Visualizing the intellectual structure and recent research trends of diabetic retinopathy

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Abstract

● **AIM:** To analyze the intellectual structure and recent research trends in diabetic retinopathy (DR) and unearth potential knowledge.

● **METHODS:** English DR publication included in this study was exported from the Web of Science Core Collection, and Chinese DR publication was exported from China National Knowledge Infrastructure from the establishment time of the database to 2019. CiteSpace and Microsoft Excel were used to visually analyze DR research, including analysis of the number of publications, highly cited publication analysis, spatial distribution analysis, and keyword co-occurrence analysis.

● **RESULTS:** A total of 23 795 English studies and 11 577 Chinese studies, including 2089 studies related to traditional Chinese medicine (TCM), were obtained. The data suggested the following: 1) The number of English and Chinese DR publications increased over time, and the growth rate of English publications was relatively fast. 2) The distribution of international scholars and institutions was close, while the distribution was scattered in China. Shanghai Jiao Tong University has the largest number of publications. Tien-Yin Wong was the core author with the largest number of publications. England and the United States are the core of international DR research cooperation. 3) Optical coherence tomography and risk factors are recent international research hot spots and trends. The difference is that TCM is a recent research trend under DR in China.

● **CONCLUSION:** DR has drawn an increasing amount of attention worldwide. The focus of research in this field has shifted from tertiary type DR treatment to secondary prevention strategies which focus on the screening and monitoring of disease progression. The advantages of TCM in the prevention of DR have attracted attention, and it is worth incorporating this with Western medicine to address this challenge.

● **KEYWORDS:** diabetic retinopathy; diabetes mellitus; retinopathy; complementary therapies; bibliometrics

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common and challenging ocular complications of diabetes mellitus and has gradually become the leading cause of blindness worldwide[1]. However, the pathogenesis of DR is complex and has not yet been fully defined, and various risk factors exist. Furthermore, there are many shortcomings in the current internationally recommended treatment, such as the administration of treatment being uncomfortable for patients, long-term side effects, high costs incurred, and limited therapeutic effect[2], while ethnomedicine has potential. Screening for DR is insufficient especially in the early stages, while emerging technology is expected to more accurately diagnose and predict the occurrence and development of DR[3-4]. To solve these problems, a large number of DR studies have been carried out worldwide, making it difficult to effectively keep up with the flow information under several fields of knowledge. Bibliometrics is an effective way to summarize the complex and growing available information set to analyze

global trends and narrow the knowledge gaps, which is why it was chosen as the knowledge analysis method[5-6]. However, to date, there has been a lack of qualitative and quantitative analyses of these published articles to sufficiently provide cutting-edge information for further cooperation and explore new ideas for the diagnosis and treatment of DR. Therefore, this study aims to analyze the structure, recent research hotspots, trends in this field by means of a scientometric analysis conducted using Microsoft Excel and CiteSpace, a Java application that includes bibliometric analysis, data mining algorithms, and visualization methods developed by Chen et al[7].

MATERIALS AND METHODS

Publication Search Data were collected from the China National Knowledge Infrastructure (CNKI) and the Web of Science Core Collection (WoSCC), which included SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-Expanded, and IC. The specific retrieval strategies in the WoSCC database were as follows: the data were retrieved according to the topic (diabetic retinopathy), time (from the establishment time to 2019), and language used (English). To improve the accuracy and validity of the data, articles and reviews were manually selected as the types of documents to be included in the study (retrieved on May 11, 2020). This study conducted two searches on CNKI. First, the specific retrieval strategies included the publication type (journal article), topic (diabetic retinopathy), time (from establishment to 2019), and language (Chinese). Second, publication related to traditional Chinese medicine (TCM) was retrieved from the results through a full-text search (retrieved on May 15, 2020).

Eligibility Criteria Original DR research retrieved from CNKI and WoSCC were included in this study. Repeated publications, unrelated studies, studies not officially published, studies collected by hand and telephone, journal introduction, popular science articles, solicitation notice, and conference news were excluded.

Study Selection The publication was screened according to title and abstract, following an inclusion and exclusion criteria. The screened results were verified by two experienced ophthalmologists.

Data Analysis Methods In this study, Microsoft Excel 2016 was used to conduct a preliminary bibliometric analysis of the included data. Microsoft Excel 2016, and CiteSpace 5.6.R5 was used to visually analyze the data in the publication from 2015 to 2019, including keywords, authors, institutions, countries, *etc*. The retrieved Chinese publication in CNKI was exported to CiteSpace 5.6.R5 in "Refworks" format, and English publication in WoSCC were exported in "plain text" format. Chinese and English publication was exported.
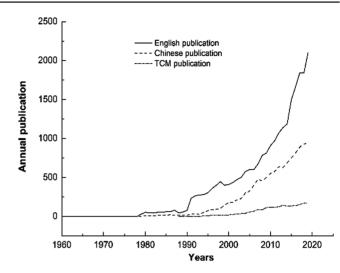

Figure 1 Annual amount of DR publication from the establishment time of database to 2019.

The parameters of the CiteSpace 5.6.R5 were as follows: time slicing (2015-2019), years per slice (1), term source (all selection), node type (choose one at a time), and selection criteria (choose one at a time).

RESULTS

Study Inclusion A total of 23 795 English studies and 11 577 Chinese studies, including 2089 studies related to TCM, were obtained following the inclusion and exclusion criteria. A total of 8955 English publication and 4339 Chinese publication and 775 studies related to TCM were included from 2015 to 2019.

