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Full Length Article

# Research trends of worldwide ophthalmologic randomized controlled trials in the 21st century: A bibliometric study

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ABSTRACT

*Background:* Randomized controlled trials (RCTs) are often considered the gold standard and the cornerstone for clinical practice. However, bibliometric studies on worldwide RCTs of ophthalmology published in the 21st century have not been reported in detail yet. This study aims to perform a bibliometric study and visualization analysis of worldwide ophthalmologic RCTs in the 21st century.

*Methods:* Global ophthalmologic RCTs from 2000 to 2022 were searched in the Web of Science Core Collection. The number of publications, country/region, institution, author, journal, and research hotspots of RCTs were analyzed using HistCite, VOSviewer, CiteSpace, and Excel software.

*Results:* 2366 institutions and 90 journals from 83 countries/regions participated in the publication of 1769 global ophthalmologic RCTs, with the United States leading in the number of volumes and research field, and the Moorfields Eye Hospital contributing to the most publications. Ophthalmology received the greatest number of publications and co-citations. Jeffrey S. Heier owned the most publications and Jost B. Jonas owned the most co-citations. The knowledge foundations of global ophthalmologic RCTs were mainly retinopathy, glaucoma, dry eye disease (DED), and cataracts, and anti-vascular endothelial growth factor (VEGF) therapy (ranibizumab), topical ocular hypotensive medication, laser trabeculoplasty. Anti-VEGF therapy for age-related macular degeneration (AMD), DME (diabetic macular edema), and DED, the use of new diagnostic tools, and myopia were the hottest research highlights. Anti-VEGF therapy, prompt laser, triamcinolone, and verteporfin photodynamic therapy for AMD, DME, and CNV (choroidal neovascularization), DED, myopia, and open-angle glaucoma were the research hotspots with the longest duration. The future research hotspots might be DED and the prevention and control of myopia.

*Conclusions:* Overall, the number of global ophthalmologic RCTs in the 21st century was keeping growing, there was an imbalance between the regions and institutions, and more efforts are required to raise the quantity, quality, and global impact of high-quality clinical evidence in developing countries/regions.

## 1. Backgrounds

Since evidence-based medicine (EBM) was first introduced in 1992 and evidence-based ophthalmology was first proposed in 2000, the use of the best ophthalmologic evidence was strongly promoted and increasingly accepted and applied in clinical practice.[1,2] According to the recommendations of EBM, randomized controlled trials (RCTs) are often considered the gold standard and the cornerstone for clinical practice due to the minimum risk of bias.[3,4] Previous studies have shown that the number of RCTs in various clinical disciplines, including in ophthalmology, has been rapidly increasing worldwide until now, especially in the 21st century.[5,6] Thus, considering the importance of RCTs in clinical evidence, the analysis of worldwide ophthalmologic RCTs published in the last 20 years can mirror the current research area of high-quality ophthalmologic clinical evidence and should be urgently required.[6]

Bibliometric analysis, which is also named scientometrics and has been constantly utilized by researchers, is a systematic analysis method to quantitatively and visually feature the characteristics of literature, such as the institutions, countries/regions, journals, and authors.[6,7] With

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its help, the discovery of available information in specific fields and the exploration of future research is becoming more achievable.[8] As an increasing number of global ophthalmologic RCTs have been published, it is necessary to conduct a comprehensive bibliometric analysis of global RCTs of ophthalmology. Ryalat et al. performed a bibliometric study of worldwide ophthalmologic RCTs, however, this study has several limitations, such as the lack of systematic searching and screening, only the annual number of publications and RCTs with the most citations were visualized, and RCTs published half a century ago were also included, which had rare inspirations for current research. The comprehensive explanation of worldwide RCTs of ophthalmology was limited due to these limitations. Thus, to reduce the above limitations, thoroughly clarify the key study features and provide a basis for further research, this bibliometric study focusing on worldwide ophthalmologic RCTs published in the 21st century was performed.

## 2. Methods

### 2.1. Data sources and search strategy

The Web of Science Core Collection (WoSCC), which is considered the key database for bibliometric studies, was searched on April 17, 2022, to avoid bias from the updates of the database. Databases included the Science Citation Index Expanded. The search terms included Ophthalmology, Eye, Randomized Controlled Trial, and so on. The detailed search strategy was shown in the Supplementary. The research field was limited to Ophthalmology. There were no further limitations on country/region and journal type. The following websites and databases were searched to identify the authors' country/region and the research areas: the official website of the author's institution, ResearchGate, PubMed, and U.S. News & World Report.

### 2.2. Study selection criteria and study screening

The inclusion criteria were as follows: (1) RCTs consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement; (2) the year of publication for RCTs was between 2000 and 2022; (3) RCTs related to ophthalmology. The exclusion criteria were as follows: (1) clinical guidelines, systematic reviews, and meta-analysis; (2) basic research or animal research. (3) cross-sectional, cohort, and case-control studies. We performed a pre-test to ensure credible inter-rater reliability. The titles and abstracts of the publications were screened independently by two researchers, the full text would be further read in case of disagreement when checking. Once the disagreement could not be resolved, a third researcher would be needed.

### 2.3. Statistical analysis

The number of yearly publications was identified utilizing HistCite (12.03.07).[9] VOSviewer (1.6.9) was used to analyze the features such as countries/regions, institutions, journals, authors, and keywords, and visually represent the connections among these features.[10] The following were the settings for VOSviewer: counting method (full counting), thresholds (T) of items were adopted based on special conditions. In addition, we employed CiteSpace (5.8.R1) to generate the dual-map overlay of journals and to specify emerging papers or keywords (defined as papers or keywords with strong citation burstness).[11] We set the CiteSpace as follows: look back years = −1, e for top N (e = 1), time span (2000–2022), years per slice, links (strength: cosine, scope: within slices), and minimum duration (MD = 2).[12] We employed Excel to analyze the trends of the number of annual publications, and manage the data. Linear regression models in Excel were used to estimate the number of articles issued from 2022 to 2025. we chose the 2021 Journal Citation Reports (Clarivate Analytics, Philadelphia, USA) to be the source of the impact factor (IF).

## 3. Results

### 3.1. Results of literature screening and yearly number of worldwide ophthalmologic RCTs

A total of 3153 publications were searched, and 1769 of them were included in the final analysis. As depicted in Fig. 1A, the number of worldwide ophthalmologic RCTs has steadily increased since 2000, firstly exceeding 100 in 2012, and significantly increased since 2015. Furthermore, the number of RCTs published in 2021 (n = 141, 7.97%), which reached a peak with the maximum number of studies, was over twice that in 2009 (n = 70, 3.96%). Fig. 1B shows the estimated number of global RCTs between 2022 and 2025. With the help of linear regression models, we assume that 133 worldwide ophthalmologic RCTs will be published in 2022, and there will be an increasing trend in the number of RCTs published from 2022 to 2025. The results of the literature search, screening, and inclusion are detailed in Supplementary Fig. 1.

### 3.2. Results of countries/regions

A total of 83 countries/regions participated in global ophthalmologic RCTs. Table 1 illustrates the top 10 countries/regions. The United States contributed the most RCTs (n = 660), followed by England (n = 257) and China (n = 154). 32 countries/regions with more than/equal to 13 RCTs (T = 13) were incorporated to form the cooperative time network of countries/regions. As depicted in Fig. 2A, the United States actively cooperated with England, Germany, and China, etc., England and Germany were more active around 2010, and China, India, and Spain were more active in the last several years.

