenge. Asia Pac J Ophthalmol (Phila) 2020;9:299-307*. Crossref
81. *Lee JG, Jun S, Cho YW, et al. Deep learning in medical imaging: general overview. Korean J Radiol 2017;18:570-84*. Crossref
82. *He J, Baxter SL, Xu J, Zhou X, Zhang K. The practical implementation of artificial intelligence technologies in medicine. Nat Med 2019;25:30-6*. Crossref
83. *Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med 2019;380:1347-58*. Crossref

REVIEW ARTICLE

Efficacy, safety, and tolerability of pharmacological treatments for moderate-to-severe dry eye disease: a systematic review

Carolyn Yu Tung Wong[1], *MBChB; Justin Man Kit Tong*[2], *MBBS, MRCSEd, M Med Sc (HK), FRCSEd (Ophth), FCOphthHK, FHKAM (Ophthalmology)*
[1]*Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*

Correspondence and reprint requests:
Carolyn Yu Tung Wong, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.
Email: carolcarol.carolyn@gmail.com

Abstract

Dry eye disease is characterized by impaired tear film homeostasis and ocular surface inflammation. Topical ocular medications for moderate-to-severe dry eye disease include hyaluronic acid (HA), cyclosporine A (CsA), serum eyedrops, and lifitegrast. Effective HA-based formulations and regimens include topical aqueous HA 0.15% and 0.18%, HA gel 0.30%, sequential administration of HA 0.30% and 0.15%, a combination of HA 0.15% and polyethylene glycol, and multi-agent eyedrops containing 0.15% HA. Preservative-free hydrocortisone and loteprednol, known as soft steroids, are effective and have a reduced risk of steroid-related adverse effects. Effective CsA formulations include 0.05% CsA gel, CsA nanoemulsions, water-free CsA, and CsA combinations with lubricants (eg, HA). Autologous, allogeneic, and umbilical cord serum eyedrops, as well as the novel lymphocyte function-associated antigen-1 antagonist lifitegrast, are also effective. Various treatment options may improve treatment adherence. Long-term and large-scale studies are required to confirm the therapeutic efficacies of these treatments.

Key words: *Cyclosporine; Dry eye syndromes; Hyaluronic acid; Lifitegrast; Ophthalmic solutions*

Introduction

Dry eye disease (DED) is characterized by tear film instability and ocular surface inflammation, resulting in ocular distress and visual impairment.[1] Despite its increasing incidence worldwide, DED is commonly underdiagnosed.[2-4] Moderate-to-severe DED can result in substantial decreases in productivity and daily activities.[5] Currently, treatments for DED are not standardized.[6,7] In this systematic review, we aimed to analyze the effectiveness and safety of five therapeutic options for moderate-to-severe DED: hyaluronic acid (HA), topical steroids, cyclosporine A (CsA), serum eyedrops, and lifitegrast. Additionally, we sought to provide guidance concerning selection of appropriate treatment options for moderate-to-severe DED. Other treatment options (eg, topical and oral secretagogues, tacrolimus, macrolides, and vitamins A and E) were not included in the analysis owing to the unavailability of secretagogues in

Hong Kong, the specific use of tacrolimus for lid eczema, the targeted nature of macrolides for meibomian gland dysfunction, and the roles of vitamin A and E as additives in lubricants and ointments, respectively.

Methods

On 30 December 2023, we searched PubMed using the keywords 'moderate to severe dry eye disease' AND 'treatment'. We identified 450 randomized controlled studies written in English and published between 2015 and 2023. After excluding duplicates, reviews, editorials, and case reports/series, as well as studies of other treatment options, we included 20 studies related to the five treatment options (HA, topical steroids, CsA, serum eyedrops, and lifitegrast) for moderate-to-severe DED, which was defined as a severity level of ≥2 according to the Dry Eye Workshop I grading scheme.[8]

Hyaluronic acid

HA is a viscoelastic anionic glycosaminoglycan that binds water and resists dehydration, thereby increasing ocular surface lubrication, tear stability, epithelium healing, and relief of DED symptoms.[9,10] Although topical HA at concentrations of 0.1% to 0.2% is effective for milder DEDs,[11-13] its therapeutic efficacy for moderate-to-severe DED remains unclear.

Topical HA at concentrations of 0.15% to 0.30% was effective for moderate-to-severe DED (**Table 1**). Topical 0.15% HA was comparable to 0.05% CsA in terms of improving tear breakup time (TBUT), corneal staining score (CSS1), strip meniscometry score, and ocular surface disease index (OSDI) after 12 weeks (all $p<0.05$).[14] In addition, topical 0.18% HA drops were effective in improving the CSS1, conjunctival staining score, TBUT,

Table 1. Studies of hyaluronic acid for moderate-to-severe dry eye disease

Study	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Lee et al,[14] 2022	438	0.15% HA drop 6 times daily vs 0.05% CsA drop twice + 0.5% carboxymethylcellulose medication 6 times daily vs 0.15% HA 6 times + 0.05% CsA twice daily	Baseline, weeks 4 and 12	0.05% CsA and 0.15% HA were comparable in terms of improvements in CSS1, TBUT, SMS, and OSDI. 0.15% HA was well-tolerated and had lower prevalence of TRAEs.	Different instillation frequencies among groups, short follow-up period, concomitant effect from co-existing carboxymethylcellulose medication
Calonge et al,[15] 2023	70	0.30% HA gel vs 0.18% HA drop 4 to 6 times daily	Baseline, days 35 and 84	0.18% HA improved CSS1, CSS2, TBUT, DEQ-5, and ODSS at 84 days (all $p<0.001$). Both 0.18% HA drop and 0.30% HA gel were comparable in terms of CSS1, CSS2, TBUT, DEQ-5, and ODSS. Both HA formulations were well-tolerated, and no serious TRAEs were reported.	Short follow-up, small sample size, lack of placebo group, different etiologies causing biased results
Jun et al,[16] 2022	76	0.30% HA drop (1 drop) followed by 0.15% HA drop (1 drop) vs 0.30% HA drop (2 drops) vs 0.15% HA drop (2 drops) 4 times daily	Baseline, weeks 4 and 8	Compared with 0.15% and 0.30% HA monotherapies, HA combination therapy is superior in terms of CSS1 ($p<0.001$) and OSDI ($p=0.037$). All formulations were well-tolerated, and no serious TRAEs were reported.	Short follow-up, lack of placebo group, open-label design (participants not blinded)
Labetoulle et al,[17] 2022	78	Polyethylene glycol solution (0.15% HA and 0.5% PEG 8000) vs sodium hyaluronate (0.18% HA) 3 to 6 times daily as needed	Baseline, days 28 and 90	Compared with 0.18% HA monotherapy, polyethylene glycol solution showed greater improvements in OSD-QoL, CSS1, and TBUT at 90 days (all $p<0.05$). Both drops were well-tolerated; no serious TRAEs were reported.	Short follow-up
Roszkowska et al,[18] 2022	4	CXHAL drops vs trehalose drops 4 times daily	Baseline, day 60	At 2 months, CXHAL drops showed significant improvements in SANDE ($p=0.001$), TBUT ($p<0.001$), and staining ($p=0.004$). Both CXHAL and trehalose were generally safe and well-tolerated; no serious TRAEs were reported.	Small sample size, short follow-up

Abbreviations: CsA=cyclosporine A, CSS1=corneal staining score, CSS2=conjunctival staining score, CXHAL=cross-linked hyaluronic acid, trehalose, liposomes, and stearylamine, DEQ-5=5-item Dry Eye Questionnaire, HA=hyaluronic acid, ODSS=ocular dryness symptoms score, OSDI=ocular surface disease index, OSD-QoL=Ocular Surface Disease-Quality of Life, PEG=poly(ethylene glycol), SANDE=Symptom Assessment iN Dry Eye, SMS=strip meniscometry score, TBUT=tear breakup time, TRAE=treatment-related adverse event.

ocular dryness symptoms score, and 5-Item-Dry-Eye-Questionnaire score after 12 weeks (all p<0.001).[15] Both 0.30% HA gel and 0.18% HA aqueous drops improved the CSS1, TBUT, ocular dryness symptoms score, and 5-Item-Dry-Eye-Questionnaire score after 12 weeks (all p<0.001); no dose-response relationship was observed.[15]

A single 0.30% HA drop followed by a single 0.15% HA drop significantly improved signs and symptoms (all p<0.05) and outperformed monotherapy with either HA drop in terms of the CSS1 (p<0.001) and OSDI (p=0.037) at 8 weeks.[16] The effectiveness of HA was not dose-dependent; the combination of 0.30% and 0.15% HA drops outperformed monotherapy with 0.30% HA drop. Compared with 0.18% HA monotherapy, a combination of 0.15% HA and polyethylene glycol resulted in greater improvements in CSS1, TBUT, and Ocular Surface Disease-Quality of Life questionnaire scores at 12 weeks (all p<0.05).[17] CXHAL drops (containing 0.15% cross-linked HA, 3% trehalose, 1% liposomes, and 0.25% stearylamine) significantly improved TBUT (p<0.001), corneoconjunctival staining (p=0.004), and Symptom Assessment in Dry Eye score (p=0.001) at 8 weeks.[18]

Concerning safety and tolerability, 0.15% aqueous HA, 0.18% aqueous HA, 0.30% HA gel, the 0.15% HA and 0.30% HA combination, polyethylene glycol, and CXHAL are well-tolerated and generally safe to use. Most treatment-related adverse events (TRAEs) have been mild to moderate; patients were satisfied with the various HA regimens, formulations, and combinations.

Topical aqueous HA at concentrations of 0.15% and 0.18% is likely to provide effective relief for moderate-to-severe DED. Aqueous HA drops at concentrations of >0.18% have better ocular surface healing effects[11,19,20] but are associated with suboptimal treatment outcomes (eg, hazy vision and ocular discomfort).[19,21,22] HA gels enable administration of higher HA concentrations in a form that patients can tolerate. However, considering the non-dose-dependent relationship, it is unclear whether a higher HA concentration will have a greater therapeutic benefit. HA gels enable longer HA retention when administered before bedtime. Alternatively, combinations of HA with different lubricants can enhance the effects of HA; all-in-one HA drops can increase HA effectiveness while improving patient convenience and satisfaction.

Topical steroids

Topical steroids exert anti-inflammatory effects by reducing cytokine expression, preserving corneal epithelium integrity, enhancing tear production, and decreasing pro-inflammatory cytokine levels in tears.[23-25] However, conventional steroid drops (eg, methylprednisolone and fluorometholone) often have adverse effects such as elevated intraocular pressure (IOP) and cataract development.[26] Newer steroid formulations, known as soft steroids, such as preservative-free hydrocortisone (PFH) and loteprednol can minimize adverse effects while maintaining anti-inflammatory efficacy by limiting penetration through the anterior chamber.[27-29] These newer drugs have reduced risks of elevated IOP and cataract development.

Regarding efficacy, in patients with Sjogren syndrome, a short-term pulsed regimen of topical 0.335% (low-dose) PFH over 3 consecutive months, followed by alternating discontinuation and resumption of treatment in a 1-month interval for 3 months, effectively improved corneoconjunctival staining, tear film osmolarity, and OSDI (all p<0.05) [**Table 2**].[30] Pulsed PFH demonstrated rapid symptom improvement and sustained anti-inflammatory

Table 2. Studies of hyaluronic acid for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Menchini et al,[30] 2023	40 with Sjogren syndrome	Topical PFH for 6 days with a pulsed posology: 3 times daily for 2 days, twice daily for 2 days, and once daily for 2 days for 3 consecutive months, followed by alternating discontinuation and resumption of treatment in a 1-month interval for 3 months	Baseline, months 3 and 6	Topical PFH regimen improved OSDI, CSS1, CSS2, and tear film osmolarity throughout the study period (all p<0.05). There was no significant change in IOP at any timepoint.	Retrospective study design, short follow-up, non-uniform concomitant topical lubricant treatments, lack of control group
Yin et al,[31] 2018	42, including 21 with chronic graft-vs-host-disease	Loteprednol etabonate 0.5% vs artificial tears twice daily	Baseline, week 4	In patients without graft-vs-host disease, loteprednol treatment decreased the mean OSDI score by 34% (p=0.001) and the mean corneal fluorescein staining score by 41% (p=0.02). In patients with graft-vs-host disease, loteprednol treatment led to minimal changes in OSDI (p=0.85) and corneal fluorescein staining (p=0.1).	Small sample size, lack of exclusion criteria concerning pre-existing ophthalmic regimens

Abbreviations: CSS1=corneal staining score, CSS2=conjunctival staining score, IOP=intraocular pressure, OSDI=ocular surface disease index, PFH=preservative-free hydrocortisone.

effects beyond the treatment period; there were no significant differences in OSDI and TBUT values at 3 and 6 months. In patients without graft-vs-host disease, twice-daily application of loteprednol etabonate 0.5% (low-dose) ophthalmic suspension for 4 weeks significantly reduced OSDI (p=0.01) and corneal fluorescein staining (p=0.02).[31] However, patients with graft-vs-host disease experienced minimal changes in OSDI (p=0.1) and corneal fluorescein staining (p=0.85).[31]

Concerning safety, both PFH with pulsed posology and loteprednol etabonate 0.5% drops are generally safe. The topical PFH regimen showed a high level of safety, with no significant changes in IOP.[30] Loteprednol etabonate 0.5% drops had low rates of TRAEs and minimal impact on IOP.[32,33] There were no specific safety concerns associated with the use of loteprednol etabonate 0.5% drops.[31]

