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# Mapping research trends in diabetic retinopathy from 2010 to 2019

## A bibliometric analysis

Yi Dong, MD[a],[*] ⓘ, Yanli Liu, PhD[b], Jianguo Yu, BS[b], Shixin Qi, MD[b], Huijuan Liu, MD[b]

**Abstract**

**Background:** Although many publications in diabetic retinopathy (DR) have been reported, there is no bibliometric analysis.

**Purpose:** To perform a bibliometric analysis in the field of diabetic retinopathy (DR) research, to characterize the current international status of DR research, to identify the most effective factors involved in this field, and to explore research hotspots in DR research.

**Methods:** Based on the Web of Science Core Collection (WoSCC), a bibliometric analysis was conducted to investigate the publication trends in research related to DR. Knowledge maps were constructed by VOSviewer v.1.6.10 to visualize the publications, the distribution of countries, international collaborations, author productivity, source journals, cited references and keywords, and research hotspots in this field.

**Results:** In total, 11,839 peer-reviewed papers were retrieved on DR from 2010 to 2019, and the annual research output increased with time. The United States ranks highest among countries with the most publications. The most active institution is the University of Melbourne. Wong, TY contributed the largest number of publications in this field. Investigative Ophthalmology & Visual Science was the most prolific journal in DR research. The top-cited references mainly investigated the use of anti-vascular endothelial growth factor (VEGF) medications in the management of DR, and the keywords formed 6 clusters:

1. pathogenesis of DR;

2. epidemiology and risk factors for DR;

3. treatments for DR;

4. screening of DR;

5. histopathology of DR; and

6. diagnostic methods for DR.

**Discussion:** With the improvement of living standard, DR has gradually become one of the important causes of blindness, and has become a hot spot of public health research in many countries. The application of deep learning and artificial intelligence in diabetes screening and anti-VEGF medications in the management of DR have been the research hotspots in recent 10 years.

**Conclusions:** Based on data extracted from the WoSCC, this study provides a broad view of the current status and trends in DR research and may provide clinicians and researchers with insight into DR research and valuable information to identify potential collaborators and partner institutions and better predict their dynamic directions.

**Abbreviations:** AMD = age-related macular degeneration, BRB = blood-retinal barrier, DME = diabetic macular edema, DR = diabetic retinopathy, FA = fluorescein angiography, FAZ = foveal avascular zone, MAs = microaneurysms, MKD = mapping knowledge domain, OCT = optic coherence tomography, OCTA = optical coherence tomography angiography, PDR = proliferative

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## 1. Introduction

Diabetic retinopathy (DR) is an important complication of diabetes that affects blood vessels in the retina and can cause vision loss and blindness.[1] It is quickly becoming a worldwide public health challenge.[2,3] A large number of research papers related to DR have been published in academic journals in recent decades. In recent decades, many reviews on the pathology, metabolomics, imaging, biomarkers, and treatment of DR have been published.[1,4–8]

However, to our knowledge, the global research trend and other related topics in DR have not yet been well studied. It is difficult to read all the publications. Therefore, there is a need to use a method and tool to investigate the global status of the research in DR. Bibliometric methods and mapping knowledge domain (MKD) methods have been used in various fields to visually highlight the most influential countries, authors, journals, publications, and identify main research topics.[9] Bibliometric analysis is a method for analyzing the literature and its accompanying citation counts over time with mathematical statistics. The MKD method provides a new way to conduct literature mining and reveal the core structure of scientific knowledge. It also enables researchers to determine the range of research topics and identify new topics and assists them in planning their research direction and predicting research trends.[10] This study aimed to use bibliometric tools to analyze DR articles retrieved from the Web of Science (WoS) (Thomson Reuters Company) database and assess the research development status of DR throughout the world. This analysis could help us to uncover the current status and global trends of DR. It was hoped that our research results could provide meaningful help to the current researchers of DR. Recently, some systematic reviews have been conducted to evaluate the efficacy of PD Other systematic reviews have analyzed the adverse events in patients treated with PD However, the status of research in the area of PD-1 and PD-L1 in the cancer field and other related topics have not been investigated.

The remainder of the paper is structured as follows. The data collection and analytical methods are described in Section 2. The distribution of publications, countries, research organizations, journals, and research hotspots are presented in Sections 3. Global trends, document citation analysis, and research frontiers are discussed in Section 4. The final section, Section 5, summarizes the findings and concludes the paper.

## 2. Materials and methods

This study followed the tenets of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Tianjin Eye Hospital and Tianjin Baodi Hospital. The search for papers to be included in this study was carried out on April 20, 2020 using the Science Citation Index Expanded (SCI-EXPANDED) database via the Web of Science Core Collection (WoSCC) provided by Thomson Reuters (Philadelphia, PA, USA). The database was searched using the term "diabetic retinopathy" in terms of "topic" (title, abstract, author's keywords, and WoS-assigned keywords, called Keywords Plus) to retrieve all articles where the expression "diabetic retinopathy" appeared, as well as other relevant expressions (e.g., diabetic retinopathies). The time span was set to between 2000 and 2019. Only articles were included as document types (nonarticle documents such as reviews, meeting abstracts, editorial materials, proceedings papers, letters were excluded). Journal articles were used for the analysis because they accounted for the majority of document types that also included complete research ideas and results. Data were downloaded from the WoS in "Full record and cited references" formats.

Visualization software can produce node-link maps that allow us to intuitively observe the publication outputs, hotspots, and other aspects of a research field. In this study, the data were imported into VOSviewer v.1.6.10 and analyzed systematically. VOSviewer (www.vosviewer.com), developed by van Eck and Waltman, is a literature visualization software that has the advantages of displaying cluster analysis results.[11] In the knowledge maps generated using VOSviewer, items are represented as nodes and links. The nodes and their labels, such as countries, organizations, authors, co-citation literature, and keywords, are proportional to the weight of the analysis components. The links between the nodes reflect the relationship between the components. CiteSpace IV (Drexel University, Philadelphia, PA) was used to capture keywords with strong citation bursts, which could be considered as predictors of research frontiers.

## 3. Results

### 3.1. Yearly quantitative distribution of publications

According to the selection criteria, we identified and included 11,839 publications on DR that were indexed in the WoSCC from 2010 to 2020. The number of publications showed a gradually increasing trend over time, from 857 in 2010 to 1573 in 2019 (Fig. 1A). Through keyword burst detection analysis (Fig. 1B), we detected 28 keywords that represented citation bursts; among these keywords, "machine learning" showed citation bursts in 2019, which is consistent with the increase in published papers.