Analysis of the Amount of Publications The change in the annual number of publications, which can directly display the change in the research enthusiasm for a certain discipline in a specific period, is an important indicator for analyzing the development trend and predicting future trends[5]. The results are shown in Figure 1. Little research had been conducted on DR before 1990, as research under this field was in its infancy. English publication began slightly earlier than that of Chinese, indicating that Chinese DR research started later. In the same way, DR research related to TCM was began later in China. Researchers began to pay more attention to DR since 1990, as indicated by the annual increase in the number of studies on DR. From 1990 to 2014, DR research had steadily increased, and the growth rate of English research has been relatively fast. DR research related to TCM has also gradually increased, but it is relatively insufficient. Since 2014, English DR research has entered the stage of rapid development, while Chinese research (especially TCM) has maintained a stable rate.

Highly Cited Publication Analysis The number of citations, known as cited frequency, is an important basis for reflecting the value of publication[6]. In order to grasp the core publication on DR and provide a solid foundation for the in-depth study of DR in the future, this study analyzed the top five highly cited publication. Table 1 lists the top five cited English DR

Table 1 Statistics of highly cited English DR publication (Top 5)

Study	Title	Cited frequency
DCCT Research Group *et al*, 1993[8]	The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus	16969
UKPDS Group, 1998[9]	Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)	13828
UKPDS Group, 1998[10]	Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38	5503
Ferrara and Davis-Smyth, 1997[11]	The biology of vascular endothelial growth factor	3473
Yancopoulos *et al*, 2000[12]	Vascular-specific growth factors and blood vessel formation	2835

DR: Diabetic retinopathy.

Table 2 Statistics of highly cited Chinese publication on DR (Top 5)

Study	Title	Cited frequency
Liang *et al*, 2014[17]	American Diabetes Mellitus Guidelines: standards of medical care in diabetes-2014	193
Xie and Wang, 1995[13]	TCM analysis on the pathogenesis of diabetic retinopathy	180
Chen and Zhu, 2006[15]	The pathologic mechanism of diabetic retinopathy	172
Yao *et al*, 2001[16]	Guidelines for prevention and treatment of diabetic fundus disease	162
Duan *et al*, 2011[14]	TCM diagnosis and treatment standards of diabetic retinopathy	153

DR: Diabetic retinopathy; TCM: Traditional Chinese medicine.

Table 3 Statistics of highly cited DR publication in TCM (Top 5)

Study	Title	Cited frequency
Xie and Wang, 1995[13]	TCM analysis on the pathogenesis of diabetic retinopathy	180
Duan *et al*, 2011[14]	TCM diagnosis and treatment standards of diabetic retinopathy	153
Duan *et al*, 2006[18]	Randomized controlled double-blind multicentric clinical trial on non-proliferative diabetic retinopathy treated by Qi-ming granule	111
Li *et al*, 2000[19]	Study on relationship between traditional Chinese medicine syndrome types of diabetes mellitus and stages of diabetic retinopathy	110
Li and Xia, 2000[20]	Clinical study on TCM syndrome differentiation of diabetic retinopathy	90

DR: Diabetic retinopathy; TCM: Traditional Chinese medicine.

publication[8-12]. The top four highly cited studies were all issued in the 1990s; and two of these were released in 1998 and were related to the United Kingdom Prospective Diabetes Study (UKPDS). In addition, the main types of articles were randomized controlled clinical trials and reviews. The Diabetes Control and Complications Trial (DCCT)[8] and UKPDS[9-10] are significant prospective clinical trials that have shown the usefulness of strict control of blood glucose and other risk factors. Both reviews focused on the vascular endothelial growth factor (VEGF). However, Ferrara and Davis-Smyth[11] paid close attention to the specific role of vascular endothelial factors in angiogenesis, while Yancopoulos *et al*[12] concentrated on the mechanism and rules. Table 2 lists the top five cited Chinese publication on DR[13-17], two of which are studies on DR in TCM. One study analyzed the pathogenesis of DR from the perspective of TCM[13], and the other aimed to formulate the TCM diagnosis and treatment standards of DR[14]. A scientific paper, extracted from the "American Diabetes Mellitus Guidelines: Standards of Medical Care in Diabetes-2014",

was cited the most frequently (193 citations)[17]. As for the remaining two articles, one is also a review of the pathologic mechanism of DR[15], and the other reviews the guidelines for the prevention and treatment of diabetic fundus disease[16]. The types of articles used were standard and review articles. Table 3 lists the top five cited studies on DR in TCM[13-14,18-20]. These articles were mainly clinical trials and theoretical discussions. In terms of content, these mainly discussed the relationship between TCM syndrome types and the stages of DR.

Spatial Distribution Analysis of Diabetic Retinopathy Research The spatial distribution and cooperation network analysis of knowledge can provide a theoretical basis for authors and national and institutional cooperation decision-making for future DR research[5]. CiteSpace was used to analyze the spatial distribution, including the authors, institutions, countries/regional distribution, and collaborative networks. The size of the nodes in the pictures analyzed by CiteSpace reflects the frequency of occurrence[7]. The nodes are connected by lines of different colors and thicknesses,
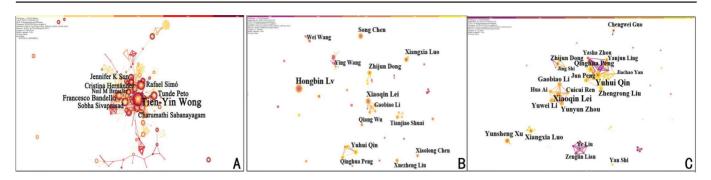
Figure 2 Map of active authors in the DR field from 2015 to 2019 A: English author's partnership network; B: Chinese author's partnership network; C: TCM author's partnership network (The font size of each author's name represents the publication counts of each author. Different colors inside the circle represent different time intervals. The thickness of the straight connecting line represents the collaborative intensity between authors).

indicating that the nodes are related[7]. The darker the color and thicker the line, the closer the relationship is[7]. Centrality describes the importance of the nodes, which is reflected in the purple circle of the nodes' outer edge on the cooperation network map[7]. The higher the centrality, the more nodes are connected to it.

