Review article

Bibliometric analysis of the research hotspots and trends of circular RNAs

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ARTICLE INFO

ABSTRACT

Background and objective: Circular RNAs (circRNAs) have garnered considerable attention in the study of various human diseases due to their ubiquitous expression and potential biological functions. This study conducts a bibliometric and visualization-based analysis of circRNA-related research in diseases, aiming to reveal the current status, hotspots and emerging trends within the field.

Methods: Literature published between 2013 and 2022 and indexed in the Web of Science core databases was retrieved. Visualizations of publication volume, countries, authors, institutions, journals, references, and keywords were performed. Microsoft Excel (2021) was used to analyze and graph publication volume and growth trends. Additionally, CiteSpace (version 6.1.R6) and VOSviewer (version 1.6.18) were employed to visualize the bibliographic information.

Results: Between 2013 and 2022, a total of 4195 relevant articles on circRNA in the context of diseases were identified. These articles covered 56 countries, 2528 institutions, 19,842 authors and 698 journals, citing 85,541 references. The annual publication volume showed an exponential growth trend, with rapid development post-2017. China, the United States and Germany emerged as the top three contributors, demonstrating high publication volume and total citations. Notably, Nanjing Medical University exhibited the highest publication volume, boasting 291 articles. Burton B. Yang and Li Yang consistently ranked among the top 10 authors in terms of publication volume and citations, emerging as core contributors in this research field. The journal *Bioengineered* ranked first in terms of published articles (160), with an impact factor of 6.832, while *Molecular Cancer* garnered the highest impact factor (41.4), solidifying its position as a top journal in this field. Furthermore, high-frequency keywords included "expression" "proliferation" "biomarker" "microRNA" "cancer", signifying the prevailing research hotspots and principal themes of this field over the past decade. As of 2022, "biomarker", "prostate cancer","drug resistance","papillary thyroid carcinoma", etc. continued as keywords during the outbreak period. At present, the value of circRNA application is mainly reflected in the two aspects of biomarkers and therapeutic targets, and the prediction of accurate diagnosis and precise treatment based on big data analysis, especially in cancer, will become a hot spot of research in the future.

Conclusion: The trajectory of circRNA research from its biological origins to its applications in diseases has been delineated from 2013 to 2022. However, the transition to disease-specific

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applications and exploration of biological functions warrants further attention in future research endeavors.

1. Introduction

Circular RNA (circRNA) represents a distinctive class of endogenous non-coding RNA molecules with a closed-loop structure. Initially discovered in viruses by Sanger et al., in 1976 [1], circRNAs have since been identified across various organisms, including prokaryotes, unicellular eukaryotes, and mammals [2]. However, circRNA has previously been regarded as a byproduct of splicing errors. The emergence of advanced RNA sequencing techniques and bioinformatics analysis has unveiled the multifaceted roles of circRNAs in cellular processes.

In contrast to linear RNAs, circRNAs exhibit remarkable stability due to their closed-loop structure, enabling their presence in diverse cellular compartments such as exosomes and plasma [3]. Moreover, circRNAs often demonstrate tissue-specific or developmental stage-specific expression patterns, underscoring their functional diversity and regulatory complexity [4]. Notably, circRNAs function as miRNA sponges, interact with proteins, and regulate gene expression at the post-transcriptional level [5]. The burgeoning interest in circRNAs stems from their implication in various human diseases, including cancer, kidney disorders, cardiovascular conditions, diabetes, preeclampsia, and cellular senescence [6–9]. Systematic reviews and meta-analyses have further highlighted the significance of circRNAs in disease pathogenesis and progression, providing comprehensive overviews of their roles as diagnostic biomarkers and therapeutic targets. For example, the systematic review by Li et al. [10] provides insights into the role of circRNAs in cancer progression and their potential as diagnostic markers, while the meta-analysis by Zhang et al. [11] explores the diagnostic accuracy of circRNAs in cardiovascular diseases. These studies underscore the growing recognition of circRNAs as key players in human health and disease.

In light of the rapidly expanding body of circRNA literature, conducting a systematic and comprehensive bibliometric analysis becomes imperative. Bibliometric analysis serves as a mature methodology for quantitatively assessing research outputs, identifying key contributors, and delineating research trends within a specific field [12,13]. By elucidating bibliometric parameters such as core authors, institutions, countries, collaborative networks, and emerging topics, this analysis facilitates a deeper understanding of the research landscape surrounding circRNAs in disease contexts [14]. Cancer as examples, a scientific publications on cancer epidemiology in Indonesia through bibliometric analysis aiming to complement the national survey data [15]. Another study used bibliometric approach to identify key research areas in pharmaceutical fields [16].

Previous studies have collectively investigated global trends in circRNA research from various perspectives and time frames. They revealed a significant surge in circRNA-related publications, particularly post-2010, with China, the USA, and Germany emerging as major contributors. Notable circRNAs, such as circCDR1as and circHIPK3, have garnered extensive attention, particularly in cancer research [17]. Themes in circRNA studies evolved towards exploring biogenesis and functional aspects [18]. Additionally, the research increasingly focused on circRNA roles in diseases, notably cancer, with circFOXO3 and circITCH among the prominently studied circRNAs [11]. These findings underscore the dynamic nature of circRNA research and its potential implications for future investigations.

2. Materials and methods

2.1. Sources and search strategies

Web of Science, a renowned and authoritative citation database with robust indexing capabilities, is widely employed in bibliometric research [14,19]. In this study, the database was employed as the data source to ensure data accuracy and comprehensiveness. The selected citation indexes were Science Citation Index Expanded and Social Sciences Citation Index. The search strategy was outlined as follows: TI=('circRNA*') OR TI=('circular RNA*') OR TI=('closed circular RNA') OR TI=('circular noncoding RNA*') OR TI=('circular non coding RNA*').

2.2. Inclusion and exclusion criteria

Inclusion and exclusion criteria were established to ensure the selection of relevant literature for this study. The time frame for inclusion ranged from January 1, 2013 to December 31, 2022, encompassing recent research within the defined period. Only articles categorized as "Article" or "Review" were considered for inclusion, reflecting the focus on primary research and comprehensive reviews. Furthermore, to maintain consistency and accessibility, only publications in the English language were included. Exclusion criteria were applied to refine the selection process. Firstly, articles from non-relevant disciplines, as determined by the Web of Science subject categories, were excluded following a thorough review of article titles, abstracts, and keywords to ensure alignment with the research theme. Secondly, retracted literature was excluded to uphold the integrity and validity of the selected publications. Lastly, literature lacking complete bibliographic information was excluded to maintain data accuracy and reliability.

2.3. Data extraction and cleaning

By applying the inclusion criteria, the search yielded a total of 5598 articles. Following the exclusion of 1403 articles, a final set of 4195 articles was obtained in plain text format. Each article contained comprehensive information such as title, authors, affiliations, journal name, publication date, abstract, keywords, research content, references and more. To ensure data reliability, the CiteSpace software was employed to eliminate erroneous and duplicate records. Keywords were standardized by merging synonymous terms; for example, "miRNA" and "microRNA" were consolidated as "microRNA". Additionally, different institution names were unified, and relevant countries were combined, such as grouping "Northern Ireland," "England," "Scotland" and "Wales" under "United Kingdom". The analysis of source publication influence relied on data from the 2022 Journal Citation Reports published by the American Institute for Scientific Information. Furthermore, supplementary bibliometric information, including citation frequency and the h-index, was obtained from the "Citation Reports" feature within the Web of Science database. In our study, keyword selectiona and data extraction were conducted independently by two authors to ensure accuracy and reliability. Each author performed the analysis separately, and any discrepancies or disagreements were resolved through discussion and consensus.