### 3.2. Distribution of productive countries in DR

According to the retrieved results, the 11,839 articles originated from 128 countries. As presented in Table 1, the top 10 countries engaged in DR research published 10,419 articles, accounting for 88.0% of the total number of publications. The United States contributed the most publications (3280, 27.7%), followed by China (2222, 18.8%) and Japan (811, 6.9%). According to citation analysis, the United States had 79,761 citations, followed by China (26,304 citations) and Japan (15,670 citations).

Country co-authorship analysis reflects the degree of communication between countries as well as the most influential

## Top 28 Keywords with the Strongest Citation Bursts

| Keywords | Year | Strength | Begin | End | 2010 - 2019 |
|---|---|---|---|---|---|
| factor expression | 2010 | 8.9197 | 2010 | 2012 | |
| intravitreal triamcinolone acetonide | 2010 | 9.3894 | 2010 | 2012 | |
| photodynamic therapy | 2010 | 8.7143 | 2010 | 2013 | |
| endothelial progenitor cell | 2010 | 8.5072 | 2010 | 2013 | |
| intravitreal bevacizumab | 2010 | 9.4817 | 2010 | 2012 | |
| myocardial infarction | 2010 | 8.2729 | 2010 | 2013 | |
| protein kinase c | 2010 | 8.3662 | 2010 | 2014 | |
| rat retina | 2010 | 8.4608 | 2010 | 2012 | |
| injection | 2010 | 8.753 | 2010 | 2011 | |
| verteporfin | 2010 | 9.7444 | 2010 | 2013 | |
| secondary | 2010 | 11.0888 | 2010 | 2012 | |
| age related maculopathy | 2010 | 8.282 | 2010 | 2013 | |
| pregnancy | 2010 | 10.014 | 2010 | 2012 | |
| vitreous | 2010 | 9.1322 | 2010 | 2011 | |
| avastin | 2010 | 26.2251 | 2010 | 2013 | |
| epithelium derived factor | 2010 | 9.4687 | 2011 | 2012 | |
| low vision | 2010 | 8.1185 | 2011 | 2013 | |
| photocoagulation | 2010 | 9.291 | 2011 | 2012 | |
| oximetry | 2010 | 8.3558 | 2012 | 2015 | |
| oxygen-induced retinopathy | 2010 | 8.0946 | 2014 | 2016 | |
| panretinalphotocoagulation | 2010 | 8.239 | 2015 | 2016 | |
| optical coherence tomography angiography | 2010 | 16.0758 | 2016 | 2019 | |
| foveal avascular zone | 2010 | 17.3489 | 2017 | 2019 | |
| level | 2010 | 8.0694 | 2017 | 2019 | |
| global prevalence | 2010 | 14.3468 | 2017 | 2019 | |
| density | 2010 | 14.5639 | 2017 | 2019 | |
| autophagy | 2010 | 7.945 | 2017 | 2019 | |
| machine learning | 2010 | 8.0694 | 2017 | 2019 | |

**Figure 1.** Annual publications and citation bursts analysis. (A) The annual number of publications in DR study from 2010 to 2019. (B) Top 28 keywords with the strongest citation bursts on DR from 2010 to 2019.

countries in this field. The larger nodes represent the more influential countries; the thickness and distance of the links between nodes represent the strength of the cooperative relationships among countries. Figure 2 shows that the United States intensely cooperated with many countries in the DR field, such as England, Australia, Germany, France, and Denmark. Although China has published a large number of articles, there is little cooperation with other countries. This indicates that geographical distance is not the primary influencing factor of cooperative relationships.

**Top 10 productive countries in diabetic retinopathy study, 2010–2019.**

| Rank | Country | Count (%) | Citations | Total link strengthen |
|---|---|---|---|---|
| 1 | United States | 3280 (27.7) | 79,761 | 2108 |
| 2 | China | 2222 (18.8) | 26,304 | 798 |
| 3 | Japan | 811 (6.9) | 15,670 | 297 |
| 4 | England | 752 (6.4) | 18,476 | 1002 |
| 5 | Germany | 657 (5.5) | 15,655 | 821 |
| 6 | Australia | 640 (5.4) | 17,188 | 966 |
| 7 | India | 578 (4.97) | 9666 | 394 |
| 8 | South Korea | 560 (4.7) | 6779 | 188 |
| 9 | Italy | 544 (4.6) | 12,545 | 575 |
| 10 | Spain | 375 (3.2) | 6439 | 343 |

Table percentages were calculated by dividing the row count by the total number of publications (n=11839).

