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Bibliometric and visualized analysis of DME from 2012 to 2022

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Abstract

Background: Diabetic macular edema (DME) is the main cause of irreversible vision loss in patients with diabetes mellitus (DM), resulting in a certain burden to patients and society. With the increasing incidence of DME, more and more researchers are focusing on it.

Methods: The papers related to DME between 2012 and 2022 from the Web of Science core Collection were searched in this study. Based on CiteSpace and VOS viewer, these publications were analyzed in terms of spatiotemporal distribution, author distribution, subject classification, topic distribution, and citations.

Results: A total of 5165 publications on DME were included. The results showed that the research on DME is on a steady growth trend. The country with the highest number of published documents was the US. Wong Tien Yin from Tsinghua University was the author with the most published articles. The journal of *Retina, the Journal of Retinal and Vitreous Diseases* had a large number of publications. The article "Mechanisms of macular edema: Beyond the surface" was the highly cited literature and "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema" had the highest co-citation frequency. The treatment, diagnosis, pathogenesis, as well as etiology and epidemiological investigation of DME, have been the current research direction. Deep learning has been widely used in the medical field for its strong feature representation ability.

Conclusions: The study revealed the important authoritative literature, journals, institutions, scholars, countries, research hotspots, and development trends in in the field of DME. This indicates that communication and cooperation between disciplines, universities, and countries are crucial. It can advance research in DME and even ophthalmology.

Abbreviations: ACI = average citations per item, BRB = blood-retinal barrier, DM = diabetes mellitus, DME = diabetic macular edema, DR = diabetic retinopathy, IF = impact factor, JCR = Journal Citation Report, OCT = optical coherence tomography, OCTA = optical coherence tomography angiograph, RPE = retinal pigment epithelium, SOTC = sum of times cited, TP = total publications, VEGF = vascular endothelial growth factor, WoSCC = Web of Science Core Collection.

Keywords: bibliometric, deep learning, diabetic macular edema, visualized analysis

1. Introduction

Diabetic macular edema (DME) is one of the ocular complications of diabetes mellitus (DM). It is also a major cause of vision loss in patients with diabetic retinopathy (DR). Given the lifelong disease of DM, macular edema can be persistent and have an extremely elevated recurrence rate after treatment.[1] According to statistics, the global age-standardized prevalence has been on the rise since 2019, and about 25% of patients could experience more severe vision loss in about 3 years without standardized treatment.[2] The macular area is like the "heart" of the eye, a sensitive area of the retina where 90% of the visual cells are concentrated, which is responsible for sharp central vision to show the colorful world. When DM occurs, the small blood vessels and microvessels will be damaged, the blood-retinal barrier (BRB) would be broken, resulting in increased leakage and fluid accumulation in the inner retinal layer of the macular area, finally causes the swelling of macular area.[3] Macular edema can lead to visual cell death and degeneration, and the visual acuity will be severely reduced and even blindness. In most studies, DME is defined as hard exudate in the presence of microaneurysms and punctate hemorrhages within the range of disc diameter of the fovea.[4] The clinically significant macular edema is the more severe

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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type of DME which is defined as edema within 500 μm of the centeral foveal, or a focal photocoagulation scar in the macular area.[5]

The mechanism of etiology and pathogenesis in DME is really complex. Hyperglycemia is the main risk factor for DME, and the primary structural change is the disruption of the BRB. High glucose environment leads to the activation of protein kinase C, increased intraretinal vascular endothelial growth factor (VEGF) concentration, impairment of tight junction proteins, alteration of vascular permeability, and BRB damage, leading to hyperpermeability and vascular leakage.[6,7] Inflammation is a major pathological feature of DME. During the inflammatory process, the increased concentrations of pro-inflammatory cytokines and inflammatory mediators, combined with elevated VEGF levels, leukocyte activation, and stasis, could lead to increased BRB catabolism and vascular permeability.[8,9] For the primary management of DME in general, it was most beneficial to start strict glycemic control early in the onset of DM and before progression to DME.[10] The trial found that there was no significant effect in prognosis improvement by controlling the blood glucose, hyperlipidemia and nonce the patients progressed to DME.[11] A large number of publications about DME have been published in recent years. DME has been discussed from various aspects in these literatures, but there is a lack of systematic summary and overall analysis. Therefore, the research status of DME can be analyzed from the collected publications, which was conducive to researchers to grasp the current research hotspots and research directions, so as to further study DME.

Bibliometrics was an independent discipline formed in the late 1970s and widely used in document analysis.[12] Its analysis, with the help of modern computer technology, can generate a clear visual knowledge map, which provided a quantitative analysis method for the review and investigation of the existing literature in specific fields. Bibliometrics focuses on literature systems and characteristics, investigates hot spots and trends in the scientific literature, describes the relationship between cited and co-cited references, and describes the contributions of different authors, countries, institutions, and journals.[13,14] The Web of Science Core Collection (WoSCC) database has been recognized as one of the most suitable high-quality digital literature resources for bibliometric analysis by numerous researchers, and it has been widely used in various fields such as medicine, geology, ecology, etc. The CiteSpace and VOSviewer are popular software tools for visualizing literature information with their own advantages when performing mapping, and researchers often use them together to play a complementary role. Based on the papers collected by WoSCC as a data sample, this study performed a bibliometric analysis of the DME-related studies published in the last decade. A quantitative and visual analysis of the literature using bibliometric methods was conducted to demonstrate the current state of DME research, to reveal research hotspots and overall development trends, and to provide references for future related research.

2. Methods

2.1. Date collection

To improve the accuracy of the search, we obtained the subject headings from MeSH. We have set the search term as "diabetic macular edema" or "DME," and searched the relevant literature in WoSCC, with the search period between January 1, 2012 and November 28, 2022. The retrieval method was advanced retrieval. The documents which defined as "Article and Review" in WoSCC were collected for analysis. There were no restrictions on language or document types. The documents unrelated to DME should be excluded. Other documents, such as meeting abstract, guidelines, letters or editorials, were excluded too.

2.2. Date analysis

After extracting the data, all documents were analyzed using Microsoft Office Excel 2019, VOSviewer (v.1.6.18), and CiteSpace (v.6.1.R3). Microsoft Office Excel 2019 was used to analyze the temporal distributions and identify highly cited DME-related studies over the past decade. Based on each set parameter, the included documents were processed by VOSviewer for large-scale data processing to construct a relational networks and visualize the knowledge maps of country/region, authors, research institutions, and discipline distributions. The CiteSpace software was used to visualize the basic knowledge and research hotspots in the field of DME research, to predict the development path and research frontiers of DME research. The CiteSpace parameters of time slicing was set as 2012 to 2022, and years per slice were set as (1), node type as cited reference, selection criteria as "$K = 25$," and pruning was set as pathfinder. The flowchart of literature screening and processing is shown in Figure 1.

3. Results

3.1. Temporal distribution map of the literature in publications and citation

A total of 6708 records comprising 11 types of documents were obtained. After excluding diseases unrelated to DME, 5165 documents which defined as "Article (n = 4347) and Review (n = 818)"in WoSCC were collected for analysis. The trend of publications of the retrieved literature was analyzed and shown in Figure 2. The number of publications on DME has generally increased in the recent decade, with the highest number published in 2020 and 2021. The number of publications was the highest in 2020 (684 of papers), but suddenly declined in 2022 (475 of papers). Herein, the number of citations is an important indicator of academic quantitative evaluation.[15] From 2012 to 2022, the frequency of literature cited increased year by year, with the highest number of cited articles published in 2021 (24,448 of papers). But the number suddenly declined in 2022. The overall trend was consistent with the number of publications. The temporal distribution of the 2 illustrates that the current research on DME is gradually becoming a research hotspot

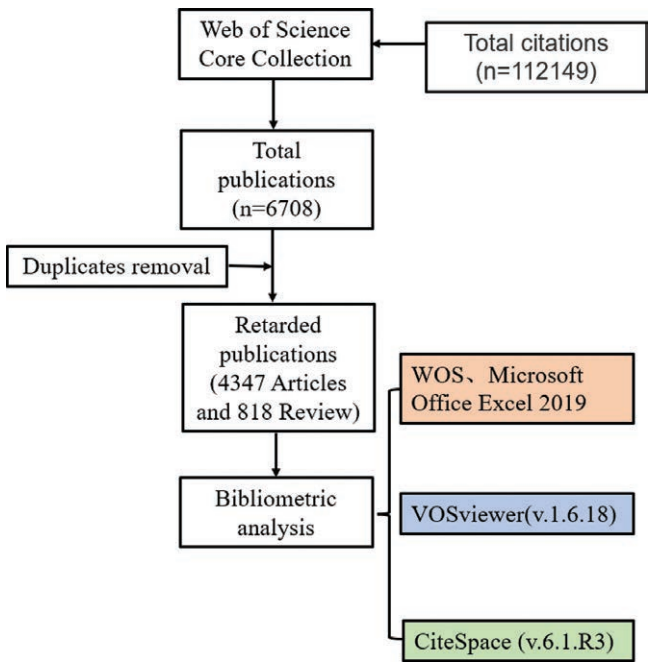

Figure 1. The flowchart of literature screening and processing.