### 3.3. Results of institutions

2366 institutions were involved in the publication of worldwide ophthalmologic RCTs. The top 10 institutions are described in Table 1. Most RCTs were from Moorfields Eye Hospital (n = 69), followed by Johns Hopkins University (n = 52) and The University of Melbourne (n = 46). Institutional collaborations between institutions were visually presented via analyzing 28 institutions with over/equal to 20 RCTs (T = 20), and the largest time sub-network with 27 institutions is shown in Fig. 2B. Close cooperation between institutions existed. Institutions such as the Moorfields Eye Hospital participated in more RCTs in 2010. Recently, institutions such as the University of Melbourne and Sun Yat-sen University contributed more RCTs.

### 3.4. Results of journals, co-cited journals, and journal dual-map overlay

90 journals participated in the publication of worldwide ophthalmologic RCTs. In the top 10 journals, three journals (*Ophthalmology*, *American Journal of Ophthalmology*, *and British Journal of Ophthalmology*) contributed to at least 100 RCTs (n = 290, 131, and 122, respectively) (Table 2). *Ophthalmology* earned the highest IF (12.1). The top 10 journals were mainly from the United States (n = 6) or England (n = 3), only *Graefes Archive for Clinical and Experimental Ophthalmology* was from Germany. We included 23 journals with a publication number over/equal to 20 (T = 20) to visualize the journal citation relationship and Fig. 3A describes the time network. *Ophthalmology*, *American Journal of Ophthalmology*, and *British journal of ophthalmology* were the main publication journals around 2010, and *BMC Ophthalmology* and *Journal of Ophthalmology* were the recent ones. Co-cited journals are journals usually cited together by other studies.[6] 4488 journals were co-cited. All of the top 10 co-cited journals were from the United States (n = 8) or England (n = 2), and each of them, except for *Eye*, earned more than 1000 co-citations. *Ophthalmology* (n = 6414) was the journal with the highest number of co-cations. The IF (2021) of these co-cited journals ranged between 12.1 (*Ophthalmology*) and 2.1 (*Optometry and Vision Science*), five journals ranked in Q1. As

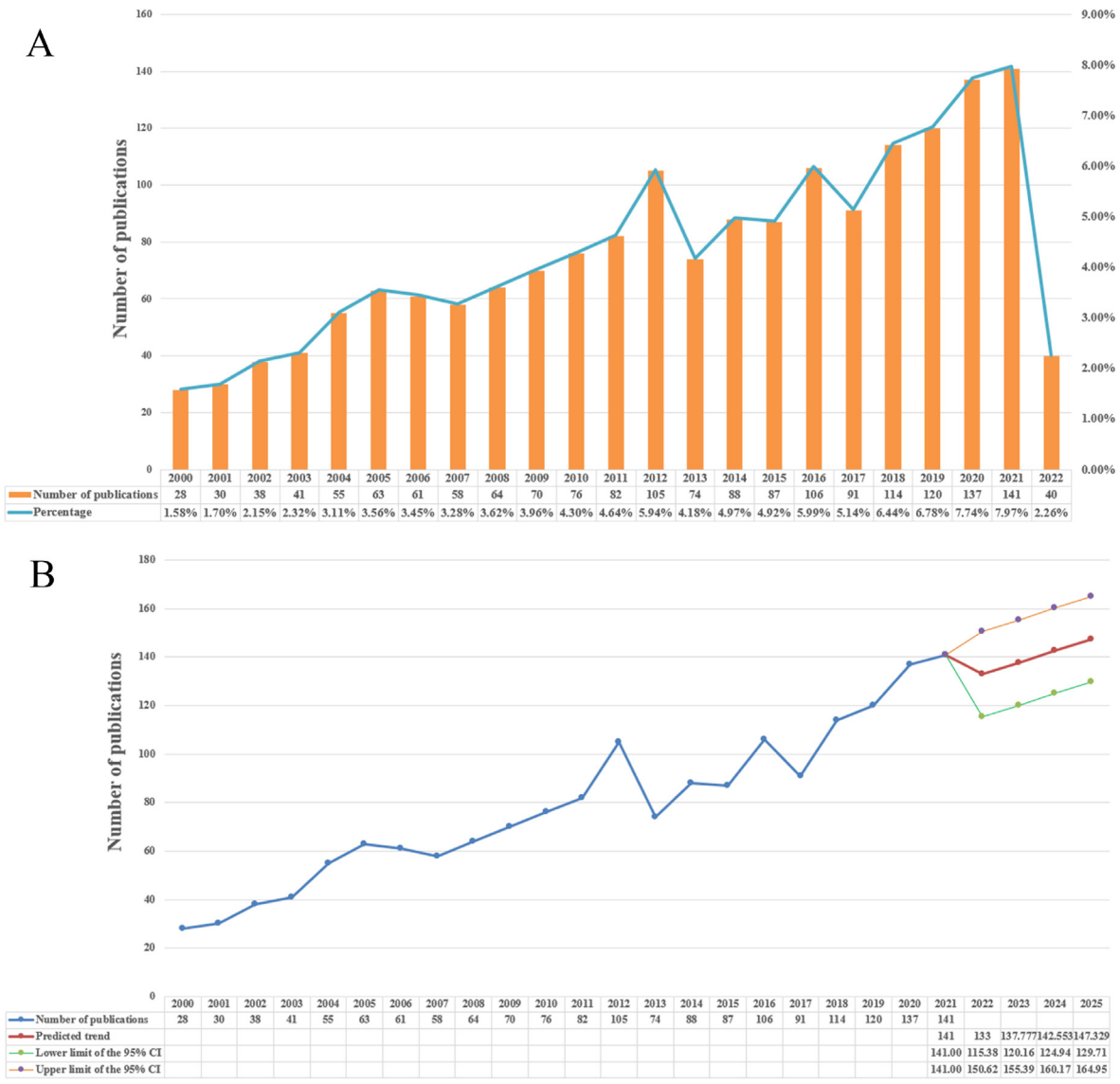


**Fig. 1.** Annual number of global ophthalmologic RCTs (A) and the predicted number of global ophthalmologic RCTs from 2022 to 2025 (B).
RCTs = randomized controlled trials.

**Table 1**
The top 10 countries/regions and institutions that contributed to worldwide ophthalmologic RCTs.

| Rank | Countries/ Regions | Numbers | Institutions (Countries/ Regions) | Numbers |
|---|---|---|---|---|
| 1 | The United States (USA) | 660 | Moorfields Eye Hospital (England) | 69 |
| 2 | England | 257 | Johns Hopkins University (USA) | 52 |
| 3 | China | 154 | The University of Melbourne (Australia) | 46 |
| 4 | Germany | 144 | The Chinese University of Hong Kong (China) | 39 |
| 5 | India | 117 | Sun Yat-Sen University (China) | 35 |
| 6 | Australia | 111 | Stanford University (USA) | 35 |
| 7 | Italy | 93 | The Singapore National Eye Centre (Singapore) | 34 |
| 8 | Iran | 74 | Tehran University of Medical Sciences (Iran) | 34 |
| 9 | Japan | 65 | National University of Singapore (Singapore) | 33 |
| 10 | Canada | 61 | Harvard University (USA) | 33 |

shown in Fig. 3B, the network map of the co-cited journals was detailed by analyzing 20 co-cited journals with greater than/equal to 350 co-citations (T = 350). A close co-cited relationship existed among these journals. The dual-map overlay of journals is shown in Supplementary Fig. 2. In this map, three chief paths were identified, showing that studies of Ophthalmology/Ophthalmic/Ophthalmoldgica journals mainly cited from publications in Neurology/Sports/Ophthalmology, Molecular/Biology/Genetics, and Health/Nursing/Medicine.

