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Research article

Trends and hot spots in research related to aqueous humor from 2014 to 2023: A bibliometric analysis☆

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ABSTRACT

Purpose: To analyze publication trends and investigate research hotspots of aqueous humor (AH) studies.
Methods: A bibliometric study was conducted based on the Web of Science Core Collection (WOSCC). VOSviewer v. 1.6.18 was utilized to create a knowledge map visualizing the number of annual publications, the distribution of countries, international collaborations, author productivity, source journals and keywords in the field.
Results: A grand total of 4020 peer-reviewed papers concerning AH were retrieved from 2014 to 2023. The United States of America secured the top position among the most published countries and Duke University emerged as the most active institution. Stamer, WD contributed the most papers in this area. *Investigative Ophthalmology & Visual Science* was the most prolific journal in AH research. Retrieved publications mainly concentrated on the correlation between AH as a biomarker carrier and different ocular disorders. Six clusters were formed based on the keywords: (1) the diagnosis of endophthalmitis and AH pharmacokinetics; (2) the association of AH with pathogenesis and prognosis of glaucoma; (3) diagnosis and treatment of AH associated with uveitis; (4) the relationship between AH and refractive diseases of the eye; (5) the association of AH with mechanism and biomarkers of ocular tumorigenesis; (6) the indicators of AH associated with fundus disease.
Conclusions: This study unveiled present patterns of global collaboration, emerging frontiers, fundamental knowledge, research hotspots and current trends in AH.

1. Introduction

Aqueous humor (AH) is secreted by the ciliary processes and exits the eye via the trabecular meshwork (TM) or uveoscleral outflow channels. The primary role of AH is to regulate intraocular pressure, supply nutrition to the lens, cornea and TM, eliminate metabolic waste and safeguard against oxidative harm [1]. AH constantly transfers substances with the bloodstream via the walls of capillaries, as well as with different ocular tissues through both direct and indirect interaction. Hence, the concentrations of proteins or cytokines in

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AH can serve as biomarkers for assessing the well-being of blood vessels or ocular tissue [2]. The latest therapeutic advancements have made it possible to safely extract AH from treated eyes, enabling the convenient and secure evaluation of disease-specific biomarkers for a range of ocular conditions, including cataract, glaucoma, diabetic retinopathy, age-related macular degeneration, uveitis and retinoblastoma [3]. In recent years, AH has garnered significant interest from academic researchers as a crucial biomarker carrier help understand the pathogenesis, severity grading, and prognosis prediction of different eye diseases. To gain a deeper understanding of the boundaries and trending topics in AH, we investigated the present state of AH research using bibliometric techniques and knowledge mapping (MKD) approaches.

Bibliometric analysis is a technique of analyzing pertinent literature using mathematical and statistical methods. Quantitative measurement can be used to assess the distribution, relevance and clustering of literature [4]. By utilizing databases and visualization technology, the MKD approach offers a novel means to conduct literature mining and uncover the fundamental framework of scientific knowledge. Co-authorship analysis reveals patterns of collaboration among authors, institutions, and countries. By analyzing the occurrence of multiple keywords in a single article, co-occurrence analysis reveals the closeness between them, effectively showcasing current subjects and patterns in the field.

Assessing research trends in an academic field holds significance for researchers. The analysis of bibliometric hotspots can serve as a visual aid in evaluating significant patterns in research, as well as identifying important areas that are not being studied. Hence, the aim of this research was to offer an all-encompassing examination of the scholarly articles regarding AH. Specifically, this study evaluated the growth of publications, global collaborations, author productivity rates, source journals, co-citation analysis and keyword co-occurrence analysis in relation to AH research.

2. Methods

2.1. Data source and research process

Data utilized in this research were obtained from the WOS CORE COLLECTION (WoSCC) on May 20, 2024. The analysis of bibliometrics was conducted utilizing the inherent functionalities of WOS and the bibliometric analysis tool, VOSviewer. The search term used was "aqueous humor" and the specified time span was "from January 1, 2014 to December 31, 2023". A grand total of 5152 publications were acquired, with the exclusion of the subsequent documents: Review Article (702 articles), Meeting abstract (332), Letter (51), Editorial Material (38), Early access (22), Proceeding Paper (22), Book Chapters (12), Retracted Publication (12), Correction (9), Publication with Expression Of Concern (1) and Data Paper (1). A grand total of 4020 articles underwent analysis. There were no limitations on the language used. The obtained outcomes were stored as "plain text" and with "full records and cited references. For every article, the subsequent fundamental details were gathered: country, author, institution, journal, references, keywords.

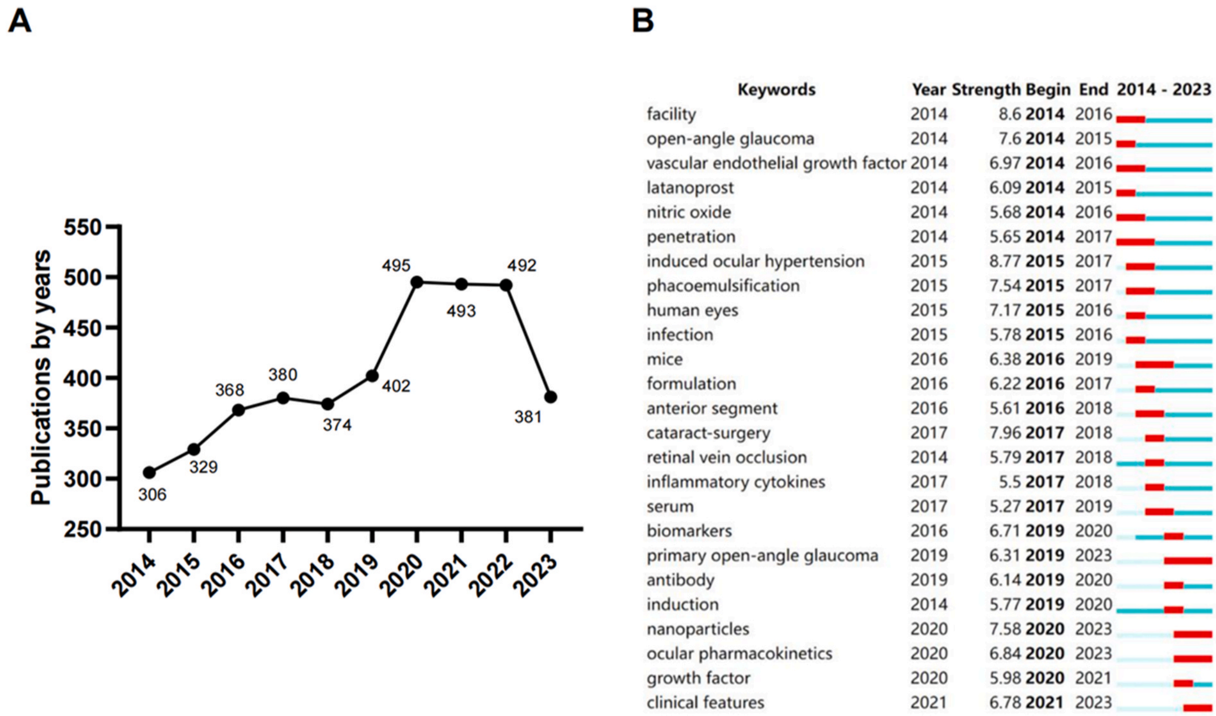

Fig. 1. (A) The annual number of publications in AH research from 2014 to 2023. (B) Burst analysis of keywords.

