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Article

A Fusion-based AI Approach for Dry Eye Disease Diagnosis using Multiple Sources of Digital Ophthalmic Data: A Bibliographic Study

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Abstract: Dry eye disease (DED) is one of the most common eye diseases. There is at least one DED patient in almost every five people. AI-based research methods increasingly become the focus of DED diagnosis research. This study utilizes a systematic review method on DED AI-based diagnosis. 2112 unduplicated records are extracted from Google Scholar, Web of Science (WOS), PubMed, China National Knowledge Infrastructure (CNKI), and Scopus databases. The most contributed countries, institutions, authors, journals, references, and disciplines are recognized. Keyword distribution and hot topics are identified. Popular databases of ophthalmic images, videos, and electronic demographic medical records are discussed. The DED diagnosis, classification, and grading criteria are identified. The major diagnosing methods are clustered, compared, and investigated. Findings show that diagnosing method research could be classified into three categories based on the relationship between AI techniques, which are (1) ground truth and/or comparable standards for AI DED diagnosis (TBUT, S I T, TMH, and OSDI), (2) potential methods for AI-based methods have a great advantage(DED detection based on meibometry Images, CASPs, IVCM Images, OCT Images, blink videos and ultrasonic imaging), (3) and the potential direction and supplemented methods for AI-based DED detection (DED detections based on tear osmolarity, proteomic analysis, TCM and demographic information). AI-based approaches based on digital ophthalmologic images play an important role in early screening. Challenges and future perspectives are discussed at the end of this article, academically and practically.

Keywords: Dry eye disease; Artificial Intelligence; diagnosis; bibliographic study

1. Introduction

Dry eye disease (DED) is one of the most common eye diseases and a primary cause of ocular surface dysfunction and inflammation. 5-30% of the world's population and more than 15 million Americans suffer from DED (Baratta, Schlumpf, Del Buono, DeLorey, & Calkins, 2022). The severity of DED varies significantly. Due to the complicated etiology, the prevalence and recurrence rates are incredibly high. The patients are unwell, and their quality of life is severely impaired (Esen Baris, Guven Yilmaz, & Palamar, 2022; Xi, Qin, & Bao, 2019). In the Covid-19 era, wearing masks has effectively stopped the spread of the virus, which has been linked to an increase in DED symptoms(Esen Baris et al., 2022). DED is a chronic disease that accumulates gradually. People who regularly use video terminals, wear contact lenses and makeup, have long-term eye drops abuse, stay up late for a long time, use their eyes for a long time, and/or are over the age of 30 can all be identified as high risk of DED. The early stage of DED includes irritation, dryness, burning, eye itching, tears, photophobia, eye fatigue, increased secretions, redness, foreign body sensation, and eye pain (Celebi & Mirza, 2016). The late stage of DED can cause corneal ulcers and even perforation, eventually leading to blindness.

The chronic eye disease of DED (Vyas et al., 2022), is described as deficiencies and hyperosmolarity of the precorneal tear film, and instabilities of the tear homeostasis controlling, which leads to ocular surface structure damage, inflammation, and neurosensory abnormalities (Baratta et al., 2022; Craig, Nelson, et al., 2017; Craig, Nichols, et al., 2017; Willcox et al., 2017; Wolffsohn et al., 2017). This eye disease could be caused by a variety of reasons, including thermal and chemical injury, meibomian dysfunction, aqueous tear secretion abnormalities, blepharitis, allergy-related irritation, instable hormonal state, gene defection, unhealthy living habits and environments, eye drops abusing, age and gender, etc. (Baratta et al., 2022). From the anatomy perspective, the tear film is covered by corneal epithelial cells and composed of three layers, which are outer oil layer, middle aqueous layer, and inner mucus layer (Mohamed, Abd El-Hamid, Fathalla, & Fouad, 2022). Problems in each layer may cause dry eyes. Diagnosis and treatments from ophthalmologists are a necessary for DED patients. Typical therapeutic interventions include reducing eye surface inflammation and inflammatory immune responses by topically using tetracycline derivatives, corticosteroids, cyclosporines, and lubricants. However, the issues of recurrent, corneal erosion, keratoconus, and dystrophies are still challenges for DED treatment(Baratta et al., 2022).

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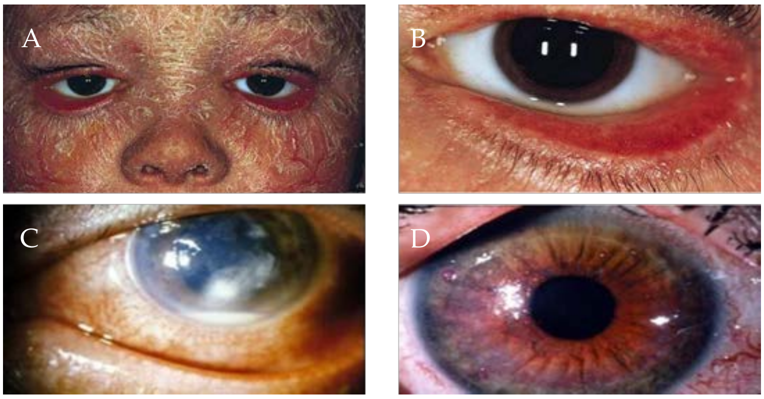

Figure 1 DED cases (A and B are related to MGD, C and D are related to the late stage of DED).

Thus, early diagnosis of DED plays an important role in its treatment. The normal DED diagnosis with Tear break-up time, Schirmer I test, meibometry images, etc. is time-consuming, labor-wasting, and low efficiency(Vyas et al., 2022). AI advanced technologies has been developing and make several remarkable achievements in the medical fields(H. Wang, 2022b; H. Wang et al., 2022; Xing, Liu, Li, et al., 2022; Xing, Liu, Liu, Li, & Wang, 2022). This method exhibits an increasing essential value for ophthalmic eye disease diagnosis. This research concluded 16 methods for AI-based DED detection, which delivers a vital reference value for related studies.

This article is organized as follows. The second chapter is related to the methodology, the third, fourth and fifth part is related to quantitative analysis of AI applied to DED, database, and DED diagnosis methods respectively. Discussions and conclusions are delivered in the last part.

2. Methods

This study utilized the bibliographic study method (H. Wang, 2022a) on the literature databases of Google Scholar, WOS, PubMed, CNKI, and Scopus. 2112 unduplicated records are extracted (Google Scholar: 1765, WOS: 9, Pubmed:148, CNKI:7 and Scopus:173). The search string is set as (dry eye) AND ((artificial intelligen*) OR (machine learning) OR (deep learning) OR (AI)), the period is not limited. The search date is 10th August 2022. The tool of CiteSpcace (R6.1)(Han, 2021; H. Wang, 2022c; H. Wang & Li, 2022) is applied for the quantitative analysis. The text mining is delivered based on the most related extracted papers, where 319 pieces of article are involved.

3. Quantitative analysis of AI applied to DED

3.1. Research developing trend

2112 unduplicated papers are recognized, and the publication developing trend is shown in Figure 2. There is a burst point in 2018, researchers' attentions of DED detection are increasingly developed since 2018.

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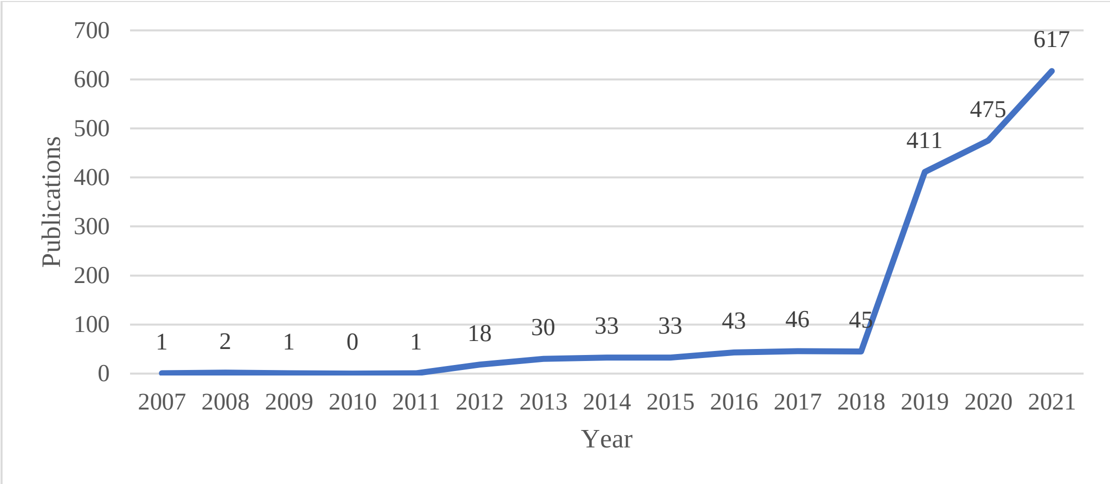

Figure 1 DED research developing trend

3.2. Contributed countries, institutions, authors, journals and cited references

As the Table 1 shown, according to the number of publications, the top-20 contributed countries are The U.S., China, India, Turkey, Japan, The United Kingdom, South Korea, Spain, Italy, Germany, France, Australia, Canada, Brazil, Singapore, Russian Federation, Poland, Saudi Arabia, Switzerland and Egypt. According to the figure 3, topics are classified into 7 clusters based on the country distribution, which are age-related macular degeneration, diabetes, supportive care, meibomian gland dysfunction, Egyptian, particular matter and retinal vascular occlusion. Nodes, links, and density are recognized as 162, 864 and 0.0663, where the cooperation level between countries is relatively low.

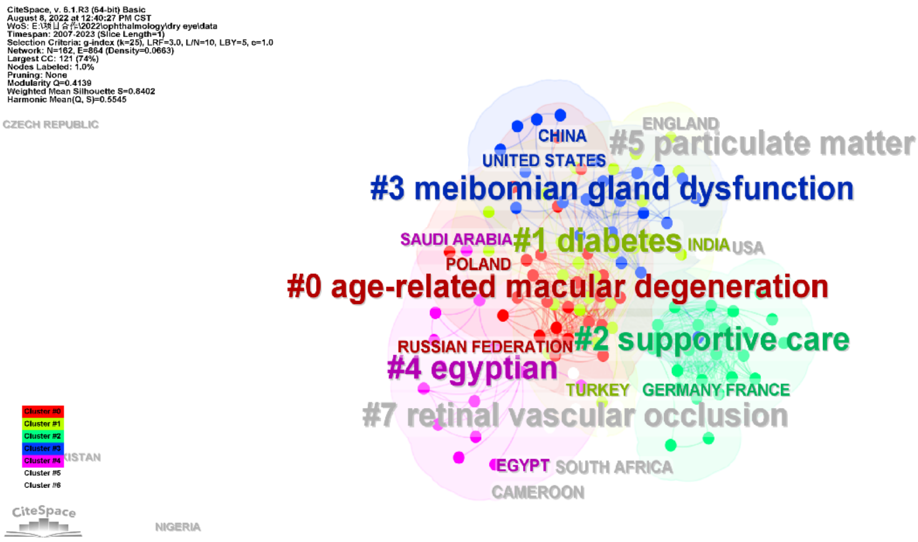

Figure 2 The topic cluster based on country distributions (The different colors represents different clusters).

The top-20 institutions are listed as the following, which are Singapore Eye Research Institute, Bascom Palmer Eye Institute, Keio University, King Saud University, Find peer reviewers from Beijing Tongren Eye Center, Beijing Tongren Hospital,Capital Medical University, Catholic University of Korea, Quinze-Vingts National Ophthalmology Hospital, Gavin Herbert Eye Institute, Beijing Key Laboratory of Restoration of Damaged Ocular Nerve, Peking University Third Hospital, Singapore National Eye Centre, Ophthalmic Research Group, Life and Health Sciences, Aston University, Yong Loo Lin School of Medicine, National University of Singapore, Fujian Provincial Key Laboratory of Ophthalmology and Visual Science, Wilmer Eye Institute, Kyoto Prefectural University of Medicine, Harvard Medical School, Francis I. Proctor Foundation for Research in Ophthalmology, International Islamic University Malaysia, Duke University, Departamento de Física Aplicada (Area de Optometriá) and Universidade de Santiago de Compostel. These institutions are from countries of Singapore, the United States, Japan, Saudi Arabia, China, South Korea, France, Singapore, The United Kingdom, Malaysia and Spain. As the figure 4 shown, topics clustered into 10 classifications based on the institution distribution, which are Sj(o)grens syndrome (SS), overactive bladder, dry eye disease, sensitive early indicator, wax ester, hay fever, pivotal randomized, corneal nerve, age-related macular degeneration characterization and localized follicular lymphoma. Nodes, links, and density are recognized as 469, 1019 and 0.0093, where the cooperation level between institutions is relatively low.

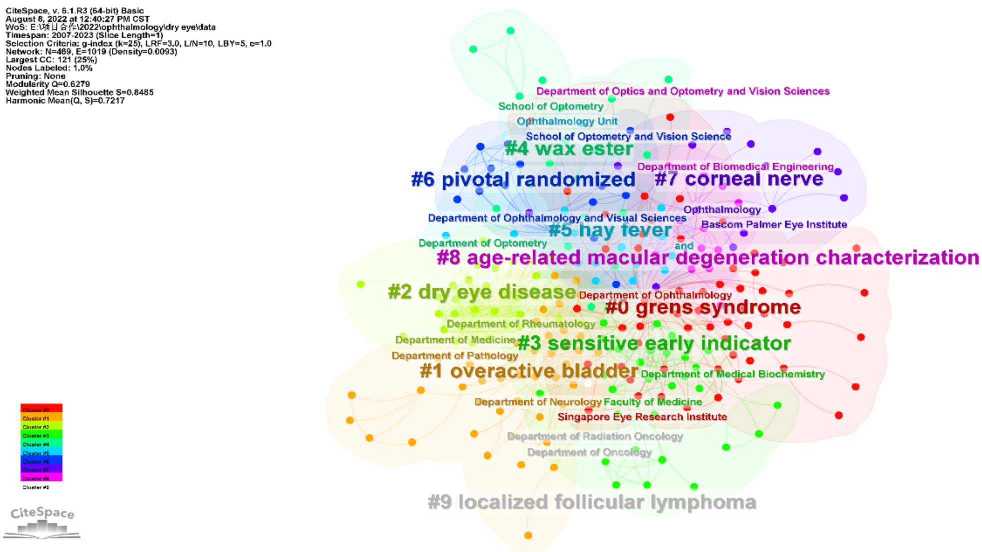

Figure 3 The topic cluster based on institution distributions (The different colors represents different clusters).

The top-20 contributed authors are Lemp, Michael A. Schiffman(M. A. Lemp et al., 2011), Rhett M. Nichols(Schiffman, Christianson, Jacobsen, Hirsch, & Reis, 2000), Kelly K. Pflugfelder(Nichols, Nichols, & Mitchell, 2004), Stephen C(Pflugfelder et al., 2005) and Bron, Anthony J(Bron et al., 2014). As the figure 5 shown, topics clustered into 13 classifications based on the author distribution, which are meibomian gland dysfunction, depression, ocular surface disease, visual function, tear substitute, higher-order aberrations, tear meniscus, retrospective study, dry eye patients (DF), tear osmolarity, covid-19, ocular graft-versus-host disease and Sjogren syndrome. Nodes, links, and density are recognized as 494, 2527 and 0.0208, where the cooperation level between authors is relatively low.

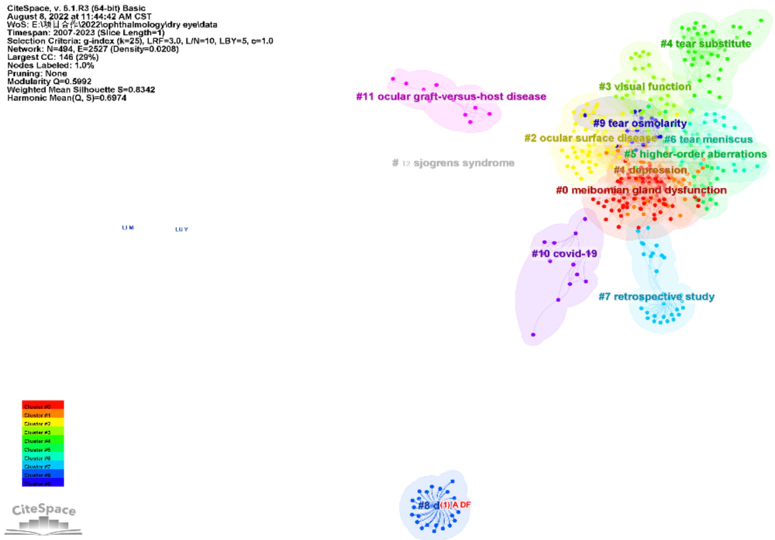

Figure 4 The topic cluster based on author distributions (The different colors represents different clusters).