### 3.5. Results of authors and co-cited authors

8266 authors participated in global ophthalmologic RCTs. The top 10 authors with the most RCTs are shown in Table 3, and each of them earned at least 10 papers. Jeffrey S. Heier (n = 17) ranked first, followed by Catey Bunce (n = 17) and David M. Brown (n = 16), etc. Most of the writers were from the United States (n = 4) and United Kingdom (n = 2). The research area of these publication authors mainly included diseases such as retinopathy, glaucoma, corneal disease, and cataracts, which was detailed in Table 3. Fig. 4A outlines the largest time sub-network map of publication authors with 12 authors, which was produced by analyzing 23 authors with greater than/equal to 10 RCTs (T = 10). Authors such as

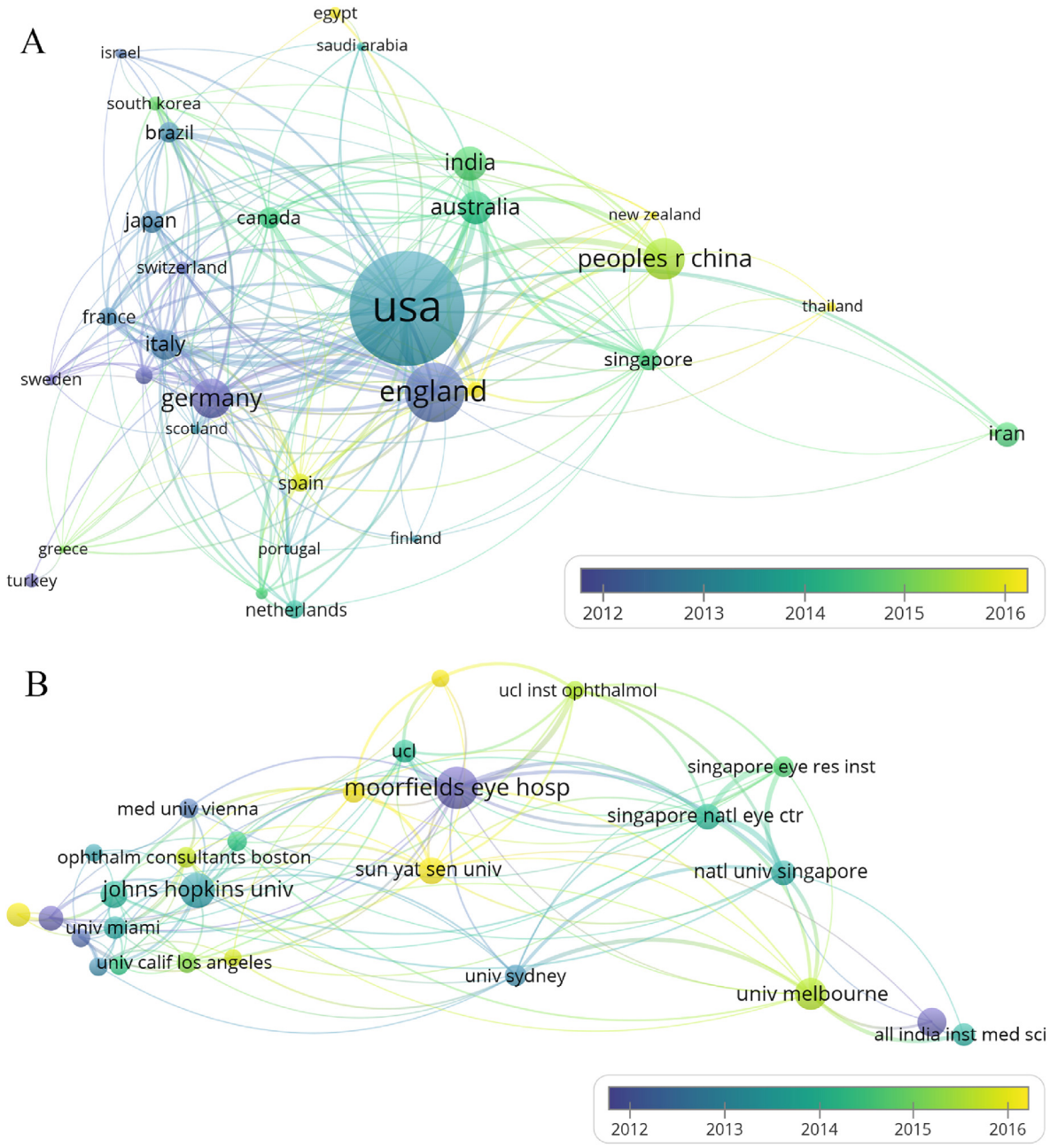


**Fig. 2.** The time network map of countries/regions (A, T = 13) and institutions (B, T = 20) contributed to worldwide ophthalmologic RCTs.
The size of the nodes stands for the numbers, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. The color of the nodes changes with their active time, which leans toward blue for the earlier time around 2012, and toward yellow for the later time around 2016. RCTs = randomized controlled trials.

Neil M Bressler and Haller, Julia A were more active in 2010, and authors such as Usha Chakravarthy and Wykoff, Charles C were more active recently. Co-cited authors can be defined as authors cited together by other papers.[6] 20,061 authors were co-cited, among whom, Jost B. Jonas(n = 165), Ronald Klein (n = 159), Jeffrey J. Walline(n = 118), Smith, EL (n = 115), and Leske, MC (n = 108) received the top five most co-citations (Table 3). 23 authors with co-cited number more than/equal to 70 (T = 70) were included to visualize the co-cited author relationship. Fig. 4B showed that these co-cited authors can be divided into 3 clusters and close co-cited relationship can be seen among them.

### *3.6. Analysis of keywords and keywords with the strongest citation burstness*

In general, 5169 keywords were found and the top 10 keywords with the most frequencies are displayed in Table 4. Glaucoma, open-angle glaucoma, and ranibizumab ranked as the top three most occurrences. All of the top 10 keywords received over 60 occurrences. As shown in Fig. 5A, we selected 20 keywords with greater than/equal to 50 occurrences and with research value (keywords without research value such as "eye" and "randomized controlled trials" were excluded) to outline the

**Table 2**
The top 10 journals and co-cited journals related to global ophthalmologic RCTs.

| Rank | Journal | Number | IF | Q | Co-cited journal | Co-citation | IF | Q |
|---|---|---|---|---|---|---|---|---|
| 1 | Ophthalmology[@] | 290 | 12.1 | Q1 | Ophthalmology [@] | 6414 | 12.1 | Q1 |
| 2 | American Journal of Ophthalmology[@] | 131 | 5.3 | Q1 | American Journal of Ophthalmology[@] | 3406 | 5.3 | Q1 |
| 3 | British journal of ophthalmology[#] | 122 | 4.6 | Q1 | Archives of Ophthalmology[@] | 3508 | 7.4 | Q1 |
| 4 | Investigative Ophthalmology & Visual Science [@] | 85 | 4.8 | Q1 | Investigative Ophthalmology & Visual Science [@] | 3249 | 4.8 | Q1 |
| 5 | Journal of Cataract and Refractive Surgery[@] | 70 | 3.4 | Q2 | British journal of ophthalmology[#] | 2678 | 4.6 | Q1 |
| 6 | Eye[#] | 67 | 4.5 | Q2 | Journal of Cataract and Refractive Surgery[@] | 2266 | 3.4 | Q2 |
| 7 | Retina-the Journal of Retinal and Vitreous Diseases[@] | 67 | 3.9 | Q2 | Optometry and Vision Science[@] | 1051 | 2.1 | Q3 |
| 8 | Acta Ophthalmologica[#] | 59 | 3.9 | Q2 | Cornea[@] | 1125 | 2.7 | Q3 |
| 9 | Graefes Archive for Clinical and Experimental Ophthalmology[&] | 50 | 7.4 | Q2 | Retina-the Journal of Retinal and Vitreous Diseases[@] | 1122 | 3.9 | Q2 |
| 10 | Archives of Ophthalmology[@] | 49 | 7.4 | Q1 | Eye[#] | 977 | 4.5 | Q2 |

