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Review article

Mapping knowledge structure and themes trends of non-surgical treatment in intervertebral disc degeneration

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ABSTRACT

Background: Intervertebral disc degeneration (IDD) is a chronic disabling disease caused by degeneration of nucleus pulposus cells, decreased activity and the number of nucleus pulposus cells, decreased extracellular matrix, and infiltration of inflammatory factors, resulting in low back and leg pain. Recent studies have shown that non-surgical treatment is of great significance in reversing the progression of degenerative disc disease, and there are more relevant literature reports. However, there is no bibliometric analysis in this area. This study aimed to describe the knowledge structure and thematic trends of non-surgical treatment methods for IDD through bibliometrics.

Methods: Articles and reviews on non-surgical treatment of disc degeneration from 1998 to 2022 were collected on the Web of Science. VOSviewer 1.6.18, CiteSpace 6.1.R3, R package "bibliometrix" and two online analysis platforms were used for bibliometric and visual literature analysis.

Results: 961 articles were screened for inclusion, including 821 articles and 140 reviews. The analysis of our study shows that publications in the non-surgical treatment of disc degeneration are increasing annually, with publications coming mainly from North America and Asia, with China and the United States dominating. Huazhong Univ Sci & Technol and Wang K are the most prolific institutions and authors, respectively, and Le Maitre CL is the most co-cited author. However, there is less collaboration between institutions in different countries. *Spine* is both the most published and the most cited journal. According to the co-citation and co-occurrence analysis results, "mesenchymal stem cells," "exosomes," "medication," and "tissue engineering" are the current research hotspots in this field.

Conclusions: This study employs bibliometric analysis to explore the knowledge structure and trends of non-surgical treatments for IDD from 2013 to 2022. Key research hotspots include mesenchymal stem cells, exosomes, medication, and tissue engineering. The number of publications, especially from China and the USA, has increased significantly, though international collaboration needs improvement. Influential contributors include Wang K and the journal Spine. These findings provide a comprehensive overview and highlight important future directions for the field.

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1. Introduction

Intervertebral disc degeneration (IDD) is a degenerative disease based on the degeneration of nucleus pulposus cells in intervertebral disc tissue, which has become one of the major diseases affecting the quality of life and disability worldwide [1]. The pathological mechanism of IDD is mainly the decrease of the number and activity of nucleus pulposus cells caused by degeneration of nucleus pulposus cells, which may accompany the decrease of extracellular matrix and infiltration of inflammatory factors. The clinical symptoms of IDD were mainly leg pain, low back pain, and lower limb weakness caused by nerve root compression. Currently, the main surgical treatment methods for IDD are discectomy and spinal fusion, which can relieve clinical symptoms. Surgery does not represent the exclusive recourse for addressing intervertebral disc disorder (IDD). Pharmacotherapy employing nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and analgesics is capable of effectively managing the pain and inflammation associated with IDD. Physical therapy, through the fortification of musculature, enhancement of flexibility, and promotion of optimal posture, serves as a pivotal modality. Techniques encompassing manual therapy, traction, and electrical stimulation are also instrumental in alleviating pain and ameliorating functional capacity. Still, biomechanical changes make the adjacent discs more susceptible to degenerative lesions [2]. In the long run, it is not conducive to long-term rehabilitation and symptom control. Therefore, the search for effective non-surgical treatment of IDD has become a promising strategy.

Non-surgical treatment methods can solve the clinical symptoms caused by intervertebral disc degeneration, thus solving deep-seated biological problems. Currently, the most common non-surgical treatment methods include tissue engineering, growth factor therapy, gene therapy, cell therapy, drug therapy, and other small molecular substances [3]. In addition, non-surgical treatment can effectively promote the proliferation and autophagy of nucleus pulposus cells [4], inhibit multiple pathological processes such as extracellular matrix degradation [5], apoptosis [6], cell scorching [7]and inflammatory response [8], and address the clinical symptoms caused by disc degeneration from the pathophysiological level, which may become the mainstream modality of IDD treatment in the future. In recent years, research on the non-surgical treatment of IDD has gradually increased and achieved good results, and many animal experiments have proved its effectiveness [9–11]. Cell therapy and tissue engineering therapy are more studied and gradually applied in clinical trials [12,13].

Many studies on the non-surgical treatment of IDD have been published, and researchers need to spend much time reading the literature to understand the corresponding IDD treatment area.

