Theme trends in research related to retinal vein occlusion: a quantitative and co-word analysis

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Abstract

Background. This study focused on plotting knowledge structure and exploring research hotspots of retinal vein occlusion (RVO). **Methods.** In this study, research articles, with subject of RVO, were acquired from PubMed. Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) was used for MeSH terms acquisition, evaluation and high-frequency MeSH term determination. Biclustering analysis and knowledge structure were conducted based on the MeSH term-source article matrix. RVO theme trends were illustrated with social network analysis (SNA), along with strategic diagrams. **Results.** A total of 3179 articles on RVO were retrieved, and the annual research output increased with time. USA ranked first with the most publications, with Retina as the most prolific journal in RVO research. MeSH terms were characterized into five different genres. As shown by the strategic diagram, the complications of RVO, the etiology of macular edema, as well as the therapeutic use of anti-VEGF, steroids and anti-inflammatory agents were well developed (Quadrant I). In contrast, epidemiology, metabolism and genetics related research on RVO were relatively immature (Quadrant III). Research on surgical treatments of vitrectomy, diagnostic methods and pathology of RVO were centralized but undeveloped (Quadrant IV). The SNA results was exhibited by the centrality chart, on which the node position was represented by the centrality values. **Conclusions.** By providing a bibliometric research, the overall RVO research trends could be revealed based on the five categories identified by this study. The mathematical bibliometric study could shed light on new perspectives for researchers.

Background

Retinal vein occlusion (RVO) ranks the second most common cause of retinal vascular disease [1]. Central (CRVO), hemiretinal (HRVO) and branch (BRVO) vein occlusion are the three major categories of RVO based on the occlusion site. Patient symptoms may generally include, depending on the classification of RVO, blurry or missing vision, floating dots or lines, and defective visual field. The main complications of CRVO include the macular edema formation, neovascularization, neovascular glaucoma, and vitreous hemorrhage, while complications of BRVO depend more on the vessel occluded [2]. Academic journals have published a vast amount of papers in RVO related research over recent decades. In order to reduce the effort and time required for a traditional systematic literature review, we applied bibliometric methods to explore the research status in an RVO study.

Bibliometry is a computational analytical method, which is based on mathematical and statistical analysis of an article's attributes, and it can be used to describe, assess and predict the current status and future development of science and technology [3]. Co-word and co-citation analyses are the common means employed in bibliometry analysis to demonstrate research trends. It is assumed that a collection of academic words from an article of interest can be used to outline this article. Based on this presumption, co-word analysis can be employed to assess the relationship of two academic words in a research literature. This study is focusing the assessment of RVO research trends with co-word analysis.

Methods

Data Collection

Medical subject headings (MeSH) is a universal terminology used in academic publications to index and categorize biomedical information. In general, approximately ten to fifteen titles and subtitles are applied to index each published paper [4]. Co-word clustering analysis can be performed based on MeSH terms. In this study we select all journal articles in English from the PubMed database with the MeSH term “retinal vein occlusion”, and 3179 articles in total were identified and used in our analysis.

Data Extraction and Bibliographic Matrix Setup

Bibliographic Item Co-occurrence Matrix Builder (BICOMB), designed and built by Prof. Cui from China Medical University, was employed to examine the distribution features including publication time, nations, journals and researchers. In addition, BICOMB was also used to obtain the main MeSH terms/MeSH subheadings of these selected literatures [5]. The inventory, acquired from the PubMed database, was implemented for the generation of a term-source and co-occurrence matrix, and these matrices were further applied for subsequent bibliometric analysis.