PFH drops exhibit efficacy and safety comparable to conventional topical steroid drops (methylprednisolone and fluorometholone) for moderate-to-severe DED, particularly among patients with Sjogren syndrome.[30] Additionally, short-term (4 weeks) use of topical 0.5% (low-dose) loteprednol etabonate was effective in patients without graft-vs-host disease.[31] PFH drops used in a pulsed regimen demonstrated prolonged efficacy despite treatment cessation.[30] Soft steroids with a pulsed and tapered dosing schedule (6 days/month) can be used in patients with moderate-to-severe DED, especially those with Sjogren syndrome for whom lubricants alone are insufficient.[30] Further research is needed to confirm the role of soft steroids as a transitional therapy before CsA eye drops take full effect. However, in patients with graft-vs-host disease, topical steroids may have reduced efficacy and necessitate more frequent or prolonged treatment.[31] Stronger anti-inflammatory medications, such as CsA and lifitegrast, may be used to manage ocular surface inflammation in these patients.[31]

Cyclosporine A

Topical CsA suppresses inflammatory activities such as interleukin-2-mediated T-cell activation and lymphocyte migration.[34] Although topical 0.05% CsA is effective for moderate-to-severe DED,[35] its aqueous formulation is associated with ocular burning and stinging,[36-38] which reduces patient adherence[39,40] and leads to lower therapeutic effectiveness.[38,41,42]

Novel gel and nanoemulsion formulations of CsA can significantly improve the signs and symptoms of moderate-to-severe DED (**Table 3**).[43-46] Compared with 0.05% aqueous CsA, all 0.05% CsA gel (CyclAGel) regimens (0.05% once daily, 0.05% twice daily, and 0.1% once daily) improved the CSS1, TBUT, and Schirmer test score (ST1) at 12 weeks (all p<0.05).[43] Furthermore, CyclAGels have greater overall effects than aqueous CsA; the once-daily regimen of 0.05% CyclAGel provided the greatest efficacy. In a phase III trial, the once-daily regimen of 0.05% CyclAGel elicited positive clinical response; a higher proportion of patients experienced at least a 1-point improvement in the inferior CSS1 (p<0.0001) and a greater improvement in the ST1 (p<0.05) by day 84, compared with the vehicle.[44] Similarly, a 0.08% CsA nanoemulsion preparation (TJO-087) significantly improved the OSDI, TBUT, CSS1, and ST1 at 32 weeks.[45] A 0.05% CsA micellar nanoparticle preparation yielded superior improvements in the CSS1, ST1, OSDI, and individual dry eye symptom scores, compared with an equivalent dose of aqueous CsA (p<0.05).[46]

In the ESSENCE-2 trial, water-free CsA (0.1%) demonstrated early therapeutic effects on the ocular surface, along with greater improvements in the total corneal fluorescein score at 15 days (p<0.05) and 29 days (p=0.03) and the central corneal fluorescein score at 15 days (p<0.05), compared with the aqueous vehicle.[47] Combinations of lower-concentration CsA with trehalose (0.01% CsA and 3% trehalose; 0.02% CsA and 3% trehalose) resulted in significant improvements in the CSS1, conjunctival staining score, TBUT, and Standard Patient Evaluation of Eye Dryness Questionnaire score (all p<0.05) at 12 weeks.[48] A combination of CsA with HA significantly reduced tear interleukin-6 levels at 1 month, compared with 0.1% CsA monotherapy (p<0.05).[49] The percentages of improvement in the OSDI, TBUT, and ocular staining were consistently greater in the combination treatment group.

All CsA gel regimens and nanoparticle formulations are safe and well-tolerated, as are water-free CsA. No serious TRAEs have been recorded. Two major adverse events were reported in the water-free CsA trial, but they were not linked to the study drug. Patients receiving CsA combination therapies reported high levels of treatment satisfaction and no TRAEs.

Novel CsA formulations and combinations may enhance the effectiveness of topical CsA. Gels and nanoemulsions may improve treatment satisfaction and drug adherence, whereas the water-free formulation enables more rapid onset of therapeutic effects, thereby increasing treatment adherence despite modest TRAEs. The reduced tear interleukin-6 levels suggest that combination therapies can enhance the anti-inflammatory effects of CsA.

Serum eyedrops

Blood derivatives supply tear components (eg, growth factors, vitamins, and proteins) to the ocular surface.[50] Blood sources are from the patient's own peripheral blood (autologous) and donor tissues, particularly allogeneic peripheral blood and umbilical cord blood.[51] These serum eyedrops are intended for patients with severe DEDs who have not responded to HA or CsA.[52]

Autologous serum eyedrops (ASEs), allogeneic serum eyedrops (HSEs), and umbilical cord serum eyedrops (USEs) are effective treatments for moderate-to-severe DED. Both 20% and 50% ASE preparations improved

Table 3. Studies of cyclosporine A for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Significant findings	Limitations
Peng et al,[43] 2021	240	0.05% CyclAGel once daily vs 0.05% CyclAGel twice daily vs 0.1% CyclAGel once daily vs 0.05% Restasis twice daily	Baseline, weeks 2, 6, and 12	Compared with 0.05% aqueous CsA, all 0.05% CyclAGel regimens improved the eye dryness score, dryness symptoms, CSS1, TBUT, and ST1 at 12 weeks (all p<0.05). 0.05% CyclAGel once daily showed the greatest overall efficacy. No serious TRAEs were noted; all CyclAGel regimens were safe and well-tolerated.	Open-label design, biased perception of symptom reporting due to formulation differences
Peng et al,[44] 2022	627	0.05% CyclAGel vs vehicle drops once nightly	Baseline, days 14, 42, and 84	Compared with patients receiving vehicle drops, more patients receiving 0.05% CyclAGel once nightly experienced at least a 1-point improvement in inferior CSS1 (p<0.0001) and a greater improvement in ST1 (p<0.05) by day 84. 0.05% CyclAGel once nightly was well-tolerated, and no serious TRAEs were reported.	Short follow-up, limited inclusion of patients with different DED etiologies
Eom et al,[45] 2023	155	0.08% nanoemulsion CsA (TJO-087) once daily vs 0.05% emulsion CsA twice daily	Baseline, weeks 8, 16, 24, and 32	TJO-087 and CsA 0.05% showed similar improvements in OSDI, TBUT, CSS1, and ST1 at 32 weeks. TJO-087 was well-tolerated, and no serious TRAEs were reported.	Possible unblinding of blinded design, confounding effect from concomitant carboxymethylcellulose medication
Rao et al,[46] 2023	90	0.05% CsA MNP twice daily for the entire period vs 0.05% CsA MNP twice daily for the first 4 weeks and once daily for the remaining period vs 0.05% Restasis twice daily for the entire period	Baseline, weeks 4, 8, 12, and 24	Compared with Restasis, both CsA MNP formulations yielded superior improvements in CSS1, ST1, OSDI, and individual dry eye symptom scores (all p<0.05). No serious TRAEs were reported, and both MNP formulations were well-tolerated.	Endpoints susceptible to bias (eg, symptom score), short follow-up
Akpek et al,[47] 2023	817	Water-free 0.1% CsA drops vs vehicle twice daily	Baseline, days 15 and 29	Water-free CsA yielded superior improvements in total corneal fluorescein score at 15 days (p<0.05) and 29 days (p=0.03) and in central corneal fluorescein score at 15 days (p<0.05). Two serious TRAEs were documented; neither was associated with the study drug.	Inclusion of mainly aqueous-deficient DED patients, short follow-up
Shin et al,[48] 2021	114	HU00701 (0.01% CsA + 3% trehalose) vs HU007 (0.02% CsA + 3% trehalose) vs placebo vs 0.05% Restasis (0.05% CsA)	Baseline, weeks 4, 8, and 12	Both HU00701 and HU007 significantly improved CSS1, CSS2, TBUT, and SPEED score by week 12 (all p<0.05). Both resulted in no major TRAEs and were well-tolerated.	Unclear minimum therapeutic dose of CsA, unclear synergistic effects between CsA and trehalose, phase II study without active competitor, Restasis only served as reference treatment
Priani et al,[49] 2023	20	0.1% CsA vs 0.1% CsA + 0.1% HA 1 drop once daily	Baseline, month 1	Compared with patients receiving CsA 0.1% monotherapy, more patients receiving combination therapy experienced improvements in OSDI, TBUT, ocular staining, and interleukin-6 levels. The CsA/HA combination was generally safe and well-tolerated.	Small sample size, short follow-up period

Abbreviations: CsA=cyclosporine A, CyclAGel=cyclosporine A gel, CSS1=corneal staining score, CSS2=conjunctival staining score, DED=dry eye disease, HA=hyaluronic acid, MNP=micellar nanoparticle, OSDI=ocular surface disease index, SPEED=Standard Patient Evaluation of Eye Dryness, ST1=Schirmer test score, TBUT=tear breakup time, TRAE=treatment-related adverse event.

the subjective and objective parameters of moderate DED (all p<0.05) [**Table 4**].[53] However, only the 50% ASE preparation was effective in improving subjective and objective parameters of severe DED at 12 weeks (all p<0.05). HSEs and ASEs demonstrated similar efficacy in terms of improving the OSDI, TBUT, punctate lesions, and visual acuity by 1 month.[54] USEs and ASEs produced persistent improvements in TBUT and tear protein levels (eg, lysozyme) at 12 weeks.[55] All three types of serum eyedrops were similarly effective in terms of improving TBUT, ST1, visual acuity, and the fluorescein staining score among patients with severe DED.[56]

All three serum eyedrops are generally well-tolerated and safe to use. Only one study reported mild transient TRAEs after the use of ASEs and HSEs.

Table 4. Studies of serum eyedrops for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Kumari et al,[53] 2023	44	20% ASE vs 50% ASE	Baseline, weeks 2, 4, 8, and 12	In moderate DED, both 20% and 50% ASE improved subjective and objective parameters ($p<0.05$), but in severe DED, only 50% ASE improved both objective and subjective parameters ($p<0.05$). Both ASE preparations were generally safe and well-tolerated. No serious TRAEs were documented.	Need for refrigeration during storage, short follow-up, lack of lissamine green and rose bengal staining, lack of impression cytology for ocular surface
van der Meer et al,[54] 2021	19	ASEs vs HSEs	Baseline, month 1	ASEs and HSEs were comparable in terms of OSDI, TBUT, tear production, punctate lesions, and visual acuity. Both were well-tolerated and safe for use. TRAEs were mild and resolved completely.	Lack of inclusion criteria regarding graft-vs-host disease or Stevens-Johnson syndrome, small sample size
Mukhopadhyay et al,[55] 2015	144 with Hansen's disease	ASEs vs USEs	Baseline, weeks 6 and 12	Both USEs and ASEs significantly improved TBUT and tear protein levels at 12 weeks. Both were well-tolerated, and no serious TRAEs were reported.	Short follow-up, possible confounding effects from systemic antileprosy therapy
Rodríguez Calvo-de-Mora et al,[56] 2022	63 (21 per arm)	ASEs vs HSEs vs USEs	Baseline, months 1 and 3	All 3 therapies had similar effects in terms of improving visual acuity, ST1, TBUT, fluorescein and lissamine green staining scores, and questionnaire scores. All 3 therapies had good tolerability and safety. No TRAEs were documented.	Limited number of molecules determined and analyzed, lack of conjunctival impression cytology, lack of control group receiving conventional treatment

Abbreviations: ASE=autologous serum eyedrop, DED=dry eye disease, HSE=allogeneic serum eyedrop, OSDI=ocular surface disease index, ST1=Schirmer test score, TBUT=tear breakup time, TRAE=treatment-related adverse event, USE=umbilical cord serum eyedrop.

The 20% ASE preparation is effective for moderate DED, whereas the 50% ASE preparation is effective for severe DED. HSEs and USEs are effective for moderate-to-severe DED in patients who are unable to provide blood owing to logistical or clinical restrictions.

Lifitegrast

Lifitegrast is a lymphocyte function-associated antigen-1 antagonist specifically designed to treat DED.[57] By suppressing T-cell adherence to intercellular adhesion molecule 1, lifitegrast prevents the interaction of integrin lymphocyte function-associated antigen-1 and intercellular adhesion molecule 1, thereby inhibiting the inflammatory cascade associated with DED.[58,59] Lifitegrast is used in the treatment of patients with severe DED who exhibit resistance to standard DED medications such as HA and CsA.[60]

Two phase III trials evaluated the efficacy of lifitegrast in patients with moderate-to-severe DED (ie, a corneal fluorescein staining score of >1.5 and an eye dryness score of ≥60) [**Table 5**].[61,62] In the OPUS-2 trial, compared with placebo, lifitegrast treatment did not lead to greater improvements in the inferior corneal fluorescein staining score ($p=0.6186$), total CSS1 ($p=0.3711$), or nasal lissamine staining score ($p=0.6982$) at 84 days; however, it significantly improved the eye dryness score ($p<0.0001$), ocular discomfort score ($p=0.001$), and eye discomfort score ($p<0.0001$) at 84 days.[61] In the OPUS-3 study, lifitegrast was superior to placebo in improving the eye dryness score, symptoms of itching ($p=0.032$), foreign body sensations ($p=0.042$), and eye discomfort ($p=0.005$) at 42 days, although lifitegrast did not exhibit greater effectiveness by day 84.[62] Post hoc analysis further demonstrated the efficacy of lifitegrast against moderate-to-severe DED at all endpoints ($p\leq0.001$).[63] The greatest improvement was observed in patients with an inferior corneal fluorescein staining score of >1.5 and an eye dryness score of ≥60 at baseline.

Lifitegrast appears to be well-tolerated and safe. There have been no reports of serious ocular TRAEs; all TRAEs have been mild to moderate.