Although there are reviews and summaries for various non-surgical treatment sub-areas at present, these reviews only focus on specific areas of IDD research, which are of great significance to some aspects such as publication volume, country, institution, The author's contribution to this field and the future research topics and hot spots are not systematically elaborated [14,15]. It has been reported that junior researchers can benefit from the knowledge structure and hot trends of related fields. However, the knowledge structure and hot trends of non-surgical treatments for IDD have rarely been reported [16,17]. Bibliometric analysis is a systematic and quantitative research method, particularly well-suited for analyzing and evaluating research dynamics and trends in specific fields. In this study, bibliometric analysis was chosen as the primary method because it allows for the systematic processing of large volumes of scientific literature, providing a clear reflection of research activities and hotspots through quantitative indicators such as publication count and citation frequency. This method effectively identifies research hotspots and frontiers, reveals collaboration patterns between international and institutional entities, assesses the quality and impact of research, and ensures the reliability and scientific validity of results by using data from authoritative databases. Therefore, bibliometric analysis is the optimal method for exploring the knowledge structure and thematic trends of non-surgical treatments for IDD.

Bibliometrics is the qualitative and quantitative analysis of the published literature in a specific field using statistical and mathematical methods [18,19]. Bibliometrics is a mature and reliable method that can describe the dynamic trend of literature and journals in a specific field, screen out the active contribution degree of author institutions, and predict the field's future development trend and hot spots [20,21]. Researchers typically use a variety of bibliometric software such as VOSviewer [22], CiteSpace [23], and R package "bibliometrix" [24]to perform bibliometric visualization of literature. In recent years, with the enrichment of visualization tools of bibliometrics and the gradual deepening of related basic research, the research of bibliometrics in the field of life science has received extensive attention [25,26], bibliometric analysis has been carried out on non-surgical treatment methods for orthopedics related diseases [27,28], liver diseases [29], osteoarthritis [30]and other diseases, but there is no study on treatment methods for intervertebral disc degeneration in articles. In recent years, non-surgical treatment in intervertebral disc degeneration has been researched more and more, with broad application prospects. To fill the gap in this research area, this study plans to conduct a bibliometric analysis of academic papers from 1998 to 2022, mainly to determine the main contributors and research status in this field and to look forward to the research hotspots and theme trends.

2. Materials and methods

2.1. Data source and search strategy

Web of Science Core Database (WoS, Clarivate Analytics, Philadelphia, PA, USA) is one of the world's most comprehensive and authoritative citation databases. It can provide comprehensive basic information and reference information of literature to evaluate academic research in the relevant field [31]. The authors conducted a literature search from the Web of Science Core Collection (WoSCC) on September 17, 2022. All relevant pieces of literature were searched by subject (TI) and author keywords (AK), and the search formula was as follows: #1:TI=("intervertebral disc degeneration") OR AK = ("intervertebral disc degeneration"); #2: TI = (treatment OR therapy) OR AK = (treatment OR therapy) OR AB = (treatment OR therapy); final dataset: #1 AND #2, a total of 984

relevant articles were retrieved. The literature language was limited to English, and the literature type was limited to articles and reviews. Only the research works of literature between 1998 and 2022 were included, and 961 valid pieces of literature were finally obtained. The specific literature screening process is shown in Fig. 1.

2.2. Data extraction

All 961 articles were exported as "Full Record and Cited References" in plain text or Win UTF-8 format. Data from all articles included annual publications, citations, countries, institutions, authors, funding agencies, journals, subject categories, highly cited articles, and keywords. The information in the WOS database was checked and consolidated. Information from each region was included in its dependent countries; e.g., publications from England, Northern Ireland, Scotland, and Wales were allocated to the United Kingdom. Information on the Hirsch index (H-index) and average citation per item (ACI) of funding institutions and authors was obtained by using the "Citation Report" function in WoSCC. Journal Impact Factor (JIF) and subject category quartiles (Q1, Q2, Q3, and Q4) rankings are from the 2021 Journal Citation Report (JCR, Clarivate Analytics, Philadelphia, PA, USA).

2.3. Data analysis

Statistical analysis and table plotting were performed using Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA) and R software (v4.2.1., R Foundation, Vienna, Austria). Microsoft Excel 2019 was used to graph the number of annual publications in the field, the most relevant subject categories, and the number of keyword occurrences.

