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A Bibliographic Study and Quantitative Analysis of Age-related Macular Degeneration and Fundus Images

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Abstract

Age-related Macular Degeneration (AMD) is regarded as one of the main causes of irreversible vision loss in the elder. The increasing number of AMD patients is expected to reach 288 million by 2040. Detecting methods based on fundus images have become the main diagnostic approach for AMD. Therefore, this paper makes a systematic review analysis of AMD diagnosis based on fundus images. Methodologies of bibliography and text mining are included. 674 non-repetitive pieces of literature (183 in Chinese and 508 in English) are extracted from databases of Web of Science, Scopus, PubMed, and CNKI. The major contributed countries, related disciplines, key authors and their major contributions, hot topics, and the developing trend are discussed in the bibliographic study. Results show that there is a significant difference in focus between Chinese scholars and international researchers. Besides, cooperation in interdisciplinary research between countries and authors is strongly encouraged. Based on the text mining result, the anatomic and pathological system of AMD is explored. AMD symptoms based on Optical Coherence Tomography (OCT), Regular Color Fundus Photography (RCFP), and Ultra-Wide Fundus (UWF) images are quantitatively analyzed. Eventually, suggestions and future directions are delivered. This study contributes a significant reference value for AMD-related scholars and practitioners.

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Introduction

In 1874, Age-related Macular Degeneration (AMD) was first proposed, which was defined as symmetric central chorioretinopathy in the elderly. Today, AMD has become one of the main causes of irreversible vision loss in the elderly, accounting for 8.7% of global blindness. About 1% of the European population suffers from advanced AMD. It is estimated that by 2040, the total number of AMD patients will increase to 288 million. Besides age, genetic factors and environmental factors are also the direct causes of AMD [1].

The visualization methods used to quantify the morphological diagnostic features of AMD mainly include Color Fundus Photography (CFP) [2], Fundus Autofluorescence (FAF) [3]-infrared imaging (Infrared Imaging-IR) [4]. Spectral-Domain Optical Coherence Tomography (SD-OCT, hereinafter referred to as OCT) [5], Optical Coherence Tomography Angiography (OCT-A) [6], and Scanning Laser Ophthalmoscopy (SLO) [7]. For color fundus imaging technology, the earliest fundus imaging began with CarlZeiss's first fundus camera in 1926 to achieve 20-degree fundus imaging photos [8], then the Optos200Tx (Optos, Dunfermline, Scotland) and Clarus 500 and 700 are developed. Today, traditional fundus cameras have a 3050-degree retinal field of vision, which has become a standard fundus screening tool [9]. Since then, cameras over 50 degrees are called wide-focus cameras [10].

However, there are still challenges and deficiencies in the quantitative research on the influence of AMD. Therefore, this paper makes a descriptive and visual analysis and discussion on the structure, pathology, inducement, characteristics, and classification of AMD on OCT, Regular Color Fundus Photography (RCFP), and Ultra-Widefield Fundus (UWF), which has a strong reference value for the diagnosis and research of AMD. The structure of this paper is as follows, the second chapter is the experimental methods, the third chapter is the results and discussion, and the last chapter is the summary.

Methodology

In this paper, bibliometrics [11,12] are used to search Web of Science (WOS), Scopus, PubMed, and China knowledge Network (CNKI). The search sentences of WOS, Scopus and PubMed are set as the following, TS = ("Age-Related Macular Degeneration") AND TS = ("fundus"); the search sentence of CNKI is set as the following, TS = ("age-related macular degeneration") AND TS = ("fundus"). The search date is February 14, 2022. This paper uses CiteSpace (5.8.R3 (64-bit)) tool [13] to make a quantitative analysis of the retrieved literature. After screening, text mining and text analysis are carried out on several typical articles at home and abroad. Finally, based on the fundus picture, this paper focuses on the AMD structure, inducement, classification (dry and wet AMD; early and late AMD,) and the diseases shown on the picture (diagnostic basis).

Results and discussion

Results of bibliometric analysis

A total of 186 articles, including WOS183, Scopus181, and PubMed144, were searched by CNKI. A total of 674 non-repetitive Chinese and English articles were obtained. The development of the literature year is shown in figure 1. As can be seen from the picture, for fundus images and related topics of age-related macular degeneration, the Chinese literature Zhi.com first appeared in 1986, and its development is relatively slow and even has a downward trend in recent years. The international English literature first appeared in 1991, which is later than the knowledge net database, but since 2012, the literature in this database has developed rapidly, and the literature review in this field is expected to continue to grow in the next few years.