Analysis of Core Authors and Cooperative Relationship Network The core authors' group refers to a cluster of authors who have numerous publications and extensive influence in a subject area[5]. Price's law, which is used to measure the distribution of literary authors in a specific subject area, indicates that $M=0.749 (NMax)^{1/2}$, where $NMax$ refers to the number of papers by the author who has the most publications, while scholars with a number of published papers above M are considered as the core authors in this field[5]. Figure 2A shows that there are 482 authors who have published English document, and there are 1524 lines of cooperation between authors (density=0.0131), indicating that the cooperation between authors is close, forming a cooperative network with Tien-Yin Wong as the core node.

The majority of the author's partnerships are in warm colors, thereby indicating that the core authors in DR have collaborated closely in recent years. CiteSpace shows that the author with the most English publications is Tien-Yin Wong (with 116 articles; $NMax$=116). Price's law states that M=8.067, thereby indicating that authors (*i.e.*,125 scholars) with over nine English articles are international core authors in DR. The 125 core authors published 2251 articles, accounting for 25.14% of the total published DR article, indicating that a group of high-yield and highly influential core authors and research teams have not been formed.

However, the distribution of Chinese authors is relatively scattered, forming multiple sub-networks, indicating that there are many research groups and insufficient cooperation intensity (Figure 2B). CiteSpace shows that Hongbin Lv (with 26 articles) is the author with the most Chinese publications.

According to Price's law, there are 115 Chinese core authors in DR and published 737 studies, accounting for 17.14% of the total DR publication, indicating that a group of high-yield and highly influential core authors and research teams have not been formed similarly. Figure 2C shows that the cooperation between team members is close, forming many research groups, including a series of core teams with Xiaoqin Lei as the mainstay, Yuhui Qin as the mainstay, and Yunsheng Xu as the mainstay, but there is very little cooperation between teams. Xiaoqin Lei (with 16 articles) was the author with the most TCM publications. According to Price's law, there are 39 core authors in the field of TCM and published 202 studies, accounting for 26.06% of the total publication, indicating that these experts play an important role in promoting the progress of DR research in TCM. There are no Chinese experts among the top 10 core authors of English publication on DR, indicating that Chinese scholars are not very active and influential in this field worldwide. Moreover, we can see that seven of the top ten Chinese core authors have conducted research on DR related to TCM.

Analysis of Institutional Distribution and Cooperation Network The results are shown in Figure 3 and Table 4. Figure 3A shows that the distribution of English institutions is similar. English DR research institutions are mainly universities, and the types of research institutions are relatively single, which shows that universities are the main force in the field of international DR research. By contrast, the distribution of Chinese institutions is scattered. Chinese DR research institutions are mainly medical schools and hospitals (Figure 3B). In addition, the cooperation of institutions is also weak in the field of TCM. The institutions with DR research in TCM are mainly composed of medical schools, comprehensive universities, hospitals, and pharmaceutical companies (Figure 3C). According to Table 5, Shanghai Jiao Tong University, which belongs to China, is the institution with the most English publication on DR. China and the United States,

Figure 3 Map of major institutions in the DR field from 2015 to 2019 A: Institutional cooperation network in English publications; B: Institutional cooperation network in Chinese publication; C: TCM institutional cooperation network (The size of each circle is proportional to the publication counts. Different colors inside the circle represent different time intervals. The thickness of the straight connecting line represents the collaborative intensity between institutions).

Table 4 Institution of top 10 on the publications of DR from 2015 to 2019

English			Chinese		
Institution	Publications (*n*)	Region	Institution	Publications (*n*)	Region
Shanghai Jiao Tong University	155	China	Department of Ophthalmology, the Affiliated Hospital of Chengde	20	Hebei Province
Johns Hopkins University	133	The United States	Chengdu University of TCM	16	Sichuan Province
National University of Singapore	131	Singapore	Hunan University of Chinese Medicine	16	Hunan Province
The University of Melbourne	129	Australia	Xi'an Fourth Hospital	15	Shaanxi Province
The University of Sydney	126	Australia	Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine	15	Shanghai
Sun Yat-sen University	122	China	Department of Ophthalmology, First Affiliated Hospital of Xinjiang Medical University	14	Xinjiang
Harvard Medical School	113	The United States	Department of Eye Center, Renmin Hospital of Wuhan University	13	Hubei Province
Capital Medical University	109	China	Department of Ophthalmology, the Affiliated Hospital of Southwest Medical University	12	Sichuan Province
University of Michigan	102	The United States	Department of Ophthalmology, the Second Affiliated Hospital of Nanchang University	12	Jiangxi Province
Singapore National Eye Centre	101	Singapore	Eye Hospital of China Academy of Chinese Medical Sciences	12	Beijing

DR: Diabetic retinopathy; TCM: Traditional Chinese medicine; Xinjiang: The Xinjiang Uygur Autonomous Region.

followed by Singapore and Australia, have the largest number of institutions, which belong to the top ten institutions on DR publications. Among the top 10 Chinese institutions, three belong to TCM. Among the top ten institutions, there are more institutions in Sichuan Province.

