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Global research trends of infantile hemangioma: A bibliometric and visualization analysis from 2000 to 2022

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ABSTRACT

Background: Infantile hemangioma (IH) has received global attention, resulting in a significant volume of literature. However, there is a lack of bibliometric analyses specifically focusing on IH publications. This study aims to fill this gap by conducting a comprehensive analysis of IH publications, investigating their characteristics, contribution distribution, and developmental trends. By enhancing our understanding of IH and identifying potential research topics and collaborators, this study will contribute to the advancement of the field.

Methods: A total of 4333 articles and reviews on IH were collected from the Web of Science (WoS) database, spanning the years 2000–2022. The study encompassed a comprehensive analysis of IH publications, evaluating their quantity and quality. Additionally, we profiled publishing groups based on country, institution, author publication records, and collaboration networks. Lastly, we identified and summarized the prominent research topics.

Results: Annual publications on IH have increased over the past 20 years. The United States has the highest number of publications and the highest total number of citations. Pediatric Dermatology was the most influential journal in the IH field. The citation analysis indicated that the articles published by Léauté-Labrèze in 2008 had the highest number of citations. The articles published by North PE in 2000 and Boye E in 2001 laid a certain research foundation for this field. Concerning institutions, most of the cooperative relationships were established in the same country/region. The United States has the largest number of scientific research institutions and IH researchers, leading most of the cross-country collaboration. The University of California, San Francisco, Medical College of Wisconsin, Harvard University, and Shanghai Jiaotong University were the research centers that published the most IH-related research. Frieden IJ, Mulliken JB, and Drolet BA were the top three most influential authors. Frieden IJ, Garzon MC, and Mulliken JB were the top three authors with the most cited frequency. In addition, keywords and keyword co-occurrence networks prompted that the pathological mechanism of IH, clinical analysis, and other vascular anomalies are research hotspots. Analysis of trending topics suggests that research on IH has evolved from treatment-focused studies towards investigations of other vascular diseases and a series of clinical case studies. Currently, clinical case studies receive the most attention in the field.

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Conclusions: This comprehensive bibliometric study provides a thorough analysis of post-2000 publications in the field of IH, offering insights into current research trends for the first time. The findings suggest that future investigations will continue to prioritize understanding IH mechanisms, treatment approaches, and treatment evaluation. Furthermore, the exploration of other vascular diseases and the inclusion of clinical case studies are expected to contribute to advancements in IH clinical practice. By identifying potential collaborators, partner institutions, and new research avenues, this study offers valuable guidance for future in-depth research on IH.

1. Introduction

Infantile hemangioma (IH) is the most common benign vascular tumor in children [1], with an incidence of 4 %–5 %. It occurs more frequently in premature and low birth weight infants, with a male to female ratio of 1:3 to 5 [2]. IH often appears on the head, neck, limbs, and trunk [3]. It is characterized by endothelial cell proliferation and neovascularization (proliferating phase), spontaneous resolution at 1-year-old (involuting phase), and complete regression at the age of 5∼10 years old (involuted phase). Although IH often regresses spontaneously, large and fast-growing IHs can lead to residual cutaneous redundancy, fibrous and fatty residues, telangiectases, and scarring after regression. In addition, about 10 % of IHs may rupture, causing hemorrhage, infection, and pain, which can affect both aesthetics and quality of life [4,5]. IHs located in specific areas may also lead to organ dysfunction, such as visual function impairment, acute respiratory failure, congestive heart failure, and other severe, life-threatening complications [6,7]. Thus, it is crucial to identify appropriate treatment strategies for different scenarios.

Currently, the therapeutic options for IH encompass surgical resection, laser therapy, medical therapy (such as oral beta blockers or steroids), intralesional injections, and various combinations [8]. Propranolol, discovered serendipitously in 2008 as an effective treatment for severe IH, has become the first-line approach [9,10]. However, it is disheartening that these treatments only provide symptomatic relief, delay progression, partially improve quality of life, and do not achieve a definitive cure in some patients. Therefore, a comprehensive understanding of the etiology, diagnosis, and treatment of IH is of paramount importance. Upon reviewing the existing research on IH, it is evident that there is a lack of studies attempting to summarize the developmental trajectory and research trends of IH, or visually depict the current research hotspots in this field. Nevertheless, these studies will hold immense value in providing valuable insights into comprehensively understanding the development of IH, identifying existing research limitations and gaps, and offering crucial perspectives for future advancements.

Bibliometrics, proposed by Helm in 1922, is a branch of library science that uses mathematical and statistical methods to quantitatively and qualitatively analyze publications [11]. By conducting multi-dimensional analyses of publications, bibliometric methods can depict the publication status (country, institution, journal, author) in the relevant research field, and identify key literature and major findings in the field [12]. In addition, it can help researchers understand the past and present of the field, grasp research priorities, and predict future trends. Currently, bibliometrics has been applied in various fields of medical research. However, to the best of our knowledge, bibliometric-based IH research is unprecedented. Considering the current impact of IH on the physical and mental health of children and their parents, as well as the continued public concern about it, conducting a bibliometric analysis of IH publications is necessary to help new scholars in the field quickly grasp the current situation of the discipline.

Based on the above situation, this research is the first study to utilize bibliometric and social network analysis methods in investigating the publication output and evolution of collaboration networks in the field of IH. The main objectives of this study were as follows: (1) to examine the publication output, distribution, and network of cited and citing publications in IH research; (2) to analyze the evolution trends and collaboration networks of countries, institutions, and authors; and (3) to identify research topics and hotspots within the field. Through these analyses, our study aims to achieve the following goals: (1) to gain a comprehensive understanding of the historical development of IH and acquire knowledge of high-quality articles across various topics; (2) to highlight research gaps among different countries and institutions, providing insights for identifying potential collaborators and securing funding support; and (3) to establish knowledge repositories for different research domains and provide guidance for future research directions and topic selection.

2. Materials and methods

2.1. Search strategy

In conducting bibliometric analysis, the Science Citation Index Expanded (SCI-EXPANDED) of Clarivate Analytics Web of Science Core Collection (WoSCC) is the most commonly used database containing the most prestigious high-impact journals and high-quality publications, which gives a perfect view of the worldwide research on science, technology, medicine, and other fields. We made the paper research on 27 December 2022, collecting infantile hemangioma (IH) related studies between 1 January 2000 and 26 December 2022. The search strategy was listed as below: (TS = hemangioma OR TS = hemangioma OR TS = hemangiom* OR TS = angiom* OR TS = chorioangioma OR TS = chorioangiomas) AND (TS = infant OR TS = infancy OR TS = infantile OR TS = neonate OR TS = newborn OR TS = child OR TS = children).

2.2. Data pre-processing

We selected "article" and "review" publication types written in English for further research. The meeting abstract, editorial material, book chapter, letter, etc., were excluded. Then, the analysis process in R 4.1.3 helps to automatically remove duplicate and inaccurate publications. Finally, 4333 publications in total were obtained. We retrieved the 4333 publications with their full records, including titles, authors, affiliations, countries, keywords, publication year, etc., and citing references for the following bibliometric analyses.

2.3. Research method

This is the first bibliometric analysis conducted specifically on the field of IH. Prior to this research, no such analysis has been undertaken. In this study, R software (version 4.1.3, https://www.r-project.org/) (the biblioshiny() function in bibliometrix package) [13], online website https://bibliometric.com/, and CiteSpace (version 6.1. R6, https://citespace.podia.com/) were used for data processing and visualization [14]. The operational steps are outlined as follows (the detailed operating procedure can be found in the appendix file):

The bibliometrix package in the R platform accurately counted the number of articles and citations as indicators to assess the publication trends in the field of IH. Specifically, the "Annual Scientific Production" and "Average Article Citations per Year" modules were utilized for evaluation, and the results were visually presented using the ggplot2 package.

To examine the publication output characteristics of IH, the total citations (TC) were employed as a measure of author and journal impact. Additionally, the quantity and quality of academic output were assessed using the h-index, which considers the most cited papers of a journal/author and the number of citations they have received in other publications. The h-index was calculated using the *Hindex* function in the bibliometrix R package, where a higher value indicates greater journal/author influence. Moreover, the latest impact factor (IF) from the Journal Citation Reports was utilized to evaluate the influence of medical journals. Regarding the distribution of cited and citing publications in IH research, the bibliographic data of the 4333 publications were uploaded to the "JCR Journal Maps" feature in CiteSpace for constructing a dual-map. The map consists of two sections: the left section represents the practical applications of IH, while the right section represents the research foundation of IH. Furthermore, a historiograph map illustrating the chronological network of the most relevant direct citations was generated using the "Intellectual Structure" module in bibliometrix and subsequently imported into PowerPoint for further enhancement [15].

To gain insights into the main academic communities within IH publications, collaborative network analyses were conducted for countries, institutions, and authors, considering their production over time. The online platform, https://bibliometric.com/, facilitated the mapping of collaborative networks between countries using the "Analysis of cooperative relations - Inter-State relations" module. Additionally, bibliometrix provided information on the top 15 countries with the highest number of IH publications through the "Corresponding Author's Countries" and "Most Cited Countries" sections. Furthermore, collaboration networks were constructed for institutions and authors using the "Walktrap" clustering algorithm. The production trends of the top 20 authors over time were visualized using the "Authors' production over time" module and the "ggplot2" R package.

In addition, a co-occurrence analysis was conducted to explore the keyword categories and trend topics within the field of IH. Notably, the utilization of "Keywords Plus" played a significant role in this part. "Keywords Plus" is an automatically generated index term derived from the titles and abstracts of cited references in a paper. It enhances traditional keyword or title-based retrieval by

Table 1
Main information of publications on IH.