Lifitegrast is superior to topical CsA among patients with moderate-to-severe DED. Lifitegrast is effective as early as day 14. In contrast, topical CsA tends to have a delayed onset, and 16% to 29% of patients who use topical CsA may experience pain/irritation/burning in the eye.[64,65]

Discussion

The optimal approach for management of moderate-to-severe DED is a stepwise and sequential approach. In patients with moderate-to-severe DED, HA drops can be used as the primary daytime treatment. Instillations of topical 0.15% HA drops six times daily for 12 weeks provides relief comparable to CsA. For nighttime therapy requiring longer retention, a 0.30% HA gel formulation is recommended. It is important to note that the effectiveness of HA is not dose-dependent. Therefore, increased concentrations may not provide greater benefits. Combination HA therapies involving different lubricants can enhance the efficacy of HA, but further research is needed to confirm this finding.

Table 5. Studies of lifitegrast for moderate-to-severe dry eye disease

Studies	No. of patients	Intervention	Evaluation timepoint	Findings	Limitations
Tauber et al,[61] 2015	718, including 413 with moderate-to-severe DED	Lifitegrast vs placebo twice daily	Baseline, days 14, 42, and 84	Compared with placebo, lifitegrast yielded superior improvements in eye dryness (p<0.0001), ocular discomfort (p=0.0005), and eye discomfort (p<0.0001). Lifitegrast was generally well-tolerated and safe. Most TRAEs were mild to moderate.	Short follow-up, selection bias (inclusion of patients actively using artificial tears), exclusion of patients with active lid margin disease
Holland et al,[62] 2017	711, including 390 with moderate-to-severe DED	Lifitegrast vs placebo twice daily	Baseline, days 14, 42, and 84	Lifitegrast yielded superior improvements in symptoms of itching (p=0.032), foreign body sensations (p=0.042), and eye discomfort (p=0.005) at 42 days. Lifitegrast was generally safe and well-tolerated. Most TRAEs were mild to moderate.	Short follow-up, exclusion of patients with a history of LASIK in preceding 12 months and patients wearing contact lenses

Abbreviations: DED=dry eye disease, LASIK=laser in situ keratomileusis, TRAE=treatment-related adverse event.

For patients who do not respond to the HA regimen, short-term use of topical soft steroids (eg, a pulsed regimen of PFH and loteprednol) is recommended. Topical soft steroids display efficacy comparable to conventional steroid drops while providing superior safety benefits with minimal effects on IOP. Short-term pulsed topical PFH is particularly beneficial for patients with Sjogren syndrome. However, topical soft steroids may be less effective in patients with graft-vs-host disease; these patients may require more frequent or longer duration of treatment.[31] Alternatively, immunomodulatory agents such as CsA and lifitegrast can be used for ocular surface inflammation in patients with graft-vs-host disease.[31] These medications have stronger anti-inflammatory effects and may be useful for patients who do not adequately respond to soft steroids.[31] The use of 5.0% lifitegrast or 0.05% CsA twice daily for at least 12 weeks can alleviate symptoms of moderate-to-severe DED.[38,62,66] Patients with intolerable adverse effects from topical aqueous CsA can switch to gel or nanoemulsion formulations of CsA. Effective regimens include 0.05% CyclAGel once daily for 12 weeks and 0.08% nanoemulsion CsA (TJO-087) once daily for 32 weeks. Lifitegrast is recommended for patients who are sensitive to the adverse effects of aqueous CsA.

Patients who do not respond to anti-inflammatory medications, such as steroids and immunomodulatory agents, may consider ASEs. For moderate DED, we recommend using a 20% ASE preparation four times daily for 2 to 4 weeks. The 20% concentration is intended to prevent excessive antiproliferative effects.[67] However, a 50% ASE preparation may be needed for patients with severe DED. ASEs are considered the last resort for the management of moderate-to-severe DED; ASEs are associated with difficulties in preparation and refrigeration and risks of contamination.[68] Human HSEs and USEs can be considered for patients who require serum eyedrops but are unable to provide their own blood because of logistical or clinical constraints.

Careful monitoring is essential to ensure patient compliance and to assess improvement in symptoms and signs. The timing of assessments for therapeutic success varies among different individuals and therapies.[69] Assessment after 1 to 3 months is recommended for most treatments, except CsA, which may require a longer duration to demonstrate therapeutic effects.[38,70,71] Patients with moderate DED may be examined every 6 weeks, whereas patients with severe DED may require more frequent monitoring (eg, every 2 to 3 weeks). Diagnostic tests, such as corneal fluorescein staining and TBUT, should be performed during follow-up visits to assess treatment response.[72-75] Patients with autoimmune disease–related DED, such as Sjogren syndrome and graft-vs-host disease, should be referred to specialists for further evaluation and treatment.

This systematic review focused on randomized controlled studies of five therapeutic options (HA, topical steroids, CsA, serum eyedrops, and lifitegrast) for moderate-to-severe DED, which is defined as a severity level of ≥2 according to the Dry Eye Workshop I grading scheme.[8] However, the scheme is not evidence-based and lacks objectivity and universality. A standardized classification system that can objectively categorize different severities of DED is necessary to facilitate personalized treatment strategies.

This systematic review had some limitations. Most included studies had short follow-up periods and relatively small sample sizes. According to the Grading of Recommendations, Assessment, Development, and Evaluations framework,[76] the quality of evidence for most included studies was moderate, owing to publication bias and corporate sponsorship. As a result, the findings should be interpreted with caution.

Contributors

Both authors designed the study, acquired the data, analyzed

the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

Both authors have disclosed no conflict of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data analyzed during the present study are available from the corresponding author upon reasonable request.

References

1. *Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf 2017;15:276-83.* Crossref
2. *Shih KC, Lai JSM, Ng ALK. Management of dry eye disease: a systematic approach for the primary care physician. Hong Kong Pract 2016;38:113-9.*
3. *O'Neil EC, Henderson M, Massaro-Giordano M, Bunya VY. Advances in dry eye disease treatment. Curr Opin Ophthalmol 2019;30:166-78.* Crossref
4. *Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. Am J Ophthalmol 2017;182:90-8.* Crossref
5. *Patel VD, Watanabe JH, Strauss JA, Dubey AT. Work productivity loss in patients with dry eye disease: an online survey. Curr Med Res Opin 2011;27:1041-8.* Crossref
6. *Aragona P, Giannaccare G, Mencucci R, Rubino P, Cantera E, Rolando M. Modern approach to the treatment of dry eye, a complex multifactorial disease: a P.I.C.A.S.S.O. board review. Br J Ophthalmol 2021;105:446-53.* Crossref
7. *Baudouin C, Aragona P, Van Setten G, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. Br J Ophthalmol 2014;98:1168-76.* Crossref
8. *The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007;5:75-92.* Crossref
9. *Ang BCH, Sng JJ, Wang PXH, Htoon HM, Tong LHT. Sodium hyaluronate in the treatment of dry eye syndrome: a systematic review and meta-analysis. Sci Rep 2017;7:9013.* Crossref
10. *Johnson ME, Murphy PJ, Boulton M. Effectiveness of sodium hyaluronate eyedrops in the treatment of dry eye. Graefes Arch Clin Exp Ophthalmol 2006;244:109-12.* Crossref
11. *You IC, Li Y, Jin R, Ahn M, Choi W, Yoon KC. Comparison of 0.1%, 0.18%, and 0.3% hyaluronic acid eye drops in the treatment of experimental dry eye. J Ocul Pharmacol Ther 2018;34:557-64.* Crossref
12. *Lemp MA. Management of dry eye disease. Am J Manag Care 2008;14(3 Suppl):S88-101.*
13. *Gomes JAP, Santo RM. The impact of dry eye disease treatment on patient satisfaction and quality of life: a review. Ocul Surf 2019;17:9-19.* Crossref
14. *Lee JE, Kim S, Lee HK, et al. A randomized multicenter evaluation of the efficacy of 0.15% hyaluronic acid versus 0.05% cyclosporine A in dry eye syndrome. Sci Rep 2022;12:18737.* Crossref
15. *Calonge M, Sahyoun M, Baillif S, et al. Sodium hyaluronate 0.30% ocular gel versus sodium hyaluronate 0.18% eye drop in the treatment of moderate to severe dry eye disease. Eur J Ophthalmol 2023;33:188-95.* Crossref
16. *Jun JH, Bang SP, Park HS, et al. A randomized multicenter clinical evaluation of sequential application of 0.3% and 0.15% hyaluronic acid for treatment of dry eye. Jpn J Ophthalmol 2022;66:58-67.* Crossref
17. *Labetoulle M, Mortemousque B; CBL-101 Study Group. Performance and safety of a sodium hyaluronate tear substitute with polyethylene glycol in dry eye disease: a multicenter, investigator-masked, randomized, noninferiority trial. J Ocul Pharmacol Ther 2022;38:607-16.* Crossref
18. *Roszkowska AM, Inferrera L, Spinella R, et al. Clinical efficacy, tolerability and safety of a new multiple-action eyedrop in subjects with moderate to severe dry eye. J Clin Med 2022;11:6975.* Crossref
19. *Hynnekleiv L, Magno M, Vernhardsdottir RR, et al. Hyaluronic acid in the treatment of dry eye disease. Acta Ophthalmol 2022;100:844-60.* Crossref
20. *Zheng X, Goto T, Ohashi Y. Comparison of in vivo efficacy of different ocular lubricants in dry eye animal models. Invest Ophthalmol Vis Sci 2014;55:3454-60.* Crossref
21. *Oechsner M, Keipert S. Polyacrylic acid/polyvinylpyrrolidone bipolymeric systems. I. Rheological and mucoadhesive properties of formulations potentially useful for the treatment of dry-eye-syndrome. Eur J Pharm Biopharm 1999;47:113-8.* Crossref
22. *Pires NR, Cunha PLR, Maciel JS, et al. Sulfated chitosan as tear substitute with no antimicrobial activity. Carbohydr Polym 2013;91:92-9.* Crossref
23. *De Paiva CS, Corrales RM, Villarreal AL, et al. Apical corneal barrier disruption in experimental murine dry eye is abrogated by methylprednisolone and doxycycline. Invest Ophthalmol Vis Sci 2006;47:2847-56.* Crossref
24. *Lekhanont K, Leyngold IM, Suwan-Apichon O, Rangsin R, Chuck RS. Comparison of topical dry eye medications for the treatment of keratoconjunctivitis sicca in a botulinum toxin B-induced mouse model. Cornea 2007;26:84-9.* Crossref
25. *De Paiva CS, Corrales RM, Villarreal AL, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. Exp Eye Res 2006;83:526-35.* Crossref
26. *Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Curr Opin Ophthalmol 2000;11:478-83.* Crossref
27. *McGhee CNJ, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf 2002;25:33-55.* Crossref
28. *Sheppard JD, Comstock TL, Cavet ME. Impact of the topical ophthalmic corticosteroid loteprednol etabonate on intraocular pressure. Adv Ther 2016;33:532-52.* Crossref
29. *Adatia FA, Michaeli-Cohen A, Naor J, Caffery B, Bookman A, Slomovic A. Correlation between corneal sensitivity, subjective*

dry eye symptoms and corneal staining in Sjögren's syndrome. Can J Ophthalmol 2004;39:767-71. Crossref