VOSviewer (v 1.6.18) is a bibliometric software developed by Professors van Eck and Waltman [32], which can extract meaningful parameters from large volumes of literature and is often used to construct collaboration, co-citation, and co-occurrence networks [33, 34]. In this study, the software was used to perform the following analyses: Institution analysis, authors and co-cited authors analysis, journals and co-cited journals analysis, and keyword co-occurrence analysis. In the map generated by VOSviewer, a node generally represents an item, such as an institution, author, or journal. The size and color of the node, respectively, represent the number and category of the item, and the thickness of the line between the nodes represents the degree of collaboration or co-citation between the items [35,36].

CiteSpace (v 6.1.R3) is another software for bibliometric analysis and visualization developed by Prof. Chaomei Chen [37], which was used in this study for institutional analysis, construction of dual-map overlay journals, Most Relevant Subject Categories analysis, analysis of references perform co-citation analysis, and identify the top 25 references with the most potent citation explosion. In the graph generated by CiteSpace, the size of the nodes and the color rings represent the number of items and the different years, and the connecting lines between the nodes represent collaboration or co-citation relationships between items [38,39].

The R package "bibliometrix" (v 4.2.1) was used to map the global distribution collaboration network of publication volume and for thematic trend analysis. In addition, the bibliometric online analysis platform (https://bibliometric.com/) was used to map inter-country collaboration networks and annual publication volume changes in the top 10 countries. Another online network (https://www.citexs.com/Summary) was analyzed for genes in the non-surgical treatment of disc degeneration; this site enables aggregated

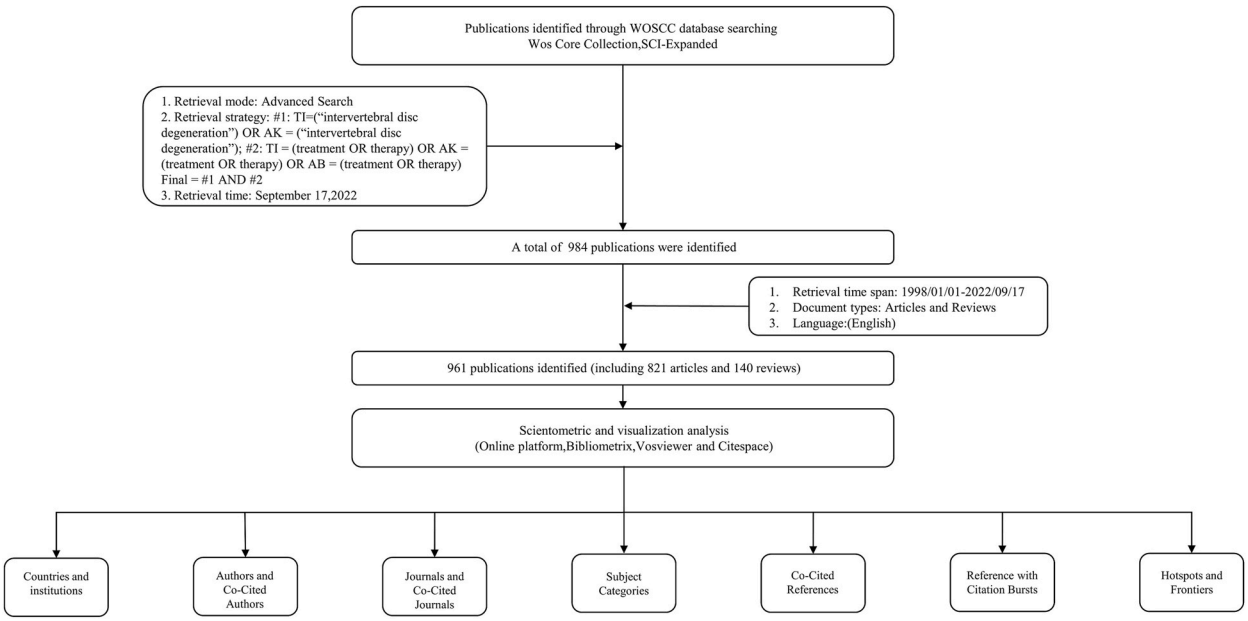

Fig. 1. Flow chart of literature search and selection.

analysis of genetic research data in a field based on the PubMed literature database.

