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A bibliometric analysis and visualization of retinopathy of prematurity from 2001 to 2021

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Abstract. – OBJECTIVE: Retinopathy of prematurity (ROP) is an eye disease with the potential to cause blindness, primarily affecting premature infants with low birth weight. This study analyzed the etiology, primary location, and research advances in ROP.

MATERIALS AND METHODS: We used bibliometric techniques and searched the Web of Science Core Collection for "retinopathy of prematurity." We found 4,018 original articles and reviews with 69,819 references. We analyzed the data using HistCite (12.03.17), VOSviewer (1.6.16), CiteSpace (6.1. R5), and the Bibliometrix Package (4.1.0).

RESULTS: The amount of literature in this area has increased between 2001-2021. An analysis of references and journal co-citations highlights this field's most influential articles and related topics. Hellström, from the University of Gothenburg (Sweden), is the most prolific researcher; Harvard University is the most prolific research institution, and the USA is the most productive country. "Threshold ROP" and "cryotherapy" are the keywords with the highest burst strength. The future research hotspots are artificial intelligence, zone II, ROP development, ranibizumab, and type 1 retinopathy.

CONCLUSIONS: This article offers a comprehensive review of the present status of ROP research, along with insights into emerging concepts and potential international collaborations in this field.

Key Words:
Retinopathy of prematurity, Bibliometric analysis, Developing trends, Hotspots, Research topics, CiteSpace, VOSviewer.

Abbreviations
AI: Artificial intelligence; EPIs: Extremely premature infants; ICROP: The International Classification of Retinopathy of Prematurity; IGF-I: Insulin-like growth factor I; OCT: Optical coherence tomography; ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor; WoSCC: Web of Science Core Collection.

Introduction

Retinopathy of prematurity (ROP) is a vascular proliferative ocular condition that impacts infants born prematurely, particularly those with low birth weight, and has the potential to lead to retinal detachment and blindness[1,2]. ROP accounts for 3-11% of the cases of childhood blindness in developed Europe and 0-42% in middle-income Europe[3]. Rapid progress in perinatal medicine in recent years has significantly increased the number of preterm infants, especially extremely premature infants (EPIs). The survival rate has also increased substantially[4,5]. Simultaneously, the number of ROP cases has continued to rise. Approximately 50,000 new ROP-blind children are diagnosed annually worldwide, and the number of children with visual impairment is innumerable.

The pathogenesis of ROP can be attributed to the halted growth of blood vessels and the abnormal proliferation of ocular vasculature. ROP typically occurs in a two-stage process[6]. In phase I, an avascular zone forms in the retina due to the disruption of normal vascularization caused by hyperoxia and post-preterm fluctuations in oxygen levels. During phase II, hypoxia in the nonvascularized retina triggers an elevation in vascular endothelial growth factor (VEGF) levels, leading to the stimulation of abnormal vascular proliferation. Consequently, these vessels become abnormally dilated and tortuous, leading to various retinal complications, including retinal detachment[7].

In the past two decades, researchers have endeavored to understand the pathogenesis of ROP and develop effective treatments and preventive

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strategies. Bibliometrics is a broad field of study that utilizes quantitative methods to measure the impact of scholarly works such as books, journals, and other forms of media[8]. It combines mathematical and statistical methods to analyze and interpret data, which can then be used to assess the importance of a particular publication. Bibliometrics can provide insights into the overall impact of a publication and research trends[9]. In particular, visualization technology applications can graphically present the research development process, status, focus, and trends[10]. Based on the Web of Science database, we performed a bibliometric analysis and visualized the cases of ROP reported between 2001 and 2021. We analyzed the relevant publications to reveal the quantity, countries/regions, institutes, authors, journals, and keywords related to ROP research and visualize these. We highlighted trends over time, research categories, and co-cited references to provide valuable insights into the current progress and future directions in ROP research.

This study differs from traditional reviews that mainly focus on a single aspect of ROP and use subjective and qualitative analysis methods. Creating a global overview of ROP from these studies is impossible.

Materials and Methods

Searching for and Screening the Literature

We used the Thomson Scientific SCI-expanded Web of Science Core Collection (WoSCC) bibliographic database in this bibliometric study. The database is frequently updated, so we limited the timeframe to ensure consistency, retrieving the data on April 20, 2022. The search strategy employed was as follows: topic = (retinopathy of prematurity) and time span = 2001-2021. We only included articles and reviews written in English. Two researchers (Changgen Liu and Yanhua Wang) independently conducted the initial search for data and reconciled any discrepancies through consensus, with the assistance of a third researcher (Jingke Cao). Finally, we reviewed 4,018 publications. The bibliometric research procedure is illustrated in Figure 1.

Data Visualization and Analysis

We completed the bibliometric analysis using HistCite (12.03.17), VOSviewer (1.6.16), CiteSpace (6.1. R4 Advanced), and the Bibliometrix 4.1.0 Package powered by R.

Garfield[11] created HistCite – a potent computer program that locates relevant scholarly papers and then records and tracks the progress of a particular area of research. Using the data, we determined the overall number of publications, Global Citations Score (GCS), Local Citations Score (LCS), and the countries with the most publications, top organizations, leading journals, and authors for each year of publication.

We employed VOSviewer, a software developed by Van Eck and Waltman[12], to visualize the intricate co-citation networks that depict collaboration and temporal correlations among countries, organizations, and individuals. In the visualization, the size of the nodes corresponds to the number of publications, the colors represent distinct clusters or periods, and the saturation of the line indicates its thickness.

CiteSpace enables users to visually analyze the knowledge domain and its patterns using clustering, dual-map citation overlays, timeline views, references, and keyword citation outbursts[13,14]. Researchers commonly use keywords and citation analysis to identify the most recent progress in their field. Cluster analysis enables researchers to categorize references and keywords, thereby revealing relevant research topics related to ROP. When the Q value is higher than 0.3, the clusters become significantly more visible, as indicated by the Modularity Q and the Mean Silhouette. Clustering results are considered reliable when the mean silhouette is above 0.5.

The Bibliometrix Package (Naples, Italy) programmed in R is an efficient tool for bibliometric analysis[15]. In this study, we used thematic evolution analysis to classify the development of ROP research into different time frames.

Results

Overall Distribution

We identified 4,018 publications on ROP in the WoSCC, including 3,530 original articles and 488 reviews. The findings from the curve fitting analysis revealed a consistent upward trend in the annual number of publications on ROP since 2001 (R^2 = 0.9757) (Figure 2a). The cumulative citations for these articles totaled 105,024, averaging 26.4 citations per article. The quality of the GCS and LCS scores of articles released in the early stages was not of a high standard because the research field was not well developed. However, the GCS score increased steadily from 2005-2008.