30. *Menchini M, Sartini F, Figus M, Gabbriellini G. Short-term results of a pulsed therapy with hydrocortisone eye drops to treat moderate to severe dry eye in primary Sjögren syndrome patients. Graefes Arch Clin Exp Ophthalmol 2023;261:1029-36.* Crossref
31. *Yin J, Kheirkhah A, Dohlman T, Saboo U, Dana R. Reduced efficacy of low-dose topical steroids in dry eye disease associated with graft-versus-host disease. Am J Ophthalmol 2018;190:17-23.* Crossref
32. *Comstock TL, Paterno MR, Bateman KM, Decory HH, Gearinger M. Safety and tolerability of loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension in pediatric subjects. Paediatr Drugs 2012;14:119-30.* Crossref
33. *Amon M, Busin M. Loteprednol etabonate ophthalmic suspension 0.5 %: efficacy and safety for postoperative anti-inflammatory use. Int Ophthalmol 2012;32:507-17.* Crossref
34. *Deveney T, Asbell PA. Patient and physician perspectives on the use of cyclosporine ophthalmic emulsion 0.05% for the management of chronic dry eye. Clin Ophthalmol 2018;12:569-76.* Crossref
35. *Periman LM, Mah FS, Karpecki PM. A review of the mechanism of action of cyclosporine A: the role of cyclosporine A in dry eye disease and recent formulation developments. Clin Ophthalmol 2020;14:4187-200.* Crossref
36. *Mah F, Milner M, Yiu S, Donnenfeld E, Conway TM, Hollander DA. PERSIST: Physician's Evaluation of Restasis(®) Satisfaction in Second Trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review. Clin Ophthalmol 2012;6:1971-6.* Crossref
37. *Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The immunological basis of dry eye disease and current topical treatment options. J Ocul Pharmacol Ther 2020;36:137-46.* Crossref
38. *Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology 2000;107:631-9.* Crossref
39. *Kim CY, Park KH, Ahn J, et al. Treatment patterns and medication adherence of patients with glaucoma in South Korea. Br J Ophthalmol 2017;101:801-7.* Crossref
40. *White DE, Zhao Y, Ogundele A, et al. Real-world treatment patterns of cyclosporine ophthalmic emulsion and lifitegrast ophthalmic solution among patients with dry eye. Clin Ophthalmol 2019;13:2285-92.* Crossref
41. *Razeghinejad MR, Katz LJ. Steroid-induced iatrogenic glaucoma. Ophthalmic Res 2012;47:66-80.* Crossref
42. *Kallab M, Szegedi S, Hommer N, et al. Topical low dose preservative-free hydrocortisone reduces signs and symptoms in patients with chronic dry eye: a randomized clinical trial. Adv Ther 2020;37:329-41.* Crossref
43. *Peng WY, Chen RX, Dai H, et al. Efficacy, safety, and tolerability of a novel cyclosporine, a formulation for dry eye disease: a multicenter phase II clinical study. Clin Ther 2021;43:613-28.* Crossref
44. *Peng W, Jiang X, Zhu L, et al. Cyclosporine A (0.05%) ophthalmic gel in the treatment of dry eye disease: a multicenter, randomized, double-masked, phase III, COSMO trial. Drug Des Devel Ther 2022;16:3183-94.* Crossref
45. *Eom Y, Yoon KC, Kim HK, Song JS, Hyon JY, Kim HM. A multicenter, randomized, double-blind evaluation of the efficacy of TJO-087 versus 0.05% cyclosporine A in moderate to severe dry eye. J Ocul Pharmacol Ther 2023;39:27-35.* Crossref
46. *Rao AT, Gupta A, Chauhan T, et al. Efficacy and safety of 0.05% micellar nano-particulate (MNP) cyclosporine ophthalmic emulsion in the treatment of moderate-to-severe keratoconjunctivitis sicca: a 12-week, multicenter, randomized, active-controlled trial. BMC Ophthalmol 2023;23:121.* Crossref
47. *Akpek EK, Wirta DL, Downing JE, et al. Efficacy and safety of a water-free topical cyclosporine, 0.1%, solution for the treatment of moderate to severe dry eye disease: the ESSENCE-2 randomized clinical trial. JAMA Ophthalmol 2023;141:459-66.* Crossref
48. *Shin J, Rho CR, Hyon JY, Chung TY, Yoon KC, Joo CK. A randomized, placebo-controlled phase II clinical trial of 0.01% or 0.02% cyclosporin A with 3% trehalose in patients with dry eye disease. J Ocul Pharmacol Ther 2021;37:4-11.* Crossref
49. *Priani D, Muhiddin HS, Sirajuddin J, Eka HB, Bahar B, Bukhari A. Effectiveness of topical cyclosporin-A 0.1% compared to combined topical cyclosporin-A 0.1% with topical sodium hyaluronate on interleukin-6 levels in the tears of patients with dry eye disease. Vision (Basel) 2023;7:31.* Crossref
50. *Higuchi A. Autologous serum and serum components. Invest Ophthalmol Vis Sci 2018;59:DES121-DES129.* Crossref
51. *Giannaccare G, Carnevali A, Senni C, Logozzo L, Scorcia V. Umbilical cord blood and serum for the treatment of ocular diseases: a comprehensive review. Ophthalmol Ther 2020;9:235-48.* Crossref
52. *Wong J, Govindasamy G, Prasath A, et al. Allogeneic umbilical cord plasma eyedrops for the treatment of recalcitrant dry eye disease patients. J Clin Med 2023;12:6750.* Crossref
53. *Kumari N, Kusumesh R, Kumari R, Sinha BP, Singh V. Comparative evaluation of effectiveness of twenty versus fifty percent autologous serum eye drops in treatment of dry eye. Indian J Ophthalmol 2023;71:1603-7.* Crossref
54. *van der Meer PF, Verbakel SK, Honohan Á, et al. Allogeneic and autologous serum eye drops: a pilot double-blind randomized crossover trial. Acta Ophthalmol 2021;99:837-42.* Crossref
55. *Mukhopadhyay S, Sen S, Datta H. Comparative role of 20% cord blood serum and 20% autologous serum in dry eye associated with Hansen's disease: a tear proteomic study. Br J Ophthalmol 2015;99:108-12.* Crossref
56. *Rodríguez Calvo-de-Mora M, Domínguez-Ruiz C, Barrero-Sojo F, et al. Autologous versus allogeneic versus umbilical cord sera for the treatment of severe dry eye disease: a double-blind randomized clinical trial. Acta Ophthalmol 2022;100:e396-e408.* Crossref
57. *Haber SL, Benson V, Buckway CJ, Gonzales JM, Romanet D, Scholes B. Lifitegrast: a novel drug for patients with dry eye disease. Ther Adv Ophthalmol 2019;11:2515841419870366.* Crossref
58. *Murphy CJ, Bentley E, Miller PE, et al. The pharmacologic assessment of a novel lymphocyte function-associated antigen-1 antagonist (SAR 1118) for the treatment of keratoconjunctivitis sicca in dogs. Invest Ophthalmol Vis Sci 2011;52:3174-80.* Crossref
59. *Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. Ocul Surf 2016;14:207-15.* Crossref
60. *Abidi A, Shukla P, Ahmad A. Lifitegrast: a novel drug for treatment of dry eye disease. J Pharmacol Pharmacother 2016;7:194-8.* Crossref
61. *Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 study.*

Ophthalmology 2015;122:2423-31. Crossref
62. *Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). Ophthalmology 2017;124:53-60*. Crossref
63. *Holland EJ, Jackson MA, Donnenfeld E, et al. Efficacy of lifitegrast ophthalmic solution, 5.0%, in patients with moderate to severe dry eye disease: a post hoc analysis of 2 randomized clinical trials. JAMA Ophthalmol 2021;139:1200-8*. Crossref
64. *Boboridis KG, Konstas AGP. Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. Expert Opin Pharmacother 2018;19:1027-39*. Crossref
65. *Leonardi A, Van Setten G, Amrane M, et al. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. Eur J Ophthalmol 2016;26:287-96*. Crossref
66. *Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. Ophthalmology 2000;107:967-74*. Crossref
67. *Rodriguez-Garcia A, Babayan-Sosa A, Ramirez-Miranda A, et al. A practical approach to severity classification and treatment of dry eye disease: a proposal from the Mexican Dry Eye Disease Expert Panel. Clin Ophthalmol 2022;16:1331-55*. Crossref
68. *Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. Ocul Surf 2015;13:118-32*. Crossref
69. *Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf 2017;15:575-628*. Crossref
70. *de Oliveira RC, Wilson SE. Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease. Clin Ophthalmol 2019;13:1115-22*. Crossref
71. *Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005;112:1790-4*. Crossref
72. *Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640-50*. Crossref
73. *Pellegrini M, Bernabei F, Moscardelli F, et al. Assessment of corneal fluorescein staining in different dry eye subtypes using digital image analysis. Transl Vis Sci Technol 2019;8:34*. Crossref
74. *Paugh JR, Tse J, Nguyen T, Sasai A, et al. Efficacy of the fluorescein tear breakup time test in dry eye. Cornea 2020;39:92-8*. Crossref
75. *Begley CG, Himebaugh N, Renner D, et al. Tear breakup dynamics: a technique for quantifying tear film instability. Optom Vis Sci 2006;83:15-21*. Crossref
76. *Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995-8*. Crossref

PERSPECTIVE

Artificial intelligence in retinopathy of prematurity: transfer learning and federated learning

Carolyn Yu Tung Wong[1], *MBChB; Wilson Wai Kuen Yip*[2], *MBChB, MMed, FRCSEd (Ophth), FCOphthHK, FHKAM (Ophthalmology); Henry Hing Wai Lau*[2], *MBChB, MMed, FRCSEd (Ophth), FCOphthHK, FHKAM (Ophthalmology); Carol Yim Lui Cheung*[2], *BSc (HK), MPhil (HK), PhD (UK)*

[1]*Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*

[2]*Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China*

Correspondence and reprint requests:

Dr Carolyn Yu Tung Wong, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.

Email: carolcarol.carolyn@gmail.com

Abstract

Artificial intelligence can help resolve the lack of specialists in retinopathy of prematurity (ROP) and its associated diagnostic subjectivity. Obstacles to the use of deep learning (DL) for ROP tasks include the condition's low prevalence, data paucity, and difficulty in multi-institutional data sharing to optimize training. Transfer learning (TL) and federated learning (FL) are advanced strategies to address DL issues. This review highlights the advantages of TL and FL applications in various ROP-related tasks. TL and FL achieve outstanding results for ROP screening, triaging, and monitoring, with certain algorithms exceeding the baseline DL models. TL assists the construction of generalizable ROP models despite little data. FL lays the groundwork for safe data exchange between institutions in TL. However, both TL and FL entail shortcomings associated with inadequate generalizability and data privacy attacks. Further research is needed to address the unsolved interpretability and liability issues in TL and FL models. Although both TL and FL have great potential to overcome DL constraints and improve the diagnosis of ROP, more work is needed to address application concerns such as model interpretability and liability.

Key words: Artificial intelligence; Deep learning; Machine learning; Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative condition involving the aberrant formation of retinal blood vessels in premature, lightweight newborns.[1] ROP can be classified by its anteroposterior position (area), severity (stage), and vascular features,[1] as well as the extent of vascularization (ie, zone 1, 2, or 3).[2] ROP classification guides treatment in clinical practice.[2,3] ROP is a leading cause of childhood blindness; an estimated 20 000 newborns with ROP become blind annually worldwide.[4,5] ROP-related blindness is mostly avoidable with early screening, proper diagnosis, and swift intervention.[6] Unfortunately, the global burden of ROP remains high because of a lack of experts to screen for the condition, particularly in middle-to-low-income countries.[7,8] Additionally, inter-clinician differences in the qualitative evaluation of ROP characteristics in images for diagnosis and severity triaging result in fluctuating standards and questionable reliability of ROP diagnoses and classifications.[9-11] Therefore, the use of artificial intelligence (AI) for data analysis and automated diagnosis is advocated.[12]

Deep learning (DL) is widely used to diagnose and classify various retinal diseases (including ROP).[13,14] Nonetheless, ROP presents greater challenges than other retinal disorders in DL-based AI. Transfer learning (TL) and federated learning (FL) can address the challenges associated with constructing AI models for ROP and better incorporate AI into ROP diagnostic pathways.

Relationships between artificial intelligence, machine learning, deep learning, transfer learning, and federated learning

The Figure shows the relationships between AI, machine learning (ML), DL, TL, and FL. Telescreening of fundus photographs for ROP facilitates the integration of computer-based image analysis.[15,16] Early systems for ROP diagnosis use manual and semi-automated ML methods to analyze data and make decisions based on learned patterns, whereas DL learns autonomously without explicit human guidance.[15,16] ML requires defining disease-specific features and training the machine for interpretation, whereas DL uses artificial neural networks to analyze images, recognize patterns, and continuously improve.[15-17] These networks, particularly convolutional neural networks (CNNs), are adept at image processing and classifying data beyond human perception.[17]

CNN is a DL architecture that learns from data, excelling in image pattern recognition for object and category identification.[18] It comprises an input layer, an output layer, and several hidden layers that transform data to uncover features.[18] Images are made of pixels arranged in a matrix, with values from 0 to 255 representing brightness and color.[19] CNNs mimic human brain function by first identifying simple patterns before progressing to complex ones, ultimately classifying images and diagnosing conditions.[19] Various architectures such as AlexNet (for large datasets) and ResNet (for deep networks) are designed for specific tasks, with differing layer configurations and parameters.[20,21] Training an ML model involves a dataset and validation processes to assess performance.[22] Metrics such as sensitivity and area under the receiver operating characteristic curve (AUROC) evaluate the algorithm.[22] The training feeds labeled data through the CNN layers, refining the model to reduce errors and requiring substantial image input for accuracy.[22]

TL utilizes knowledge from a previous task to improve performance on related tasks.[22,23] Common CNNs for TL include ResNet, ImageNet, U-Net, and VGG-16.[22,23] Fine-tuning a pretrained network requires less data than training from scratch, enabling the use of pretrained features for new tasks.[18] For example, a network trained on millions of images can be adapted for new classification tasks with just a few hundred images.[18]

In FL, multiple clients train a model collectively while keeping their data decentralized.[24] FL trains algorithms on local datasets without sharing data samples.[25] Local models are trained on local data, and parameters such as weights and biases are exchanged periodically among nodes to create a shared global model.[25]

Transfer learning for diagnosing retinopathy of prematurity

ROP is uncommon, and collecting adequate data to generate potent DL diagnostic classifiers is challenging.[26] Many ROP data for DL training are affected by class imbalances, low label quality owing to disparities in annotators' clinical experience and interpretations, and intrinsic biases towards

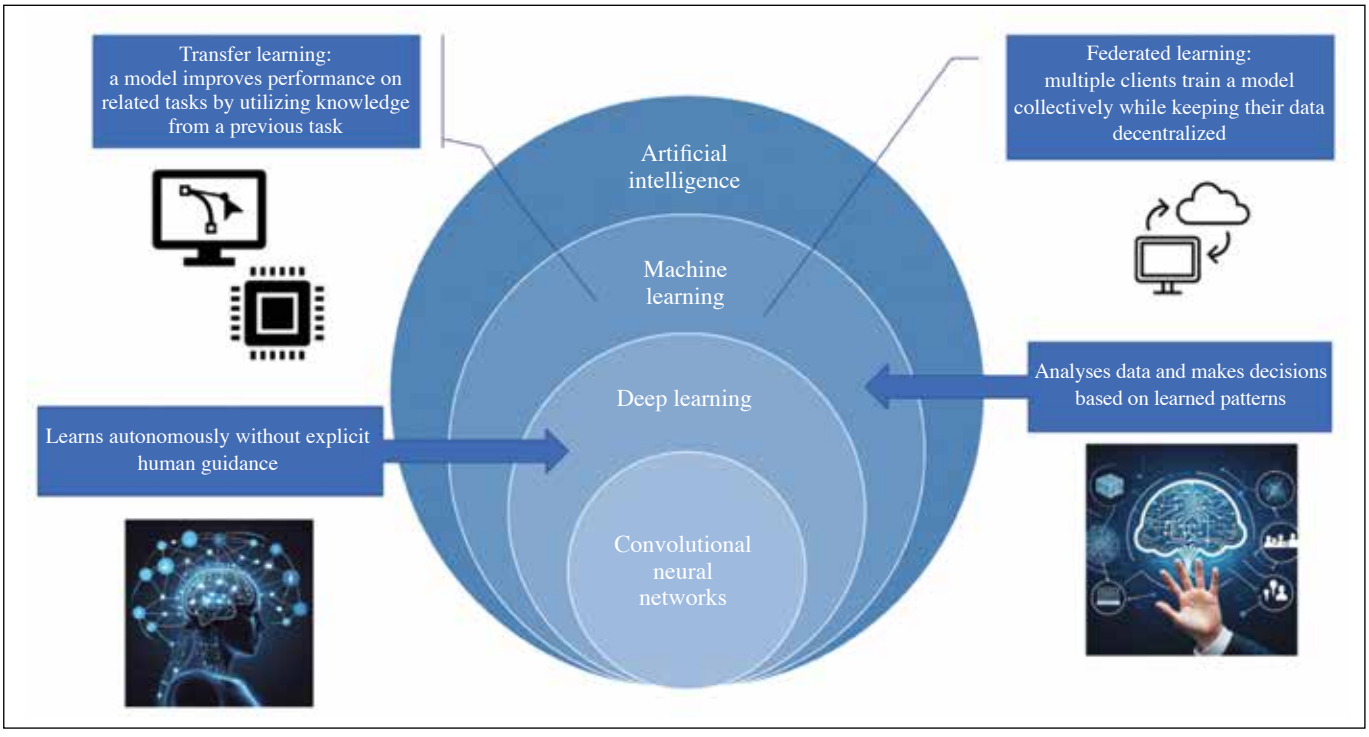


Figure. Relationships between artificial intelligence, machine learning, deep learning, transfer learning, and federated learning

the traits reflected in most single-ethnic datasets.[26,27] ROP models trained on a single population may not generalize well to different populations, whereas ROP models trained on populations in various institutions are limited because of privacy concerns.[26] Even if more ROP data can be accumulated over time to increase the database size, a new DL system will have to be built from scratch with different parameter settings owing to differences in image distribution in the new ROP training data.[28] Traditional DL requires model rebuilding, which increases expenditures on system maintenance and modifications to adapt to the population's ever-changing ROP scenario.[28] Furthermore, the process of searching for appropriate network parameters via an extensive trial-and-error procedure is time-consuming and costly while adjusting the dynamic ROP scene.[28] This decreases the incentive to create and incorporate DL systems for ROP classification.