Description	Results
Main information about data	
Timespan	2000:2022
Sources (Journals, Books, etc)	978
Documents	4333
Annual growth rate %	3.22
Document average age	10.2
Average citations per document	19.29
References	63616
Document contents	
Keywords plus (ID)	5624
Author's keywords (DE)	6056
Authors	
Authors	15916
Authors of single-authored documents	125
Authors collaboration	
Single-authored documents	147
Co-authors per document	5.26
International co-authorships %	13.06
Document types	
Article	3733
Review	600

incorporating multiple occurrences and organizing them in a sequential arrangement from multi-word phrases to individual search terms. This approach enhances the inclusiveness of key terms and aids researchers in gaining a comprehensive understanding of prominent issues within a specific field. The thematic map of "Keywords Plus", generated using the bibliometrix package, was employed to visualize the classification and evolution of research hotspots in the IH discipline. Furthermore, the bibliometrix package facilitated the identification of specific trend topics since year 2000 through the "Most Frequent Words", "WordCloud", and "Trend Topics" items under the "Documents-Words" module and the construction of the co-occurrence network of keywords plus through the "Walktrap" Clustering Algorithm under the "Conceptual Structure-Network Approach" module. Additionally, the CiteSpace software was used to analyze and visualize the top 20 keywords exhibiting the strongest citation bursts in the scientific literature, providing insights into the hotspots and frontiers within the IH field.

3. Results

3.1. Characteristics of IH publications

3.1.1. Document types and main information included in the study

Between 1 January 2000 and 26 December 2022, 4333 publications on infantile hemangioma (IH) met the inclusive conditions and were appropriate for subsequent bibliometric analyses, involving 3733 original articles and 600 reviews. The average citation per document was 19.29. The main information on IH publications is provided in Table 1.

3.1.2. Trends in annual publication volume and citation frequency

The publications on IH have increased significantly from 2001 (84) to 2011 (273) and have remained stable (more than 200) until the present day. Between 2000 and 2022, 2015 saw the highest number of publications with 290 documents published. As Fig. 1A shows, the annual scientific production has gradually increased, with an annual growth rate of 3.22 % since the beginning of the millennium. Fig. 1B illustrates the average number of article citations per year, with five peaks observed in 2004, 2011, 2013, 2015, and 2019, respectively. Considering the fluctuations in these years, the publications on IH are likely to remain relatively stable in the future.

3.1.3. Journal distribution of IH publications

Table 2 presents a list of the top 20 influential journals based on the total number of publications related to IH. Pediatric Dermatology tops the list with 248 IH-related papers, with the highest h-index (33) and the largest number of total citations (4097). Notably, Pediatrics ranks sixth with only 60 publications but receives the highest number of citations (5197). In second place is Pediatric Radiology with 78 publications, a h-index of 19, and 1211 citations. Third on the list is Childs Nervous System with 76 publications, a h-index of 15, and 756 citations. It is worth mentioning that these two journals were established in Germany and most of the top journals were established in America (14/20). These 20 journals collectively contribute 1115 publications, accounting for 25.7 % of the included papers. Fig. S1 shows the source dynamics, where Pediatric Dermatology has published the most relevant papers, especially since 2010. Most of the journals listed in the top 10 have maintained an overall growth trend in recent years.

3.1.4. Network analysis of cited and citing publications in IH research

To provide a more detailed explanation of the cited and citing publications network for IH research, we created a journal dual-map overlay visualization on a global map of science in Fig. 2. The figure consists of two basic modules: the journals of citing papers are illustrated on the left (the application fields), and the journals of cited papers are illustrated on the right (the research foundations).

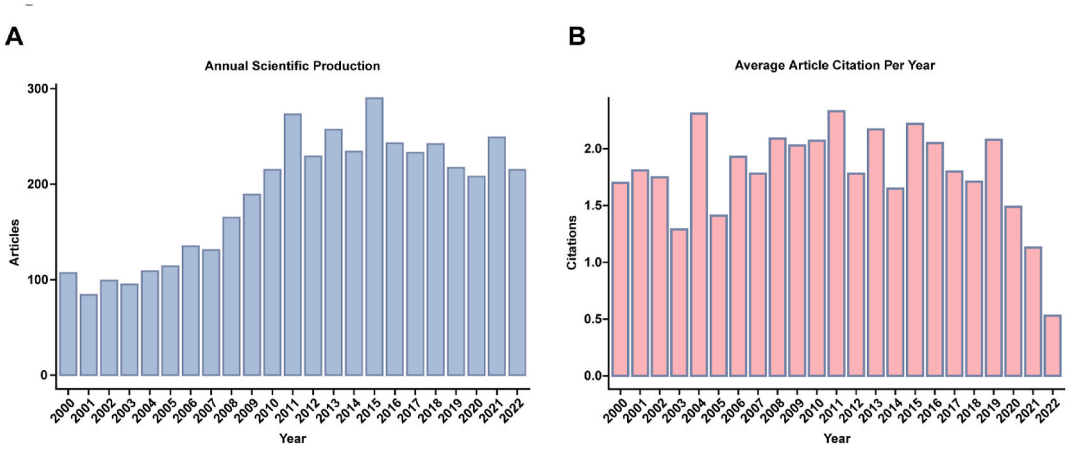

Fig. 1. Annual number of publications of infantile hemangioma (IH). (**A**), number of publications in each year from 2000 to 2022. (**B**), number of citations in each year from 2000 to 2022.

Table 2
The top 20 journals with the most publication in IH field.

Rank	Journal	NP	Country	h_index	TC	IF[a]	Category
1	Pediatric Dermatology	248	America	33	4097	1.997	Q3
2	Pediatric Radiology	78	Germany	19	1211	3.005	Q2/Q3
3	Childs Nervous System	76	Germany	15	756	1.532	Q4
4	International Journal of Pediatric Otorhinolaryngology	74	Ireland	22	1410	1.626	Q4
5	Journal of Craniofacial Surgery	64	America	11	437	1.172	Q4
6	Pediatrics	60	America	33	5197	9.703	Q1
7	Journal of the American Academy of Dermatology	59	America	28	2478	15.487	Q1
8	Journal of Pediatric Surgery	53	America	15	882	2.549	Q2/Q3
9	Pediatric Surgery International	40	Germany	11	478	2.003	Q3
10	British Journal of Dermatology	37	England	20	1537	11.113	Q1
11	Journal of Neurosurgery-Pediatrics	37	America	14	508	2.713	Q2/Q3
12	Journal of Pediatric Hematology Oncology	37	America	10	511	1.17	Q4
13	Plastic and Reconstructive Surgery	36	America	18	1237	5.169	Q1
14	American Journal of Medical Genetics Part A	35	America	13	737	2.578	Q3
15	Annals of Plastic Surgery	32	America	9	275	1.763	Q3
16	Archives of Dermatology	30	America	22	2008	–	–
17	European Journal of Pediatrics	30	Germany	13	722	3.86	Q1
18	Medicine	30	America	11	439	1.817	Q3
19	Pediatric Blood \& Cancer	30	America	14	952	3.838	Q1/Q2/Q3
20	Pediatric and Developmental Pathology	29	America	12	386	2.266	Q3

[a] The IF of journals were obtained from the 2022 Web of Science Journal Citation Reports (JCR); TC: total citation; NP: number of publication.

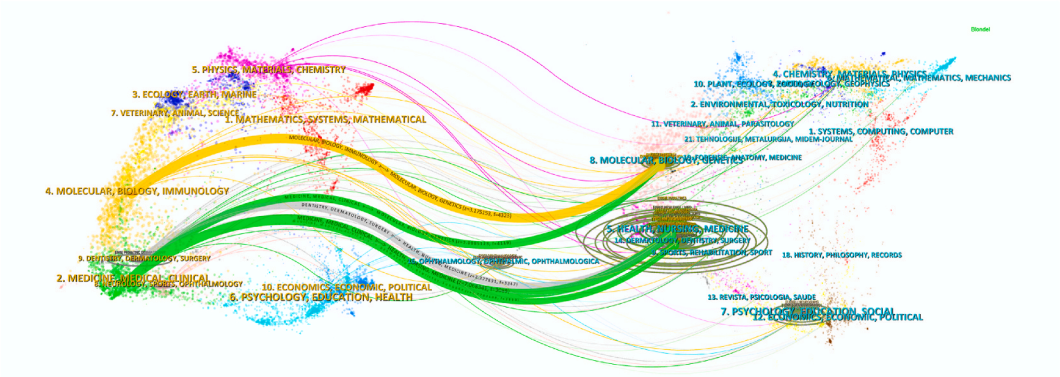

Fig. 2. Publication portfolio of IH. The map consists of two sections: the left section (yellow font) represents the practical applications of IH, while the right section (blue font) represents the research foundation of IH.

Each journal is represented as a circle, with lines between circles indicating citations and the width of the lines indicating the connection strength between different disciplines. The height of the ovals represents the number of articles, and the width denotes the number of authors. Five paths, including one yellow, one gray, and three green, were identified. The main citing papers are categorized into three disciplines: Molecular/Biology/Immunology, Dentistry/Dermatology/Surgery, and Medicine/Medical/Clinical. The

Table 3
The top 10 cited publications of IH.