### 3.3. Distribution of main research organizations

According to the retrieved results, 11,839 articles were published by 8642 organizations. The top 10 organizations published 1852 articles, accounting for 15.64% of the total number of publications (Table 2). Based on co-authorship analysis, Figure 3 displays the knowledge domain map of the research organizations' distribution in DR research. The size of the node corresponds to the number of published articles. The links between nodes represent the collaborations. The thicker and longer the node-link, the closer the collaboration is between the 2 organizations.
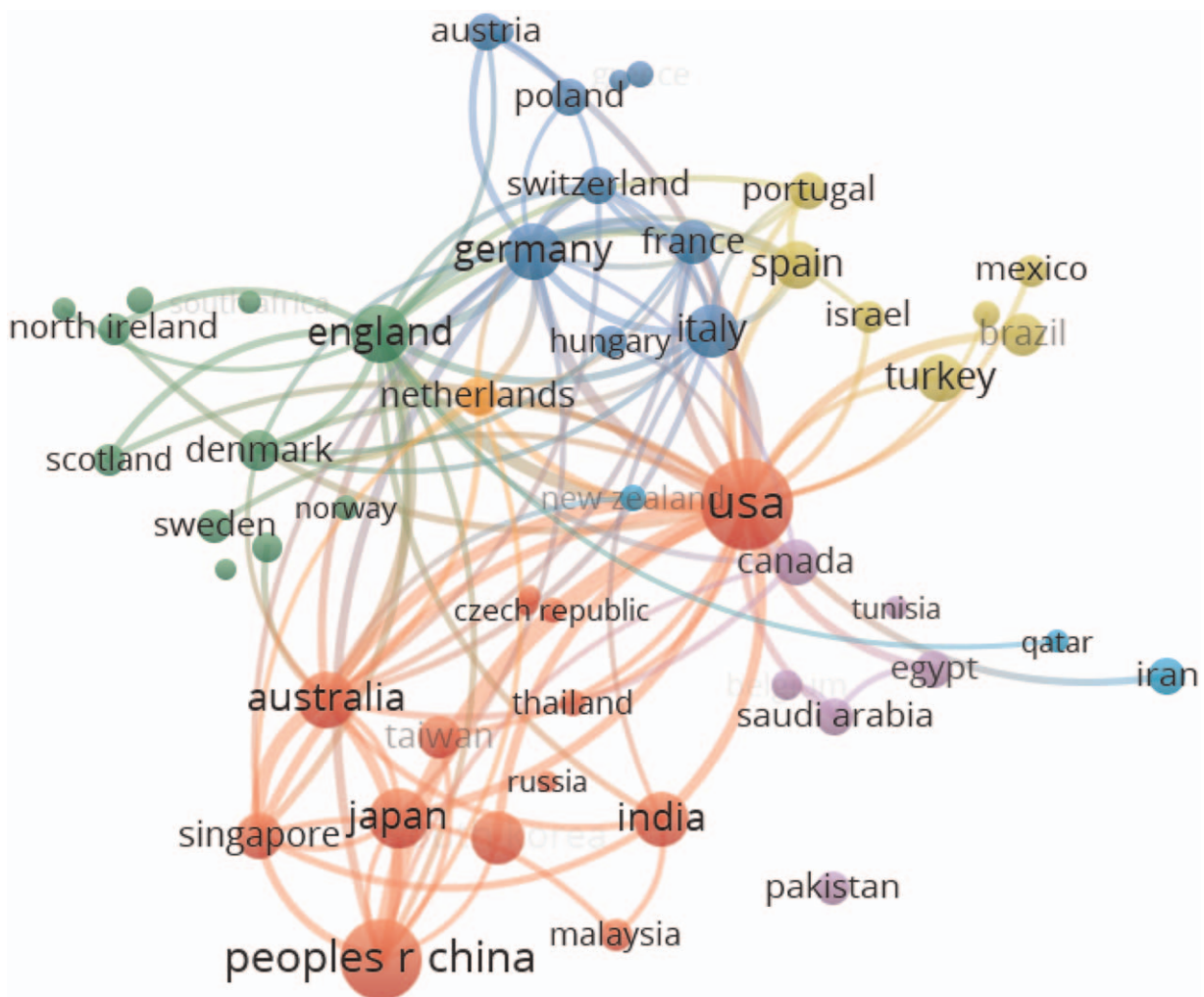


**Figure 2.** Network visualization map of countries' collaboration in DR research during the period 2009 to 2018. The size of the node represents the number of publications of the country and the thickness of lines signifies the size of collaboration between the countries. The minimum number of documents of a country was set as 25. Of the 128 countries that were involved in DR research, 52 countries met the threshold.

**Table 2**

**TOP 10 productive organizations in diabetic retinopathy study, 2010 to 2019.**

| Rank | Organization | Country | Count (%) | Citations |
|---|---|---|---|---|
| 1 | University of Melbourne | Australia | 2.13 | 7499 |
| 2 | Shanghai Jiao Tong University | China | 1.82 | 2416 |
| 3 | Johns Hopkins University | USA | 1.76 | 8658 |
| 4 | University of Sydney | Australia | 1.72 | 7147 |
| 5 | National University of Singapore | Singapore | 1.71 | 5809 |
| 6 | University of Wisconsin | USA | 1.57 | 5893 |
| 7 | Sun Yat-Sen University | China | 1.39 | 2644 |
| 8 | Capital Medical University | China | 1.25 | 1707 |
| 9 | Harvard university | USA | 1.21 | 5152 |
| 10 | Singapore National Eye Center | Singapore | 1.09 | 2766 |

### 3.4. Distribution of authors and co-authorship of research groups

According to the retrieved results, over 111,933 authors contributed to DR research. Among all authors, Wong Tienyin (91 publications) ranked first, followed by Wong Tieny (82 publications) and Klein Ronald (79 publications), indicating their productive contribution to DR research. Information on author co-citations was analyzed as well. Among all co-cited authors, Klein, R (3199 co-citations) ranked first, followed by Kowluru, RA (1618 co-citations), and Aiello, LP (1423 co-citations), indicating their relative influence on DR research (Table 3).

According to the co-authorship analysis, Figure 4 displays the knowledge domain map of the authors in DR research. The size of the node corresponds to the number of published articles. The links between nodes represent the cooperative relationship between authors.

The greater the link strength, the greater the density of cooperation was between the linked authors.