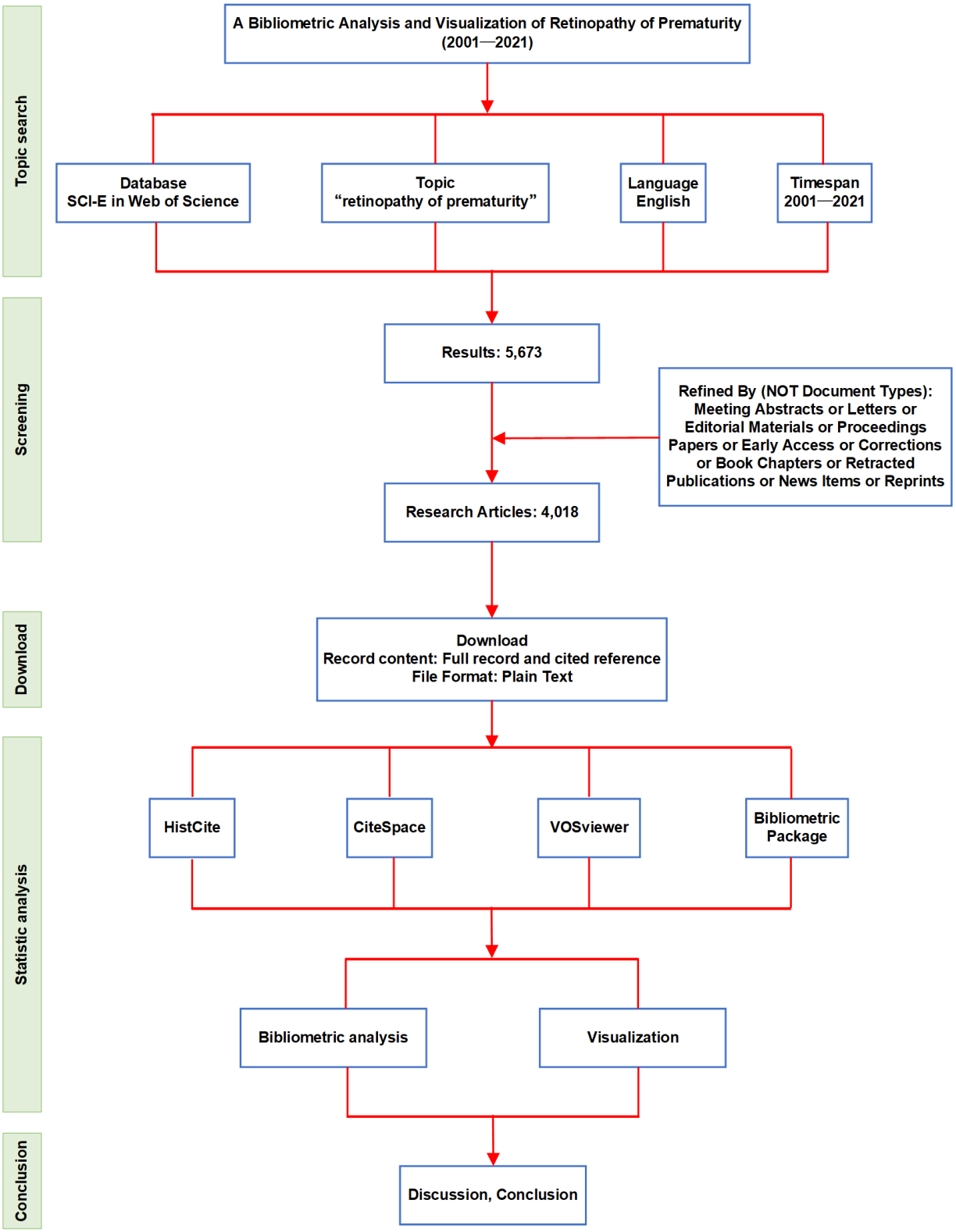


Figure 1. Flow chart of bibliometric analysis.

The Total Global Citations Score (TGCS) has stabilized since 2009, suggesting that ROP studies have matured (Figure 2b).

Leading Countries/Regions

Between 2001 and 2021, research articles on ROP were published by 97 countries/regions. The global productivity of articles is depicted in Figure 3a. Approximately 93.2% of worldwide articles were generated by the top 10 countries, as shown in Table I. The USA had the highest output, publishing 1,511 (38%) articles related to ROP, followed by China (n = 390; 9.8%) and the UK (n = 306; 7.7%). This is illustrated in Figure 3b. The USA topped the list with the highest number of cited articles (51,236 citations), followed by

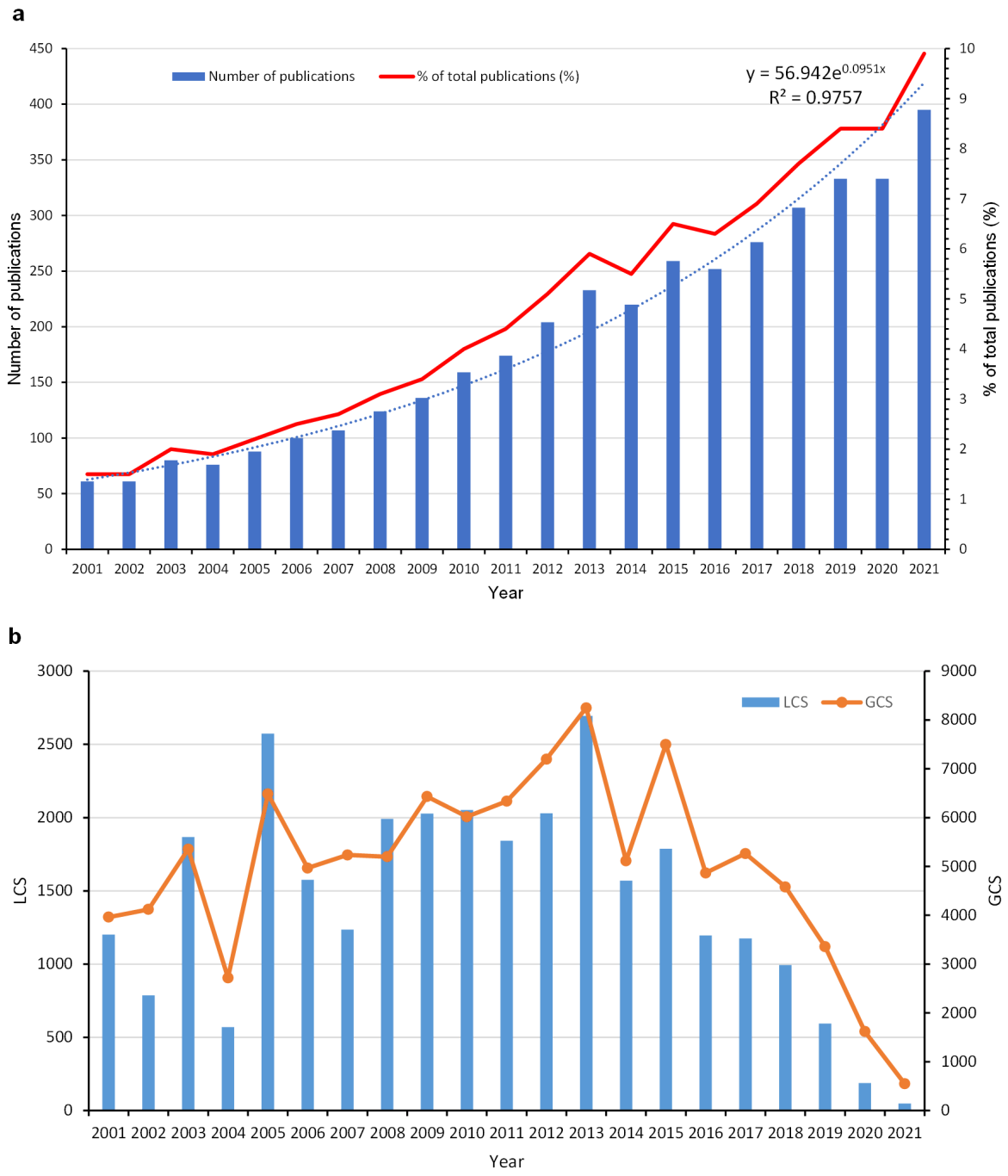


Figure 2. Overall distribution of publication outputs on ROP. **a**, Global annual output trends; (**b**), LCS, GCS.

Table I. The 10 most productive countries/regions in ROP research.

Rank	Country/Region	Number of publications (%)	Centrality	LCS	GCS	Average citation
1	USA	1,511 (38%)	0.11	14,097	51,236	33.91
2	China	390 (9.8%)	0.04	998	4,229	10.84
3	UK	306 (7.7%)	0.35	3,539	13,394	43.77
4	Canada	278 (7%)	0.15	1,650	9,971	35.86
5	India	250 (6.3%)	0.04	1,138	3,154	12.62
6	Turkey	227 (5.7%)	0	942	2,274	10.02
7	Australia	220 (5.5%)	0.15	1,304	8,476	38.53
8	Sweden	194 (4.9%)	0.04	2,982	8,628	44.47
9	Germany	174 (4.4%)	0.04	1,678	6,218	35.74
10	Japan	157 (3.9%)	0.04	998	3,256	20.74

Local Citations Score (LCS), Global Citations Score (GCS).

Table II. The 10 most productive institutions in ROP research.

Rank	Institution	Country	Number of publications (%)	Centrality	LCS	GCS	Average citation
1	Harvard University	USA	122 (3.1%)	0.09	2,832	7,739	63.43
2	University of Pennsylvania	USA	115 (2.9%)	0.12	1,461	4,819	41.9
3	University of Toronto	Canada	114 (2.9%)	0.12	468	4,270	37.46
4	Oregon Health and Science University	USA	94 (2.4%)	0.03	1,275	3,030	32.23
5	University of Gothenburg	Sweden	94 (2.4%)	0.1	1,940	4,195	44.63
6	Duke University	USA	90 (2.3%)	0.11	1,263	4,192	46.58
7	Children's Hospital of Philadelphia	USA	86 (2.2%)	0.12	2,388	4,496	52.28
8	University of Utah	USA	73 (1.8%)	0.14	857	2,598	35.59
9	Harvard Medical School	USA	72 (1.8%)	0.01	357	1,219	16.93
10	Stanford University	USA	72 (1.8%)	0.02	865	3,974	55.19

Local Citations Score (LCS), Global Citations Score (GCS).

the UK (13,394) and Canada (9,971). Sweden had the highest average number of citations per publication, with a mean of 44.47, followed by the UK and Australia, with averages of 43.77 and 38.53, respectively. The visualized network of international collaboration demonstrates a close cooperation between countries. The USA and Canada cooperated more closely, followed by Sweden, the UK, and Germany (Figure 3c). The overlay visualization network shows that the UK (2012), Australia (2013), India (2016), and China (2017) previously had the highest average publications per year (Figure 3d).

Active Institutions and Authors

A total of 14,785 authors from 4,078 institutions contributed to the publication of articles on ROP. The top 10 institutions with the highest research output in ROP are presented in Table II. Harvard University in the USA emerged as the leading institution with the most output (n = 122), followed by the University of Pennsylvania in the USA (n = 115), and the University of Toronto in Canada (n = 114). The highest Global Citations Score (GCS) was achieved by Harvard University in the USA (7,739 citations), followed by the University of Pennsylvania (4,819) and the Children's Hospital of Philadelphia (4,496). Collaboration between institutions was relatively strong and could be categorized into four clusters. The University of Pennsylvania-led cooperation groups exhibited the closest collaboration with other institutions (Figure 4a).