Document	DOI	Year	Citations
Propranolol for severe hemangiomas of infancy	10.1056/NEJMC0708819	2008	807
Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics	10.1097/00006534-198203000-00002	1982	588
GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas	10.1016/S0046-8177 (00)80192-6	2000	307
Growth characteristics of infantile hemangiomas: implications for management	10.1542/PEDS.2007-2767	2008	299
Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment	10.1542/PEDS.2006-0413	2006	262
Propranolol for severe infantile hemangiomas: follow-up report	10.1542/PEDS.2008-3458	2009	257
Hemangiomas in children	10.1056/NEJM199907153410307	1999	243
Infantile hemangiomas: how common are they? A systematic review of the medical literature	10.1111/J.1525–1470.2008.00626.X	2008	239
A randomized, controlled trial of oral propranolol in infantile hemangioma	10.1056/NEJMOA1404710	2015	236
Cellular markers that distinguish the phases of hemangioma during infancy and childhood	10.1172/JCI117241	1994	216

citation lines of these three disciplines point to Molecular/Biology/Genetics, Health/Nursing/Medicine, and Dermatology/Dentistry/Surgery fields. Additionally, Table 3 lists the ten most highly cited papers in this field, which deserve a spotlight.

3.1.5. Distribution of the top 20 influential publications

Fig. 3 displays a historiograph that shows the direct citation network of the top 20 influential studies in the field of IH. The study by North PE in 2000 and Boye E in 2001 were the most cited studies in subsequent developments, even up to 2015. These studies focused on exploring the cellular and molecular mechanisms underlying IH, making them pioneering research in this field. From 2000 to 2008, influential studies focused on the clinical findings such as the characteristics, complications, and management of IH, along with the exploration of mechanisms such as the function of endothelial cells (Yu Y, 2004) and VEGFR signaling (Jinnin M, 2008). After 2008, studies tended to report on the efficacy and safety of β-blockers in curing IH. The papers by Metry DW in 2006 and Metry D in 2009 made remarkable contributions in advancing the research on PHACE syndrome. The work of Wassef M in 2015 on the classification of vascular anomalies also gained significant attention. Additionally, the review of IH by French doctor Léauté-Labrèze, who discovered the inhibitory effect of propranolol on IH growth in 2008, published in 2017, is a significant work in this field worth reading. Table S1 provides further details on the 20 most influential papers in the field of IH.

3.2. Major academic communities in IH publications

3.2.1. Country-wise distribution of publication output

As depicted in Fig. 4, 83 countries/regions worldwide contributed to the 4333 IH documents. Besides, America has established cooperative relations on IH with many countries. It has the most publications and collaborative relationships among the 83 countries/regions. Moreover, most of the cross-country collaboration of China and Spain was associated with America. Table 4 further lists the top 15 countries with the most publications from the "Corresponding Author's Country" view. In Table 4, America dominated in the IH field, possessing 1394 of the 4333 papers and made the most comprehensive collaboration with other countries, leading nearly one-third of the collaborations (0.322 frequency), which account for more than 10 % (0.131 MCP_Ratio, MCP: Multiple Country Publications) of its publications. And China ranked second, contributing 658 of the 4333 papers, with 15 % (0.152 frequency) international cooperation and accounting for 5 % (0.052 MCP_Ratio) in its publications. Italy followed this, publishing 195 articles, and nearly 5 % (0.045 frequency) collaborations, accounting for its 17 % (0.169 MCP_Ratio) publications. Moreover, the barplot in Fig. 5A helps us intuitively grasp the complex numerical data in Table 4 with single country publications (SCP) in green and multiple country publications (MCP) in red.

According to the number of total citations (TC) perspective, the top 20 most cited countries are plotted in Fig. 5B. It is obvious that behind America, China and France rank in second and third place, respectively. Specifically, the TC of America (TC = 39231) was roughly 6.4 times that of China (TC = 6132) and 7.9 times that of France (TC = 4997). Concerning the average citations per year (AC), the AC of publications in France leaped to first with 35.95 citations, which is followed by Austria (AC = 34.08), America (AC = 28.14), and Sweden (AC = 26.00) after removing outliers (Fig. 5C).

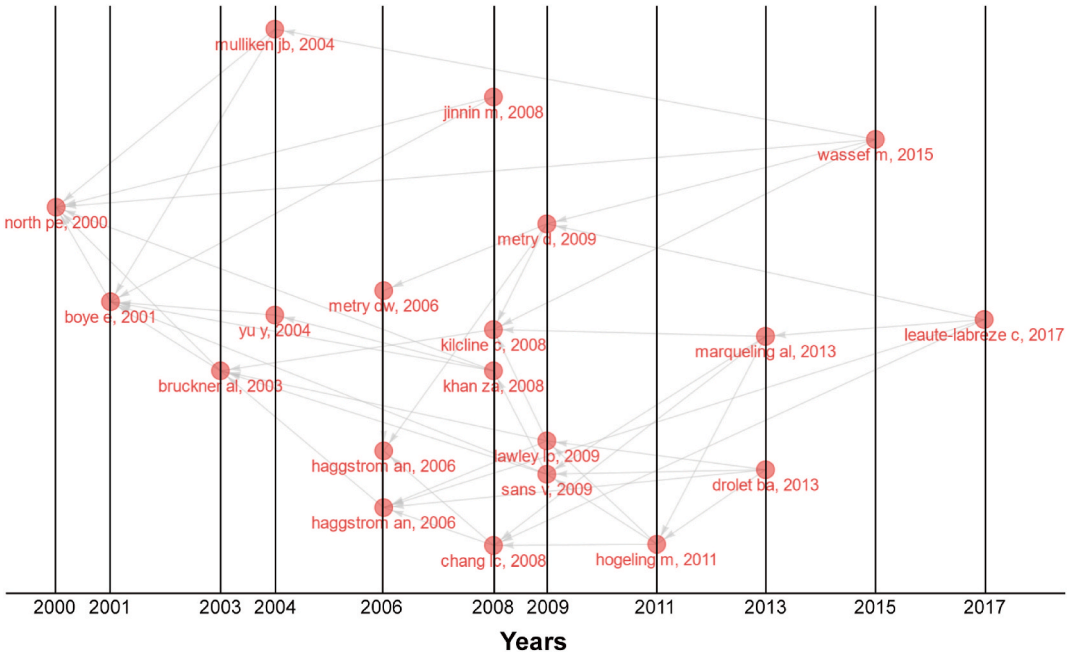

Fig. 3. Historical citation network of the top 20 influential papers within the IH field.

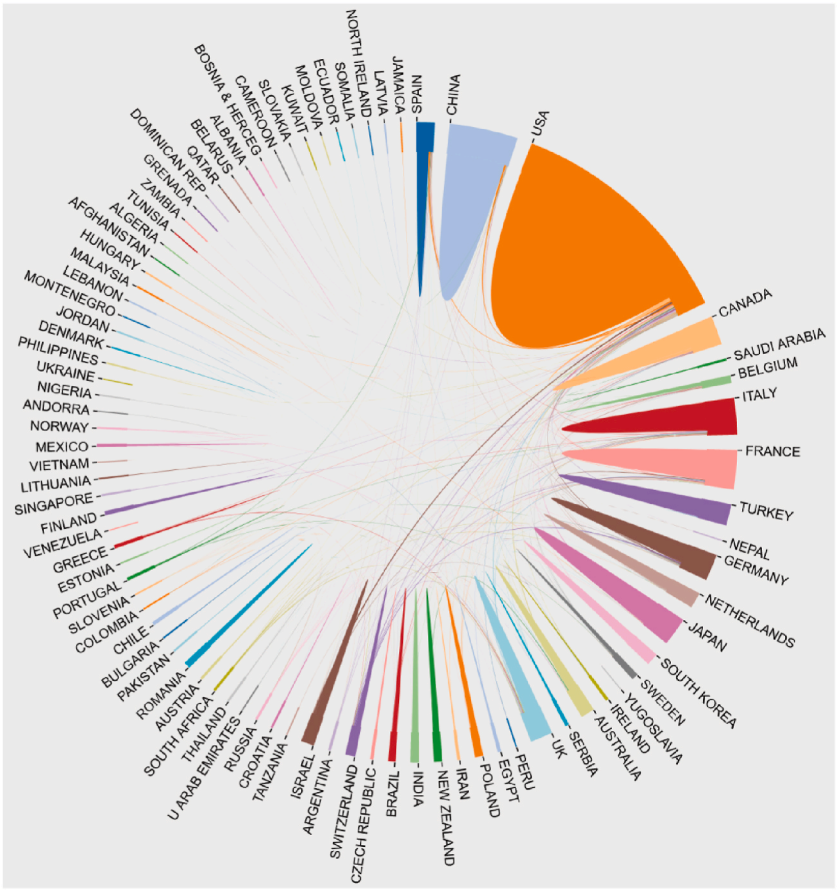

Fig. 4. The cooperative network map of countries that involved in IH. The thickness of the line connecting countries reflects the frequency of cooperation.

Table 4
The top 15 countries with most publications on IH.

Country	Articles	SCP	MCP	Freq	MCP_Ratio
USA	1394	1212	182	0.322	0.131
CHINA	658	624	34	0.152	0.052
ITALY	195	162	33	0.045	0.169
UNITED KINGDOM	190	157	33	0.044	0.174
JAPAN	184	176	8	0.042	0.043
CANADA	155	120	35	0.036	0.226
GERMANY	154	120	34	0.036	0.221
TURKEY	148	140	8	0.034	0.054
FRANCE	139	114	25	0.032	0.18
INDIA	112	102	10	0.026	0.089
SPAIN	107	89	18	0.025	0.168
KOREA	81	76	5	0.019	0.062
AUSTRALIA	63	56	7	0.015	0.111
NETHERLANDS	63	57	6	0.015	0.095
BRAZIL	62	59	3	0.014	0.048

SCP: Single Country Publications; MCP: Multiple Country Publications; MCP_Ratio = MCP/Articles.