The top-20 contributed journals (the retrieval time is 11st October 2022) Impact score(IS) according to Academic Accelerator (https://www.resurchify.com/)(Y. Chen, Li, & Wang, 2022) are Ophthalmology(IS=5.21, overall rank=335), Cornea(IS=2.35, overall rank=2566), American Journal of Ophthalmology(IS=4.1, overall rank=982), Investigative Ophthalmology & Visual Science(IS=4.05, overall rank=2361), The ocular surface(IS=5.56, overall rank=1711), JAMA Ophthalmology(IS=3.00, overall rank=973), British Journal of Ophthalmology(IS=4.91, overall rank=1498), Clinical Ophthalmology(IS=2.19, overall rank=4765), Optometry and Vision Science(IS=, overall rank=), Acta Ophthalmologica(IS=1.75, overall rank=8911), Current Eye Research(IS=3.3, overall rank=2635), Eye(IS=3.62, overall rank=2277), Survey of Ophthalmology(IS=5.24, overall rank=1178), Eye & Contact Lens(IS=2.58, overall rank=9902), Plos One(IS=3.58, overall rank=5222), Experimental Eye Research(IS=3.49, overall rank=5169), Contact Lens & Anterior Eye(IS=3.43, overall rank=8554), Current Opinion in Ophthalmology(IS=3.94, overall rank=1785), Journal of Ophthalmology (IS=1.97, overall rank=6330) and BMC Ophthalmology (IS=2.13, overall rank=5854). Publishers of Academic Press Inc., American Medical Association, Association for Research in Vision and Ophthalmology Inc., BioMed Central Ltd., BMJ Publishing Group, Dove Medical Press Ltd., Elsevier Inc., Hindawi Publishing Corporation, Lippincott Williams and Wilkins Ltd., Nature Publishing Group, Public Library of Science, Taylor and Francis

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Ltd. and Wiley-Blackwell Publishing Ltd are identified. Publish places are located in the United States, the United Kingdom, New Zealand and Netherlands. Categories and scopes are recognized as the following, which are Ophthalmology (Q1 and Q2), Arts and Humanities (miscellaneous) (Q1), Medicine (miscellaneous) (Q1 and Q2), Sensory Systems (Q1 and Q2), Optometry (Q2), Multidisciplinary (Q1), Cellular and Molecular Neuroscience (Q2 and Q3). As the figure 6 shown, topics clustered into 13 classifications based on the journal distribution, which are Sjogren syndrome, autoantibodies, graft-versus-host disease, tear substitute, depression, DED, smartphone, tropicamide, Sezary syndrome, trehalose, graduate and candida albicans. Nodes, links and density are recognized as 555, 3061 and 0.0199, where the cooperation level between authors is relatively low.

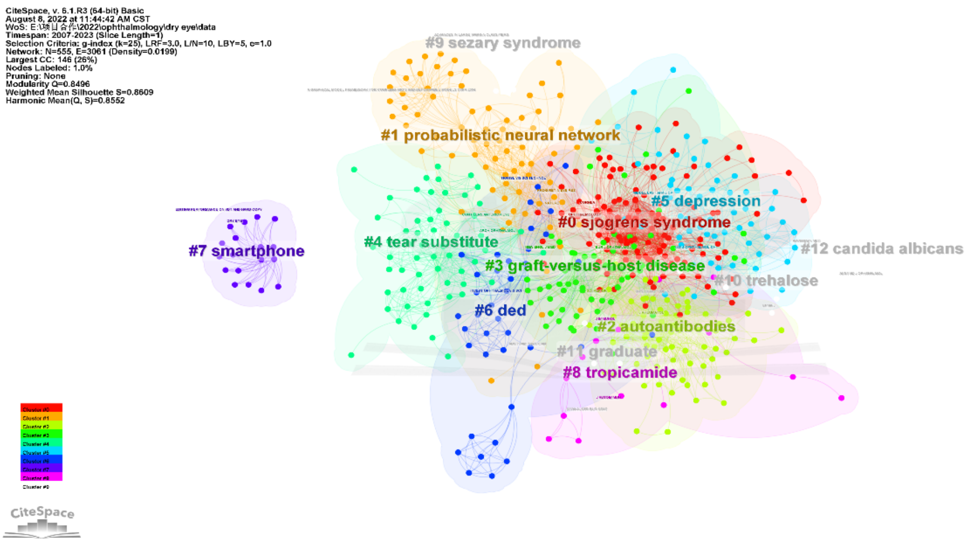

Figure 5 The topic cluster based on journal distributions (The different colors represents different clusters).

The top-20 cited references are TFOS DEWS II Definition and Classification Report(Craig, Nichols, et al., 2017), TFOS DEWS II diagnostic methodology report(Wolffsohn et al., 2017), Prevalence and associated factors of depression in general population of Korea: results from the Korea National Health and Nutrition Examination Survey, 2014(Shin et al., 2017), Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life(Paulsen et al., 2014), TFOS DEWS II epidemiology report(Stapleton et al., 2017). As the figure 7 shown, topics clustered into 5 classifications based on the reference distribution, which are ocular surface disease, diquafosol ophthalmic solution, ocular surface disease index, intense pulsed light, and depression. Nodes, links and density are recognized as 493, 1326 and 0.0109, where the cooperation level between authors is relatively low.

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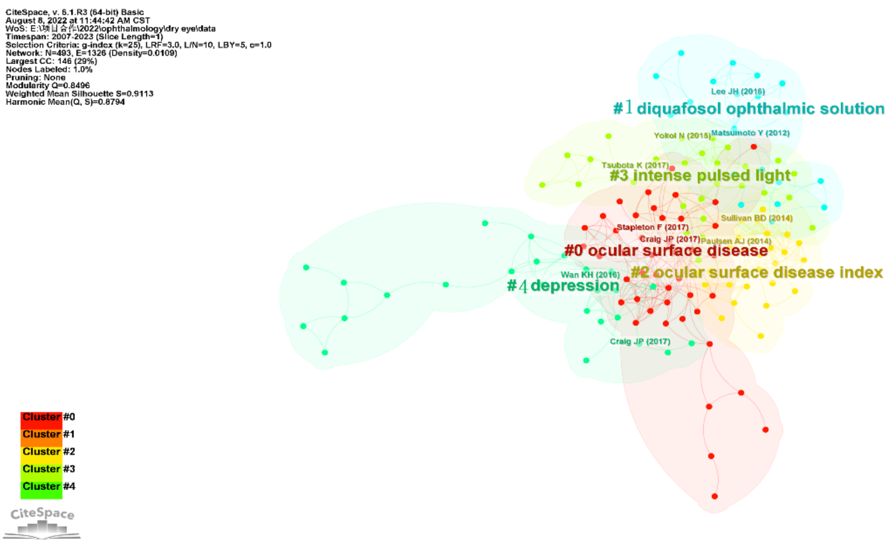

Figure 7. The topic cluster based on literature distributions (The different colors represents different clusters).

3.3. Keywords distribution and latest studies

The keyword distribution is illustrated as the Figure 8 shown, the latest topics of 2022 fall on bacterial eye infection, bacterium culture, blood cell count, cerebrospinal fluid analysis, chill, confusion, connective tissue disease, creatine kinase, creatinine blood level, daily life activity, demographics, diabetes, drug substitution, epistaxis, evaporative dry eye, fibrosis, foreign body, graft versus host disease, graves' disease, graves ophthalmopathy, histology, loss of appetite, medical record, meibum, optical tomography, vancomycin, visual analog scale, visual field defect. According to the number of publications, the hottest topics (count≥200) are related to human, dry eye, article, female, male, adult, middle aged, dry eye syndrome, controlled study, aged, major clinical study, clinical article, lacrimal fluid, tear, priority journal, diagnostic imaging, follow up, case report, dry eye disease, retrospective study, Schirmer test, prevalence, complication, Sjogren syndrome, meibomian gland dysfunction, meibomian gland, young adult, diagnosis.

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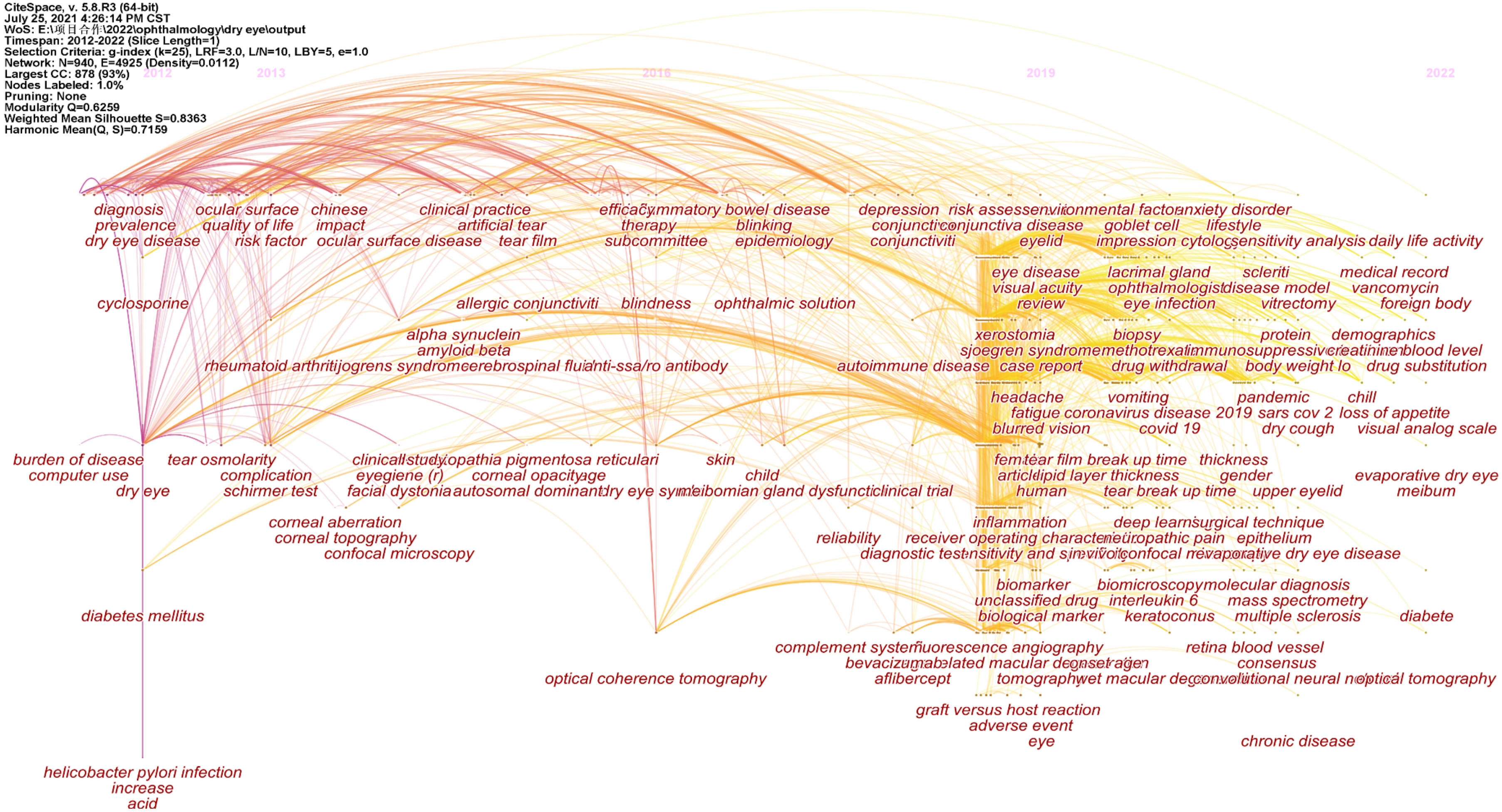

Figure 6 Keywords distribution

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Tab. 1 The quantitative analysis of top-20 contributed countries, institutions, authors, journals and references related to DED diagnosis

Index	Publications	Countries	Publications	Institutions	countries	Cited Frequencies	Authors	Cited Frequencies	Journals	IS	Publisher	Country	Overall Rank	Categories	Cited Frequencies	References
1	439	The U.S.	20	Singapore Eye Research Institute	Singapore	113	Lemp, Michael A(M. A. Lemp et al., 2011)	234	Ophthalmology (ISSN: 15494713, 01616420)	5.21	Elsevier Inc.	United States	335	Ophthalmology (Q1)	30	TFOS DEWS II Definition and Classification Report(Craig, Nichols, et al., 2017)
2	278	China	20	Bascom Palmer Eye Institute	The United States	66	Schiffman, Rhett M(Schiffman et al., 2000)	232	Cornea (ISSN: 15364798, 02773740)	2.35	Lippincott Williams and Wilkins Ltd.	United States	2566	Ophthalmology (Q1)	27	TFOS DEWS II Epidemiology Report(Stapleton et al., 2017)
3	146	India	8	Keio University	Japan	60	Bron, Anthony J(Bron et al., 2014)	227	American Journal of Ophthalmology (ISSN: 00029394, 18791891)	4.1	Elsevier USA	United States	982	Ophthalmology (Q1)	20	TFOS DEWS II diagnostic methodology report(Wolffsohn et al., 2017)
4	128	Turkey	7	King Saud University	Saudi Arabia	51	Nichols, Kelly K(Nichols et al., 2004)	199	Investigative Ophthalmology & Visual Science (ISSN: 01460404, 15525783)	4.05	Association for Research in Vision and Ophthalmology Inc.	United States	2361	Ophthalmology (Q1); Sensory Systems (Q1); Cellular and Molecular Neuroscience (Q2)	11	New Perspectives on Dry Eye Definition and Diagnosis: A Consensus Report by the Asia Dry Eye Society(Tsubota et al., 2017)
5	126	Japan	6	Find peer reviewers from Beijing Tongren Eye Center, Beijing Tongren Hospital,Capital Medical University	China	51	Moss, Scot E.(Moss, Klein, & Klein, 2008)	191	The ocular surface (ISSN: 15420124)	5.56	Elsevier Inc.	United States	1711	OPHTHALMOLOGY - SCIE(Q1)	10	TFOS DEWS II Management and Therapy Report (Jones et al., 2017)
6	114	The United Kingdom	6	Catholic University of Korea	South Korea	48	Pflugfelder, Stephen C(Pflugfelder et al., 2005)	178	JAMA Ophthalmology	3	American Medical Association	United States	973	Ophthalmology (Q1)	9	Dry eye in the beaver dam offspring study: prevalence, risk

									(ISSN: 21686173, 21686165)							factors, and health-related quality of life(Paulsen et al., 2014)
7	104	South Korea	6	Quinze-Vingts National Ophthalmology Hospital	France	47	Schaumberg, D. A.(Uchino & Schaumberg, 2013)	165	British Journal of Ophthalmology (ISSN: 14682079, 00071161)	4.91	BMJ Publishing Group	United Kingdom	1498	Ophthalmology (Q1);	9	TFOS DEWS II management and therapy report(Jones et al., 2017)
8	96	Spain	6	Gavin Herbert Eye Institute	The United States	45	Craig, J. P.(Agarwal, Craig, & Rupenthal, 2021)	102	Clinical Ophthalmology (ISSN: 11775467, 11775483)	2.19	Dove Medical Press Ltd.	New Zealand	4765	Ophthalmology (Q1)	7	Prevalence and associated factors of depression in general population of Korea: results from the Korea National Health and Nutrition Examination Survey(Shin et al., 2017)
9	94	Italy	5	Beijing Key Laboratory of Restoration of Damaged Ocular Nerve, Peking University Third Hospital	China	35	Miljanović, B.(Miljanović, Dana, Sullivan, & Schaumberg, 2007)	98	Optometry and Vision Science (ISSN: 15389235, 10405488)	1.75	Lippincott Williams and Wilkins Ltd.	United States	8911	Ophthalmology (Q2); Optometry (Q2)	7	Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications(Sullivan et al., 2014)
10	93	Germany	5	Singapore National Eye Centre	Singapore	32	Galor, Anat.(Galor et al., 2018)	96	Acta Ophthalmologica (ISSN: 1755375X, 17553768)	3.3	Wiley-Blackwell Publishing Ltd	United Kingdom	2635	Medicine (miscellaneous) (Q1); Ophthalmology (Q1)	7	Tear osmolarity in the diagnosis and management of dry eye disease (M. A. Lemp et al., 2011)
11	72	France	4	Ophthalmic Research Group, Life and Health Sciences, Aston University	The United Kingdom	30	Uchino, Miki(Uchino et al., 2014)	90	Current Eye Research (ISSN: 14602202, 02713683)	2.63	Taylor and Francis Ltd.	United Kingdom	5805	Ophthalmology (Q2); Sensory Systems (Q2); Cellular and Molecular Neuroscience (Q3)	6	TFOS DEWS II Report Executive Summary(Craig, Nelson, et al., 2017)