### 3.5. Distribution of source journals

Based on the retrieved results, articles on DR research were published in 1524 journals. The top 10 journals that publish on
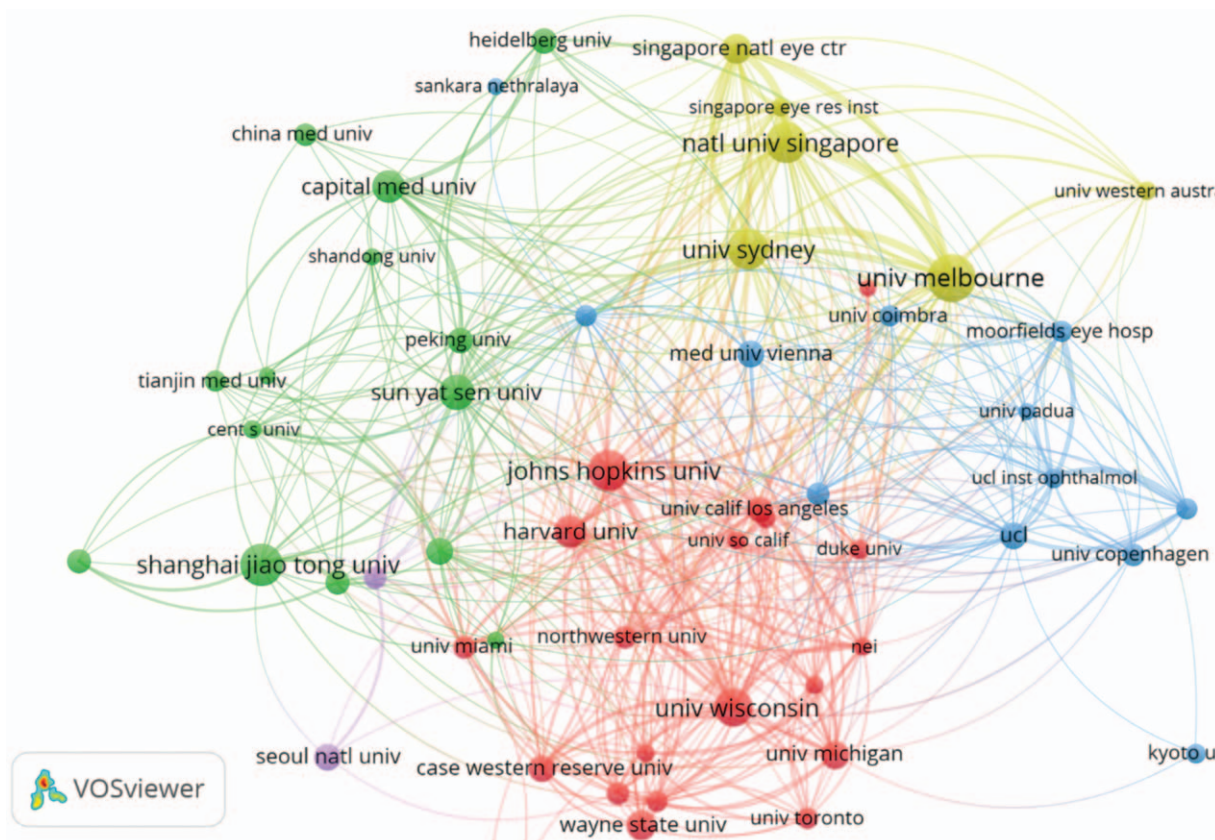


**Figure 3.** Network visualization map of main research organizations in DRstudy from 2009 to 2018. The size of each node is determined by the number of publications from each institution. The width of each line represents the strength of links between institutions. The minimum number of documents of an organization was set as 60. Of the 8642 organizations that were involved in DR research, 54 organizations met the threshold.

Top 10 productive authors and co-cited authors in diabetic retinopathy study, 2010 to 2019.

| Rank | Author | Count | Co-cited author | Count |
|------|--------|-------|-----------------|-------|
| 1 | Wong, TY | 173 | Klein, R | 3199 |
| 2 | Klein, R | 79 | Kowluru, RA | 1628 |
| 3 | Lamoureux, EL | 73 | Aiello, LP | 1423 |
| 4 | Mitchell, P | 59 | Wong, TY | 1370 |
| 5 | Bandello, F | 59 | Barber, AJ | 1113 |
| 6 | Kowluru, RA | 58 | Cheung, N | 1060 |
| 7 | Peto, T | 57 | Antonetti, DA | 984 |
| 8 | Simo, R | 56 | Joussen, AM | 885 |
| 9 | Wang, JJ | 55 | Yau, JWY | 785 |
| 10 | Kern, TS | 53 | Spaide, RF | 764 |

this topic are listed in Table 4. Investigative Ophthalmology & Visual Science published the greatest number of articles (782, 6.6%), followed by PLOS ONE (464, 3.9%) and Retina-The Journal of Retinal and Vitreous Diseases (455, 3.8%). Articles

published in these 3 journals accounted for 14.36% of all publications included in this study.

### 3.6. Distribution of cited references: knowledge bases of DR research

Through co-citation analysis of the cited references, a knowledge base of DR research can be efficiently constructed. The minimum number of citations for a cited reference was set to 200. Of the 337,162 cited references, 305 met the threshold. The top 10 co-cited references are presented in Table 5.

### 3.7. Distribution of keywords hotspots of DR research

Through the co-occurrence analysis of high-frequency keywords, the research hotspots of DR were identified. The minimum number of co-occurrences of a keyword was set to 20. Of the 13,415 extracted keywords involved in DR, 226 met the threshold. Based on the network, the keywords with similarities were clustered, and the 6 main clusters were denoted using the
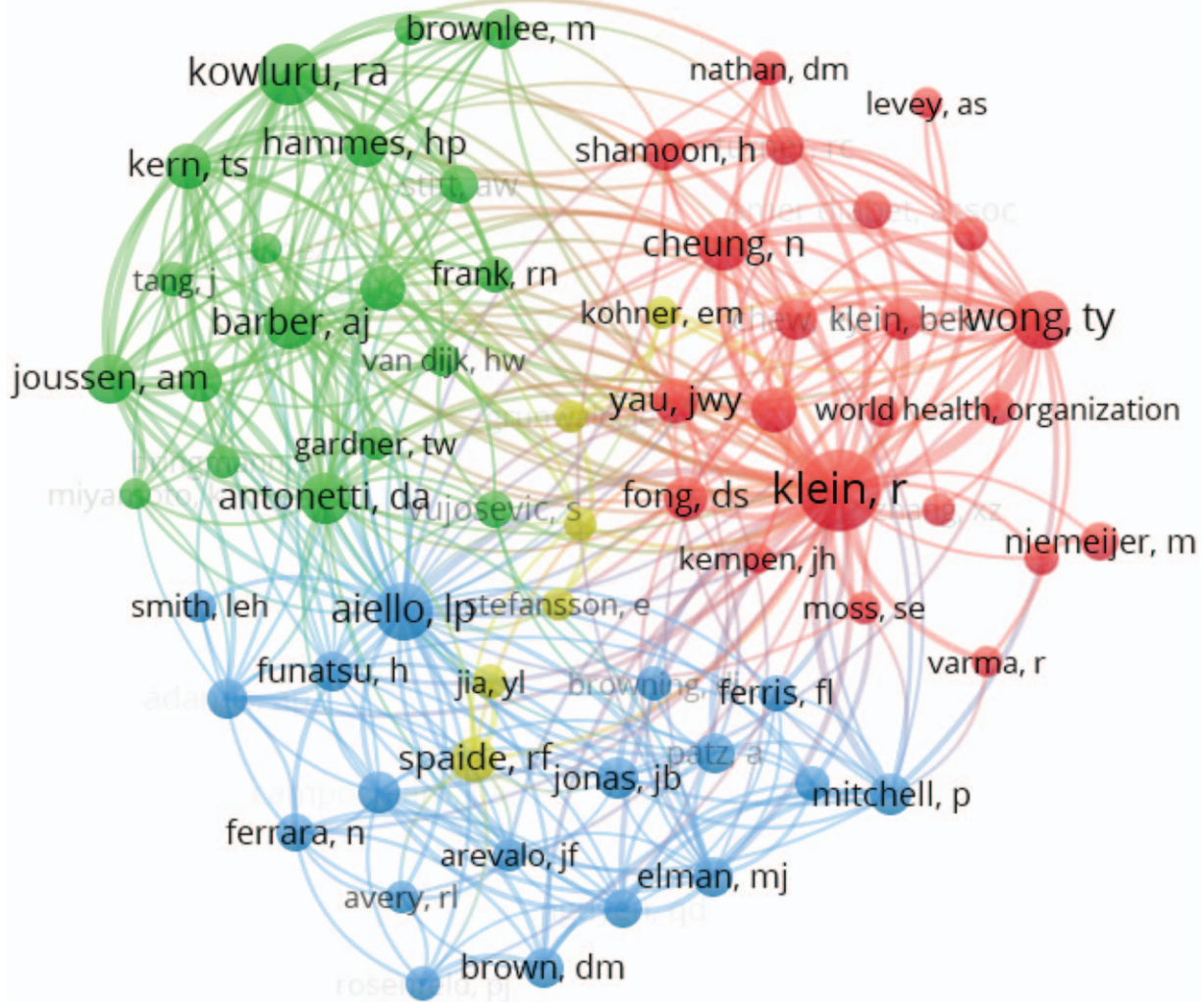