3. Results

3.1. Quantitative analysis of publication

Based on our search strategy, there were 961 literature studies on non-surgical treatment modalities for IDD from 1998 to 2022, including 821 articles and 140 reviews. Fig. 2 shows the specific annual publications on the non-surgical treatment modalities for IDD. In terms of the growth rate of the number of publications per year, the entire annual publication volume can be divided into Three periods: the first period (1998–2007), the second period (2008–2012), and the third period (2013–2022). From the first period, it could be seen that there were fewer studies in general in this period, and the number of literature was below 10. The number of literature in the second period increased but grew more slowly, with an average of 13 published studies per year, in a flat period of overall research. In the third period, the amount of literature began to proliferate, with an average of 86.1 publications annually. The average number of publications in this period was 6.6 times the average in the second period, which was a period of rapid growth in overall research.

3.2. Country and institutional analysis

These publications are mainly from 49 countries and 405 institutions. As seen in Table 1, the top 15 countries are mainly located in Europe, Asia, and North America, with Europe (n = 7) and Asia (n = 4) accounting for the majority. Among these countries, the most prolific country is China (n = 601, 51.6 %), with more than half of the total publications, followed by the United States, Japan, and the United Kingdom. Furthermore, the vast majority of the top 15 institutions came from China (n = 13), followed by the United States (n = 1) and the United Kingdom (n = 1).

Fig. 3A shows a visualization depicting each country's contribution to the volume of publications. Based on the gradient of color shades, it can be seen that most of the research is concentrated in the Asian and North American regions. Fig. 3B shows the publication volume of the top 10 countries from 1998 to 2022, where the United States mainly dominated the number of publications in this field until 2013. From 2014 onwards, the number of publications in China started to increase rapidly yearly, with the number of publications until it took first place in 2022. Fig. 3C shows the analysis of international cooperation between different countries. Fig. 3D summarizes the top 10 funding agencies, with the central funding agencies for research in this area originating from China and the United States. Fig. 4A and **B** shows the visualization of institutional collaborations generated by CiteSpace and Vosviewer. It can be seen that Huazhong Univ Sci & Technol (n = 52,4.4 %) has the most research and is in the center, with more collaboration with Zhengzhou Univ, followed by Shanghai Jiao Tong Univ (n = 43,3.6 %) studied more, and collaborated more with Tongji Univ, Soochow Univ, and Zhejiang Univ. It can be seen from Fig. 4B that Huazhong Univ Sci & Technol and Shanghai Jiao Tong Univ do not collaborate. However, they are the first and second institutions in terms of the number of publications. However, Wenzhou Med Univ and Zhejiang Univ, which have more publications, cooperated closely.

3.3. Authors and co-cited authors

4765 authors have been involved in research on the non-surgical treatment of disc degeneration. Fig. 5A shows the top 10 prolific authors, with Wang K having the highest number of publications, followed by Yang C and Zhang Y. Fig. 5B shows the annual output

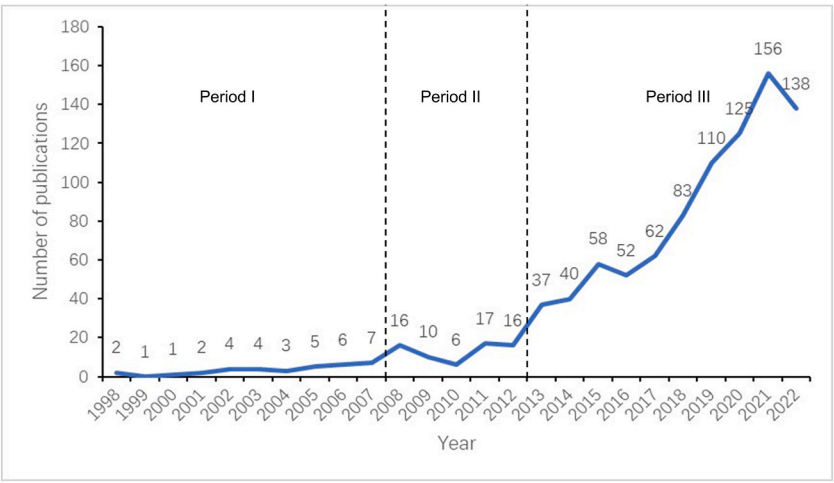

Fig. 2. Annual publication volume of studies on the non-surgical treatment of intervertebral disc degeneration.

Table 1
Top 15 countries and institutions on research of non-surgical treatment in IDD.