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12	64	Australia	4	Yong Loo Lin School of Medicine, National University of Singapore	Singapore	28	Wolffsohn, James S.(Wolffsohn et al., 2017)	83	Eye (ISSN: 0950222X, 14765454)	3.62	Nature Publishing Group	United Kingdom	2277	Arts and Humanities (miscellaneous) (Q1); Medicine (miscellaneous) (Q1); Ophthalmology (Q1); Sensory Systems (Q1)	6	Importance of tear film instability in dry eye disease in office workers using visual display terminals: the Osaka study(Yokoi et al., 2015)
13	61	Canada	4	Fujian Provincial Key Laboratory of Ophthalmology and Visual Science	China	28	Schein, Oliver D.(Schein, MUÑO, Tielsch, Bandeen-Roche, & West, 1997)	69	Survey of Ophthalmology (ISSN: 00396257, 18793304)	5.24	Elsevier USA	United States	1178	Ophthalmology (Q1)	6	TFOS DEWS II tear film report(Willcox et al., 2017)
14	54	Brazil	4	Wilmer Eye Institute	The United States	27	Fiona Stapleton(Stapleton et al., 2017)	64	Eye & Contact Lens (ISSN: 1542233X, 15422321)	2.58	Lippincott Williams and Wilkins Ltd.	United States	9902	Medicine (miscellaneous) (Q2); Ophthalmology (Q2)	5	Dry eye disease, dry eye symptoms and depression: the Beijing Eye Study(Labbé et al., 2013)
15	44	Singapore	4	Kyoto Prefectural University of Medicine	Japan	26	Tsubota, Kazuo(Tsubota et al., 2017)	61	Plos One (ISSN: 19326203)	3.58	Public Library of Science	United States	5222	Multidisciplinary (Q1)	5	Prevalence and risk factors of dry eye symptoms in a Saudi Arabian population(Alshamrani et al., 2017)
16	41	Russian Federation	3	Harvard Medical School	The United States	26	Tomlinson, A.(Bron et al., 2014)	55	Experimental Eye Research (ISSN: 00144835, 10960007)	3.49	Academic Press Inc.	United States	5169	Ophthalmology (Q1); Sensory Systems (Q2); Cellular and Molecular Neuroscience (Q3)	5	Depression and anxiety in dry eye disease: a systematic review and meta-analysis(Wan, Chen, & Young, 2016)
17	40	Poland	3	Francis I. Proctor Foundation for Research in Ophthalmology	The United States	24	Sullivan, B. D(Sullivan et al., 2014)	49	Contact Lens & Anterior Eye (ISSN: 14765411, 13670484)	3.43	Elsevier	Netherlands	8554	Medicine (miscellaneous) (Q2); Ophthalmology (Q2); Optometry (Q2)	5	The definition and classification of dry eye disease(M. A. Lemp & Foulks, 2007)

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18	39	Saudi Arabia	3	International Islamic University Malaysia	Malaysia	21	Lin, Pei-Yu(Chou, Fan, & Lin, 2019)	48	Current Opinion in Ophthalmology (ISSN: 10408738, 15317021)	3.94	Lippincott Williams and Wilkins Ltd.	United States	1785	Medicine (miscellaneous) (Q1); Ophthalmology (Q1)	4	Is dry eye an environmental disease?(Alves, Novaes, Morraye, Reinach, & Rocha, 2014)
19	34	Switzerland	3	Duke University	The United States	19	Smith, Janine A(Smith, 2007)	45	Journal of Ophthalmology (ISSN: 2090004X, 20900058)	1.97	Hindawi Publishing Corporation	United States	6330	Ophthalmology (Q2)	4	Dry eye disease and work productivity loss in visual display users: the Osaka study(Uchino et al., 2014)
20	31	Egypt	3	Departamento de Física Aplicada (Area de Optometriá), Universidade de Santiago de Compostel	Spain	19	McCarty, Cathy A.(McCarty & Taylor, 2011)	45	BMC Ophthalmology (ISSN: 14712415)	2.13	BioMed Central Ltd.	United Kingdom	5854	Medicine (miscellaneous) (Q2); Ophthalmology (Q2)	4	Depression, stress, quality of life, and dry eye disease in Korean women: a population-based study(Na, Han, Park, Na, & Joo, 2015)

Tab. 2 The latest publications of AI-based method on DED detection.

Index	Year	References	Data Set	Involved AI-based methods	Results and conclusions	Advantages	Disadvantages
1	2022	A deep learning model established for evaluating lid margin signs with colour anterior segment photography(Y. Wang, Jia, Wei, & Li, 2022)	832 color anterior segment photographs of 428 DED patients.	VGGNet-13	Results: (1) lid margin irregularity: AUC:0.979, Sentiment:0.930, Specificity:0.938; (2) lid margin vascularization: AUC:0.977, Sentiment:0.923, Specificity:0.961; (3) meibomian gland orifice: AUC:0.968, Sentiment:0.889, Specificity:0.948; (MGO) retroplacement: AUC: 0.963, Sentiment:0.979, Specificity:0.909; (4) MGO plugging: AUC:0.968, Sentiment:0.8867, Specificity:0.967 ;(5) mucocutaneous junction (MCJ) anteroplacement: AUC:0.950, Sentiment:0.875, Specificity:0.966; (6) MCJ retroplacement:0.978, Sentiment:0.966, Specificity:0.888.	A high AUC, sentiment and specificity for the DLM training and testing, which exhibits a high reliable level for the results.	There are 8 individual models involved, which is resource wasting. The dataset is too small for a DLM predicting.

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					Conclusions: Deep learning models play a significant role for DED detection based on lip margin symptom evaluations.		
2	2022	Impact of Incomplete Blinking Analyzed Using a Deep Learning Model With the Keratograph 5M in Dry Eye Disease(Zheng et al., 2022)	50 DED patients and 50 normal participants are involved, where symptom questionnaires, blink videos (collected by Keratograph 5M, Wetzlar, Germany) and ocular surface assessments are collected from Hospital of Wenzhou Medical University.	Unet	Results: (1) DL models based on blink videos of 30 frames per second (FPS) under white light presented a low error and a high sensitivity for DED detection. (2) DED patients present a high value for the average relative interpalpebral height (IPH) and the frequency proportion of incomplete blinking (IB).	A high relationship between IPH and the IB frequency proportion and the other Parameters increasing the confidence of this proposed parameters.	The calculation method and threshold of IPH and the IB proportion are not experimentally discussed before. Different source of blink videos collected from different equipment should be considered.
3	2022	Tear film breakup time-based dry eye disease detection using convolutional neural network(Vyas et al., 2022)	TBUT videos	Inception	A high performance is exhibited for DED frame classification (normal, break-up, blink, noise) and DED detection. The accuracy of DED severity grading based on TBUT is 83%. The correlation efficient value between DLM and ophthalmologist decisions is 90%.	It presented an advantage for timesaving and a high accuracy of DED.	More ophthalmologists should be considered when it comes to comparison between AI models and manually detections.
4	2022	Change patterns in the corneal sub-basal nerve and corneal aberrations in patients with dry eye disease: An artificial intelligence analysis(Jing et al., 2022)	The oculus keratography (Wetzlar, Germany) based on In vivo confocal microscopy and ocular surface disease index questionnaire are collected from 177 participants, where 155 DED patients (53 males and 102 females; mean age: 68.54 ± 7.64 years) of 229 eyes and 20 normal subjects(8 males and 12 females; mean age: 64.35 ± 9.53 years) with 40 eyes.	Corneal nerve segmentation network (CNS-Net)(Wei, Shi, Wang, Chou, & Li, 2020)	The corneal sub-basal nerve is extracted and average density and maximum length in corneal nerve morphology are calculated by AI algorithms. Their results show that the cutoff of Strip Meniscometry (SMT) and lower tear meniscus height (LTMH) and lower tear meniscu depth (LTMD) are < 5 mm (AUC 0.994, sensitivity 96.7% and specificity 96.7%), 204.96 μm (AUC of 0.998, sensitivity of 98.3% and specificity of 96.7%) and 190 μm (AUC of 0.995, sensitivity of 96.7% and specificity of 95%) respectively.	It presents a strength of automation and timesaving, high reliability and efficiency, continual learning and refinement alongside concurrent improvement, and good correlation with measurement of experts.	The training dataset is not big enough. The size of the input data is resized as 384*384*3, which is too small and different from the practical situations. According to the architecture of this CNS-net model, global image features are not considered in this model.
5	2022	Infrared Imaging Meibomian Gland Segmentation System Based on Deep Learning(Zhang, Yao, Ding, Pei, & Fu, 2022)	Meibomian gland images	Mobile-U-Net network	Meibomian gland region is segmented. The similarity coefficient of mobile-U-Net network and dry eye detection instruments is 92.71%.	Comparing to the existed dry eye equipment, it is an efficient deep learning model for meibomian ROI segmentations.	A big number of training database is needed for the proposed U-net architecture. The explainable level of this method is relatively low.
6	2022	Automated quantification of meibomian gland	1000 meibomian gland images of 572 eyes of 320 patients (107 men and 213 women) from Yeouido St. Mary's	Improved CNN deep learning model	Meiboscore classification accuracy of 73.01% for DL models on the validation set.	The Dl model presents an advantage of accuracy comparing to	The proposed DL model present a low accuracy for images from

		dropout in infrared meibography using deep learning(Saha et al., 2022)	Hospital (The database is available at https://mgd1k.github.io/).		Meiboscore classification accuracy of 59.17% and 53.44% of the DL model and labelling by ophthalmologists for images from independent centers. The reflection is removed from original MG images.	the manual MGD detection. The reflection is removed from original MG images without affecting meiboscore grading.	independent centers and real word situations
7	2022	EE-Net: An edge-enhanced deep learning network for jointly identifying corneal micro-layers from optical coherence tomography(L. Wang et al., 2022)	1712 OCT images from the Wenzhou Medical University Eye Hospital	edge-enhanced convolutional neural network (EE-Net)	Epithelium layer, Bowman's layer, and stroma layer are delineated at the same time. Comparing to the BiO-Net network, the average dice similarity coefficient (DSC) is 0.9314, the average intersection over union (IOU) is 0.8839, the average Matthew's correlation coefficient (MCC) is 0.9314, and the average sensitivity value is 0.9320.	This method is relatively weight-lighted, resource-saving, and high interpreted level with high accuracy, when it comes to a small size of training database.	It takes more time when it comes to a large size of dataset, comparing to the normal CNN model.
8	2022	Meibomian Gland Density: An Effective Evaluation Index of Meibomian Gland Dysfunction Based on Deep Learning and Transfer Learning(Y. Zhang et al., 2022)	4006 meibomian images of 85 eyes are collected, where 1620 and 2386 images related to the upper and lower eyelid respectively. The data is captured by Oculus Keratograph 5M (K5M; Oculus, Wetzlar, Germany)from Eye Hospital, Wenzhou Medical University.	The 50-layer residual neural network and U-net (ResNet50_U-net) is utilized for image segmentation (cutoff value is set as 0.275). 11 models are utilized for data enhancements (https://github.com/aleju/imgaug#citation, 6 February 2020).	The average processing time of per image is 0.01 second. The value of accuracy, AUC, sensitivity, and specificity is 92%, 0.900, 0.88 and 0.81 respectively.	This model transfer for preprocessing, which is time saving and resource saving. The ResNet50 is for feature extraction and U-net for up-sampling and ROI segmentation, which is with higher accuracy rather than using Resnet or U-Net only.	The quality of generated images by data enhancement models are relatively low with noises, with the fake training images, it may be different when it comes to the real-word data.
9	2022	Comparison of Autonomous AS-OCT Deep Learning Algorithm and Clinical Dry Eye Tests in Diagnosis of Dry Eye Disease (Chase et al., 2021)	27180 AS-OCT images (14040 images of DED and 13140 images of normal) of 151 eyes of 91 subjects, which are collected by using the equipment of HD-OCT (Envisu R2210, Bioptigen, Leica, Buffalo Grove, IL, USA) from the cornea department of the Bascom Palmer Eye Institute.	VGG19 DL model (single GeForce GTX 1080 Ti GPU, parameters are set as the following: learning rate: 0.0001; regularization weight: 0.0001; momentum: 0.9).	For classifying the DED from normal subjects, the DL model presents a sensitivity of 86.36%, a specificity of 82.35%, and accuracy of 84.62%.	This model is an automatic DED detection model by learning the local features, exhibiting an advantage of fast speed when it comes to a large size of database.	This model is a black-box model which is not considering the global features of the images. The dataset is limited by taking by only one equipment.
10	2022	Random Forest Algorithm-Based Ultrasonic Image in the Diagnosis of Patients with Dry Eye Syndrome and Its Relationship with Tear Osmotic Pressure(Jiang, Sun, Chen, & Sun, 2022)	3D ultrasonic images centered on macular for 100 DED patients (42 males and 58 females) aged in the range of 43 to 57.	Random forest (RF) segmentation algorithm	By applying the RF classification algorithm (the number and depth of trees is 16 and 12 respectively), the images were classified into seven categories, which are macular holes (MH), cystoid macular edema (CME), and four retinal structures (L1: NFL; L2: GCL, IPL, INL, and OPL; L3: ONL, ISL; L4: CL, OSL, VM, and RPE) and background region. Based on the ground	RF method is a typical machine learning algorithm, which is quick predictive with high explainable level.	RF machine learning method is a simple model with low efficiency for large number of testing datasets, especially for diversified data the real-world sceneries.

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		truth of central corneal thickness (CCT) measurement, DL model exhibits a greater performance than conventional graph cut, measuring by the values of true positive volume coefficients (TPVF), deiss similarity coefficient (DCS) and false positive volume coefficients (FPVF). The confidence interval of DED patients' CCT value is 22.7-34.2 μm, the average tear osmotic pressure (TSP) for moderate and severe DED are 316.5 mOsm/kg and 403.6 mOsm/kg respectively, CCT value is highly related to TSP(r=0.779;P=0.05).

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4. Database review

Databases of AI based methods for DED detection are classified into three clusters, which are ophthalmic images, videos, and electronic demographic medical records. According to the existing research, it could be concluded as the following types, which are Tear break-up time (TBUT) videos, Cornea Fluorescein Staining (CFS) images, ultrasonic image, interferometry and slit-lamp images, in vivo confocal microscopy (IVCM) images, meibometry images, blink videos, colorful anterior segment photographs (CASP), optical coherence tomography (OCT) images, demographic data, and Ocular Surface Diseast Index (OSDI) questionnaire. Some of the popular databases are concluded in the table 3, descriptions, references and data available policies of TBUT video database, CFS digital image database, in vivo confocal microscopy (IVCM) image database, MGD-1k Dataset, Meibomian Gland image database, Blink video database, colorful anterior segment photograph database, Corneal OCT dataset, AS-OCT database, Ultrasonic Image database, Dry Eye Disease in Medical Students are provided.

Tab. 3 Database of AI applied to DED

Database	Type of Database	Descriptions	References	Data available policies
TBUT video database	Tear break-up time (TBUT) videos	TBUT videos were collected from Vaikunth Eye Clinic, Ahmedabad, Gujarat, India.	(Vyas et al., 2022)	TBUT videos provided by Dr. Ravish Kinkhabwala (M.D. OPHTH, AIIMS, New Delhi) from Vaikunth Eye Clinic, Ahmedabad, Gujarat, India.
CFS digital image database	Interferometry and slit-lamp images of cornea fluorescein staining (CFS)	Slit-lamp photographs of CFS collected from 40 DED patients from Cornea Service of the S.Orsola-Malpighi University Hospital (Bologna, Italy)., where half are related to Sjögren syndrome (SS), and others are related to ocular graft-versus-host disease (oGVHD), whose mean age is 60.7 ± 12.3 years.	(Pellegrini et al., 2019a)	N/A
In vivo confocal microscopy (IVCM) image database	In vivo confocal microscopy (IVCM) images and OSDI questionnaire	The oculus keratography (Wetzlar, Germany) based on In vivo confocal microscopy and OSDI questionnaire are collected from 177 participants, where 155 DED patients of 229 eyes and 20 normal subjects with 40 eyes.	(Jing et al., 2022)	N/A
MGD-1k Dataset	Meibometry images	1000 meibomian gland images of 572 eyes of 320 patients (107 men and 213 women) from Yeouido St. Mary's Hospital. 59 of 1000 images were marked as ungradable at least in one out of 6 rounds. All 941 images contain full gradings. Age: Men (mean 51, std 19), Women (mean: 55 years, std 19) Men/Women ratio: 322(32.2%) / 678 (67.8%) Number of Meibomian Gland Images: 1000 Upper Eyelid images: 467 Lower Eyelid images: 533 Gradable Image number: 941 [94.1%] Color Channel: Single/Grayscale Imaging Device: LipiView II Ocular Surface Interferometer Duration of data collection: 2019 April to 2020 April (1 year) Open source: the database is available at https://mgd1k.github.io/.	(Saha et al., 2022)	This dataset is provided by Gwangju Institute of Science and Technology, The Catholic University of Korea, Yeouido St. Mary's Hospital, College of Medicine.
Meibomian Gland image database	Meibomian Gland images with TUBT, OSDI and lid margin score information	4006 meibomian images of 85 eyes are collected, where 1620 and 2386 images related to the upper and lower eyelid respectively. The data is captured by Oculus Keratograph 5M (K5M; Oculus, Wetzlar, Germany) from Eye Hospital, Wenzhou Medical University.	(Z. Zhang et al., 2022)	The datasets generated during and/or analyzed during the current study are available from the corresponding author(Zuhui Zhang, School of Ophthalmology and Optometry, The Eye Hospital of Wenzhou Medical University, 270 Xueyuanxi Road, Wenzhou 325027, China.) on reasonable request.
Blink video database	One-minute blink videos, OSDI questionnaire, DEQ-5 questionnaire, tear meniscus	50 DED patients and 50 normal participants are involved, where symptom questionnaires, blink videos (collected by Keratograph 5M, Wetzlar,	(Zheng et al., 2022)	N/A