Bi-clustering analysis of the high-frequency main MeSH terms/MeSH subheadings

Threshold value, $T = (1+)/2$, was used to evaluate the quantity of high-reoccurrence main MeSH terms/MeSH subheadings, and in this equation, “i” represents the quantity of key MeSH terms/MeSH subheadings with single appearance. RVO hot spots were explored with bi-clustering analysis which was based on the evaluation of high-reoccurrence MeSH terms and RVO-associated research articles. A binary matrix, with its rows built with high-reoccurrence key MeSH terms and its columns composed of source article, was developed. Then, the term-source article matrix was used to conduct co-occurrence double cluster analysis with gCLUTO software which can be retrieved from <http://glaros.dtc.umn.edu/gkhome/cluto/gcluto>. For hill diagram visualization, peaks are in accordance with the hotspots of the theme, which can be used to roughly estimate the clustering results. The different color appearing on the hill diagram represents different standard deviation (SD), the height of the hill is proportional to the similarity in intra-class and the hill volume is correlated with the quantity of MeSH terms. For dendrogram, high-reoccurrence key MeSH terms were displayed as the row labels and the PubMed Unique Identifiers (PMIDs) of the source publications were listed as the column names.

Strategic diagram analysis

The strategic diagram analysis is based on themes of centrality and density. Centrality is represented by the external cohesion index, indicating the theme position in the framework, and density is illustrated by the internal cohesion index, reflecting the progression of the themes. With X-axis representing centrality and Y-axis illustrating density, four quadrants were developed. Based on the biclustering assessment, different clusters generated were distributed in different quadrants of this strategic diagram generated by Graph.

Social network analysis

SNA network was developed using Ucinet 6.0 (Analytic Technologies Co., Lexington, KY, USA) software according to the high-reoccurrence key MeSH terms/MeSH subheadings co-occurrence matrix. A two-dimensional map, for visualization, was generated with the key MeSH terms/MeSH subheadings using NetDraw 2.084 software. On this map, the key MeSH terms/MeSH subheadings were shown as the nodes and the frequency of their co-occurrence was displayed as the links. Furthermore, closeness, betweenness and degree centralities were employed to examine the location of the key MeSH terms/MeSH subheadings, in order to obtain in-depth understanding of RVO network organization.

Results

Distribution characteristics of relevant literatures

With the searching criteria described above, 3179 publications in total were included in this study. As displayed in Fig.1A, research articles published yearly in the RVO field has gradually increased from 90 in 2004, to over 200 in 2015. Among all the first authors involved in this topic, Noma H ranked first by publishing 52 articles (Fig.1B). As for the amount of RVO research output, the United States ranked first with 1,544 publications, making up almost 50% of the research in this specific area (Fig.1C). Among the top 10 most productive journals displayed on Fig.1D, Retina, American Journal of Ophthalmology and Ophthalmology are listed as the top three, and these identified top journals are considered to be the principal journals in RVO field.

Research hot spots identification with MeSH term clusters

According to Table 1, 73 MeSH terms, representing 57.6% all MeSH terms, were identified as the high-reoccurrence MeSH terms. These 73 high-reoccurrence MeSH terms could be used to reveal the hot spots of studies in the field of RVO.

The visualization of the key MeSH terms/MeSH subheadings using the hill diagram and dendrogram, based on biclustering analysis, are presented on Fig. 2. According to the evaluation of the MeSH terms, RVO research hot spots were classified into five categories (Table 2). These categories mainly include the following content: (1) Research related to the epidemiology and metabolism of RVO (cluster 0); (2) Studies on the complications of RVO, and the etiology of macular edema; the therapeutic use of monoclonal/humanized antibodies, glucocorticoids, triamcinolone acetonide, dexamethasone and anti-inflammatory agents (cluster 1); (3) Surgical treatment of vitrectomy (cluster 2); (4) Genetics related research on RVO (cluster 3); and (5) Pathology of RVO and diagnostic methods including fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) (cluster 4). The key research topics of RVO could be revealed by the above mentioned five clusters.

Table 2 Cluster analysis of high-frequency major MeSH terms/MeSH subheadings of retinal vein occlusion