2.4. Research methodology

Microsoft Excel (2021) was employed for analyzing and graphing publication volume and growth trends. Additionally, CiteSpace (version 6.1.R6) and VOSviewer (version 1.6.18) were utilized for visualizing the bibliographic information.

CiteSpace, developed by Chaomei Chen's research team at Drexel University in the United States [20], constructs knowledge networks among documents based on temporal dimensions. It visually represents the structure, patterns and distribution of scientific knowledge within a specific discipline or between different disciplines. CiteSpace reveals research status, identifies popular research themes and predicts emerging trends [21]. The software's configuration parameters included: a time span from January 2013 to December 2022, with one year per time slice. It employed the "pathfinder" modification algorithm and set the initial g-index (k) threshold at 25, adjusted as required. Node types such as "Country," "Institution," "Author," "Keyword," and "Source" were represented, with node size reflecting their frequency. Thicker lines between nodes indicated stronger collaborations, while node color and thickness represented different years and their respective publication volumes [22]. Betweenness centrality, calculated by CiteSpace, measures the proportion of the shortest paths passing through a certain point to the total number of shortest paths between these points [23]. It identifies highly connected nodes in a network, reflecting their significance and influence. In the network graph, nodes with a centrality >0.1 were indicated with purple circles [24]. Cluster analysis employed the Log Likelihood Ratio (LLR) algorithm to cluster and name keywords, with modularity (Q) and average silhouette score (S) evaluating clustering quality. Q > 0.3 indicates significant clustering structures, S > 0.5 indicates reasonable clustering and S > 0.7 signifies reliable clustering [25,26]. The timeline graph depicted the chronological evolution of keywords categorized by clusters, facilitating the analysis of research evolution [20]. Keyword burst analysis predicted research frontiers [27], with red lines in the graph representing periods of keyword bursts and indicating burst
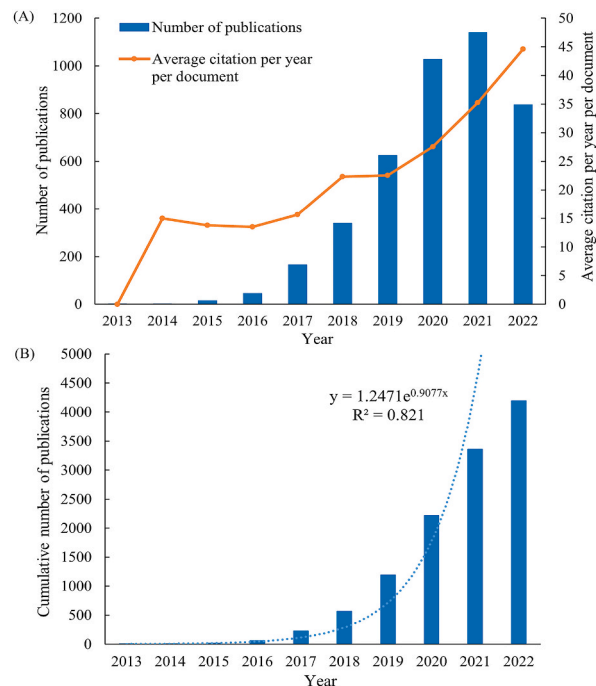

Fig. 1. Distribution of the number of publications related to circRNA research in disease areas.

strength. Keywords with high burst strengths and closer burst years represented research frontiers.

VOSviewer, developed by Eck and his team at Leiden University, Netherlands, visualizes knowledge unit networks in literature. It excels in clustering analysis of knowledge units based on association strength or similarity [28]. In this study, VOSviewer was utilized to conduct a co-citation analysis on references. Different colors represented distinct clusters, with the same colour indicating similar research directions.

3. Results

3.1. Publication trend analysis

This study included 4195 relevant articles on circRNA within the field of disease research, from 2013 to 2022. Among these, 3393 constituted research papers (80.88 %), with the remaining 802 being reviews (19.12 %). Based on citation analysis, the total number of citations for the 4195 articles reached 131,119 (including 58,884 self-citations). The average citations per paper stood at 31.26, accompanied by an h-index of 153. Between 2013 and 2021, the annual publication volume of circRNA-related research in diseases exhibited a consistent upward trend. There was a rapid increase in publication volume post-2017, surging beyond 1000 articles in both 2020 and 2021. Notably, after the onset of the COVID-19 pandemic, relevant publications increased by approximately 64 %, with 625 papers in 2019 and 1027 papers in 2020.However, in 2022, a minor decline in publication volume was observed. The average citations

Fig. 2. Country distribution of circRNA and disease research.(A)Co-occurrence network map, each node represents a country, the nodes are displayed in the form of a yearly wheel, the width of the wheel represents the number of papers published by the country in that year, and the size of the node represents the frequency of occurrence.(B) Cooperation network map, the connection between nodes represents cooperation, and the thickness of the line represents the strength of cooperation.

per paper increased over the years, except for a minor dip in 2015–2016, ultimately reflecting an overall rising trend (Fig. 1A). The cumulative annual publication volume during this period demonstrated an exponential growth trend ($y = 1.2471e^{0.9077x}$, $R^2 = 0.821$; Fig. 1B).

3.2. National and institutional analysis of publications

The 4195 articles originated from 56 different countries, as depicted in the co-authorship network analysis (Fig. 2A). Among these, five countries contributed over 50 articles, 16 countries contributed between 10 and 50 articles, and 35 countries contributed fewer than 10 articles. Moreover, the distribution of publication output across countries was disparate, showing a pronounced top-heavy effect, with a majority of articles concentrated within a limited number of countries. The top 10 countries by publication volume are listed in Table 1. The top three countries in both publication volume and total citations were China (3770 articles, constituting 80.8 %, with 104,318 citations), the United States (240 articles, constituting 5.1 %, with 19,559 citations), and Germany (73 articles, constituting 1.6 %, with 6103 citations). The collaboration relationships between countries are illustrated in Fig. 2B, with China exhibiting close collaboration with other countries, particularly the United States. The top three countries with the highest average citations per paper were Denmark (177.4 citations), followed by Germany (83.6 citations) and Canada (83 citations). The top three countries in terms of betweenness centrality were China (0.44), the United States (0.28) and Germany (0.21).

The 4195 articles originated from 2528 different institutions. As shown in Table 2, the institution with the highest publication output was Nanjing Medical University (291 articles), followed by Sun Yat-sen University (165 articles) and Fudan University (162 articles). Notably, the top 10 institutions in terms of publication output were all from China, contributing between 96 and 291 articles. Their betweenness centrality ranged from 0.03 to 0.12, with significantly high values for institutions such as Nanjing Medical University, Sun Yat-sen University, Fudan University, and Shanghai Jiao Tong University, all exceeding 0.1. Harvard Medical School ranked 65th in terms of publication volume (18 articles), but exhibited the highest betweenness centrality value (0.13).