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	height (TMH), and first noninvasive tear film breakup time (NIBUT)	Germany) and ocular surface assessments are collected from Hospital of Wenzhou Medical University.		
colorful anterior segment photograph database	colorful anterior segment photographs	832 color anterior segment photographs of 428 DED patients.	(Y. Wang et al., 2022)	The datasets are available from the corresponding author (Xuemin Li., Department of Ophthalmology, Beijing Key Laboratory of Restoration of Damaged Ocular Nerve, Peking University Third Hospital, Beijing, China) upon reasonable request.
Corneal OCT dataset	optical coherence tomography (OCT) images.	1712 OCT images (sized 2048×1365 pixels) acquired from the Wenzhou Medical University Eye Hospital	(L. Wang et al., 2022)	N/A
AS-OCT database	Anterior segment optical coherence tomography (AS-OCT) images with information of corneal International Classification of Diseases, 10th Revision (ICD-10) diagnosis,	27180 AS-OCT images (14040 images of DED and 13140 images of normal) of 151 eyes of 91 subjects form December 2016 to October 2019, which are collected by using the equipment of HD-OCT (Envisu R2210, Bioptigen, Leica, Buffalo Grove, IL, USA) from the cornea department of the Bascom Palmer Eye Institute.	(Chase et al., 2021)	N/A
Ultrasonic Image database	3D ultrasonic images with information of	3D ultrasonic images centered on macular collected from June 2018 to June 2021 for 100 DED patients (42 males and 58 females) aged in the range of 43 to 57.	(Jiang et al., 2022)	The data used to support the findings of this study are available from the corresponding author (Lei Jiang, Department of Ophthalmology, The Third Peoples' Hospital of Changzhou, Changzhou, 213001 Jiangsu, China.) upon request.
Dry Eye Disease in Medical Students	Tear break-up time (TBUT) videos and OSDI questionnaire.	Purpose: Explore the DED of the medical students during lockdown time due to the convid-19. Size of dataset: 126 KB Columns: timestamp. Age, gender, academic year, OSDI questions (What type of Digital display device do you use; How many hours in a day do you spend on your smartphones, laptops, etc.; Eyes that are sensitive to light; Eyes that feel gritty (itchy and Scratchy); Painful or Sore eyes). Open source available at: https://www.kaggle.com/datasets/shankar24397/dry-eye-disease-in-medical-students Publish time:2020 Retrieval time: 29th October 2022	https://www.kaggle.com/datasets/shankar24397/dry-eye-disease-in-medical-students	The dataset is provided by Shankar AJ (a Software Engineer at LTI, Mumbai, Maharashtra, India)

5. DED diagnosis methods

16 DED diagnosis methods are concluded in this study (table 4), which are tear break-up time (TBUT), schirmer I test (SIT), ocular surface disease index (OSDI) questionnaire, tear meniscus height(TMH), cornea fluorescein staining (CFS) score, proteomic analysis, lid margin abnormalities based on colorful segment anterior photographs (CASPs), traditional Chinese medicine (TCM) diagnosis and DED detection based on In Vivo Confocal Microscopy (IVCM) Images, meibometry Images, OCT Images, blink videos, tear osmolarity, ultrasonic imaging and Demographic Factors. Based on the previous research, this study clusters these methods into three categories (figure 9). (1) TBUT, S I T, TMH, and OSDI are the most acceptable, conventional, and typical methods for DED detection, which are usually regarded as the ground truth and comparable criteria for AI methods research. (2) AI-based methods have a great advantage for cornea fluorescein Staining (CFS) images, meibometry Images, colorful segment anterior photographs (CASPs), IVCM Images, OCT Images, blink videos and ultrasonic imaging. (3) The DED detection based on tear osmolarity, proteomic analysis, TCM and demographic information are regarded as the potential direction and supplemented methods, especially for AI-based ophthalmic applications.

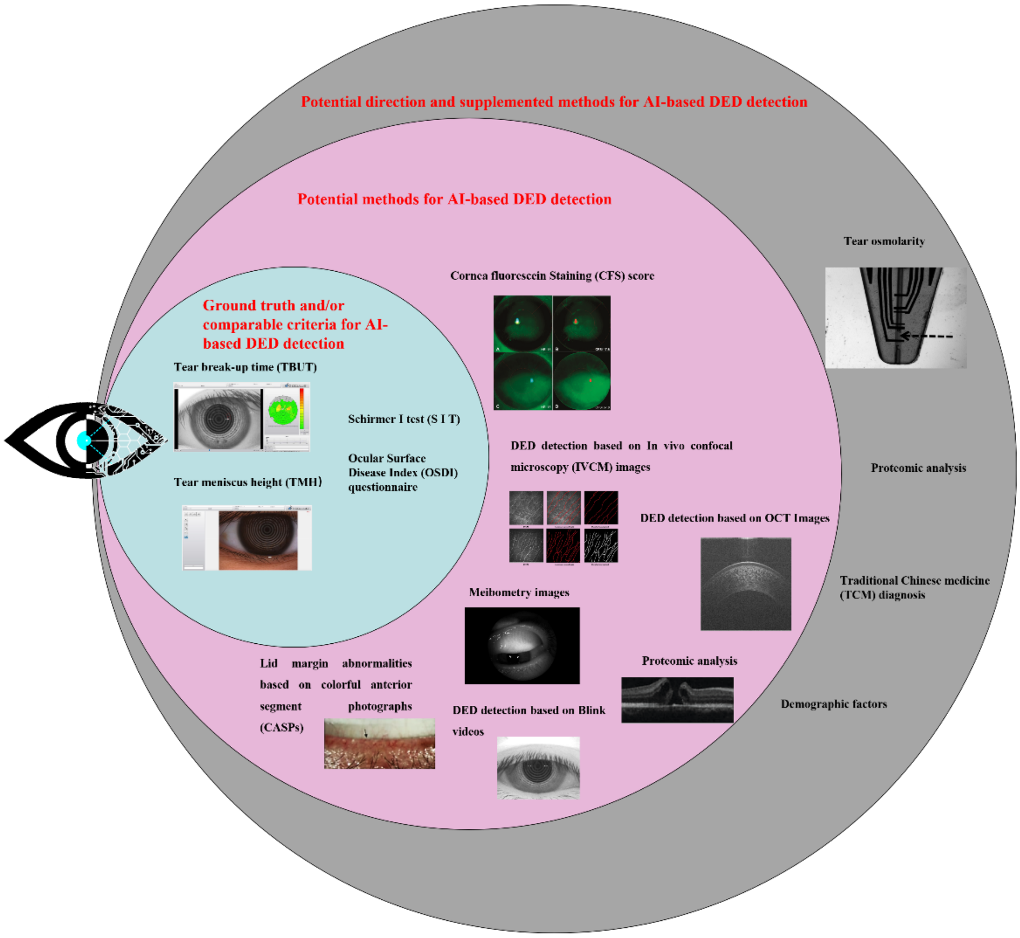

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Figure 7 AI-based DED diagnosis methods clusters(Amparo, Wang, Yin, Marmalidou, & Dana, 2017; Celebi & Mirza, 2016; Jiang et al., 2022; Jing et al., 2022; Karasu & Celebi, 2022; Sebbag et al., 2017; Y. Wang et al., 2022).

5.1. Ground truth and/or comparable criteria for AI-based DED detection

5.1.1. Tear break-up time (TBUT)

TBUT is one of the most common clinical diagnostic standards of DED, it is always be regarded as the ground truth for DED detection (Jones et al., 2017; Xiaocong et al., 2022). It is measured on the tear film by calculating the time the first breakup pattern emerges(Vyas et al., 2022). TBUT is tested and evaluated based on Cornea Fluorescein Staining (CFS) and slit-lamp images or AI-based dry eye detection devices (e.g., Keratograph 77000), where a process of fluorescein instillation may be involved. After the sodium fluorescein strip wet with preservative-free saline, it touches subjects' inferotemporal bulbar conjunctiva. Subjects are requested to blink, the precorneal tear film is measured by a biomicroscope with a 10 times objective under blue-light illumination. Then record the interval between the first black spot or interruption in precorneal fluorescein tear layer. Each eye was read three times and average the results as the final TBUT result (De Paiva & Pflugfelder, 2004). The shorter the TBUT, the more unstable the tear film, and the higher the probability of DED. Machine learning (ML) has been used to detect region of interests (ROI) of TBUT, which is most used for DED early screening (Storås et al., 2022). The advantages of AI-based method for DED diagnosis based on TBUT are timesaving and resource-saving. However, because of lack of public datasets and low quality of obtained data, especially for blurred video, illuminated videos, constant blinking of eyes in the videos, the challenges and issues are difficult to be solved(Vyas et al., 2022). Zhang et. al. (2022) (Z. Zhang et al., 2022) utilized the mean value of 3 TBUT measuring records as the final TBUT result. The normal range of TBUT is from 5.00 to 7.75, DED is 1.33-3.67. TBUT is a significant indicator for DED diagnosis, which is usually regarded as grounded truth for DED detection (the cutoff is ≤ 10 seconds). However, TBUT method is criticized for the weakness of time-costing, resource-consuming, low reproducibility, and high variations in values (Chase et al., 2021). Furthermore, when it comes to the real world, the result could be not accurate under specific situations, for instance, patients could be nervous when using an equipment for TBUT test. Besides, some of hospitals still using the interferometry and slit-lamp and CFS images for DED detection, this method is mildly invasive, the injection of fluorescent agent may cause eye allergy and discomfort (Chase et al., 2021). The figure 10 is captured by Keratograph 77000 (Wetzlar, Germany) of a female patient from Aier eye hospital in China (capture time: 5th March, 2022), the TBUT result is 9.75, the tear break-area is emerged at the 9.75 second illustrated as the red box shown, the break-up degree and the area during the test time is exhibit as the chart figure.

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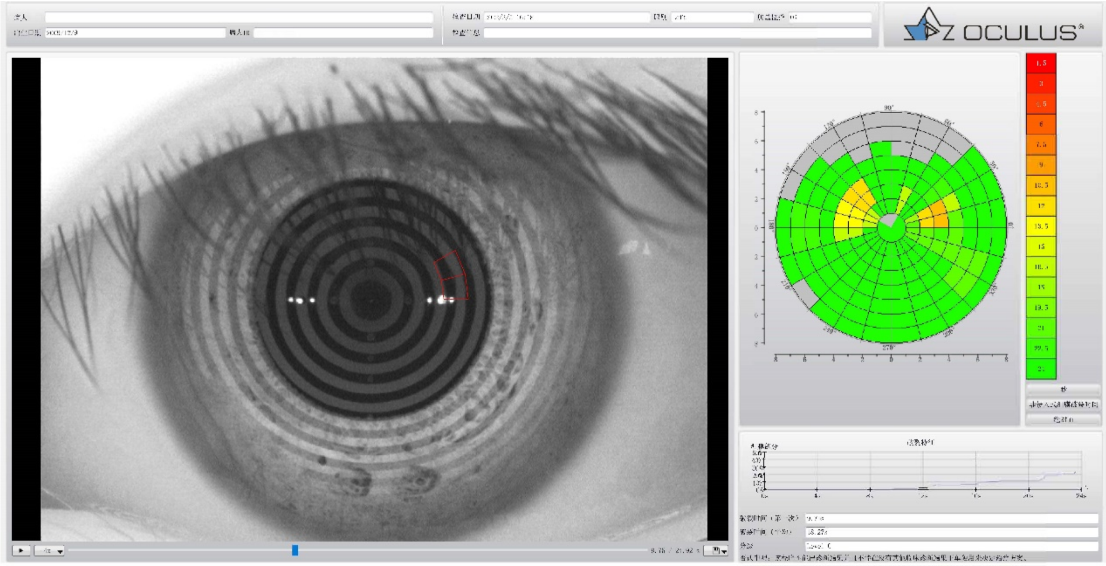

Figure 8 TBUT result of a DED patient captured and analyzed by Keratograph 77000 (Wetzlar, Germany) .

5.1.2. Schirmer I test (S I T)

S I T is one of the most typical approaches for DED diagnosis, it is always be regarded as the ground truth for DED detection(Jones et al., 2017; Wolffsohn et al., 2017). S I t could be tested via wetting strips after topical anesthesia with 0.5% proparacaine hydrochloride eye drops. The cutoff of DED is ≤10mm of wetting strips counted in 5 minutes, it is diagnosed as severe DED while ≤5mm(Li, Deng, & He, 2012). It is one of the most common, acceptable, and typical indicators for DED detection. However, it is time-costing and resource resuming, patients are not comfortable for the testing process.

5.1.3. Tear meniscus height (TMH)

TMH is a significant indicator for aqueous-deficient DED detection(Craig, Nichols, et al., 2017; Jones et al., 2017; Stapleton et al., 2017; Willcox et al., 2017; Wolffsohn et al., 2017). There are multiple available ways for TMH measuring, including reflective meniscometry, slit-lamp evaluation, Keratograph(M. Chen, Wei, Xu, Zhou, & Hong, 2022) and Kowa DR-1α Tear Interferometer (Tolyo, Japan)(Arita et al., 2019). Findings of Jiang et al (2022) show that the DED and normal subjects' TMH scale is 0.16–0.23mm and 0.17–0.24mm respectively (Jiang et al., 2022). Arita et al. (2019) performed a research on 59 subjects (aged 50.0 ± 14.0 years), findings indicate that the cutoff value is 0.18mm(Arita et al., 2019). Findings of chen et al. (2022) shows that the cutoff of DED detection is 0.29(M. Chen et al., 2022). The figure 11 is captured by Keratograph 77000 (Wetzlar, Germany) of a female patient from Aier eye hospital in China (capture time: 5th March, 2022), the TMH is illustrated as the wight box shown (value=0.14).

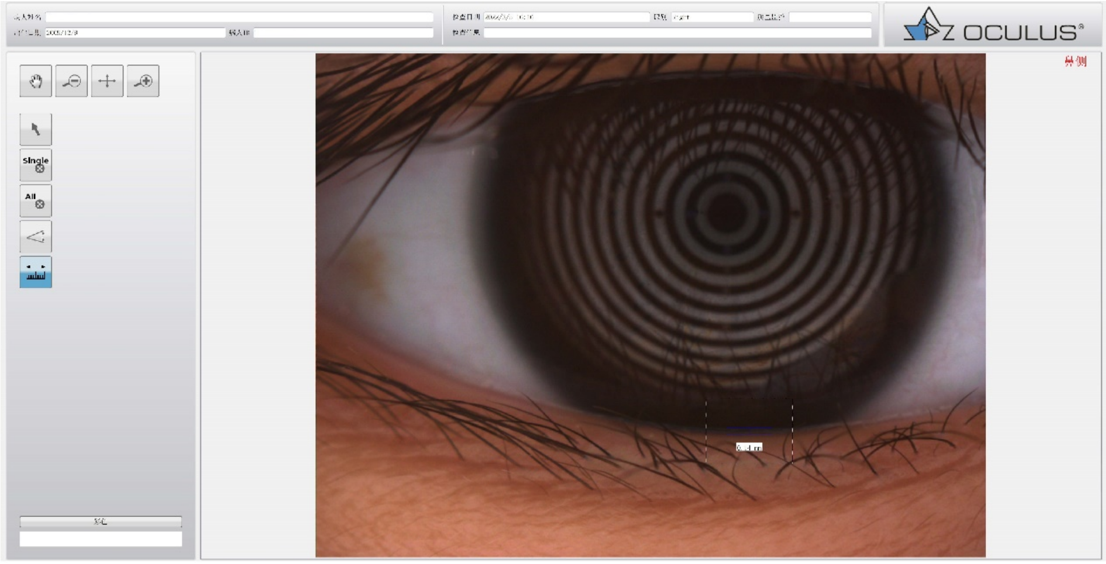

Figure 9 TMH result of a DED patient captured and analyzed by Keratograph 77000 (Wetzlar, Germany)

5.1.4. Ocular Surface Disease Index (OSDI) questionnaire

OSDI is one of the most typical ways for DED detection. Jiang et al. (2022) utilizes this method for DED diagnosis and grading. 12 questions for 5 severe level identification are utilized, which are related to eye discomfort, blurred vision, foreign body sensation, decreased vision, and fear of light symptoms, especially when subjects are night driving, in air conditioning rooms, using blue light screen, reading papers and encountering sandstorm weather. Five degrees includes "no discomfort", "occasional occurrence", "half probability", "frequent occurrence" and "always happens", scores are listed as 0, 1. 2, 3 and 4. OSDI score is calculated by the average value of each question (Jiang et al., 2022). This method is harmless for testing, which is the most acceptable way for early screening of DED patients. However, the questionnaire results may be subjective with low accuracy, which is also time-costing and resource-consuming.