2.2. Analysis tools and methods

VOSviewer, a literature visualization software created by Van Eck & Waltman (2010) [5], utilizes cluster analysis to present the outcomes. The study involved importing data into VOSviewer and conducting a systematic analysis by generating node-link diagrams which can help visualize the distribution of studies, identify hot spots, and determine the direction of research development. The weight of the analyzed components determines the size of nodes and their labels, such as country, organization, author, co-cited literature, and keywords and the relationships between these elements are represented by the links between nodes.

CiteSpace is an online Java tool used for analyzing and visualizing data. CiteSpace possesses a distinctive characteristic of displaying the abrupt surge of terms within a specific field of study during particular time intervals, thereby indicating the potential focal points and trends during each time period.

In this research, VOS viewer was utilized to construct co-authorship analysis, co-occurrence analysis, co-citation analysis, and network visualization of papers. The literature can be characterized by keywords and the knowledge structure and research hotspots of the area can be uncovered.

3. Results

3.1. Annual distribution of publications

A total of 4020 articles on AH collected in WoSCC were identified and included from 2014 to 2023 based on the specified selection criteria. Fig. 1 (A) displays the annual publications associated with AH, which have risen from 306 in 2014 to 492 in 2022. Despite a decline in the number of publications over the last couple of years, the overall trajectory continues to exhibit a consistent upward trend over time. Burst analysis was performed to elucidate the research hotspot and the increasing trend of publications and the results were shown in Fig. 1 (B). The terms 'primary open-angle glaucoma', 'nanoparticles', 'ocular pharmacokinetics' and 'clinical feature' experienced a surge in citations between 2019 and 2023, indicating their significance in recent years and aligning with the increasing number of published papers.

3.2. Country analysis

Based on the obtained findings, a total of 4020 publications were generated from a diverse range of 92 countries. According to Table 1, the most publications was contributed by The United States of America (USA) (1,103, 27.4 %), with China (946, 23.5 %) and Japan (396, 9.85 %) following closely behind. Base on the citation analysis, the published papers from the United States received the highest number of citations (22,509), followed by China (10,964) and Japan (5,916). In this field, The United Kingdom of Great Britain and Northern Ireland (UK) has released a total of 222 papers, but it stood out in terms of the average number of citations with 21.45, suggesting the considerable acknowledgement of English publications.

The analysis of co-authorship among countries demonstrates the influence of each country and the level of collaboration between countries in the research field. Larger nodes indicate the greater contribution of the country in the field, while the cooperation between countries is represented by the thickness and distance of the links between nodes. The nodes' color indicates the average year of publication; the darker color signifies an earlier average year of publication, while a lighter shade signifies a later average year.

The analysis of co-authorship examined 53 countries that had published more than five times in the field (Fig. 2) excluding three unlinked items and demonstrated the collaboration of 50 institutions. As shown in Supplemental Table 1, the top three countries in terms of total link strength were USA (578 total link strength), China (240) and UK (238). Likewise, according to Fig. 2, the United States has established the most comprehensive academic connections with various countries, including Germany, Japan, Korea, and Argentina, with China being the closest. This suggests that cooperation relationships are not primarily influenced by geographical distance.

Table 1
Top 10 productive countries in aqueous humor study, 2014–2023.

Rank1	Country	Count (%)	Citations	Average Citation/Publication
1	USA	1103(27.4)	22509	20.41
2	China	946(23.5)	10964	11.59
3	Japan	396(9.85)	5916	14.94
4	Germany	253(6.29)	4107	16.23
5	UK	222(5.52)	4762	21.45
6	Korea	182(4.53)	2306	12.67
7	Italy	175(4.35)	2875	14.88
8	India	173(4.3)	2129	16.43
9	Spain	143(3.56)	1905	13.42
10	Turkey	133(3.31)	1120	7.78

Notes. Percentages (%) were calculated by dividing the row count by the total number of publications (n = 4, 020). USA, The United States of America; UK, The United Kingdom of Great Britain and Northern Ireland.

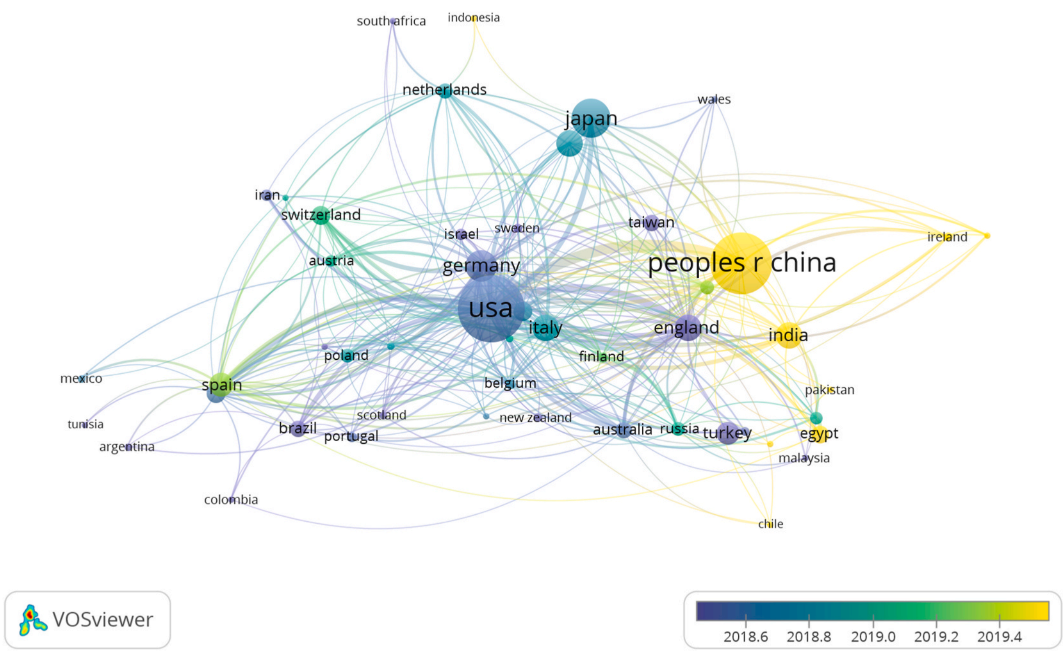

Fig. 2. Global AH research landscape and the collaborative network among leading countries. (The minimum number of documents of a country was set as 5. Of the 90 countries that involved in AH research, 52 countries meet the threshold.)