3.3. Contribution of top journals

The 4195 articles were sourced from 698 different journals, primarily concentrated in the fields of medicine and biology. Table 3 displays the top 10 journals with the highest publication volume in this field, each with 50 articles or more, collectively constituting 1266 articles, which accounts for 30.2 % of the total publication output. *Bioengineered* (160 articles, 3.8 % of the total), with an impact factor of 6.832, emerged as the journal with the highest publication volume. It is a fully open-access interdisciplinary journal covering topics such as bioengineering and biotechnology, including research on biological processes, biomaterials, miRNA, other biomolecules and cancer. The second-highest publication volume was contributed by *Frontiers in Oncology* (104 articles, 2.5 %), which had an impact factor of 5.738. It primarily focuses on cancer research across all stages, from basic research to clinical studies. *Frontiers in Genetics* (97 articles, 2.3 %), with an impact factor of 4.772, was the third-highest publication volume journal. It primarily focuses on genes and genomics related to biological processes. Among the top 10 journals, *Molecular Cancer* had the highest impact factor (41.4), with 95 related articles published, contributing to 2.3 % of the total publication volume. It emerges as one of the top journals in this field.

Fig. 3 illustrates the relationship between citing and cited journals through a dual map representation. The cited papers predominantly fall within two major fields: (1) Molecular Biology and Genetics, and (2) Health, Nursing, and Medicine. On the other hand, the citing papers are primarily clustered in two distinct areas: (1) Molecular Biology and Immunology, and (2) Medicine, Medical Sciences, and Clinical Research. These findings indicate the frontiers of knowledge exploration and innovation.

Bradford's Law is used to quantitatively describe the concentration and dispersion distribution pattern of scientific papers in journals [29]. It involves arranging journals in descending order based on the number of papers published within a specific subject domain. This arrangement aids in delineating a core zone with the highest publication rate, followed by several zones (related zones and peripheral zones). The number of papers in each zone is approximately equal, and the number of journals in the core zone and subsequent zones follows a proportional relationship of 1: a:a^2:... .Table 4 summarizes the distribution of circRNA-related research papers within the landscape of diseases, employing Bradford's Law. According to this law, the number of papers in each zone should be roughly equal, resulting in a journal ratio of 1:3.8:36.3. However, the *1:a:a²* proportionality is not adhered to, indicating the absence of a consolidated core zone for journals focused on circRNA-related research within the domain of diseases. Consequently, no pronounced

Table 1
Top 10 countries with circRNA research publications in diseases.

| Rank	Country	Number of publications	proportion (%)	Total citation frequency	Average citation frequency per paper	Centrality
1	China	3770	80.8	104,318	27.7	0.44
2	USA	240	5.1	19,559	81.5	0.24
3	Germany	73	1.6	6103	83.6	0.23
4	Iran	64	1.4	806	12.6	0.1
5	Italy	55	1.2	3440	62.5	0.13
6	Canada	43	0.9	3569	83.0	0.00
7	Australia	38	0.8	1475	38.8	0.07
8	United Kingdom	37	0.8	1503	40.6	0.15
9	Denmark	28	0.6	4966	177.4	0.09
10	India	28	0.6	1894	67.6	0.02

Table 2
Top 10 institutions with circRNA research publications in diseases.

Rank	Institution	Country	Number of publications	Proportion (%)	Total citation frequency	Average citation frequency per paper	Centrality
1	Nanjing Med. Univ.	China	291	11.5	10,344	35.5	0.12
2	Sun Yat-sen Univ.	China	165	6.5	5863	35.5	0.1
3	Fudan Univ.	China	162	6.4	6612	40.8	0.12
4	Shanghai Jiao Tong Univ.	China	142	5.6	6181	43.5	0.12
5	China Med. Univ.	China	126	5.0	2164	17.2	0.03
6	Zhengzhou Univ.	China	122	4.8	2397	19.6	0.06
7	Southern Med. Univ.	China	121	4.8	3216	26.6	0.09
8	Cent. South Univ.	China	113	4.5	3480	30.8	0.06
9	Zhejiang Univ.	China	100	4.0	2867	28.7	0.08
10	Harbin Med. Univ.	China	96	3.8	3211	33.4	0.05

Table 3
Top 10 journals with circRNA research publications in diseases.

Rank	Journal	Number of publications	Proportion (%)	Total citation frequency	Average citation frequency per paper	Impact Factor	JCR[a]
1	Bioengineered	160	22.9	699	4.4	4.9	Q1
2	Frontiers in Oncology	104	14.9	1034	9.9	4.7	Q2
3	Frontiers in Genetics	97	13.9	863	8.9	3.7	Q2
4	Aging-US	96	13.8	1863	19.4	5.2	Q2
5	Molecular Cancer	95	13.6	10,350	108.9	37.3	Q1
6	Biochemical And Biophysical Research Communications	91	13.0	4843	53.2	3.1	Q2
7	Cancer Management and Research	79	11.3	1199	15.2	3.3	Q3
8	Molecular Therapy-Nucleic Acids	77	11.0	2425	31.5	8.8	Q1
9	Cell Death & Disease	72	10.3	2565	35.6	9.0	Q1
10	Cancer Cell International	70	10.0	1120	16.0	5.8	Q1

[a] JCR: Journal Citation Reports.
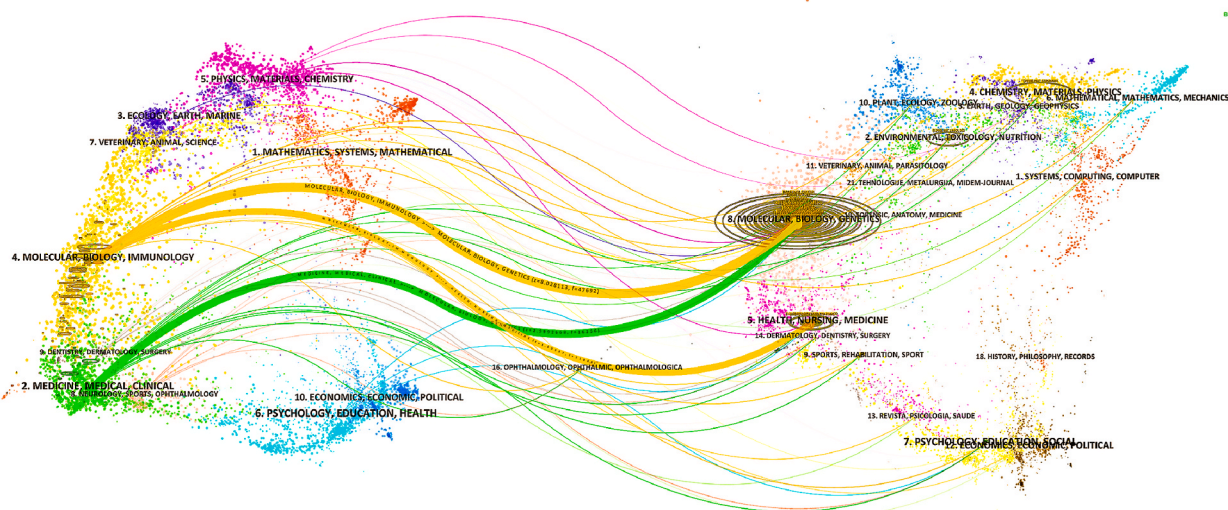
Fig. 3. The dual-map overlay of journals. Publications on this field primarily appeared from two regions of the citing map: Molecular/Biology/Immunology in orange and Medicine/Medical/Clinical in green. The orange-colored curve indicated that the publications belonging to Molecular/Biology/Immunology journals primarily cited those in Molecular/Biology/Genetics journals and Health/Nursing/Medicine. The green-colored curve revealed that the publications from Medicine/Medical/Clinical journals mainly cited thuse in Molecular/Biology/Genetics journals.