(Fig. 2). However, it will show a decreasing trend in 2022 due to the impact of the Corona Virus Disease 2019.

3.2. Country/region distribution

As shown in Table 1, the country with the highest number of published documents was the United States (US) with 28.75% of the total reports, followed by China and Italy, accounting for 14.54% and 7.09%, respectively. The total number of studies in these 3 countries accounted for half of the total number of reports, indicating that DME research has received wide attention in these 3 countries. England (54.97) and Italy (52.38) had the highest average reference times of single item, indicating that these 2 countries may be relatively mature and authoritative for DME researches.

The VOSviewer parameter "Minimum number of documents for a country" was set to 10. The results were obtained from 100 countries, of which 44 reached the threshold value. Based on the co-occurrence analysis, VOSviewer divided the countries into 4 clusters. Figure 3 shows the cooperation among countries. The US worked mainly with Germany, Brazil, South Korea, and Sweden; China worked closely with Russia, Iran, Poland, Saudi Arabia, and the Czech Republic; and Italy tends to work more closely with Portugal, Switzerland, and Spain.

3.3. Distribution of authors and research institutions

As shown in Table 2, Wong Tien Yin from Tsinghua University was the author with the most published articles, followed by Jennifer K Sun from Harvard University and Ernesto Rodriguez from the JAEB Center for Health Research. Of the remaining 7 authors, 4 were from US universities and research institutions, 1 was from Austria, 1 was from Italy and 1 was from Israel. Although the overall authors were closely related to each other, no clear core group of authors was seen.

The VOSviewer parameters "Minimum number of documents of an author" with the method (Linlog/modularity), were set as 15. The results obtained were for 18,465 authors, and 98 of which met the thresholds. As shown in Figure 4, the different clusters represented the collaboration among authors. The results were shown in close collaboration between Wong Tien Yin, Mitchell Paul, Lamoureux Ecosse L, Sabanayagam Charumathi, Meriaudeau Fabrice, Klein Ronald. Glassman Adam R worked closely with Silva Paolo S, Gardner Thomas W, Melia Michele, and Aiello Lloyd Paul.

As seen in Table 3, the University of California System (176 of papers) was the institution that published the most research papers. It was closely followed by the University of London (175 of papers) and Johns Hopkins University (173 of papers). University of London was the research institution with the highest ACI (57.91), followed by University College London (55.78) and Moorfields Eye Hospital NHS Foundation Trust (55.68). In terms of institutional affiliation, most of them originated from universities and research institutions, with fewer links to enterprises, hospitals, or other administrative institutions.

The VOSviewer parameters "the minimum number of documents of an institution" with method (Linlog/modularity), were set as 20. Results were obtained from 5184 institutions, 108 of which met the threshold. As shown in Figure 5, it could be seen that the institutions were relatively closely linked to each other, forming a cooperative relationship with Johns Hopkins University, Singapore National Eye Centre, University Sydney, and Universita Vita-Salute San Raffaele MILANO as the main clusters, and the DME was studied earlier in these organizations.

3.4. Distribution of disciplines and journals

Regarding the number of published papers, Ophthalmology (58.10%), Computer Science Information Systems (7.18%) and Biochemical Research Methods (6.93%) were the top 3 disciplines as shown in Table 4. Since DME was the leading cause of irreversible vision loss in DM, it was more studied in specialties. However, cross-discipline collaboration was also likely to promote progress and win-win between disciplines. The study of Computer Science Information Systems and Biochemical Research Methods was also on the rise.

As shown in Table 5, Retina the Journal of Retinal and Vitreous (305 of articles) was the most published journal in the field of DME, followed by Investigative Ophthalmology Visual Science (179 of articles) and Ophthalmology

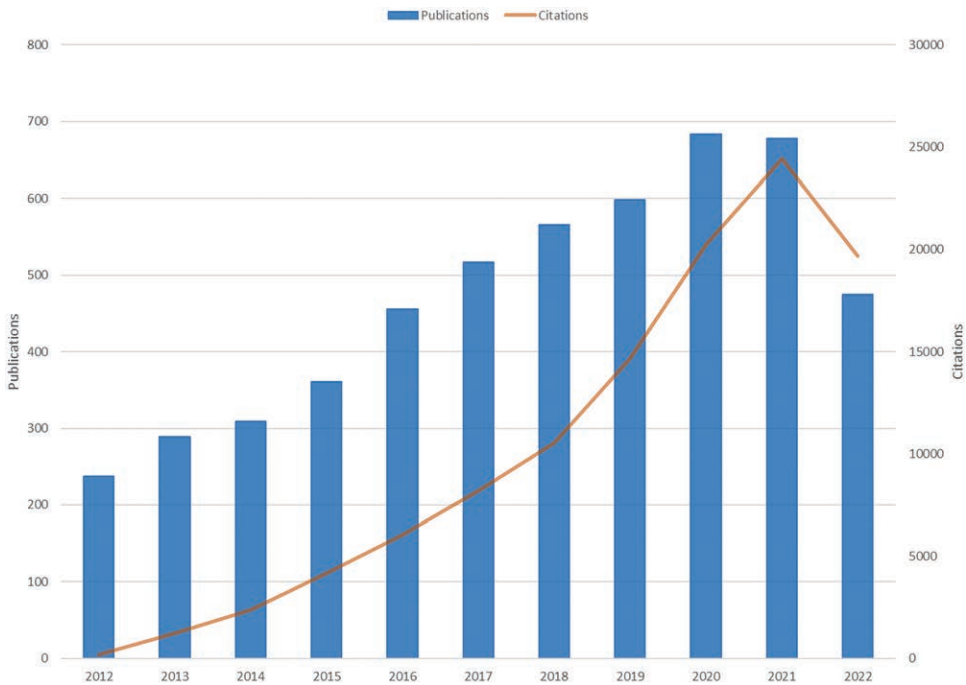

Figure 2. Trends in the growth of publications and citations worldwide from 2012 to 2022.

Table 1

Top 10 productive countries regarding the researches on DME.

Rank	Country	Region	Quantity	Proportion/%	ACI	H-index	Total link strength
1	USA	North America	1485	28.75	49.25	475	1141
2	China	East Asia	751	14.54	44.14	505	376
3	Italy	South Europe	366	7.09	52.38	469	526
4	India	South Asia	354	6.85	42.24	355	392
5	Japan	East Asia	349	6.76	42.54	400	160
6	England	West Europe	343	6.64	54.97	400	658
7	Germany	Central Europe	319	6.18	48.63	400	560
8	Turkey	East Europe	239	4.63	32.96	168	145
9	South Korea	East Asia	234	4.53	35.32	166	109
10	France	West Europe	209	4.05	40.16	532	438

ACI = average citations per item, DME = diabetic macular edema.