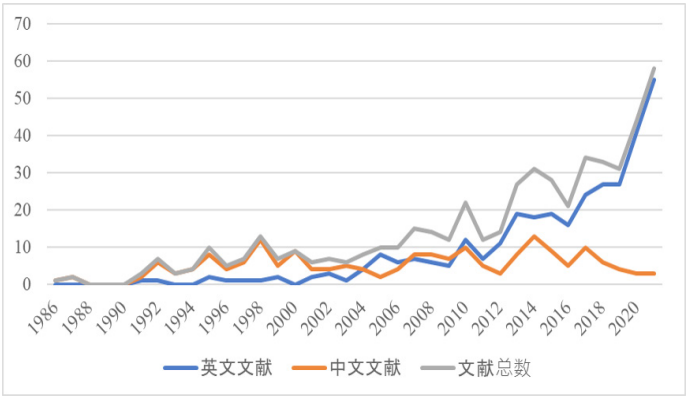

Figure 1: The developing trend of publications.

Literature analysis

According to the regional analysis based on the publication of English literature, it can be obtained from figure 2 and Table 1 that the top 10 countries and regions are mainly contributed by China, while the articles of WOS are more extensive. Among them, the United States contributed the most to the total number of English and Chinese documents (nodes: 64), followed by Germany (nodes: 20) and Turkey (nodes: 17). According to the number of nodes in figure 2 (nodes: 118) and the connection coefficient, it is known that cooperation between countries in this area is weak.

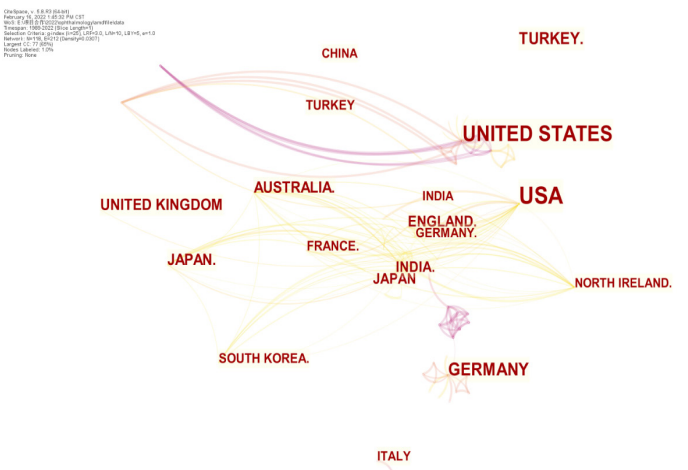

Figure 2: The distribution map of countries.

Table 1: The top 7 regions listed according to numbers of publications

Index	Number of publications	Regions
1	64	The U. S
2	20	Germany
3	17	Turkey
4	13	Australia
5	13	Japan
6	12	The U. K
7	11	India

According to the quantitative analysis of English literature, the classification of disciplines is shown in figure 3, and the subjects involved are Ophthalmology, Medicine, Computer science and engineering, Imaging science, Healthcare, Anthropology, Multidisciplinary, Rheumatology, Pathology, and Geriatrics & gerontology. Among them, only 1% are interdisciplinary, and 88% are ophthalmology, medicine, and health care. Therefore, the application of computer engineering and imaging science in the field of ophthalmology and medicine needs to be encouraged and promoted in future research.