Analysis of Countries Distribution and Cooperation Network Figure 4 shows that the distribution of the countries is close. The country with the highest centrality is England (0.27), followed by the United States (0.21), and Australia (0.14). The country with the largest published volume is the United States (2278), followed by China (1748), India (720), and England (609). Evidently, England and the United States have an advantage in terms of importance and volume. England and the United States are the core of international DR research cooperation, maintaining close ties with other countries. China has a large published volume, but its centrality
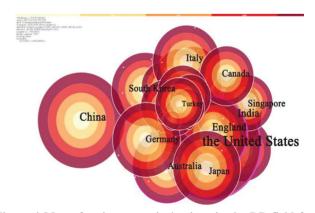

Figure 4 Map of active countries/regions in the DR field from 2015 to 2019 The font size of each country's name represents the number of publication in the country. Different colors inside the circle represent different time intervals. The thickness of the straight connecting line represents the collaborative intensity between countries.
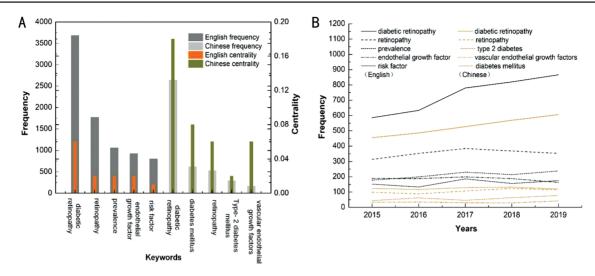
Figure 5 The top 5 high-frequency keywords in the DR field from 2015 to 2019 A: The total frequency and centrality of English and Chinese keywords; B: Annual frequency of English and Chinese keywords.

Table 5 Top 10 English and Chinese keywords with the strongest citation bursts in the DR field from 2015 to 2019 (sorted by the ending year of burst)

English				Chinese			
Keywords	Strength	Begin	End	Keywords	Strength	Begin	End
Spectral domain	4.7006	2017	2019	Optical coherence	3.0089	2017	2019
Release	4.4239	2017	2019	Tomography	3.0089	2017	2019
Intravitreal implant	4.1474	2017	2019	Diabetic retinopathy	2.735	2017	2019
Gene therapy	4.1474	2017	2019	TCM	2.735	2017	2019
Variability	3.8708	2017	2019	Blood lipids	2.6581	2017	2019
Blue mountains eye	3.8708	2017	2019	Xiaoke	1.9137	2017	2019
Methodology	3.8708	2017	2019	Vitreous cavity	1.9137	2017	2019
Disruption	3.5942	2017	2019	DR/surgery	1.8337	2015	2017
Nerve head	3.5942	2017	2019	Clinical research	1.8337	2015	2017
Vascular leakage	3.5783	2017	2019	Proliferative diabetic retinopathy	2.7651	2016	2017

is 0, indicating that China has made a significant contribution, but China has little cooperation with other countries.

Recent Hotspots and Trends Analysis of DR Research

High-frequency keywords analysis The analysis of research hotspots plays an important role in promoting the progress of research and discovering hidden knowledge, which means that the problems are discussed and solved in a large number of related documents in a time. Co-keyword analysis, the most important content of bibliometric analysis for the co-occurrence relationship between the two words, can extract research hotspots in the field to summarize the development of trends and predict the future direction of development[5]. The more this occurs simultaneously, the stronger the relationship[5]. To analyze recent research hotspots and trends in the field of DR, CiteSpace was used to obtain keyword co-occurrence networks. Among all the keywords, high-frequency keywords better represent the frontiers of research on DR. Figure 5A shows that the most frequent and central keyword in English and Chinese publication is "diabetic retinopathy," which means

a series of studies are carried out around this keyword. In addition, the annual frequency of DR is increasing, which also indicates that DR has drawn an increasing amount of attention (Figure 5B). In general, the frequency of English keywords was higher than that of Chinese. Aside from the keyword "diabetic retinopathy," the keywords with high frequency and increasing trend are "prevalence" and "risk factor" in English publication, while "type 2 diabetes" and "vascular endothelial growth factors" in Chinese publication, respectively reflecting the recent research hotspots and trends.

Burst keywords analysis Burst keywords that emerge within a certain period of time are considered indicators of emerging trends[21]. Therefore, this study analyzed keywords showing remarkable bursts from 2015 to 2019 to reveal emerging trends and provide directions for future research. The strength of the burst keywords represents the sudden growth rate of the keyword. As seen in Table 5, the strongest English and Chinese burst keywords that lasted until 2019 were both related to optical coherence tomography (OCT), indicating that

Table 6 English and Chinese keywords clustering of DR research from 2015 to 2019

English					Chinese				
Cluster ID	Size	Silhouette	Mean (y)	Topic	Cluster ID	Size	Silhouette	Mean (y)	Topic
0	290	0.74	2015	Oxidative stress	0	74	0.648	2015	Diabetes mellitus
1	168	0.787	2015	Type 2 diabetes	1	73	0.616	2016	Calcium dobesilate
2	154	0.831	2015	Ranibizumab	2	69	0.623	2016	Vitrectomy
3	135	0.764	2015	Optical coherence tomography	3	42	0.749	2016	Vascular endothelial growth factor
4	88	0.8	2015	Blindness	4	42	0.764	2016	Nursing intervention
5	68	0.919	2016	Exudates	5	40	0.686	2015	Macular edema
					6	35	0.839	2016	Optical coherence
					7	27	0.85	2016	Fundus fluorescein angiography

the screening of DR is the latest trend worldwide. There are high-strength burst keywords, including "release," "variability," "disruption," "nerve head," and "vascular leakage," among others, indicating that research on the mechanism of DR is still an international hotspot and is one of the latest trends. The keywords in English publication "intravitreal implant" and "gene therapy" belong to international treatment, and "blue mountains eye" and "methodology" refer to the research method.

As for Chinese DR research, diagnosis, risk factors, treatment, and method are the recent research hotspots and trends, separately reflected by the keywords "optical coherence," "tomography," "blood lipids," "vitreous cavity," "surgery," "clinical research." In addition, TCM has played an increasingly important role and has attracted more and more attention, as reflected by the keywords "TCM" and "xiaoke".