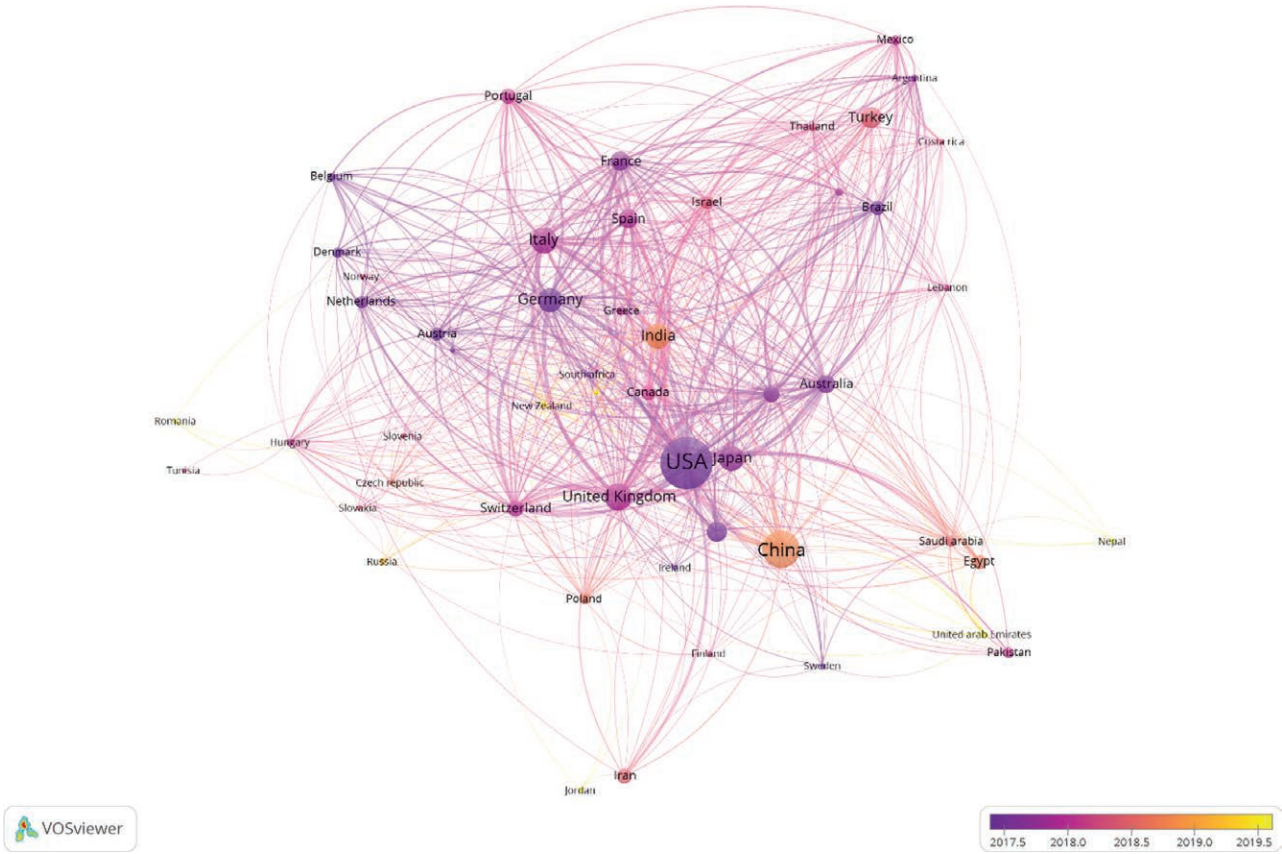

Figure 3. Cooperation map of countries of DME. The coloring is done according to the time course of their appearance, superimposing the time on the network of co-occurring countries. The different colors corresponded to different years, with the more purple color corresponding to an earlier appearance of the country, and the yellow color corresponded to a later. The closer 2 countries were located to each other, the stronger their correlation. DME = diabetic macular edema.

(137 of articles). The journals with the highest ACI were Clinical Medicine, Ophthalmologica, and Investigative Ophthalmology Visual Science in order. From the impact factors of the journals, most of them were dominated by Q1 and Q2, indicating that the relevant papers in DME were of high academic value.

3.5. Highly cited literature and co-cited references

3.5.1. Highly cited literature The citation frequency of a literature is the gold standard for evaluating the literature and assessing the quality and influence of scholarship.[15] Ten highly cited papers are listed in Table 6. The articles including "Mechanisms of macular edema: Beyond the surface," "Ocular Disease Therapeutics: Design and Delivery of Drugs for Diseases of the Eye" and "Photoreceptor cells and retinal pigment epithelium contribute to the development of diabetic retinopathy" were the top 3 articles in terms of number of citations. The article "Mechanisms of macular edema: Beyond the surface" was the most cited paper, reviewed the mechanisms of macular edema formation comprehensively that mainly related to dysregulation of retinal aqueous ion homeostasis.[16] The second cited "Ocular Disease Therapeutics: Design and Delivery of Drugs for Diseases of the Eye," which focused on major advances in drugs for various ophthalmic diseases, described the chemical activity of related drugs and the structure-activity relationships of various chemical classes.[17] The third most cited article "Photoreceptor cells and retinal pigment epithelium contribute to the development of diabetic retinopathy" evaluated the different cell types in the retina in which outer retinal cells played an influential role (directly or

Table 2

Top 10 authors in the studies of DME.

Rank	Author	Country	Institution	TP	ACI	H-index
1	Tien Yin Wong	China	Tsinghua University	62	57.08	216
2	Jennifer K. Sun	USA	Harvard University	56	41.48	136
3	Ernesto Rodriguez	USA	JAEB Center For Health Research	55	17.25	48
4	Charles Wykoff	USA	The Methodist Hospital System	55	32.15	91
5	Neil M. Bressler	USA	Johns Hopkins Medicine	51	19.94	147
6	Ursula Schmidt-Erfurth	Austria	Medical University of Vienna	50	47.74	304
7	Srinivas Sadda	USA	Doheny Eye Institute	49	52.49	375
8	Francesco Bandello	Italy	IRCCS Ospedale San Raffaele	48	41.27	207
9	Quan Dong Nguyen	USA	Stanford University	44	41.11	141
10	Anat Loewenstein	Israel	Tel Aviv University	41	50.80	171

ACI = average citations per item, DME = diabetic macular edema, TP = total publications.