To overcome these issues, TL enables a new model to reuse knowledge already acquired in another domain, task, or distribution in another model supplied with a more robust and diversified training dataset.[28] For example, the ImageNet dataset consists of millions of diverse images for CNNs; AlexNet trains on them to produce robustly learned model parameters and weights for training a new model using this knowledge via TL.[29] Fine-tuning the last fully connected layers using TL enables the retrained network to better adapt to the new task domain.[29] It is faster to set up a ROP system with TL, which transfers part of the established model settings, than to train a CNN from scratch, which requires developers to decide on each model setting.[29]

Table 1 summarizes studies of TL models for ROP. Rao et al[30] used TL to develop an ROP screening model using the limited number of ROP images available. The ImageNet-pretrained model was leveraged to construct the ROP diagnostic DL system using TL. The TL method yielded an AUROC of 0.970, with 91.46% sensitivity and 91.22% specificity in ROP.[30] When used correctly with appropriate networks, TL enables quicker convergence and highly accurate achievements.[30] The TL algorithm can decentralize care and increase ROP screening coverage, freeing up human experts for treatment planning.[30]

Wang et al[31] built an ROP screening and severity triaging system by using another ImageNet-pretrained model with TL. The TL-based screening and triaging systems achieved 96.62% sensitivity and 99.32% specificity for ROP screening, and 88.46% sensitivity and 92.31% specificity for ROP grading.[31]

Chen et al[32] used TL to devise AI models to classify ROP stages using the robust ImageNet-pretrained model. The TL-based models retrained on a North American dataset and a Nepali dataset demonstrated excellent staging performance when tested on data from the same population, with AUROCs of 0.99 and 0.98 and sensitivities of 94% and 73%, respectively.

Subramaniam et al[33] developed another ROP staging system (no-plus and plus categories) using the ImageNet-pretrained model via TL. The resulting TL-based ROP diagnostic algorithm achieved an AUROC of 0.9754, 96% accuracy, 100% specificity, and 71.43% sensitivity. The algorithm can be used in telemedicine for ROP using smartphone fundus photographs.

Brown et al[34] used TL to establish an ROP staging classifier based on the ImageNet-pretrained model. The TL-based algorithm attained AUROCs of 0.94 and 0.98 for normal and plus class recognition, respectively. In an independent test set, the sensitivity was 100% and specificity was 94% for pre-plus or worse diagnosis. TL helped create a continuous ROP scoring system, providing greater granularity in determining disease progression and improvement.

Mao et al[35] used the ImageNet-pretrained network to train an ROP staging system using TL. The TL-based system could diagnose plus-stage disease with 95.1% sensitivity and 97.8% specificity, and pre-plus-stage disease or worse with 92.4% and 97.4% sensitivity, respectively. The quadratic weighted kappa of the system, a metric that measures the agreement between the predicted and actual outcome (varying from 0 [random agreement] to 1 [complete agreement]), was 0.9244.[36] The TL method may provide useful second opinions after ophthalmologists' diagnoses.

Yildiz et al[37] used TL to generate an ROP staging system based on the robust ImageNet-pretrained network. The resulting TL system achieved an AUROC of 99% and 94% for plus and not-plus stages on the internal and external datasets, respectively. The internally and externally verified AUROC for predicting pre-plus or worse stages versus normal stages were 99% and 88%, respectively.

Tong et al[38] used TL to create an ROP triage system that classifies patients based on disease severity (normal, mild, semi-urgent, or urgent) and stage (1 to 4). The TL method obtained an accuracy of 0.903 for severity and 0.957 for ROP staging. TL effectively improved the competency, efficiency, and consistency of ROP screening.

TL enables accurate ROP identification and triaging for personalized treatment and follow-up plans. It reduces the need to gather vast quantities of ROP data and conduct high-quality image capturing and expert-led data labeling as in traditional DL model development.[28] TL models can screen and classify patients with ROP across various subgroups, despite the limited volume of training data.[29]

However, TL has limitations to ROP AI tasks. Despite ImageNet's ability to shape robust model settings for the initial phase of ROP model training, the image properties differ between ROP medical images and natural images. This could result in unrealistic and inaccurate knowledge transferring from the pretrained network.[39] ImageNet may fail to depict complex pathological structures in two or three

Table 1. Transfer learning (TF) retinopathy of prematurity (ROP) models

Study	Task	Algorithm	Dataset	Operations
Rao et al,[30] 2023	Differentiate between ROP (stage 1-3) and non-ROP eyes	EfficientNet-B0	227 326 wide-field retinal images	Involved pretraining on ImageNet; the EfficientNet-BO initialized was retrained as a binary.
Wang et al,[31] 2018	Classifying ROP and non-ROP, followed by grading on identified ROP-positives into minor or severe ROP	Inception BN as the ROP identification network (ROP vs non-ROP); Gr-Net as the ROP severity grading network (minor vs severe ROP)	Id-Net trained on an identification dataset and Gr-Net trained on a grading dataset	Training processes of Id-Net and Gr-Net were identical except for the training datasets. An Inception–BN network was first pretrained on ImageNet. The learned parameters were used as the initial parameters of Id-Net and Gr-Net, which were later fine-tuned.
Chen et al,[32] 2021	Classifying non-staged and staged ROP (1 to 3) images	Three CNNs trained on three different image datasets	5943 images from 711 patients in the North American dataset and 5009 images from 541 patients from the Nepali dataset	Three types of CNN models were trained using three datasets: North American alone, Nepali alone, and both. A ResNet-152 architecture pretrained on the ImageNet dataset was incorporated into the training of the three CNNs through TL.
Subramaniam et al,[33] 2023	Classifying plus and no plus	Algorithm developed from pretrained GoogLeNet	5000 images from EyePACS	The ImageNet- pretrained GoogLeNet was leveraged. In the training, the first 20 layers were frozen, and the last learnable layer and the final classification layer were replaced with layers relevant to our dataset.
Brown et al,[34] 2018	Classifying normal, pre-plus, and plus disease in ROP	U-Net architecture as the vessel segmentation network; Inception version 1 architecture as the network to classify preprocessed images into normal, pre-plus, and plus	Pretraining of Inception version 1 involves ImageNet. Training of the TL algorithm involves 5511 retinal photographs, with 4535 (82.3%) being normal, 805 (14.6%) being pre-plus disease, and 172 (3.1%) being plus disease.	The second CNN (Inception version 1) architecture was previously pretrained on the ImageNet database of 1.2 million images from 1000 classes. In the training of the algorithm, the two networks were presented with corresponding reference standard diagnoses, which were used to adjust the network's numerous internal parameters to output the correct diagnoses.
Mao et al,[35] 2020	Classifying normal, pre-plus, and plus disease	Three deep CNNs, including a U-Net for vessel segmentation, another U-Net for optic disc segmentation and a DenseNet for the three-class classification	5711 images for training, 450 images for testing, and 63 images for treatment	The input of the DenseNet was the output of the modified U-net that segmented the blood vessels. For the DenseNet, the weights were initialized using TL based on the ImageNet.
Yildiz et al,[37] 2020	Classifying plus vs not-plus; classifying pre-plus or worse vs normal	Three classifiers: logistic regression, support vector machine, and neural networks	5512 images (163 plus, 802 pre-plus, and 4547 normal) for training and validation; 100 images (15 plus, 34 pre-plus, and 51 normal) for external validation	The pipeline of the system begins with segmenting the vessels in a color retina image. The system incorporated a pretrained U-Net CNN architecture for segmentation. Using the segmented images and optic disc centers, vessels were traced and vessel tree information was extracted. Using the outputs from previous steps, features of the retina were extracted, and these features were used for classification in the system.
Tong et al,[38] 2020	Classifying ROP severity (normal, mild, semi-urgent and urgent); classifying ROP into stages (stages 1 to 5) and detecting plus disease	Two CNNs: the 101-layer ResNet as classification network) and the Faster R-CNN as an identification network	36 231 fundus images	A ResNet-101 CNN architecture was pretrained on the ImageNet. It was then retrained on the study's dataset using TL, while the fine-tuning technique was applied to transfer the connection weights from the pretrained model to the study's model, and the model was retrained to the present task.

Results	Remarks	Added value to the ROP clinical pathway	Limitation
91.46% sensitivity, 91.22% specificity, 0.970 AUROC, 81.72% positive predictive value, and 96.14% negative predictive value	TL enabled faster convergence, potential higher diagnostic accuracy acquisitions, and lower operational demand for training networks.	The highly accurate TL model can be used as an objective ROP screening tool, facilitating broader screening coverage and care decentralization (ie, moving triaging away from an ophthalmologist-led system).	Limited generalizability owing to single ethnicity (South Asian) population; uncertain generalizability for stage 4 & 5 ROP disease detection owing to remaining class imbalance (ie, inadequate representation of the very advanced stages)
In test dataset, the Id-Net achieved 96.62% sensitivity and 99.32% specificity for ROP identification, whereas Gr-Net achieved 88.46% sensitivity and 92.31% specificity for ROP grading. In 552 cases, the deep neural networks outperformed some human experts and achieved 84.91% sensitivity and 96.90% specificity for ROP identification, whereas the corresponding values for ROP grading were 93.33% and 73.63%, respectively.	TL demonstrated its capability to derive high-performing deep neural networks. Although TL is less sensitive to the size of training dataset, the quality and quantity of pretraining and retraining datasets are still relevant. The dataset plays a crucial role in avoiding overfitting the algorithm.	TL helped the ROP screening system to reach ROP-expert comparable performance, facilitating ROP diagnostic consistency. The system could be used to detect and triage ROP into different grades for individualized management plans.	Limited generalizability owing to insufficient severe ROP cases (ie, remaining class imbalance) and persistently limited data availability
Both the North American- and Nepali-trained models demonstrated high performance on the test set from the same population, with 0.99 AUROC, 0.98 area under precision-recall curve, and 94% and 73% sensitivity, respectively. Compared to the models trained on individual datasets, the model trained on a combined dataset had better performance on each test set, with 98% sensitivity in the North American test set and 82% sensitivity in the Nepali test set.	Internal and external performance of the algorithm was most improved by increasing the heterogeneity of the training dataset features (eg, by combining images from different populations and cameras).	CNNs could be trained to detect stages 1 to 3 ROP with high accuracy, facilitating triaging patients with ROP for differential interventions and management.	Limited generalizability due to the filtered images not being adequately representative of the real-world population; absence of expandability provided for the CNN imaging features associated with stages 1 to 3
In the held-out test set of 50 images, 0.9754 AUC, 96% accuracy, 100% specificity, and 71.43% sensitivity were obtained. Precision was 1, recall was 0.7143, and the F1 score was 0.833.	Despite TL, the limited number of cases of plus disease necessitated further collaboration with other countries in the SP-ROP project and improved access to more smartphone images.	The successful performance of the TL-trained solution suggested the potential for more accurate diagnosis using smartphone fundus images and the future utilization of these images for telemedicine-based diagnoses.	Limited generalizability remained caused by the limited access to diverse and vast amounts of images.
The mean AUROC was 0.94 for the normal diagnosis and 0.98 for the plus-stage diagnosis. In an independent test set of 100 retinal images, the algorithm achieved 93% sensitivity and 94% specificity for plus-stage diagnosis. For the detection of pre-plus disease or worse, sensitivity was 100% and specificity was 94%. On the same test set, the algorithm reached a quadratic weighted κ coefficient of 0.92, outperforming 6 of 8 ROP experts.	By enabling the network to learn highly generalizable image features from an unrelated yet large and highly diverse dataset of images, TL was conducive to the acceleration of classification performance in the algorithm.	The TL-based system allowed continuous scoring, providing more granularity in determining relative disease progression or regression and facilitating the formulation of management plans for patients with progression monitoring. Incorporating the TL model into fundus camera systems and telemedicine platforms for ROP and other image-based diseases may improve the objectivity, accuracy, and efficiency of healthcare delivery.	The robustness of the TL algorithm remained constrained by persistent data limitations (eg, image quality, resolution, camera systems, and field of view). Biased training might have remained owing to the limited data variations. It is a poorly interpretable 'black box' model.
The trained network achieved 95.1% sensitivity with 97.8% specificity for the diagnosis of plus disease. For the detection of pre-plus or worse, the sensitivity was 92.4% and specificity was 97.4%. The quadratic weighted κ was 0.9244.	The TL training in DenseNet contributed to better generalizability and robustness in the classifier. The selection of the appropriate network was equally important for allowing easier training and alleviating overfitting issues.	The proposed system provides an accurate diagnosis of plus disease and can act as an assistive diagnostic tool to validate ophthalmologists' judgements.	Limited generalizability remained owing to the persistent lack of labelled images.
The AUCs on the first and second datasets were 99% and 94%, respectively, for predicting plus vs not-plus categories, and 99% and 88%, respectively, for predicting pre-plus or worse vs normal categories.	The CNN can identify more discriminative features given the exposure to a large dataset for training in pretraining during the TL training process.	This fully automated system, which combines retinal vessel segmentation, tracing, feature extraction and classification stages, diagnosed plus disease in ROP with performance on par with recent publications reporting on the use of CNNs. It is likely to benefit holistic ROP diagnostic practices.	Uninterpretable black-box nature; quality of input images distorted by image resizing
The system achieved 90.3% accuracy for classification of ROP severity. Specifically, the accuracies in discriminating normal, mild, semi-urgent, and urgent were 88.3%, 90.0%, 95.7%, and 87.0%, respectively, whereas the corresponding accuracies of the two experts were 90.2% and 89.8%. The model also achieved 95.7% accuracy for detecting the ROP stage and 89.6% accuracy for detecting plus disease. The accuracies in discriminating stages I to stage V were 0.876, 0.942, 0.968, 0.998, and 0.999, respectively.	After TL, the proposed ROP classifier system performed well without requiring a novel database of millions of images. It allowed the two CNN models to be applied as the study's classification and identification algorithms, which perform screening functions with proficiency comparable to or better than that of ROP experts.	The most prominent advantage is that the TL attempt promoted the identification of ROP stage and plus disease presence, along with disease severity. This functionality enables clinical review and verification of the automated diagnosis, rather than simply identifying the presence of ROP. TL benefits also include consistent prediction and instantaneous reporting of results.	Limited generalizability owing to the persistently limited number of ROP stage V fundus images (ie, bias) and an inadequately large patient cohort.

