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

*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-1α, -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 /                                             | 170       | 1.3763                      | 32.3106                   |
|   | Title                                                                 | Page | Frequency1 | Frequency2 |
|---|-----------------------------------------------------------------------|------|------------|------------|
| 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 /                                                         | 64   | 0.5181     | 45.8954    |
|   | therapeuti c use                                                                 |   |   |   |
|---|--------------------------------------------------------------------------------|---|---|---|
|  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 |
|   | Topic                                                                 | Page | Position | Score  |
|---|-----------------------------------------------------------------------|------|----------|--------|
| 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 / therapeutic use                         | 28   | 0.2267   | 53.5946|
| 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|
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    |

VEGFA: Vascular Endothelial Growth Factor A; VEGFR: Vascular Endothelial Growth Factor Receptors; NADPH2: Methylene tetrahydrofolate Reductase
| # | Topic                                      | Value 1  | Value 2  | Value 3  |
|---|-------------------------------------------|---------|---------|---------|
| 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  |
|   | Description                                      | Value   | Value 1 | Value 2 |
|---|-------------------------------------------------|---------|---------|---------|
| 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| Electoretinography                               | 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  |
|   | Topic                                                                 | Value 1 | Value 2 | Value 3 |
|---|-----------------------------------------------------------------------|---------|---------|---------|
| 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  |
|   | Description                                | Value 1 | Value 2 | Value 3 |
|---|--------------------------------------------|---------|---------|---------|
| 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; **NAPDH2**: Methylene-tetrahydrofolate Reductase

Table 3B Descriptive statistics for centrality measure about retinal vein occlusion
| Centralization | Mean ± SD | Min   | Max   | Network centralization |
|----------------|-----------|-------|-------|------------------------|
| Degree         | 220.219 ± 346.829 | 17.000 | 1894.000 | 6.044%                |
| Betweenness    | 25.534 ± 42.030   | 0.000  | 204.590 | 7.140%                |
| Closeness      | 47.895 ± 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

This is a list of supplementary files associated with the primary manuscript. Click to download.
table S1.xlsx