Keyword clusters analysis A cluster is a group of closely coupled documents representing different directions of research[7]. Figure 6A-6C) shows the main clusters labeled by the representative keywords. To better understand the meaning and scope of each cluster, it is meaningful to consider other factors in the cluster shown in Table 6, including cluster ID, silhouette, size, and year (mean). Furthermore, cluster size is the number of terms included in each cluster. Figure 6D-6F shows the timeline views which reflect the evolution of keywords in different clusters over time.
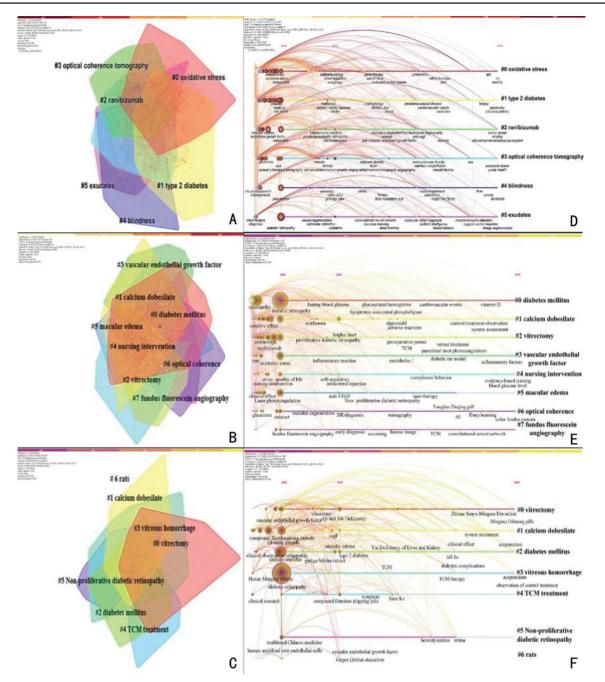
In Figure 6A, 6D and Table 6, the major topics of DR research are related to the mechanism according to the size and number of nodes. The representative terms are "oxidative stress" with the largest size but the lowest silhouette, and "exudates". As suggested by the timeline view (Figure 6D), the cluster "#0 oxidative stress" is related to the mechanism behind the evolution from gene expression to protein expression to toxicity. The silhouette score of cluster #1 is 0.787, showing it is highly credible, and the representative terms is "type 2 diabetes", considered to the research on risk factors of DR. The representative term "ranibizumab" with a highly credible cluster is connected with the treatment of DR. Cluster #3 with the representative term "optical coherence tomography", has

something to do with the diagnosis and management. The representative term "blindness" indicates that it is related to the consequences, management, and efficacy indicators of DR. It shows that international research in this field is relatively comprehensive.

As can be seen in Table 6, the silhouettes in Chinese clusters ranged from 0.616 to 0.85, indicating that all clustering results are reasonable. The representative terms are "diabetes mellitus" with the largest size, indicating the research related to the risk factors of DR as the same topic as international. As suggested by the timeline view (Figure 6E), the cluster "#0 diabetes mellitus" evolved from hyperglycemia to hyperlipidemia to vitamin D deficiency. Figure 6B shows that calcium dobesilate, vitrectomy, and nursing intervention are Chinese DR research hotspots related to treatment in recent years.

Clearly, optical coherence and fundus fluorescein angiography are also Chinese research hotspots in the diagnosis and management of DR. Vascular endothelial growth factor is also a hotspot in Chinese research on the mechanism of DR. As can be seen in Figure 6C, the cluster "#0 Vitrectomy", the cluster "#1 calcium dobesilate" and the cluster "#4 TCM treatment" indicate that the major topics of DR researches in TCM are related to the treatment. It also shows that the combination of TCM and Western medicine (WM) is a research trend of DR in China, indicating that TCM is inclusive and can be further developed.

As suggested by the timeline view (Figure 6F), TCM treatment methods, including acupuncture and Mingmu Dihuang pills and Zhixue Sanyu Mingmu decoction, are the latest hotspots and research trends in the field of TCM for DR. The cluster "#2 diabetes mellitus" indicates that TCM also focuses on risk factors for DR, which are consistent with international. The classification and diagnosis of DR in WM has a certain connection with the understanding of TCM, as shown in cluster #5, which is also a research hotspot of TCM. It can better integrate TCM and WM. The cluster "#6 rats" shows that a large number of studies have been conducted to comprehend TCM from a micro-perspective.

Figure 6 Map of keywords clustering of DR research from 2015 to 2019 A: The cluster views of English co-keywords analysis; B: The cluster views of Chinese co-keywords analysis; C: The cluster views of TCM co-keywords analysis (The convex hulls of different colors represent different clusters; the brighter the convex hull is, the more recently it appears. The number of nodes each convex hull covers is proportional to the number of keywords of each cluster. The thickness of line each convex hull covers is proportional to the co-occurrence frequency of keyword of each cluster.); D: The timeline view of English co-keywords analysis; E: The timeline view of Chinese co-keywords; F: The timeline view of TCM co-keywords (Time is set as the horizontal axis, and the cluster is set as the vertical axis. This view clearly presents the differences in the appearance time point and time span of each cluster.).

DISCUSSION

In this study, scientometric analysis was conducted to summarize the intellectual structure and recent research hotspots and trends of DR. Overall, there are three stages according to the annual number of documents: the period of preliminary development before 1990, the period of steady development from 1990 to 2014, and the period of rapid development from 2014 to the present. As the annual number of English and Chinese DR documents has been increasing, it can be concluded that DR has become a subject of growing study and an increasingly important area of research in the world. DR research related to TCM has increased, but it is relatively insufficient. With the co-occurrence analysis of authors, institutions, and countries, it can be concluded that international cooperation is relatively close, while cooperation is relatively weak in China. There has not

yet been a group of high-yield and highly influential core authors and research teams worldwide. China possesses the institution with the largest volume of English DR publications, Shanghai Jiao Tong University, while there is a shortage of high-yielding Chinese scholars in the international arena, implying the decentralization of power and the deficiency of core competitiveness. A large number of core authors and institutions have recently carried out DR research related to TCM in China, showing that DR experts have paid attention to and affirmed the effect of TCM. However, it is obvious that national support for TCM and cooperation is relatively lacking and must be further strengthened in China.