dimensions.[39] Thus, leveraging the power of large amounts of non-realistic big data may shift the model's focus to non-generalizable image attributes that are unrelated to the disease or clinical anatomy in a given collection of medical images.[39] Consequently, biased training may undermine the algorithm's capacity to recognize disease patterns in new data.[39] Therefore, gathering massive volumes of raw ROP medical images is paramount in generalizable training. Furthermore, the selection of the TL technique, the backbone architecture, and the fine-tunable layers are critical in guiding the success of a smooth and accurate conveyance of generalizable characteristics.[40,41] However, most key decisions in TL were based primarily on ophthalmologists' intuition or personal experience.[42] There is presently no agreement or defined procedure for making such training decisions in TL. This puts TL-trained models at risk of incurring uncalculated decision making, which may limit the performance boost that TL provides.[42]

Federated learning for diagnosing retinopathy of prematurity

Data sharing among institutions fosters generalizable training. Multicenter research is increasingly important in developing robust ROP DL algorithms that can be used in real-world applications.[43,44] The most common approach is centralized learning, in which data from multiple institutions are pooled in a centralized model. However, exchanging data among institutions increases the risk of data breaches and privacy violations.[45]

To protect data privacy and reduce the risk of raw ROP data leakage, the distributed learning method allows ROP data to be disseminated among institutions rather than combined into a single pool.[46] FL enables multiple medical institutions to cooperatively train AI systems without sharing data.[47-49] Thus, FL promotes ROP AI research and development, necessitating multicenter collaboration and access to large-scale data for performance excellence.

Table 2 summarizes studies of FL models for ROP. Lu et al[50] used FL to create a no plus, pre-plus, and plus ROP classification model. After training with 1145 color fundus photographs, both the FL and centralized learning models performed well, with AUROCs ranging from 0.93 to 0.96. In four of seven sites, FL outperformed locally trained models that used a single-institution dataset. FL can generate higher-quality models by leveraging larger and more diverse training datasets from multiple sources while maintaining a high standard of data privacy.

Hanif et al[51] applied FL to develop a vascular severity scoring system for three ROP subclasses (no plus, pre-plus, and plus). They compared the average DL-generated vascular severity score for each ROP class across institutions to determine inter-institutional variability. There were no significant inter-institutional disparities between the pre-plus and plus groups; however, there were significant disparities in the mean vascular severity score for the no-plus group. The vascular severity scoring system for ROP can be an objective measure for inter-clinician diagnostic variability. FL has the potential to improve ROP screening uniformity, objectivity, and consistency, as well as intervention triage.

However, FL for ROP has limitations. Despite the FL models' superior overall performance, locally trained DL models are not inferior to the FL models. 43% of the participating sites likely gained no advantage from the FL approach, especially when FL models are more vulnerable to data breaches (inference attacks and model inversion attacks). Furthermore, despite the inclusion of real-life clinical data, FL models remain stimulated models that fail to address practical FL challenges such as different privacy restrictions among participating institutions, varying accessibility, extensive communication and overhead expenses, and unpredictable reliability among participating sites in terms of supplying high-quality input data.

Real-world use of models

The i-ROP DL is the first DL model to receive breakthrough designation from the United States Food and Drug Administration for real-world ROP screening. The i-ROP DL system was trained on over 5000 deidentified posterior retinal images captured using a RetCam camera as part of the multicenter Imaging and Informatics in Retinopathy of Prematurity (i-ROP) cohort study.[34] All eight study centers used a standard imaging protocol, capturing images in five standard fields of view (posterior, nasal, temporal, superior, and inferior).[34] However, the analysis focused solely on wide-angle images of the posterior retina, excluding images without an optic nerve present.[34] Subsequent studies developing ROP DL systems also adopted this approach of analyzing only posterior retinal images.[52,53]

To ensure quality control in the images used for model training, it is recommended that a reference standard diagnosis is assigned to each image.[54] This involves independent image-based diagnoses by three trained graders (two ophthalmologists and one study coordinator) and a clinical diagnosis by an expert ophthalmologist.[54] The images are classified as normal, pre-plus disease, or plus disease according to the international classification of ROP, which includes zone, stage, and plus disease.[34,52] The reference standard diagnosis serves as the foundation for training the DL system.[34] Images are excluded if at least two of the three graders deem them unacceptable for diagnosis or if they exhibit stage 4 or 5 ROP.[52] In these advanced stages, the relevance of diagnosing plus disease for ROP screening diminishes, as visualizing retinal blood vessels becomes challenging.[34] The effectiveness of incorporating a reference standard diagnosis consensus procedure for training highly accurate ROP DL systems has been demonstrated.[52,53]

Brown et al[34] reported that the i-ROP-DL system demonstrated expert-level automated performance, with 91% accuracy in diagnosing plus disease in premature infants from a North American population.[34] The i-ROP DL

Table 2. Federated learning (FL) retinopathy of prematurity (ROP) models

Study	Task	Algorithm	Dataset	Operations	Results	Remarks	Added value to the ROP clinical pathway	Limitation
Lu et al,[50] 2022	Classifying three level plus in ROP	ResNet-18	5255 wide-angle retinal images in the neonatal intensive care units of 7 institutions	Model averaging was used. At the start of each round of training, a copy of the global model was shared with each of the 7 institutions to initialize that institution's local model. Each local model was then trained for 10 epochs, and the model checkpoint with the best validation performance, as measured by AUROC, was chosen to be aggregated into the global model at the end of the round. Upon the completion of all the federation rounds, a copy of the global model was finally transferred to each individual site for the prediction of new, unseen data.	Four (57%) of the seven models trained on local institutional data performed inferiorly to the FL models.	FL has been promising for allowing multiple institutions to leverage their individual data resources to collaboratively develop DL models without directly sharing data while reducing time and costs and protecting patient privacy. Each contributing entity eventually benefits from an aggregated model trained on a larger and more heterogeneous distribution of cases, which often gives far more generalizable models with greater performance than that of standalone models trained using only a single institution's data.	FL trained on point-of-care labels performed comparably to models trained on centralized datasets with consensus-expert labels, supporting the feasibility of the approach in clinical settings. FL approach is more secure and convenient than the more commonly used collaborative approach and is a beneficial alternative.	Datasets contributed by each institution were not entirely based on the population, causing insufficient generalizability; absence of assessment in the practical obstacles to implementing this method, such as limited communication bandwidth; sole focus on the performance aspect of FL without taking into account practical attacks on FL in a real-world setting that may require additional privacy-preserving measures
Hanif et al,[51] 2022	Classifying plus, pre-plus and no plus	-U-Net	Wide-angle retinal images in 5245 patients from the neonatal intensive care units of 7 institutions	Model averaging was used. At the beginning of each round of training, a copy of the global model was shared with each institution to initialize that institution's local model. The local model is then trained for a set number of epochs, and the model checkpoint from the epoch with the best validation performance, (as measured by AUROC), is chosen to be aggregated into the global model at the end of the round.	The proportion of patients diagnosed with pre-plus disease varied significantly between institutions ($p<0.00l$). A significant inverse relationship between the institutional vascular severity score and the mean gestational age was found ($p=0.049$, adjusted $R2=0.49$).	This is likely to represent a generalizable approach to assess clinician diagnostic paradigms as well as disease severity for epidemiological evaluation across institutions without the need for sharing sensitive patient data.	In comparison to a centrally hosted trained model, FL model training eliminates the need for a central process or consensus of ROP experts, making it more feasible to implement.	Each institution's datasets were not completely population based. There were also variations in the participating sites' enrolment protocols, potentially introducing population bias into the cohorts. These factors led to persistent inadequate generalizability.

can also provide a quantitative severity score (1 to 9) based on a single photograph, correlating with full zone, stage, and plus disease classification.[52,55-57] It is highly sensitive in detecting treatment-requiring ROP in a North American population.[52,58]

Campbell et al[59] assessed the diagnostic performance of the i-ROP-DL system-based ROP severity score using data from an Indian ROP telescreening program.[59] The system demonstrated sustained high diagnostic accuracy at the individual eye examination level, with an AUROC of 0.98, 100% sensitivity, and 78% specificity for identifying treatment-requiring ROP in diverse patient groups. At the population level, the system identified higher ROP severity in neonatal care units lacking resources for oxygen monitoring and titration.[59] These findings suggest that the system can enhance ROP screening efficiency and serve as an epidemiological tool for monitoring ROP severity across different regions and time periods.[59] As an autonomous screening device, the system can effectively expand ROP screening coverage across large geographic areas, provide automated real-time referral decisions, and reduce the screening workload by 60% to 80%.[59] Additionally, the i-ROP-DL system could aid in resource allocation to neonatal care units caring for high-risk infants susceptible to treatment-requiring ROP and aggressive posterior ROP.[59]

Table 3 summarizes the advantages and disadvantages of TL and FL, as well as the overall effect of AI, ML, and DL on ROP screening.

Future directions

Poor transparency is seen in advanced AI techniques' decision-making. Most ROP models are black boxes, making it difficult for ophthalmologists to understand how they arrive at their decisions.[60] To completely trust AI's clinical rationality, future ROP AI research should follow the explainable AI strategy, in which the AI system is divided into numerous components (eg, pre-diagnostic

Table 3. Pros and cons of artificial intelligence (AI), machine learning (ML), deep learning (DL), transfer learning (TL), and federated learning (FL) for retinopathy of prematurity (ROP) screening

	Pros	Cons
AI	Improved decision support: AI can aid healthcare providers by offering diagnostic assistance, thereby enhancing the precision of ROP screening.	Interpretability concerns: AI systems can be intricate and may lack clarity, making it challenging for clinicians to comprehend the reasoning behind decisions.
	Process automation: AI can streamline routine tasks including image analysis, saving time and lessening the burden on clinicians.	Reliance on data quality: The success of AI systems depends significantly on the quality and quantity of the training data.
	Multimodal data integration: AI can evaluate different types of data (such as clinical, imaging, and demographic information) to deliver a thorough assessment of ROP risk.	Challenges in implementation: Incorporating AI into current clinical workflows can be difficult and may necessitate substantial adjustments to existing practices.
ML	Predictive analytics: ML algorithms can detect patterns in data that may elude human observers, potentially facilitating earlier identification of ROP.	Data constraints: ML models need substantial, well-annotated datasets for training, which can pose challenges in specialized areas like ROP.
	Flexibility: ML models can be updated with new data, enabling them to enhance their performance over time as additional information becomes available.	Overfitting concerns: Without proper management, ML models may become overly tailored to the training data, resulting in poor performance on new, unseen data.
	Resource efficiency: ML can swiftly analyze extensive datasets, allowing for the efficient screening of a large number of patients.	Data bias: If the training dataset contains biases, the ML model may generate biased results, negatively impacting patient care.
DL	High accuracy in image analysis: DL, especially convolutional neural networks, is highly effective in evaluating medical images and often achieves impressive accuracy in identifying ROP.	High computational demand: DL requires considerable computational resources for both training and inference, which may not be accessible in every clinical environment.
	Automated feature learning: DL models can automatically extract relevant features from raw data, minimizing the need for manual feature selection.	Data intensive: DL models generally need substantial labelled datasets to perform effectively, which can be a drawback in ROP screening contexts.
	Scalability: DL models are capable of processing large datasets and recognizing complex patterns, making them ideal for extensive ROP screening initiatives.	Limited interpretability: DL models often function as 'black boxes', making it challenging to understand their decision-making processes, a critical aspect in clinical settings.
TL	Shorter training time: Utilizing pretrained weights from existing models significantly reduces the time needed to train a new model on ROP data.	Domain shift challenges: If the source domain (where the model was pretrained) differs considerably from the target domain (ROP images), the model's performance might suffer.
	Enhanced performance: Leveraging knowledge from related tasks can improve the model's effectiveness, particularly when the dataset for ROP is limited.	Risk of overfitting: Overfitting is a possibility if the model is not adequately fine-tuned for the specific ROP dataset.
	Reduced data dependency: The TL model can yield satisfactory results with smaller datasets, which is advantageous in medical imaging where annotated data may be hard to obtain.	Limited explainability: Employing pretrained models can complicate the understanding of how decisions are made in relation to ROP.
FL	Data privacy: FL facilitates the training of ROP models on decentralized data while keeping sensitive patient information secure, which is essential.	Complex setup: Implementing federated learning systems can be technically demanding and necessitates strong infrastructure.
	Varied data sources: It allows the local ROP model to learn from diverse datasets across multiple institutions, enhancing the model's generalization and robustness.	Increased communication needs: Regular interactions between the central server and local devices may result in higher latency and greater resource usage.
	Ongoing learning: The ROP model can be continuously updated as new data from various sources becomes available, improving its performance over time.	Challenges of heterogeneous data: Differences in the quality and distribution of ROP data across institutions can complicate the training process and impact model performance.

module, picture segmentation module, and final diagnosis module) for ophthalmologists to visualize.