The three most productive authors were Hellström, from the University of Gothenburg (93 articles); Quinn, from the Children's Hospital of Philadelphia (84 articles); and Chiang, from the National Institutes of Health (81 articles) (Table III). Quinn was the most cited author (n = 7,338),

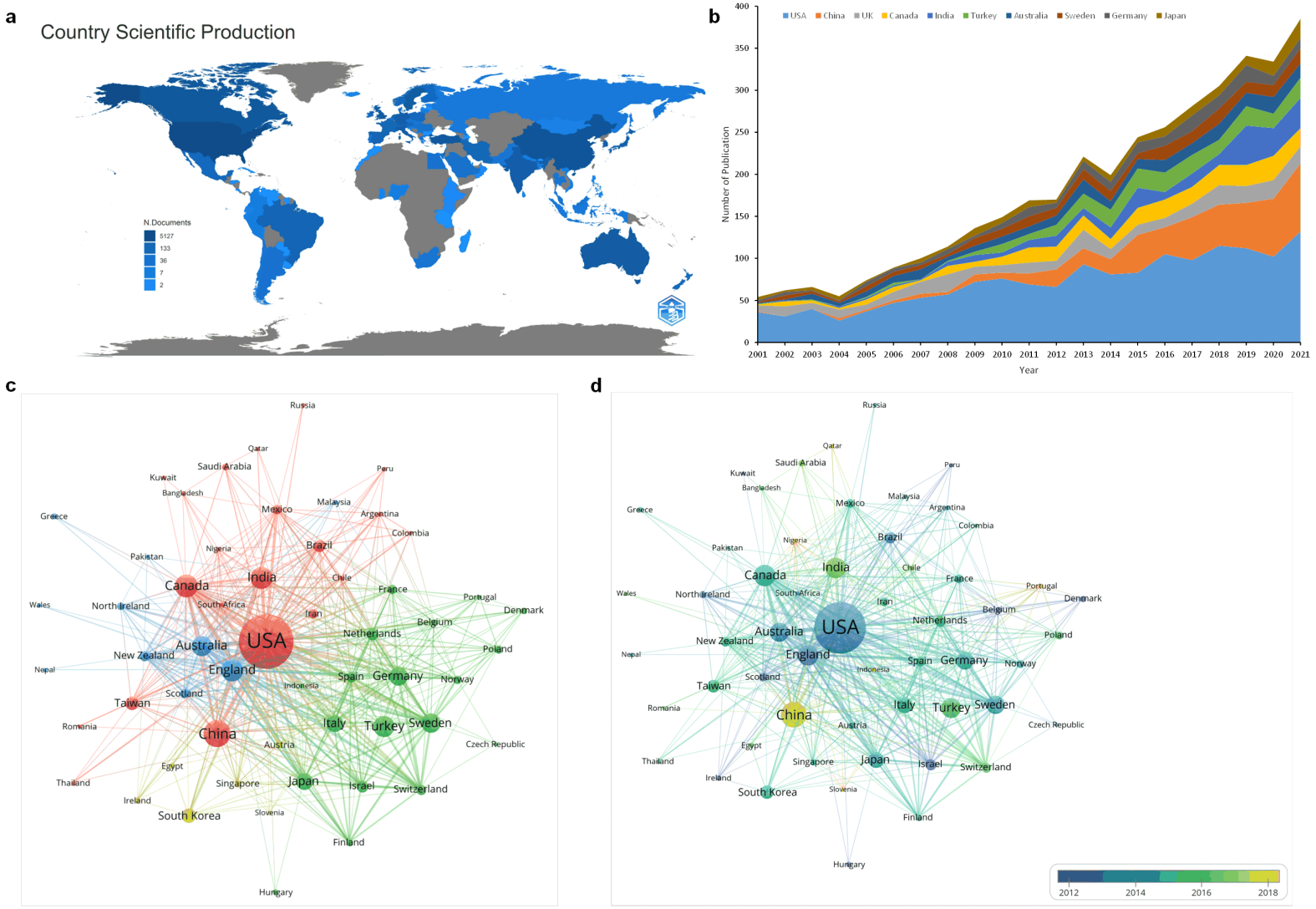


Figure 3. Leading countries/regions in ROP research. **a**, Geographical distribution of global output; (**b**), Annual output trend of the top 10 productive countries; (**c**), Visual cluster analysis of the cooperation between countries; (**d**), Timeline visualization of the cooperation between countries.

Table III. The 10 most productive institutions in ROP research.

Rank	Author	Country	Institution	Number of publications (%)	LCS	GCS	H-index
1	Hellström, A	Sweden	University of Gothenburg	93 (2.3%)	2,191	4,762	33
2	Quinn, GE	USA	Children's Hospital of Philadelphia	84 (2.1%)	4,554	7,338	35
3	Chiang, MF	USA	National Institutes of Health	81 (2.0%)	1,478	2,711	29
4	Chan, RVP	USA	University of Illinois at Chicago	55 (1.4%)	543	1,197	21
5	Ying, GS	USA	University of Pennsylvania	55 (1.4%)	611	950	17
6	Smith, LEH	USA	Boston Children's Hospital	54 (1.4%)	1,751	4,423	30
7	Shah, PS	Canada	University of Toronto	52 (1.3%)	156	1,660	23
8	Hartnett, ME	USA	University of Utah	50 (1.3%)	957	2,236	25
9	Wallace, DK	USA	Indiana University	48 (1.2%)	1,863	3,791	24
10	Holmstrom, G	Sweden	Uppsala University	44 (1.1%)	1,583	3,539	20

Local Citations Score (LCS), Global Citations Score (GCS).

followed by Hellström (n = 4,762) and Smith (n = 4,423). The level of collaboration among authors was relatively modest, mainly taking place within institutions (Figure 4b). Hellström, Quinn, and Smith, from the Boston Children's Hospital, were early researchers on ROP. They have worked in this field for more than 20 years (2001-2021) (Figure 4c).

Core Journals

All the ROP articles were published in 621 different journals. Around 25.5% of these articles were published in the most productive journals (Table IV). "Investigative Ophthalmology & Visual Science" was the most prolific journal, publishing 157 articles, followed by the "Journal of AAPOS" (n = 155) and the "British Journal of Ophthalmology" (n = 108). In total, we obtained 69,106 citation references from various journals. The top 10 most cited journals are provided in Table IV, among which "JAMA Ophthalmology" (formerly "Archives of Ophthalmology") was the leading journal (n = 2,488), followed by "Pediatrics" (n = 2,483) and "Ophthalmology" (n = 1,859). The dual-map overlay presents the five primary citation pathways (Figure 5). Most articles were published in molecular science, biology, immunology, medicine, clinical medicine, sports neurology, and ophthalmology journals. By contrast, the articles with the highest number of citations were published in journals focusing on molecular science, biology, genetics, health, nursing, and medicine. The sub-disciplines involved in ROP research were primarily molecular biology and immunology.

Research Categories

Research categories are an essential part of bibliometric analysis. We initially examined the scientific disciplines of the ROP-cited literature utilizing the Web of Science (WoS) (Field: WoS Categories). The ROP theme was present in 97 branches of international scientific inquiry, including ophthalmology, pediatrics, and obstetric gynecology. The top 20 are listed in Figure 6. We observed the highest concentrations in ophthalmology (1,796), pediatrics (1,220), obstetrics gynecology (370), medicine general internal sciences (264), biochemistry molecular biology (138), multidisciplinary sciences (136), medicine research experimental sciences (131), cell biology (99), pharmacology pharmacy (82), and surgery (64). In summary, ROP is a multidisciplinary field.