Rank	Country	Counts	ACI	H-index	Institution	Counts	ACI	H-index
1	China (Asia)	601 (51.6 %)	15.69	46	Huazhong Univ Sci &Technol (China)	52 (4.4 %)	21.71	22
2	The United States (North America)	175 (15.0 %)	43.05	45	Shanghai Jiao Tong Univ (China)	43 (3.6 %)	18.24	16
3	Japan (Asia)	54 (4.6 %)	34.98	22	Wenzhou Med Univ (China)	32 (2.7 %)	17.09	15
4	United Kingdoms (Europe)	34 (2.9 %)	73.65	17	Soochow Univ (China)	29 (2.5 %)	14.37	13
5	Italy (Europe)	32 (2.7 %)	31.15	15	Sun Yat Sen Univ (China)	26 (2.2 %)	20.13	15
6	Netherlands (Europe)	30 (2.6 %)	24.97	17	Zhejiang Univ (China)	25 (2.1 %)	16.16	13
7	South Korea (Asia)	29 (2.5 %)	19.24	13	Fudan Univ (China)	22 (1.9 %)	15.09	11
8	Germany (Europe)	29 (2.5 %)	41.71	16	Hebei Med Univ (China)	21 (1.8 %)	10.43	9
9	Australia (Oceania)	24 (2.1 %)	42.88	13	Southern Med Univ (China)	17 (1.4 %)	10.53	6
10	Canada (North America)	23 (2.0 %)	29.91	14	Qingdao Univ (China)	16 (1.4 %)	11.29	8
11	Switzerland (Europe)	21 (1.8 %)	55.71	13	Univ Pittsburgh (The United States)	15 (1.3 %)	60.17	16
12	India (Asia)	12 (1.0 %)	15.75	7	Univ Manchester (United Kingdom)	15 (1.3 %)	85.5	11
13	Brazil (South America)	9 (0.8 %)	8.33	5	Southeast Univ (China)	14 (1.2 %)	26.56	11
14	France (Europe)	9 (0.8 %)	27.78	5	Shandong Univ (China)	14 (1.2 %)	12.71	9
15	Spain (Europe)	7 (0.6 %)	19	6	Lanzhou Univ (China)	13 (1.1 %)	5.67	5