It is unclear if healthcare providers, developers, suppliers, or regulators should be held responsible for AI system errors in real-world clinical practice despite being properly clinically verified. The distribution of liability clarifies not just whether and from whom patients should seek restitution but also if AI systems may find their way into clinical practice.[60] Before AI may be used in clinical settings, ethical frameworks must be developed that outline the legal responsibility of various parties in ensuring that AI functions in a specified manner and implementing proper compensating actions if and when harm happens.

Conclusion

TL and FL are useful in improving generalizability,

repeatability, and data safety when creating ROP models. However, the benefits of TL and FL for ROP AI training may not always result in improved ROP diagnosis and triaging. Future attempts to narrow the interpretability and liability gaps are needed.

Contributors

CYTW and HHWL designed the study, acquired the data, analyzed the data, and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflict of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

References

1. *Dogra MR, Katoch D, Dogra M. An update on retinopathy of prematurity (ROP). Indian J Pediatr 2017;84:930-6.* Crossref
2. *Kumar V, Patel H, Paul K, Surve A, Azad S, Chawla R. Deep learning assisted retinopathy of prematurity screening technique. HEALTHINF 2021;234-43.* Crossref
3. *Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome—structure and function. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Arch Ophthalmol 1990;108:1408-16.* Crossref
4. *Good WV, Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-50.*
5. *Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res 2013;74(Suppl 1):35-49.* Crossref
6. *Campbell JP, Chiang MF, Chen JS, et al. Artificial intelligence for retinopathy of prematurity: validation of a vascular severity scale against international expert diagnosis. Ophthalmology 2022;129:e69-76.* Crossref
7. *Campbell JP, Ryan MC, Lore E, et al. Diagnostic discrepancies in retinopathy of prematurity classification. Ophthalmology 2016;123:1795-801.* Crossref
8. *Prakalapakorn SG, Greenberg L, Edwards EM, Ehret DEY. Trends in retinopathy of prematurity screening and treatment: 2008-2018. Pediatrics 2021;147:e2020039966.* Crossref
9. *Fleck BW, Williams C, Juszczak E, et al. An international comparison of retinopathy of prematurity grading performance within the Benefits of Oxygen Saturation Targeting II trials. Eye 2018;32:74-80.* Crossref
10. *Gschließer A, Stifter E, Neumayer T, et al. Inter-expert and intra-expert agreement on the diagnosis and treatment of retinopathy of prematurity. Am J Ophthalmol 2015;160:553-60.e3.* Crossref
11. *Chiang MF, Jiang L, Gelman R, Du YE, Flynn JT. Interexpert agreement of plus disease diagnosis in retinopathy of prematurity. Arch Ophthalmol 2007;125:875-80.* Crossref
12. *Peng Y, Chen Z, Zhu W, et al. ADS-Net: attention-awareness and deep supervision based network for automatic detection of retinopathy of prematurity. Biomed Opt Express 2022;13:4087-101.* Crossref
13. *Tan Z, Simkin S, Lai C, Dai S. Deep learning algorithm for automated diagnosis of retinopathy of prematurity plus disease. Transl Vis Sci Technol 2019;8:23.* Crossref
14. *Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 2019;103:167-75.* Crossref
15. *Scruggs BA, Chan RVP, Kalpathy-Cramer J, Chiang MF, Campbell JP. Artificial intelligence in retinopathy of prematurity diagnosis. Transl Vis Sci Technol 2020;9:5.* Crossref
16. *Gensure RH, Chiang MF, Campbell JP. Artificial intelligence for retinopathy of prematurity. Curr Opin Ophthalmol 2020;31:312-7.* Crossref
17. *Ramanathan A, Athikarisamy SE, Lam GC. Artificial intelligence for the diagnosis of retinopathy of prematurity: a systematic review of current algorithms. Eye 2023;37:2518-26.* Crossref
18. *Indolia S, Goswami AK, Mishra SP, Asopa P. Conceptual understanding of convolutional neural network: a deep learning approach. Procedia Comput Sci 2018;132:679-88.* Crossref
19. *Taye MM. Theoretical understanding of convolutional neural network: concepts, architectures, applications, future directions. Computation 2023;11:52.* Crossref
20. *Anwar A. Difference between AlexNet, VGGNet, ResNet, and inception. Towards Data Science. Accessed 27 July 2024. Available from: https://towardsdatascience.com/the-w3h-of-alexnet-vggnet-resnet-and-inception-7baaaecccc96.*
21. *Nabil M. Unveiling the diversity: A comprehensive guide to types of CNN architectures Medium. Accessed 27 July 2024. Available from: https://medium.com/@navarai/unveiling-the-diversity-a-comprehensive-guide-to-types-of-cnn-architectures-9d70da0b4521.*
22. *Maitra P, Shah PK, Campbell PJ, Rishi P. The scope of artificial intelligence in retinopathy of prematurity (ROP) management. Indian J Ophthalmol 2024;72:931-4.* Crossref
23. *Bai A, Carty C, Dai S. Performance of deep-learning artificial intelligence algorithms in detecting retinopathy of prematurity: a systematic review. Saudi J Ophthalmol 2022;36:296-307.* Crossref
24. *Kairouz P, McMahan HB, Avent B, et al. Advances and open problems in federated learning. Foundations Trends Machine Learning 2021;14:1-210.* Crossref
25. *Federated learning. Wikipedia. Accessed 27 July 2024. Available from: https://en.wikipedia.org/w/index.php?title=Federated_learning&oldid=1236419947.*
26. *Coyner AS, Chen JS, Chang K, et al. synthetic medical*

images for robust, privacy-preserving training of artificial intelligence: application to retinopathy of prematurity diagnosis. Ophthalmol Sci 2022;2:100126. Crossref

27. *Kalpathy-Cramer J, Campbell JP, Erdogmus D, et al. Plus disease in retinopathy of prematurity: improving diagnosis by ranking disease severity and using quantitative image analysis. Ophthalmology 2016;123:2345-51.* Crossref
28. *Ruamviboonsuk P, Kaothanthong N, Ruamviboonsuk V, Theeramunkong T. Transfer Learning for Artificial Intelligence in Ophthalmology. In: Yogesan K, Goldschmidt L, Cuadros J, Ricur G, editors. Digital Eye Care and Teleophthalmology: a Practical Guide to Applications. Springer International Publishing; 2023: 181-98.* Crossref
29. *Al-Timemy AH, Ghaeb NH, Mosa ZM, Escudero J. Deep transfer learning for improved detection of keratoconus using corneal topographic maps. Cognit Comput 2022;14:1627-42.* Crossref
30. *Rao DP, Savoy FM, Tan JZE, et al. Development and validation of an artificial intelligence based screening tool for detection of retinopathy of prematurity in a South Indian population. Front Pediatr 2023;11:1197237.* Crossref
31. *Wang J, Ju R, Chen Y, et al. Automated retinopathy of prematurity screening using deep neural networks. EBioMedicine 2018;35:361-8.* Crossref
32. *Chen JS, Coyner AS, Ostmo S, et al. Deep learning for the diagnosis of stage in retinopathy of prematurity: accuracy and generalizability across populations and cameras. Ophthalmol Retina 2021;5:1027-35.* Crossref
33. *Subramaniam A, Orge F, Douglass M, et al. Image harmonization and deep learning automated classification of plus disease in retinopathy of prematurity. J Med Imaging (Bellingham) 2023;10:061107.* Crossref
34. *Brown JM, Campbell JP, Beers A, et al. Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. JAMA Ophthalmol 2018;136:803-10.* Crossref
35. *Mao J, Luo Y, Liu L, et al. Automated diagnosis and quantitative analysis of plus disease in retinopathy of prematurity based on deep convolutional neural networks. Acta Ophthalmol 2020;98:e339-45.* Crossref
36. *Understanding the quadratic weighted kappa. Kaggle. Accessed 17 July 2024. Available from: https://www.kaggle.com/code/reighns/understanding-the-quadratic-weighted-kappa.*
37. *Yildiz VM, Tian P, Yildiz I, et al. Plus disease in retinopathy of prematurity: convolutional neural network performance using a combined neural network and feature extraction approach. Transl Vis Sci Technol 2020;9:10.* Crossref
38. *Tong Y, Lu W, Deng QQ, Chen C, Shen Y. Automated identification of retinopathy of prematurity by image-based deep learning. Eye Vis (Lond) 2020;7:40.* Crossref
39. *Cadrin-Chênevert A. Moving from ImageNet to RadImageNet for improved transfer learning and generalizability. Radiol Artif Intell 2022;4:e220126.* Crossref
40. *Ayana G, Dese K, Choe SW. Transfer learning in breast cancer diagnoses via ultrasound imaging. Cancers (Basel) 2021;13:738.* Crossref
41. *Iman M, Arabnia HR, Rasheed K. A review of deep transfer learning and recent advancements. Technologies 2023;11:40.* Crossref
42. *Li W, Huang R, Li J, et al. A perspective survey on deep transfer learning for fault diagnosis in industrial scenarios: theories, applications and challenges. Mech Syst Signal Process 2022;167:108487.* Crossref
43. *Campbell JP, Lee AY, Abràmoff M, et al. Reporting guidelines for artificial intelligence in medical research. Ophthalmology 2020;127:1596-9.* Crossref
44. *Ting DSW, Wong TY, Park KH, Cheung CY, Tham CC, Lam DSC. Ocular Imaging Standardization for Artificial Intelligence Applications in Ophthalmology: the joint position statement and recommendations from the Asia-Pacific Academy of Ophthalmology and the Asia-Pacific Ocular Imaging Society. Asia Pac J Ophthalmol (Phila) 2021;10:348-9.* Crossref
45. *Tom E, Keane PA, Blazes M, et al. Protecting data privacy in the age of ai-enabled ophthalmology. Transl Vis Sci Technol 2020;9:36.* Crossref
46. *Chang K, Balachandar N, Lam C, et al. Distributed deep learning networks among institutions for medical imaging. J Am Med Inform Assoc 2018;25:945-54.* Crossref
47. *Yang Z, Chen M, Wong KK, Poor HV, Cui S. Federated learning for 6G: applications, challenges, and opportunities. Proc Est Acad Sci Eng 2022;8:33-41.* Crossref
48. *Konečný J, Brendan McMahan H, Yu FX, Richtárik P, Suresh AT, Bacon D. Federated learning: strategies for improving communication efficiency. Accessed 27 July 2024. Available from: http://arxiv.org/abs/1610.05492.*
49. *Rieke N, Hancox J, Li W, et al. The future of digital health with federated learning. NPJ Digit Med 2020;3:119.* Crossref
50. *Lu C, Hanif A, Singh P, et al. Federated learning for multicenter collaboration in ophthalmology: improving classification performance in retinopathy of prematurity. Ophthalmol Retina 2022;6:657-63.* Crossref
51. *Hanif A, Lu C, Chang K, et al. Federated learning for multicenter collaboration in ophthalmology: implications for clinical diagnosis and disease epidemiology. Ophthalmol Retina 2022;6:650-6.* Crossref
52. *Redd TK, Campbell JP, Brown JM, et al. Evaluation of a deep learning image assessment system for detecting severe retinopathy of prematurity. Br J Ophthalmol 2018:bjophthalmol-2018-313156.* Crossref
53. *Sharafi SM, Ebrahimiadib N, Roohipourmoallai R, Farahani AD, Fooladi MI, Khalili Pour E. Automated diagnosis of plus disease in retinopathy of prematurity using quantification of vessels characteristics. Sci Rep 2024;14:6375.* Crossref
54. *Ryan MC, Ostmo S, Jonas K, et al. Development and evaluation of reference standards for image-based telemedicine diagnosis and clinical research studies in ophthalmology. AMIA Annu Symp Proc 2014;2014:1902-10.*
55. *Bellemo V, Lim ZW, Lim G, et al. Artificial intelligence using deep learning to screen for referable and vision-threatening diabetic retinopathy in Africa: a clinical validation study. Lancet Digit Health 2019;1:e35-44.* Crossref
56. *Ting DSW, Wu WC, Toth C. Deep learning for retinopathy of prematurity screening. Br J Ophthalmol 2018:bjophthalmol-2018-313290.* Crossref
57. *Taylor S, Brown JM, Gupta K, et al. Monitoring disease progression with a quantitative severity scale for retinopathy of prematurity using deep learning. JAMA Ophthalmol 2019;137:1022-8.* Crossref
58. *Greenwald MF, Danford ID, Shahrawat M, et al. Evaluation of artificial intelligence-based telemedicine screening for retinopathy of prematurity. J AAPOS 2020;24:160-2.* Crossref
59. *Campbell JP, Singh P, Redd TK, et al. Applications of artificial intelligence for retinopathy of prematurity screening. Pediatrics 2021;147:e2020016618.* Crossref
60. *Li Z, Wang L, Wu X, et al. Artificial intelligence in ophthalmology: The path to the real-world clinic. Cell Rep Med 2023;4:101095.* Crossref