**Figure 4.** Co-cited authorship network in DR study from 2009 to 2018. The size of the frame represents the number of publications of the author and the thickness of lines signifies the size of collaboration between the authors. The minimum number of documents of an author was set as 300. Of the 111,933 authors that were involved in DR research, 65 authors met the threshold.

**Table 4**

**Top 10 main source journals in diabetic retinopathy study, 2010 to 2019.**

| Rank | Journal | Country | Count | % of 11,839 |
|------|---------|---------|-------|-------------|
| 1 | Investigative ophthalmology & Visual Science | United States | 782 | 6.61 |
| 2 | PLOS ONE | United States | 464 | 3.92 |
| 3 | Retina-The Journal of Retinal and Vitreous Diseases | United States | 455 | 3.84 |
| 4 | Ophthalmology | United States | 283 | 2.39 |
| 5 | Acta ophthalmologica | Den Mark | 245 | 2.07 |
| 6 | Graefe's Archives for Clinical and Experimental Ophthalmology | United States | 216 | 1.83 |
| 7 | British Journal of Ophthalmology | England | 201 | 1.70 |
| 8 | American Journal of Ophthalmology | United States | 186 | 1.57 |
| 9 | Scientific Reports | England | 185 | 1.56 |
| 10 | International journal of ophthalmology | China | 176 | 1.49 |

colors red, green, brown, yellow, purple, and blue, respectively (Fig. 5). The top 10 keywords for each cluster are listed in Table 6.

## 4. Discussion

### 4.1. Global trends in research on DR

The variation in the number of academic papers is an important research index that can reflect the development trend of the corresponding field. As shown in Figure 1, a total of 11,839 papers were retrieved on DR from 2010 to 2019, and the annual research output increased with time. In the analysis of the most productive countries shown in Table 1, the United States accounted for 27.7% of publications and ranked first in the number of publications. This indicates that the United States is the international scientific center of DR research.

Through the analysis of the distribution of research organizations, the most productive organizations and cooperation within the groups in a certain field can be identified. As shown in Table 2, the most productive research institution was the University of Melbourne (252 documents), followed by Shanghai Jiao Tong University (216 documents) and Johns Hopkins University (208 documents), indicating that these research

organizations are at the core of the entire research network. In terms of the number of links, the National University of Singapore presented the highest number (406 links), followed by the University of Melbourne (386 links), which indicated that these organizations are key nodes in the collaboration network (shown in Fig. 3).

The establishment of a co-authorship network knowledge map can provide valuable information to individual researchers seeking collaboration opportunities. The co-authorship groups are shown in Figure 4: the red-colored group has Professor Klein as the center; the green-colored group has Professor Kowluru as the center; the blue-colored group has Professor Aiello as the center, and the yellow-colored group has Professor Spaide as the center.

A distribution analysis of academic journals helps determine the core journals in a certain research field. To this end, Investigative Ophthalmology & Visual Science, which has published the highest number of articles, is the most prolific journal on DR research.

### 4.2. Intellectual base

Based on the premise that high-quality research will be extensively cited, citation parameters were used to describe