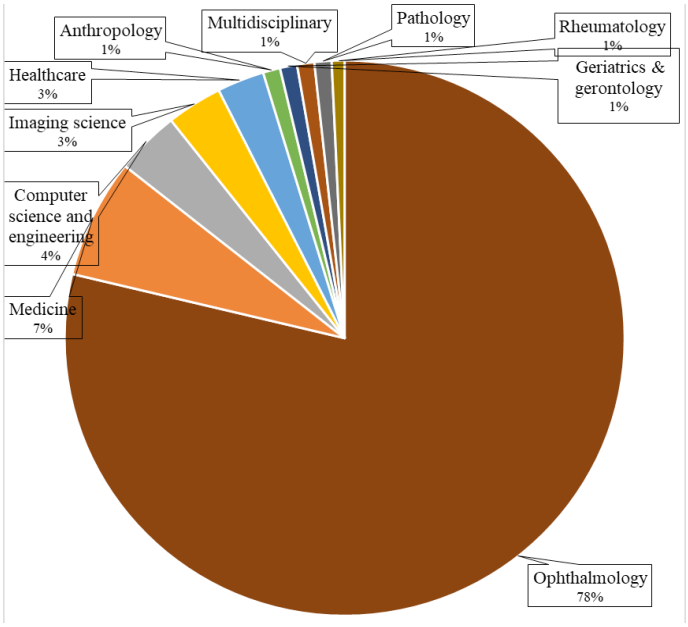

Figure 3: The category classification.

As can be seen from the following figure, based on the authors of the English literature, the number of nodes in figure 4 (Number 538) and the connection coefficient (Epist 999) show that the cooperation between authors in this field needs to be strengthened. As shown in Table 2, according to the ranking of the number of articles published, the study analyzed the representative contributions of the top 5 authors. International scholars pay more attention to (1) the manifestation of AMD in pictures, and (2) recognition and diagnosis based on artificial intelligence algorithms (deep learning and machine learning).

Figure 4: The category classification.

Table 2: The top 5 key authors of WOS, Scopus, and PubMed according to the number of publications.

Index	Number of publications	Authors	References	Conclusions
1	9	FG HOLZ	Mesopic And Dark-Adapted Two-Color Fundus-Controlled Perimetry in Geographic Atrophy Secondary to Age-Related Macular Degeneration [14].	For the dry AMD, the morphological characteristics of the geographical atrophy area can be obtained by detecting the two-color fundus control visual field in the visual field grid of patients with fundus images.
2	6	AMITHA DOMALPALLY	Multimodal, multitask, multiattention (M3) deep learning detection of reticular pseudodrusen: Toward automated and accessible classification of age-related macular degeneration	The multi-mode, multi-task, multi-attention (M3) deep learning framework based on color fundus pictures and fundus autofluorescence (FAF) has good performance in the detection of reticular pseudoretinopathy (RPD).
3	6	Chew, Emily Y.	Principal Cause of Poor Visual Acuity after Neovascular Age-Related Macular Degeneration: Age-Related Eye Disease Study 2 Report Number 23 [15].	Based on the clinical fundus photos of wet AMD, 60% of the visual acuity decline in wet AMD is due to macular atrophy and 40% is due to subretinal fibrosis. This conclusion is helpful to guide the treatment of wet AMD.
4	6	Schmitz-Valckenberg	OCT Signs of Early Atrophy in Age-Related Macular Degeneration: Interreader Agreement: Classification of Atrophy Meetings Report 6 [16].	To explore the correlation between incomplete Retinal Pigment Epithelium (RPE) and Outer Retinal Atrophy (iRORA), complete RPE and Outer Retinal Atrophy (cRORA) based on AMD fundus images.
5	4	Schmidt-erfurth, Ursula	Comparison of macular pigment in patients with age-related macular degeneration and healthy control subjects – a study using spectral fundus reflectance [17].	The dependence of macular pigment optical density on age was studied based on the fundus reflectance spectrum. Compared with the healthy control group, the macular pigment light density of AMD patients was lower.

Chinese literature analysis

As the Figure 4. And Table 3. Shown, the main topics and years of domestic research on AMD and fundus imaging are Age-related Macular Degeneration (AMD) (1996), fundus disease (2008), fluorescein angiography (1998), Compaq (2014), neovascularization (1998), wet age-related macular degeneration (2010), visual field (1997), diabetic retinopathy (2012, 2015), a follow-up study (1998), Liangxue Huayu recipe (2010), vitreous wart (2001), Retinal Pigment Epithelium (RPE) (2017), clinical study (2010), Photodynamic Therapy (PDT) (2014), central visual acuity (2019), Jianpi Huazhuo recipe (2010), optical coherence tomography (2007), injection (2014), fundus examination (2015), early examination (2001), fovea (2001).