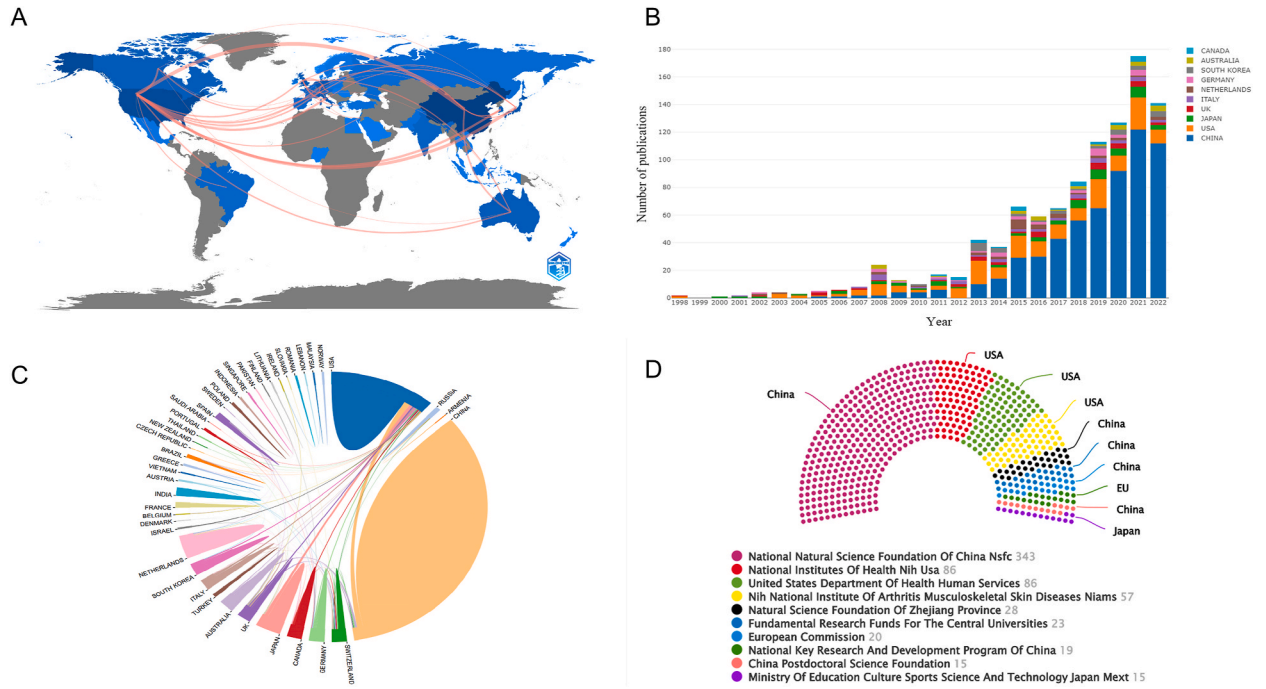

Fig. 3. (A) Spatial distribution of publications by country (B) Annual number of publications in the top 10 countries from 1998 to 2022 (C) Analysis of international cooperation between different countries (D) Sources of funding agencies in the top 10 in this field.

and citations of the top 10 authors for the years 1998–2022. We created a cluster density plot of author co-authorship analysis based on the number of publications greater than or equal to 8. We included 40 author co-authorship analysis (Fig. 5C), which can be seen to include 8 cluster classes. The co-citation network was plotted with a minimum co-citation equal to 90 (Fig. 5D). The most cited intensities are Le Maitre CL, Risbud MV, Sakai D, and Gruber HE.

3.4. Journals and co-cited journals

A total of 295 journals published publications related to the non-surgical treatment of disc degeneration, of which *Spine* published the most papers (n = 54,5.6 %), followed by *Spine Journal* (n = 33,3.4 %), *Journal of Orthopaedic Research* (n = 32,3.3 %) and *Molecular Medicine Reports* (n = 32,3.3 %). Among the top 15 journals in terms of the number of publications, the highest impact factor is *Osteoarthritis and Cartilage* (IF = 7.507), followed by *Oxidative Medicine and Cellular Longevity* (IF = 7.310), with the vast majority classified as Q1 or Q2 JCR divisions. We then filtered 30 journals with a minimum number of publications to 8 to draw a journal network diagram (Fig. 6A), which shows a strong citation relationship between journals, especially between *Spine*, *Spine Journal*, and

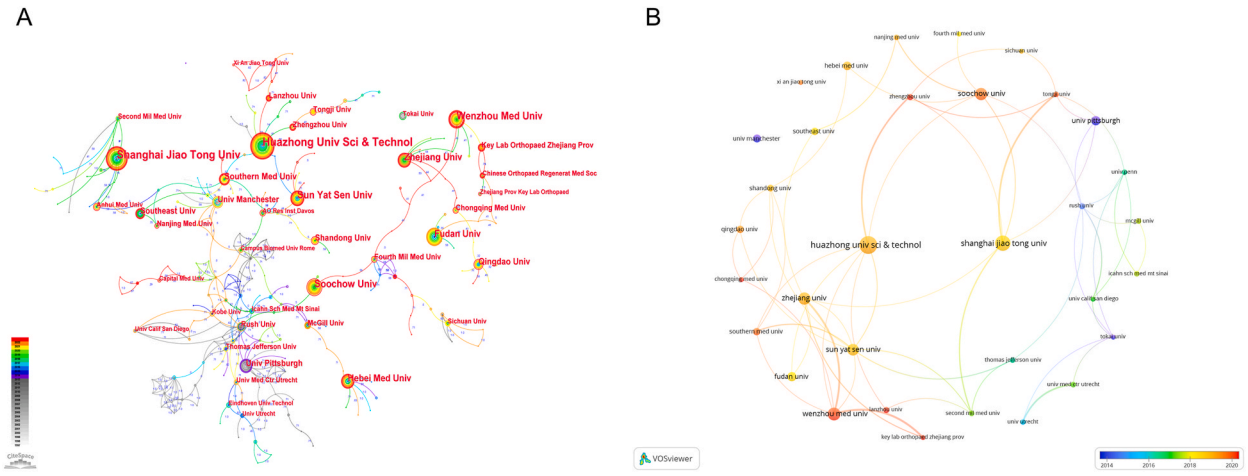

Fig. 4. (A) Visual mapping of institutional collaboration generated by CiteSpace (B) Visual mapping of institutional collaboration generated by Vosviewer.

Journal of Orthopaedic Research.