**Table 5**

**Top 10 co-cited references in Diabetic Retinopathy research, 2010 to 2019.**

| Rank | Title | Author | Cluster | Citations |
|------|-------|--------|---------|-----------|
| 1 | A survey on deep learning in medical image analysis | Litjens, Geert | 4 | 1402 |
| 2 | Global Prevalence and Major Risk Factors of Diabetic Retinopathy | Yau, Joanne W. Y. | 2 | 1389 |
| 3 | Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs | Gulshan, Varun | 4 | 1077 |
| 4 | Diabetic retinopathy | Cheung, Ning | 4 | 1020 |
| 5 | Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema | Elman, Michael J. | 3 | 776 |
| 6 | The RESTORE Study Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema | Mitchell, Paul | 3 | 740 |
| 7 | Ranibizumab for Diabetic Macular Edema Results from 2 Phase III Randomized Trials: RISE and RIDE | Quan Dong Nguyen | 3 | 737 |
| 8 | Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. | Chew, Emily Y. | 3 | 660 |
| 9 | Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema | Wells, John A | 3 | 592 |
| 10 | Inflammation in diabetic retinopathy | Tang, Johnny | 1 | 499 |
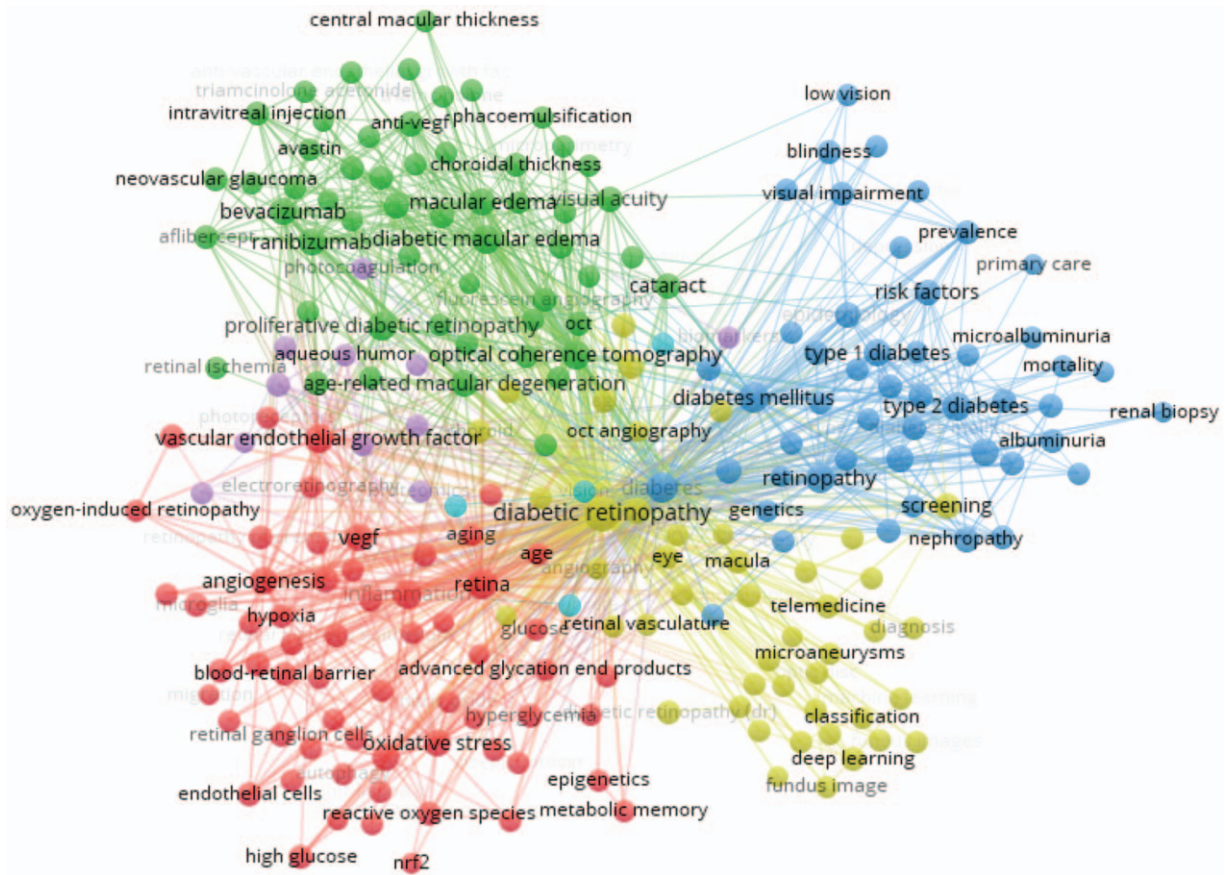
**Figure 5.** Co-occurrence network of keywords in DR study. The size of the points represents the frequency, and the keywords are grouped into 6 clusters: (Cluster 1-Red) pathogenesis of DR; (Cluster 2-Green) epidemiology and risk factors for DR; (Cluster 3-Brown) treatments for DR; (Cluster 4-Yellow) screening of DR; (Cluster 5-Purple) histopathology of DR; and (Cluster 6-Blue) diagnostic methods for DR. The minimum number of occurrences of a keyword was set as 20. Of the 13,415 keywords that were involved in DR research, 226 keywords met the threshold.

related topics within the selected articles. As shown in Table 5, "A survey on deep learning in medical image analysis" ranked first in both citations and link strength. Through co-citation analysis, a large number of cited references can effectively show the background of a study. Therefore, we conducted a cluster

analysis to explore the main topics in DR research. As shown in Table 5, the 4 co-cited references list various clinical trials that mainly investigated the use of anti-VEGF medications in the management of DR. The publications entitled "A survey on deep learning in medical image analysis" and "Global Prevalence and

**Table 6**

Co-occurrence analysis of keywords. Top 10 keywords in the 6 clusters.

| Cluster 1 Red | Cluster 2 Green | Cluster 3 Brown | Cluster 4 Yellow | Cluster 5 Purple | Cluster 6 Blue |
|---|---|---|---|---|---|
| diabetes (675) | diabetic retinopathy (2940) | diabetic macular edema (838) | glaucoma (311) | vascular endothelial growth factor (269) | optical coherence tomography (854) |
| retina (524) | diabetes mellitus (497) | proliferative diabetic retinopathy (518) | screening (261) | age-related macular degeneration (195) | optical coherence tomography angiography (229) |
| inflammation (272) | retinopathy (343) | bevacizumab (541) | telemedicine (139) | ranibizumab (179) | cataract (228) |
| angiogenesis (243) | type 2 diabetes (311) | macular edema (459) | ophthalmology (106) | visual acuity (137) | fluorescein angiography (153) |
| oxidative stress (225) | type 2 diabetes mellitus (203) | vitrectomy (292) | diabetic retinopathy (dr) (51) | neovascularization (104) | foveal avascular zone (105) |
| vegf (222) | diabetic nephropathy (179) | anti-vegf (232) | deep learning (95) | choroidal thickness (72) | imaging (104) |
| apoptosis (200) | type 1 diabetes (167) | panretinal photocoagulation (126) | macula (106) | oct (71) | phacoemulsification (83) |
| polymorphism (83) | risk factors (138) | diabetic macular edema (125) | eye (103) | retinal neovascularization (60) | retinal thickness (83) |
| hypoxia (78) | epidemiology (109) | intravitreal injection (177) | retinal imaging (66) | choroidal neovascularization (58) | epiretinal membrane (71) |
| Neurodegeneratio (76) | nephropathy (84) | retinal vein occlusion (161) | classification (70) | aflibercept (54) | retinal vasculature (73) |

OF = occurrence frequency.

Major Risk Factors of Diabetic Retinopathy" ranked in the top 2 in both frequency count and link weight, respectively, and are thus considered the core position of the whole knowledge map.