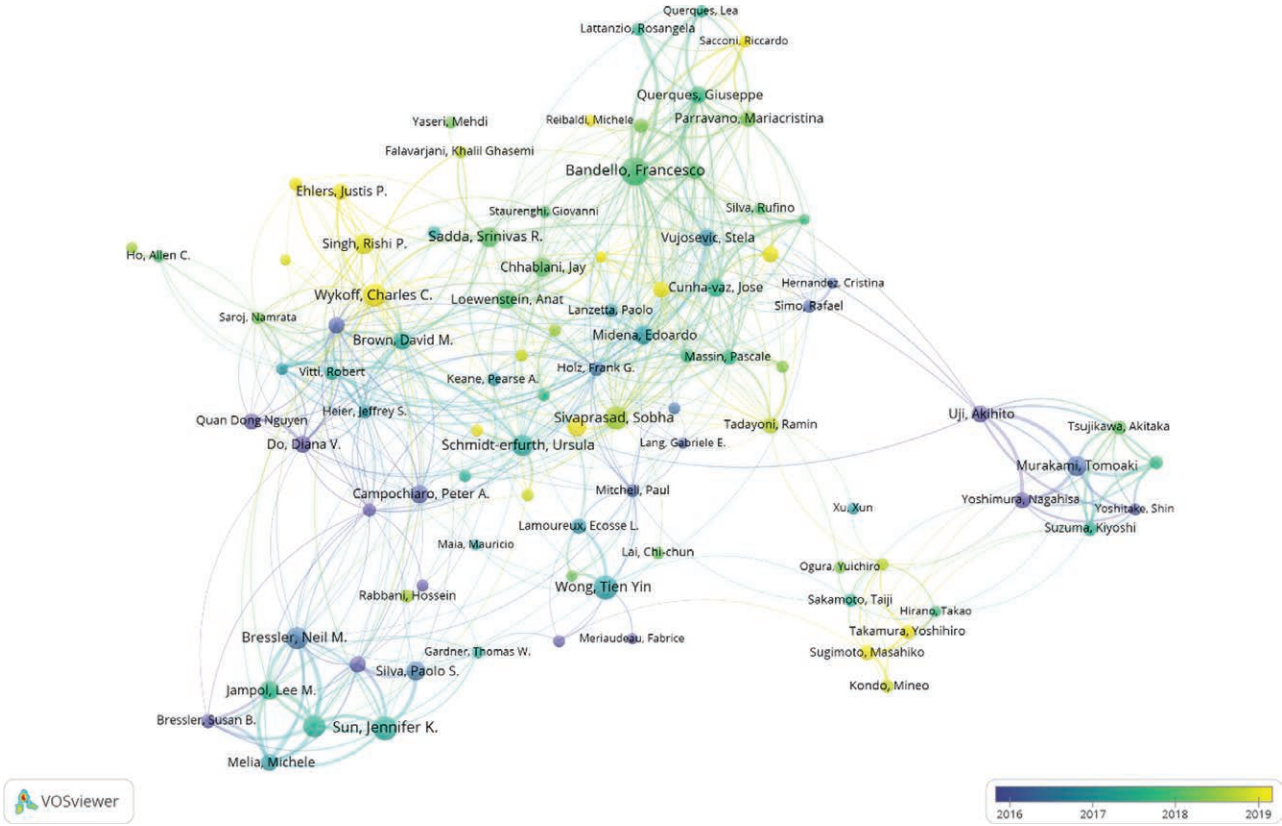

Figure 4. Cooperation map of authors.

Table 3

Top 10 institutions in the studies of DME.

Rank	Institution	Country	Quantity	SOTC	ACI	H-index
1	University of California System	USA	176	9091	51.65	475
2	University of London	England	175	110,134	57.91	400
3	Johns Hopkins University	USA	173	6554	37.88	292
4	Harvard University	USA	157	8394	53.46	469
5	Johns Hopkins Medicine	USA	148	5337	36.06	292
6	University College London	England	144	8033	55.78	400
7	Harvard Medical School	USA	139	7447	53.58	469
8	Moorfields Eye Hospital NHS Foundation Trust	England	117	6514	55.68	395
9	Udice French Research Universities	France	113	5000	44.25	532
10	Egyptian Knowledge Bank EKB	Egypt	111	4905	44.19	343

ACI = average citations per item, DME = diabetic macular edema, SOTC = sum of times cited.

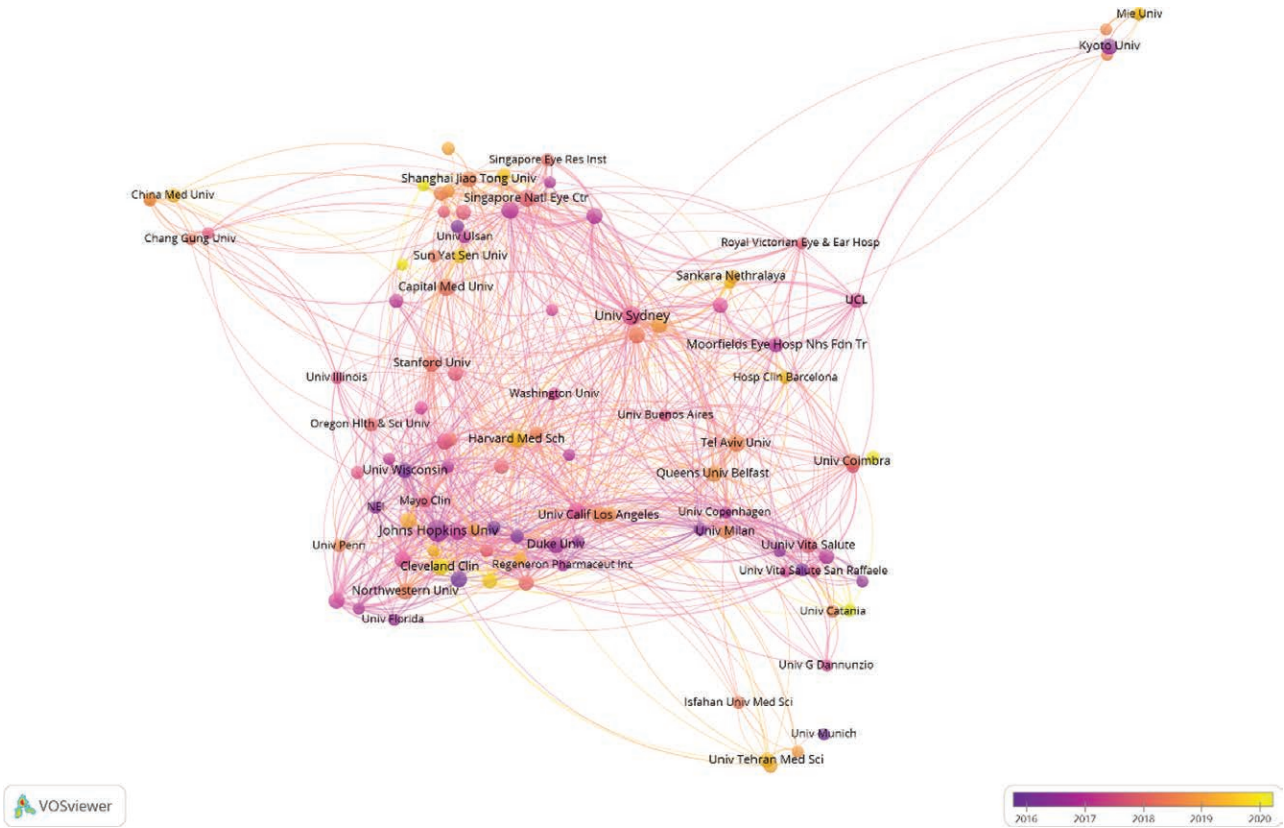

Figure 5. Cooperation map of research institutions.

Table 4

Disciplines within the top 20 in the studies of DME.

Rank	Quantity	WoSCC categories	Percentage/%
1	3001	Ophthalmology	58.10
2	371	Computer Science Information Systems	7.18
3	358	Biochemical Research Methods	6.93
4	328	Pharmacology Pharmacy	6.35
5	241	Multidisciplinary Sciences	4.67
6	215	Medicine Research Experimental	4.16
7	141	Biochemistry Molecular Biology	2.73
8	141	Surgery	2.73
9	132	Engineering Biomedical	2.56
10	105	Engineering Electrical Electronic	2.03
11	97	Radiology Nuclear Medicine Medical Imaging	1.88
12	88	Cell Biology	1.70
13	82	Optics	1.59
14	72	Health Care Sciences Services	1.39
15	69	Computer Science Interdisciplinary Applications	1.39
16	66	Computer Science Artificial Intelligence	1.28
17	63	Chemistry Multidisciplinary	1.22
18	62	Computer Science Information Systems	1.20
19	60	Biochemical Research Methods	1.16
20	51	Chemistry Medicinal	0.99
21	47	Computer Science Theory Methods	0.91

DME = diabetic macular edema.

indirectly) in the pathogenesis of diabetic retinal vascular and neuronal damage or dysfunction.[18]

From Table 6, 6 of the most cited documents were reviews and 4 were articles. Judging by the number of citations, the guidelines were more frequently cited. As far as the time of publication of the greatly cited literature, the highly cited literature was more between 2018 and 2021.