Co-Cited References

The majority of articles emphasized the clinical characteristics, treatment, and outcomes related to ROP. The top 10 most co-cited references included two reviews and eight original articles (Table V). The article with the highest number of citations was authored by Gole et al[16], who was a member of the International Classification of Retinopathy of Prematurity (ICROP). The author documented the collaborative efforts of international pediatric ophthalmologists and retinal specialists in creating a consensus document that modified certain aspects of the ICROP (with 682 co-citations). Subsequently, Good et al[17], who were members of the Early Treatment for Retinopathy of the Prematurity Cooperative Group, discovered that early treatment of high-risk pre-threshold ROP

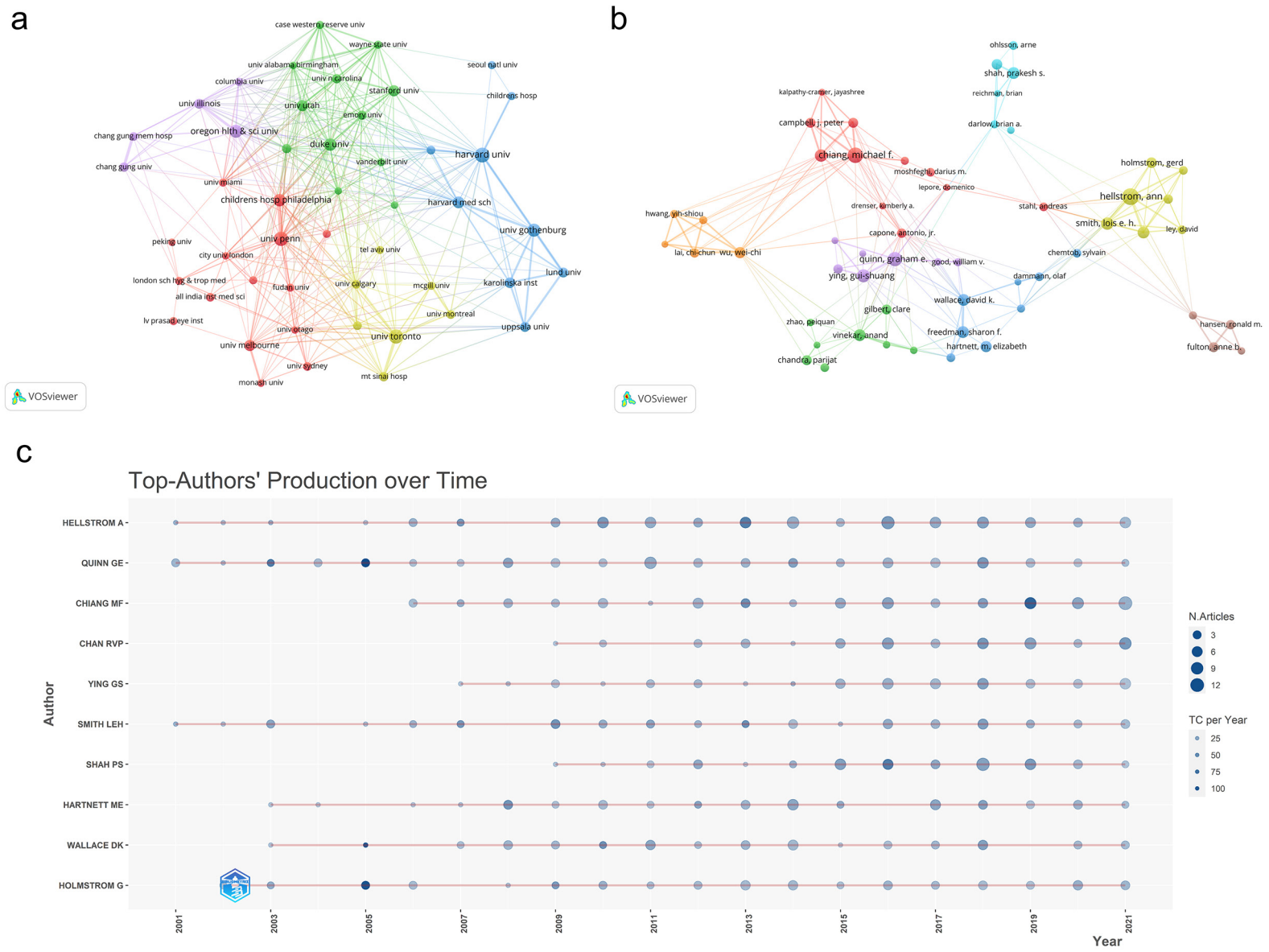


Figure 4. Visualization of active institutions and author analysis. **a**, Cluster analysis of the cooperation between institutions; (**b**), Timeline distribution of the top 10 most productive authors; (**c**), Cluster analysis of the cooperation between authors.

Table IV. The 10 core and most cited journals in ROP research.

Rank	Journal	Number of publications (%)	IF/JCR (2022)	Rank	Cited Journal	Freq	IF/JCR (2022)
1	Investigative Ophthalmology & Visual Science	157 (3.9%)	4.925/Q1	1	JAMA Ophthalmology (formerly Archives of Ophthalmology)	2,488	0
2	Journal of AAPOS	155 (3.9%)	1.325/Q4	2	Pediatrics	2,483	9.703/Q1
3	British Journal of Ophthalmology	108 (2.7%)	5.908/Q1	3	Ophthalmology	1,859	14.277/Q1
4	Pediatrics	104 (2.6%)	9.703/Q1	4	British Journal of Ophthalmology	1,748	5.908/Q1
5	Retina-the Journal of Retinal and Vitreous Diseases	88 (2.2%)	3.975/Q2	5	Investigative Ophthalmology & Visual Science	1,734	4.925/Q1
6	Indian Journal of Ophthalmology	86 (2.2%)	2.969/Q3	6	New England Journal of Medicine	1,628	176.079/Q1
7	Journal of Pediatric Ophthalmology & Strabismus	85 (2.1%)	1.330/Q4	7	American Journal of Ophthalmology	1,403	5.488/Q1
8	Journal of Perinatology	82 (2.1%)	3.225/Q2	8	Journal of AAPOS	1,373	1.325/Q4
9	JAMA Ophthalmology (formerly Archives of Ophthalmology)	77 (1.9%)	0	9	Journal of Pediatrics	1,271	6.314/Q1
10	Cochrane Database	77 (1.9%)	12.008/Q1	10	Archives of Disease of Systematic Reviews in Childhood-Fetal and Neonatal Edition	1,218	6.643/Q1

significantly reduced unfavorable outcomes to a clinically meaningful extent (with 636 co-citations); this was a substantial advance in the field and stimulated further developments.

Subsequently, we performed a reference burst analysis. Figure 7a displays the top 25 references with the highest citation bursts. Among these, nine references continued to have strong citation bursts till 2021. Among them, the work of Hellström[1] had the highest burst strength from 2017-2021 (38.22). The studies included a review of developments in the pathological mechanisms of ROP, factors influencing ROP development, preventive strategies, and treatment. Blencowe et al[5] also had a strong citation burst strength (36.84). They conducted a systematic review and meta-analysis to assess the risk of ROP and potential visual impairment in preterm infants who survive. Fierson et al[25] ranked third in citation burst strength (34.46). In 2013, they issued a revised statement on the screening of preterm infants for ROP, updating their previous statement.

Furthermore, we visually represented the cited references and conducted a clustering analysis. We identified 14 clusters with a modularity Q score of 0.6915 and a weighted mean silhouette value of 0.8731 (Figure 7b). The high modularity and silhouette values indicated 1) that the identified clusters were well-defined and distinct and 2) that the data organization was meaningful and interpretable. The 14 clusters with the highest K values included "angiogenesis," "telemedicine," and "bevacizumab" (Table VI, Figure 7b). Finally, we developed a visualized landscape for clusters (Figure 7c) and found that cluster 3 "risk factors," cluster 8 "NBSP," cluster 9 "oxygen saturation," and cluster 0 "angiogenesis" were the earliest fields in ROP. At the time of writing (April 20, 2022), the hotspots of ROP were cluster 13 "artificial intelligence," cluster 2 "bevacizumab," cluster 11 "inflammation," cluster 7 "winrop," and cluster 1 "telemedicine."

Keyword Analysis

We extracted keywords from the titles and abstracts of 4,018 publications and generated an overlay visualization map for keywords with more than 50 co-occurrences. We included 108 keywords (Figure 8a). In the overlay visualization map, VOSviewer differentiated the keywords using different colors based on their average publication year. Purple indicated earlier appearing

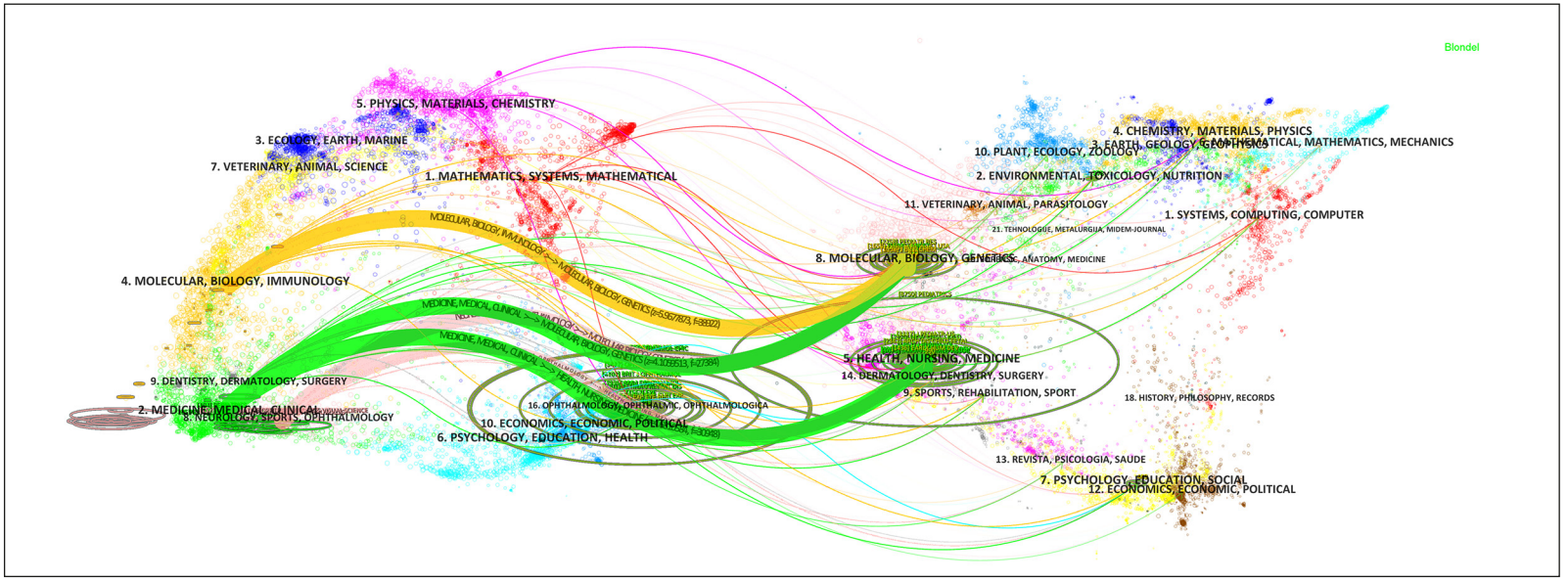


Figure 5. The dual-map overlay of articles cited on ROP research. The left side lists the citing journals, the right side lists the cited journals, and the line path represents the citation relationship.