Cluster	Number of MeSH terms*	Cluster analysis
0	41,18,46,39,40,44,38,65,20	<p>1.Retinal vein occlusion metabolism and epidemiology</p> <p>2.Aqueous humor, macular edema, vitreous body and iris metabolism</p>
1	29,3,53,37,13,9,10,4,2,1,28,26,52,55,19,64	<p>1.Retinal vein occlusion complications and macular edema etiology 2.Retinal vein occlusion and macular edema drug therapy</p>
2	70,61,57,16,59,32,31,14,6,54,33,45,60,69	<p>1.Retinal and choroid neovascularization</p> <p>2.Ophthalmologic Surgical Procedures</p>
3	66,51,22,73,48,23,43,34,42,24,5,50,25	<p>1.Retinal vein occlusion etiology and genetics: point mutation, factor V and NADPH2</p> <p>2.Retinal vein occlusion complications: hyperhomocysteinemia, antiphospholipid syndrome and vision disorders</p> <p>3.Retinal artery occlusion etiology and complications</p>
4	68,71,27,7,36,49,17,63,56,72,67,58,8,62,11,21,15,35,47,14,30	<p>1.Retina and vessels physiology and physiopathology</p> <p>2.Pathology of retinal vein occlusion</p> <p>3.Retinal diseases diagnosis and methods</p>

*Represents the serial number of high-frequency major MeSH terms/MeSH subheadings shown in Table S1.

Theme trends of RVO

Themes in Quadrant I with the features of intensive centrality and density are considered as the motor themes. Quadrant II, located at the upper-left quadrant, containing with specialized themes with low centrality but intensive density. The bottom-left quadrant, Quadrant III, includes themes with inadequate

density and centrality, and the themes in the quadrant are generally regarded to be either emerging or fading. The bottom-right quadrant, Quadrant IV, holds themes with intensive centrality but inadequate density, indicating themes without internal maturation. These themes were distributed in the quadrants of the strategic diagram with spherical shapes and their location was based on the value of density and centrality indicating the internal and external correlation, respectively (Fig. 3A). As shown in Fig. 3B, Cluster 1 includes studies on the complications of RVO, the etiology of macular edema, and the therapeutic use of monoclonal/humanized antibodies, steroids and anti-inflammatory agents and it is assigned to Quadrant I, indicating their pivotal position with significant centrality and density. Cluster 0 and 3 are assigned to Quadrant III, consisting of studies on the metabolism, epidemiology and genetics of RVO that are still immature, especially in the peripheral regions of current studies. Whereas, Cluster 2 and 4 are located in Quadrant IV, representing that studies that include ophthalmologic surgical procedures, diagnostic methods and the pathology of RVO are undeveloped while in the central position.

Social network analysis of RVO

SNA network organization was defined by centrality parameters including degree, betweenness and closeness centralities (Table 3A&3B).

The top ten MeSH terms with high-reoccurrence exhibits higher degree centralities comparing to the average of 220.219 ± 346.829 . "Macular edema/drug therapy" is listed as a MeSH term with the highest reoccurrence rate showing the greatest degree centrality as 1,894. "Retinal vein occlusion/complications" and "Retinal vein occlusion/diagnosis" are listed with the highest betweenness centrality with the value of 204.59 and 177.057, respectively, and indicating most intensive mediating roles in the network. Whereas, with the average betweenness centrality determined as 25.534 ± 42.030 (Table 3B), MeSH terms "Dexamethasone/ therapeutic use" "VEGFA/ antagonists & inhibitors" and "Ranibizumab/ therapeutic use" show relative lower betweenness centrality values as 8.775, 19.518 and 16.643, respectively. However, these three MeSH terms show higher degree centralities values as 442, 279 and 246, respectively, comparing with the degree centrality mean value of 220.219. Meanwhile, MeSH terms "Retinal vein occlusion/complications" have the top closeness centrality of 66.

To better understand this, the betweenness centrality was used to develop the SNA. As shown in Fig. 4, the betweenness centrality is represented by the node size and co-occurrence frequency is displayed by line width.

Discussion

Based on the assumptions that literature content can be represented by selected MeSH terms, research status of a specific theme can be revealed by an aggregation of MeSH terms. Statistical evaluation using BICOMB software indicates that the overall trend of research articles on "retinal vein occlusion" [MeSH] is featured as an increase peaked in 2015. Furthermore, US and England are identified as the two countries with the most publications on RVO, and one of the reasons for this could be that their native language is English.