### 4.3. Research frontiers

The co-occurrence analysis of keywords is a common bibliometric research method in which the assigned keywords are considered to represent the search theme. Thus, the internal structure of the related literature and the frontier discipline can be revealed. As shown in Table 6, DR topics mainly formed 6 clusters, and keywords in the same cluster showed greater similarity to a specific research topic than keywords in different clusters. Combined with the characteristics and current status of DR research, the 6 clusters are described as follows:

Cluster #1 (red) represents keywords mainly related to the pathogenesis of DR. The extracted co-occurrence keywords include "inflammation", "angiogenesis", "oxidative stress", "apoptosis", "hypoxia", and "neurodegeneration". Chronic hyperglycemia leads to increased inflammation and oxidative stress in the retina, which seems causally related to the development of at least diabetes-induced leakage and the degeneration of retinal capillaries. The incubation of retinal cells in high glucose causes the upregulation of proinflammatory factors, such as Inducible nitric oxide synthase, cyclooxygenase-2, and leukotrienes.[12–16] Inflammatory processes play an important role in the development of early and possibly later stages of DR, and the inflammatory pathogenesis of DR is based on the molecular characteristics of inflammation, as opposed to the classical cellular definition of inflammation.[17] Diabetes-induced oxidative stress plays a role in the development of inflammatory processes in the retina.[18,19] Two months of diabetes in rats significantly increased retinal levels of interleukin-1β and nuclear factor kappa-B, and antioxidants inhibited those increases.[20] Other research has shown that inhibition of interleukin -6 trans-signaling significantly reduces diabetes-induced oxidative damage in the retina.[21] Early proinflammatory changes, such as the appearance of microglia, the formation of advanced glycation endproducts, and the overproduction of VEGF, can directly cause hypoxia in the retina and not necessarily via reactive oxygen species.[22] VEGF is known to be a proinflammatory molecule whose vitreal levels are highly correlated with retinal neovascularization and edema. Many studies have evaluated the association of enzymes or gene polymorphisms with DR; for example, the nitric oxide synthase 3 gene rs869109213 polymorphism alone or in combination with the endothelin receptor B gene rs10507875 polymorphism may be associated with DR in Slovenian patients with type 2 diabetes mellitus,[23] and the methylenetetrahydrofolate reductase C677T polymorphism may contribute to DR development in multiethnic groups.[24] Researching the pathogenesis of DR could provide new therapeutic targets for inhibiting or preventing retinopathy.

Cluster #2 (green) represents keywords related to the epidemiology of and risk factors for DR. Age-standardized to the 2010 population, there are approximately 93 million people with DR, 17 million with proliferative DR, and 21 million with diabetic macular edema (DME). The overall prevalence is 34.6% for any DR, 6.96% for proliferative DR, 6.81% for DME, and 10.2% for vision-threatening DR.[25] The most common risk factors for DR are longer diabetes duration and poorer glycemic and blood pressure control.[26,27] Moreover, the overall prevalence is higher in people with type 1 diabetes than in those with

type 2 diabetes.[25] In China in 2010, the pooled prevalence rates of any DR, nonproliferative DR, and proliferative DR were 1.14%, 0.90%, and 0.07% in the general population and 18.45%, 15.06%, and 0.99% in people with diabetes, respectively. A total of 13.16 million Chinese individuals aged 45 years and above live with DR, and the risk factors include residing in rural China, insulin treatment, elevated fasting blood glucose levels, and higher glyeosylated hemoglobin concentrations.[2] Other risk factors for DR include poor blood pressure and lipid control, high body mass index, puberty, pregnancy, and cataract surgery. There are weaker associations with some genetic and inflammatory markers. DR has become a serious global public health problem.[28] Diabetic nephropathy is another major public health problem with social and economic burdens. The prevalence of nephropathy among individuals with retinopathy is 35.6%, and there is a significant association between nephropathy and the development of retinopathy. Two abso ute risk factors for DR are nephropathy and hypertension.[29]

Cluster #3 (brown) represents keywords related to treatments for DR, such as "intravitreal injections" of "anti-VEGF", "vitrectomy" and "panretinal photocoagulation" (PRP). DME is very common in proliferative diabetic retinopathy (PDR) and is characterized by metamorphopsia and loss of visual acuity (VA). Anti-VEGF intravitreal injections can benefit most patients. Aflibercept, bevacizumab, and ranibizumab are 3 commonly used anti-VEGF agents whose molecular structure and properties differ.[30] Many clinical trials have been conducted to determine the optimal anti-VEGF drug among the 3 listed above, as well as to elucidate their efficacy and guide their administration frequency for patients with DME. The Diabetic Retinopathy Clinical Research Network conducted a comparative effectiveness study for center-involved DME for all 3 drugs at a 2-year follow-up visit. Among eyes with better VA at baseline, no difference was identified in vision outcomes through the 2-year follow-up. For the eyes with worse VA at baseline, the advantage of aflibercept over bevacizumab for mean VA gain persisted through the 2 years, although the difference at 2 years was diminished. The VA difference between aflibercept and ranibizumab for eyes with worse VA at baseline that was noted at 1 year had decreased at 2 years.[31,32] The disadvantages are frequent injection, high medical costs, and poor results in some patients after multiple injections. Compared with anti-VEGF drugs, dexamethasone implants significantly improve anatomical outcomes. However, this does not translate to improve VA, which may be due to the progression of cataracts. Therefore, the dexamethasone implant may be recommended as the first choice for select cases, such as for pseudophakic eyes, anti-VEGF-resistant eyes, or patients reluctant to receive frequent intravitreal injections.[33] PDR is the worst stage of DR. For decades, PRP and vitrectomy have been the standard of care for the treatment of PDR. Recently, anti-VEGF has provided a new standard of care in PDR.[34] Tractional macular detachment occurs in 10% of eyes after anti-VEGF agent pretreatment before vitrectomy for complicated PDR. The main risk factors are days between anti-VEGF injection and vitrectomy, vitreous hemorrhage, and age.[35] However, preoperative intravitreal injections of anti-VEGF agents are effective and safe for complicated PDR.[36,37]