3.5.2. Co-cited references The network community structure of this study is shown in Figure 6, which indicates that this study was well clustered and its network community structure was high homogeneous and reliable.[19]

In Table 7, the article "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema" had a significant impact in the field and had the highest co-citation frequency that showed the larger node in Figure 6. This article demonstrated in 2015 through a clinical trial study that in the treatment of DME intravitreal injections of abciximab, bevacizumab, or ranibizumab all improved vision loss due to DME, with no significant difference in the degree of improvement, but abciximab was more effective in improving vision in the presence of poor initial vision levels.[20] The article "Ranibizumab for DME: results from 2 phase III randomized trials: RISE and RIDE" was the second most cited one while "The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema" was the third most cited article.[21] The first 2 papers demonstrated the efficacy of ranibizumab for the treatment of DM. The third most cited article found no significant difference in effectiveness of ranibizumab monotherapy versus laser combination.[22] The second most cited article indicated that ranibizumab rapidly and sustainably improved macular edema and reduced the risk of further loss of strength in patients with DME, with a low rate of complications from ocular and nonocular damage.[23]

Figure 7 displays the top 25 papers with the strongest citation bursts. The strongest citation burst was the article published for 2011 "The Restore study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema," which had an intensity of 93.86.

3.6. Research hotspots and frontier analysis

3.6.1. Research hotspots analysis Keywords were highly summarized articles whose frequency reflected the hot spots

Table 5

Journals within top 20 the studies of DME.

Rank	Quantity	Journal	ACI	IF (2022)	JCR
1	305	*Retina the Journal of Retinal and Vitreous*	32.25	3.975	Q2
2	179	*Investigative Ophthalmology Visual Science*	41.23	4.925	Q1
3	137	*Ophthalmology*	32.44	14.277	Q1
4	128	*Graefes Archive for Clinical and Experimental Ophthalmology*	35.33	3.535	Q2
5	120	*European Journal of Ophthalmology*	30.52	1.922	Q4
6	118	*Plos One*	39.86	3.752	Q2
7	110	*Clinical Ophthalmology*	39.53	4.383	Q1
8	103	*Scientific Reports*	40.88	4.996	Q1/3
9	100	*American Journal of Ophthalmology*	33.01	5.488	Q1
10	98	*Ophthalmic Surgery Lasers Imaging Retina*	24.77	1.296	Q4
11	96	*JAMA Ophthalmology*	26.57	8.253	Q1
12	93	*Journal of Ophthalmology*	40.20	1.974	Q4
13	91	*International Journal of Ophthalmology*	31.75	1.645	Q4
14	89	*Indian Journal of Ophthalmology*	36.57	2.969	Q3
15	84	*Ophthalmologica*	43.11	3.757	Q2
16	82	*BMC Ophthalmology*	32.54	2.086	Q3
17	82	*International Ophthalmology*	31.46	2.029	Q3
18	69	*Ophthalmology Retina*	29.38	0.000	N/A
19	67	*Eye*	41.00	4.456	Q1
20	58	*Journal of Clinical Medicine*	58.79	4.964	Q2
21	58	*Ophthalmic Research*	32.09	3.031	Q3

ACI = average citations per item, DME = diabetic macular edema, IF = impact factor, JCR = Journal Citation Report.

Table 6

Top 10 highly cited literature.

Rank	Title	Journal	Type	Author	Year	SOTC
1	Mechanisms of macular edema: beyond the surface	*Prog Retin Eye Res*	Review	Alejandra Daruich	2018	532
2	Ocular disease therapeutics: design and delivery of drugs for diseases of the eye	*J Med Chem*	Article	Kuei-Ju Cheng	2020	505
3	Photoreceptor cells and RPE contribute to the development of diabetic retinopathy	*Prog Retin Eye Res*	Review	Deoye Tonade	2021	475
4	Retinal applications of swept source OCT and OCTA	*Prog Retin Eye Res*	Review	Inês Laíns	2021	469
5	Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions	*Prog Retin Eye Res*	Article	Ingeborg Klaassen	2013	434
6	Targeting RGD-binding integrins as an integrative therapy for diabetic retinopathy and neovascular age-related macular degeneration	*Prog Retin Eye Res*	Review	Inge Van Hove	2021	401
7	VEGFR1 signaling in retinal angiogenesis and microinflammation	*Prog Retin Eye Res*	Review	Akiyoshi Uemura	2021	400
8	Preclinical challenges for developing long acting intravitreal medicines	*Eur J Pharm Biopharm*	Article	Sahar Awwad	2020	395
9	Connexin43 in retinal injury and disease	*Prog Retin Eye Res*	Article	Helen V. Danesh-Meyer	2016	387
10	Optical coherence tomography angiography	*Prog Retin Eye Res*	Review	Richard F. Spaide	2018	375

OCT = optical coherence tomography, OCTA = optical coherence tomography angiography, RPE = retinal pigment epithelium, SOTC = sum of times cited.

in a particular research field. A map of keyword co-occurrence analysis was consisted by nodes and concatenated lines of keywords after the software processing. Keywords from 5616 retrieved documents were analyzed for co-occurrence and similar items were combined to obtain Figure 8. The VOSviewer parameters "Minimum number of occurrences of a keyword" with method of Linlog/modularity was set to 50. There were 10,056 keywords and 142 of them satisfied the threshold. For each of the 142 keywords, the total strength of co-occurring links with other keywords was calculated, and the top 20 keywords with the greatest total link strength were selected to form Table 8. Since the search term for this study was DME, it was logical that it should appear most frequently. The next most frequent term was DR. In general, DR stage III and above were combined with macular edema in the macular region, which can severely affect the patient's visual acuity.

Figure 8 divides the keywords into 4 clusters, which represented the 4 major research directions of DME at present. Red cluster focused on the treatment of DME as a main research direction. Keywords were mainly drugs used for the treatment of DME such as ranibizumab, aflibercept, bevacizumab, triamcinolone acetonide, dexamethasone, growth-factor therapy, etc. All of the above treatments are currently the first line of clinical treatment for anti-VEGF drugs with intravitreal injection and conventional treatment with laser therapy. Green cluster focused on the diagnosis of DME, including clinical symptoms and detection tools. Clinical symptoms included age, visual acuity, degeneration, retinopathy, macular degeneration, edema, venous occlusion, and glaucoma, etc. Detection tools included coherence tomography angiography, fluorescein angiography, choroidal neovascularization, and foveal avascular zone. Blue cluster has been associated with the pathogenesis of DME, including VEGF, inflammation, proliferative DR, oxidative stress, BRB, neovascularization, and neurodegeneration. Yellow cluster focused on studies related to the etiology and others on DME. Its keywords were mainly risk factors, macular edema, epidemiology, progression, DM, management, and complications, etc.

3.6.2. Research frontiers identification Based on the keywords co-occurrence network, we conducted the keywords emergent word detection. Keyword emergence referred to a significant increase in the keyword frequency over a relatively short period of time. By conducting keyword emergence