With the focus on investigating the structures of RVO knowledge systemically, co-word evaluation, biclustering examination, strategic diagram and bibliometric SNA were included in this study. Clusters were formed and identified with MeSh terms that are associated closely through the co-word and biclustering evaluation. Cluster 1 was identified to be associated with studies on the complications of RVO, the etiology of macular edema and the therapeutic use of monoclonal/humanized antibodies, corticosteroids and anti-inflammatory agents. Age and systemic disorders were identified as the top two risk factors for RVO. RVO prevalence increases significantly with age but does not differ by gender [6], probably due to atherosclerosis. Systemic diseases such as hypertension, diabetes mellitus, hyperlipidemia, thrombophilia, hypercoagulation and inflammatory diseases are strongly associated with RVO [7]. RVO patients may suffer a variety of complications, the most significant of which is macular edema. Other serious complications include vascularization of the retina and optic disc (which can result in vitreous hemorrhage), retinal detachment, neovascular glaucoma and even blindness [8]. Cystoid macular edema (CME), which is caused by capillary congestion, may result in the metamorphopsia and even loss of visual acuity. A multicenter, randomized clinical trial examined the efficacy and safety of 1-mg and 4-mg doses of intravitreal triamcinolone acetonide (IVTA) in comparison with standard grid photocoagulation for BRVO. Investigators reported similar improvement in OCT thickness over 1-year observation in all groups. In terms of complications, cataract progression rate was higher in the 4mg IVTA group, thus IVTA is less commonly used than anti-VEGF therapy [9]. VEGF is an inflammatory cytokine that promotes vascular permeability and is upregulated in eyes with vein occlusion [10]. Ranibizumab and bevacizumab are humanized monoclonal antibodies that are active against the VEGF-A molecule. Different clinical trials on anti-VEGF injections suggest that intraocular anti-VEGF injection can significantly improve vision acuity in eyes with BRVO [11]. These topics in Cluster 1, positioned in Quadrant I, are the centralized and matured hotspots in the RVO field.

Cluster 0 is associated with research on epidemiology and the metabolism of RVO. The prevalence of RVO has been reported to range between 0.4% and 4.6%. Of the two main types of RVO, BRVO is four to six times more prevalent than CRVO [12]. The balance between inflammatory cytokines and angiogenesis in eye fluid is disturbed in patients with RVO. Exposure of endothelial cells to proinflammatory cytokines can cause oxidative stress and apoptosis, aggravating leukocyte efflux and thrombosis. Significantly increased concentrations of IL-1 α , -6, and -8; IP-10; and PDGF-AA were observed in RVO patients when compared to control patients [10]. Macular edema secondary to RVO is associated with increased levels of VEGF in the aqueous humor. Therefore, the management of macular edema secondary to RVO, especially in the presence of capillary non-perfusion areas, should aim at reducing ocular VEGF concentration [13]. Cluster 3 relates to genetic studies on RVO. Thrombophilic diseases like factor V Leiden mutation, hyperhomocysteinemia and anticardiolipin antibodies increase the risk of RVO [14]. Proteomic studies suggest that RVO is associated with the remodeling of the extracellular matrix and adhesion processes. However, many areas of proteome changes in RVO remain unstudied. Future studies may address long-lasting retinal changes following intervention with anti-VEGF agents, such as dexamethasone intravitreal implants [15]. These two clusters, assigned to Quadrant III, represents research hotspots which are marginal and immature, and future research on these topics is suggested.