3.2.2. Institutional distribution of publication output

After retaining institutions with more than 10 inter-agency collaborations, the study identified 23 institutions involved in collaborative publications, which were clustered into six groups based on the level of cooperation. The clusters are represented in Fig. 6 by different colors, with the dots and lines indicating the institutions and the strength of mutual collaboration, respectively. Upon investigation of the institutional affiliations, we observed that institutions within the same cluster were largely from the same country or region. For instance, Shandong University and Shanghai Jiao Tong University, both located in China, were clustered together in

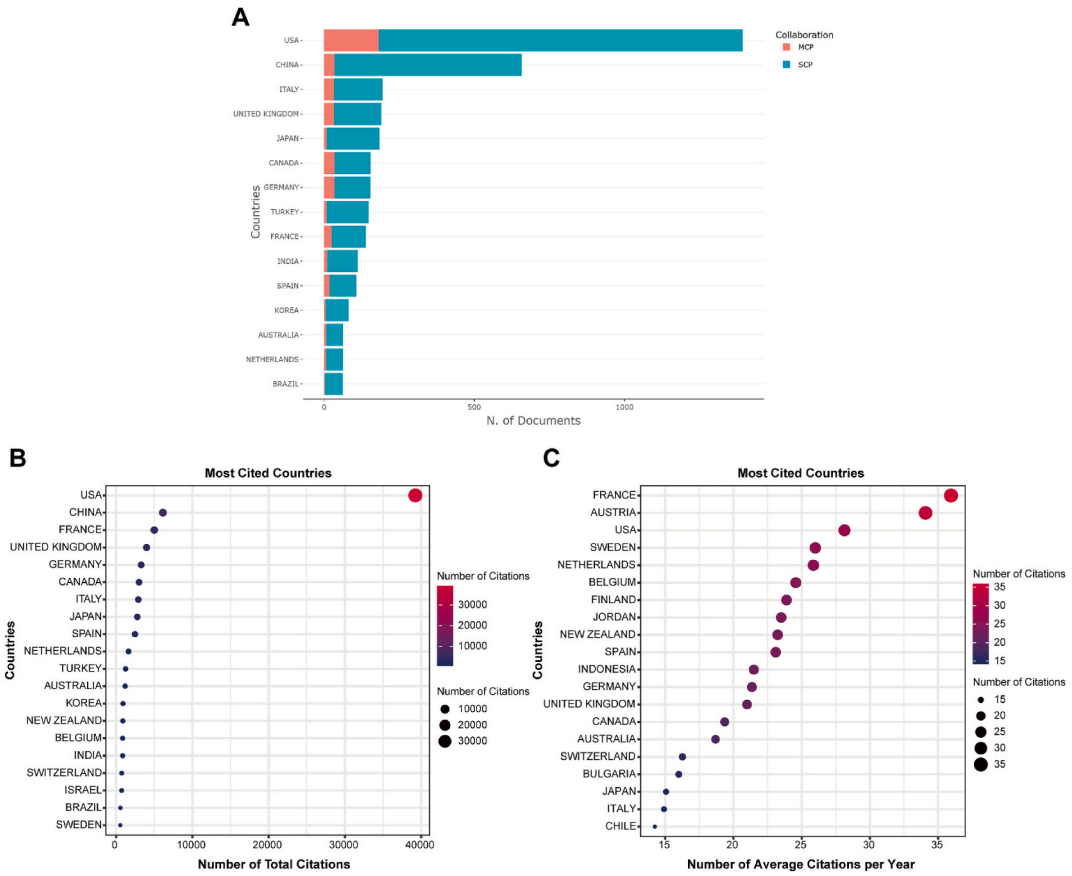

Fig. 5. Country analysis of publications of IH. (**A**), the barplot of the top 15 countries with the most publications in the IH field. (**B**), top 20 most cited countries ranked by the number of total citations. (**C**), top 20 most cited countries ranked by the number of citations per year. SCP: Single Country Publications, MCP: Multiple Country Publications.

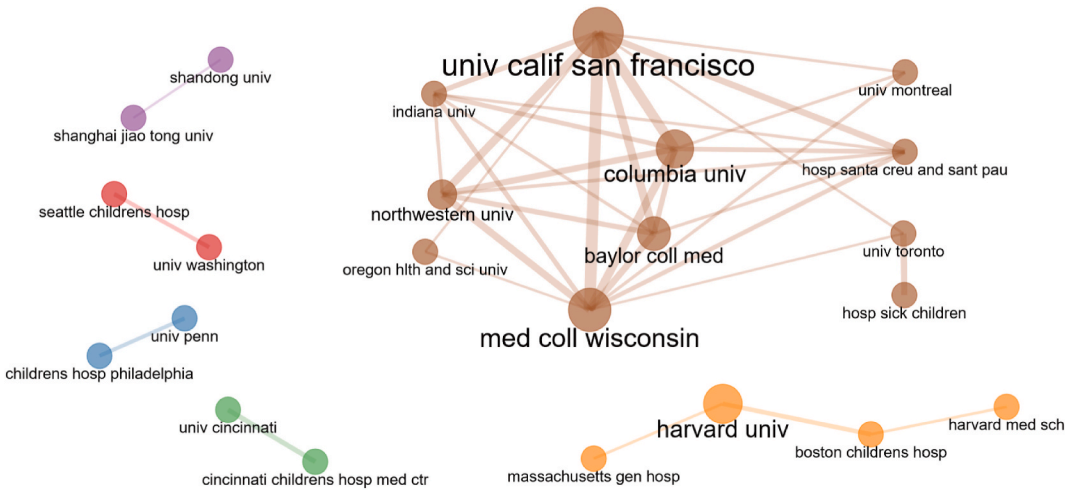

Fig. 6. The analysis of institutional collaboration network in IH (displaying only collaboration relationships with more than 10 occurrences).

purple. In contrast, the red, blue, green, and orange clusters comprised institutions from the United States, where universities and children's hospitals in close proximity developed strong collaborations. The largest cluster, brown, consisted of eleven institutions, with seven from the United States (Indiana University, Northwestern University, Oregon Health & Science University, University of California, San Francisco, Columbia University, Baylor College of Medicine, Medical College of Wisconsin) that worked closely with

each other. In addition, this cluster included Hospital de la Santa Creu i Sant Pau from Spain, and the University of Toronto, Université de Montréal, and The Hospital for Sick Children from Canada. Of these four institutions, Hospital de la Santa Creu i Sant Pau from Spain had extensive collaboration with six of the seven American institutions in the cluster. Université de Montréal and the University of Toronto from Canada primarily collaborated with the University of California, San Francisco, and the Medical College of Wisconsin.

Fig. S2 provides a more detailed view of institutional collaborations without limitations on collaboration strength. The figure reveals that Shanghai Jiao Tong University is at the forefront of IH research in China, engaging in extensive cooperation with numerous domestic universities, such as Wuhan University, Capital Medical University, Zhejiang University, Fujian Medical University, Fudan University, Sichuan University, and China Medical University. Meanwhile, the University of California, San Francisco, and Medical College of Wisconsin are the primary international cooperation hubs, leading the most collaborations across universities, research institutes, and hospitals.

3.2.3. *Author-wise distribution of publication output*

We selected 37 authors who co-authored more than five publications on IH to construct the authors' collaboration network, as shown in Fig. 7A. The results revealed that collaborators from the same regions or hospitals tend to work together more closely. For example, Lin XiaoXi, Ma Gang, Qiu YaJing, Jin Yunbo, and Chen Hui, all affiliated with Shanghai Jiaotong University in China, exhibit the closest collaboration with each other. The pink module includes Chen Siyuan and Ji Yi from West China Hospital of Sichuan University and Li Lizhi from Shengli Clinical Medical College of Fujian Medical University. In the green cluster, Zheng JiaWei and Zhang Ling come from Shanghai Jiao Tong University, and Wang Xuan is from Shandong Provincial Hospital affiliated with Shandong University. Meanwhile, Huo Ran from Shandong University and Li Xiaoyang from Wenzhou Medical University were found in the orange cluster.