A co-citation relationship is formed when two journals appear in the bibliography of a third journal's cited literature. In Table 2, among the top 15 co-cited journals, a total of 5 of them had more than 1000 citations, with *Spine* (n = 7374) being the most cited journal, followed by *European Spine Journal* (n = 1649), *Journal of Orthopaedic Research* (n = 1322), *Spine Journal* (n = 1317) and *Arthritis Research & Therapy* (n = 1221). In addition, the journal with the highest impact factor was *Lancet* (IF = 202.731), followed by *Nature Reviews Rheumatology* (IF = 32.286) and *Biomaterials* (IF = 15.304). A minimum of 250 was set to plot the co-citation network, and 30 journals were included (Fig. 6B). Fig. 6B shows positive citation relationships between *Spine* and *Spine Journal*, *European Spine Journal*, and *Journal of Orthopaedic Research*.

The double graph overlay of journals clearly shows the citation relationships between journals and co-cited journals, as shown in Fig. 6C, with clusters of cited journals on the left, clusters of co-cited journals on the right, and the colored bars in the middle indicating the primary citation relationships between them, where the yellow bars indicate that studies published in journals in Molecular/Biology/Immunology usually cite studies published in Molecular/Biology/Genetics journals. The pink bars indicate that studies published in Neurology/Sports/Ophthalmology journals tend to cite papers published in Molecular/Biology/Genetics journals.

3.5. Analysis of the most relevant subject categories

Subject categories of publications in this field can be obtained in the "Citation Report" function in the WoSCC database. Each literature has one or more subject categories. The top 10 subject categories ranked according to the number of publications under each subject are shown in Fig. 7A, where the Orthopedics (n = 254) subject category had the most significant number of publications, followed by Cell biology (n = 204), Medicine Research Experimental (n = 204), Clinical Neurology (n = 180), and Biochemistry Molecular Biology (n = 141) received significant attention. Subsequently, a thematic category network was constructed using CiteSpace (Fig. 7B), and it can be seen that Orthopedics is cross-linked with Cell biology and Clinical Neurology. At the same time, Medicine Research Experimental is also closely cross-linked with Cell biology, and Oncology is also closely cross-linked.

3.6. Co-cited references and reference burst

As shown in Fig. 8A, the co-citation analysis of references is performed using CiteSpace. All points representing references in the figure are divided into different clusters, and different clusters may have cross-cutting research topics. From Fig. 8A, we can see that "cell-derived exosome" (#0) is the largest cluster, followed by "nucleus pulposus cell" (#1), "mesenchymal stem cell" (#2), and "tissue engineering approaches" (#3). At the same time, the author also uses CiteSpace to construct the timeline chart of the main clusters (Fig. 8B). According to the time axis trend in the figure, it can be seen that the research focus in recent years has changed from "tissue engineering approaches" (#3) , "inflammatory kinetics" (#4), and "direct cell-based tissue regeneration therapy" (#5) to "cell-derived exosome" (#0), "nucleus pulposus cell" (#1), "mesenchymal stem cell" (#2), and "circular RNA" (#9). In Table 3, we provide information on the top 10 co-cited references, all cited more than 40 times and two more than 60 times [40,41].

The citation burst of references refers to the references frequently cited by researchers in a particular field during a specific period. We used CiteSpace to identify the 25 references with the most potent citation bursts (Fig. 8C). The dark blue bars represent the citation years, and the red bars represent the intense citation bursts [42]. The citation explosion of references occurred as early as 2011 and as late as 2020. The most substantial outbreak (strength = 26.4) was cited by Risbud MV et al. in 2014, followed by Vergroesen PPA (strength = 16.17) and Sakai D (strength = 13.76). Overall, the burst duration of the 25 articles was 2–5 years, and the intensity range for bursting was 7.71–26.4. Table 4 summarizes the main research contents of 25 references according to the literature sequence in