keywords compared to the green and yellow ones within the specified time frame. This visual representation highlighted numerous ROP-related research hotspots that were identified, including "impact," "prediction," "preterm," "inflammation," "mechanisms," "VEGF," "oxidative stress," "optical coherence tomography," "telemedicine," "ranibizumab," "intravitreal bevacizumab," "bevacizumab," "laser treatment," "aggressive posterior retinopathy," and "efficacy," indicating that ROP research is evolving rapidly. The trend of balanced development in these clusters over the past few years is shown in Figure 8a.

We analyzed clusters of high-frequency (> 50 times) keywords. The results are shown in Figure 8b. After filtering out common keywords, we identified 108 nodes and 4,114 links on the network map. We classified all the keywords into four clusters: Cluster 1 (clinical features of ROP; bottom left, red); Cluster 2 (animal model and pathogenesis of ROP; bottom right, green); Cluster 3 (screening and diagnosis of ROP; upper left, blue); and Cluster 4 (treatment and follow-up of ROP; upper right, yellow) (Figure 8b). Cluster 1 was the largest and included 39 items. The prominent keywords were "prematurity" (566), "preterm infants" (491), "retinopathy" (482), "outcomes" (354), "low birth weight infants" (293), "risk factors" (262), "bronchopulmonary dysplasia" (214), and "mortality" (206). In Cluster 2, the primary keywords were "endothelial growth factor" (503), "oxygen-induced retinopathy" (322), "angiogenesis" (297), "expression" (204), "neovascularization" (191), "oxidative stress" (117), and "inflammation" (89). In Cluster 3, the primary keywords were "retinopathy of prematurity" (1,264), "infants" (575), "children" (259), "management" (146), "trial" (137), "diagnosis" (108),

Table V. The top 10 co-cited references.

Rank	Frequency	Centrality	First Author	Year	Title	Cluster-ID
1	682	0.11	Gole et al[16]	2005	The international classification of retinopathy of prematurity revisited	1
2	636	0.15	Good et al[17]	2003	Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial	1
3	349	0.15	Garner[18]	1984	An international classification of retinopathy of prematurity	1
4	326	0.03	Mintz-Hittner et al[19]	2011	Efficacy of intravitreal bevacizumab for stage 3+retinopathy of prematurity	2
5	324	0.05	Smith et al[20]	1994	Oxygen-induced retinopathy in the mouse	0
6	250	0.04	Gilbert et al[21]	2005	Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: Implications for screening programs	3
7	239	0.03	Papile et al[22]	1978	Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm	4
8	224	0.08	Palmer et al[23]	1991	Operational aspects of terminating randomization in the multicenter trial of cryotherapy for retinopathy of prematurity	3
9	220	0.04	Gilbert[4]	2008	Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control	3
10	209	0.06	Cryotherapy for Retinopathy of Prematurity Cooperative Group[24]	1988	Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results	1

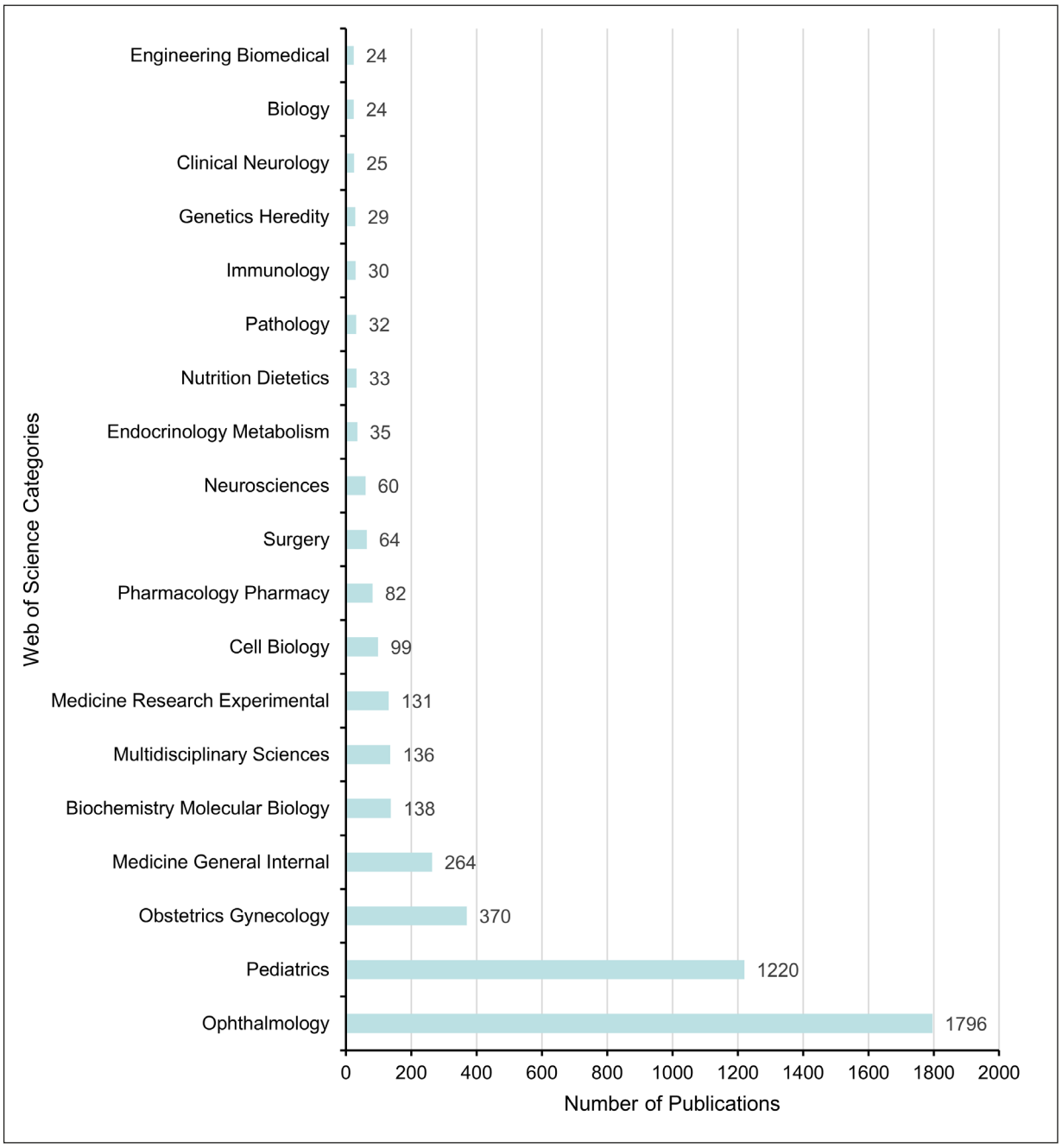


Figure 6. Distribution of research categories.

"plus disease" (105), "telemedicine" (98), and "optical coherence tomography" (93). The primary keywords in Cluster 4 were "bevacizumab" (214), "threshold retinopathy" (188), "therapy" (172), "cryotherapy" (155), "efficacy" (123), "ranibizumab" (115), "laser photocoagulation" (114), "follow-up" (108), "myopia" (89), and "aggressive posterior retinopathy" (67).

Keywords with a high burst strength served as valuable indicators for identifying research hotspots, frontiers, and emerging trends, as depicted in Figure 8c. The three keywords with the strongest citation bursts were "threshold ROP" (strength 26.88, 2001-2010), "cryotherapy" (strength 25.35, 2001-2010), and "early treatment" (strength 14.83, 2006-2013). Most notably,

five keywords continued to have strong citation bursts till 2021: "type 1 retinopathy" (strength 13.77, 2018-2021), "ranibizumab" (strength 11.45, 2018-2021), "ROP development" (strength 11.08, 2018-2021), "zone II" (strength 9.38, 2018-2021), and "artificial intelligence" (strength 10.57, 2019-2021). The bursts continued, indicating that these research directions have been the new areas of focus in recent years and are potential future research hotspots.