3.3. Distribution of main research organizations

Based on the obtained findings, a total of 4020 articles were released by 3927 different establishments. Duke University published the most papers (114, accounting for 2.8 % of all papers), followed by Fudan University (105, 2.6 %) and Sun Yat-sen University (88, 2.2 %) (Table 2).

We performed the co-authorship analysis among 3927 organizations that have produced over 20 publications. Three unlinked projects were excluded, showing the cooperation of 64 organizations. Fig. 3 and Supplemental Table 2 displayed the knowledge domain map of research institution distribution in the AH study, as per the co-author analysis. The node's size is proportional to the quantity of published articles. Collaboration is symbolized by the connections between nodes. The stronger the link, the closer the collaboration.

3.4. Distribution of authors and co-authorship of research groups

Based on the obtained findings, the AH study involved over 17203 authors in its contribution. Among all authors, Stamer, W. Daniel (63 papers) was the top-ranked author among all authors, with Overby, Darryl R. (34) and Inoue, Toshihiro (32) following closely behind, indicating their significant contribution to AH research. Additionally, an analysis was conducted on the co-citations of the authors. Quigley, HA (625 co-citations) emerged as the top-ranked among all co-cited authors, with Stamer, WD (460) and Weinreb, Rn (460) following closely behind, signifying their significant impact on AH research (Table 3). Prof. Stamer, W. Daniel ranks among the top in terms of both the quantity of published works and citations. He is a leading expert in the field of glaucoma, specializing in the

Table 2
Top 10 productive organizations in aqueous humor study, 2014–2023.

Rank1	Organization	Country	Count	Citations
1	Duke University	USA	114	3353
2	Fudan University	China	105	1395
3	Sun Yat-sen University	China	88	1327
4	Capital medical university	China	80	779
5	Shanghai Jiaotong University	China	75	753
6	The University of Tokyo	Japan	45	717
7	Wenzhou Medical University	China	45	486
8	Oregon Health and Science University	USA	43	883
9	Miami University	USA	43	931
10	University of North Texas	USA	43	767

USA, The United States of America.

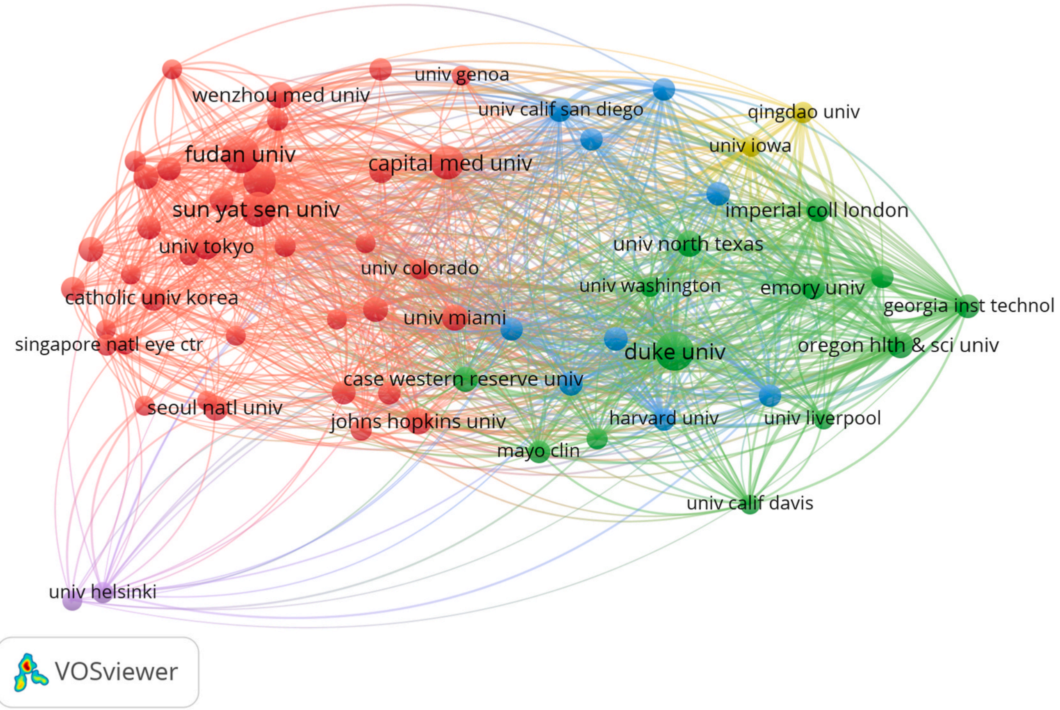

Fig. 3. Global AH research landscape and the collaborative network among leading organizations. (The minimum number of documents of an organization was set as 20. Of the 3796 organizations that involved in AH research, 54 organizations meet the threshold.)

examination of the correlation between the dynamics of AH outflow and the development of glaucoma.

Among a total of 17,203 authors, we analysis collaboration between authors who have published more than 10 times. Thirty-seven unlinked items were excluded, showing collaborations between 64 authors. Fig. 4 displayed the map of knowledge domains of the collaboration of the researchers in the AH study, as determined by the co-authorship analysis. The magnitude of the nodes is proportional to the quantity of articles that have been published. The connections among nodes symbolize the cooperative associations among authors and the collaboration density increases with higher link strength. Stamer, WD (total link strength 85), Overby, DR (73), Noma, H (69), Shimura, M (69), and Yasuda, K (66) were the top five authors based on their total link strength (Supplemental Table 3). By fostering increased cooperation among researchers worldwide, the field is certain to experience enhanced vitality and future value.

3.5. Distribution of source journals

Based on the obtained findings, research papers on the study of AH were published across 793 different journals. The top 10 journals publishing on this subject are listed in Table 4. *Investigative Ophthalmology & Visual Science* had the largest number of articles published (298,7.4 %), with *Experimental Eye Research* coming in second (220, 5.5 %), followed by *Scientific Reports* (134 articles, 3.3 %), *PLOS ONE* (129 articles, 3.2 %) and *Current Eye Research* (91, 2.3 %). Articles published in these five journals accounted for 21.7 % of all publications included in this study. The top 3 journals with the highest number of citations were *Investigative Ophthalmology & Visual Science* (7,385), *Experimental Eye Research* (3,525), and *Scientific Reports* (2,350). The journal '*Investigative Ophthalmology &*

Table 3
Top 10 productive authors and co-cited authors in aqueous humor study, 2014–2023.