Cluster 2 relates to the surgical treatment of RVO. Macular grid laser photocoagulation is an effective treatment for macular edema in patients with BRVO. Other treatment options for reducing edema are intravitreal steroids, anti-VEGF drugs and vitrectomy. It has also been reported that vitrectomy is effective for reducing macular edema and improving visual acuity in patients with BRVO. Vitrectomy probably reduces macular edema by allowing oxygenated fluid to circulate in the vitreous cavity, improving perifoveal microcirculation, and increasing the clearance of VEGF in the vitreous cavity. A five-year follow-up of vitrectomy for macular edema associated with BRVO revealed that vitrectomy may evade the risks associated with repeated injections; however, the incidences of postoperative RD were higher than that of intravitreal injections [16]. Cluster 4 is associated with the pathophysiology and RVO diagnosis. In RVO patients, signs of oxidative stress, such as enhanced plasma lipid peroxidation and decreased antioxidant activity of paraoxonase, have been reported [17]. M. Becatti, et al. compared ROS production and membrane lipid peroxidation in RVO patients and control subjects. The results indicated that erythrocyte oxidative stress is an essential factor in the pathogenesis of RVO disease [18]. Suzuki et al. reported that anti-VEGF therapy might improve retinal deep ischemia in the retinal deep layer of patients with RVO [19]. In clinical practice, treatment decisions commonly depend on OCT measurements. OCT provides high-resolution imaging of the fovea and is helpful in detecting the presence of macular edema, vitreoretinal interface changes, neurosensory retinal detachment and subretinal fluid. Optical coherence tomography angiography (OCTA) can evaluate the retinal hemodynamics in patients with RVO. FFA is able to detect peripheral capillary nonperfusion, macular ischemia, and subtle neovascularization. Eyes with more capillary nonperfusion have a greater risk of ocular neovascularization. FFA may also help to distinguish collateralization from neovascularization, since the former does not leak fluorescein, whereas the latter does [20]. These two clusters are assigned to Quadrant IV and include immature but centralized research topics.

According to the RNA analytical outcome, MeSH terms ranked the top three are “Macular edema/drug therapy”, “Antibody, monoclonal, humanized/therapeutic use” and “Retinal vein occlusion/drug therapy”, showing high degree centralities. These MeSH terms are with the most directly links with other components, pioneering the progress of the RVO research. With regard to the betweenness centrality analysis, “Retinal vein occlusion/complications”, “Retinal vein occlusion/diagnosis” and “Retinal vein occlusion/physiopathology” are identified to be located at the network center, representing the key components with the highest influence in the determination of other components’ co-occurrence. “Retinal vein/pathology” and “Retina/pathology” are among the top ten MeSH terms with betweenness centrality; however, these two components are located in the IV quadrant and are not included in the MeSH terms listed with the top ten high-reoccurrence. This demonstrates that although these two components are important in the network stability, but the research on this topic is not well developed.

Conclusions

In summary, the structure and maturity of an identified field can be evaluated and revealed with clustering analysis and strategic diagrams. SNA has the advantage of identifying the associations among the high-reoccurrence MeSH terms. The key foci on current research include drug therapy and pathogenesis

alterations, and genetics-based studies are the novel developing areas. The purpose of this bibliometric study is to shed some light on research topic selection for researchers in the RVO field. However, potential methodological limitations should also be evaluated by researchers. First, the publications extracted from PubMed may not be comprehensive enough to cover all of the topics in RVO literature. Secondly, research article and journal qualities are not consistent, with articles from top tier journals showing significant impact in comparison with those of little influence from inferior journals. Thus, the contribution should have not be considered the same in the knowledge structure during analysis. Finally but not lastly, high-reoccurrence MeSH terms were used for the co-word analysis and novel research topics may be excluded from the analysis due to low-reoccurrence, which may introduce bias during the analysis. Due to the above potential limitations, future analyses should take the newly emerging topics and multiple databases into consideration.

Declarations

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Availability of data and materials

The datasets included in this study are available in the PubMed database.

Author contributions

FL conceived the research, finished the manuscript and reviewed the final version. XC and MZ extracted data and prepared figures/ tables. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

No competing interests.

Abbreviations

RVO: retinal vein occlusion; CRVO: central retinal vein occlusion; HRVO: hemiretinal retinal vein occlusion; BRVO: branch retinal vein occlusion; BICOMB: Bibliographic item co-occurrence matrix builder; SNA: social network analysis; MeSH: Medical subject headings; FFA: fundus fluorescein angiography; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; CME: cystoid macular edema; IVTA: intravitreal triamcinolone acetonide.