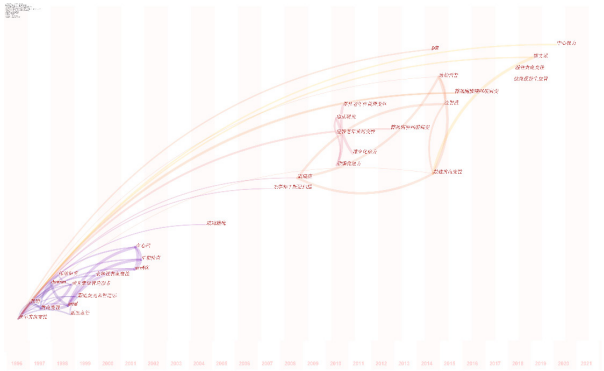

Figure 5: The time zone of the keyword development of CNKI.

Table 3: The top 22 keywords of CNKI according to the number of publications.

Index	Number of publications	Centralization	Keywords	Index	Number of publications	Centralization	Keywords
1	134	1.03	AMD	12	2	0	drusen
2	5	0.03	fundus disease	13	2	0	RPE
3	5	0.04	fluorescein angiography	14	2	0	clinical study
4	4	0.03	Compaq	15	2	0	PDT
5	4	0	neovascularization	16	2	0	central visual acuity
6	4	0	wet age-related macular degeneration	17	2	0	Jianpi Huazhuo recipe
7	4	0.05	visual field	18	2	0	OCT
8	2	0	diabetic retinopathy	19	2	0	injection
9	2	0	follow-up study	20	2	0	fundus examination
10	2	0	Liangxue Huayu recipe	21	2	0	early examination
11	2	0	diabetic retinopathy	22	2	0	fovea

Result of text mining

Fundus structure of senile maculopathy

By comparing the RPE structures of a 3-year-old child and an 80-year-old patient, The outer segments of the rods and cones are embedded in the photoreceptor matrix and partially surrounded by the Apical Pseudopod Retinal Pigment epithelial process (APRP). The exfoliated disc is wrapped in phagosomes and digested by phagosomes in the cytoplasm of the omental pigment epithelium. Macrophages and fused macrophages remove cell fragments around the cells. Light-induced toxicity occurs when light is absorbed by various chromophores in lipofuscin particles. This destroys DNA and cell membranes, leading to inflammation and apoptosis. Lipofuscin particles increased, glass membrane thickened, and choroidal capillaries decreased. With the increase of age, the central elastic membrane of the glass film becomes more porous. This is defined as the main cause of AMD, thus, the retinal pigment epithelium is the main reason for the diagnosis of age-related macular degeneration [18].

The early clinical symptom of AMD is the appearance of yellow precipitate between the RPE and the glass membrane (Bruch's membrane, BM), called drusen. The components of vitreous warts include proteins, lipids, cholesterol, and cell fragments of the retinal pigment epithelium. In the early stages of the disease, the number of glass warts is limited and will not affect visual function. When the number of the vitreous body increases, or when there is a significant pigment change in the retina due to the degeneration of RPE cells, the disease develops from early to middle AMD, or even to late AMD. The visual symptoms of early AMD patients are not obvious, and they usually show blurred central visual field or visual distortion. Over time, the central field of vision may become blurred, eventually leading to advanced AMD, or central vision loss (scotoma). Early age-related macular degeneration is characterized by vitreous warts, pigmentation, hypopigmentation, or no visible choroidal vessels. Glass warts can be classified according to size, appearance, biochemical composition, and examination techniques. When the diameter of the glass wart is more than 25 μm, the glass wart can be seen under the fundus camera. The larger the number of vitreous warts, the larger the area covered, and the greater the area of retinal pigmentation and hypopigmentation in the macula, the higher the risk of advanced age-related macular degeneration. Dry and wet age-related macular degeneration are independent and interchangeable. In addition, both can be found in the same patient, that is, dry and wet age-related macular degeneration can occur in the same or different eyes of the same patient [18].

Advanced age-related macular degeneration can be divided into two types: Neovascular Age-related Macular Degeneration (Neovascular AMD) or Wet Age-related Macular Degeneration (wet AMD), and Geographic Atrophy AMD or dry age-related macular degeneration [19-20,18]. Wet age-related macular degeneration is characterized by the infiltration of abnormal blood vessels from the choroidal vascular system into the ret-