Cluster #4 (yellow) represents keywords related to the screening of DR. DR results in vision loss if not treated early. However, the interpretation of retinal images requires specialized knowledge and expertise in DR, and capital- and labor-intensive

screening programs are difficult to rapidly scale up and expand to meet the needs of this growing global epidemic. Many artificial intelligence and deep learning-based methods have been developed from large image datasets in the assessment of retinal photographs for the detection and screening of DR as well as in the segmentation and assessment of optic coherence tomography (OCT) images for the diagnosis and screening of DME.[38] A hospital-based cross-sectional study showed that non-mydriatic funduscopic screening photography was practical and useful for the detection of DR in patients with type 1 and type 2 diabetes.[39] Telemedicine services facilitate the evaluation, diagnosis, and management of remote patients. In ophthalmology, telemedicine is in its infancy, particularly in its application to DR, as current models are largely performed via "store and forward" methods, but remote monitoring and interactive modalities exist. Telemedicine has the potential to improve access to care, decrease the cost of care, and improve adherence to evidence-based protocols.[40]

Cluster #5 (purple) represents keywords related to the histopathology of DR. The blood-retinal barrier (BRB) is a particularly tight and restrictive physiological barrier that regulates ion, protein, and water flux into and out of the retina. It consists of inner and outer components, the inner BRB being formed of tight junctions between retinal capillary endothelial cells and the outer BRB of tight junctions between retinal pigment epithelial cells. OCT is widely used to evaluate the BRB. DR and age-related macular degeneration (AMD) are the 2 most frequent and relevant retinal diseases that are directly associated with alterations of the BRB.[41] DR is a result of retinal neovascularization, and wet AMD is initiated by choroidal neovascularization.[41] It is well known that intravitreal injections of anti-VEGF agents are effective and safe in minimizing neovascularization.[42] Aflibercept and ranibizumab can both reduce macular edema and improve the VA of patients; these drugs are more commonly used in DME.[32] Swept-source OCT demonstrates a significant reduction in choroidal thickness of eyes with PDR compared with that of controls. In the foveal region, the choroid appears to be thinner in DR eyes than in diabetic eyes without retinopathy.[43]

Cluster #6 (blue) represents diagnostic methods for DR, such as "OCT", "optical coherence tomography angiography (OCTA)", and "fluorescein angiography (FA)". FA is a dye-based ocular angiography and has been used in clinical practice for over 50 years. Only the superficial vascular plexus can be seen with it, and it provides limited information about the choroidal circulation. Despite these limitations, FA imaging offers many other advantages, including dynamic information regarding the transit of blood as well as identification of dye leakage from disruptions of BRB by disease. OCT constitutes one of the greatest advances in ophthalmic imaging and is capable of showing structural images of the retina and choroid. Building on this platform, OCTA provides depth-resolved images of blood flow in the retina and choroid with levels of detail far exceeding those obtained with FA. OCTA can generate high contrast, well-defined images of the microvasculature. Besides, OCTA images can be viewed in cross-section to confirm the depth location of vascular pathologies. Finally, OCTA can be performed much more rapidly than FA or indocyanine green angiography, streamlining the clinical workflow. At the same time, OCTA has important limitations. First, the fields of view that can be imaged by OCTA are smaller than those imaged by FA. Second, OCTA signals have a limited dynamic range.[44] Many studies have been conducted to compare OCTA with FA in patients with DR.[45–47]

These studies have found good agreement for the size of the foveal avascular zone (FAZ) and weak agreement regarding the number of microaneurysms (MAs) in both imaging modalities. It is better to assess the FAZ with OCTA and MAs with FA. Complementary use of FA and OCTA is the best diagnostic approach.[46] Diabetic macular ischemia grade, the size of the FAZ on OCTA, ellipsoid zone disruption, and disorganization of the retinal inner layers with OCT are associated with VA. The use of OCTA and OCT can predict VA in DR.[48] With the development of newer, wide-angle imaging technologies, wide-angle OCT, wide-angle OCTA, ultrawide-field FA, longitudinal wide-field swept-source OCTA, and en face OCTA have gradually been used in DR.[49–51] The multimodal imaging approach keeps the findings of any one modality in perspective by integrating that information with potentially useful data obtained by other imaging methods, which allows clinicians to gain the most information from each modality and thereby optimize patient care.[52]

## 5. Conclusions

We constructed a series of science maps of the annual number of publications, the distribution of countries, international collaborations, author productivity, source journals, cited references, and keywords in DR research. The results of this study may be helpful for ophthalmologists in choosing appropriate journals for publication and organizations or authors for collaborations. The extracted keywords enable researchers to identify new topics and assist them in predicting research directions. However, some limitations should be considered. First, the publications were extracted from the WoSCC between 2010 and 2019, which may not sufficiently represent all of the topics in DR research. Second, the primary data were extracted from WoSCC, which is a database more suited for performing citation analysis. Third, because most publications in the WoSCC were in English, a linguistic bias may exist. Last but not least, the collaboration network analysis successfully displayed the co-occurrence (distance between the 2 nodes/items) and the co-authorship of the institutions (the strength of the links). However, the strength of each pair of linked items is not shown in the final exported file, and VOSviewer was unable to generate a geographical map of co-authorship. Thus, a visualization of geographical location and co-authorship cannot be generated, and an understanding of the relationship thereof cannot be determined.

## 6. Future studies

Future studies may consider exploring a specific aspect of DR research, such as medicine and surgery. We will use different document databases and other bibliometric methods (such as bibliographic coupling analysis) to study other aspects of DR. In addition, Altmetrics, a new and comprehensive bibliometric method for evaluating the academic and social influences of research outputs, can also be applied in combination with scientometric analysis to better understand the trends and new areas of research in the field. It can be predicted that there will be an increasing number of papers in the coming year. In particular, studies about medicine and imaging will be the next popular hotspots and should receive more attention in the future.

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## Author contributions

Conceptualization: Yi Dong, Shixin Qi.
Data curation: Yi Dong, Huijuan Liu.
Formal analysis: Yi Dong.
Investigation: Yi Dong, Jianguo Yu.
Methodology: Yi Dong, Yanli Liu, Shixin Qi.
Project administration: Yi Dong, Yanli Liu, Jianguo Yu, Huijuan Liu.
Resources: Yi Dong, Yanli Liu.
Software: Yi Dong.
Supervision: Yi Dong, Jianguo Yu.
Validation: Yi Dong, Shixin Qi.
Visualization: Yi Dong.
Writing – original draft: Yanli Liu.
Writing – review & editing: Yi Dong, Yanli Liu.

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