*Archives of Ophthalmology* is now called *JAMA Ophthalmology*.
[@]This journal belongs to the United States.
[#]This journal belongs to the United Kingdom.
[&]This journal belongs to Germany. IF = impact factor, based on the 2021 Journal Citation Reports (JCR) and retaining 1 decimal place. Q = Quartile in Category. RCTs = randomized controlled trials.

relationships between keywords. The research highlights were open-angle glaucoma, ocular hypertension, injection, etc., approximately a decade ago, which changed to dry eye, phacoemulsification, ranibizumab, and bevacizumab in these years. Keywords with burstness means that received specific attention, characterizing hotspots over a while.[6] CiteSpace was employed to explore the keywords with burstness from 2000 to 2022, and 32 keywords were found (Supplementary Fig. 3). The red or blue block, each of which represented one year, and the red one means the citation burstness, formed the keyword straight line.[6] Table 4 shows the top 10 keywords with the strongest burstness and worth exploring (we excluded keywords with no research value such as "eye" and "randomized controlled trials", see Supplementary Fig. 3 for more details). Management, acetonide, and injection received the strongest burstness strength (11.45, 9.4, and 8.35, respectively.) Each of the top 10 keywords with the strongest burstness and research value earned a burstness strength over 5. The burstness of four keywords with exploring worth lasted at least 10 years (maculopathy, photodynamic therapy, choroidal neovascularization, and verteporfin). The burstness of keywords such as meibomian gland dysfunction (MGD), dry eye disease (DED), management, symptom, and myopia control lasted until 2022, these keywords might be the future research hotspots (Supplementary Fig. 3).

### 3.7. Results of co-cited references and references with citation burstness

Co-cited references are those co-cited by other publications together.[6] 33,609 articles were co-cited and the one from *New England Journal of Medicine* published by Rosenfeld, P. J. in 2006 earned the most co-citations (n = 74).[13] Table 5 presents the top 10 co-cited references with the details.[13–22] 20 references, co-cited at least 20 times (T = 20), were involved in the visualization of co-cited papers. Fig. 5B presents the largest sub-network map with 18 co-cited references and extensive co-citation relationships can be discovered among these references. References with burstness can be defined as publications focused on a particular time period, which could basically outline the research center.[6] We utilize CiteSpace to explore the references with burstness in 21 century, and 20 references were found (Supplementary Fig. 4). The red or blue block, each of which represented one year, and the red one means the citation burstness, formed the keyword straight line.[6] Supplementary Table 1 details the top 10 references with the strongest burstness (from 12.62 to 7.81),[13,19,21,23–29] the top 22 references with the longest burstness time (at least 5 years)[13,14,19,21,23,24,27,28,30–43] and 9 references with the burstness continue to 2022.[23,24,27–29,32,33,44,45]

## 4. Discussion

### 4.1. General characteristics of worldwide ophthalmologic RCTs

Overall, 2366 institutions, 90 journals, and 8266 authors from 83 countries/regions contributed to 1769 global ophthalmologic RCTs from 2000. The number of worldwide ophthalmologic RCTs has been basically increasing annually and there would be still an increasing trend until 2025 according to the prediction, in line with previous studies.[5] This result indicates that the worldwide ability to produce ophthalmology high-quality clinical evidence is progressively improving.[5] In terms of countries/regions, the developed countries such as the United States and England absolutely contributed to the most studies and led the field of ophthalmologic high-quality clinical evidence. However, it was worth noting that developing countries such as China, India, and Iran also played important roles in producing ophthalmologic high-quality clinical evidence. The reasons for these phenomena could be explained as follows: firstly, developed countries are the world-leading engines of medicine.[6] Secondly, the implementation of RCTs usually requires abundant financial support,[46–48] and the better economy and expenditure funds for scientific research from developed countries/regions significantly provided support for the implementation of ophthalmologic RCTs.[49] Thirdly, with the speedy economic growth of developing countries such as China and India,[50–52] the capacity of producing ophthalmologic high-quality clinical evidence was also increasing in developing countries. Moreover, active and extensive collaboration can be observed among these countries/regions, which may contribute to better research quality of RCTs. Institutions such as Moorfields Eye Hospital, Johns Hopkins University, and the University of Melbourne contributed to more ophthalmologic RCTs, showing the outstanding capabilities of these institutions and the necessity of cooperation with these institutions for other institutions to produce ophthalmologic high-quality clinical evidence. *Ophthalmology* published the most RCTs and received the most co-cations, for which it could be designed as the most important journal in the field of worldwide ophthalmologic RCTs, and this result was in line with previous results.[5] All of the top 10 journals and co-cited journals, except for *Graefes Archive for Clinical and Experimental Ophthalmology* which was from Germany and received a lower IF, and a lower quartile in the category compared with other journals, were from the United States or the United Kingdom. To some extent, these results also suggest that journals from the United States and the United Kingdom were the main international platform for global ophthalmologic RCTs. In terms of authors, the majority of the publication or co-cited authors were from the