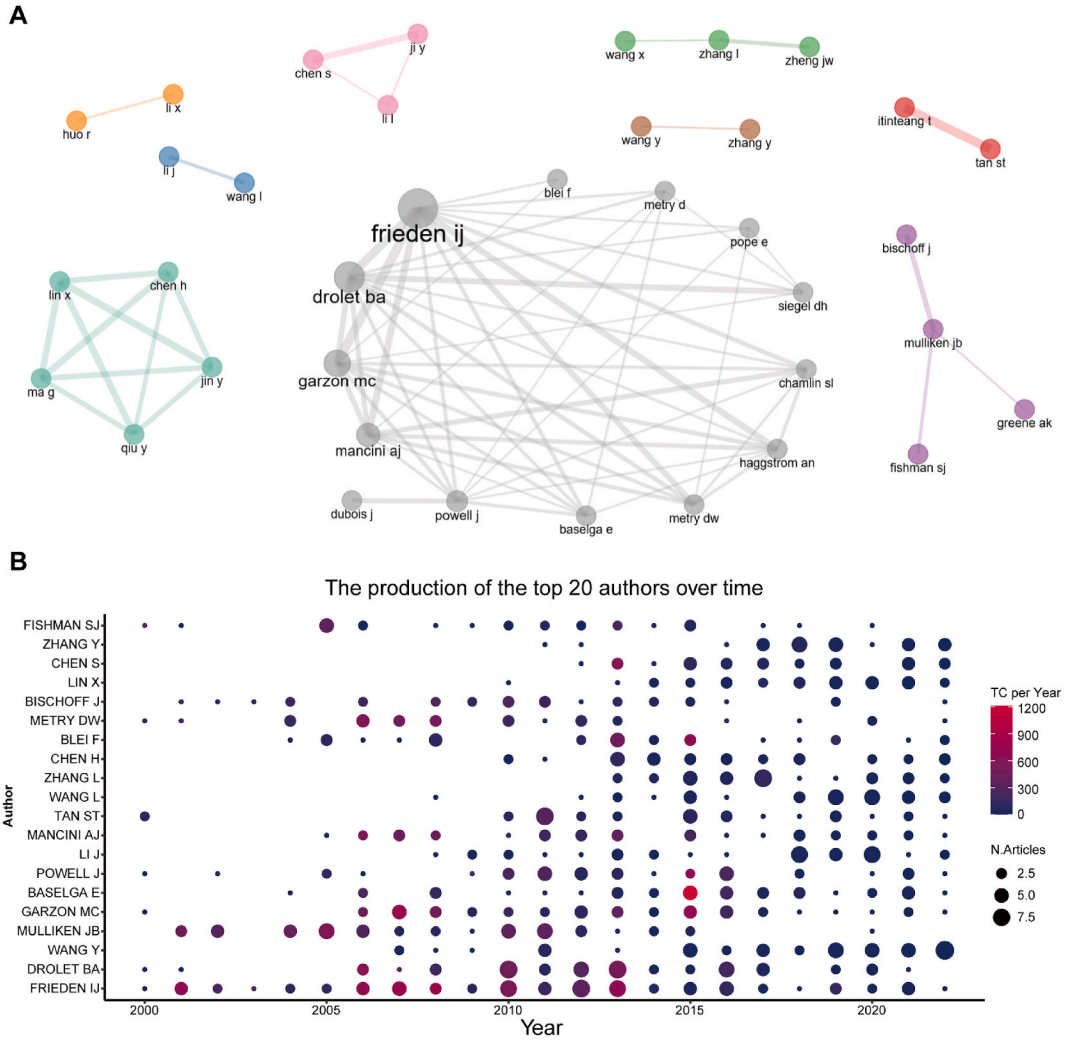

Fig. 7. Author analysis of publications of IH. (**A**), the analysis of author collaboration network (displaying only author relationships co-authored in five or more publications). (**B**), the production of the top 20 authors over time.

In the largest gray cluster, authors from American institutions dominate, including Frieden IJ, Drolet BA, Garzon MC, Mancini AJ, Chamlin SL, Metry DW, Haggstrom AN, Siegel DH, Metry D, and Blei F. Dubois J and Powell J (Sainte-Justine University Hospital Center; University of Montreal) are from Canada, and Baselga E works in Hospital de la Santa Creu i Sant Pau in Spain. Collaborators in the purple cluster are all affiliated with Boston Children's Hospital and Harvard Medical School, including Bischoff J, Mulliken JB, Fishman SJ, and Greene AK. In the red cluster, Itinteang T and Tan ST are from New Zealand (Fig. 7A).

In addition, we analyzed the yearly productivity of the top 20 authors with the highest number of publications in IH research (Fig. 7B). The size of each circle in the figure represents the number of papers published by the author in that year, while the color indicates the number of citations received. Notably, before 2004, only nine authors (Frieden IJ, Drolet BA, Mulliken JB, Garzon MC, Powell J, Tan ST, Metry DW, Bischoff J, and Fishman SJ) contributed to IH research, indicating their role as pioneers in the field. From 2005 to 2013, other authors began publishing in varying years. After 2013, most of the top 20 authors maintained a consistent level of annual publication output. Frieden IJ and Drolet BA were the most productive authors with the highest number of publications from 2000 to 2022, and Frieden IJ received the most citations during this period. Interestingly, papers of Baselga E in 2015 received the most citations, indicating its important role in this field.

The data in Table 5 corroborates the findings in Fig. 7, providing a ranking of the top 20 authors by their h-index in descending order. Frieden IJ tops the list with an h-index of 39, TC of 5837, and NP of 76 (TC: total citation; NP: number of publications). Mulliken JB (h-index = 32, TC = 3055, NP = 46) and Drolet BA (h-index = 24, TC = 2804, NP = 54) followed closely. These 20 authors contributed a total of 640 publications, representing 14.8 % of the included papers in our study.

3.3. Keywords and trending topics in IH publications

3.3.1. Frequency and network analysis of IH keywords

Fig. 8A shows a word cloud map of the top keywords plus in IH research, with the font size indicating the frequency of occurrences. The top 20 keywords plus are presented in Fig. 8B, which includes "management", "therapy", "propranolol", "malformations", "diagnosis", "classification", "vascular malformations", "expression", "tumors", "anomalies", "growth", "head", and "angiogenesis". These keywords represent the hotspots in IH research.

Furthermore, Fig. 8C displays the co-occurrence network of keywords plus, with three colored modules indicating different research themes. The red module is focused on basic research, exploring the cellular and molecular mechanisms underlying IH. The green module concentrates on clinical research, including risk factors, features, therapies, and complications of IH, as well as evaluating the effectiveness of treatment regimens. The blue module, the largest one, covers not only hemangiomas but also other vascular anomalies, highlighting the importance of "classification". This indicates that IH is just a part of vascular anomalies and more research is needed in this field.

3.3.2. Analysis of trending topics in IH research

A thematic map of keywords plus was divided into four topological regions and characterized by two parameters: density and centrality (Fig. S3). The first parameter, denoted by the horizontal axis, is "centrality", which represents the theme's external connectivity strength with other themes. It serves as a measure of the theme's importance in the overall development of the research field. The second parameter, represented by the vertical axis, is referred to as "density", reflecting the interconnectivity strength between keywords within the theme. This parameter gauges the level of cohesion within the theme [16]. In this context, the upper right

Table 5
The top 20 authors with the highest h_index in IH field.

Authors	h_index	TC	NP
Frieden IJ	39	5837	76
Mulliken JB	32	3055	46
Drolet BA	24	2804	54
Bischoff J	21	1732	28
Powell J	21	2165	36
Garzon MC	20	3386	42
Metry DW	20	2575	29
Baselga E	19	2209	37
Fishman SJ	19	1315	26
Mancini AJ	17	2547	33
Blei F	16	1790	29
Tan ST	16	813	33
Boscolo E	15	1255	15
Dubois J	15	704	25
Haggstrom AN	15	1939	21
Itinteang T	15	697	25
Adams DM	14	1137	19
Chen S	14	1010	27
Greene AK	14	731	18
Waner M	14	1202	21

TC: total citation; NP: number of publication.

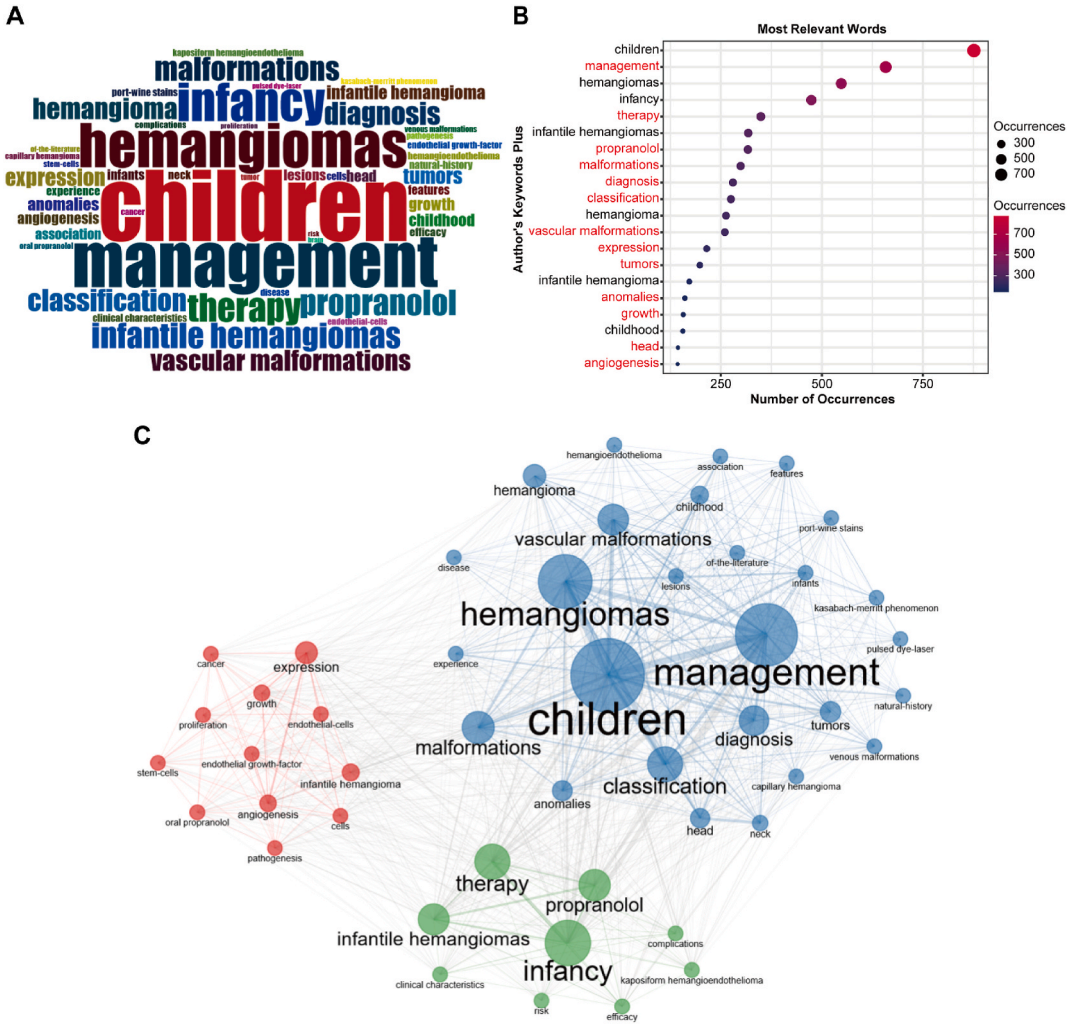

Fig. 8. Keywords analysis on IH. (**A**), word cloud map of keywords plus in IH articles ranked by their frequencies. The larger the font size, the more times it appears. (**B**), top 20 most relevant words evaluated by the number of occurrences in the bubble chart. (**C**), co-occurrence analysis of the keywords plus. The red module is focused on basic research. The green module concentrates on clinical research, and the blue module highlights the importance of "classification".