5.2. Potential methods for AI-based DED detection

5.2.1. Cornea fluorescein Staining (CFS) score

CFS score is calculated by counting the number dots in CFS, ranged in the scale of 0-40. The observed CFS is divided into five zones, which are superior, central, nasal, temporal, and inferior. The rule is proposed by Paiva and Stephen (2004) as the following. When the number of dots is in the range of 0, 1-5,6-15, 16-30, and over 30, CFS score is 0, 1, 2, 3 and 4. When one zone is involved, add 1 to the score. Two or more zones are involved, add 2. Corneal filaments are involved, add 2(De Paiva & Pflugfelder, 2004). Zhang et. al. (2022) (Z. Zhang et al., 2022) utilized CFS for DED detection, CFS score is graded according to the Baylor grading scheme from 0 to 40(De Paiva & Pflugfelder, 2004). Paiva proposed 2 or greater of CFS score is a marker of DED diagnosing. A computer-aided centesimal scoring system named Corneal Fluorescein Staining Index (CFSi), and National Eye Institute/Industry (NEI) grading scale are also applied for DED detection

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based on CFS images (Amparo et al., 2017). Amparo et al. (2017) utilized this method for CFS score calculation. Four severity quartiles are recognized by the NEI scale and CFSi, which are lowest quartile of 0-3/15 and 0–25/100(CFSi), the second quartile of 4–7/15 and 25–50/100(CFSi), the third quartile of 8–11/15 and 50–75/100(CFSi), and the highest quartile of 12–15/15 and 75–100/100(CFSi). As the figure 12 shown, A and C are the CFS images measured by NEI, B and D are calculated by CFSi. The CFS score is illustrated as the number shown at the bottom right of the sub-figures. CFS score is a significant indicator for DED diagnosis, which is usually regarded as comparable indicators for DED detection. However, there is a kind of risk to use this method because the injection of fluorescent agent may cause eye allergy.

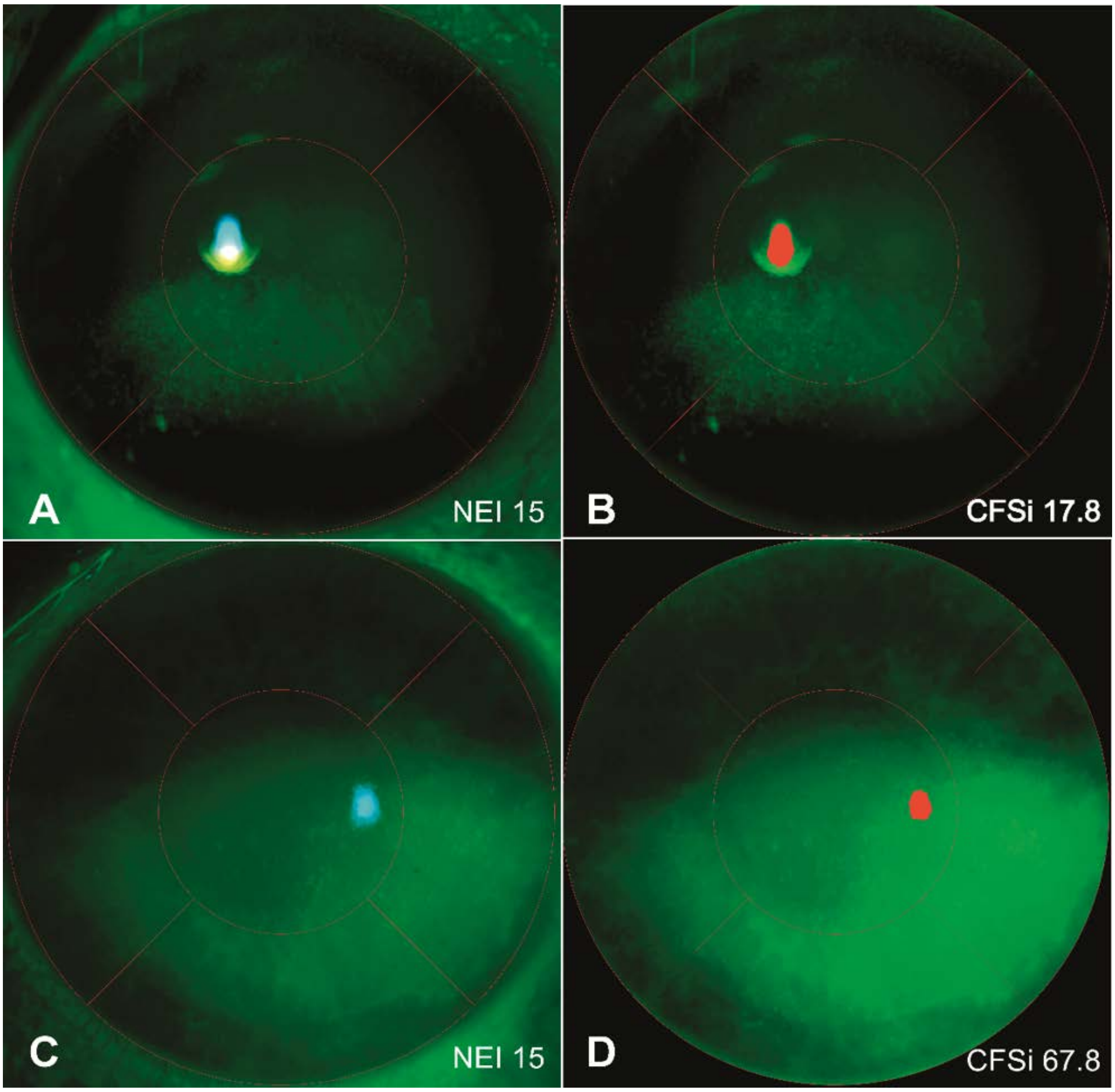

Figure 10 CFS score calculated by NEI and CFSi(Amparo et al., 2017).

5.2.2. DED detection based on In vivo confocal microscopy (IVCM) images

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Based on DED signs and symptoms collected by IVCM and OSDI questionnaire, DED could be diagnosis based on AI methods and sub-basal corneal nerve fibre parameters (CNF). Jing et al. (2022) demonstrated that CNF parameters are extracted by deep learning model based on IVCM images. The corneal intrinsic aberrations and corneal surface regularity indicators could be generated by pentacam HR system. Increasing anterior and total corneal aberrations and decreased average density and maximum length of corneal nerve could be utilized for DED detection (Jing et al., 2022). Their results show that the cutoff of strip meniscometry (SMT) and lower tear meniscus height (LTMH) and lower tear meniscu depth (LTMD) are < 5 mm (AUC 0.994, sensitivity 96.7% and specificity 96.7%), 204.96 μm (AUC of 0.998, sensitivity of 98.3% and specificity of 96.7%) and 190 μm (AUC of 0.995, sensitivity of 96.7% and specificity of 95%) respectively. The AI method based on nerve fibre segmentations (as the figure 13 shown) and calculations is an effective way for DED early screening, which is time saving and resource saving than manually diagnosis. However, the data of IVCM may not be able to be obtained, especially in developing areas. There is a significant difference between individuals on the sub-basal nerve fibre, more experiments should be implemented for finding the threshold between DED and the control group.

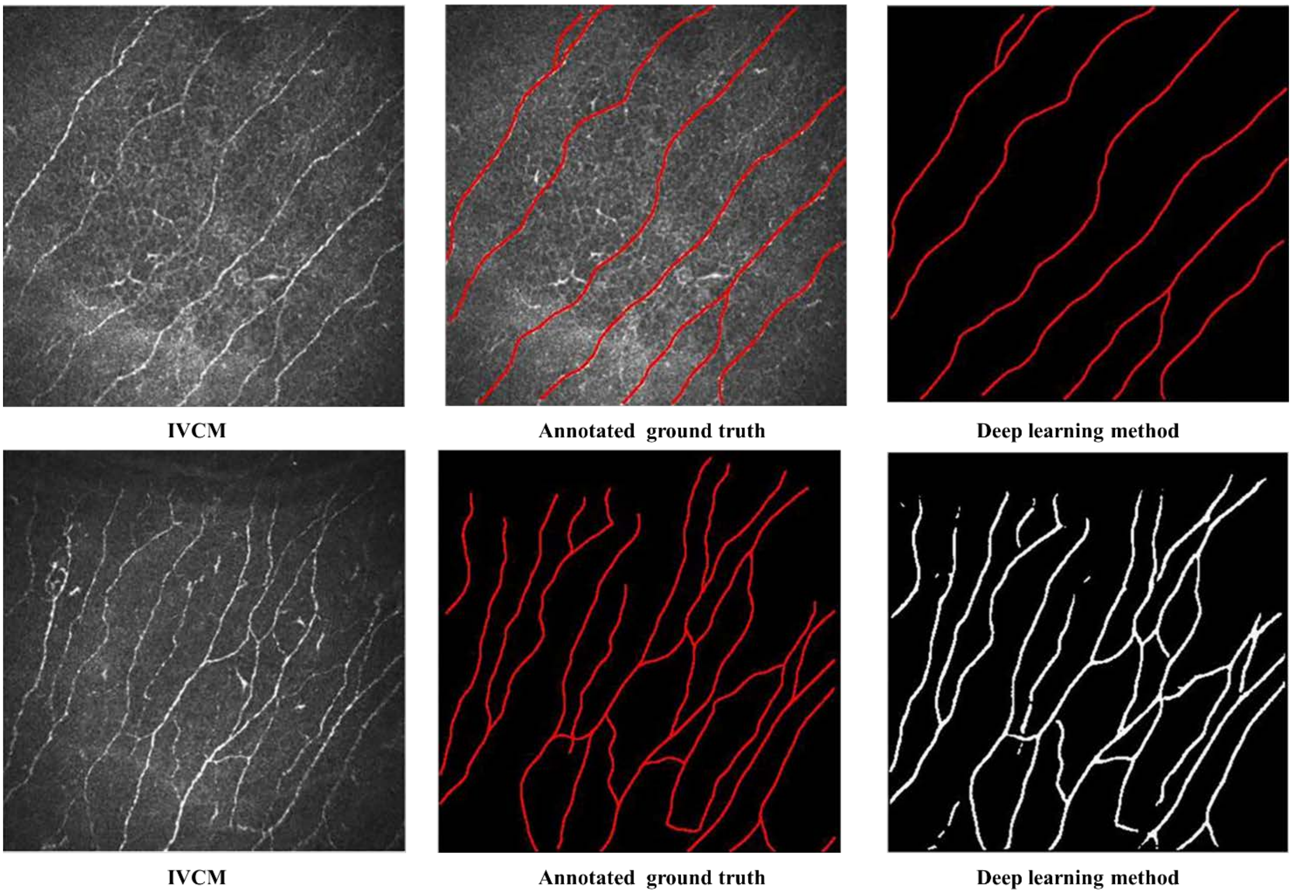

Figure 11 Automated Segmentation and Evaluation of CNF based on IVCM images(Jing et al., 2022).

5.2.3. Meibometry images

Meibomian gland dynamics (MGD) is one the major cause for DED, it could lead to ocular surface inflammation and tear film instability, which could eventually damage the cornea and visual function. Meibomian images are significant evidence for MGD diagnosing (Z. Zhang et al., 2022), which could be captured by Oculus Keratograph 5M (K5M; Oculus, Wetzlar, Germany) (Markoulli, Duong, Lin, & Papas, 2018). García-Marqués et al. (2021) proposed that MGD detection based on the MG images is a complementary solution and more powerful than other single metrics (García-Marqués, García-Lázaro, Talens-Estarelles, Martínez-Albert, & Cerviño, 2021). AI methods are applied to segmenting meibomian gland (MG) regions. MG function parameters are used for MGD degree calculating, including OSDI questionnaire (the scale is 0-100), corneal fluorescein staining (CFS, the scale is 0-20), tear meniscus height (TMH, the unit is mm), lid margin score (the scale is 0-4), meiboscore (the scale is 0-6), and meibum expressibility score (the scale is 0-45). OSDI questionnaire is applied for calculating the DED symptom score, where 14 MGD-related ocular symptoms are involved. Meiboscore is measured for the MG dropout degree. The meiboscore could be calculated by the baseline proposed by Arita et al.(Arita, Itoh, Inoue, & Amano, 2008), i.e., no loss of MG is regarded as meiboscore of 0, loss region of MG is less than one-third of the total area, which is regarded as meiboscore of 1, the lost MG area is between one-third and two-thirds of the total area is regarded as meiboscore of 2, and the MG lost area is over two-thirds of the total area. Including upper and lower lids, the scale is decided as 0-6. MG density is also a significant indicator for MGD, the lower MG density is, the more serious the MGD is, which could be calculated by the formular (1). P_t is the total pixels of the tarsus, the sum of pixels of MG areas is regarded as $\sum_{i=1}^{n} P_{MG_i}$. Zhang et al. (2022) (Z. Zhang et al., 2022) proposed that MG density has a significant relationship between OSDI($r = -0.404$, $p < 0.001$), TBUT($r = 0.601$, $p < 0.001$), lid margin score($r = -0.416$, $p < 0.001$), meiboscore ($r = -0.805$, $p < 0.001$), and meibum expressibility score ($r = 0.480$, $p < 0.001$). Thus, the higher the MG density is, the higher possibility of MGD is. As the figure 14 shown, the MGD is graded into four levels, which are meiboscore 0 to 3, the MG density is illustrated at the bottom of sub-figures. This method is one of the most common, visualizable, and useful approaches for MGD detection and grading. However, the level of automatic grading of MGD equipment is still relatively low, especially in the developing areas.

$$MG\ density = \frac{\sum_{i=1}^{n} P_{MG_i}}{P_t} \quad (1)$$

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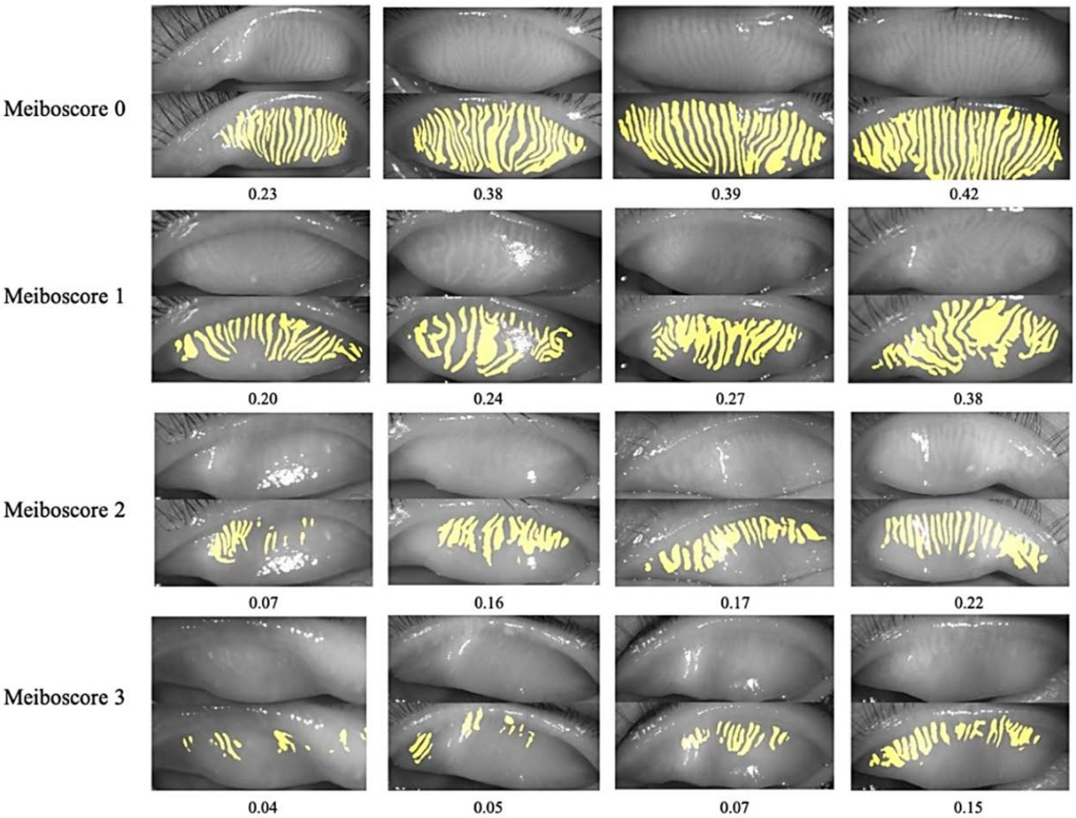

Figure 12 MGD grated by the meiboscore and MG density(Z. Zhang et al., 2022).

5.2.4. Lid margin abnormalities based on colorful anterior segment photographs (CASPs)

Based on CASPs, DED could be early screened by detecting lid margin signs. As the figure 15 shows, eight types of DED lid margin are identified by researchers, which are rounding of posterior lid margin (A), lid margin irregularity(B), lid margin vascularization(C), lid margin hyperkeratinization(D), meibomian gland orifice (MGO) retroplacement(E), MGO plugging(F), mucocutaneous junction (MCJ) anteroplacement(G) and MCJ retroplacement(H)(Y. Wang et al., 2022). The advantage of this method is that it will be a good way for DED early screening since the figures are relatively easy to be obtain. However, the sentiment and specific values are relatively low since differences between lid margin in figure level are difficult to be detected. An error of diagnosis may occur when it comes to the clinical situations. Zhang et. al.(2022) (Z. Zhang et al., 2022) graded the margin DED related symptoms as four levels (0-4) based on the number of these abnormalities, evidence includes anterior or posterior replacement of the mucocutaneous junction, plugged meibomian gland orifices, irregular lid margin, and vascular engorgement(Arita et al., 2009).