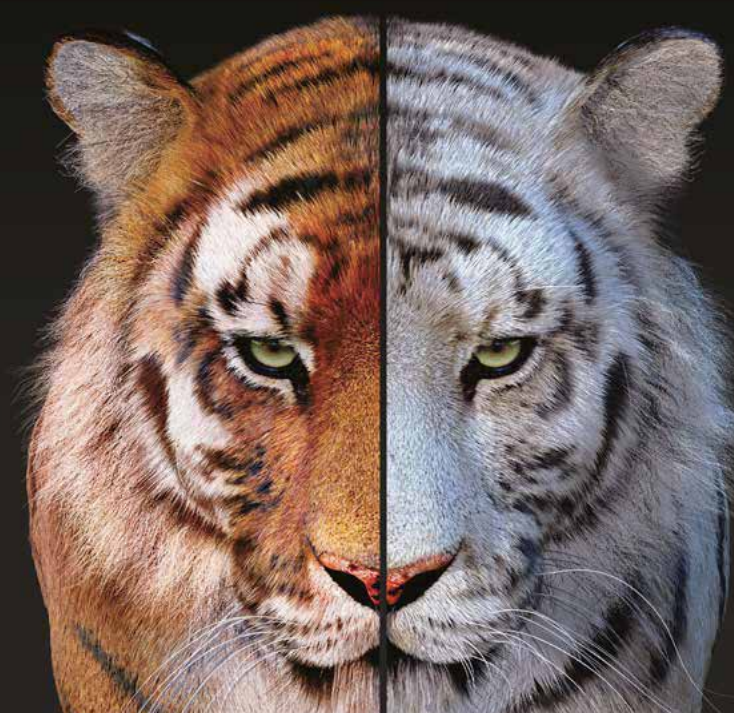
Acknowledgements

The Editor-in-Chief is grateful to the following individuals who acted as reviewers for the Journal during the past year.

Sunny Chi Lik Au
Karen Chan
Carol YL Cheung
Kelvin Chong
Derek Chung
Jonathan Ho
Andrew Kuk
Nai Man Lam
Stacey Lam
Jacky Lee
Dexter Leung
Peter Leung
Felix Li
Fiona Luk
Andrew Mak
Alex Ng
Christopher See
Kendrick Shih
Daniel Wong
Emily Suhan Wong
Hon Wah Yung

REDUCTION OF INTRAOCULAR PRESSURE (IOP) IN PATIENTS WITH OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION
WHO ARE INSUFFICIENTLY RESPONSIVE TO TOPICAL BETA-BLOCKERS OR PROSTAGLANDIN ANALOGUES

STRONGER TOGETHER



NEW

Fixapost®

latanoprost 50 micrograms/ml + **timolol** 5 mg/ml
eye drops, solution in single-dose container

The first PRESERVATIVE-FREE
Latanoprost/Timolol fixed combination[1]

1st choice
in 2nd line treatment

For patients insufficiently controlled with monotherapy
→ Higher IOP reduction with good tolerability profile

For previously treated patients with preserved fixed combinations
→ Significant improvement in main ocular symptoms[2]

Non-inferior IOP reduction to BAK-preserved latanoprost-timolol fixed combination[3]

Superior tolerability to BAK-preserved latanoprost-timolol fixed combinations[2,3]

Maintain patient's quality of life with 0% preservatives[4]

One drop a day[5]

Stored at room temperature[5]

HMS WORLD'S LOCAL PARTNER

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
E-mail: sales@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

REFERENCES:
1. Market data, March 2024 (SU and values) 2. Jandroković, S. et al. Tolerability in Glaucoma Patients Switched from Preserved to Preservative-Free Prostaglandin-Timolol Combination: A Prospective Real-Life Study. Clinical ophthalmology, 2022. 16, 3181–3192. 3. Aptel F. et al. Non-inferiority of Preservative-free versus BAK-preserved Latanoprost-timolol Fixed Combination Eye Drops in Patients with Open-angle Glaucoma or Ocular Hypertension. Journal of Glaucoma. 2019 Mar 26. 28(6):498–506. 4. Thygesen J. Glaucoma Therapy: Preservative-free for All?. Clinical Ophthalmology. 2018:12-707-717 5. Marketing authorisation file; SPC Fixaprost.

Théa let's open our eyes

HMS-FIXTHEA-AD/202311

REDUCTION OF ELEVATED INTRAOCULAR PRESSURE
IN PATIENTS WITH OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION

Monopost®

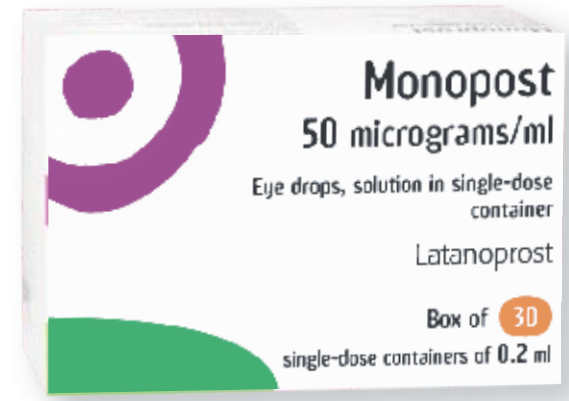
Eye drops solution in single dose container

Latanoprost 0.005%

The first preservative-free latanoprost formulation[1]

with PROVEN[2] EFFICACY

U.S. FDA APPROVED



- **N°1** Prostaglandin in Europe[1]
- Supported by **20 publications**[3]
- More than **1.5 million patients** treated with Monopost® every month in more than **40 countries**[4]
- Good tolerability profile[2]
- Innovative & preservative-free formulation
- Stored at room temperature[5]

HMS-MNPTHEA-AD/202405

HMS WORLD'S LOCAL PARTNER

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
E-mail: sales@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

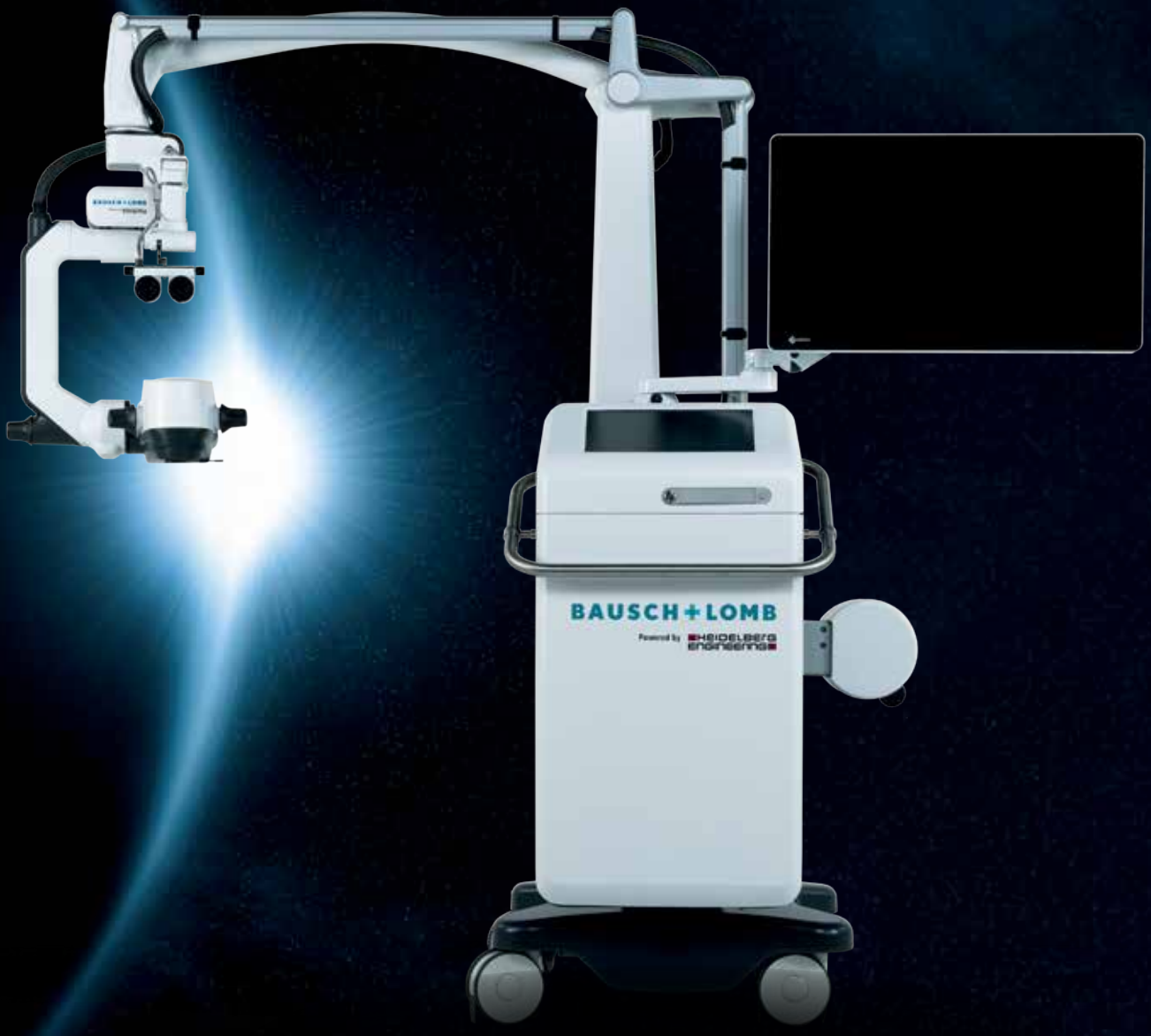
REFERENCES

1. Market Data, March 2024 **2.** Rouland JF. et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. Br J Ophtalmol 2013;97(2):196-200.5. **3.** Data available upon request. **4.** Laboratoires Théa, Internal data, December 2023. **5.** Marketing authorisation file; SPC Monoprost.

Théa let's open our eyes

THE NEW DIMENSION

FULLY DIGITAL VISUALIZATION



SEE LUMA™

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road, Tsim Sha Tsui, Kowloon, Hong Kong. Tel: 2213 3333
HK-SU-2023-10-012

BAUSCH+LOMB
See better. Live better.

ELEVATE
THE EVERYDAY

enVista HYDROPHOBIC ACRYLIC IOL ASPIRE™

Transcend the boundaries of standard monofocals and deliver your patients an IOL designed for the modern world.

BROADER DEPTH OF FOCUS
COMPARED TO THE AO MONOFOCAL OPTIC [1]

3C CONTROLLED CURVATURE CHANGE TECHNOLOGY

Uncompromised distance contrast sensitivity compared to the AO monofocal optic.[1]

A 1.5mm central zone on the posterior surface designed to create a broader depth of focus.[1]

The original glistening-free optic material.[2]

enVista ASPIRE
HYDROPHOBIC ACRYLIC IOL

References:
1. enVista Aspire Directions for Use, Bausch & Lomb. 2. enVista Directions for Use, Clinical Data [May 2017].

Bausch & Lomb (HK) Ltd.
Suites 3901 & 3912-14, 39/F, Tower 6, The Gateway, 9 Canton Road,
Tsim Sha Tsui, Kowloon, Hong Kong Tel: +852 2213 3333 HK-SU-2024-11-010

BAUSCH+LOMB

VYZULTA™
(latanoprostene bunod ophthalmic solution),0.024%

20 YEARS
OF BREAKTHROUGH IN GLAUCOMA TREATMENT

Indication

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1]

One molecule, two pathways

Lowers IOP by increasing outflow through both the trabecular meshwork and uveoscleral pathway[1]

Remarkable efficacy

Reduced the mean IOP up to 9.0 mmHg from baseline[2*]

Demonstrated safety

<1% discontinuation rate due to ocular adverse effects[1]

***VOYAGER study design:** a randomized, parallel-group, phase 2 study, which compared the efficacy and safety of 4 doses of VYZULTA™ and latanoprost 0.005% in 413 patients with open-angle glaucoma or ocular hypertension. Primary endpoint was the change of mean diurnal IOP at day 28 from baseline. The mean IOP at baseline was 26.0 mmHg in the VYZULTA™ 0.024% group and 26.2 mmHg in the latanoprost 0.005% group.[2]

IOP=intraocular pressure.

References: 1. VYZULTA Hong Kong prescribing information. **2.** Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. Br J Ophthalmol 2015; 99(6): 738-45.

INDICATION VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. **DOSAGE AND AMINISTRATION** The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect. If VYZULTA™ is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart. **IMPORTANT SAFETY INFORMATION** • Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. • Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation. • Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA™ should generally not be used in patients with active intraocular inflammation. • Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. • There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients. • Contact lenses should be removed prior to the administration of VYZULTA™ and may be reinserted 15 minutes after administration. • The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation. Please refer to full package insert for the detail.

For healthcare professional only.
Please refer to full Prescribing Information and additional Important Safety Information for VYZULTA™.

BAUSCH + LOMB
See better. Live better.

Bausch & Lomb (H.K.) Ltd.
Suites 3901 & 3912-14, 39/F
Tower 6, The Gateway, 9 Canton Road
Tsim Sha Tsui, Kowloon, Hong Kong
Tel: (+852) 2213 3333