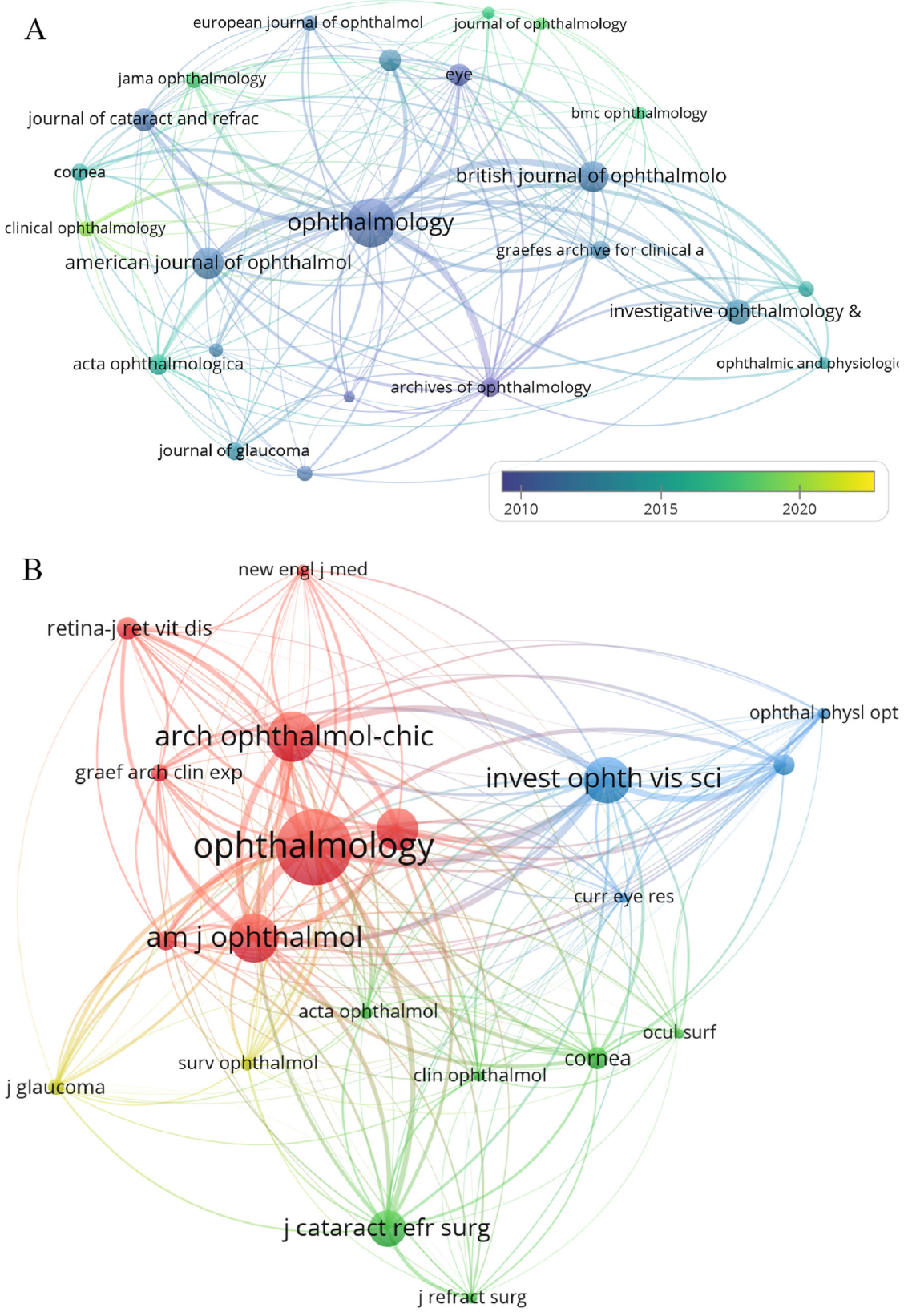


**Fig. 3.** The time network map of journals (A, T = 20) and network map of co-cited journals (B, T = 350) for global ophthalmologic RCTs.
(A) The size of the nodes stands for the numbers, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. The color of the nodes changes with their active time, which leans toward blue for the earlier time around 2010, and toward yellow for the later time around 2020. (B) The size of the nodes stands for the co-occurrence frequencies, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. Different colors of the nodes and links mean different clusters. RCTs = randomized controlled trials.

**Table 3**
The top 10 authors and co-cited authors of global ophthalmologic RCTs.

| Rank | Author | Number | Country/ Region | Research Field | Co-cited author | Co-citation | Research Field | County/ Region |
|---|---|---|---|---|---|---|---|---|
| 1 | Jeffrey S. Heier[!] | 17 | United States | Retinopathy | Jost B. Jonas* | 165 | Glaucoma | Germany |
| 2 | Catey Bunce[@] | 17 | United Kingdom | Retinopathy and Glaucoma | Ronald Klein[!!] | 159 | Retinopathy | United States |
| 3 | David M. Brown[#] | 16 | United States | Retinopathy | Jeffrey J. Walline[@@] | 118 | Myopia prevention and control | United States |
| 4 | Usha Chakravarthy[$] | 16 | United Kingdom | Retinopathy | Smith, EL | 115 | Myopia prevention and control | United States |
| 5 | Dennis S. C. Lam | 15 | China | Retinopathy, Surgery, and Glaucoma | Leske, MC | 108 | Glaucoma and cataracts | United States |
| 6 | Jennifer Rose-Nussbaumer[%] | 13 | United States | Corneal disease and cataracts | Philip J. Rosenfeld | 94 | Age-related macular degeneration | United States |
| 7 | Aung Tin | 13 | Singapore | Glaucoma | David M. Brown | 90 | Retinopathy | United States |
| 8 | David S. Boyer | 12 | United States | Retinopathy | David S. Friedman | 90 | Glaucoma | United States |
| 9 | Namrata Sharma[^] | 11 | India | Corneal diseases, cataracts, and refractive surgeries | Neil M Bressler[##] | 90 | Retinopathy | United States |
| 10 | Rasik Vajpayee[&] | 11 | Australia | Corneal diseases, cataracts, and refractive surgeries | Anastasios G P Konstas | 88 | Retinopathy, and Glaucoma | Greece |

The following websites and databases were searched to identify the authors' country/region and the research areas: the official website of the author's institution, ResearchGate, PubMed, and U.S. News & World Report. Congdon, Nathan, who was affiliated with Queen's University Belfast and the Eye Center of Sun Yat-sen University, also contributed to 11 RCTs, and focused on the design and evaluation of high-quality, low-cost models of eye care delivery in areas of limited resources, particularly rural Asia, and frequently involves NGOs working together with academic institutions in Asia and the west. Findl, Oliver, who was affiliated with Moorfields Eye Hospital, also contributed to 11 RCTs, and focused on Glaucoma, cataract, and myopia prevention and control.

[!]The author's research fields included exudative and non-exudative MD, DME, VOD, vitreoretinal surgical techniques and instrumentation, and diagnostic imaging of the retina.

[@]The author's research fields included DR, corneal transplantation, glaucoma, and RCTs.

[#]The author's research fields included AMD, DR and VOD.

[$]The author's research fields included DR and VOD.

[%]The author's research fields included lamellar keratoplasties such as UT-DSAEK, DMEK, and DALK (Boston Keratoprosthesis and cataract surgery).

[^]The author's research fields included all aspects of corneal diseases (including Keratoconus, Fuchs dystrophy, Chemical Injuries, Corneal Ulcers and Steven Johnson Syndrome) cataract and refractive surgeries as well as laboratory-based stem cell-based therapies. The author mainly focused on phacoemulsification surgeries and foldable intraocular lens implantation and excimer laser refractive procedures such as LASIK, PRK, SMILE and lamellar surgeries (DALK, DSAEK, anterior segment reconstructive procedures, ocular surface surgeries and keratoprosthesis).

[&]The author's research fields included corneal diseases and cataract, mainly focused on laser cataract surgery, complex cataract surgery, corneal surgery, corneal transplantations, keratoconus, Fuchs' dystrophy, pterygium (Surfer's Eye) and laser eye surgery for vision correction.

*The author's research fields included the intravitreal application of medication as treatment of intraocular edematousn proliferative and neovascular diseases, the intravitreal cell-based (drug) therapy, the homologous intravitreal bone-marrow transplantation, the retinal microglial cell system, the contact lens associated ophthalmodynamometry for measurement of the retinal arterial and venous blood pressure and cerebrospinal fluid pressure, the morphologic diagnosis of optic nerve diseases including the glaucomas, the association between the cerebrospinal fluid pressure and ocular disorders, the process of emmetropization and myopization, population-based studies.

[!!]The author's research fields included ocular complications of diabetes such as diabetic retinopathy and age-related eye diseases.

[@@]The author's research fields included myopia prevention and control, mainly the efficacy and safety of atropine and soft multifocal contact lenses.