Rank1	Author	Count	Co-cited author	Count
1	Stamer, WD	63	Quigley, HA	625
2	Overby, DR	34	Stamer, WD	460
3	Inoue, T	32	Weinreb, RN	460
4	Aihara, M	29	Noma, H	364
5	Sun, XH	27	Keller, KE	336
6	Tao, Y	26	Jonas, JB	331
7	Noma, H	25	Tripathi, RC	289
7	Shimura, M	25	Toris, CB	286
7	Tanihara, H	25	Johnson, M	257
10	Millar, JC	23	Fuchshofer, R	250
10	Yasuda, K	23	Tamm, ER	250

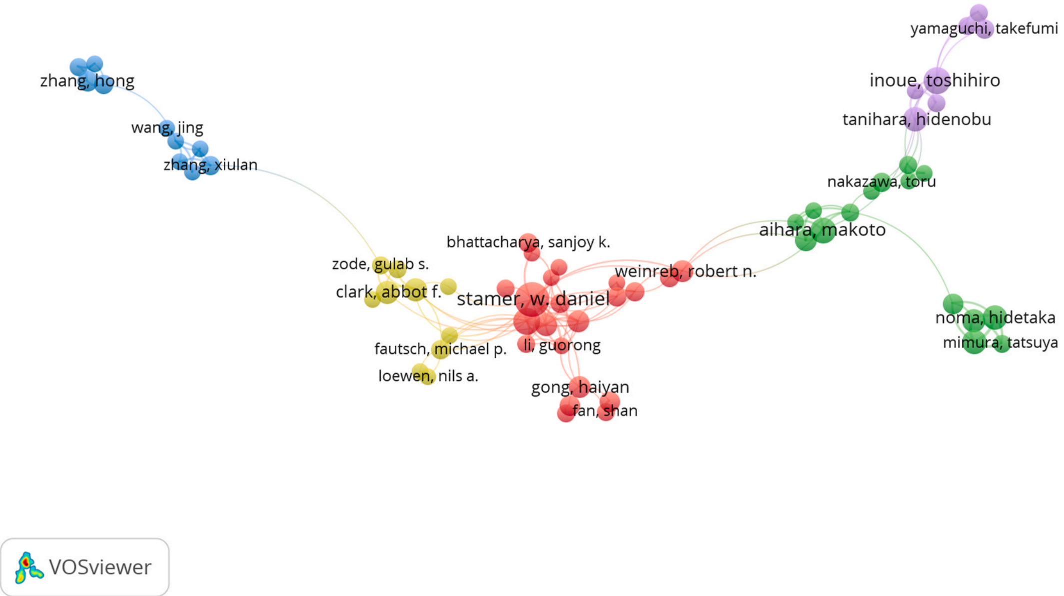

Fig. 4. Global AH research landscape and the collaborati11ve network among influential authors. (The minimum number of documents of an author was set as 10. Of the 16,537authors that involved in AH research, 62 authors meet the threshold.)

Table 4
Top 10 main source journals in aqueous humor study, 2014–2023.

Rank1	Journal	Count (%)	Citations	Average Citation/Publication
1	Investigative Ophthalmology & Visual Science	298(7.4)	7385	24.78
2	Experimental Eye Research	220(5.5)	3525	16.02
3	Scientific Reports	134(3.3)	2350	17.54
4	PLOS ONE	129(3.1)	2153	16.69
5	Current Eye Research	91(2.3)	911	10.01
6	BMC Ophthalmology	87(2.2)	819	9.41
7	Journal of Ocular Pharmacology and Therapeutics	81(2.0)	1190	14.69
8	Graefe's Archive for Clinical and Experimental Ophthalmology	75(1.9)	722	9.63
9	Ocular Immunology and Inflammation	67(1.7)	483	7.21
10	Translational vision science & technology	64(1.6)	526	8.22

Notes. Percentages (%) were calculated by dividing the row count by the total number of publications (n = 4020).

Visual Science' is highly regarded in the ophthalmic community, as evidenced by its impressive impact factor of 4.4 and its classification as a top-tier Journal Citation Reports (JCR) Division 1 journal.

3.6. Distribution of keywords: hotspots of AH study

By analyzing the high-frequent keywords, the research hotspots of AH research were determined through co-occurrence analysis. The minimum co-occurrence number of keywords was set to 15, and the minimum size of each cluster was set to 60. Out of the 12,585 keywords extracted related to AH, 470 keywords satisfied the threshold requirement. The keywords were clustered based on the network and the six main clusters were denoted as red, green, blue, yellow, purple and grey, respectively (Fig. 5). The top 10 keywords for each cluster are displayed in Table 5.

4. Discussion

4.1. Global trends in research on AH

The utilization of bibliometrics is increasingly gaining popularity as a means of demonstrating the current trend of research. By employing a blend of bibliometric analysis and network visualization, we elucidate the present state of AH research, scrutinize the involvement of countries, institutions, journals and authors, and hot spots of research are forecasted for the coming years. The quantitative measurement of academic papers is a crucial research indicator that reflects the evolving trajectory of the field. Fig. 1 (A) illustrates the gradual increase in annual research output from 2014 to 2023, with a total of 4020 papers retrieved during this period.