Table 4
The distribution of journals.

Partition	Number of articles in journals	Number of Journals	Number of papers	Proportion (%)
1	≥54	17	1375	32.8
2	11–51	64	1405	33.5
3	≤10	617	1415	33.7
SUM	–	698	4195	100

concentration advantage in terms of publication output was discernible.

3.4. Authors and their collaborations

The 4195 articles were contributed by 19,842 authors (Fig. 4A). The distribution of authors was relatively concentrated, and a high degree of collaboration strength was observed. Among them, Professor Burton B. Yang from Sunnybrook Health Sciences Centre at the University of Toronto in Canada authored 24 papers, accumulating a total of 2555 citations and an average citation per paper of 106.5. His research primarily focuses on the regulatory roles and mechanisms of circRNA and miRNA in tumour initiation, progression and angiogenesis. Additionally, Researcher Yang Li (Yang, L) from the Institute of Biomedical Sciences at Fudan University authored 22 papers, earning a total of 3577 citations and an average citation per paper of 162.6. His work centers around employing cutting-edge techniques such as non-coding RNA and genome editing, to explore areas such as exonic circRNA processing, novel functional mechanisms, base editing and regulatory networks. Burton B. Yang and Yang Li consistently maintained their positions among the top 10 authors in both publication volume and citation frequency, establishing themselves as core authors in this research field (Table 5). Chen Lingling (Chen, LL), from the Centre of Excellence for Molecular Cell Science at the Chinese Academy of Sciences, holds the highest citation frequency among authors in this field. She has authored eight papers and garnered a total of 4385 citations, with an average citation per paper of 548. Her research primarily focuses on RNA processing, metabolism and functional mechanisms.

Using VOSviewer, a collaborative network analysis was conducted on authors with publication volumes of 5 or more. The software categorizes authors with similar research content or directions into clusters (Fig. 4B). Table 6 summarizes key collaborative clusters among researchers in circRNA-related research, highlighting their main research areas and key partnerships, facilitating a better understanding of the interdisciplinary collaborations and thematic foci within the field.

3.5. Analysis of funding institutions

The analysis of funding institutions reveals important insights into the financial landscape surrounding research on the topic. Among the 4195 papers examined, a total of 3038 papers received funding support (Fig. 5). This indicates the significance of financial backing in facilitating research endeavors within the field. Leading the list of funding institutions is the National Natural Science Foundation Of China, which contributed to the largest number of papers, totaling 1596. Additionally, prominent Chinese institutions such as the National Key Research And Development Program Of China, as well as provincial-level natural science foundations such as those of Guangdong, Jiangsu, and Hunan, featured prominently in funding support. Interestingly, international funding bodies such as the National Institutes Of Health and the United States Department of Health and Human Services also played a role in supporting research, highlighting the global collaboration and exchange of resources in advancing knowledge on the topic. Overall, this analysis underscores the importance of funding institutions in driving scientific research forward and sheds light on the diverse sources of financial support contributing to the advancement of knowledge in this field.

3.6. Citation analysis and Co-citation analysis

A total of 4195 articles garnered a total of 131,119 citations, with self-citations accounting for 58,884 citations (44.9 %). The average citation per article stood at 31.26. Notably, 269 articles garnered over 100 citations, constituting 6.4 % of the total, while 522 articles remained uncited, comprising 12.4 % of the total. Table 7 presents the top 10 highly cited papers in the field, with citation counts ranging from 901 to 1864. Among these, eight papers surpassed 1000 citations. Among them, three were published in Molecular Cell, one in Nature Reviews Molecular Cell Biology, one in Nature Reviews Genetics, one in Molecular Cancer and one in Cancer Letters, which are prestigious journals within the medical and biological sciences domains. The most highly cited article, published in 2014 in Molecular Cell titled "circRNA Biogenesis Competes with Pre-mRNA Splicing" [30], delves into the biological genesis of circRNA. The article titled "The biogenesis, biology and characterization of circular RNAs" [31], published in 2019 in the journal Nature Reviews Molecular Cell Biology, ranks second in terms of citation frequency. This article primarily expounds on the biogenesis, biological characteristics and identification methods of circRNA, providing a comprehensive summary of the circRNA-related biological functions and the methodologies used to elucidate their functions. The article published in 2013 in the journal PLoS Genetics titled "Cell-Type Specific Features of Circular RNA Expression" [32] ranks third in terms of citation frequency. The article used refined bioinformatics and statistical methods to identify circRNAs, revealing that the regulation of splicing sites during RNA circularization displays both gene-specific and cell-type-specific features.

The 4195 articles collectively cited 85,541 references (Fig. 6). The top 10 most cited references primarily encompass the biological origin, characteristics, and functions of circRNAs, along with their significance as diagnostic biomarkers for cancer. The frequency of
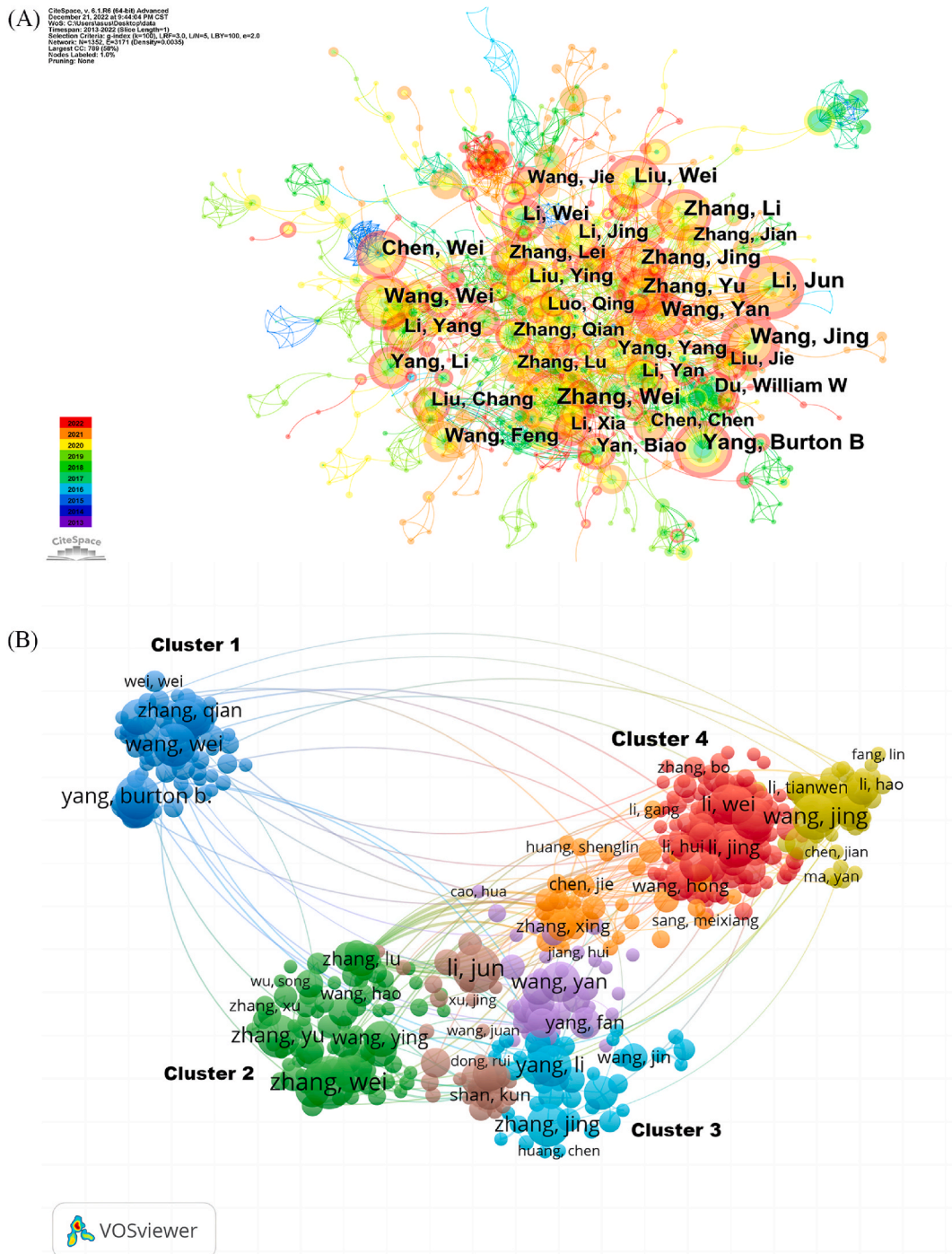
Fig. 4. Author distribution of circRNA and disease research.(A)Co-occurrence of authors network map, nodes represent different authors, node size represents the number of author posts, the thickness of the connecting line between nodes represents the strength of cooperation. (B)Cooperation network map, the color represents different clusters, and the same color represents similar research directions.