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Tables 1 & 3

Table 1 High-frequency MeSH terms/MeSH subheadings from the included papers on retinal vein occlusion

Rank	Major MeSH terms/ MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
1	Macular Edema / drug therapy	603	4.8818	4.8818
2	Antibodies, Monoclonal, Humanized / therapeutic use	594	4.8089	9.6907
3	Retinal Vein Occlusion / complications	548	4.4365	14.1273
4	Retinal Vein Occlusion / drug therapy	510	4.1289	18.2562
5	Retinal Vein Occlusion / etiology	391	3.1655	21.4216
6	Retinal Vein Occlusion / surgery	367	2.9712	24.3928
7	Retinal Vein Occlusion / physiopathology	290	2.3478	26.7406
8	Retinal Vein Occlusion / diagnosis	276	2.2345	28.9751
9	Glucocorticoids / therapeutic use	242	1.9592	30.9343
10	Triamcinolone Acetonide / therapeutic use	170	1.3763	32.3106
11	Retinal Vein / pathology	153	1.2387	33.5492
12	Visual Acuity / physiology	139	1.1253	34.6745
13	Dexamethasone / therapeutic use	136	1.1010	35.7756
14	Laser Coagulation / methods	125	1.0120	36.7876
15	Tomography, Optical Coherence / methods	115	0.9310	37.7186
16	Vitrectomy / methods	98	0.7934	38.5120
17	Retinal Vein Occlusion / pathology	88	0.7124	39.2244
18	Retinal Vein Occlusion / metabolism	84	0.6801	39.9045
19	VEGFA / antagonists & inhibitors	83	0.6720	40.5764
20	Retinal Vein Occlusion / epidemiology	82	0.6639	41.2403
21	Fluorescein Angiography / methods	80	0.6477	41.8880
22	Retinal Vein Occlusion / genetics	78	0.6315	42.5194
23	Retinal Vein Occlusion / blood	78	0.6315	43.1509
24	Retinal Artery Occlusion / etiology	75	0.6072	43.7581
25	Retinal Vein Occlusion / chemically induced	69	0.5586	44.3167

26	Ranibizumab / therapeutic use	66	0.5343	44.8510
27	Macular Edema / physiopathology	65	0.5262	45.3773
28	Bevacizumab / therapeutic use	64	0.5181	45.8954
29	Macular Edema / etiology	63	0.5100	46.4054
30	Retina / pathology	61	0.4938	46.8993
31	Retinal Vein / surgery	57	0.4615	47.3608
32	Choroid / blood supply	57	0.4615	47.8222
33	Optic Nerve / surgery	56	0.4534	48.2756
34	Retinal Artery Occlusion / complications	45	0.3643	48.6399
35	Macular Edema / diagnosis	44	0.3562	48.9961
36	Electroretinography	40	0.3238	49.3199
37	Anti-Inflammatory Agents / therapeutic use	38	0.3076	49.6276
38	Tissue Plasminogen Activator / therapeutic use	37	0.2995	49.9271
39	Vitreous Body / metabolism	36	0.2915	50.2186
40	VEGFA / metabolism	36	0.2915	50.5100
41	Aqueous Humor / metabolism	35	0.2834	50.7934
42	Vision Disorders / etiology	35	0.2834	51.0767
43	Hyperhomocysteinemia / complications	35	0.2834	51.3601
44	Iris / blood supply	33	0.2672	51.6273
45	Decompression, Surgical / methods	33	0.2672	51.8944
46	Macular Edema / metabolism	33	0.2672	52.1616
47	Macula Lutea / pathology	31	0.2510	52.4126
48	Homocysteine / blood	31	0.2510	52.6635
49	Retina / physiopathology	30	0.2429	52.9064
50	Antiphospholipid Syndrome / complications	29	0.2348	53.1412
51	Factor V / genetics	28	0.2267	53.3679
52	Recombinant Fusion Proteins /	28	0.2267	53.5946