Table VI. Summary of co-cited reference cluster analysis in ROP research.

Cluster ID	Size	Silhouette	Label (LLR)	Average Year	Top 3 co-cited references
#0	161	0.89	Angiogenesis (8794.6, 1.0E-4)	2001	Smith et al[20] (1994); Hellstrom et al[1] (2013); Pierce et al[26] (1996)
#1	139	0.903	Telemedicine (4843.19, 1.0E-4)	2008	Gole et al[16] (2005); Good et al[17] (2003); Garner[18] (1984)
#2	132	0.859	Bevacizumab (6951.79, 1.0E-4)	2012	Mintz-hittner et al[19] (2011); Hartnett and Penn[27] (2012); Sato et al[28] (2012)
#3	113	0.762	Risk factors (6838.55, 1.0E-4)	2000	Gilbert et al[21] (2005); Gilbert[4] (2008); Palmer et al[29] (1991)
#4	93	0.803	Mortality (8512.02, 1.0E-4)	2003	Papile et al[22] (1978); Bell et al[30] (1978); Jobe and Bancalari[31] (2001)
#5	91	0.928	Myopia (3288.33, 1.0E-4)	1997	Cryotherapy for Retinopathy of Prematurity Cooperative Group[32] (2001); O'connor et al[33] (2002); Palmer[34] (1990)
#6	85	0.935	Optical coherence tomography (1974.82, 1.0E-4)	2008	Fulton et al[35] (2009); Wu et al[36] (2012); Hammer et al[37] (2008)
#7	83	0.87	Winrop (2213.71, 1.0E-4)	2010	Hellstrom et al[38] (2001); Hellstrom et al[39] (2003); Lofqvist et al[40] (2006)
#8	67	0.83	Nbsp (1243.35, 1.0E-4)	2008	Gilbert et al[41] (1997); Gilbert and Foster[42] (2001); Vinekar et al[43] (2007)
#9	67	0.88	Oxygen saturation (2575.49, 1.0E-4)	2002	The STOP-ROP Multicenter Study Group[44] (2000); Chow et al[45] (2003); SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network[46] (2010)
#10	38	0.892	Propranolol (1305.76, 1.0E-4)	2005	Chen and Smith[47] (2007); Capone and Trese[48] (2001); Mutlu and Sarici[49] (2013)
#11	28	0.941	Inflammation (545.76, 1.0E-4)	2011	Sood et al[50] (2010); Lee and Dammann[51] (2012); Sato et al[52] (2009)
#12	26	0.978	Polymorphism (744.82, 1.0E-4)	2001	Bizzarro et al[53] (2006); Cooke et al[54] (2004); Shastry[55] (2010)
#13	9	0.99	Artificial intelligence (373.75, 1.0E-4)	2016	Quinn[56] (2016); De Fauw et al[57] (2018); Wong et al[58] (2014)

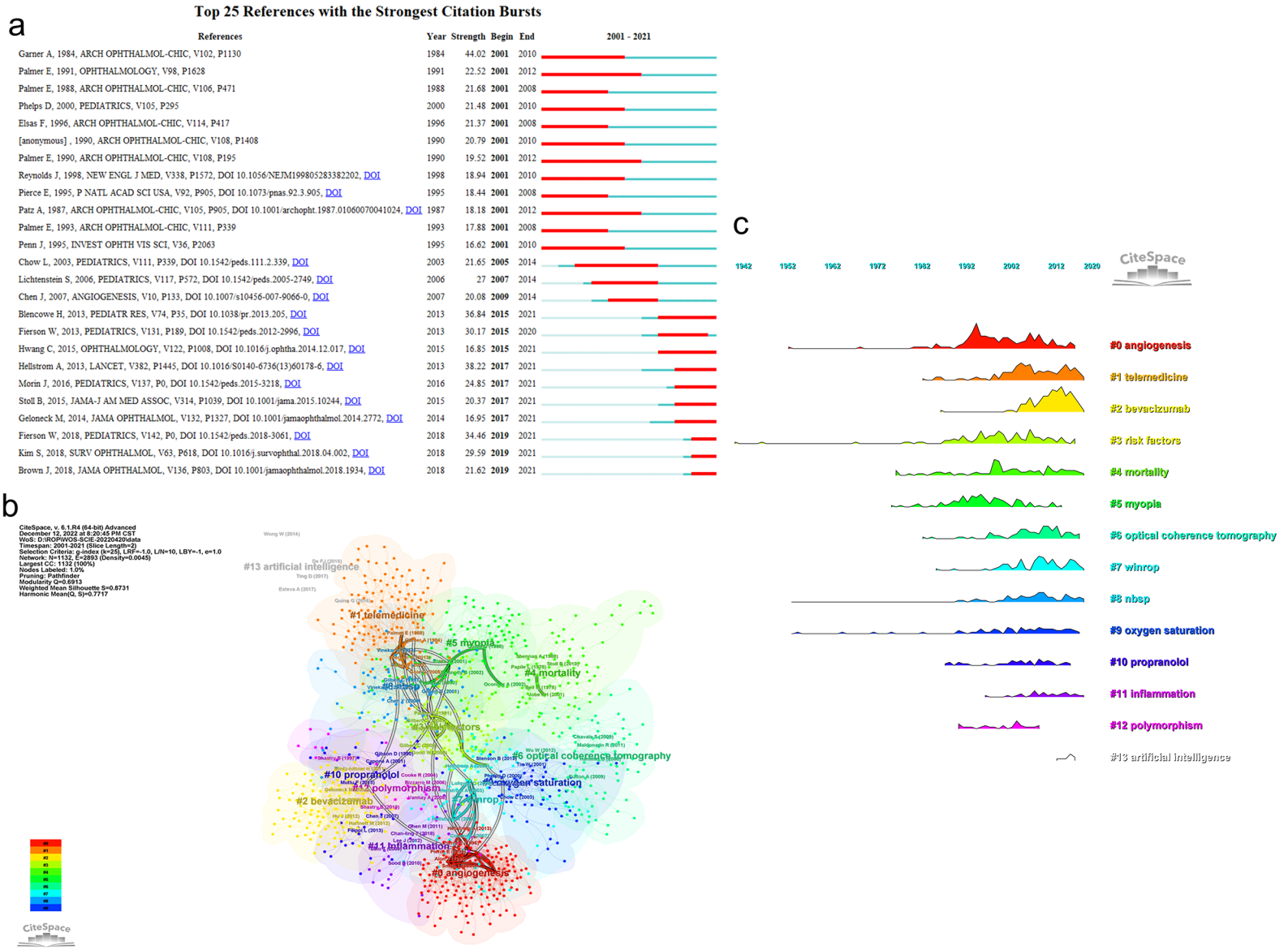
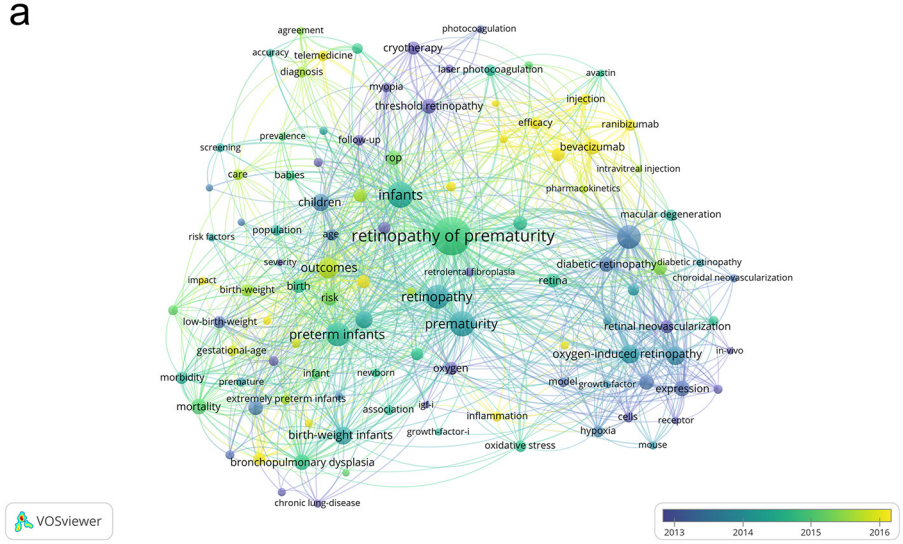
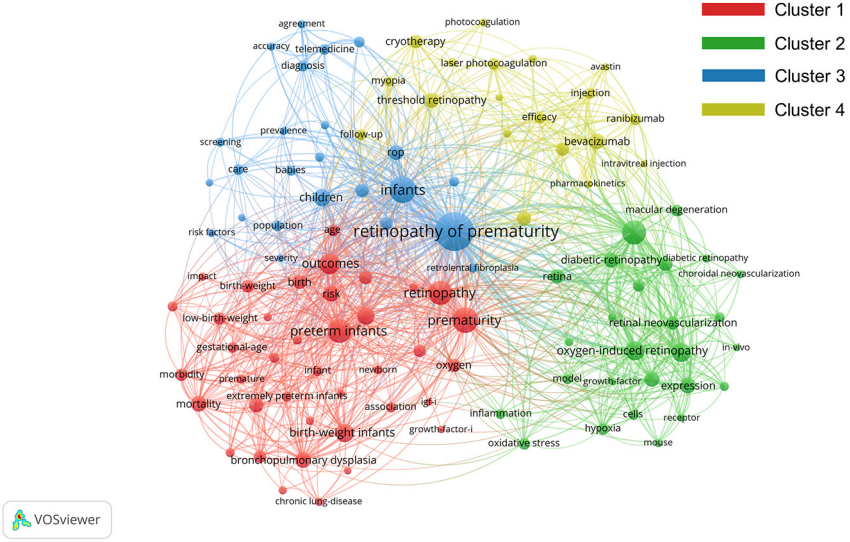