co-citations between articles reflects the degree of similarity in the concepts, theories, or methodologies they present [33]. Nodes of the same color in the graph indicate similar themes across publications. Furthermore, each cluster represents a distinct research domain: the red cluster focuses on the biological functions of circRNA; the green cluster emphasizes the biogenesis and biological characteristics of circRNA; and the blue cluster predominantly addresses the regulatory roles and diagnostic prognostic values of dysregulated circRNA in diseases.

Table 5

Top 10 authors with circRNA research publications in diseases.

Rank	Author	Number of publications	Total citation frequency	Average citation frequency per paper
1	Zhang, W	30	898	29.9
2	Li, J	27	415	15.4
3	Wang, J	25	390	15.6
4	Yang, BB	24	2555	106.5
5	Zhang, L	23	278	12.1
6	Zhang, J	23	742	32.3
7	Wang, W	23	504	21.9
8	Zhang, Y	23	700	30.4
9	Liu, W	23	431	18.7
10	Yang, L	22	3577	162.6

Table 6

Key collaborative clusters and research focus in circRNA-related studies.

| Cluster	Colour	Key partnership	Main research area
1	🟦	Anchored by Professor Burton B. Yang from Sunnybrook Health Sciences Centre at the University of Toronto, includes collaborations with colleagues such as William W Du, Yang WN and Awan Faryal Mehwish from the same institution.	To explore the biological functions of circRNA and its regulatory role in tumours (mainly breast cancer) and cardiovascular diseases.
2	🟩	Composed of Luo Q, Zhang L, Huang ZK, Li JM and Guo Y from Nanchang University.	To investigate differentially expressed circRNA in rheumatoid arthritis, systemic lupus erythematosus and tuberculosis as potential biomarkers for diagnosis and treatment.
3	🟦	Yang Li, Researcher, Institute of Biomedical Research, Fudan University, and Professor Chen Lingling, Center of Excellence for Molecular and Cellular Sciences, Chinese Academy of Sciences, are the center.	To explore the generation and processing of circRNA and their characteristics.
4	🟥	Huang Jie from Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Lin Tiantian from Sun Yat-sen University, and Liu Huawei from Jinan University are the center authors.	To investigate the regulatory role of differentially expressed circRNA as miRNA sponges in bladder cancer.
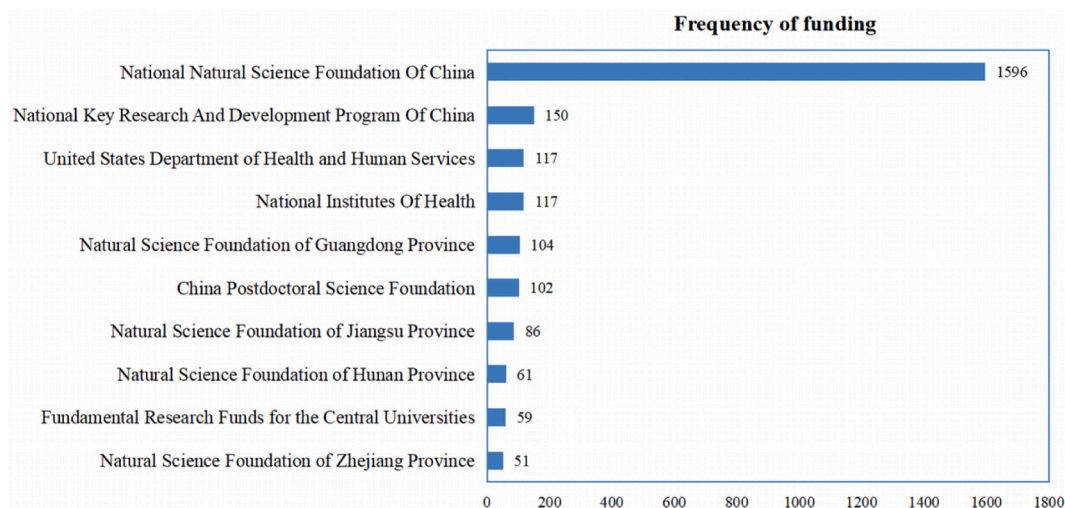
Fig. 5. Funding support landscape for research on circRNA in diseases.

3.7. Analysis of research hotspots and frontiers

Utilizing CiteSpace for keyword analysis, synonym merging, co-occurrence, clustering and burst analysis, a co-occurrence knowledge map was constructed (Fig. 7A), containing 388 nodes and 317 edges. The frequently occurring keywords were as follows: expression (1243 occurrences), proliferation (938 occurrences), biomarker (908 occurrences), microRNA (775 occurrences), cancer (711 occurrences), invasion (654 occurrences), progression (613 occurrences), migration(516 occurrences), metastasis (483 occurrences), biogenesis (448 occurrences), and apoptosis (426 occurrences). These keywords collectively represent the major research themes of circRNAs in diseases from 2013 to 2022. Notably, expression (0.33), transcripts (0.3), cell(0.31), and regulation

Table 7
Top 10 studies with the most citation frequencies related to circRNA research in diseases.