To clarify the basic knowledge and research trends of DR, highly cited documents were analyzed. The main types of highly cited articles were clinical trials and reviews. DCCT and UKPDS, which are randomized clinical trials that can be considered as the "milestones" in diabetes mellitus fields, showed that intensive control of blood glucose and other risk factors has beneficial effects on retinal microvessels[8-10]. At present, the clinical trial goal of Roshandel *et al*[22] has shifted from research on the efficacy of intensive treatment to epigenetic research on diabetic retinopathy in type 1 diabetes. The UKPDS group focuses on studying risk prediction and its model construction of DR[23-24]. VEGF plays a key role in the DR mechanism[11-12]. It is now recognized that DR is mainly caused by hyperglycemia- and glucolipotoxicity-induced oxidative stress, epigenetic changes, neurodegeneration, and inflammation, which mediate the expression and pathological effects of VEGF to promote angiogenesis[25]. Moreover, anti-VEGF therapies are currently one of the main treatment methods for DR. Recent studies related to VEGF in the field mainly focused on the effect of anti-VEGF therapy on improving visual acuity. Anti-VEGF therapy has remarkable clinical benefits, but fails to achieve clinically significant visual improvement for most DR patients, especially its limited efficacy in early damage to neurovascular units[26].

The difference in the basic knowledge of DR in China is to understand DR from the perspective of TCM. TCM, a characteristic medicine in China, has had definite effects on the prevention and treatment of DR[27]. TCM believes that prevention is more important than treatment, and this thinking has guided health maintenance and disease treatment for thousands of years with its own unique system of theories, diagnostics, and therapies[28]. Undoubtedly, TCM has unique advantages in the prevention and early damage intervention of DR. DR belongs to the category of "Shi-zhan-hun-miao", "Yun-wu-yi-jing", and "Bao-mang" in TCM, considering that the basic pathogenesis of DR evolves from deficiency of Qi and Yin to deficiency of liver and kidney, and then to deficiency of Yin and Yang[14]. TCM believes that the early

stage of DR is mainly due to the lack of Qi and Yin, the material basis of the human body, and Qi cannot push Yin up to nourish the eyes[19]. Blood stasis, a pathogenic factor, is often involved in the disease process[14]. Promisingly, TCM has been demonstrated to be effective in treating the early stage of DR by tonifying Qi and nourishing Yin, as well as activating blood and removing blood stasis[29].

Obviously, the way of thinking about DR is different between TCM and WM. Because of the origins and driving forces of development, practicing WM requires an understanding of the body for fixed somatic structures, while TCM maintained the practice of tracing symptoms and study patterns of underlying disharmony by assessing the human body as a whole[30]. Although the approaches of TCM and WM differ significantly, their clinical efficacy goals and targets are the same, indicating that there is a certain correlation between them.

Through the analysis of the English publication of core authors and teams, we can further understand the recent progress and trends of international DR research. Recent research tends to predict and screen the occurrence and development of DR, including risk prediction indicators and machine learning technology. Specifically, serum measures including genomic, proteomic, and metabolomic biomarkers, ocular biomarkers including vitreous and retinal vascular structural changes, and other risk factors are being studied as risk prediction indicators[31-33]. Ting *et al*[34] were committed to a deep learning system for automatically detecting referable DR and screening vision-threatening DR.

In terms of intelligent auxiliary diagnosis and risk prediction, the most different point in China is the TCM indicator. However, this approach has its limitations. For example, there is no unified standard for TCM data[35], and this is difficult to obtain, is regarded as an isolated island, and there is little data on the connection between retinal images and TCM. According to keyword co-occurrence analysis, DR research is very comprehensive worldwide, but each has its own focus. With respect to the mechanism of DR, international research was mainly devoted to further investigation of the underlying molecular mechanisms, especially for neurodegeneration in the early stage, while it was still focused on VEGF in China.

Regarding the diagnosis of DR, the development and verification of new equipment and processing technologies with stronger imaging capabilities and image processing capabilities are recent hotspots and trends in international research, including studies on three-dimensional diagnostic scan with a novel deep learning architecture[36], fractal analysis of fundus photographs[37], and a trained Bayesian model based on these textures for DR screening[38]. However, Chinese research mainly focuses on the clinical use of equipment and image analysis. This may be mainly caused by the lack

of interdisciplinary talent, scientific research platforms, and supporting funds.

With regard to the prevention of DR, international research has shown solicitude for innovative strategies and new technologies, which have been shown to increase diabetic eye screening rates. In China, screening for DR is lacking because of the economic burden and inadequate education for complications. The main difference in Chinese research on the prevention of DR is that it focused on the efficacy of Chinese patent medicines, such as Qi-ming granules[18], and nursing intervention.

Concerning the therapeutic method of DR, the international ophthalmology community has focused their efforts on improving the delivery of laser photocoagulation treatment and ocular surgery, but also increasingly committed to research on anti-VEGF therapies[39] and gene therapy[40]. Chinese research is mainly devoted to combination therapy, including combined surgical treatment, anti-VEGF assisted surgery, anti-VEGF combined with laser photocoagulation, and TCM combined with laser photocoagulation.

Whether it is the analysis of highly cited publication, core authors and institutions, or keyword co-occurrence analysis, these all show that TCM plays an important role in Chinese DR research. A large number of studies have shown that TCM treatments, including Chinese medicine extract[41], Chinese patent medicine[27], acupuncture[42], decoction[43], etc., are clinically effective in improving ocular fundus lesions, inducing the regression of neovascularization, and improving patients' vision, which deserves further study.