Figure 7. Visualization of co-cited reference analysis. **a**, Representative burst references among the top 25 references with the strongest citation bursts; (**b**), Cluster analysis of co-cited references; (**c**), Landscape of the co-cited reference evolution of ROP research.

a



b



c

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2001 - 2021
threshold rop	2001	26.88	**2001**	2010	
threshold retinopathy	2001	17.9	**2001**	2011	
room air	2001	14.66	**2001**	2009	
chronic lung disease	2001	13.33	**2001**	2009	
receptor	2001	12.27	**2001**	2009	
eye	2001	11.06	**2001**	2005	
follow up	2001	11	**2001**	2010	
retinal neovascularization	2001	10.11	**2001**	2005	
cryotherapy	2002	25.35	**2002**	2010	
threshold disease	2002	11.7	**2002**	2010	
significant increase	2002	9.86	**2002**	2012	
retrolental fibroplasia	2003	14.6	**2003**	2010	
retinal vasculature	2001	12.27	**2004**	2011	
oxygen	2002	9.71	**2005**	2009	
early treatment	2002	14.83	**2006**	2013	
avascular retina	2002	11.07	**2008**	2014	
j aapo	2011	11.37	**2011**	2012	
avastin	2011	10.48	**2011**	2016	
pharmacokinetics	2015	12.06	**2015**	2019	
randomized controlled trial	2015	10.61	**2015**	2018	
type 1 retinopathy	2018	13.77	**2018**	2021	
ranibizumab	2012	11.45	**2018**	2021	
rop development	2018	11.08	**2018**	2021	
zone ii	2014	9.38	**2018**	2021	
artificial intelligence	2019	10.57	**2019**	2021	

Figure 8. Visualization of keyword analysis. **a**, Timeline distribution of the cluster analysis of keywords; (**b**), Landscape of the keyword evolution of ROP research; (**c**), Representative burst keywords among the top 25 references with the strongest citation bursts.

Discussion

We quantitatively analyzed publications on ROP from 2001 to 2021 using bibliometric analysis and provided an overview of ROP research, topics, fundamentals, and future research hotspots.

General Trends in Publications

We analyzed original articles and reviews on ROP published from 2001 to 2021 and presented the information visually. Before 1984, there was a substantial variation in the classification and diagnostic criteria utilized to characterize ROP, which posed challenges to the external validity of scoping efforts. The ICROP is a consensus statement that creates standard nomenclature for ROP classification. Originally published in 1984[19], it was expanded in 1987[59] and revised twice, once in 2005[16] and once in 2021[60]. A unified nomenclature for classification is critical as it serves as the fundamental prerequisite for the diagnosis and treatment of clinical diseases in the future. We found a steady increase in the number of scientific research publications over the past two decades. However, the number of papers published before 2006 was small (< 100), as shown in Figure 2a.

The USA contributed the most to ROP publications, accounting for 38% (1,511/4,018) over the past two decades. The analysis of the author nodes revealed cooperation between the authors. Hellström [Professor of Pediatric Ophthalmology at Sahlgrenska College, University of Gothenburg (Sweden) and Chief Physician at Sahlgrenska University Hospital] emerged as the most prolific researcher in the field, focusing on investigating the pathophysiological research of ophthalmology and eye diseases[61]. These studies[1,61] on ROP and its impact on the psychological well-being of preterm infants are internationally recognized (with a high H-index of 33). Harvard University was the most productive (122 publications) and influential (mean citation: 63.43) research institution. Furthermore, Harvard University formed collaborations in ROP research with highly central institutions, including the University of Utah, the University of Pennsylvania, the University of Toronto, and the Children's Hospital of Philadelphia. Notably, eight out of the top ten institutions in this field were based in the United States, affirming the country's prominent position in ROP research.

Research Topics

In a co-citation network, the references cited by a specific article offer valuable insights into the intellectual interrelations among different scientific concepts[61]. We categorized the literature depicted in the co-citation network into 14 clusters, with each node representing a cited article and each cluster representing a specialized or thematically focused area. The silhouette value of a cluster serves as a measure of the clustering configuration's quality, ranging from -1 to 1. A higher silhouette score (recommended value > 0.70) indicates greater consistency among the cluster members, assuming the comparison is made between clusters of similar sizes[62].

The underlying pathology of ROP consists of two critical phases: vessel loss and hypoxia-driven destructive pathological angiogenesis (neovascularization)[6]. In the last twenty years, extensive investigations have been carried out on angiogenesis in ROP. Neovascularization is a hallmark of ROP[63] and has become a focus in ROP research. The establishment of animal models for oxygen-induced retinopathy and assessment of the associated pathology offers an opportunity to investigate the etiology of ROP and identify potential treatment strategies. Given the impact of VEGF on retinal angiogenesis, Aiello et al[64] proposed using an anti-VEGF treatment for ROP; this is a significant contribution to the field of ophthalmology because it provides a novel insight into the pathogenesis of ROP and suggests a promising intervention for this condition. With a further understanding of the role of VEGF in retinal angiogenesis, the findings of Aiello et al[64] may enable the development of a therapy that can improve the clinical outcomes for infants affected by ROP.

The primary risk factors for ROP are low birth weight and premature gestational age[2]. Further, infection, inflammation, and oxidative stress potentially contribute to ROP development[51,65]. There is ample evidence[66] that these three factors can lead to various cellular and tissue alterations in the eyes of premature infants, including incompletely formed vessels. Additionally, studies[67] have shown that these changes can lead to scar tissue formation, which can cause permanent vision loss if left untreated. Thus, it is essential to closely monitor prenatal and neonatal infants to assess their risk of developing ROP and take appropriate preventative measures.

The use of oxygen is widespread in the care of premature infants, especially extremely premature infants (EPIs). Defining the optimal oxygen

saturation range for premature infants is critical to reducing the incidence of ROP and preventing high mortality. Research[68] conducted in the 1950s demonstrated that providing preterm infants with excess oxygen increased the risk of severe ROP. However, the mortality rate increased with decreasing oxygen levels[46], which presented a clinical challenge. A trial[69] on the initial benefits of oxygen saturation targeting revealed that preterm infants still subjected to high-concentration oxygen inhalation at 32 weeks of gestation relied more on oxygen for an extended period. Further, observational evidence[70-72] indicated a potential correlation between elevated levels of oxygen and an escalated risk of ROP.

Genetic polymorphism may contribute to the pathogenesis of threshold ROP in premature infants[54]. Abundant research is currently available on *VEGF* polymorphisms and their involvement in the pathogenesis of ROP[73,74]. According to a meta-analysis, the *VEGF* gene -460 T/C polymorphism was found to be associated with the development of advanced ROP[75]. Additionally, polymorphisms in genes related to oxidative stress and some inflammatory molecules are associated with the risk of ROP, including endothelial nitric oxide synthase[76,77], angiopoietin 2[77], angiotensin-converting enzyme[78], antioxidant enzymes[79], *TNF-alpha*[80], and the insulin-like growth factor 1 (*IGF-I*) receptor[81]. Interestingly, a recent study[82] found that infants with the rs 12600817 polymorphism in the *TIMP-2* gene were at a higher risk of developing severe ROP requiring therapy. In addition, among infants with ROP requiring treatment, the AG+GG genotype of the rs 2889529 TIMP-2 polymorphism was associated with treatment response. The rs 12600817 polymorphism of TIMP-2 could help predict the risk of ROP in premature infants. Additionally, the rs 2889529 polymorphism could be used as a genetic marker to evaluate the therapeutic effect of ROP.

Screening for and early identification of ROP have always been key research directions. However, the shortage of ROP ophthalmologists remains a severe and growing problem. Telemedicine and artificial intelligence (AI) provide synchronous solutions to the challenges that ophthalmologists and healthcare providers face worldwide[83]. A six-year study[84] by the Stanford University Network for Diagnosis of Retinopathy of Prematurity showed that telemedicine screening is highly sensitive and specific, with good diagnostic accuracy. Telemedicine is a secure, dependable, and cost-effective supplement to the initiatives of ROP experts because it can increase the availability of screening for patients and concentrate existing ophthalmology community resources on infants with vision-threatening conditions[85]. There are also developments integrating AI into ROP screening programs that may improve care for ROP secondary prevention and contribute to disease epidemiology and the assessment of neonatal care unit resources[86].