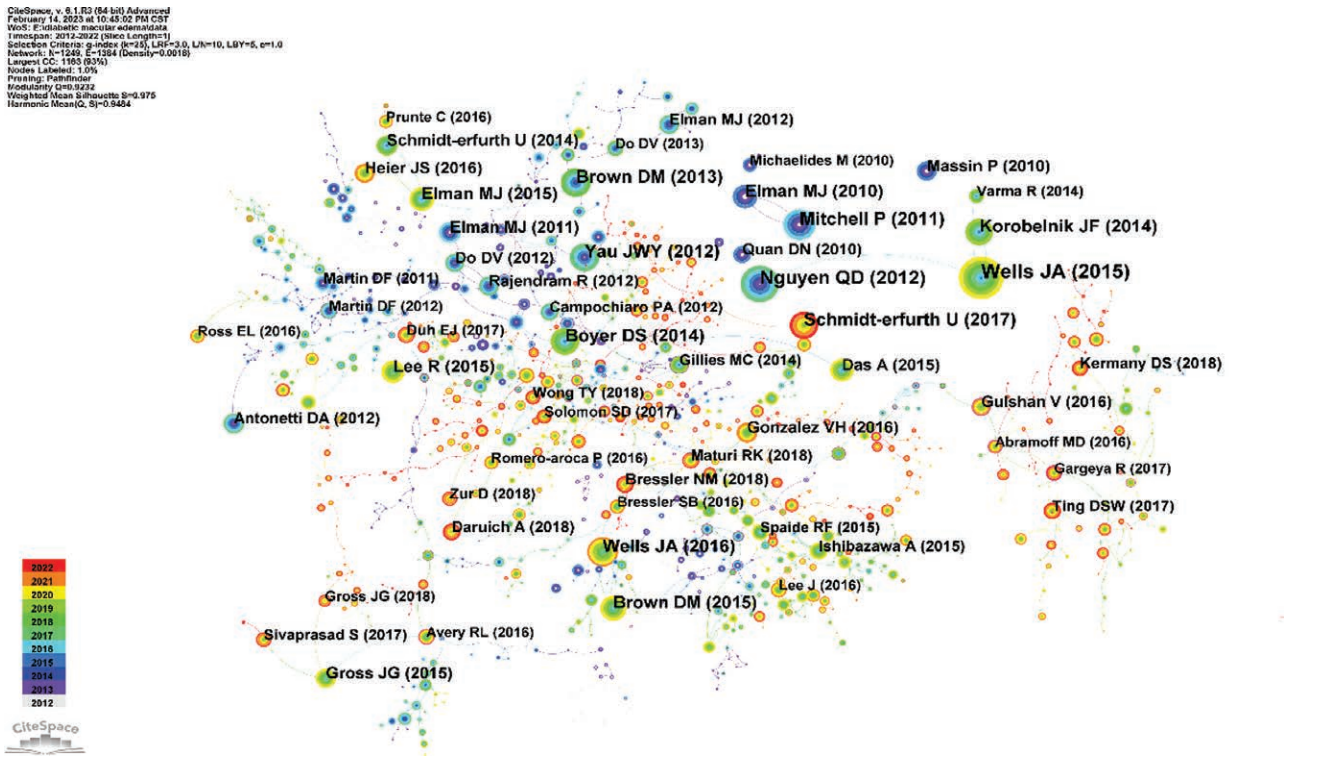

Figure 6. References co-citation network. According to the parameters, a network with 1249 nodes, 1384 connections, and 0.0018 density was obtained. The value Modularity *Q* was 0.77, and Silhouette *S* was 0.90. Modularity is an evaluation index for network modularity. The larger the Modularity value of a network, the better its clustering. The value space of *Q* was set as "[0, 1]," The value *Q* > 0.3 meant that the obtained clustering structure was significant, and when the value of *S* was set above 0.5, the clustering is generally considered reasonable, and at 0.7, it means that the clustering is convincing. The closer the *S* value is to 1, the better the network homogeneity is indicated.

analysis, we can more clearly understand the research hotspots in a certain time period and judge the development direction of research. Figure 9 reports the top 25 keywords with the strongest citation explosion in the last decade of DME research. "Strength" indicates the strength of the keyword mutation, which is proportional to the impact of the keyword. These were Avastin, validation, artificial intelligence (AI), reproducibility, etc. Early targets of attention in the last decade of research on DME have been retinal thickness, epithelium-derived factors, proliferative DR, and intravitreal triamcinolone. Notably, deep learning had the strongest burst of citations. Deep learning as multilayer neural networks is a machine learning method that is a novel element in the field of ophthalmology and has shown greater application advantages and promise in the research process of ophthalmic diseases. In addition to topic terms, keywords shown so far in AI, transfer learning, and subthreshold micropulse lasers were closely related to computers with strong prospects for application in ophthalmic treatment and diagnosis. This also suggested that cross-discipline is also a hot spot in current DME research.

4. Discussion

4.1. General information

Our study showed that the number of publications and citations frequency of DME had increased significantly since 2014, reaching a peak value in 2020. The Royal Society of Ophthalmologists in the UK had revised the new guidelines in 2020, which are based on the guidelines released by the Royal College of Ophthalmology in 2013 and the European Ophthalmology Guidelines in 2017. The guidelines summarized the pathogenesis of DR and DME, and also reviewed their treatment methods.[24] With the deepening of research, more researchers have turned their attention to DME, and more and more relevant literature has been published.

This was an indication of the high international interest in the study of DME. Currently, China holds an important place in terms of research attention and research achievements, and has a high academic reputation. However, our study found that the current research on DME was not closely linked between countries. Developed countries or European countries were not closely linked to developing countries. No obvious core group was formed between authors and institutions. Communication between institutions was only limited to the regional or domestic context of their respective countries. Therefore, it is important to strengthen international cooperation, exchange results, break down international barriers, form an international core research team, and then promote the further development of DME. In addition, this study found that DME was closely related to research in AI, computer science information, and biochemistry. Currently, digital medical technology can enable intelligent communication of information during medical process. The routine diagnosis of ophthalmic diseases in clinical practice increasingly relies on various forms of ophthalmic machinery and equipment. They can capture ophthalmic images during the course of the disease, which can reflect changes in the course of the disease and thus be used for clinical assessment of the diseases.

4.2. The hotspots and frontiers

Through keyword clustering analysis, it was found that the current research hotspots in DME were divided into 4 main aspects, including treatment, diagnosis, pathogenesis and etiology, and others of DME. Currently, deep learning is in an explosive period, and will become a hot frontier in the DME field.

Table 7

Top 10 co-cited references.

Rank	Frequency	Centrality	Title	Journal	Author	Year
1	436	0.01	Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema	*New Engl J Med*	John A. Wells	2015
2	326	0.01	Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE	*Ophthalmology*	Quan Dong Nguyen	2012
3	258	0.01	The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema	*Ophthalmology*	Paul Mitchell	2011
4	231	0.01	3-y, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema	*Ophthalmology*	David S. Boyer	2014
5	221	0.02	Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: 2-y results from a comparative effectiveness randomized clinical trial	*Ophthalmology*	John A. Wells	2016
6	218	0	Guidelines for the management of diabetic macular edema by the EURETINA	*Ophthalmology*	Ursula Schmidt-Erfurth	2017
7	216	0.01	Global prevalence and major risk factors of diabetic retinopathy	*Diabetes Care*	Joanne W. Y. Yau	2012
8	213	0	Intravitreal aflibercept for diabetic macular edema	*Ophthalmology*	Jean-François Korobelnik	2014
9	207	0.02	Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-mo results from 2 phase III trials: RISE and RIDE	*Ophthalmology*	David M. Brown	2013
10	186	0.06	Intravitreal aflibercept for diabetic macular edema: 100-wk results from the VISTA and VIVID studies	*Ophthalmology*	David M. Brown	2015

EURETINA = European Society of Retina Specialists.

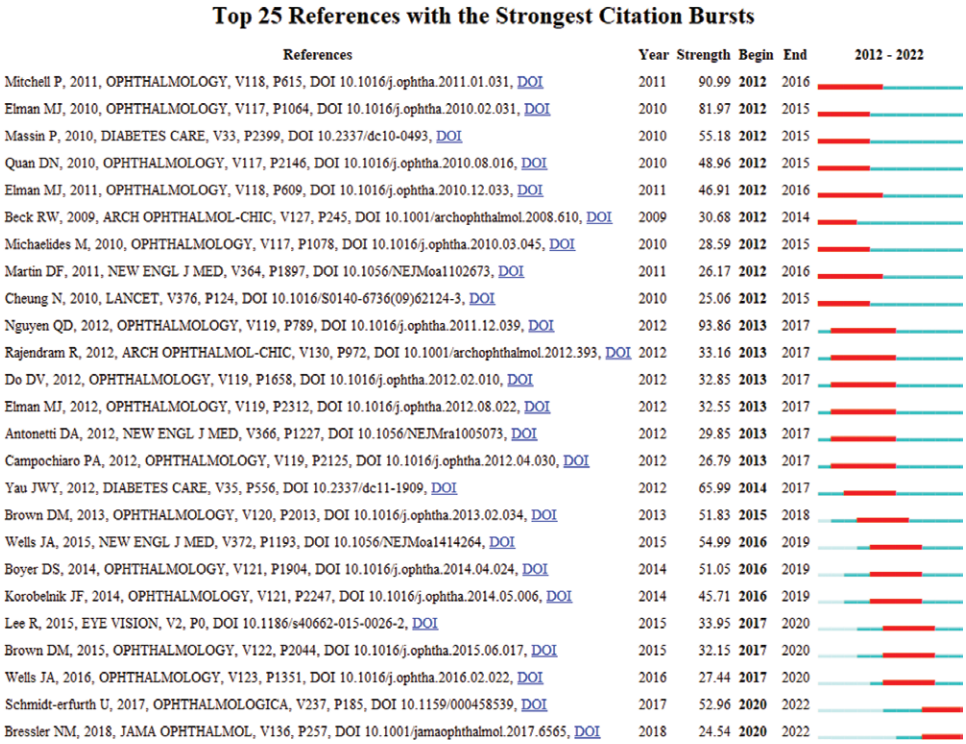

Figure 7. Top 25 references with the strongest citation bursts.