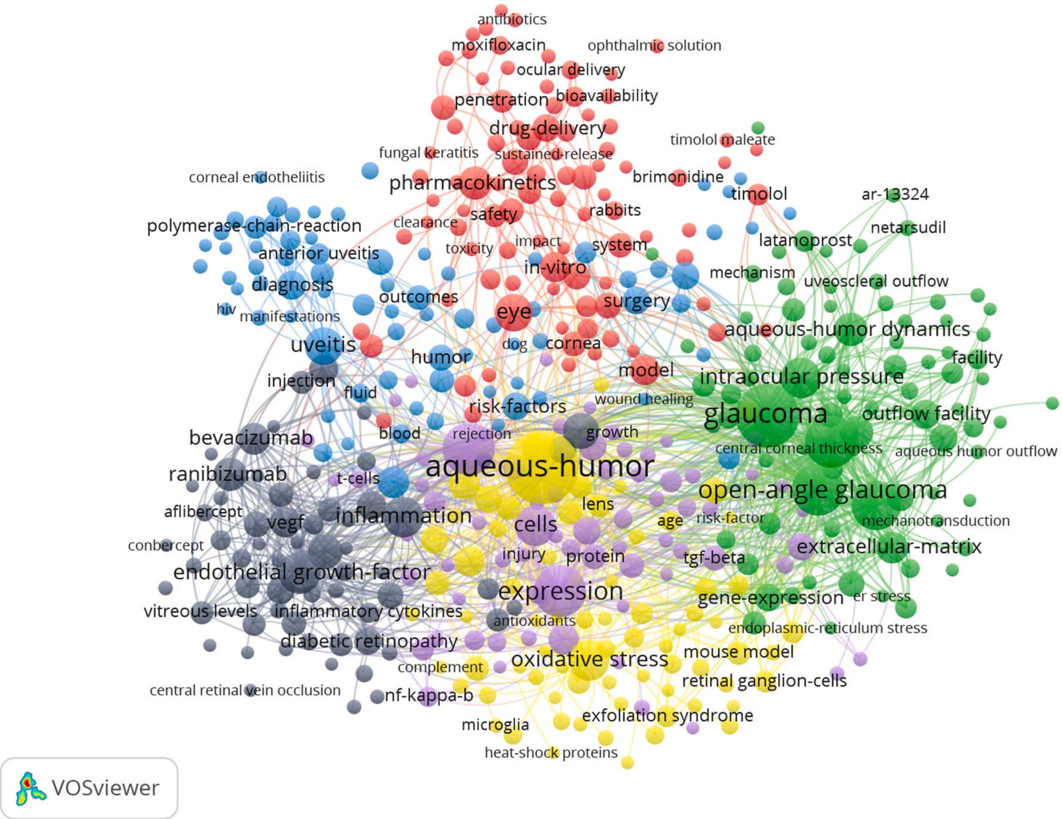

Fig. 5. Co-occurrence network of keywords in AH study. (The minimum number of occurrences of a keyword was set as 15. Of the 12,371 keywords that involved in AH research, 454 keywords meet the threshold.)

Table 5
Co-occurrence analysis of keywords. Top 10 keywords in the 6 clusters.

Cluster 1 (red)	Cluster 2 (green)	Cluster 3 (blue)	Cluster 4 (Yellow)	Cluster 5 (purple)	Cluster 6 (grey)
Pharmacokinetics (159)	Glaucoma (820)	Uveitis (214)	Aqueous-humor (1130)	Expression (504)	Endothelial growth-factor (288)
Model (137)	Intraocular-pressure (470)	Disease (136)	Oxidative stress (258)	Activation (122)	Inflammation (255)
In-vitro (114)	Open-angle glaucoma (435)	Therapy (113)	Cataract (166)	Biomarkers (114)	Cytokines (182)
Drug-delivery (107)	Trabecular meshwork (413)	Diagnosis (111)	Prevalence (134)	Mechanisms (103)	Ranibizumab (153)
Rabbit (84)	Aqueous-humor dynamics (169)	Risk-factors (95)	Association (119)	Identification (97)	Bevacizumab (147)
Dexamethasone (83)	Ocular hypertension (157)	Management (93)	Pathogenesis (72)	TGF-beta (79)	VEGF (132)
Efficacy (77)	Extracellular-matrix (156)	Infection (60)	Progression (63)	TNF-alpha (57)	Macular degeneration (115)
Release (71)	Outflow facility (102)	Anterior uveitis (51)	Matrix metalloproteinases (60)	Cancer (43)	Diabetic retinopathy (99)
Endophthalmitis (70)	Aqueous-humor outflow (100)	Clinical-features (47)	High myopia (47)	Migration (26)	Retinopathy (96)
Nanoparticles (68)	Schlemm's canal (60)	Epidemiology (36)	Age (45)	Retinoblastoma (23)	Macular edema (86)

NOTE. The numbers in brackets represent the frequency of keywords according to **the co-occurrence analysis**.

According to Fig. 1 (B) Since 2019, keywords such as primary open-angle glaucoma, nanoparticles, ocular pharmacokinetics and clinical feature have become more and more relevant, which provides current researches with an idea on the latest research trends to a certain extent. This means that the future field of AH research will pay more attention to transforming laboratory research results into actual clinical applications. In the future, highly sensitive and specific AHdetection technology based on nanomaterials may be further developed to provide strong support for the early detection and prevention of diseases. Colloidal dispersions such as nanoemulsions, nanoparticles, and liposomes have great potential in innovative systems for ophthalmic delivery and deserve further investigation [6].

The United States holds a prominent position in AH-related research globally currently, leading in terms of the highest number of publications and citations among the countries mentioned in Table 1. Additionally, it secures the top spot in the analysis of co-authors by country. These results suggest that the potential influence of the United States on the course of research in this area is significant and the United States is an international science hub for AH research.

By analyzing of the distribution of research organizations, we can identify the cooperation within the most productive organizations and groups in a given field. As shown in Supplemental Table 2, the three institutions with the highest total link strength are Duke University (total link strength 88), Emory University (66) and Georgia Institute of Technology (55). This is an indication that these research institutions are at the core of the overall research network.

Creating a knowledge map of the co-authorship network can help researchers discover potential collaboration prospects. Fig. 4 displays the red group with Prof. Stamer, WD (Duke University, USA) at its core, the green group with Prof. Noma, H (Tokyo Medical University, Japan) at its core, the blue group with Prof. Zhang, XL (Sun Yat-Sen University, China) at its core, the yellow group with Prof. Millar, JC (University of North Texas Health Science Center, USA) at its core, and the purple group with Prof. Inoue, T (Kumamoto University, Japan) at its core.

Identifying the core journals in a specific field is facilitated by analyzing the distribution of academic journals. Based on our findings, *Investigative Ophthalmology & Visual Science* has emerged as the leading publisher with the highest volume of publications and the most citations in this particular area of research.

4.2. Research frontiers

The co-occurrence analysis of keywords facilitates the classification of the main knowledge structures and hotspots in the research area. As shown in Fig. 5, the topics of AH form six main clusters, and keywords with similarities in research topics are grouped together. The six clusters were analyzed in relation to the characteristics and current status of AH study as follows:

Cluster#1, which is colored red, consisted of keywords primarily connected with the diagnosis of endophthalmitis and AH pharmacokinetics, including pharmacokinetics (159), model (137), in-vitro (114), drug-delivery (107), rabbit (84). dexamethasone (83) efficacy (77), release (71). endophthalmitis (70), nanoparticles (68).

Endophthalmitis, a highly severe eye infection, can lead to permanent blindness in the affected eye within a matter of hours or days after symptoms appear. Traditionally, the gold standard for diagnosing endophthalmitis is microbial culture. Nevertheless, conventional microbiological techniques are not ideal since a negative culture does not completely exclude the diagnosis, and up to 60 % of AAH aspirates yield negative results for culture [7]. In recent years, molecular methods like PCR have emerged as leading techniques for quickly and accurately detecting important bacteria in clinical samples due to their speed, specificity, and high sensitivity. Multiple study demonstrated that the combination of conventional cultures and the 16SrDNA sequencing technique for screening endophthalmitis pathogens yields higher efficacy in terms of both positive detection rate and number of identified bacteria compared to the conventional culture method alone [8–10].