ina. These newly formed blood vessels are fragile and easily ruptured, leaking blood in the retina, causing the neuroretina or retinal pigment epithelium to detach from the glass membrane, which disturbs the fine arrangement of photoreceptors and leads to visual deformation [20-21, 16]. These new subretinal vessels tend to grow toward the fovea, and within days or months, more extensive bleeding and scars may occur, causing sudden vision loss. Dry age-related macular degeneration is caused by the gradual degeneration of retinal pigment epithelium and photoreceptor cells and the contraction of choroidal vessels mainly manifested as well-defined round or oval hypopigmented spots, usually located near the fovea. Large choroidal vessels can be seen. Each year after the initial diagnosis, about 15% of patients with unilateral wet age-related macular degeneration were found to have wet age-related macular degeneration on the opposite side. If left untreated, wet age-related macular degeneration usually leads to legal blindness within a few months after the second eye is affected (visual acuity ≤ 0.1 min 6max 60) [18]. In contrast, patients with dry age-related macular degeneration may take several years, during which the peripheral visual field around the central scotoma is complete, so they still have enough vision to support their daily activities [20,22].

The macular fovea is shown by the arrow in the following picture. The layered structures are vitreous, nerve fiber layer, ganglion cells, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, inner segment, outer segment, retinal pigment epithelium, and choroid. Among them, the retinal pigment epithelium is relatively flat, and there is no effusion between layers [23].

The area within the outer white circle (the diameter of the retina is about 6 mm) is considered the macular area (Macular Lutea), which in Latin means yellow spots or spots. The inner circle (0.8 mm in diameter) is the foveal area of the macula and the area with the largest cone-rod cell ratio. The curve superimposed on this normal fundus shows the relationship between visual acuity and fovea distance, as a measure of the effect of the location and area of fundus macular (scar) coverage on visual acuity in age-related macular degeneration. The closer the distance from the macular fovea, the greater the damage to vision. The picture in the lower right corner shows the solution of the posterior pole of the eyeball. The retina has 10 layers, and the illustration shows the outer layers of two layers, mainly consisting of photosensitive rod-shaped and cone-shaped photoreceptor cells supported by Miller cells (purple part in the picture), all embedded in the intercellular matrix and close contact with the retinal pigment epithelium. There are two kinds of extracellular matrix around the retinal pigment epithelium, namely the photoreceptor matrix and the glass membrane. Between the retinal pigment epithelium and the outer wall of the eye (sclera) are the vitreous membrane, choroidal capillaries, and choroid (a larger vascular layer). The choroidal capillary layer (Ruysch's Complex) mainly includes retinal pigment epithelium, vitreous membrane, and choroidal capillaries [20].

Quantitative characteristics of senile maculopathy based on OCT

High-resolution OCT imaging is regarded as the gold standard of anatomical biomarkers in senile macular degeneration [23]. Quantified dry AMD in the following dimensions: (1) choroidal hyperpermeability; (2) RPE attenuation or destruction; and (3) photoreceptor degeneration, characterized by lack of cross-section, ellipse, and outer boundary membrane, and thinning of the outer nuclear layer. Moraes et al. (2021) segmented the fundus features on OCT images that are of clinical significance for the diagnosis of AMD: Neurosensory retina (NSR), vitreous body (drusen), Intraretinal Fluid (IRF), Subretinal Fluid (SRF), subretinal hyperreflective substance (Subretinal Hyperreflective Material-SHRM), and retinal pigment epithelium (Retinal Pigment Epithelium-RPE), Hyperreflective Foci (HRF), Fibrovascular Pigment Epithelium Detachment (FvPED), and serous pigment epithelium detachment (SPED).

Quantitative characteristics of age-related macular degeneration based on common color fundus photos