[##]The author, who also published 11 RCTs, mainly focused on diabetic retinopathy and macular degeneration. NGO = Non-Governmental Organization. MD = macular degeneration. DME = diabetic macular edema. DR = diabetic retinopathy. VOD = venous occlusive disease. RCTs = randomized controlled trials. AMD = age-related macular degeneration. UT-DSAEK = Ultrathin-Descemet Stripping Automated Endothelial Keratoplasty. DMEK = Descemet Membrane Endothelial Keratoplasty. DALK = Deep Anterior Lamellar Keratoplasty. LASIK = Laser in situ keratomileusis. PRK = Photorefractive Keratectomy. SMILE = Small incision Lenticule Extraction. DSAEK = Descendant's Stripping Automated Endothelial Keratoplasty.

United States or the United Kingdom, which also partly suggested the dominant position of the United States and the United Kingdom in the area of global RCTs. The research highlights of the publication or co-cited authors were mainly retinopathy, glaucoma, corneal diseases, cataract, myopia prevention, etc., which might be considered the research basement of worldwide ophthalmologic RCTs. As for the keywords, worldwide ophthalmologic RCTs mainly focused on glaucoma, phacoemulsification, retinopathy, DED, photodynamic therapy, MGD, and anti-vascular endothelial growth factor (VEGF) therapy (ranibizumab and bevacizumab).

### *4.2. Knowledge foundations of global ophthalmologic RCTs*

According to the definition of co-cited articles, a better understanding of the intellectual foundations of global ophthalmologic RCTs could be confirmed by analysis of the top 10 co-cited papers.[53] The first, seventh, and tenth papers focused on the age-related macular degeneration (AMD),[13,19,22] with the first one exploring the efficacy and safety of ranibizumab compared with sham injection,[13] the seventh one comparing the efficacy and safety of ranibizumab with verteporfin photodynamic therapy,[19] and the tenth one comparing the efficacy and safety of verteporfin photodynamic therapy versus placebo.[22] The research highlights of the second, third, and fourth RCTs were open-angle glaucoma,[14–16] among them, the second RCT explored the efficacy and safety of topical ocular hypotensive medication,[14] and the third RCT compared the efficacy and safety of argon laser trabeculoplasty with trabeculectomy,[15] and the fourth RCT compared the efficacy and safety of laser trabeculoplasty plus topical betaxolol hydrochloride with no initial treatment.[16] The fifth paper focused on the comparison of the efficacy and reliability of the Ocular Surface Disease Index (OSDI) questionnaire for dry eye patients.[17] Diabetic macular edema (DME) was the topic of the sixth and ninth papers,[18,21] the former researched the efficacy and reliability of immediate focal argon laser photocoagulation versus deferral of photocoagulation,[18] and the latter explored the efficacy

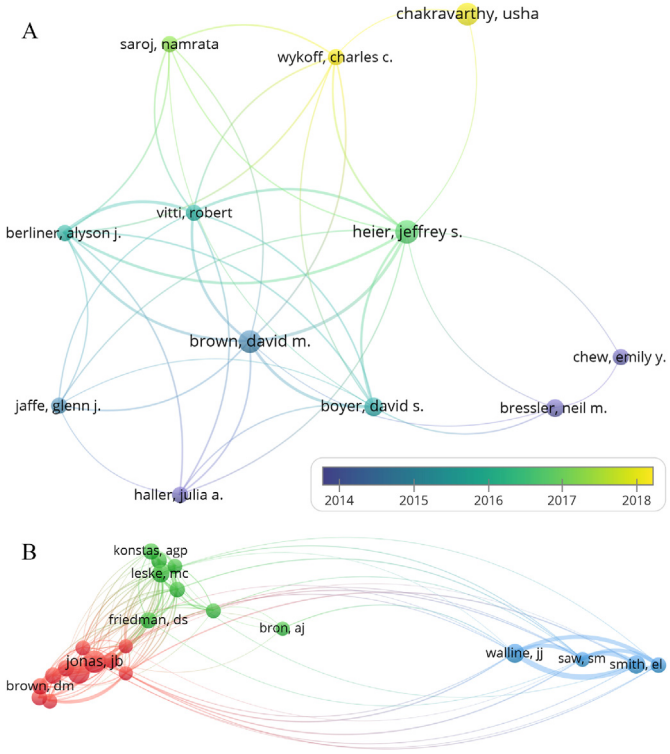


**Fig. 4.** The time network map of authors (A, T = 10) and network map of co-cited authors (B, T = 70) for global ophthalmologic RCTs.
(A) The size of the nodes stands for the numbers, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. The color of the nodes changes with their active time, which leans toward blue for the earlier time around 2010, and toward yellow for the later time around 2018. (B) The size of the nodes stands for the co-occurrence frequencies, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. Different colors of the nodes and links mean different clusters. RCTs = randomized controlled trials.

**Table 4**
The top 10 keywords with the most occurrences and keywords with the strongest burstness of global ophthalmologic RCTs.

| Rank | Keyword with the most occurrences | Occurrence | Keywords with the strongest burstness | Burst strength |
|---|---|---|---|---|
| 1 | glaucoma | 121 | management | 11.45 |
| 2 | open-angle glaucoma | 110 | acetonide | 9.4 |
| 3 | ranibizumab | 109 | injection | 8.35 |
| 4 | intraocular-pressure | 102 | dry eye disease | 8.16 |
| 5 | surgery | 98 | ocular hypertension | 7.56 |
| 6 | children | 83 | photodynamic therapy | 6.99 |
| 7 | cataract-surgery | 80 | age-related macular degeneration | 6.64 |
| 8 | bevacizumab | 75 | open angle glaucoma | 6.55 |
| 9 | phacoemulsification | 69 | triamcinolone acetonide | 6.23 |
| 10 | retinopathy | 66 | meibomian gland dysfunction | 5.46 |

Keywords with no research interest, such as eye, randomized controlled trials, fellow up, etc., were excluded from the ranking of keywords with the strongest burstness and not further researched. Keywords with no research interest were detailed in Supplementary Figure 3.

and reliability of following different treatments: 0.5 mg ranibizumab + prompt laser, Sham injection + prompt laser, 0.5 mg ranibizumab + deferred laser, and 4 mg triamcinolone + prompt laser.[21] The eighth reference analyzed the efficacy and reliability of the Lens Opacities

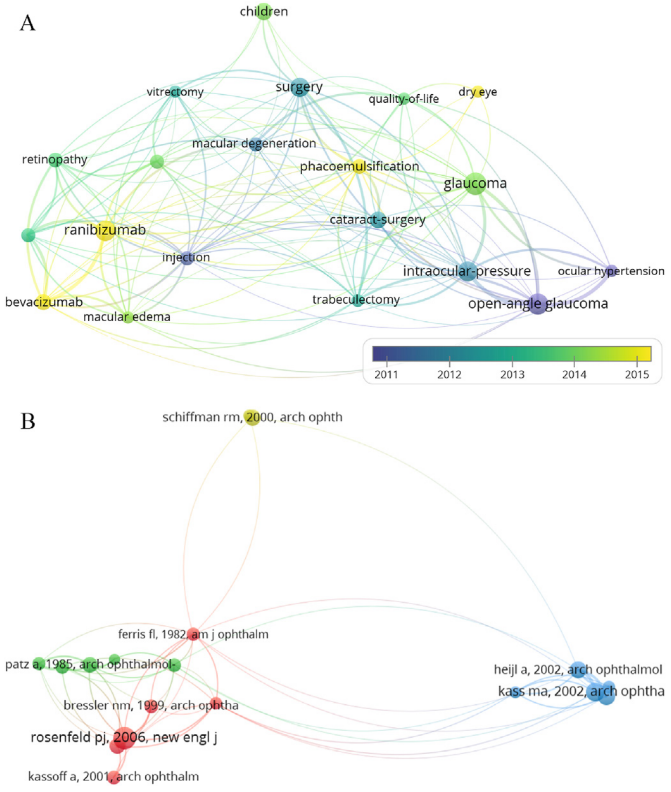


**Fig. 5.** The time network map of keywords with the most occurrences (A, T = 50) and network map of co-citation references (B, T = 7) for global ophthalmologic RCTs.
(A) The size of the nodes stands for the numbers, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. The color of the nodes changes with their active time, which leans toward blue for the earlier time around 2010, and toward yellow for the later time around 2018. (B) The size of the nodes stands for the co-occurrence frequencies, the links among these nodes mean co-occurrence connections, and the sizes of which mean co-occurrence frequencies. Different colors of the nodes and links mean different clusters. Keywords with no research interest, such as eye, randomized controlled trials, fellow up, etc., were excluded from the ranking of keywords with the strongest burstness and not further researched. Keywords with no research interest were detailed in Supplementary Figure 3.. RCTs = randomized controlled trials.