Broadly speaking, the focal point of DR research has shifted from treatment measures, which include surgery and drugs, to screening and monitoring for the process. TCM has played an important role in the treatment and prevention of DR. It has been proven that the complementary advantages of combined TCM and WM can significantly improve the efficacy of treatment and enable precise prevention of diseases[44-45]. The advantages and research trends of TCM and WM are new meaningful entry points for the combination to face the challenge; for instance, acupuncture can be applied alongside gene therapy, TCM syndromes can be associated with retinal image changes, etc. In particular, TCM has unique advantages for disease prevention[46]. In other words, the effective prevention measures of DR in TCM can be used as a key to decrypt the molecular mechanisms underlying retinal neurodegeneration in the early stages of DR.

This study had several strengths. To the best of our knowledge, this is the first attempt to conduct a bibliometric study which compares current DR research in China and abroad. The research structure included core teams, institutions, and countries, which can provide information to research scholars

and aid them in targeting relevant figures. On top of this, recent hot topics and their trends may be obtained, specifically through burst detection, which can provide dynamic information for the development of this field. Furthermore, the findings of this study provide valuable information for further research and TCM development policies in this field, as well as new entry points for the integration of TCM and WM.

However, this study also has some limitations. First, the data analyzed in our study only included those from WoSCC and CNKI, and the publication types were limited. Thus, the identified publication may not fully represent all the DR research. However, CNKI and WoSCC collect the most important publication under the sciences, social sciences, and humanities, both locally and abroad. Moreover, it is very difficult for current software to analyze data from multiple databases simultaneously. Second, the included studies were restricted to those published in English and Chinese, resulting in some linguistic bias. Nonetheless, English remains the most widely used language for international academic articles, and Chinese is the most representative language in China. Next, bias, including homonyms of the authors, may also exist because all information was extracted by scientometric tools. These problems may be addressed in future studies.

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REFERENCES

1 Kong DQ, Li L, Liu Y, Zheng GY. Association between endoplasmic *Reticulum* stress and risk factors of diabetic retinopathy. *Int J Ophthalmol* 2018;11(10):1704-1710.

2 Rodríguez ML, Pérez S, Mena-Mollá S, Desco MC, Ortega ÁL. Oxidative stress and microvascular alterations in diabetic retinopathy: future therapies. *Oxidative Med Cell Longev* 2019; 2019:4940825.

3 Powers M, Greven M, Kleinman R, Nguyen QD, Do D. Recent advances in the management and understanding of diabetic retinopathy. *F1000Research* 2017;6:2063.

4 Yang QH, Zhang Y, Zhang XM, Li XR. Prevalence of diabetic retinopathy, proliferative diabetic retinopathy and non-proliferative diabetic retinopathy in Asian T2DM patients: a systematic review and Meta-analysis. *Int J Ophthalmol* 2019;12(2):302-311.

5 Gu D, Li T, Wang X, Yang X, Yu Z. Visualizing the intellectual structure

and evolution of electronic health and telemedicine research. *Int J Med Inform* 2019;130:103947.

6 Brandt JS, Hadaya O, Schuster M, Rosen T, Sauer MV, Ananth CV. A bibliometric analysis of top-cited journal articles in obstetrics and gynecology. *JAMA Netw Open* 2019;2(12):e1918007.

7 Chen QB, Fan GL, Na W, Liu JM, Cui JG, Li HY. Past, present, and future of groundwater remediation research: a scientometric analysis. *Int J Environ Res Public Heal* 2019;16(20):3975.

8 Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329(14):977-986.

9 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837-853.

10 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317(7160):703-713.

11 Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev* 1997;18(1):4-25.

12 Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature* 2000;407(6801):242-248.

13 Xie XJ, Wang MF. TCM analysis on the pathogenesis of diabctic retinopathy. *Zhongguo Zhong Yi Yan Ke Za Zhi* 1995;5(2):86-88.

14 Duan JG, Jin M, Jie CH, Ye HJ. TCM diagnosis and treatment standards for diabetic retinopathy. *Shi Jie Zhong Xi Yi Jie He Za Zhi* 2011;6(7):632-637.

15 Chen Y, Zhu XH. The pathologic mechanism of diabetic retinopathy. *Guo Ji Yan Ke Za Zhi* 2006;6(2):433-435.

16 Yao Y, Zhao JP, Ma ZZ, Wang CG. Guidelines for prevention and treatment of diabetic fundus disease. *Zhongguo Shi Yong Yan Ke Za Zhi* 2001;19(2):83-95.

17 Liang F, Hu DY, Shen ZJ. American Diabetes Mellitus Guidelines: standards of medical care in diabetes-2014. *Zhonghua Lin Chuang Yi Shi Za Zhi* 2014;8(06):1182-1190.

18 Duan JG, Liao PZ, Wu L, Li YM, Yu YG, Qiu B, Li CK. Randomized controlled double-blind multicentric clinical trail on non-proliferative diabetic retinopathy treated by Qi-ming granule. *Cheng Du Zhong Yi Yao Da Xue Xue Bao* 2006;29(2):1-5.

19 Li ZY, Yu YG, Zhang C, Wang Y, Wang XC. Study on relationship between traditional Chinese medicine syndrome types of diabetes mellitus and stages of diabetic retinopathy. *Zhongguo Zhong Yi Yan Ke Za Zhi* 2000;10(1):31-34.

20 Li H, Xia JS. Clinical study on TCM syndrome differentiation of diabetic retinopathy. *He Nan Zhong Yi* 2000;20(5):33.

21 Zheng KY, Dai GY, Lan Y, Wang XQ. Trends of repetitive transcranial magnetic stimulation from 2009 to 2018: a bibliometric analysis. *Front*

Neurosci 2020;14:106.