therapeutic use

53	Glucocorticoids / adverse effects	27	0.2186	53.8131
54	Optic Disk / surgery	27	0.2186	54.0317
55	VEGFR / therapeutic use	27	0.2186	54.2503
56	Retinal Vessels / physiopathology	27	0.2186	54.4689
57	Retinal Detachment / etiology	26	0.2105	54.6794
58	Retinal Artery Occlusion / diagnosis	26	0.2105	54.8899
59	Retinal Vein / physiopathology	25	0.2024	55.0923
60	Ophthalmologic Surgical Procedures	25	0.2024	55.2947
61	Optic Disk / blood supply	24	0.1943	55.4890
62	Ischemia / diagnosis	24	0.1943	55.6833
63	Optic Disk / pathology	23	0.1862	55.8695
64	Diabetic Retinopathy / drug therapy	23	0.1862	56.0557
65	Fibrinolytic Agents / therapeutic use	23	0.1862	56.2419
66	Point Mutation	23	0.1862	56.4281
67	Retinal Diseases / diagnosis	22	0.1781	56.6062
68	Retina / blood supply	22	0.1781	56.7843
69	Retinal Vein / physiology	21	0.1700	56.9543
70	Retinal Neovascularization / etiology	21	0.1700	57.1244
71	Retinal Vessels / physiology	21	0.1700	57.2944
72	Vitreous Body / pathology	21	0.1700	57.4644
73	NADPH2 / genetics	21	0.1700	57.6344

VEGFA: Vascular Endothelial Growth Factor A; VEGFR: Vascular Endothelial Growth Factor Receptors;
NADPH2: Methylenetetrahydrofolate Reductase

Table 3A Individual centrality of retinal vein occlusion research

Rank	Major MeSH terms/ MeSH subheadings	Degree	betweenness	Closeness
1	Macular Edema / drug therapy	1894.000	80.059	60.000
2	Antibodies, Monoclonal, Humanized / therapeutic use	1619.000	94.753	62.000
3	Retinal Vein Occlusion / complications	1013.000	204.59	66.000
4	Retinal Vein Occlusion / drug therapy	1369.000	133.827	64.000
5	Retinal Vein Occlusion / etiology	282.000	124.109	57.500
6	Retinal Vein Occlusion / surgery	684.000	94.747	62.000
7	Retinal Vein Occlusion / physiopathology	364.000	136.091	61.500
8	Retinal Vein Occlusion / diagnosis	442.000	177.057	62.500
9	Glucocorticoids / therapeutic use	801.000	42.612	57.000
10	Triamcinolone Acetonide / therapeutic use	557.000	40.277	56.500
11	Retinal Vein / pathology	296.000	83.365	57.500
12	Visual Acuity / physiology	423.000	35.901	56.000
13	Dexamethasone / therapeutic use	442.000	8.775	49.500
14	Laser Coagulation / methods	352.000	34.94	55.500
15	Tomography, Optical Coherence / methods	351.000	31.979	56.000
16	Vitrectomy / methods	239.000	35.908	55.000
17	Retinal Vein Occlusion / pathology	96.000	14.796	51.000
18	Retinal Vein Occlusion / metabolism	144.000	38.806	49.500
19	VEGFA / antagonists & inhibitors	279.000	19.518	51.000
20	Retinal Vein Occlusion / epidemiology	60.000	19.197	49.000
21	Fluorescein Angiography / methods	219.000	19.706	53.500
22	Retinal Vein Occlusion / genetics	73.000	12.664	43.833
23	Retinal Vein Occlusion / blood	39.000	2.870	41.000
24	Retinal Artery Occlusion / etiology	114.000	22.276	48.500
25	Retinal Vein Occlusion / chemically induced	17.000	1.772	41.833
26	Ranibizumab / therapeutic use	246.000	16.643	50.500
27	Macular Edema / physiopathology	138.000	11.415	50.167
28	Bevacizumab / therapeutic use	225.000	25.401	52.500