Classification System III (LOCS III) for cataract patients.[20] Possible explanations for these findings are as follows. First, diseases such as cataracts, glaucoma, AMD, and diabetic retinopathy were the leading global causes of blindness or moderate and severe vision impairment (MSVI),[54–57] the worldwide enormous number of patients and the heavy disease burden primarily and strongly required high-quality evidence, especially evidence from RCTs, to guide clinical practice.[48,58] In addition, the rise of innovative treatments particularly targeted therapy like anti-VEGF therapy (ranibizumab) which has revolutionized the treatment of vasoproliferative ophthalmologic disease, altered the prognosis of patients, and been one of the greatest achievements in ophthalmology,[59,60] also highlighted the requirements for high-quality evidence on novel therapies. Taken together, the top 10 co-cited references 13–22 were mainly related to diseases like retinopathy, glaucoma, DED, and cataracts, and therapies such as anti-VEGF therapy (ranibizumab), topical ocular hypotensive medication, laser trabeculoplasty, focal argon laser photocoagulation, and verteporfin photodynamic therapy (Table 5), which could be considered as the knowledge foundations of global ophthalmologic RCTs.

**Table 5**
The top 10 co-cited references of global ophthalmologic RCTs.

| Rank | Author | Year | Journal | Count | PICOS structure | | | | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | P | I | C | O | S | |
| 1[!] | Rosenfeld, P. J. | 2006 | N Engl J Med | 74 | AMD patients | Ranibizumab injection | Sham injection | Patients losing fewer than 15 letters from baseline visual acuity | RCT | Intravitreal administration of ranibizumab for 2 years improved age-related macular degeneration patients' visual acuity without vision loss and serious adverse events |
| 2[@] | Kass, Michael A. | 2002 | Archives of Ophthalmology | 58 | Patients with elevated intraocular pressure | Commercially available topical ocular hypotensive medication | Observation | The development of reproducible visual field abnormality or reproducible optic disc deterioration attributed to open-angle glaucoma | RCT (the Ocular Hypertension Treatment trial) | Topical ocular hypotensive medication was effective and safe in delaying or preventing the onset of open-angle glaucoma in patients with elevated intraocular pressure. |
| 3 | Van Veldhuisen PC | 2000 | Am J Ophthalmol | 52 | Patients with open-angle glaucoma | Argon laser trabeculoplasty | Trabeculectomy | The relationship between intraocular pressure and progression of visual field damage | RCT (the AGIS trial) | Lower intraocular pressure reduced the progression of visual field defect |
| 4 | Heijl, A. | 2002 | Arch Ophthalmol | 50 | Patients with open-angle glaucoma | Laser trabeculoplasty plus topical betaxolol hydrochloride | Without initial treatment | Glaucoma progression defined by specific visual field and optic disc outcomes. | RCT (the Early Manifest Glaucoma trial) | Initial treatment can significantly delay the progression of glaucoma and provide considerable benefit |
| 5 | Schiffman, R. M. | 2000 | Arch Ophthalmol | 48 | Dry eye patients and normal controls | Ocular Surface Disease Index (OSDI) questionnaire | N/A | The efficacy and reliability of OSDI questionnaire | Cohort study | The efficacy and reliability to measure the severity of dry eye disease of OSDI questionnaire are excellent |
| 6 | Patz A | 1985 | Archives of Ophthalmology | 46 | Patients with DR and ME | Immediate focal argon laser photocoagulation | Deferral of photocoagulation | The efficacy and safety of focal argon laser photocoagulation | RCT (the ETDRS trial) | The efficacy and safety of focal argon laser photocoagulation are excellent, which suggest that all patients with clinically significant diabetic macular edema should be considered for focal photocoagulation. |
| 7[@] | Brown, D. M. | 2006 | N Engl J Med | 45 | Patients with neovascular AMD | Ranibizumab plus sham verteporfin photodynamic therapy | Sham intravitreal injections plus active verteporfin photodynamic therapy | Patients losing fewer than 15 letters from baseline visual acuity | RCT (the ANCHOR trial) | Intravitreal treatment of ranibizumab was superior to verteporfin when treating neovascular age-related macular degeneration without serious ocular adverse events |
| 8 | Chylack LT | 1993 | Arch Ophthalmol | 39 | Patients with cataracts | N/A | N/A | The efficacy and reliability of the Lens Opacities Classification System III (LOCS III) | Cross-sectional study (LOCS III) | The LOCS III is an improved LOCS system for grading slit-lampand retroillumination images of age-related cataract. |
| 9[#] | Elman MJ | 2010 | Ophthalmology | 38 | Patients with DME | 0.5 mg ranibizumab + prompt laser | Sham injection + prompt laser, 0.5 mg ranibizumab + deferred laser, 4 mg triamcinolone + prompt laser | Best-corrected visual acuity and safety at 1 year | RCT | Intravitreal ranibizumab with prompt or deferred laser is more effective than prompt laser alone for DME involving the central macula. |
| 10 | Bressler NM | 1999 | Arch Ophthalmol | 37 | Patients with CNV caused by AMD | Verteporfin photodynamic therapy | Placebo photodynamic therapy | The efficacy and safety of verteporfin photodynamic therapy in 12 months | RCT (the TAP trial) | Verteporfin photodynamic therapy can safely reduce the risk of vision loss of patients with CNV from AMD, which should be recommend as the primary treatment. |

PICOS structure: A structure for standardized description of clinical studies. P = Patients, I = Intervention, C = Comparison, O = Outcomes, S = Study type. BCVA = best-corrected visual acuity. DME = diabetic macular edema. OCT = optical coherence tomography. FA = fluorescein angiography. AMD = age-related macular degeneration. CNV = choroidal neovascularization. DR = diabetic retinopathy. ME = macular edema. RCTs = randomized controlled trials. N/A = Not applicable.

[!]This study was also the one with the strongest burstness (burst strength = 12.62).

[@]This study was also the one with the longest burstness time (5 years).

[#]This study was also the one with the one with the fourth strongest burstness (burst strength = 9).