Evaluating the pharmacokinetic parameters of drugs aid in assessing the ideal level and administration method for a singular dosage, as well as exploring various methods of delivery [11]. Therefore, it is necessary to conduct studies on drug characteristics like the highest tolerable level, rate of absorption, distribution, elimination, and duration of the drug [12]. To prevent endophthalmitis, fluoroquinolones are frequently prescribed and used as antibiotics during intraocular surgery. Alhusban and colleagues conducted a pharmacokinetic analysis with the AH of patients undergoing cataract surgery and the result implied that moxifloxacin is the preferred option for preventing postoperative endophthalmitis [13]. Ketoconazole is an antifungal drug used to treat endophthalmitis. Shilpa Kakkar et al. developed solid lipid nanoparticles (SLN) to solve the problem of its low bioavailability in the eye. The pharmacokinetic analysis showed that the bioavailability of Ketoconazole was 2.5 times higher in the AH when administered as SLN compared to the free drug suspension [14]. The progress and practical use of novel ophthalmic medications could be enhanced by these.

Cluster#2, which is colored green, consisted of keywords primarily connected with the association of AH with the pathogenesis and prognosis of glaucoma, including: glaucoma (820), intraocular-pressure (470), open-angle glaucoma (435), trabecular meshwork (413), aqueous-humor dynamics (169), ocular hypertension (157), extracellular-matrix (156), outflow facility (102), aqueous-humor outflow (100) and Schlemm' s canal (60).

Glaucoma is mainly characterized by chronic degeneration of the optic nerve, and the level of intraocular pressure (IOP) is the primary risk factor that can be modified for the progression and occurrence of glaucoma. The amount of IOP is determined by the equilibrium between the speed at which AH is produced (inflow) and the resistance it faces during its exit from the eye (outflow) [15, 16]. There is a substantial amount of evidence indicating that reducing intraocular pressure (IOP) has a neuroprotective effect by delaying or potentially halting the structural and functional harm to the axons of the optic nerve in individuals diagnosed with glaucoma. AH exits the eye through two routes, one responsive to IOP (conventional trabecular meshwork pathway) and the other independent of IOP (unconventional uveoscleral and uveovortex pathway) [17]. The maintenance of normal IOP heavily relies on the barrier and filtration functions controlled by the trabecular pathway, and any impairment to these functions will lead to an elevation in intraocular pressure. Consequently, there is significant curiosity in comprehending the diverse molecular mechanisms that govern AH drainage via trabecular meshwork (TM) to advance the creation of effective and focused treatments for controlling IOP in individuals with glaucoma. Various external signals, such as growth factors and the extracellular matrix (ECM), can influence the outflow of AH by changing the arrangement of actin cytoskeleton, cellular adhesion, contractile properties, and the rigidity of the trabecular meshwork [18,19]. The uveoscleral drainage route is a widely recognized element of the non-traditional pathway, possessing notable and possibly advantageous adaptive characteristics. Considering that this route is not fully utilized in typical circumstances, it holds significant promise and benefits from the ability to naturally amplify in case of damage to the traditional route or can be utilized through medical and surgical approaches prior to the occurrence of injury related to IOP [20].

The study of glaucoma related biomarkers has numerous benefits when using AH. Because AH is in direct contact with the TM, it reflects the functional status of the TM. At present, there is a lack of a precise molecule target for screening the high-risk population of glaucoma, making an early specific diagnosis, grading the severity, monitoring the progression, and assessing the postoperative risk. Proteomic methods are primarily used to discover disease-related protein or polypeptide biomarkers, which are essential for understanding disease mechanisms, diagnosing diseases, and developing novel therapeutic strategies. With the continuous development of proteomics technology, the screening of differential proteins in eye diseases is simpler and more accurate. In the examination of the proteome in AH from individuals with glaucoma and cataract, it was found that glaucoma patients had increased proportions of abnormal collagen and fibronectin in AH, as well as key proteins related to tissue vascular remodeling and immune response pathways, indicating that the makeup of the trabecular matrix is considerably changed in the presence of the illness [21,22]. TGF-β2 is acknowledged as a versatile growth factor involved in diverse cellular functions, including cell movement, cell division, cell demise, and protein creation. It also aids in enhancing ECM production and suppressing cell proliferation [23]. A meta-analysis of comprehensive data affirms that levels of total TGF-β2 are notably elevated in open-angle glaucoma compared to controls [24]. In another research, it was found that the levels of TGF-β1 and TGF-β2 were elevated in eyes experiencing acute primary angle closure. Abnormal accumulation of ECM in the trabecular network, caused by alterations in these protein levels, can cause an elevation in resistance to the outflow of AH [25]. Hence, exploring the potential use of anti-TGF-2β treatment in managing glaucoma holds significant importance.

The gold standard for surgically treating medically uncontrollable glaucoma, which can be defined as surgical trauma, is Glaucoma filtration surgery. It aims to regulate IOP by establishing a synthetic drainage pathway from the anterior chamber to the subconjunctival space. The overproduction of ECM and the formation of scars will result in the closure of the AH outflow channel, ultimately causing the failure of the surgical procedure. Multiple studies on AH in individuals with primary glaucoma revealed a notable rise in the levels of various cytokines linked to fibrosis, including monocyte chemoattractant protein-1 (MCP-1), Secreted Protein Acidic and Rich in Cysteine (SPARC), transforming growth factor-B (TGF-β) and vascular endothelial growth factor (VEGF) [26–30]. These factors are crucial in determining the prognosis of glaucoma filtration surgery.

Cluster#3, which is colored blue, consisted of keywords primarily connected with the diagnosis and treatment of uveitis associated with AH, including: uveitis (214) disease (136), therapy (113), diagnosis (111), risk-factors (95), management (93), infection (60), anterior uveitis (51), clinical-features (47) and epidemiology (36).