29	Macular Edema / etiology	172.000	19.417	53.000
30	Retina / pathology	173.000	43.715	57.000
31	Retinal Vein / surgery	132.000	6.812	45.833
32	Choroid / blood supply	128.000	21.483	50.500
33	Optic Nerve / surgery	134.000	16.381	50.000
34	Retinal Artery Occlusion / complications	67.000	5.589	44.000
35	Macular Edema / diagnosis	125.000	5.003	47.500
36	Electroretinography	70.000	3.634	46.500
37	Anti-Inflammatory Agents / therapeutic use	128.000	2.351	44.167
38	Tissue Plasminogen Activator / therapeutic use	67.000	2.167	43.000
39	Vitreous Body / metabolism	90.000	3.881	45.000
40	VEGFA / metabolism	106.000	2.239	45.500
41	Aqueous Humor / metabolism	90.000	4.245	45.500
42	Vision Disorders / etiology	60.000	4.384	46.000
43	Hyperhomocysteinemia / complications	65.000	5.171	41.833
44	Iris / blood supply	45.000	5.346	45.500
45	Decompression, Surgical / methods	84.000	3.642	45.000
46	Macular Edema / metabolism	87.000	3.332	43.833
47	Macula Lutea / pathology	88.000	4.964	47.000
48	Homocysteine / blood	55.000	3.908	40.833
49	Retina / physiopathology	96.000	2.991	47.000
50	Antiphospholipid Syndrome / complications	32.000	0.255	39.167
51	Factor V / genetics	41.000	0.283	37.167
52	Recombinant Fusion Proteins / therapeutic use	129.000	0.174	39.833
53	Glucocorticoids / adverse effects	31.000	0.640	40.500
54	Optic Disk / surgery	66.000	4.719	44.000
55	VEGFR / therapeutic use	126.000	0.174	39.833
56	Retinal Vessels / physiopathology	53.000	8.830	47.500
57	Retinal Detachment / etiology	46.000	4.854	45.000

58	Retinal Artery Occlusion / diagnosis	57.000	3.530	45.000
59	Retinal Vein / physiopathology	38.000	0.350	42.000
60	Ophthalmologic Surgical Procedures	57.000	1.365	41.667
61	Optic Disk / blood supply	44.000	4.631	45.500
62	Ischemia / diagnosis	80.000	10.025	47.000
63	Optic Disk / pathology	35.000	1.299	42.333
64	Diabetic Retinopathy / drug therapy	74.000	3.540	41.667
65	Fibrinolytic Agents / therapeutic use	35.000	0.471	39.667
66	Point Mutation	37.000	1.600	39.333
67	Retinal Diseases / diagnosis	41.000	0.983	42.167
68	Retina / blood supply	23.000	0.000	35.333
69	Retinal Vein / physiology	39.000	2.148	41.833
70	Retinal Neovascularization / etiology	30.000	1.697	40.667
71	Retinal Vessels / physiology	47.000	1.931	43.000
72	Vitreous Body / pathology	31.000	1.771	42.833
73	NADPH2 / genetics	44.000	1.017	38.000

VEGFA: Vascular Endothelial Growth Factor A; VEGFR: Vascular Endothelial Growth Factor Receptors;
NADPH2: Methylene tetrahydrofolate Reductase

Table 3B Descriptive statistics for centrality measure about retinal vein occlusion

Centralization	Mean $\pm$ SD	Min	Max	Network centralization
Degree	220.219 $\pm$ 346.829	17.000	1894.000	6.044%
Betweenness	25.534 $\pm$ 42.030	0.000	204.590	7.140%
Closeness	47.895 $\pm$ 7.168	35.333	66.000	51.35%

Figures

Figure 1

Temporal distribution of publications on retinal vein occlusion in PubMed. A. Number of publications in recent 15 years. B. The top 15 first authors. C. The top 15 countries. D. The top 15 journals.

Figure 2

Biclustering analysis of 73 high-frequency major MeSH terms/MeSH subheadings and articles on retinal vein occlusion. A Mountain visualization of biclustering of 73 high-frequency major MeSH terms/MeSH subheadings and articles. B Matrix visualization of biclustering of 73 high-frequency major MeSH terms/MeSH subheadings and PubMed Unique Identifiers (PMIDs) of articles. The number before each major MeSH terms/MeSH subheadings represents serial number of them as shown in Table 1.

Figure 3

Strategic diagrams for ADSCs. A The meaning of strategic diagram. B Strategic diagram for retinal vein occlusion. Clusters in each strategic diagram refer to biclustering results shown in Table 2. The size of a signal node represents the number of major MeSH terms/MeSH subheadings involved in each cluster.

Figure 4

SNA for 73 high-frequency major MeSH terms/MeSH subheadings in retinal vein occlusion. The size of nodes indicates the MeSH terms centrality. The thickness of the lines indicates the co-occurrence frequency of MeSH terms pairs.

Supplementary Files

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- [tableS1.xlsx](#)