The normal fundus color photograph with AMD positive is shown in figure 5 [18]. With the increase of age, the glass warts become fused and enlarged, sometimes crystalline, with unclear boundaries, or accompanied by RPE pigmentation or hypopigmentation. Figure A shows early age-related macular degeneration in two maculae: small glass warts in the left macular region (at the arrow shown), large, blurred glass warts in the fovea (at the arrow shown), and more glass warts and focal pigmentation in the right macular region (at the arrow shown). Figure B shows early age-related macular degeneration on the left, characterized by extensive small but large glass warts in and around the macular region, and late dry age-related macular degeneration on the right. It is mainly reflected in the well-defined round or oval hypopigmented spots (arrows) in the fovea of the macula, accompanied by large choroidal vessels. The left side of the C figure shows early age-related macular degeneration with crystallization and calcification of the vitreous body (at the arrow shown); on the right (also early age-related macular degeneration), large fused vitreous bodies can be seen, resulting in RPE detachment and hyperpigmentation (at the arrow shown). Figure D shows advanced dry age-related macular degeneration with a complete annular scotoma around the residue of the central small visual field, that is, the photoreceptors in the visual center are still functioning (arrowhead). Figure E shows advanced wet age-related macular degeneration, showing massive serous RPE detachment (edge marked with arrows), caused by fluid exudating from the subretinal neovascularization membrane. Figure F shows advanced wet age-related macular degeneration with subfoveal hemorrhage and surrounding RPE detachment (at the arrow shown). Figure G shows advanced dry age-related macular degeneration (black arrow), with orange lines of large choroidal vessels surrounded by glial scar tissue (at the arrow shown), caused by massive subretinal hemorrhage and a small amount of residue (white arrow). Figure H shows advanced wet age-related macular degeneration with a glial scar in the macular area and bleeding residue in the temporal margin (at the arrow shown) [18].

Quantitative characteristics of age-related macular degeneration based on ultra-wide-angle fundus images

For UWF images, this image has a wider fundus shooting area, and many studies have shown that other fundus diseases have a positive inducing effect on macular degeneration. Therefore, for the diagnosis of fundus diseases in ultra-wide-angle fundus images, it plays an important role in the prediction and early screening of macular degeneration. The use of this image in the follow-up of eye diseases or diseases is of great significance for early screening of fundus diseases in the community [1,8]. Rengin and Rengin (2021) pointed out that the characteristics of AMD in ultra-wide-angle fundus images can be expressed as choroidal neovascularization, hyperpigmentation, retinal pigment epithelial detachment, reticular pseudo erythe-

ma, and senile reticular pigmentation. The repeatable recording of peripheral retinal changes in AMD may lead to a more comprehensive classification of the disease. As Figure 6 shown, plot a is submacular hemorrhage caused by exudative age-related macular degeneration (left eye); b is non-exudative age-related macular degeneration (right eye); c is choroidal neovascularization membrane (left eye); d is non-exudative age-related macular degeneration with vitreous and chorioretinal atrophy (right eye). E is choroidal neovascularization membrane and associated pigment epithelial tear (right eye); f is choroidal neovascularization membrane (left eye); g is the presence (right eye); h is choroidal neovascularization membrane (left eye) [1].