Uveitis is a complicated inflammation within the eye that has various causes differing among populations because of variances in geography, ethnicity, and socioeconomic factors [31]. AH is a potential reservoir of proteomic biomarkers in uveitis. Different subtypes and severity of uveitis release different concentrations of proteins that can be used as biomarkers. Currently, anti-TNFα therapy is the only FDA-approved biologic therapy for uveitis. The identification of proteins by mass spectrometry can help improve the understanding of the pathogenesis of uveitis and may also serve as future diagnostic and drug targets. T helper (Th) 17 cells are important for maintaining normal mucosal health and immune function, whereas pathological Th17 cells play a driving role in the occurrence and maintenance of uveitis [32]. The functions of cytokines including IL-6, IL-17 and IL-23 etc. are closely related to the regulation and differentiation of Th17 cells. Therefore, targeted therapy for these cytokines, such as IL-6, IL-23, is being actively developed [33]. Juvenile idiopathic arthritis-associated uveitis (JIAU), a form of chronic uveitis in children, is frequently seen and affects the iris and ciliary body. It starts gradually with flare-ups and often leads to serious eye problems like posterior synechiae, cataracts, glaucoma, and macular edema [34]. In Lena Wildschütz's study, the analysis of cytokines in AH revealed notable elevations in the levels of B cell-activating factor (BAFF), a proliferation-inducing ligand (APRIL), and IL-6 in the AH of JIAU These findings suggest that these cytokines could potentially play a role in the persistence of plasma cells in the affected tissues [35]. All of them have the potential to be therapeutic targets for uveitis, aiding in the stratification and customization of treatment for each individual patient.

Cluster#4, which is colored yellow, consisted of keywords primarily associated with the connection between AH and refractive alteration diseases of the eye, including: Aqueous-humor (1130), Oxidative stress (258), Cataract (166), Prevalence (134), Association (119), Pathogenesis (72), Progression (63), Matrix metalloproteinases (60), High myopia (47), and Age (45).

Cataract, as the primary cause of treatable blindness globally, is one of the foremost ocular ailments resulting in loss of vision, with a prevalence of 71.8 % [36]. The damage caused by oxidative stress to the cells that make up the lens epithelium is the cellular foundation for the formation of age-related cataract (ARC). Furthermore, the intensification of oxidative stress further accelerates the demise of these cells, potentially leading to ARC once a specific threshold of cell death is reached [37]. Since oxidative stress is related to the entire process of cataract formation, it is a potential indicator that can objectively evaluate the occurrence and severity of cataracts [38]. Research has verified that the level of glutathione peroxidase (GSH-Px) in the AH of individuals with cataracts is lower compared to that of individuals without cataracts. This suggests an imbalance in the antioxidant status within the AH, potentially leading to abnormal oxidative metabolism of the lens [39]. Tsao et al. explores the relationship between the antioxidant (ascorbic acid) in AH and the severity of cataracts. The results suggested that total antioxidant capacity of AH and ascorbic acid correlate better with cataract severity than traditional method [40]. Consequently, it indicates a significant association between oxidative stress and the progression of cataracts. Hence, it is of importance to identify the levels of GSH-PX and ascorbic acid in the AH of individuals with cataracts for the purpose of disease surveillance. The aforementioned findings from the study can offer a fresh perspective on the development of cataracts, as well as present potential indicators for diagnosing and tracking the condition. Collecting samples of AH from healthy individuals is challenging due to the distress caused by the process of sampling the AH and the ethical limitations involved. In studies related to other ocular diseases, researchers often use the AH from cataract patients undergoing surgery as a reference or comparison.

High myopia, characterized by a refractive error exceeding −6.00 diopters or an axial length surpassing 26 mm, has a higher prevalence in Asian population [41]. There is strong evidence indicating that individuals with high myopia are at a significantly greater risk of developing eye conditions, including retinal detachment, macular degeneration and glaucoma, which can severely impact patients' eyesight [42]. The qualitative and quantitative search on small molecule metabolites in samples, known as metabolomics studies, can play an active role in searching for relevant biomarkers for various diseases. Yinghong Ji et al. detected 242 metabolites in AH from high myopia patients using a non-targeted metabolomics technique. The development of high myopia was confirmed to be significantly influenced by the metabolism of amino acids, as evidenced by the substantial increase in four amino acids: glutamine 1, N-alpha-Acetyl-L-ornithine 3, Nicotinoylglycine 2, and *o*-Hydroxyhippuric acid 2 [43]. Among them, glutamine 1 is related to the generation of reactive oxygen species, which may indicate that oxidative stress may be involved in the onset of high myopia. A review on AH has demonstrated that the presence of certain substances in the AH of myopia is associated with the breakdown of the scleral matrix, chronic eye inflammation, pro-fibrotic activity, vascular formation, and suppression [44]. These results can not only provide biomarkers for the prediction of high myopia, but also provide a further understanding of the etiological mechanism. Choroidal atrophy caused by long axial length in patients with high myopia can lead to decompensation of the retinal pigment epithelium, which in turn causes upregulation of VEGF and the formation of CNV [45]. Intraocular injection of anti-VEGF drugs can effectively improve best-corrected visual acuity in CNV patients associated with high myopia [46]. In addition, the analysis of potential differential metabolites and proteins in the AH of such patients demonstrated that TGF, D-citramalic acid, etc. may be involved in the formation of CNV and have the potential to be used as disease markers [47,48].

Cluster#5, which is colored purple, consisted of keywords primarily connected with the association of AH with mechanism and biomarkers of ocular tumorigenesis, including: expression (504), activation (122), biomarkers (114), mechanisms (103), identification (97), TGF-beta (79), TNF-alpha (57), cancer (43), migration (26) and retinoblastoma (23).

Retinoblastoma (RB) is a prevalent form of ocular cancer globally, making up 6 % of all cancers in children below the age of 5 [49]. Due to concerns about the spread of tumors, traditional biopsies are still not recommended, and the molecular analysis of RB is only conducted on excisional tumor samples. The AH biopsy technique overcomes numerous challenges and hazards associated with acquiring conventional tissue biopsies, offering fresh opportunities for investigating cancer mechanisms that prevent the use of direct tissue biopsies. Multiple research studies have shown that AH, as the primary source of liquid biopsy, provide the greatest amount of tumor-derived cell-free tumor DNA (cfDNA) and other retinoblastoma biomarkers. This makes it the most promising biofluid for the purposes of diagnosis, prognosis, and therapy monitoring [50–52]. While most RB cases result from biallelic inactivating mutations of the RB1 oncogene, around 13 % of non-inherited RB exhibit RB1 promoter methylation and subsequent silencing. The disruption of tumor-promoting pathways through epigenetic changes has been demonstrated to have a greater impact on the development and advancement of RB tumors compared to the inactivation of RB1 gene [53]. Hongtao Li et al. revealed that the DNA methylation profiles of tumor-derived cfDNA in the AH accurately represent RB tumor tissue. This demonstrates that the AH is a dependable biofluid for methylation profiling of the tumor. The findings establish a basis for future utilization in the clinical assessment and prediction of RB, along with the possibility of employing precision medicine for treatment strategies [54].