### 4.3. Emerging information of global ophthalmologic RCTs

Interpretation of articles with citation burstness can better represent research hotspots and development trends.[53] Thus, we specifically focused on the top 10 references with the strongest burstness,[13,19,21,23–29] the top 22 references with the longest burstness time (at least 5 years)[13,14,19,21,23,24,27,28,30–43] and the top 9 references with the burstness continues to 2022[23,24,27–29,32,33,44,45] (Supplementary Table 1). As for the top 10 references with the strongest burstness,[13,19,21,23–29] the first, fourth, fifth, and sixth references specifically focused on retinopathy such as AMD and DME and anti-VEGF therapy (ranibizumab).[13,19,21,25] The second, third, eighth, and ninth references (The TFOS DEWS II report) elaborated on DED in different fields like definition, classification, epidemiology characteristics, etc.[23,24,27,28] The authors of the seventh paper detailed the new ophthalmologic diagnostic tools such as optical coherence tomography (OCT).[26] The tenth article investigated the efficacy and safety of atropine with different concentrations in myopic children.[29] In the top 22 references with the longest burstness time (at least 5 years),[13,14,19,21,23,24,27,28,30–43] 12 references were related to retinopathy such as AMD, DME, choroidal neovascularization (CNV).[13,19,21,30,31,34,36,37,39,40,42,43] Among them, the one with a 6-year burstness duration explored the efficacy and safety of verteporfin photodynamic therapy compared with a placebo.[30] Nine references analyzed the efficacy and safety of anti-VEGF (ranibizumab, pegaptanib, or bevacizumab) monotherapy or plus other treatments compared with sham injection, prompt laser, triamcinolone, or verteporfin photodynamic therapy.[13,19,21,31,36,37,39,42,43] Better efficacy and safety were shown in the anti-VEGF groups. Interestingly, ranibizumab and bevacizumab were compared and no significant differences existed between these two groups.[43] Intravitreal triamcinolone acetonide was explored in the thirteenth and nineteenth literature.[34,40] Among the remaining papers, four articles elaborated on DED (The TFOS DEWS II report),[23,24,27,28] and four articles paid attention to myopic in incidence, efficacy, and safety of various methods for myopia control such as multifocal contact lens and atropine.[32,33,35,38] The efficacy and safety of topical ocular hypotensive medication such as latanoprost were highlighted in the remaining two articles.[14,41] Among the top 9 references, the burstness continues to 2022, five articles elaborated on DED (The TFOS DEWS II report),[23,24,27,28,44] and the remaining four references mainly analyzed the incidence and control strategies (especially the use of atropine) for myopia.[29,32,33,45] In light of those findings, several explanations can be offered. First, consistent with the above explanations, the heavy burden caused by the high incidence of glaucoma, AMD, DME, and the rise of innovative treatments like anti-VEGF therapy both requested higher quality evidence to guide ophthalmologic clinical practice.[54–60], [48] Second, in the field of retinopathy, a treatment trend from the laser, triamcinolone, or verteporfin photodynamic therapy to anti-VEGF therapy could be seen in these references with research burstness. As the revolution in the treatment of retinal diseases,[59,60] since ranibizumab received FDA approval for the treatment of AMD,[13] anti-VEGF therapy not only revolutionized the treatment of AMD, CNV, and DME but also holds potential for over 50 ocular diseases, including neovascular glaucoma and retinopathy of prematurity.[59,60] Nowadays, the highlights of clinical practice and research for anti-VEGF therapy are beyond the efficacy, and safety but the selection of the optimal treatment and the balance for health economics between the risks and benefits, for example, the prefer for ranibizumab or bevacizumab in neovascular AMD,[43] and the choices between aflibercept monotherapy or bevacizumab first in DME.[61] Third, with the high and increasing incidence, and the heavy disease burden of DED, MGD, and myopia,[27,62–66] especially the rapidly increasing of DED, MGD, and myopia related to more reliance on electronic screens and DED or MGD related to more reliance on the mask during the COVID-19 pandemic,[67–71] and with the novel therapies for myopia, DED, and MGD such as orthokeratology, atropine and botanical formula,[29,72] the requirement for high-quality evidence of interventions for DED, MGD and myopia has increased rapidly in recent years, which could explain in part the recent and future hotspots of DED, MGD and myopia in the field of worldwide ophthalmologic RCTs. Taken together, over the past two decades, anti-VEGF therapy for retinopathy such as AMD and DME, DED, the use of new ophthalmologic diagnostic tools, and myopic were the hottest research highlights. Different treatments like anti-VEGF therapy, prompt laser, triamcinolone, and verteporfin photodynamic therapy for retinopathy such as AMD, DME, and CNV, DED, myopic, and open-angle glaucoma were the research hotspots with the longest duration. The research focus on DED and the prevention and control of myopia were still popular in 2022, which could point out the research directions of high-quality clinical evidence in ophthalmology in the future.

### 4.4. Strengths and limitations

First of all, the present study comprehensively visualized the research field of worldwide ophthalmologic RCTs in the 21st century, which was more comprehensive and detailed compared to previous studies,[5] and provided a research foundation for the further ophthalmologic high quality clinical evidence. Secondly, similar to the systematic review and meta-analysis,[73] we rigorously screened and included the RCTs, which largely ensured the reliability of our results and minimized the risk of bias. Finally, three bibliometric tools were used for the analysis, making our results more comprehensive and objective when comparing to the traditional expert reviews.[74]

Nevertheless, a few limitations existed in this study. Firstly, only data from WoSCC database was analyzed, resulting in the possibility of the loss for some important studies, which might thus reduce the capability of study promoting. However, this was also limited by the current research method, because WoSCC database is the most widely used database currently for bibliometric analysis, and it is extremely difficult to integrate and analyze data from different databases at the same time by current bibliometric software.[75] Secondly, only bibliometric characteristics of global ophthalmologic RCTs were analyzed, further research on quality of global ophthalmologic RCTs would be required to analysis the ophthalmologic high-quality evidence from a standpoint of evidence-based medicine.

## 5. Conclusions

Overall, the number of global ophthalmologic RCTs in the 21st century was keeping growing, the United States contributed the most RCTs and earned the dominant region. Moorfields Eye Hospital published the most studies, Ophthalmology could be considered as the most important journal, and authors such as Jeffrey S. Heier and Catey Bunce played key roles. The knowledge foundations of global ophthalmologic RCTs were mainly diseases like retinopathy, glaucoma, DED, and cataracts, and therapies such as anti-VEGF therapy (ranibizumab), topical ocular hypotensive medication, laser trabeculoplasty, focal argon laser photocoagulation, and verteporfin photodynamic therapy. Anti-VEGF therapy for retinopathy such as AMD and DME, DED, the use of new ophthalmologic diagnostic tools, and myopic were the hottest research highlights. Anti-VEGF therapy, prompt laser, triamcinolone, and verteporfin photodynamic therapy for retinopathy such as AMD, DME, and CNV, DED, myopic, and open-angle glaucoma were the research hotspots with the longest duration. The possible future research hotspots might be DED and the prevention and control of myopia. However, there was an imbalance between the regions and institutions, more efforts are required to raise the quantity, quality, and global impact of high-quality clinical evidence in developing countries/regions.

## Study approval

Not Applicable. As a bibliometric analysis and a retrospective pooled analysis, this study did not require study approval.

## Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: Hao Wang, Wenfang Zhang; Data collection: Hao Wang, Qiang Ye; Analysis and interpretation of results: Hao Wang, Weihe Xu, Jing Wang; Drafting the manuscript: Hao Wang, Jing Wang, Jianhan Liu, Xintong Xu; All authors reviewed the results and approved the final version of the manuscript.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Abbreviations

| | |
|---|---|
| DED | dry eye disease |
| VEGF | vascular endothelial growth factor |
| AMD | age-related macular degeneration |
| CNV | choroidal neovascularization |
| DME | diabetic macular edema |

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aopr.2023.07.003.

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