The red cluster involved the intravitreal injections of anti-VEGF drugs of DME. It had been found that intravitreal injections of anti-VEGF drugs had gradually replaced surgery and laser photocoagulation as the new standardized treatment methods for DME according to keywords. This method was more effective than before and could reduce side effects.[25] Ranibizumab was a recombinant humanized monoclonal antibody fragment that could bind to all subtypes of VEGF-A with high affinity. Ranibizumab entered clinical trials for neovascular age-related macular degeneration in 2000 and was approved by the US Food and Drug Administration in the same year. It has been found that this drug had a significant therapeutic effect on DME, with relatively small side effects and complications, and could quickly improve patients' vision.[26] Aflibercept was a key structural domain of human VEGF receptors 1 and 2, fused with the fragment of human immunoglobulin G and bound to various subtypes of VEGF-A, VEGF-B, and placental growth factor.[27] Ron Hashmonay found that the treatment of intravitreal aflibercept was significantly superior to laser in terms of function and anatomical endpoints, and had a longer duration of action in the eyes and excellent tolerance.[28] Bevacizumab is a full-length, humanized monoclonal antibody that targets all subtypes of VEGF. Bevacizumab has a lower cost and is more commonly used in clinical practice compared with ranibizumab.[29] Currently, anti-VEGF drug therapy is considered the most promising treatment for vision loss due to DME. The above

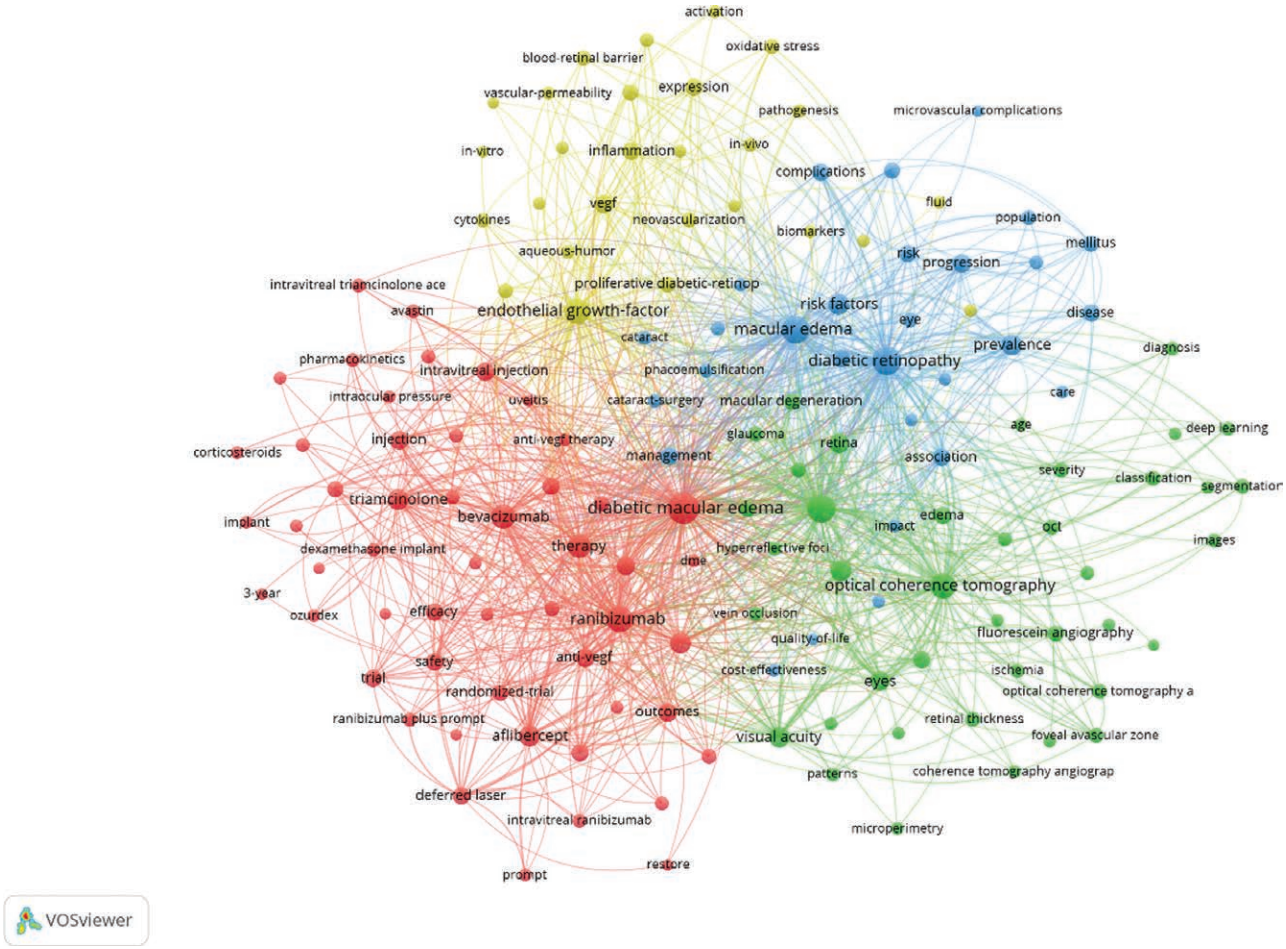

Figure 8. Map of keyword clustering in the studies of DME. Larger nodes in the analysis of keyword visualization map indicated greater frequency of keyword occurrences. The different colors indicated the keyword clustering maps. DME = diabetic macular edema.

Table 8

Keywords within the top 20 in the studies of DME.

Rank	Keywords	Occurrences	Total link strength	Rank	Keywords	Occurrences	Total link strength
1	diabetic macular edema	2008	10,538	12	visual acuity	457	2883
2	diabetic retinopathy	1478	7815	13	prevalence	444	2398
3	macular edema	1370	6935	14	photocoagulation	443	2704
4	retinopathy	1254	7230	15	risk factor	429	2549
5	ranibizumab	1100	7148	15	triamcinolone	407	2798
6	optical coherence tomography	983	5156	16	diabetes	394	2292
7	endothelial growth factor	863	5394	17	aflibercept	393	2750
8	bevacizumab	711	4881	18	vascular endothelial	388	2527
9	therapy	611	3800	19	degeneration	373	2093
10	eye	487	2727	20	retina	234	1891

DME = diabetic macular edema.

3 drugs of anti-VEGF were commonly used in clinical practice to treat DME.[30] If systemic risks such as cardiovascular events and financial burden will not tolerated, local corticosteroid therapy is preferred, commonly including triamcinolone acetonide and dexamethasone. By analyzing the above keywords, we can understand the current main therapeutic drugs for DME and provide theoretical support for clinical diagnosis and treatment.