22 Roshandel D, Chen Z, Canty AJ, Bull SB, Natarajan R, Paterson AD, DCCT/EDIC Research Group. DNA methylation age calculators reveal association with diabetic neuropathy in type 1 diabetes. *Clin Epigenetics* 2020;12(1):52.

23 Maddaloni E, Coleman RL, Agbaje O, Buzzetti R, Holman RR. Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86). *Lancet Diabetes Endocrinol* 2020;8(3):206-215.

24 Basu S, Sussman JB, Berkowitz SA, Hayward RA, Bertoni AG, Correa A, Mwasongwe S, Yudkin JS. Validation of risk equations for complications of type 2 diabetes (RECODe) using individual participant data from diverse longitudinal cohorts in the U.S. *Diabetes Care* 2018;41(3):586-595.

25 Sinclair SH, Schwartz SS. Diabetic retinopathy-an underdiagnosed and undertreated inflammatory, neuro-vascular complication of diabetes. *Front Endocrinol* 2019;10:843.

26 Wang W, Lo A. Diabetic retinopathy: pathophysiology and treatments. *Int J Mol Sci* 2018;19(6):1816.

27 Xu ZH, Gao YY, Zhang HT, Ruan KF, Feng Y. Progress in experimental and clinical research of the diabetic retinopathy treatment using traditional Chinese medicine. *Am J Chin Med* 2018;46(7): 1421-1447.

28 Li LR, Yao HQ, Wang J, Li YS, Wang Q. The role of Chinese medicine in health maintenance and disease prevention: application of constitution theory. *Am J Chin Med* 2019;47(3):495-506.

29 Ai X, Yu P, Hou Y, Song X, Luo J, Li N, Lai X, Wang X, Meng X. A review of traditional Chinese medicine on treatment of diabetic retinopathy and involved mechanisms. *Biomed Pharmacother* 2020;132:110852.

30 Wang WJ, Zhang T. Integration of traditional Chinese medicine and Western medicine in the era of precision medicine. *J Integr Med* 2017;15(1):1-7.

31 Sun Z, Tang F, Wong R, Lok J, Szeto SKH, Chan JCK, Chan CKM, Tham CC, Ng DS, Cheung CY. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: a prospective study. *Ophthalmology* 2019;126(12):1675-1684.

32 Gasecka A, Siwik D, Gajewska M, Jaguszewski MJ, Mazurek T, Filipiak KJ, Postuła M, Eyileten C. Early biomarkers of neurodegenerative and neurovascular disorders in diabetes. *J Clin Med* 2020;9(9):2807.

33 Haider S, Sadiq SN, Lufumpa E, Sihre H, Tallouzi M, Moore DJ, Nirantharakumar K, Price MJ. Predictors for diabetic retinopathy progression-findings from nominal group technique and Evidence review. *BMJ Open Ophthalmol* 2020;5(1):e000579.

34 Ting DSW, Cheung CY, Lim G, *et al*. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA*

2017;318(22):2211-2223.

35 Deng WX, Zhu JP, Li J, Yuan ZY, Wu HY, Hua YZ, Zhang YG, Wen-An Z, Huang HY. Research on text mining of syndrome element syndrome differentiation by natural language processing. *Digit Chin Med* 2019;2(2):61-71.

36 De Fauw J, Ledsam JR, Romera-Paredes B, *et al*. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med* 2018;24(9):1342-1350.

37 Lim LS, Chee ML, Cheung CY, Wong TY. Retinal vessel geometry and the incidence and progression of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2017;58(6):BIO200-BIO205.

38 Cao K, Xu J, Zhao WQ. Artificial intelligence on diabetic retinopathy diagnosis: an automatic classification method based on grey level co-occurrence matrix and naive Bayesian model. *Int J Ophthalmol* 2019;12(7):1158-1162.

39 Yang QH, Zhang Y, Jiang J, Wu MM, Han Q, Bo QY, Yu GW, Ru YS, Liu X, Huang M, Wang L, Zhang XM, Fang JM, Li XR. Protective effects of a novel drug RC28-E blocking both VEGF and FGF2 on early diabetic rat retina. *Int J Ophthalmol* 2018;11(6):935-944.

40 Wang JH, Roberts GE, Liu GS. Updates on gene therapy for diabetic retinopathy. *Curr Diab Rep* 2020;20(7):22.

41 Mei XY, Zhou LY, Zhang TY, Lu B, Ji LL. *Scutellaria barbata* attenuates diabetic retinopathy by preventing retinal inflammation and the decreased expression of tight junction protein. *Int J Ophthalmol* 2017;10(6):870-877.

42 Ang L, Song E, Jun JH, Choi TY, Lee MS. Acupuncture for treating diabetic retinopathy: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med* 2020;52:102490.

43 Ou C, Yang YJ, Peng QH. Yiqi Yangyin Huoxue method in treating diabetic retinopathy: a systematic review and meta-analysis. *Evid Based Complement Alternat Med* 2019;2019:6020846.

44 Aggarwal M, Aggarwal B, Rao J. Integrative medicine for cardiovascular disease and prevention. *Med Clin North Am* 2017;101(5):895-923.

45 Wang RY, Sun QH, Wang F, Liu Y, Li X, Chen TH, Wu XK, Tang HJ, Zhou MY, Zhang SZ, Xiao Y, Huang WJ, Wang CC, Li L. Efficacy and safety of Chinese herbal medicine on ovarian cancer after reduction surgery and adjuvant chemotherapy: a systematic review and meta-analysis. *Front Oncol* 2019;9:730.

46 Wang J, Ma Q, Li Y, Li P, Wang M, Wang T, Wang C, Wang T, Zhao B. Research progress on Traditional Chinese Medicine syndromes of diabetes mellitus. *Biomed Pharmacother* 2020;121:109565.