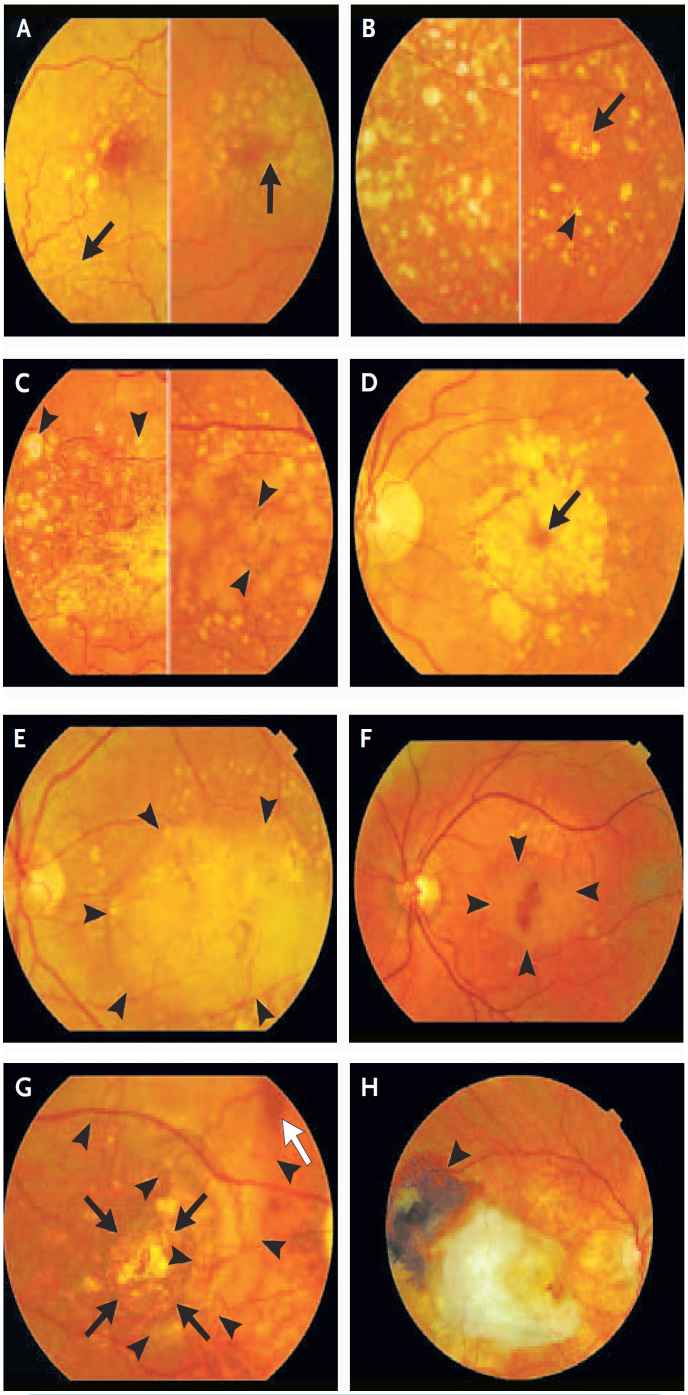

Figure 6: CFP of AMD cases [20,18].

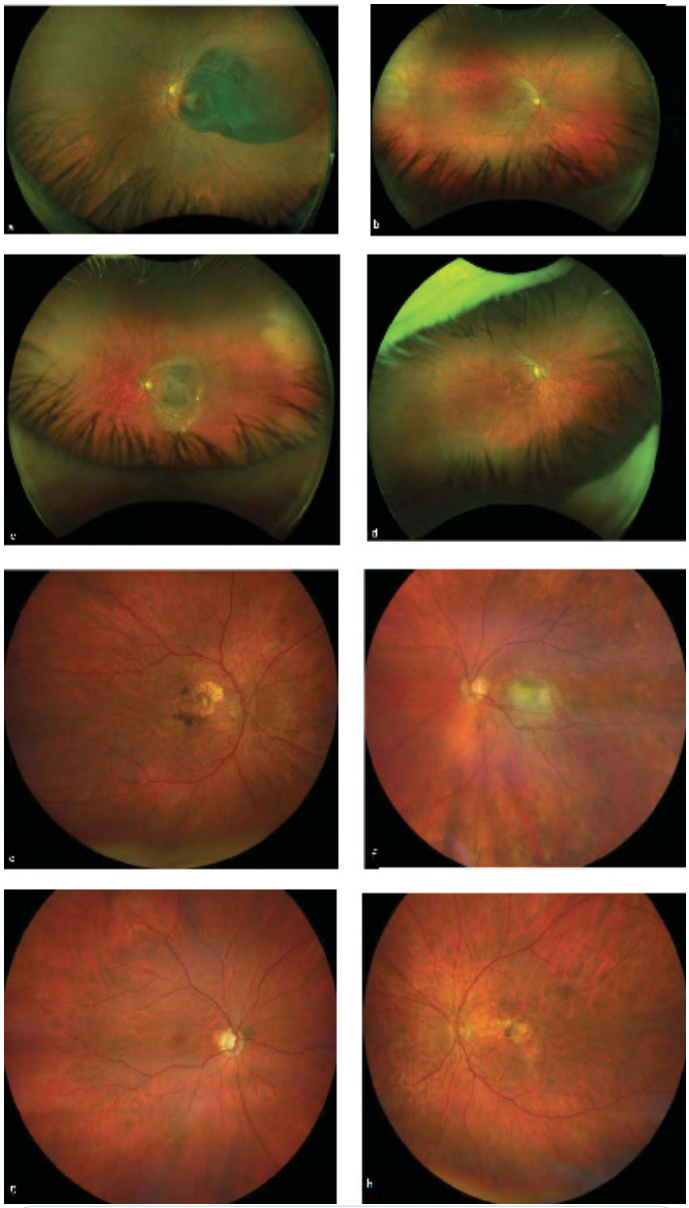

Figure 7: UWF of AMD cases [1].