Optical coherence tomography (OCT) is a three-dimensional noncontact imaging technique used to characterize the topology and internal microstructure of a sample[87]. OCT can be configured as a conventional microscope, ophthalmic scanner, or endoscope with a small-diameter catheter for assessing internal biological organs. OCT is an emerging intracoronary imaging mode. In 2006, Professor Patel of the Oxford Eye Hospital used OCT to detect *in vivo* microscopic changes in stage 4 ROP[88]. Since then, OCT has gained popularity worldwide because of its safety and extremely high resolution[89-91].

In 2006, Löfqvist et al[40] developed an algorithm called the WINROP Screening Algorithm. It utilized postnatal longitudinal systemic factors such as levels of IGF-I, levels of IGF-binding protein 3, and postnatal weight gain to forecast the likelihood of subsequent development of ROP that necessitates treatment in individual infants. Subsequently, the algorithm has been applied in many countries and regions, including Mexico[92], Brazil[93], Korea[94], China[95], the Czech Republic[96], Australia[97], and South Africa[98]. A multicenter validation study[99] of the WINROP algorithm demonstrated moderate sensitivity as it failed to detect many treatable ROP cases. Additional criteria need to be incorporated into the algorithm to enhance its sensitivity.

Bevacizumab is a humanized monoclonal antibody produced through genetic engineering that hinders the process of angiogenesis by attaching to and obstructing VEGF[100]. In February 2004, the US Food and Drug Administration approved Avastin for the first time for treating metastatic colorectal cancer. In 2006, a case report[101] described the combined use of intravitreal bevacizumab administration and laser photocoagulation to treat aggressive zone I ROP. The concurrent application of indirect laser photocoagulation and intravitreal bevacizumab injection was well-tolerated and resulted in rapid regression of aggressive zone I ROP. In 2011, the BEAT-ROP Cooperative Group[19] published the first prospective controlled randomized stratified multicenter trial

in the "New England Journal of Medicine". The study compared the efficacy and safety of the bevacizumab 0.625 mg intravitreal injection and laser treatment for stage 3+ ROP. Infants with stage 3+ ROP treated with intravitreal bevacizumab monotherapy showed more progress and fewer adverse reactions than those treated with conventional laser therapy. Intravitreal injections of bevacizumab contribute to a low recurrence rate and help restore physiological retinal angiogenesis[102]. Other anti-VEGF drugs – ranibizumab[103], conbercept[104], and aflibercept[105] – have also been used to treat ROP. Further, propranolol has also been used to treat ROP.

In 2010, Professor Filippi from Meyer University Children's Hospital published a pioneering protocol[106] to explore the possible therapeutic role of the beta-blocker propranolol in ROP treatment. This clinical trial aimed to identify a simple, inexpensive, and well-tolerated treatment with few adverse effects that could combat one of the main preterm birth complications. Three years later, the results of this study proved that oral propranolol was effective in stopping ROP progression. Safety remained a significant concern[107], but Filippi et al[106] established a solid basis for using propranolol in ROP treatment. Concurrently, several animal studies[108-110] were conducted. A meta-analysis[111] of randomized controlled trials revealed that the risk of disease progression was reduced when propranolol was administered orally to preterm newborns, particularly those with stage 2 ROP.

If left untreated, severe ROP can cause serious vision issues and potential blindness[112]. Therefore, ROP outcomes have been the focus of research. ROP treatment has become increasingly safe, the success rate for vision preservation has skyrocketed, and treatments are becoming more uniform. This progress is attributed to advancements in medicine, the implementation of new tests, and improvements in treatment protocols. The prognosis and follow-up for children have become more dependable[21]. Although non-proliferative ROP is often resolved without treatment, it can result in vision deficits, including myopia[113], amblyopia[114], and refraction[115].

Research Foundation

Top co-cited articles serve as the fundamental pillars of a specific research area. Utilizing co-citation networks, we conducted a comprehensive analysis of the most frequently co-cited publications to explore the knowledge foundation within the field of ROP. We found that the revised version of the ICROP[16] published in JAMA Ophthalmology (formerly Archives of Ophthalmology) and the clinical trial[17] concerning revised indications for the therapy of ROP published in the journal by the Early Treatment for Retinopathy of Prematurity Cooperative Group are the foundations of the research in this field. The top 10 co-cited references in Table V contain two guidelines, four clinical trials, one oxygen-induced animal model, and three other original articles in this field that play fundamental and instructive roles in ROP research.

Emerging Trends and Hotspots

The hot spots have evolved from threshold ROP – the burst keyword with the highest strength – to cryotherapy, early treatment, avascular retina, pharmacokinetics, randomized controlled trials, and finally, to type 1 retinopathy, ranibizumab, ROP development, zone II, and AI (Figure 8c). The research focus of ROP has shifted from general pathological and clinical features to clinical trials and specific diagnostics (Figure 8a). The treatment options for ROP have shifted from cryotherapy and laser therapy to bevacizumab and ranibizumab. In addition, research on ROP has concentrated more on clinical treatment than on exploring the basic mechanisms. The evolution of keyword bursts suggests the following future research trends in this field:

1) Type 1 ROP refers to a severe form of ROP characterized by the involvement of zone I (any stage of ROP plus disease), zone I (stage 3 with or without disease), or zone II (stage 2 or 3 ROP plus disease). Among these, zone II lesions worsened or improved over time, entering zones I and III, respectively. Therefore, it is essential to elucidate the clinical risk factors for ROP development that play vital roles in preventing ROP progression. Many case-control and longitudinal cohorts have been reported recently[116], and type 1 retinopathy, ROP development, and zone II will become future hotspots.
2) AI is an umbrella term for tasks performed primarily by computers, with minimal human involvement, widely understood as robotics[117]. AI may help alleviate the shortage of ROP ophthalmology professionals and improve the efficiency of ROP screening. Additionally, AI can provide an automated, quantifiable, and objective diagnosis of ROP[118]. The diagnosis can be subdivided by regions, stages, and additional disorders, with each

region exhibiting significant subjectivity and inconsistency within and between experts. The AI-based combination of telemedicine and highly automated systems will play an essential role in ROP screening, early diagnosis, grading, and individualized treatment. It is an emerging research frontier.

3) Ranibizumab, the first anti-VEGF medication to be authorized for the treatment of ROP, is a monoclonal antibody fragment that targets VEGF-A[119,120]. In a major randomized phase III RAINBOW study[121] of babies with ROP, 80% of the children who received intravitreal ranibizumab at a dosage of 0.2 mg experienced effective therapy at 24 weeks. This was higher than the success rate in the laser therapy group (66%), although no statistically significant benefit was evident. The long-term effect of ranibizumab treatment on vision is unclear. However, a preliminary analysis from the RAINBOW extension study did not indicate any signs of impaired vision[122]. Adverse reactions to ranibizumab in pediatric patients were akin to those observed in adults, with the majority of adverse reactions attributable to the intravitreal injection procedure. Furthermore, no systemic VEGF inhibition was noted in clinical trials[123], which aligns with the rapid systemic elimination of ranibizumab. Studies have shown that ranibizumab is a safe and effective therapy for ROP. Although no data on the long-term effects of ranibizumab on vision were available during this study, it represents a viable option for laser treatment.

Strengths and Limitations

This study is the first review to use the bibliometric approach to analyze ROP-related studies published in the past two decades comprehensively. Compared with traditional reviews, the bibliometric method offers a fresh and unbiased view of the dynamic changes in research trends and directions. Simultaneously, we used different bibliometric research tools to obtain reliable results in different dimensions. This study shows the seriousness of ROP as a health problem in infants, provides scholars with a comprehensive view of ROP research, and illustrates detailed and unbiased directions for upcoming developments in this field. Nevertheless, this study has some limitations. First, we only searched English literature from the WoSCC database, excluding non-English or non-WoSCC entries. However, WoSCC English articles are the most used data source for evaluating bibliographies, so they probably represent the primary directions in this field. Second, several research reports have suggested that philometric methods may be unable to avoid bias because they rely on natural language processing. However, our results are comparable to the conventional review process and provide comprehensive and unbiased data.

Conclusions

Over the past 21 years, there have been a lot more publications in this area, which suggests that ROP has become more popular. Despite the relatively close international cooperation between institutions and authors in this field, academic exchange and cooperation need further strengthening. Several topics have emerged, including "artificial intelligence," "inflammation," "bevacizumab," "angiogenesis," and "telemedicine." These are important foundations for future research. Frontier topics are "type 1 retinopathy," "ranibizumab," "ROP development," "zone II," and "artificial intelligence." Overall, this is the first bibliometric study to shed an objective and systematic light on ROP. We hope the data presented in this article will serve as a valuable guide for future research.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and Informed Consent

Not applicable.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

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Authors' Contribution

ZF and QL designed the study. CL and JC collected data. CL, YW, and DW analyzed the data. CL wrote the manuscript. CL, JC, YW, DW, and TH prepared the figures and tables. ZF and QL reviewed and revised the manuscript. All the authors contributed to the manuscript and approved the submitted version.

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