Rank	Article Title	First Author	Source Journal	Impact Factor	Year	Citation Frequency
1	circRNA Biogenesis Competes with Pre-mRNA Splicing	Ashwal-Fluss, Reut	Molecular Cell	16/Q1	2014	1864
2	The Biogenesis, Biology and Characterization of Circular RNAs	Kristensen, Lasse S.	Nature Reviews Genetics	42.7/Q1	2019	1718
3	Cell-Type Specific Features of Circular RNA Expression	Salzman, Julia	PLoS Genetics	4.5/Q1	2013	1319
4	Circ-ZNF609 Is a Circular RNA that Can Be Translated and Functions in Myogenesis	Legnini, Ivano	Molecular Cell	16/Q1	2017	1251
5	Circular RNA: A New Star of Noncoding RNAs	Qu, Shibin	Cancer Letters	9.7/Q1	2015	1176
6	Regulation of circRNA Biogenesis	Chen, Ling-Ling	RNA Biology	4.1/Q2	2015	1169
7	The Biogenesis and Emerging Roles of Circular RNAs	Chen, Ling-Ling	Nature Reviews Molecular Cell Biology	112.7/Q1	2016	1049
8	The Biogenesis, Functions, and Challenges of Circular RNAs	Li, Xiang	Molecular Cell	16/Q1	2018	1028
9	CircRNA: Functions and Properties of a Novel Potential Biomarker for Cancer	Meng, Shujuan	Molecular Cancer	37.3/Q1	2017	970
10	Circular RNAs in Cancer: Opportunities and Challenges in the Field	Kristensen, Lasse S.	Oncogene	8.0/Q1	2018	901
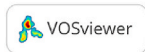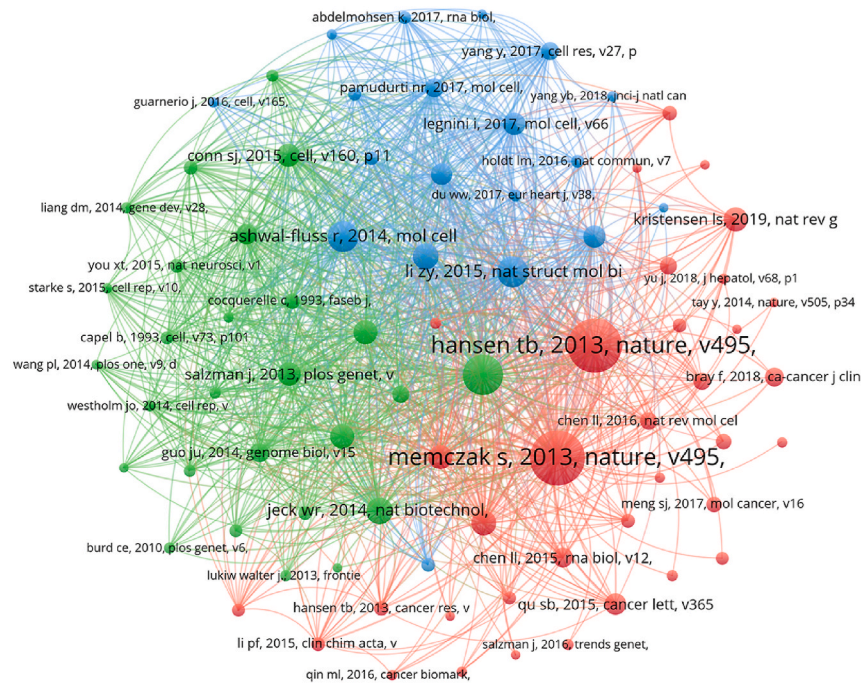
Fig. 6. Co-citation analysis of references used in publications on circRNA-related research in diseases, The color represents different clusters, and the same color represents similar research directions.

(0.28) were among the highest centrality nodes, indicating their pivotal role as "bridges" to various keywords in the field. The clustering analysis results are illustrated in Fig. 7B and 8. The module value (Q value) was elucidated to be 0.522, and the average silhouette (S value) was 0.7842. A total of 10 distinct hotspot topic clusters were identified: Clusters #0, #1, #3, #4, #5 and #6 explored the primary disease types associated with circRNA research. Cluster #2 mainly centred on the biogenesis of circRNA. It revolves around the formation of circRNA through the reverse splicing of pre-mRNAs. Cluster #8, titled "microarray analysis" primarily concentrated on research methodologies. Microarray analysis is a key technique for identifying differentially expressed circRNA in tissues. Clusters #7 and #9 primarily focused on the application of circRNA. Characteristics such as specific expression, high conservation and stability highlight the potential of circRNAs as prognosis and diagnostic biomarkers, as well as their potential as novel therapeutic targets for diseases.

Fig. 9 presents the top 35 keywords with the highest burst strengths. Over the period from 2013 to 2022, keywords such as
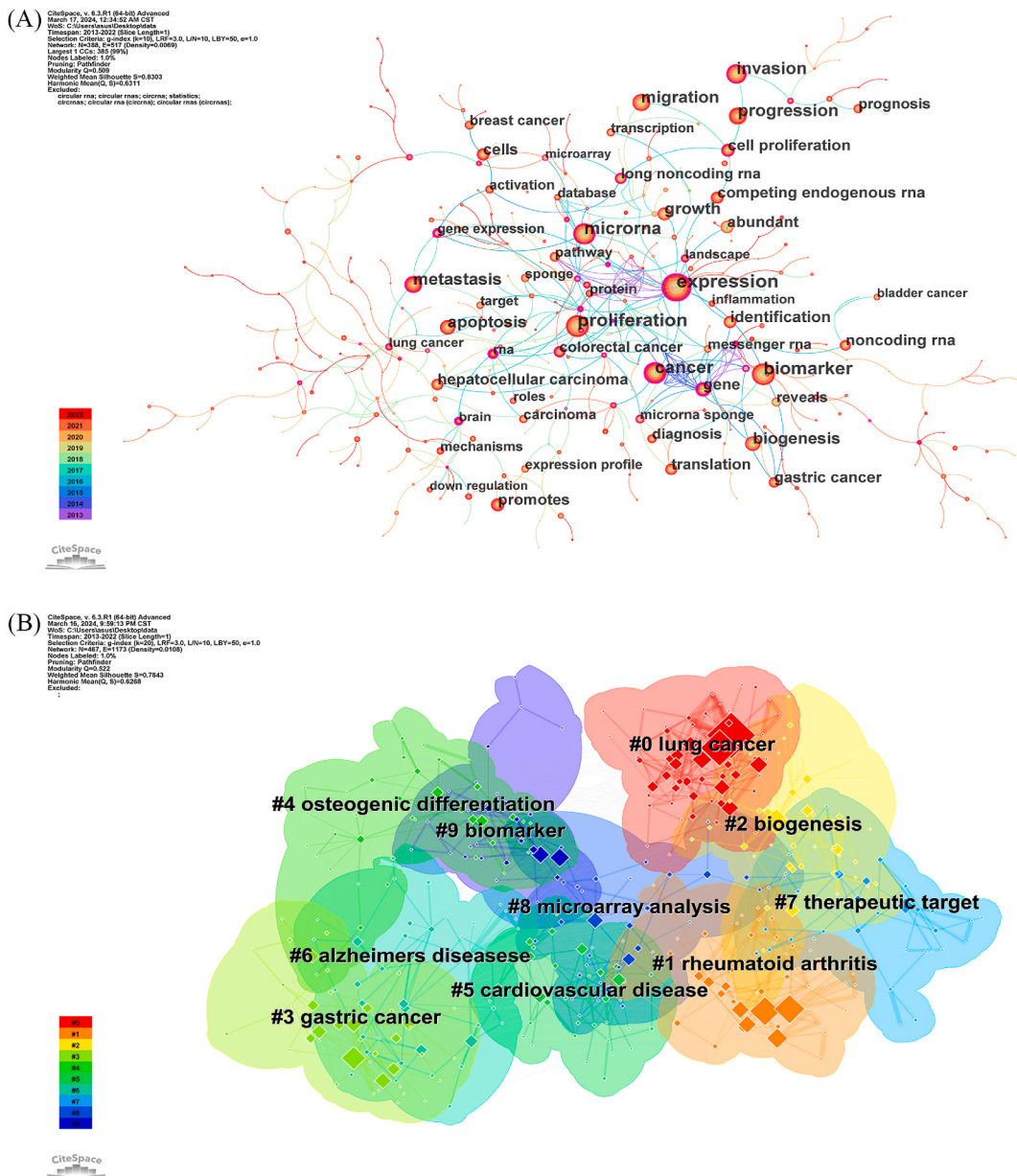
Fig. 7. Keyword distribution of circRNA and disease research.(A)Co-occurrence of keywords, each node represents a keyword, and the size of the node represents the frequency of their occurrence, and the line between nodes represents the intensity of co-occurrence.(B) Keyword clustering map, CiteSpace uses Log-likelihood rate(LLR) to cluster closely related keywords. Different patterns represent a cluster. Tag # was assigned to the cluster, and the smaller the number is, the more keywords are in the cluster.