Conclusion

Based on the bibliometric results, a total of 674 non-repetitive articles were obtained, including 183 Chinese articles and 508 English literature. Through the bibliometric analysis of the retrieved literature, the results show that: (1) macular lesions based on fundus images have been studied for more than 30 years. International English papers first appeared in 1991), in which the research of international scholars in this field has been rising since 2012, and this trend is expected to continue to develop in the next few years. (2) about the regional distribution of contributions in this field, the United States, Germany, Turkey, Australia, Japan, the United Kingdom, and India contribute the most to this field, and the cross-regional cooperation is weak (the number of nodes is 118; connection coefficient is 212). (3) the subjects involved in English literature are mainly ophthalmology, medicine, computer engineering, imaging science, health care, anthropology, interdisciplinary, paralysis, pathology, geriatrics, and geriatrics. Interdisciplinary research needs to be strengthened. (4) through the analysis of the contribution of the top five international scholars, the cooperation of many scholars who are more concerned with international scholars is still relatively weak, and we need to pay attention to the manifestation of AMD in pictures and the recognition and

diagnosis based on artificial intelligence algorithms (deep learning and machine learning). By exploring the research contributions of 12 scholars who expect to be ranked first in the examination, the results show that Chinese scholars in this field are mainly concerned with the clinical characteristics, inducement, self-test methods, treatment plans, and guidelines of AMD. In addition, the cooperation between domestic and foreign scholars in this field needs to be paid attention to (international scholars: the number of nodes is 538, the number of connections is 999; domestic scholars: the number of nodes is 13, the coefficient of connections is 10). (5) through the analysis of the subject outbreak time axis of Chinese literature, the time points of AMD disease concern structure outbreak are as follows: a) neovascularization (1998), vitreous wart (2001), choroidal neovascularization (2017), central visual acuity (2019) and fovea (2001). B) fluorescein angiography (1998), optical coherence tomography (2007); c) the time points of treatment and prevention were as follows: Kangbuxipu (2014), Liangxue Huayu recipe (2010), photodynamic therapy (PDT) (2014), Jianpi Huazhuo recipe (2010), injection (2014), fundus examination (2015), early examination (2001). D) the outbreak time points of the study methods were follow-up study (1998) and clinical study (2010); e) the outbreak time points of other mutual fundus diseases were diabetic retinopathy (2012, 2015).

Based on the results of text mining, the AMD diagnosis based on the fundus image is quantified into the following feature dimensions. For OCT fundus photos, the main manifestations are: 1) accumulation of intraretinal fluid; 2) accumulation of subretinal fluid; 3) suspected polyposis (subretinal hyperreflective substance) 4) vitreous warts; 5) detachment of retinal pigment epithelium. For color fundus photos (including ordinary fundus photos and ultra-wide-angle fundus photos), it can be reflected as follows: 1) hard/soft/calcified crystalline glass warts in the macular region; 2) focal pigmentation in the macular region (focal hyperpigmentation); 3) fused basal layer glass warts in the macular region; 4) choroidal neovascularization membrane; 5) complete circular scotoma (Ring Scotoma) around the residue of the central small field of vision. 6) retinal pigment epithelial (RPE) detachment; 7) subretinal neovascularization membrane oozing; 8) sub-foveal hemorrhage; 9) large choroidal vessels in the macular region and glial scar tissue in the perimacular area; 10) subretinal hemorrhage with residue in the perimacular region; 11) glial scar in the macular region; 12) temporal margin hemorrhage residue in the macular region.

To sum up, through the bibliometrics and text mining analysis of this paper, the research process and focus of domestic and foreign scholars in this field are very different. In this regard, this paper puts forward the following suggestions for future scholars: (1) to strengthen the cooperative research among interdisciplinary and cross-regional authors and institutions; (2) with the development of computer artificial intelligence, this technology has obvious advantages in many aspects such as resource-saving and efficiency improvement and pays attention to the application and innovative research of machine learning and deep learning in the field of ophthalmology. (3) fundus pictures have strong guiding significance for AMD early screening, detection, and evaluation, pay attention to the quantitative study of AMD fundus diseases based on OCT, OCTA, RCFP, and UWF, and have strong guiding significance for AMD early screening, prevention, and treatment. (4) combined with electronic medical records, follow-up records, and clinical manifestations, to explore the diagnosis and treatment of AMD.

Of course, many areas need to be strengthened and improved. For example, this article only focuses on the Chinese and English literature of WOS, Scopus, PubMed, and China knowledge Network. For future scholars, they can pay attention to more databases and multi-language literature. In addition, there will be some deviations in the process of translating English nouns into Chinese in the mining and understanding of the text.

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