quadrant of the map corresponds to themes with high density and centrality, which are both well-developed and crucial for the advancement of the IH field, including "children", "management", and "hemangiomas". The lower right quadrant contains themes with high centrality but low density, including "expression", "infantile hemangioma", and "growth" in cluster 1 and "infancy", "therapy", and "infantile hemangiomas" in cluster 2. While these themes play a significant role in the field's development, they are not yet fully developed and generally represent foundational aspects of research. On the other hand, the upper left quadrant comprises themes with high density but low centrality, including "angiomyolipoma", "epilepsy", and "multicenter" in cluster 1 and "fusion" in cluster 2. These themes have experienced considerable development but have limited overall impact on the research field. They often represent peripheral or highly specialized areas of study. Lastly, the lower left quadrant, including "association", "abnormalities", and "arterial anomalies", represents themes with low density and centrality. These themes possess weak importance and development, and they may indicate emerging or declining areas within the field. Overall, by utilizing the thematic map, researchers can gain valuable insights into the positioning and dynamics of different research themes within the IH field, facilitating a better understanding of their significance and impact on the research landscape.

Based on Fig. S3, Fig. 9A provides an additional visualization of the IH research trends over time, showcasing the prominent topics explored in the field since the year 2000. In the initial years, the focus was mainly on therapy, with topics like "interferon alfa-2a", "argon-laser", "ok-432 therapy", and "ND-YAG laser" being prominent. Subsequently, in 2011, attention was paid to "malformations" alongside "hemangiomas". The year 2013 saw significant exploration of "angiogenesis" as a mechanism underlying IH development. In 2014, "management", "diagnosis", and "classification" emerged as crucial topics, emphasizing standardized diagnosis and treatment of IH. Since 2016, there has been a surge in studies investigating "propranolol" and its "efficacy", "safety", and mechanism

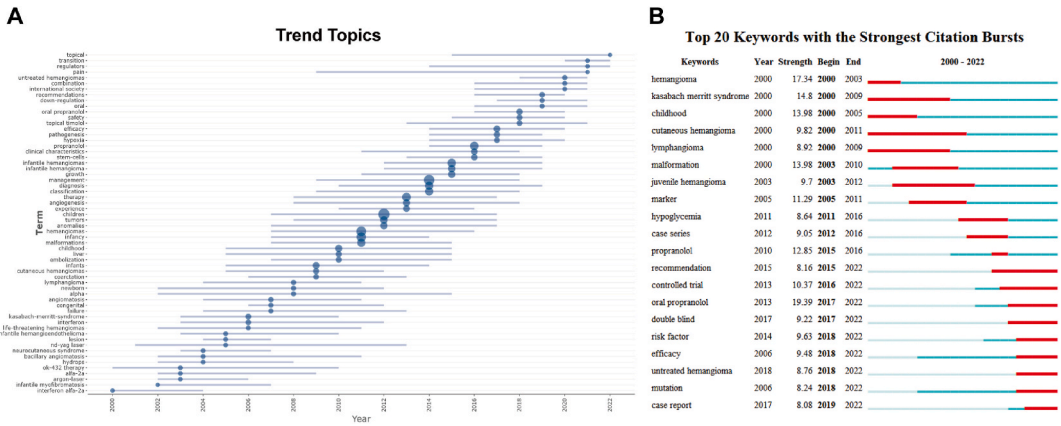

Fig. 9. Trend topics of IH. (**A**), trend Topics of Keywords on IH research from 2000 to 2022. (**B**), top 20 keywords with the strongest citation bursts in the IH discipline. These keywords were analyzed and visually represented in a burst map, highlighting their temporal impact. Each short line on the map corresponds to a specific year, while the presence of a red line indicates a burst detection year. Notably, keywords with red lines extending up to the most recent year signify potential research frontiers in the near future.

("pathogenesis" and "hypoxia"), as well as its competitor, "timolol". Furthermore, to identify emerging research topics and trends, we employed the CiteSpace algorithm-based analytical tool to generate a keywords burst map in IH field. This map visualized keywords with the strongest citation bursts in the scientific literature, arranged based on their appearance over time (Fig. 9B). The keywords burst map encompassed two crucial aspects: the strength of the burst and the year it began or ended. Among them, the strength represents the intensity or prominence of keyword bursts. It measures the level of activity and prominence of a keyword during a specific time period. A higher strength value indicates that the keyword has received greater attention and importance in the research field and has experienced a significant burst during a specific time period. It is calculated based on factors such as the frequency of keyword occurrence in the citation network and its temporal distribution. Besides, the year provides insight into both the duration of the burst and the shift in research focus. By analyzing the combined information from the keywords burst map, researchers could gain a comprehensive understanding of the emerging research topics and their evolution within the IH field. In this study, the map included the top 20 keywords exhibiting the strongest citation bursts. From 2000 to 2012, research on IH focused on the classification of vascular anomalies, like "kasabach merritt syndrome", "cutaneous hemangioma", "lymphangioma", "malformation", and "juvenile hemangioma", and researchers tried to use different "marker" to distinguish these vascular anomalies. From 2012 to 2017, the research related to IH in this stage was transformed into research on the treatment, including the application of "propranolol", the "recommendation" of the medicaments and its dosage. Since 2017, research on IH has begun to report the cases and clinical trials on the basis of previous studies, especially the risk factor of IH and the efficacy evaluation of the drug administration. This transformation revealed a deeper understanding and notable progress on the study of IH. The three burst words with the highest strength were "oral propranolol" (19.39), "hemangioma" (17.34), and "kasabach merritt syndrome" (14.8).

4. Discussion

Infantile hemangioma (IH) may not pose an immediate threat to life, but it can significantly impact a patient's quality of life and mental health [17]. Thus, it is crucial to comprehend the occurrence, development, potential pathological mechanisms, and treatment approaches for IH. Unfortunately, limited information is currently available on this topic. In this study, we conducted a comprehensive bibliometric analysis of 4333 literature sources related to IH after 2000. Our objective was to provide an overview of current research findings in the field of IH, analyze journal output and the contributions of countries, institutions, and authors, and highlight the research hotspots in IH science. Through our analysis, we have identified key trends in terms of publication output characteristics, prominent academic communities, and active research topics in IH. These findings will be particularly valuable for new researchers, enabling them to quickly grasp the historical and current landscape of IH, acquire essential knowledge, and broaden their research perspectives.

From 2000 to 2022, the annual scientific production related to IH exhibited a steady growth rate of 3.22 %. The most impactful output was primarily driven by international cooperation led by the United States, forming an America-centered multinational network that highlights its leadership in this field. Notably, the number of publications and citations from the United States far exceeded those of other countries. Although China ranked second in terms of the total number of published IH articles and citations, the average number of citations per article was comparatively low, and it did not rank among the top 20 countries. This suggests that while China has extensive publication output, it lacks high-quality articles, in part due to a lack of collaboration with internationally renowned research institutes and language barriers. Among the top ten institutions that published the most papers, only Shanghai Jiao Tong University and Sichuan University were from China, while the others were primarily from Europe and the United States. The level of cooperation between research institutions in Western countries is high, whereas cooperative relationships between China and these institutions are limited. Even between Asian countries, there is little collaboration. That is to say, in both institutional and author

collaboration networks, a regional cooperation trend was observed, with most institutions and authors tending to collaborate within their own countries/regions. This trend may be attributed to geographical constraints, language barriers, and limited academic exchanges. This highlights the importance of strengthening global cooperation and exchanges related to IH in the future, particularly with countries and institutions in the Asian region.

In terms of journals, Pediatric Dermatology is the leading publisher of IH research articles. Many of the top 20 journals in this field are based in the United States, with most being classified as Q1 journals. Articles published in Q1 or high-impact factor journals tend to receive more citations, and therefore, new researchers may prioritize reading articles from these journals. IH research has also become increasingly dependent on the fields of Health/Nursing/Medicine (Fig. 2). While some journals, such as Pediatric Dermatology and International Journal of Pediatric Otorhinolaryngology continue to maintain their influence in this area (Fig. S1). Notably, besides pediatrics and dermatology, research has also been published in the field of neurosurgery, possibly due to the rare occurrence of IHs in the neuraxis. Roughly 30 % of large facial IHs are associated with PHACE syndrome, which includes intracranial arteriopathy [18,19]. The rupture of such hemangiomas in the central nervous system can lead to challenging situations, such as quadriplegia and stroke, which must be taken seriously [20,21].