"transcript," "growth factor receptor," "microrna 7," and "biomarker" exhibited the longest burst durations, indicating sustained interest and research focus. Additionally, the keyword "reveal" showed the most intense burst strength during this timeframe. As of 2022, keywords such as "biomarker," "prostate cancer," "drug resistance," "papillary thyroid carcinoma," "liquid biopsy," "RNA binding protein," "esophageal cancer," "chondrocyte," "thyroid cancer," and "gestational diabetes mellitus" continue to experience bursts, indicating their ongoing significance and relevance in this field.

4. Discussion

Since 2013, research on circRNAs has witnessed remarkable growth, driven by its unique structure and biological characteristics, particularly in the field of human disease research. The quantity and trajectory of papers published within a specific academic field over time serve as crucial indicators for assessing the field's current status [26]. It is evident that circRNA has emerged as a hotspot in
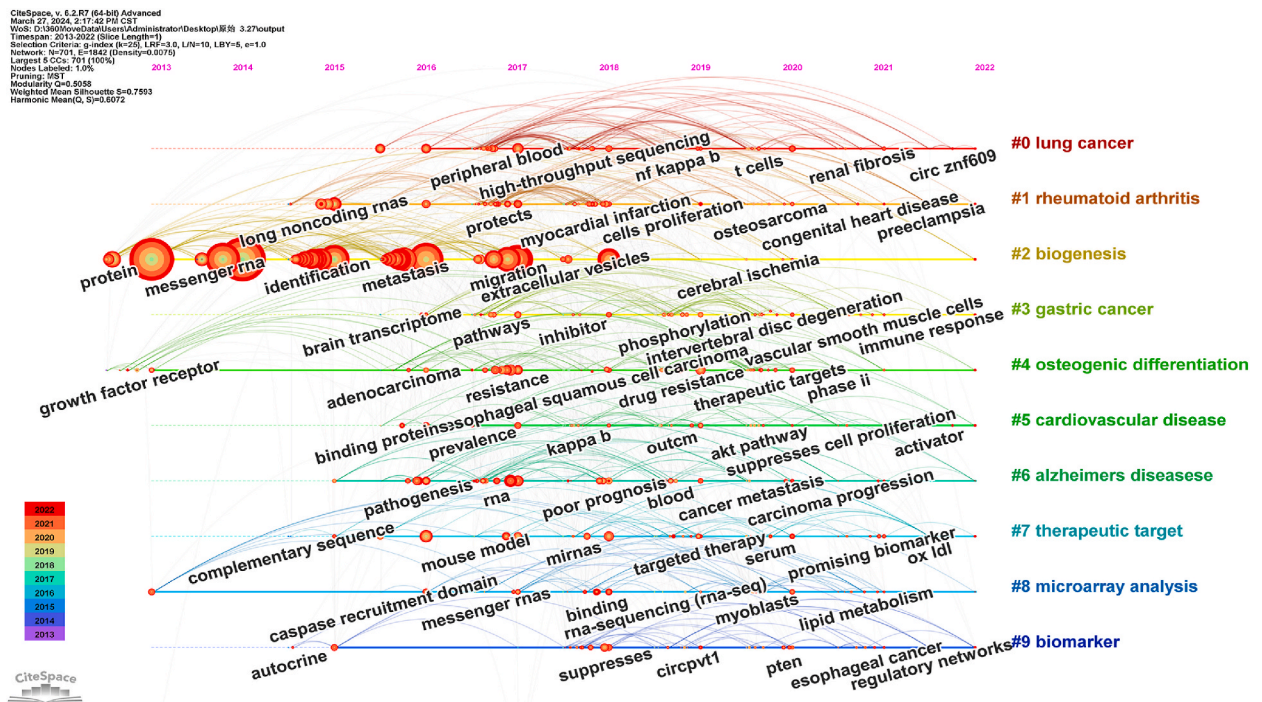
Fig. 8. Timeline view of keyword clustering, in the timeline view, the keywords on the same horizontal line belong to the right cluster. The colors of lines and keywords in the view correspond to the colors of the time bar in the lower left corner.

the field of disease research. From 2013 to 2022, the annual average citation frequency, which is a representative metric used in citation analysis for scientific evaluation, has consistently increased. This metric is also indicative of academic influence and research quality. Thus, based on bibliometric analyses, circRNA research in the context of diseases can be inferred to be continuously advancing, with the quality of papers in this field improving annually.

The countries with the highest publication volume are primarily China, the United States and Germany. China ranks first in terms of publication quantity, total citation frequency and intermediary centrality, highlighting its active and prominent roles in this field. However, the average citation frequency per paper is relatively low, at 28, reflecting a trend where many top Chinese authors have lower citation frequencies. This trend may be attributed to the large number of articles being published, which could dilute the proportion of high-quality papers. Additionally, Chinese research tends to focus more on the biological roles of circRNA in diseases rather than on investigating circRNA mechanisms and functions directly. Nonetheless, certain Chinese researchers have made significant contributions to the field of circRNA research. Professor Chen Lingling, for instance, ranks first in terms of citation frequency and represents a prominent figure in the field. Her team's work on circRNA biogenesis and mechanisms contributes significantly to this field [10,34–37]. Furthermore, Germany consistently ranks within the top three in terms of publication quantity, total citation frequency, average citation frequency and intermediary centrality, highlighting its robust research capabilities and international influence. The top journals in this field are predominantly distributed within the domains of basic research and oncology. Notably, the top 10 institutions contributing to publication volume were all from China, indicating the pivotal role of collaborative efforts among institutions in driving circRNA-related research in the context of human diseases. Harvard Medical School, with the highest intermediary centrality, serves as a crucial contributor to fundamental circRNA research.