The green cluster was mainly associated with DME diagnosis. DME can be effectively diagnosed through clinical manifestations and examination methods. DME is a relatively common retinal disease, which may be caused by retinal vein occlusion, diabetes retinopathy, and other reasons.[31] It is commonly manifested as macular edema, visual cell death, and degeneration. The visual acuity will be seriously reduced, even blindness, and optical atrophy may also be caused without timely treatment. It had been shown that the prevalence of DME in patients with DR range from 2.7% to 11.0%.[4] In addition, the prevalence of DME was associated with gender, disease courses, and glycemic control in diabetics.[4,32] The patients with DME were mainly elderly, so the age was also one of the factors affecting DME.[33] Fluorescein fundus angiography, as a diagnostic method for DME, can be used to identify non-perfusion areas, leakage microaneurysms, and diffuse leakage areas. When injecting fluorescein into the circulatory system, the image was

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2012 - 2022
avastin	2012	12.18	2012	2014	
reproducibility	2012	10.51	2012	2017	
intravitreal triamcinolone	2012	9.17	2012	2013	
retinal thickness	2012	8.42	2012	2012	
epithelium derived factor	2012	7.41	2012	2016	
permeability	2012	7.29	2012	2016	
posterior vitreous detachment	2012	7.19	2012	2014	
protein kinase c	2012	7.06	2012	2014	
pars plana vitrectomy	2012	6.81	2012	2014	
proliferative diabetic retinopathy	2012	6.28	2012	2013	
vegf trap eye	2012	7.13	2013	2016	
endothelial growth factor	2012	8.86	2014	2014	
significant macular edema	2012	6.16	2014	2016	
controlled trial	2012	8.66	2015	2016	
prompt	2012	9.17	2016	2018	
validation	2012	11.29	2019	2022	
coherence tomography angiography	2012	8.45	2019	2022	
vessel density	2012	7.98	2019	2022	
convolutional neural network	2012	7.34	2019	2022	
anti-vascular endothelial growth factor	2012	6.15	2019	2022	
deep learning	2012	22.24	2020	2022	
artificial intelligence	2012	10.59	2020	2022	
transfer learning	2012	6.17	2020	2022	
subthreshold micropulse laser	2012	6.17	2020	2022	
diabetic macular edema (dme)	2012	9.3	2021	2022	

Figure 9. Top 25 keywords with the strongest citation burst.

captured by the fundus camera to observe the changes in the intensity of fluorescein and identify the leakage area.[32] Optical coherence tomography angiography (OCTA) can observe the superficial and (or) deep capillary plexus of diabetes retinopathy, such as microangioma, vascular loop, nonperfusion, neovascularization, expansion of the microvascular zone in the fovea of the macula, and beaded veins in several different capillary beds.[33] In addition, OCTA has been used for quantitative tracking of intravitreal injection of anti-VEGF and laser coagulation therapy currently.[34] According to the above keyword analysis, the elderly people with DM should be of high concern. And they can regularly review OCTA and fluorescein fundus angiography to be alert to the occurrence of DME.

The blue cluster depicted the current dominant pathogenesis of DME. DME was the leading cause of vision loss in DM. Its pathogenesis was complex and influenced by a number of factors. When DME occurred, reactive oxygen species in cell mitochondria excessively deposited due to the elevated blood sugar, leading to oxidative stress response. In addition, reactive oxygen species can promote the production of inflammatory factors such as nuclear factor κ-B, protein kinase C and mitogen activated protein kinase exacerbates inflammation.[35] When long-term hyperglycemia damages retinal microvessels, cell hypoxia led to increased expression of hypoxia inducible factor-1, and activated the VEGF gene and promoted VEGF expression, then subsequently affected a series of retinal cells including retinal capillary epithelial cells, pericytes, retinal pigment epithelial cells, retinal glial cell.[36] Especially in the early stages, white blood cells adhered to retinal vascular endothelial cells on account of DME. That led to endothelial cell apoptosis, vascular leakage, and capillary closure. Eventually, the retinal became ischemic and hypoxic, and further damage to the BBR and failure of neurovascular units would break out.[37] Endothelial cell apoptosis can lead to retinal neovascularization, which in turn can cause damage to astrocytes or glial cells, leading to macular edema.[24] The blue cluster depicted the current dominant pathogenesis of DME. Many recent studies suggested that among the numerous pathogenic factors of DME, the most significant factor was the increase in VEGF concentration.[38,39] Based on in-depth studies of DME, multiple treatment plans have been developed, but the systematic treatment plans for DME remained limited. It was hoped that additional in-depth research into the pathogenesis of DME would lead to the development of more effective treatment regimens for DME.

Yellow cluster focused on studies related to the etiology and management on DME. Among the etiology for DME, diabetics had a lengthy course of disease and their blood sugar is poorly controlled for most of the time. The type 2 of DM accounted for a large proportion, but it was worth noting that the prevalence of DME in patients with diabetes type 1 was higher than that in patients with type 2 of DM.[40] The keyword of DM, the leading cause and risk factor for DME, appeared more frequently in the yellow cluster analysis in this study. In addition to DM, most of these patients were complicated with hypertension, hyperlipidemia, and other diseases.[41] Disease management of DME was also critical due to the prolonged course of the disease. Calabrò et al[42] increased the use of dexamethasone implants in Italian healthcare environments to improve vision and quality of life for DME patients, reducing the burden of injection on patients and social costs. Hoxhaj et al[43] believed that in clinical practice, the capacity building and technological innovation by healthcare professionals in this area should also be strengthened to implement evidence-based healthcare options. They also thought that should ensure appropriate health governance and value-based applications of technological innovation in clinical practice.[43]

Currently, deep learning is in an explosive phase of development and will be a hot research direction for DME in the future. The concept of deep learning originates from the research of artificial neural networks, whose algorithm was a new type of automatic image analysis method based on AI, allowing for the evaluation of large amounts of data.[44] Deep learning can be used to improve the accuracy of DME diagnosis, evaluate the treatment response, and further deepen the clinical research on DME. Roberts et al[45] used deep learning algorithms to quantify and objectively evaluate intra retinal fluid and subretinal fluid. They have found that the presence and quantity of intra retinal fluid and subretinal fluid can serve as a measure of individual treatment response. Han et al[46] found that the 05D-CNN algorithm through deep learning can significantly improve the accuracy and sensitivity of magnetic resonance imaging image recognition and segmentation in DME patients, markedly improve the diagnostic accuracy of magnetic resonance imaging in DME patients, and have good clinical application value. Varadarajan's et al[47] research had shown that deep learning can be used to predict DME models through simple two dimensional images, from fundus photographs, and can reduce false negatives in diagnosing DME. The application of deep learning in ophthalmic diseases have gradually becoming widespread.[48] By leveraging deep learning models, better performance can be achieved through end-to-end automatic feature optimization to assist physicians in diagnosing ophthalmic diseases and improving accuracy. Previous studies on DR had shown that the development and validation of deep learning algorithms have made major breakthroughs in the early diagnosis of DR, and were also at the forefront of current DR Research.[49] It showed the importance of deep learning and AI in ophthalmology research, and the integration of multiple disciplines can better promote the development of ophthalmology.

5. Strengths and limitations

In this study, literature on DME was analyzed for the first time using bibliometric and visualization techniques. Compared with

the traditional literature review, the bibliometric visualization analysis provides a more intuitive and comprehensive picture of the research hotspots and frontiers of DME.[50,51] However, our study also had some limitations. First, it was difficult to merge and analyze data from different databases, such as PubMed, Scopus, or Embase, due to the limitations of the visual analysis software.[52] We only searched the WoSCC database, which was the most well-known database for scientific publications in many research topics. Other databases may provide wider coverage,[53,54] and therefore some relevant studies may be missed. Second, CiteSpace and VOSviewer cannot completely replace systematic searching. Last but not least, the continuously updated nature of the databases, there was a discrepancy between the number of studies obtained and the actual number of literature. Hence the most recent data were not included in this study. Despite these limitations, our findings were still of significant reference value. Visual analysis based on literatures lays a foundation for understanding the research topics, research hotspots, and development trends in the field of DME, which is of great significance in promoting the development of the research field and guiding future research directions.

6. Conclusion

This study provided a quantitative analysis of the literature related to DME over the past decade, elaborating on its research progress, hotspots, and frontiers. At the same time, it was found that the major current research trends in DME lied in treatment, diagnosis, pathogenesis, etiology, and others. This study shed light on relevant authoritative literature, journals, institutions, scholars, and countries that played influential roles in the field of DME, which could provide directions for additional research on DME and enhance cooperation and exchange among various institutions and international organizations. Interdisciplinary collaboration, especially for the development of AI and the establishment of deep learning models, was of great significance and guidance for the diagnosis and treatment of DME. In short, we hope that with further research on DME, it can alleviate the suffering patient and advance the discipline.

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