When it comes to authors and references in the IH research field, Frieden IJ, Mulliken JB, and Drolet BA are the most productive and highly cited authors, establishing their leadership positions in the field. Their work is essential reading for new researchers. These authors came from various universities in the United States, with Frieden IJ and Drolet BA having a strong collaborative research history, while Mulliken JB conducts more collaborative research within his own units at Boston Children's Hospital. Researchers from various countries and regions have also contributed significantly to the IH discipline. For example, Bischoff J, a member of Mulliken JB's team, and her colleagues discovered the function of endothelial cells in IH. They characterized hemangioma-derived stem cells (HemSCs) [22] and studied the behavior of key regulators in HemSCs, such as VEGF-A, VEGFR-1, NOTCH and JAGGED1, SOX18, and NGBR [23–28]. These discoveries have advanced our understanding of IH pathogenesis and opened up new avenues for therapy. Powell J and Garzon MC, co-workers of Frieden IJ, have recently focused on PHACE syndrome, highlighting the importance of monitoring extracutaneous anomalies in children with facial segmental or periorbital focal IH [29,30]. Tan ST and Itinteang T have made significant contributions to exploring the microenvironment of hemangioma, investigating various molecular disorders and cell functions in IH, including the mesenchymal differentiation of capillary endothelial cells during the proliferating phase and the regulatory roles of angiotensin I (ATI) and ATII in promoting IH cell proliferation and the anti-apoptotic role of osteoprotegerin (OPG) during IH development through the TRAIL pathway [31–34]. They have also explored the roles of mast cells, lymphocyte subpopulations, and myeloid cells in IH [35–37]. In China, Professor Lin Xiaoxi and his team conducted extensive research on the applications of propranolol in IH. Prior to this, they conducted a seven-year follow-up study on untreated deep or mixed facial infantile hemangioma, which revealed a significant difference in the complete regression rate between the central facial area (33.3 %) and the perifacial area (66.7 %) ($P = 0.025$) [38]. After the propranolol application, they confirmed the safety of propranolol (2 mg/kg per day) in significantly reducing hemangioma volume in Chinese children [39], but also noted potential complications, such as sleeping disorders, diarrhea, decrease in fasting glucose, bronchial hyperactivity, and hyperkalemia [40]. A long-term follow-up study of IH with oral propranolol also identified common types of sequela, including telangiectasia, fibrofatty tissue, and erythema [41].

After analyzing the countries, journals, and authors that have published literature on IHs, we conducted a further exploration of the highly cited articles in this field. Table 3 presents the top 10 highly cited articles, which we will briefly explore in chronological order. In 1982, Mulliken JB and Glowacki J proposed a comprehensive classification of pediatric vascular lesions (hemangiomas and vascular malformations) through analyzing IH surgical specimens at the cellular level. This classification has been updated and improved over time [42,43]. In 1994, Mulliken JB's team proposed using biomarker differences to distinguish infantile and childhood hemangioma phases (proliferating, involuting, involuted phases) [44], providing insights into the pathogenesis of hemangiomas and targeting therapies. Various potential therapeutic targets, such as PRR (accumulating in the proliferative phase), AQP1 (driver of propranolol antitumor response), and hypoxia-associated downstream targets (VEGF-A, GLUT-1, and IGF-2) were discovered through this approach [45–49]. Subsequently, in 1999, Drolet BA and Frieden IJ team published a study on IH pathogenesis (angiogenesis and vasculogenesis), clinical manifestations, diagnostic imaging studies (doppler US, CT, MRI), complications, and managements (systemic corticosteroids, recombinant interferon alfa, laser systems), which further promoted the development of the discipline [50]. The following year (2000), North PE and co-workers reported that high GLUT1 endothelial immunoreactivity is a specific feature and diagnostically useful marker of juvenile hemangiomas in all clinical phases different from malformations [46]. In 2006, Haggstrom et al. conducted a prospective cohort study and identified the most important predictors of poor short-term outcomes. They found that large size, facial location, and segmental morphology are significant risk factors [51]. In 2008, the same research team published another report on the management of IHs, highlighting that the first few weeks to months of life are a critical period for IH growth, necessitating close monitoring, prompt referral, and early specialty care intervention, if needed [52]. Later that year, a groundbreaking discovery was reported in The New England Journal of Medicine, indicating that propranolol can inhibit the growth of infantile capillary hemangiomas, based on a series of 11 children [9]. In the following year, Professor Léauté-Labrèze's follow-up report further demonstrated the consistent, rapid, and therapeutic effect of oral propranolol with good clinical tolerance [53]. In 2015, the research team summarized a randomized controlled trial, recommending a dose of 3 mg per kilogram per day for six months, thereby establishing propranolol as the first-line treatment for IHs [54]. Overall, the top 10 highly cited articles have provided insight into the evolution of the field of IH. Initially, the focus was on understanding the nature of IH, while later studies aimed to determine the most effective treatment methods. By organizing this information, researchers can anticipate future trends and strategically adjust their research directions.

The blue cluster in Fig. 8C indicates that research on the "diagnosis" and "classification" of IHs are major research hotspots. For a long time, the definition of congenital vascular lesions has been confusing in various countries. In the mid-19th century, researchers

began to focus on the classification and diagnosis of hemangiomas. Virchow categorized vascular anomalies into angiomas and lymphangiomas in 1863 [55], and subsequent scholars improved the morphological classification by adding congenital vascular nevi and telangiectasia ten years later. However, these earlier classifications mainly focused on the appearance and histomorphological features of hemangiomas, without considering cell biological characteristics. A more ideal classification should explain embryonic histopathology, clinical signs, and biological behavior, to guide treatment selection, determine the appropriate timing for treatment, and assess treatment efficacy. Mulliken and Glowacki made a seminal contribution to this issue by defining the nature of vascular anomalies and classifying them into hemangiomas and vascular malformations based on multiple features [42]. Later on, in 1993, Jackson et al. further divided vascular malformations into high-flow and low-flow based on blood flow rate and arteriovenous shunt rate, which facilitated the selection of sclerotherapy and embolization for vascular malformations in clinical practice [56]. Consequently, in 1995, Waner and Suen proposed a new classification system based on Mulliken-Glowacki's classification, which divided vascular anomalies into vascular tumors and malformations and was widely recognized by international peers. This new classification method became a standard for academic exchange among researchers in different disciplines worldwide [57]. In summary, the classification of vascular malformations has become more detailed and practical, and protein and mRNA expression analyses in IH tissue aid in differential diagnosis. High expression of proliferating cell nuclear antigen, type IV collagenase, and VEGF define the proliferating phase, while bFGF and urokinase are highly expressed in both the proliferating and involuting phases of IH, but not in vascular malformations [44]. In recent years, bioinformatics has enabled the discovery of molecular markers related to IH diagnosis and prognosis, including FOXF1, CTNNB1, IL6, CD34, IGF2, and MAPK11 [58,59]. Additionally, APLN, APLNR, TMEM132A were identified as potential anti-angiogenesis therapeutic targets for IH, and FYN, KIF20A, POLD1, RAD54L, TYMS were involved in distinguishing proliferative and regressive IH lesions [60,61]. Furthermore, the circRNA-related ceRNA regulation mechanism in the pathogenesis of IH has also been explored [62]. In conclusion, the understanding of molecular expression differences of IH at different stages through sequencing methods and mining public databases promotes the development of diagnosis and treatment.

Based on the red cluster highlighted in Fig. 8C, this section emphasizes the importance of "endothelial cells", "stem cells", and "angiogenesis" in the IH microenvironment. Despite extensive research, the mechanisms underlying hemangioma hyperplasia and degeneration remain incompletely understood. Existing studies suggest that hemangioma endothelial cells (HemECs) and angiogenesis are crucial to this process [63], which involves HemEC migration and proliferation, extracellular matrix production, protein breakdown of the extracellular matrix, vascular structure formation, and luminal recanalization [64,65]. HemEC proliferation is a hallmark of hemangioma pathology, exhibiting exceptional proliferative potential compared to normal vascular endothelial cells or vascular malformed endothelial cells, greater uptake of 3H-thymidine, and stronger angiogenesis promotion, as demonstrated in vitro experiments. Moreover, the ultrastructural thickening of the multilayer basement membrane of HemECs indicates their active performance [42]. However, the precise relationship between HemECs and IH remains unclear. Studies have shown that mature endothelial cell markers CD31 and vWF are only sparsely expressed or not expressed at all in the involuted phase but exhibit clear manifestations in the involuting phase [44], consistent with the fact that premature HemECs in the proliferating phase continue to proliferate to achieve volumetric growth. As HemECs mature, the tumor enters the involuting phase and begins to degenerate.

In addition to HemECs, the relationship between mast cells and IH has long attracted attention. Researchers have found that hemangioma proliferation is directly proportional to the number of mast cells, which can release angiogenesis factors such as heparin and histamine, stimulating endothelial cell growth and hemangioma proliferation. Once the stimulation is lost, hemangiomas begin to degenerate [66]. However, some scholars have found that mast cells proliferate significantly in the early stage of degeneration in IH, and their granules contain angiogenesis inhibitors such as interferon, transforming growth factor, and prostaglandins, contributing to hemangioma degeneration [35].