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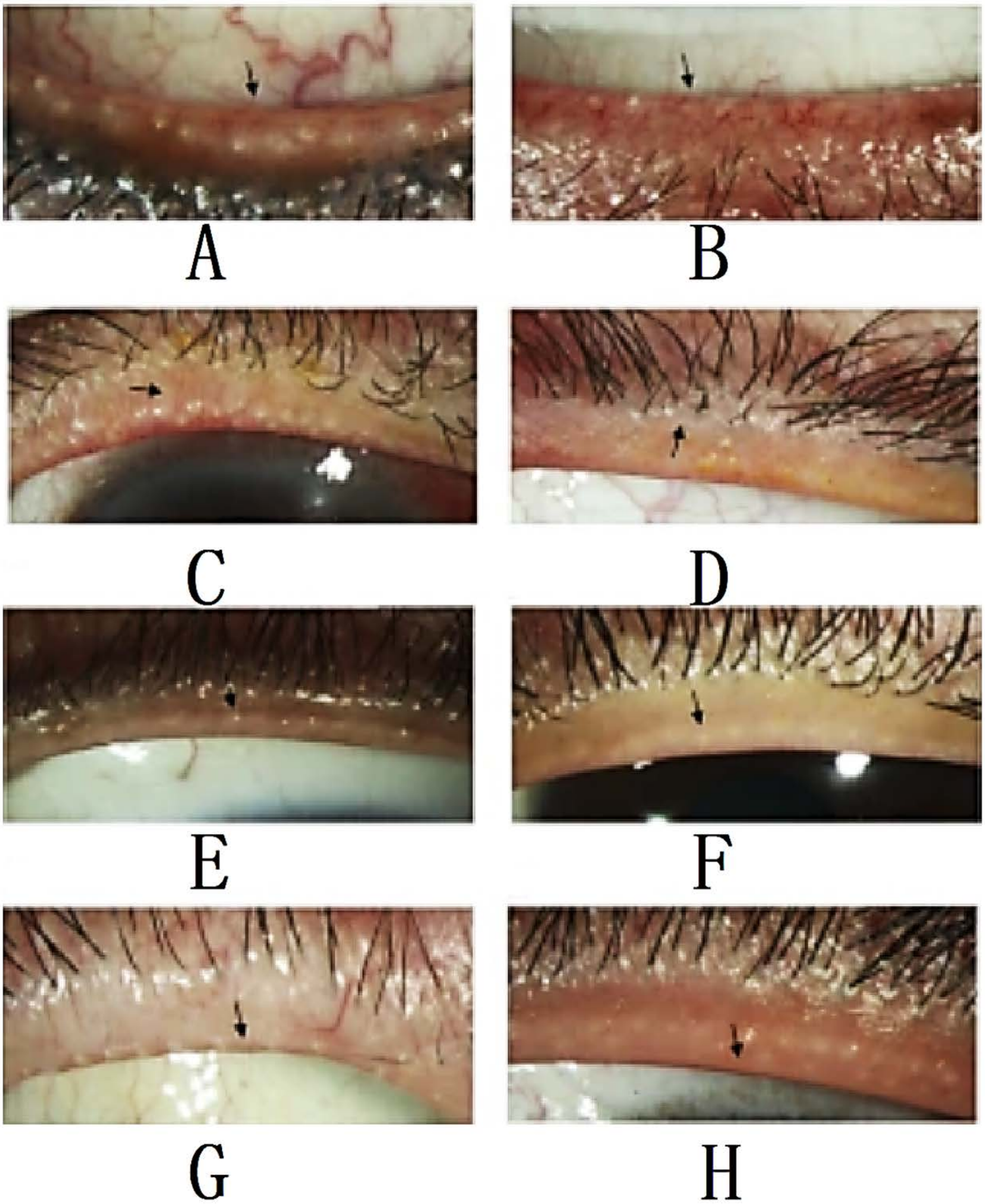

Figure 13 Eight types of DED lid margin signs(Y. Wang et al., 2022)

5.2.5. DED detection based on blink videos

The average relative interpalpebral height (IPH) and the frequency proportion of incomplete blinking (IB) could be obtained by analyzing blink videos, which have a high relationship with DED diagnosing symptoms. One time of blink is shown as the figure 16, the interpalpebral zone (green area) and the IPH (the blue line) are decreasingly changing during this period. The average relative IPH is regarded as the mean of the minimal IPH for all blinks during the period. The IB frequency proportion is calculated by the frequency of incomplete blinking divide the complete blinking. The incomplete blinking is identified by the

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rule that the minimal IPH is more than 30% of the maximal IPH. According to the research of Zheng etc. (2022) (Zheng et al., 2022), IPH of DED patients is 16.96±13.77%, IB proportion is 21.19±22.99%. IPH has a strong relationship with DED. The strength of this approach is that it will be a good way for DED early screening since the data is relatively easy to be obtain and there is less harmless and lower incompletable level for patients. However, it is relatively different for different individuals. A low accuracy may appear clinically and practically.

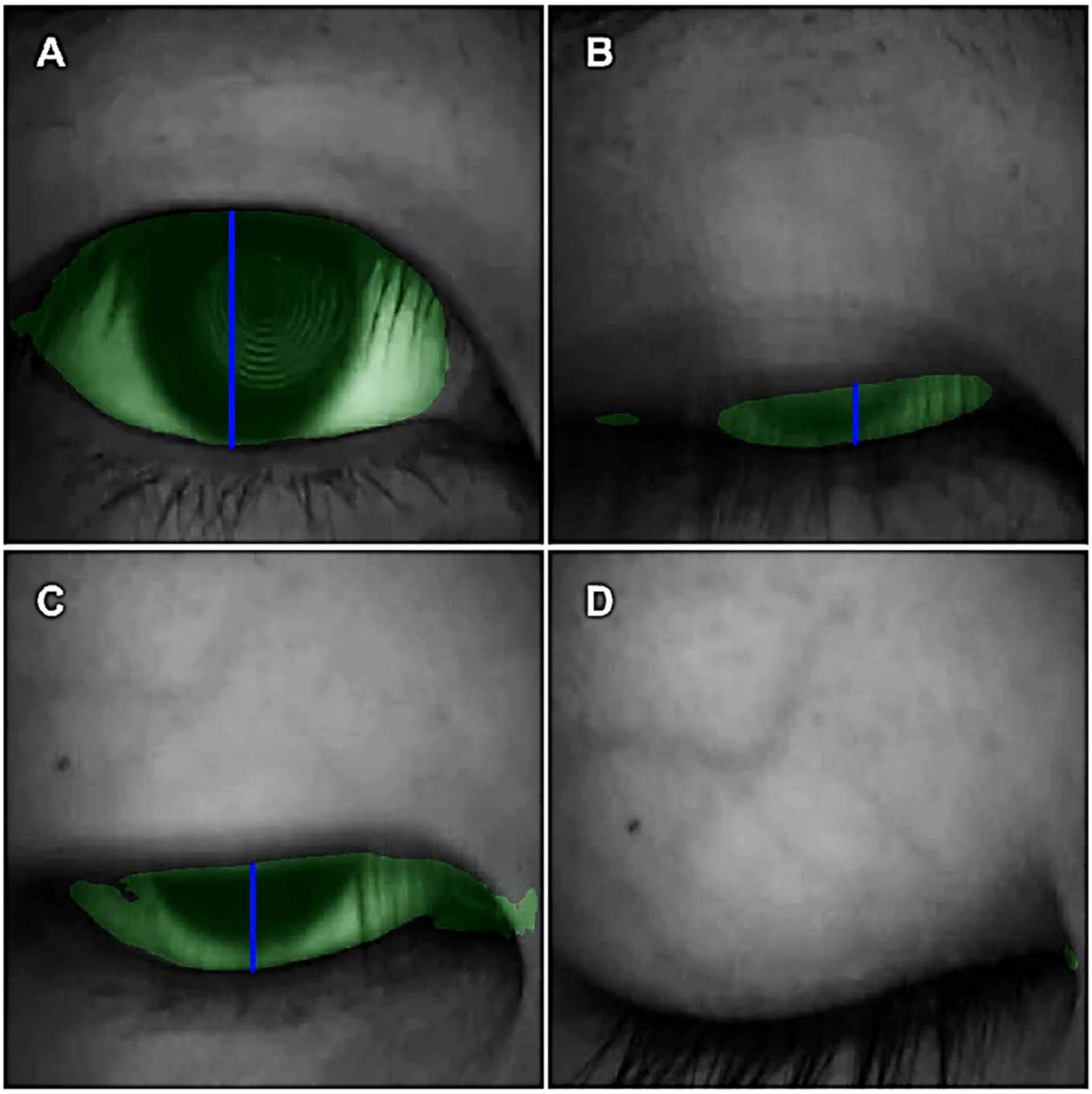

Figure 14 A screenshot of blink video

5.2.6. DED detection based on OCT Images

Based on OCT images, there is a significant difference between DED and normal subjects of patterns in the corneal epithelium and tear film layer, which was regarded as evidence for DED detection (Chase et al., 2021). As the figure 17 shown, features on epithelial layer and tear film on anterior segment OCT (AS-OCT) images are the highlighted (the purple area) with the highest weight of DL model DED detection. The correlation between the ratio of CFS and epithelial areas is also could be detected by AS-OCT (Sher et al., 2019). The irregularity of epithelial surface symptom of DED patients could be detected by AS-OCT, which is also be applied for prognosis and assisting DED treatments (Abou Shousha et al., 2020). Tear film measurements based on OCT exhibits a positive relationship between the Schirmer's test (Werkmeister et al., 2013). High tear film-corner interface reflectivity detection based on OCT images is regarded as evidence of hyperosmolar tears, which is also a method for DED detection (Deinema, Vingrys, Chinnery, & Downie, 2017). Celebi et al. (2016) measured CCT values by cirrus SD-OCT based on 56 eyes of 28 severe DED patients (mean age of 50.9 ±11.3 years)(Celebi & Mirza, 2016; Karasu & Celebi, 2022). Findings show that CCT value is 520.67±33.58μm for females and 533.00±20.49μm for males respectively. DED detection based on CCT measure and SD-OCT imaging is an effective way for DED severity degree prediction (Celebi & Mirza, 2016). Deep learning based on OCT is an autonomic, resource-saving, timesaving, highly reproducible, objective, non-invasive testing, and low-risk for testing subjects. However, comparing to other DED typical methods (TBUT, S I T, CFS and OSDI), the accuracy is relatively low especially to the real-word data. Furthermore, there is a difference between OCT images of different devices. The normalization level of ground truth for DED detection based on OCT is relatively low. The AI-based method for DED detection is Blackbox with low level of explanation.

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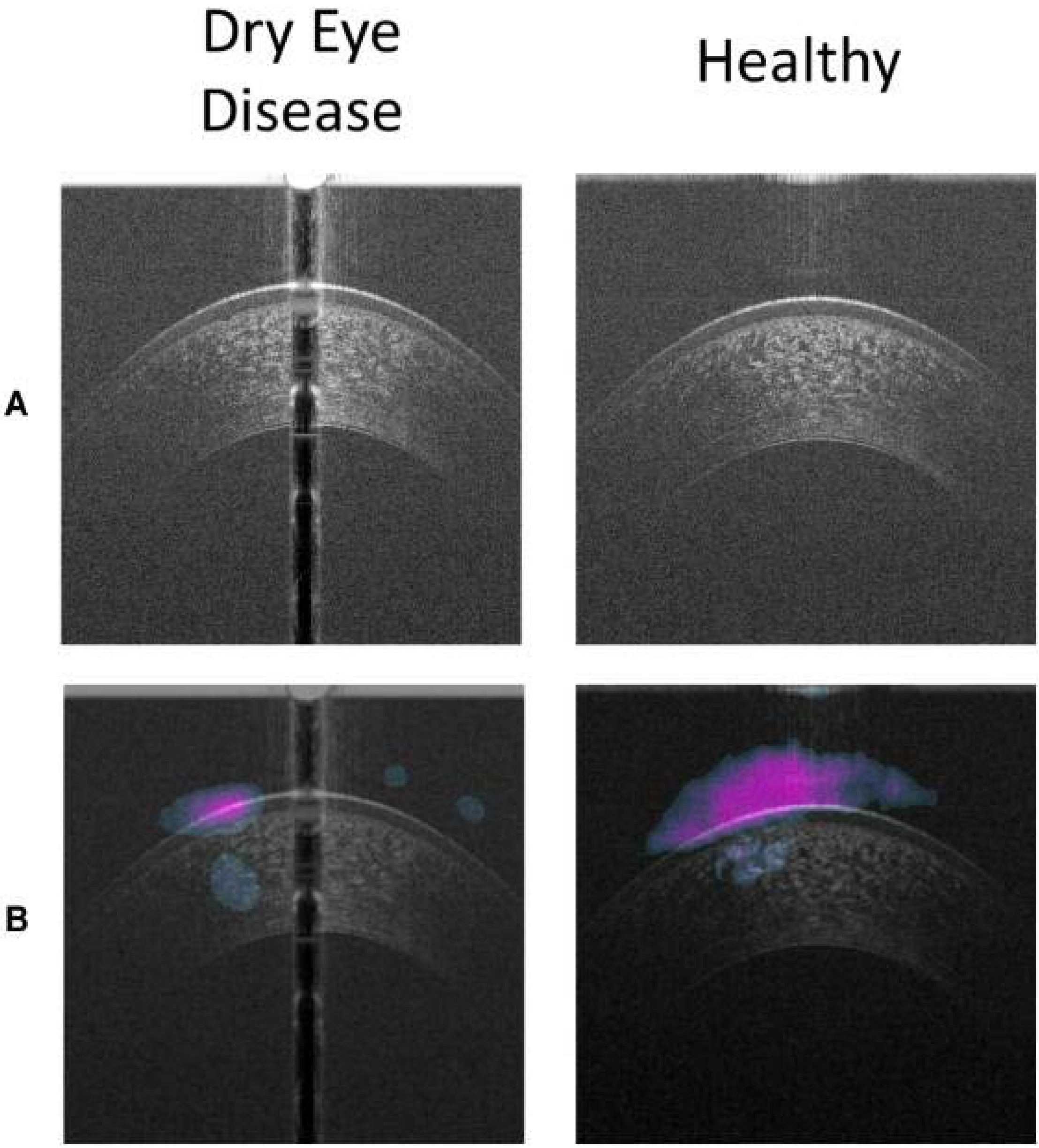

Figure 15 AS-OCT images between DED and normal subjects(Celebi & Mirza, 2016; Karasu & Celebi, 2022).

5.2.7. DED diagnosis based on ultrasonic imaging

Ophthalmic ultrasound images are one of the most significant tools for eye disease diagnosis (Jiang et al., 2022). Central corneal thickness (CCT) could be measured by A-ultrasound and ultrasound (figure 18), it is also could be measured by AI-based methods (Jiang et al., 2022). Tear osmotic pressure and DED severity degree could be predicted based on CCT results. DED detection based on ultrasonic imaging is an effective way for DED severity degree prediction. The CCT value of DED is in the range of 22.7–34.2/100 μm (43-57 years cold, reference only). Ultrasound imaging has become a novel way for eye disease detection, which could deeply analyze DED patients' symptoms from the perspective of anatomy, higher the accuracy of DED diagnosis and assists the treatment. However, the standard level of DED

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detection is based on ultrasound imaging is relatively low and not common. CCT values measured by different devices (e.g., Cirrus SD-OCT, ultrasonic pachymetry, etc.) for different clusters of individuals (classified by age, sex, geography, etc.) are different. AI-based imaging classification methods is a great way to solve the problem, however, it is still lack of research to verify the efficiency on this field. Jiang et al (2022) utilized the RF classification algorithm (the number and depth of trees is 16 and 12 respectively), the ultrasound images were classified into seven categories, which are macular holes (MH), cystoid macular edema (CME), and four retinal structures (L1: Nerve fiber layer (NFL); L2: Ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), and outer plexiform layer (OPL); L3: outer nuclear layer (ONL), Inner sensitive layer (ISL); L4: retinal layer (CL), outer sensitive layer (OSL), vitreous macula (VM), and retinal pigment epithelial cells (RPE) and background region. Based on the ground truth of central corneal thickness (CCT) measurement, DL model exhibits a greater performance than conventional graph cut, measuring by the values of true positive volume coefficients (TPVF), deiss similarity coefficient (DCS) and false positive volume coefficients (FPVF). The confidence interval of DED patients' CCT value is 22.7-34.2 μm, the average tear osmotic pressure (TSP) for moderate and severe DED are 316.5 mOsm/kg and 403.6 mOsm/kg respectively, CCT value is highly related to TSP($r=0.779$;$P=0.05$). Celebi et al. (2016) utilized ultrasonic pachymetry for CCT measurement on 56 eyes of 28 severe DED patients (mean age of 50.9 ±11.3 years). Results show that CCT value is 527.46±35.07μm for females and 540.00±20.94μm for males respectively(Celebi & Mirza, 2016).