Co-citation analysis serves as a tool to elucidate the foundational knowledge within a specific research domain by examining cited references. It facilitates the exploration and analysis of the interconnectedness and developmental context among cited documents. Building upon the insights derived from co-citation analysis, research on circRNA within the context of diseases encompasses three key areas. Firstly, investigations into the biogenesis and biological characteristics of circRNA have revealed its formation through back-splicing of pre-mRNAs, regulated by *cis*-acting elements and *trans*-acting factors, as proposed by Salzman et al. [38]. Despite ongoing research, the complete mechanism of circRNA formation remains unclear, with reported models including intron-pairing-driven circularization, circularization mediated by RNA binding proteins (RBPs), and loop-driven circularization. Notably, circRNA exhibits highly conserved sequences and stable structures, with diverse expression patterns across cells and tissues [39]. Secondly, circRNA demonstrates various biological functions. In the cell nucleus, it influences RNA splicing and indirectly regulates parent gene transcription. In the cytoplasm, circRNA acts as microRNA (miRNA) sponges, modulating mRNA expression [40]. Additionally, it mediates translation via internal ribosome entry sites (IRES) and N6-methyladenosine (m^{6}A) modifications [5], and interacts with proteins or protein complexes to exert specific function [41]. Lastly, circRNA plays crucial regulatory roles in diseases and holds diagnostic and prognostic significance, particularly in cancer. Noteworthy examples include CDR1as [42–46],

Top 35 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2022
transcript	2013	15.62	2013	2018	
growth factor receptor	2013	6.77	2013	2018	
microrna 7	2013	6.32	2013	2018	
gene	2013	5.71	2013	2016	
messenger rna	2014	8.4	2014	2017	
reveal	2015	33.35	2015	2018	
exon circularization	2015	12.06	2015	2018	
identification	2015	11.18	2015	2017	
microrna sponge	2015	10.4	2015	2018	
abundant	2016	25.75	2016	2019	
efficient	2016	10.93	2016	2019	
biogenesis	2015	8.08	2016	2017	
sequence	2016	3.8	2016	2017	
cell growth	2017	10.66	2017	2019	
pathway	2013	6.39	2017	2017	
decreased expression	2017	6.03	2017	2018	
human gastric cancer	2017	6.03	2017	2018	
p53	2017	3.52	2017	2019	
fatty liver disease	2017	3.11	2017	2019	
circhipk3	2018	5.95	2018	2019	
microarray expression profile	2018	4.81	2018	2019	
regulatory role	2018	4.17	2018	2018	
plasma	2018	3.05	2018	2019	
rna-untranslated	2018	3.05	2018	2019	
lung cancer	2017	2.5	2018	2018	
biomarker	2015	9.08	2017	2022	
prostate cancer	2017	4.38	2021	2022	
drug resistance	2019	4.23	2021	2022	
papillary thyroid carcinoma	2018	3.91	2021	2022	
liquid biopsy	2021	3.16	2021	2022	
rna binding protein	2021	3.14	2021	2022	
esophageal cancer	2021	3.14	2021	2022	
chondrocyte	2021	3.14	2021	2022	
thyroid cancer	2021	2.9	2021	2022	
gestational diabetes mellitus	2021	2.63	2021	2022	

Fig. 9. Top 35 keywords with the strongest citation bursts. From left to right, the first column represents the year in which this keyword first appeared. The second column represents the bursts' strength of the keyword. The third column represents the year in which this keyword begins and ends the burst. The fourth column in red represents the period during which the keyword is burst.

CircFoxo3 [47–50], CircPABPN1 [51,52], circHIPK3 [53–55] and circZNF609 [56–58], which are implicated in various tumor types. These insights underscore the multifaceted roles and clinical relevance of circRNA in disease contexts.

Keywords serve as concise summaries and encapsulations of the main topics covered in an article. Analyzing circRNA-related keywords in the context of disease research highlights "biomarker" as a consistent research focal point throughout the study period. CircRNA, due to its ubiquity, stability, specificity, and conservation, and circRNA can be detected and quantified through liquid biopsies in body fluids (including blood, saliva and urine), which are easy to repeat sampling, less invasive and more feasible, and more convenient and efficient than tissue biopsies. Therefore, it has potential as an vital biomarker for diagnosising and predicting disease progression and prognosis [59,60]. Over the past decade, circRNA research has transitioned from exploring its biogenesis, transcription, and functional mechanisms to investigating its application in disease. Dysregulation of circRNA expression has been linked to a variety of diseases, including cancer, cardiovascular disease, autoimmune disease, and Alzheimer's disease. Thus, endogenous circRNAs have been investigated as prospective therapeutic targets, particularly in tumor contexts. For instance, circRNAs function as competitive endogenous RNAs by competitively binding with miRNAs, thereby regulating the expression of their target mRNAs and participating in various disease pathways such as cell proliferation, apoptosis, invasion, metastasis and differentiation [61]. This regulatory mechanism has consistently been a central focus in research related to circRNA-mediated gene expression regulation [62]. In terms of research methodologies, microarray analysis has been the primary means for identifying and screening circRNAs. However, the circRNAs detected using microarrays are limited. With the continuous advancement of RNA sequencing technology and bioinformatics tools, the identification and in-depth exploration of circRNAs show promise. Foundational research aspects of circRNA, encompassing identification, biogenesis and biological characteristics, have been well-established. Future research is expected to focus

on the specific applications of circRNA in particular diseases, emphasizing their biological functions. This includes exploring the pivotal roles of circRNA in cancer cells, including proliferation, apoptosis, and differentiation, as well as their function as miRNA sponges and diagnostic biomarkers.

While our study offers a comprehensive and objective bibliometric analysis of circRNA's relevance to diseases, it is important to acknowledge several limitations. Firstly, our analysis was confined to literature sourced exclusively from the Web of Science databases, namely the Science Citation Index Expanded and Social Sciences Citation Index, and was limited to publications in English. This approach may have overlooked relevant studies not indexed in these databases or published in languages other than English. Despite the Web of Science's reputation as a widely recognized citation database, it does not encompass all research outputs within the field, potentially resulting in the omission of pertinent publications [63]. However, given its prominence, the impact of such omissions on the overall findings is expected to be minimal. To mitigate these limitations, future research endeavors could incorporate data from additional sources and languages, facilitating a more comprehensive analysis of circRNA's relevance to diseases [64]. Nevertheless, future research on circRNA could explore its specific roles in disease pathways, particularly cancer, and validate circRNA biomarkers for various diseases to enhance early diagnosis and prognosis prediction. Investigating novel therapeutic strategies targeting circRNA, such as modulating circRNA expression or activity, could lead to innovative treatments. Integrating circRNA research with precision medicine initiatives and exploring its cross-talk with other regulatory networks can provide comprehensive insights into disease pathogenesis. Advancements in circRNA detection technologies and translation of research findings into clinical practice are also crucial for realizing the diagnostic and therapeutic potential of circRNA in disease management.

5. Conclusion

In summary, this study presents a comprehensive and objective analysis of circRNA in the field of disease research, facilitated by the use of CiteSpace and VOSviewer software. The advancement of high-throughput RNA sequencing technology and bioinformatics analysis has enabled extensive exploration of circRNA, spanning its biogenesis, biological characteristics, functional mechanisms, and applications in diseases. With its significant potential in clinical therapy, future research endeavors may focus on uncovering novel functions, elucidating formation processes, and understanding the mechanisms of action of circRNA in diseases.

Funding

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Reyila Tuerdi: Writing – original draft, Visualization, Software, Methodology, Conceptualization. **Hui Zhang:** Writing – review & editing, Validation, Supervision. **Wenxin Wang:** Validation. **Minghui Shen:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition. **Xingmin Wei:** Writing – review & editing, Methodology, Formal analysis, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31478.

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