In 2008, researchers identified a multipotent stem cell in more than 30 different proliferative hemangioma specimens, which they termed hemangioma-derived stem cells (HemSCs). These cells possess robust proliferative and clonogenic capability and can differentiate into multiple lineages. Unlike endothelial cells, HemSCs do not express CD31/PECAM-1 or VE-cadherin but express CD90, a mesenchymal cell marker. Therefore, HemSCs are phenotypically more similar to mesenchymal cells than endothelial cells. When implanted into immunodeficient nude mice, HemSCs form GLUT1-positive hemangiomatous blood vessels and adipocytes [22,63]. Additionally, studies have demonstrated that HemSCs can differentiate into pericytes in vivo and in vitro when co-cultured with endothelial cells, a process driven by the upregulation of the Notch ligand JAGGED1 in proliferating phase endothelium [26,67,68]. However, pericytes in IH are less well studied. Although they cannot stabilize endothelial cell growth and migration, pericytes in hemangioma exhibit low levels of angiopoietin 1, which prevents vascular formation [69]. In the microenvironment of hemangioma, in addition to some working cells, angiogenesis factors such as peptide growth factor, fibroblast growth factor, vascular endothelial cell growth factor, and extracellular matrix, including proteases and their inhibitors, are also worth investigating [24,70,71].

In Fig. 8C, the green cluster depicts important clinical aspects of hemangioma, including "risk" factors, "complications", and "therapy" with its "efficacy". Although various factors influence the development of hemangioma, there is no universally accepted explanation. It is generally believed that genetic predisposition, endocrine irregularities during pregnancy, maternal high blood pressure, environmental pollution, and microbial infections may affect fetal blood vessel development. A recent matched case-control study with a large sample size also suggests that maternal and perinatal factors are closely associated with IH occurrence, particularly a history of miscarriage and anemia during pregnancy [72]. The study also found a positive correlation between maternal estrogen levels (increased in mothers who took birth control pills before pregnancy) and the incidence of IH. High maternal estrogen levels increase the likelihood of developing IH [73–75]. Therefore, many researchers propose that as the infant is born and weaned off breast milk, the hormones transferred from the mother to the infant gradually decrease, leading to the spontaneous regression of IH. Consequently, hormone and estrogen receptor inhibitors have been recommended as potential treatment options for hemangiomas [76,77]. Ulceration is a common complication mainly occurring in the proliferating phase in the above, lower lip, and perineal parts [78].

Additionally, complications include visual compromise, bleeding, airway obstruction, auditory canal obstruction, cardiac compromise, etc. [79–81]. The Kasabach-Merritt syndrome, reported in 1940, is a severe complication presented as hemangioma with platelet aggregation and a thrombocytopenic coagulopathy [82]. The treatment of IH should be comprehensively considered based on the child's age, IH phase, lesion depth, and severity, as well as the onset site, with the aim of achieving optimal treatment outcomes with minimal trauma and economic cost. Currently, three main types of treatment for hemangiomas are available (drug, surgery, and laser), with drug therapy being the primary choice. Glucocorticoids were previously the first-line treatment for IH. However, since 2008, numerous clinical studies have assessed the efficacy and safety of propranolol, which has now replaced glucocorticoids as a recognized first-line treatment drug worldwide, and included in guidelines [9,83–85]. The FDA approved HEMANGEOL® as the first drug specifically designed to treat proliferative IH in 2014, and it was approved by the China NMPA in 2021, providing substantial benefit to most infant patients. Therefore, further research focusing on drug mechanisms, new drug development, and novel drug delivery methods will contribute to the diagnosis and treatment of IH.

Although Fig. 8C displays three main clusters, we can observe that there are also connections between clusters, albeit weaker than within-cluster connections. This observation aligns with their practical significance, as clinical research and basic research are inherently interconnected. No basic research can be completely detached from clinical applications, and conversely, certain clinical findings necessitate exploration through basic experimental research, such as comparing treatment methods and evaluating therapeutic efficacy.

The thematic map provides an overview of the positioning of each topic in a quadrant, based on the density and centrality measures (Fig. S3). The upper left quadrant and the lower right quadrant exhibited the highest level of representation. The upper left quadrant comprises topics that have received limited investigation but demonstrate rapid development. This quadrant includes keywords such as "angiomyolipoma", "epilepsy", "multicenter", and "fusion". It is noteworthy that the term "fusion" and "epilepsy" may not be readily comprehensible in a literal sense. Specifically, "fusion" refers to research on genetic fusion or embryological fusion, focusing on the genetic aspects of investigation [86,87]. Additionally, "epilepsy" pertains to investigations concerning central nervous system infantile hemangiomas, with a specific focus on segmental cutaneous infantile hemangiomas, predominantly occurring on the head, neck, upper trunk, lumbar, or sacral region [88]. These topics exhibit significant development characterized by high density but relatively low centrality. Consequently, these areas are actively progressing in IH research. Conversely, the lower right quadrant consists of fundamental topics with high centrality but low density. This quadrant encompasses topics such as "expression", "therapy", and "infantile hemangioma(s)". While the level of development may not be as advanced as in the upper left quadrant, the substantial occurrence of these terms indicates their widespread usage. Moreover, this suggests the potential for further development through addressing existing research gaps and offering more comprehensive insights. Taking into account the aforementioned information, the thematic map effectively delineates the distribution of topics based on their density and centrality. The upper left quadrant represents topics with rapid development despite limited investigation, while the lower right quadrant comprises fundamental themes with high centrality.

After summarizing the current status of several research themes in IH, we proceeded to analyze the evolving trends using keyword-based analysis, thereby enhancing our understanding of the IH field. Fig. 9B demonstrates that previous studies mainly concentrated on various vascular diseases, including the Kasabach-Merritt syndrome. However, recent studies have increasingly emphasized propranolol, with clinical trials, dosage recommendations, efficacy evaluations, and case reports, indicating that research on oral propranolol for IH treatment has become a hot topic, consistent with Fig. 9A. To date, extensive clinical data have confirmed that propranolol has a fast action, a definite therapeutic effect, minor individual differences, and fewer adverse reactions for IH patients. However, its treatment mechanism remains unclear. The literature roughly divides the mechanism into three aspects: immediate, intermediate, and long-term effects [89]. Propranolol's immediate effect involves acting on the β-adrenergic receptor (β-AR) located on the IH's capillary wall, which reduces NO synthesis and release, causing tumor vasoconstriction, reducing vascular density, and blood flow. This is manifested as rapid IH shrinkage, darkening of color, and tumor softening [90,91]. The intermediate effect inhibits cell proliferation and blocks angiogenesis-related signaling pathways, including (1) regulating the HemEC cell cycle and inhibiting proliferation; (2) blocking the Rac/MAPK pathway, the PI3K signaling pathway, and DLL4/Notch1/Akt signal transduction, downregulating VEGF and bFGF, and inhibiting angiogenesis [92–94]; (3) Reducing HIF-1α and its downstream endothelial cell proliferation related growth factors such as VEGF, IGF, MMP [95]; (4) Downregulating the level of ATI, ACE or ATII in RAS system to reduce the tumor volume [32]. The long-term effect induces apoptosis of vascular endothelial cells by reducing the expression of STAT3 and Bcl-2, promoting the expression of caspase 3,8,9, P53, and HemECs' aliphatization [96–99]. Recent studies have also revealed that the R (+) enantiomer of propranolol, which has weak anti-β-adrenergic activity, acts as a small molecule inhibitor of SOX18 and HemSC-to-EC differentiation by interfering with *trans*-activation of SOX18 target genes, such as VCAM1 and NOTCH1 [27,100]. Furthermore, oral atenolol can be an alternative treatment option for IH patients requiring systemic therapy [101]. Future research should focus on the molecular mechanisms and microenvironmental changes after using propranolol to maximize the advantages of targeted therapy.

To our knowledge, this is the first bibliometric analysis of IH-related studies in the last 20 years. However, our study has some limitations. Firstly, we only included original articles and review articles in English. Secondly, we restricted our analysis to literature data from the WoSCC database, while papers from other databases were excluded. Thirdly, it should be noted that studies published in earlier years may have higher citation counts than high-quality articles published in recent years, which may introduce research bias. Finally, due to the constant updating of the WoSCC database, the results of bibliometric analyses may not fully reflect the actual research situation. Nevertheless, we believe that our work provides an overview of the IH field's development trends and can be useful for future research in this area.

5. Conclusions

In conclusion, infantile hemangioma (IH) is a growing research topic, attracting increasing attention from scholars. Through this study, we have analyzed the publication output characteristics of IH and provided a historical perspective. It is anticipated that future research will continue to focus on understanding the mechanisms and treatment of IH, as well as evaluating treatment effectiveness. Additionally, investigations into other vascular diseases and clinical case studies will contribute to advancements in IH clinical practices. The United States has been at the forefront of IH research and is expected to maintain its leading position. However, there is a need to strengthen research collaboration, particularly among countries. Notably, established research teams such as Lin XiaoXi's team, Tan ST's team, Frieden IJ's team, Mulliken JB's team, Drolet BA's team, and Garzon MC's team serve as valuable academic groups to learn from and collaborate with in the long term. This study offers potential guidance and contributes to further research in the field of IH.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Qian Lin: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Beichen Cai:** Conceptualization, Investigation, Methodology, Project administration, Validation, Writing – original draft. **Xiuying Shan:** Data curation, Supervision, Validation, Writing – review & editing, Visualization. **Xuejun Ni:** Software, Supervision, Writing – original draft, Validation. **Xuanfeng Chen:** Resources, Supervision, Validation. **Ruonan Ke:** Data curation, Software, Validation. **Biao Wang:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2023.e21300.

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