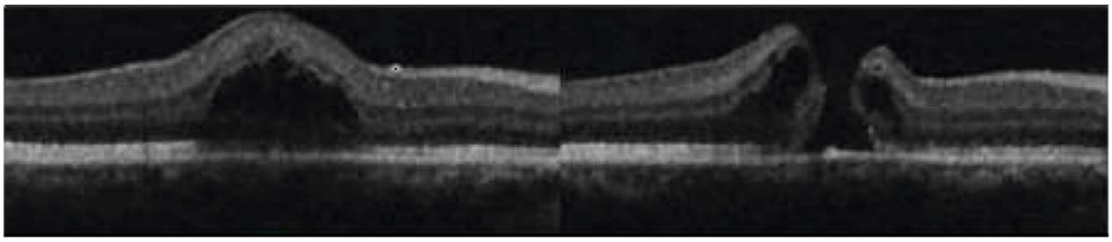
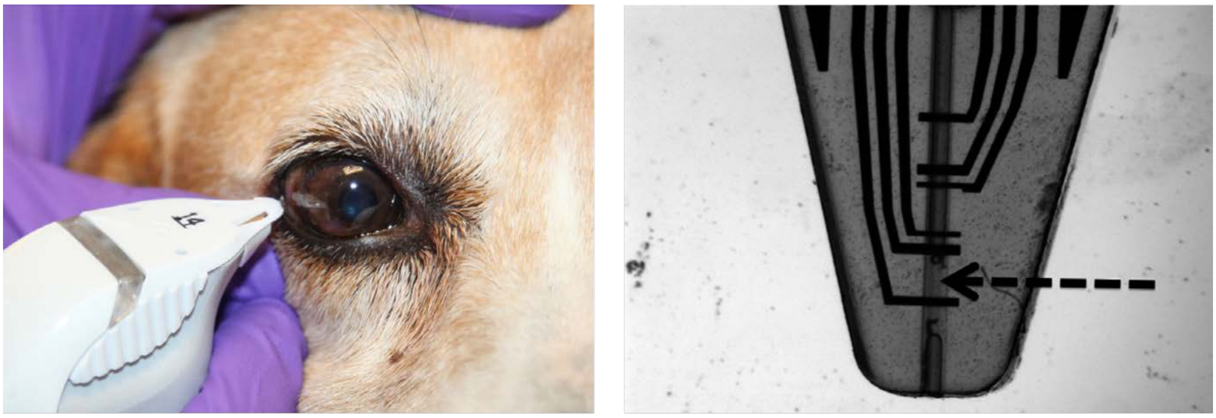


Figure 16 The sectional view for 3D ultrasonic Image circled by macular fovea of DED patients(Jiang et al., 2022).

5.3. Potential direction and supplemented methods for AI-based DED detection

5.3.1. Tear osmolarity

Tear osmotic pressure is regarded as an indicator for DED syndrome severity diagnosis for some researchers (M. A. Lemp et al., 2011). The cutoff of osmolarity is proposed as > 311 mOsms/L by Lemp et al. (M. A. Lemp et al., 2011). By analyzing the ultrasonic images, Jiang et al. (2022) proposed that, osmolarity has a strong relationship between DED(Jiang et al., 2022). This indicator exhibits a relationship connection between DED, which could be obtained by equipment. However, the equipment would report a mistake result when it is used in the wrong way. For instance, as the figure 19 shown, the TearLab is used on a dog(A), the air bubble in the microchip (dashed arrow) would lead a low osmolarity readings(B)(Sebbag et al., 2017). Besides, this method is also be challenged by the stativity and effectiveness by other researchers, which is not a grounded indicator to distinguish the DED patients and the normal (Tashbayev et al., 2020). Bethod et al. (2020) explored tear osmolarity measured with TearLab osmometer (San Diego, CA, USA) on 1514 eyes of 757 subjects, where 58 eyes are normal. They proposed that there is a low sensitivity and can't be used for DED detection (Tashbayev et al., 2020).



A B

Figure 17 TearLab testing case for osmolarity on a dog(Sebbag et al., 2017).

5.3.2. Proteomic analysis

Tear is an important biomarker for DED detection, proteomic analysis on tear fluid is a significant approach for DED detection. Zhu et al. (2018) utilized LC-Q-orbitrap-MS analysis with in-strip digestion based on tear fluid collected by Schirmer's strips. By analyzing the tear proteome of dry eye patients, they concluded that compared to the normal, 18 proteins ($P < 0.05$) are different for DED patients. Proteins of lactotransferrin (LTF), lysozyme (LYZ), lipocalin 1 (LCN1), zinc-alpha-2-glycoprotein (AZGP1), secretoglobin, family 2A, member 1 (SCGB2A1), deleted in malignant brain tumors 1 (DMBT1), lacritin (LACRT) and proline rich 4 (PRR4) are decreased. Proteins of transferrin (TF), Keratin 1 (KRT1), polymeric immunoglobulin receptor (PIGR), Complement component 3 (C3), S100A8, S100A9, orosomucoid 1 (ORM1), Annexin A1 (ANXAI), Immunoglobulin J polypeptide (IGJ) and Heat shock 27kDa protein 1 (HSPB1) are increased(Huang, Du, & Pan, 2018). Grus et al compared tear proteins in diabetic DED patients, non-diabetic DED patients and healthy controls to distinguish different groups(Jung et al., 2017). This method is useful for DED early screening. However, it is not a typical way for DED diagnosis.

5.3.4. Traditional Chinese medicine (TCM) diagnosis

The symptoms of dry eyes were evaluated according to TCM syndrome scale of deficiency of "lung yin", TCM syndrome scale of yin deficiency of damp-heat, TCM syndrome scale of spleen and kidney yang deficiency and TCM syndrome scale of yin deficiency of liver and kidney. In the research of using dry eye as TCM syndrome to diagnose other diseases, most of them are binarization of syndrome and prediction and diagnosis based on machine learning (Hu, Li, Huang, Yan, & Huang, 2020). Yang Xie et al. (2020) collected 1713 records are extracted from electronic medical records (EMR) of rheumatoid arthritis patients during the period of 2012 to 2015 in the first affiliated hospital of Anhui university of Chinese medicine, where information of demographic information, personal medical history and patients' symptoms are involved. They utilized K-nearest neighbor (KNN), support vector machine (SVM), secision tree (DT), RF, artificial neural network (ANN)and AdaBoost algorithms for feature selection and syndrome classification. They concluded that factors as following are helpful for DED detection, which are the tongue nature, coat of the tongue, pulse diagnosis, other information related to the demographic information and medical histories, such as gender, age, puffiness of the eyelid and dry eye (Xie et al., 2020). TCM methods are unique for dry eye diagnosis and treatment. However, the quantitative criteria are complex, the normalization level is low, and time-costing.

As far as CTM for DED diagnosis and treatment is concerned, the connections between organs and eyes have been discovered in multiple types of research, physiologically and pathologically. One theory of TCM is related to "liver resuscitation in the eyes"(Yuan, Yue, Zhang, Wang, & Dou, 2021). Research from Sun. et al(2015) (Xuezheng, Qinghua, & xiangdong, 2015) indicated that there is a stable connection between feeble liver and kidney and dry eye. Therefore, it is regarded as a clinical TCM solution for liver-kidney-nourishment and anti-inflammation for dry eye treatment. Chenet al.(2021) (Aiju, Tao, & Jing, 2021)proposed the treatment of Qi-Ju-Di-Huang-Van solution, which is aimed at reducing dryness and recurrence rate by enhancing the secretion of tears and prolonging the tear film rupture time. Studies by Zou et al. (Dehui et al., 2020) and Guo et al.(Xiaocong et al., 2022) show that dry eyes are closely related to the conditions of liver, kidneys, spleen, stomach and lungs, which are keys to tear production and eye moistening.

Acupuncture and moxibustion is proposed to be another effective way for DED treatments. Results from a study of Zou et al. (Dehui et al., 2020) show that he support value of acupuncture points of Zanzhu and Sizhukong is 53.125, which is the highest, the confidence value of this combination is 95.588, indicating there is a potential treatment solution by combining these two acupuncture points. They proposed that Acupuncture treatment for dry eyes focuses on the points of Sun, Yangming and Shaoyang meridians, and the selection of acupuncture points decided by the localization and stimulation of nerves, where a role of "local distal syndrome differentiation" should be followed. Guo et al.(Xiaocong et al., 2022) delivered a study about 373 Acupuncture-related clinical therapy records collected from literature databases of CNKI, Chinese Science and Technology Journal Database, Chinese Academic Journal Database, Chinese Biomedical

Literature Database, PubMed and Web of Science (the period is from January 1st, 2010 to December 1st, 2020), With the methods of Pearson hierarchical clustering and Apriori correlation analysis, findings show that the acupoints could be clustered into 3 categories, which are Sanyinjiao, ZuSanli, Taichong, Taixi and Fengchi, Zanzhu, Shibai and Sun, and Miming, Hegu, Shengwu and Shijukong. Parameters of Apriori are set as minimum support=35%, minimum confidence =80%, maximum number of priors=2. 12 combinations of acupoints are extracted. They concluded that the 12 commonly used acupoints are Zanzhu, Miming, Sun, Sanyinjiao, Fengchi, Sizhukong, Hegu, Sibai, Taichong, Chengwu, Shisanli, and Taixi. The commonly used ear points are liver, eye, endocrine, spleen, kidney, pre-pancreatic, post-pancreatic, and Shen Men. Treatment is based on acupuncture or acupuncture with medication.

Besides, some of the studies have shown that, compared with traditional Chinese medicine or western medicine alone, the method of integrated traditional Chinese and western medicine has obvious advantages in this field(Xiaocong et al., 2022). However, due to the different diagnosis and treatment methods of dry eyes in hospital of traditional Chinese and western medicine, the diagnosis and treatment standards, basis and schemes of traditional Chinese and western medicine are even more different, such as the medication mode, type and dose of western medicine, the quantitative standard of syndrome of traditional Chinese medicine, the distribution and frequency of acupuncture points, etc., resulting in great differences in diagnosis and treatment data.

Thus, the advantages of TCM on DED detection and treatment are concluded as the following. (1) Unique advantages of acupuncture and moxibustion is that it could induce patients to secrete tears on their own to moisten the eyes, prolong tear film rupture time and promote blood circulation around the eyes. (2) The characteristics of Chinese medicine in selecting points for treating diseases at their root and identifying evidence. For instance, acupuncture treatment on points of Sanyinjiao, Taichong and Taixi is a significant solution for nourishing the liver and kidneys. Challenges and weakness are concluded as the following. (1) The standard value of Acupuncture and moxibustion is quite low. (2) There are still some side effects are not considered, like subcutaneous bruising, artificial tear allergy, stinging sensation, nauseas, diarrhe, eye dryness, vomiting, ear skin breakage due to magnetic beads, eye itching, needle allergy, and motion sickness. (3) The dry-eye measurement indicators of tear breakup time (BUT), SchirmerItest(SIT) and cornea fluorescein staining (CFS) may not good as other medicine related therapeutic methods.

5.3.5. Demographic factors

The study on the prevalence of DED based on the demographic survey is helpful to detect the risk factors of the disease and achieve DED early screening. Japan realized automatic early screening for DED detection based on demographic survey in 2015(Kaido et al., 2015). This method is useful for early screening

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and higher patients' DED prevention awareness. However, results could not be regarded as the basis of DED diagnosis. Abdulaziz et al. (2017) performed research on 1858 Saudi adults with mean age of 39.3 ± 14.1 years. Findings show that People who are female gender, older age (>56 years), current smoking and history of diabetes mellitus, have a high-risk rate of DED(Alshamrani et al., 2017).

Tab. 4 AI-based DED detection methods based on different evidence

Index	DED diagnosis symptoms and evidence	References	Methods	Results	Detection biomarkers		Advantages and strengths	Disadvantages and challenges
					Normal	DED		
1	Tear break-up time (TBUT)	(De Paiva & Pflugfelder, 2004; Z. Zhang et al., 2022)	TBUT is measured by Cornea Fluorescein Staining (CFS), Interferometry and slit-lamp images or AI-based dry eye detection devices (e.g. Keratograph 77000), where the process of fluorescein instillation is involved. After the sodium fluorescein strip wet with preservative-free saline, it touches subjects' inferotemporal bulbar conjunctiva. Subjects are requested to blink, the precorneal tear film is measured by a biomicroscope with a 10 times objective under blue-light illumination. Then record the interval between the first black spot or interruption in precorneal fluorescein tear layer. Each eye was read three times and average the results as the TBUT result.	TBUT is an effective method for DED detection	10 second or higher.	Lower than 10 seconds.	TBUT is a significant indicator for DED diagnosis, which is usually regarded as grounded truth for DED detection.	This method is criticized for time-costing, resource-consuming, low reproducibility, and high variations in values. When it comes to the real world, the result could be not accurate under specific situations, for instance, patients could be nervous when it come to a TBUT test. Besides, some of the hospitals still using the Interferometry and slit-lamp images and CFS for DED detection, this method is mildly invasive, the injection of fluorescent agent may cause eye allergy and discomfort.
2	Schirmer I test (SIT)	(Jones et al., 2017; Wolffsohn et al., 2017)	S I t could be tested via wetting strips after topical anesthesia with 0.5% proparacaine hydrochloride eye drops.	S I T is one of the most typical approaches for DED diagnosis, it is always be regarded as the ground truth for DED detection,	Wetting strips counted ≥ 10 in 5 minute.	Wetting strips counted < 10 in 5 minute.	It is one of the most common, acceptable, and typical indicators for DED detection.	it is time-costing and resource resuming. Patients are not comfortable for the testing process.
3	Cornea Fluorescein Staining (CFS) score	(De Paiva & Pflugfelder, 2004; Z. Zhang et al., 2022)	CFS score is calculated by counting the number dots in CFS, ranged in the scale of 0-40. The observed CFS is divided into five zones, which are superior, central, nasal, temporal, and inferior. The rule is proposed by Paiva and Stephen (2004) as the following. When the number of dots is in the range of 0, 1-5,6-15, 16-30, and over 30, CFS score is 0, 1, 2, 3	CFS score is an effective method for DED detection	CFS score is Lower than 2.	CFS score is 2 or greater.	CFS score is a significant indicator for DED diagnosis, which is usually regarded as comparable indicator for DED detection.	Clinically, there is a kind of risk to use this method since the injection of fluorescent agent may cause eye allergy.

			and 4. When one zone is involved, add 1 to the score. Two or more zones are involved, add 2. Corneal filaments are involved, add 2					
		(Amparo et al., 2017)	A computer-aided centesimal scoring system named Corneal Fluorescein Staining Index (CFSi), and National Eye Institute/Industry (NEI) grading scale are also applied for DED detection based on CFS images.		Both of NEI and CFSi are 0.	Four severity quartiles are recognized by the NEI scale and CFSi, which are lowest quartile of 0-3/15 and 0–25/100(CFSi), the second quartile of 4–7/15 and 25–50/100(CFSi), the third quartile of 8–11/15 and 50–75/100(CFSi), and the highest quartile of 12–15/15 and 75–100/100(CFSi).		
4	Ocular Surface Disease Index (OSDI) questionnaire	(Jiang et al., 2022)	12 questions for 5 severe level identification are utilized, which are related to eye discomfort, blurred vision, foreign body sensation, decreased vision, and fear of light symptoms, especially when subjects use blue light screen, reads papers, are night driving, in air conditioning rooms and encounter sandstorm weather. Five degrees includes no discomfort, occasional occurrence, half probability, frequent occurrence and always happens, scores are listed as 0, 1. 2, 3 and 4. OSDI score is calculated by the average value of each question.	OSDI is one of the most typical ways for DED detection.	OSDI score is 0	OSDI score is 1,2,3 or 4.	This method is harmless for patients, and the most acceptable way for early screening of DED patients.	The questionnaire results may be subjective with low accuracy, which is also time wasting and resource-consuming.
5	Tear meniscus height (TMH)	(Jiang et al., 2022) (Arita et al., 2019) (M. Chen et al., 2022)	TMH could be measured by methods of reflective meniscometry, slit-lamp evaluation, Keratograph and Kowa DR-1α Tear Interferometer.	TMH is a significant indicator for aqueous-deficient DED detection	TMH scale > 0.17mm TMH scale > 0.18mm TMH scale > 0.29mm	TMH scale ≤0.17mm TMH scale is ≤0.18mm TMH scale ≤0.29mm	TMH is an significant way for DED diagnosis, the measuring method, equipment and techniques are mature with good performances.	
6	DED detection based on In Vivo Confocal Microscopy (IVCM) Images	(Jing et al., 2022)	DED signs and symptoms are collected by In vivo confocal microscopy and ocular surface disease index questionnaire. Sub-basal nerve fibre parameters extracted by deep learning model.	Results: Comparing the DED patients and control group, especially for the higher-order aberrations, (1) the anterior and total corneal aberrations are increased ($P < 0.05$), (2) the average density and maximum	Strip Meniscometry (SMT) ≥ 5 mm; Lower <tear meniscus height (LTMH) ≥ 204.96 μm ;	Strip Meniscometry (SMT) < 5 mm; Lower <tear meniscus height (LTMH) <204.96 μm ; Lower tear meniscus depth (LTMD) <190 μm	The AI method based on nerve fibre segmentations and calculations is an effective way for DED early screening, which is time saving	The data of IVCM may not be able to be obtained, especially in developing areas. There is a significant difference between individuals on the sub-basal nerve fibre, more experiences should be carried on

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			The corneal intrinsic aberrations and corneal surface regularity indicators are generated by pentacam HR system.	length of corneal nerve are decreased ($P < 0.01$), (3) the number of Langerhans cells (LCs) is negatively correlated with maximum length (CC = −0.19, $P = 0.01$) of the sub-basal nerve fibre, (4) the corneal nerve average density is negatively correlated with IHD, and anterior, posterior, and total corneal aberrations ($P < 0.05$). Conclusions: AI methods based on the oculus keratography (Wetzlar, Germany) have a potential value for DED detection. Increasing anterior and total corneal aberrations and decreased average density and maximum length of corneal nerve could be utilized for DED detection.	Lower tear meniscus depth (LTMD) ≥190 µm		and resource saving than manually diagnosis.	finding the threshold between DED and the control group.
7	Meibometry Images	(Arita et al., 2008; Arita et al., 2009; Setu, Horstmann, Schmidt, Stern, & Steven, 2021)	The meiboscore is calculated by the baseline proposed by Arita et al.(Arita et al., 2008), i.e., no loss of MG is regarded as meiboscore of 0, loss region of MG is less than one-third of the total area, which is regarded as meiboscore of 1, the lost MG area is between one-third and two-thirds of the total area is regarded as meiboscore of 2, and the MG lost area is over two-thirds of the total area. Including upper and lower lids, the scale is decided as 0-6.	The meibomian image is significant evidence for MGD diagnosing, MGD detection based on the MG images is a complementary solution and more powerful than other single metrics The higher the MG density is, the higher possibility of MGD is.	Meiboscore is 0.	Meiboscore scale is 1-6.	This method is one of the most common, visualizable, and useful approaches for MGD detection and grading.	The level of automatic grading of MGD equipment is still relatively low, especially in the developing areas.
8	Tear Osmolarity	(Z. Zhang et al., 2022)	Tear osmolarity measured with TearLab osmometer (San Diego, CA, USA)	Tear osmotic pressure is one of the most effective indicators for DED syndrome severity diagnosis	311 mOsms/L	> 311 mOsms/L	This indicator exhibits a relationship connection between DED, which could be obtained by equipment.	The equipment would report a mistake result when it is used in the wrong way. Besides, this method is also be challenged by the stativity and effectiveness by other researchers, which is not a grounded indicator to distinguish the DED patients and the normal(Tashbayev et al., 2020).