Uveal melanoma (UM) is the most common primary malignant intraocular tumor in adults. Despite improvements in its local treatment, the prevention and treatment of metastatic diseases remain still unsolved, and nearly 50 % of the patients eventually die of tumor spread [55]. Proteomic studies have shown that several angiogenic, inflammatory and chemotactic cytokines levels were increased in AH in UM patients, suggesting that the progression and spread of UM involves multiple different pathways of angiogenesis, immune response, and inflammation [56]. Wierenga et al. conducted a study to assess the feasibility of utilizing a liquid biopsy for distinguishing between high- and low-risk UM. The findings indicated that the group with the most unfavorable prognosis exhibited the greatest level of inflammation-associated biomarkers expression. Significantly large tumors that involve the ciliary body and exhibit monosomy showed a strong correlation with numerous cytokines, particularly cytokines related to apoptosis [57]. In addition, UM somatic copy number alterations and genetic alterations can be detected from the AH, which can function as a liquid biopsy for UM [58].

Cluster#6, which is colored grey, consisted of keywords primarily connected with the indicators of AH associated with fundus disease , including: endothelial growth-factor (288), inflammation (255), cytokines ranibizumab (182), Ranibizumab (153), Bevacizumab (147), VEGF (132), macular degeneration (115), diabetic retinopathy (99), retinopathy (96) and macular edema (86).

Diabetic retinopathy (DR) is a prevalent microvascular complication of diabetes mellitus (DM), leading to visual impairment and avoidable blindness in working-age adults in developed nations.Approximately one-third of the diabetic population has DR, with 10 % experiencing vision-threatening conditions like diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), and neovascular glaucoma (NVG), which can result in significant vision loss [59]. Vitreous sampling may not be an option for patients in the preclinical stages of DR, as vitrectomy is not a standard procedure in this scenario. AH appears to be more suitable when compared to the vitreous humor, both of which demonstrated significance and dependability [60]. Several studies have performed a metabolomic approach to examine the AH in patients with DR and DME. After a series of analyses, it detected a variety of differential metabolites, such as succinate, lactate etc., suggesting that the onset and progression of DR involve potential pathophysiological mechanisms of mitochondrial dysfunction, oxidative stress, and endothelial damage [61,62]. Shuang Song et al. demonstrated that the concentrations of the cytokines in AH such as IL-6, VEGF, TGF-β rose in correlation with the severity of DR, particularly in NVG and PDR. One of the factors contributing to the elevated risk of NPDR and PDR progressing into NVG is the significant rise in TGF-β levels. This implies that exploring anti-TGF-β therapy could offer a novel approach to treat NVG [63].

Age-related macular degeneration (AMD) is responsible for significant and permanent loss of central vision among older individuals globally [64]. The development of AMD involves both genetic and environmental factors, including aging, diet, inflammation, and oxidative stress. However, the exact cause of this intricate condition is still unknown. VEGF has a crucial function in the regulation of angiogenesis and facilitates the formation of new blood vessels in AMD. Over the past few years, the standard approach to treating wet AMD has shifted to anti-VEGF therapy, leading to notable enhancements in the central eyesight of individuals with exudative AMD [65]. However, this benefit requires regular monthly injections for patients to maintain, and ocular gene transfer is a potential strategy for sustained inhibition of VEGF. Jeffrey S Heier et al. demonstrate that intravitreal injection of a polyglycine 9-mer to human IgG1-Fc, a secreted VEGF-neutralising protein packaged in AAV2 (AAV2-sFLT01) has a favorable safety and tolerability profile and is a promising new therapy for the treatment of AMD [66]. However, several studies have found that levels of intraocular VEGF are within the normal range [67] or only slightly increased in individuals with neovascular AMD when compared to controls [68]. As a result, researchers have been motivated to explore alternative factors that may impact the development of AMD. In view of this, Tatsuya Mimura et al. assessed the concentrations of VEGF and diverse additional elements, encompassing molecules associated with inflammation, within the AH of both individuals with AMD and the control group. In the AMD group, it was discovered that VEGF, sVEGFR-1, sVEGFR-2, along with inflammatory markers (MCP-1, IL-6, IL-8), exhibited notably elevated levels compared to the cataract group. The development of AMD may potentially involve all of these inflammatory factors [69].

The clusters mentioned in this paper include the high-frequency keywords on AH that can be retrieved in the past ten years. The method brings new directions and possibilities for the study of pathophysiological mechanism and prognosis of various ophthalmic diseases. However, this method is not restricted in the ophthalmic field. Multiple pieces of evidence suggest that there are connections between Alzheimer's disease (AD) and different ocular conditions like cataracts, neovascular age-related macular degeneration (nAMD), glaucoma, and diabetic retinopathy. This indicates that these ocular diseases and AD might have shared risk factors and molecular-level pathological mechanisms [70,71]. Fluid exchange occurs between cerebrospinal fluid (CSF) and AH, leading to significant variation in AH composition based on the plasma and CSF composition. Prior research primarily concentrated on the diagnostic effectiveness of protein indicators in CSF and blood plasma for the early identification of AD. However, the most recent study investigated the manifestation of protein biomarkers associated with AD in the AH [72]. The presence of important proteins like NFL, Aβ40, Aβ42, GFAP, and p-tau181 in AH which potentially involve in the early detection of dementia in individuals at high risk of Alzheimer's disease was found. Hence, it is imperative for neurologists, ophthalmologists, and basic researchers to delve deeper into the pathophysiological mechanism of AD biomarkers in AH.

Nevertheless, there are certain methodological constraints that should be taken into account, which impact the outcomes of our analysis. Firstly, only documents ranging from 2014 to 2023 were obtained from WoSCC, potentially lacking comprehensiveness in capturing all aspects of AH investigation. Secondly, the main data utilized for the analysis was obtained from WoSCC, a database that is better suited for advanced citation analysis. Hence, our examination was conducted with data obtained from WoSCC, excluding data obtained from other search engines like PubMed, Scope, or Google Scholar. Thirdly, it appears that we exclusively incorporate research conducted in the English language from WoSCC. However, we conducted a literature search without any language restrictions. There may be a linguistic bias as most WHA publications are in English. Last but not least, we are unable to give information pertaining to the specific institutions, countries, and individuals that are prominent in researching particular keywords due to data limitations.

5. Conclusion

As far as we know, this is the first bibliometric analysis of the trend in AH research. The findings of this study may be helpful for ophthalmologists to choose suitable publications journals for publishing and foster collaboration with other authors or organizations. By utilizing the extracted keywords, researchers can discover novel subjects and anticipate the future of research. Future research topics should focus on AH-related nanotechnology, clinical translation and drug distribution, so as to provide more advanced and effective means for the diagnosis and treatment of eye diseases.

Data availability statement

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

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CRediT authorship contribution statement

Weichen Yuan: Writing – original draft. **Xin Xu:** Data curation, Visualization. **Fangkun Zhao:** Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

The authors have no conflicts to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33990.

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