9	Proteomic Analysis	(Huang et al., 2018)	LC-Q-orbitrap-MS analysis with in-strip digestion based on tear fluid collected by Schirmer's strips	Tear is an important biomarker for DED detection, proteomic analysis on tear fluid is a significant approach for DED detection.	N/A	Proteins of lactotransferrin (LTF), lysozyme (LYZ), lipocalin 1 (LCN1), zinc-alpha-2-glycoprotein (AZGP1), secretoglobin, family 2A, member 1 (SCGB2A1), deleted in malignant brain tumors 1 (DMBT1), lacritin (LACRT) and proline rich 4 (PRR4) are decreased. Proteins of transferrin (TF), Keratin 1 (KRT1), polymeric immunoglobulin receptor (PIGR), Complement component 3 (C3), S100A8, S100A9, orosomucoid 1 (ORM1), Annexin A1 (ANXAI), Immunoglobulin J polypeptide (IGJ) and Heat shock 27kDa protein 1 (HSPB1) are increased.	This method is useful for DED early screening.	It is not a typical way for DED diagnosis.
10	DED diagnosis based on OCT Images	(Chase et al., 2021)	DL classification models based on anterior segment OCT (AS-OCT) images	AI-based image classification DL model delivers a comparable accuracy and high speed for DED diagnosis based on AS-OCT images.	Sighs could be detected by ultra-high resolution OCT images, including irregularity of epithelial surface, corneal reflectivity of hyperosmolar tears and high reproducibility of tear film.	OCT images without irregularity of epithelial surface and low reproducibility of tear film.	Deep learning based on OCT is an autonomic, resource-saving, timesaving, highly reproducible, objective, non-invasive testing, and low-risk for testing subjects.	Comparing to other DED typical methods(TBUT, S I T, CFS and OSDI), the accuracy is relatively low especially to the real-word data. There is a difference between OCT images of different devices. The normalization level of ground truth for DED detection based on OCT is relatively low. The AI-based method for DED detection is Blackbox with low level of explanation.
		(Celebi & Mirza, 2016)	CCT values are measured by cirrus SD-OCT based on 56 eyes of 28 severe DED patients (mean age of 50.9 ±11.3 years).	DED detection based on CCT measure and SD-OCT imaging is an effective way for DED severity degree prediction.	N/A	CCT value is 520.67±33.58μm for females and 533.00±20.49μm for males respectively.		
11	Lid margin abnormalities based on colorful segment anterior photographs (CASPs)	(Y. Wang et al., 2022)	The lid margin score is graded as four levels (0-4) based on the number of these abnormalities, evidence includes anterior or posterior replacement of the mucocutaneous junction, plugged meibomian gland orifices, irregular lid margin, and vascular engorgement	The deep learning model based on CASPs is an efficient method for lid margin score measuring and DED detection.	Lid margin score scale is 0–1.00/4.00.	Lid margin score scale is 1.00-4.00/4.00.	It will be a good way for DED early screening since the figures are relatively easy to be obtain.	The sentiment and specific values are relatively low since differences between lid margin in figure level are difficult to be detected. An error of diagnosis may occur when it comes to the clinical situations.

12	DED diagnosis based on blink videos	(Zheng et al., 2022)	Analyzing blink videos to calculate the average relative interpalpebral height (IPH) and the frequency proportion of incomplete blinking (IB).	IPH has a strong relationship with DED, which is an effective way for DED detection.	IPH is equal to or more than 30% of the maximal IPH.	IPH is less than 30% of the maximal IPH.	It will be a good way for DED early screening since the data is relatively easy to be obtain and there is less harmless and lower incompletable level for patients.	There is a difference between individuals. A low accuracy may appear clinically and practically.
13	DED diagnosis based on ultrasonic imaging	(Jiang et al., 2022)	The average central corneal thickness (CCT) values are measured by type A-ultrasound CCT test and AI algorithm based on ultrasonic images. Tear osmotic pressure and DED severity degree could be predicted based on CCT results.	DED detection based on ultrasonic imaging is an effective way for DED severity degree prediction.	N/A	The CCT value is in the range of 22.7–34.2/100 μm (43-57 years cold, reference only).	Ultrasound imaging has become a novel way for eye disease detection, which could deeply analyze DED patients' symptoms from the perspective of anatomy, higher the accuracy of DED diagnosis and assists the treatment.	The standard level of DED detection is based on ultrasound imaging is relatively low and not common. CCT values measured by different devices (e.g. Cirrus SD-OCT, ultrasonic pachymetry, etc.) for different clusters of individuals (classified by age, sex, geography, etc.) are different. AI-based imaging classification methods is a great way to solve the problem, however, it is still lack of research to verify the efficiency on this field.
		(Celebi & Mirza, 2016)	CCT values are measured by ultrasonic pachymetry based on 56 eyes of 28 severe DED patients (mean age of 50.9 ±11.3 years).		N/A	CCT value is 527.46±35.07μm for females and 540.00±20. 49μm for males respectively.		
14	Traditional Chinese Medicine (TCM) Diagnosis	(Xie et al., 2020)	Traditional Chinese Medicine (Tcm) Diagnosis	The symptoms of dry eyes were evaluated according to TCM syndrome scale of deficiency of lung yin, TCM syndrome scale of yin deficiency of damp-heat, TCM syndrome scale of spleen and kidney yang deficiency and TCM syndrome scale of yin deficiency of liver and kidney.	N/A	N/A	TCM methods are unique for dry eye diagnosis and treatment.	The quantitative criteria are complex, the normalization level is low, and time-costing.
15	Demographic Factors	(Kaido et al., 2015) (Alshamrani et al., 2017)	Demographic survey	Demographic survey is helpful to detect the risk factors of the disease and achieve DED early screening	People who are male gender, younger age (≤56 years), not current smoking and without history of diabetes mellitus.	People who are female gender, older age (>56 years), current smoking and history of diabetes mellitus.	This method is useful for early screening, analyzing the factors, and higher patients' DED prevention awareness.	Results could not be regarded as the basis of DED diagnosis.

6. Discussions

DED is a universal eye disease around the global. Challenges of low level of awareness, high incident and recurrent rate makes it a significant problem for academic and society. It is still hard to be radical cured. AI-based DED detection and treatment research is increasingly developing during the recent 5 years, which has accomplished lots of achievements, especially for DED detection based on digital ophthalmic data. Countries of the U.S., China, India, Turkey, and Japan are the top-5 contributed countries. Most of the contributed institutions are related to hospitals, universities, and ophthalmic equipment companies. The top five institutions are identified as Singapore Eye Research Institute, Bascom Palmer Eye Institute, Keio University, King Saud University, Find peer reviewers from Beijing Tongren Eye Center. The top five contributed authors are identified as Lemp, Michael A. Schiffman(M. A. Lemp et al., 2011), Rhett M. Nichols(Schiffman et al., 2000), Kelly K. Pflugfelder(Nichols et al., 2004), Stephen C(Pflugfelder et al., 2005) and Bron, Anthony J(Bron et al., 2014). They have great contributions for DED diagnosing and grading standard research. The top three cited references fall on TFOS DEWS II Definition and Classification Report(Craig, Nichols, et al., 2017), TFOS DEWS II diagnostic methodology report(Wolffsohn et al., 2017), Prevalence and associated factors of depression in general population of Korea: results from the Korea National Health and Nutrition Examination Survey, 2014(Shin et al., 2017), which are all related to DED quantitative diagnostic criteria published in 2017. These criteria are regarded as the ground truth after then, and a burst of AI-based DED research was emerged in 2018. Thus, this study concluded that the quantitative diagnostic standard from the perspective of ophthalmology is a basis for interdisciplinary research developing, especially for AI and medical studies. Furthermore, based on the quantitively review analysis results, the cooperation between countries, institutions, and authors, especially from different research areas should be encouraged.

The hottest topics fall on bacterial eye infection, bacterium culture, blood cell count, cerebrospinal fluid analysis, chill, confusion, connective tissue disease, creatine kinase, creatinine blood level, daily life activity, demographics, diabetes, drug substitution, epistaxis, evaporative dry eye, fibrosis, foreign body, graft versus host disease, graves' disease, graves ophthalmopathy, histology, loss of appetite, medical record, meibum, optical tomography, vancomycin, visual analog scale, visual field defect, dry eye syndrome, controlled study, age, major clinical study, clinical article, lacrimal fluid, tear, priority journal, diagnostic imaging, follow up, case report, dry eye disease, retrospective study, Schirmer test, prevalence, complication, Sjogren syndrome, meibomian gland dysfunction, meibomian gland and young adult, diagnosis. Thus, this study concluded that the symptoms, demographic factors, treatments and diagnostic methods, especially based on medical digital evidence, clinical studies and real-world data are the former studies most focused on. It is still the vital direction for future research.

The DED diagnosis standards of Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II(Chase et al., 2021; Craig, Nichols, et al., 2017) is the most acceptable guideline for DED detection. Ocular surface disease index (OSDI) is the most typical questionnaire for DED detection and early screening(Pellegrini et al., 2019a). Oxford scale(A. Lemp, 1995), Bijsterveld scale (van Bijsterveld, 1969), the Sjögren's International Collaborative Clinical Alliance ocular staining score(Whitcher et al., 2010) and National Eye Institute/Industry (NEI) grading scales(Amparo et al., 2017; Chun & Park, 2014; Pellegrini et al., 2019b) are the most recommended guideline for DED detection and grading, especially for CFS images. DED could be classified into Sjögren syndrome (SS), and ocular graft-versus-host disease (oGVHD). SS diagnosis could be decided by American-European Consensus Group Criteria (AECGC). Six indicators are included, which are positivity of autoantibodies Anti-SSA (Ro) or Anti-SSB (La), ocular symptom evaluation (foreign body sensation, dry eye symptoms, use of artificial tears three or more times per day), ocular sign identification (Schirmer test < 5 mm/5′, positive ocular surface staining), oral symptom detection (swollen salivary glands, dry mouth, need for liquids to swallow dry foods), histopathology of salivary glands positive for focal lymphocytic sialadenitis and oral symptom measurement (unstimulated whole salivary flow ≤1.5 mL/15′, abnormal parotid sialography, abnormal salivary scintigraphy). The cutoff is ≥ 4(Vital, 2002; Vitali & Del Papa, 2016). The diagnosis of chronic oGVHD could be decided by the International Consensus Criteria on Chronic Ocular GVHD Group (ICCGVHD) based on Schirmer test, CFS and ocular surface disease index (OSDI), and conjunctival injection score, the cutoff is a total score ≥ 6 in the presence of systemic GVHD, and ≥ 8 in the absence of systemic GVHD(Ogawa & Tsubota, 2013; Pellegrini et al., 2019b).

Databases for AI-based DED detection are listed as ophthalmic images, videos and electronic demographic medical records. Digital diagnostic data types for DED detection could be classified as TBUT videos, CFS images, ultrasonic image, interferometry and slit-lamp images, IVCM images, meibometry images, blink videos, colorful anterior segment photographs, OCT images, demographic data and OSDI questionnaire structured data. Data with high quality are rare and hard to find on the open-source platform. It is also hard to be obtained in the real world. Ethics and trust issues are still challenges for researchers. And still, in most of the developing areas, the data is not stored on purpose, videos are illuminated and blurred. Patients are constantly blinking of eyes.

DED detection methods are clustered into three categories, which are ground truth and/or comparable standards for AI DED diagnosis (TBUT, S I T, TMH, and OSDI), potential methods for AI-based methods have a great advantage(DED detection based on meibometry Images, CASPs, IVCM Images, OCT Images, blink videos and ultrasonic imaging) and the potential direction and supplemented methods for AI-based DED detection (DED detections based on tear osmolarity, proteomic analysis, TCM and demographic information). The typical and conventional methods are the most acceptable with high standard level of DED detection. However, it is verified time-costing, resource wasting and sometimes with low accuracy, risk and discomfort for patients. AI-based methods based on ophthalmic digital images are autonomic, resource-saving, timesaving, highly reproducible, objective, non-invasive testing, and low-risk. It presents a hug potential for DED factor analysis, early screening and prognosis. However, lack of dataset, ethic approval and low levels of diagnosis standard normalization and explain ability of AI algorithms are still challenges. Moreover, there still are some debates and disagreement on the potential direction and supplemented methods, like tear osmolarity, proteomic analysis, TCM and demographic information, which need more studies and attention for interdisciplinary scholars to focus on. Thus, from the overall consideration, it more collaboration should be encouraged between engineers and ophthalmologists. Form the aspect of ophthalmology, more qualified data should be collected on research purpose and more attention should be paid for DED diagnosing classification. From the engineering and computer science research aspects, advanced deep learning and machine learning algorithm design considering the specific research objects and role guided should be focused, including innovation research on the robustness and explainable mechanism, optimal model fusion mode, algorithm selection, the explainable feature extraction and optimization mechanisms.

By exploring the literature opinions and communicating with more than10 ophthalmologists who have more than 5-year-clincal experiences, this study concluded four directions for the future research. (1) DED is one of the most common eye diseases. Usually, it can be detected under most of the circumstances by asking questions from OSDI questionnaires. But normalization level of the diagnosing standard is relatively low. It is hard to detect DED types (SS or oGVHD) and measure grades without dry eye evaluation equipment. Thus, AI research should be paid more attention to the DED type classification and grade measuring. (2) Besides, the prevalence rate of DED is increasing for groups who are with fundus diseases or had refractive surgeries. AI-based methods for multiple ophthalmic digital evidence evaluation should be encouraged, such as OCT, CFS and ultrasonic images. And studies related to the relationship between DED and specific fundus diseases, or refractive surgery operation conditions (like the surgery environment) should be focused. (3) Moreover, with the improvement of people's quality of life and deterioration of their living habits, the mean age of DED patients has decreased, especially during the COV-19 era. In this case, early screening for DED based on AI techniques and demographic factors and the OSDI questionnaire should be further explored. (4) Furthermore, the most challenge of DED is related to its treatment. Usually, it is suggested to use the eye drop medicine, fumigation atomization, hot/cold compress, meibomian gland massage, intense pulsed light treatment, daily care with the eye patch. But there is no standard approach for curing this disease in a stable and complete level. Thus, AI-based methods can play an important role for treatment evaluation and prognosis, especially for measuring DED severe grades during the treatment time, assisting ophthalmologists to adjust treatment plans, and helping patients by enhancing their confidence and reminding them of daily care.

7. Conclusions

This study makes a bibliographic analysis on the topic of DED diagnosis. 2131 pieces of articles are recognized during the period of 2012 to 2022. The developing trend, most contributed countries, institutions, authors, journals and cited references, keywords distribution and latest studies are explored. After texting mining on the 319 related literature, popular databases and DED methods are discussed. Advantages and disadvantages, the potential value and AI-method applications to each method for DED detection are investigated. The DED diagnosis, classification and grading standards are identified. Challenges of AI-based DED detection research are listed. Suggestions from the overall thinking, ophthalmic aspects and computer science aspects are illustrated. This article is based on the limited literature, which could be enriched in the future by considering more literature database in more languages.

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