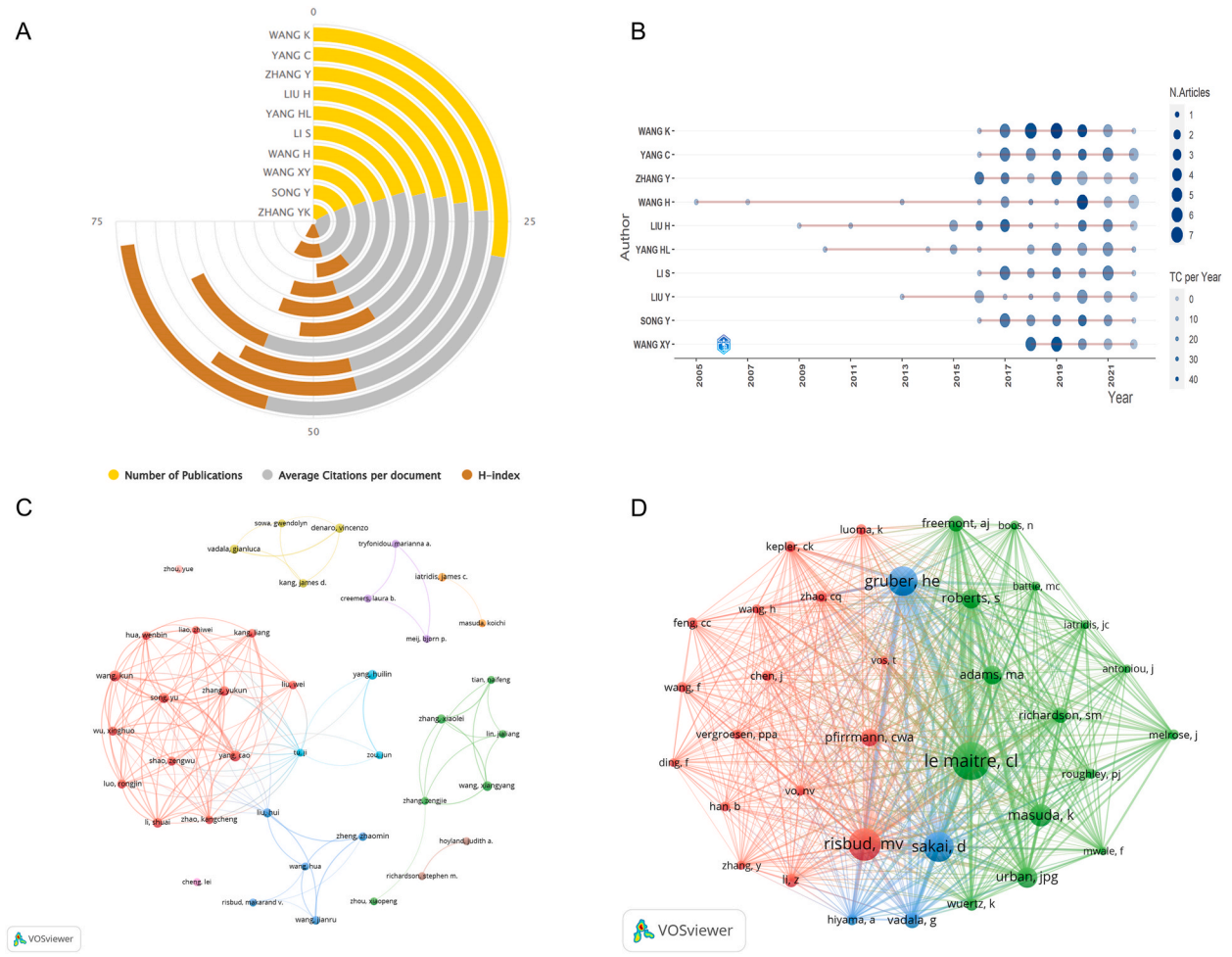

Fig. 5. (A) Publication volume, average citations per article and Hirsch index for the top 10 authors in the field (B) Annual publication volume and citation counts for the top 10 authors during 2005–2022, with the size of the circle indicating the number of articles and the depth of the circle indicating the total number of annual citations (C) author co-authorship analysis network by VOSviewer, with authors who collaborate closely sharing a common colour (D) generated by VOSviewer Author co-citation analysis network, a node indicates an author, the size of the node is proportional to the number of citations, the line between indicates the citation relationship, the smaller the distance between nodes indicates higher relevance and is classified as the same colour.

Fig. 8C.

3.7. Analysis of co-occurring keywords and related genes

We extracted 43 author keywords and drew an overlay visualization map (Fig. 9A) by manually merging keywords with the same meaning after filtering out keywords with a number greater than or equal to 6 by VOSviewer, in which different colours can reflect the research hotspots in different years. The size of nodes is consistent with the frequency of keywords. The thicker the line between the nodes, the stronger the connection between the keywords. Fig. 9A shows that intervertebral disc degeneration is closely related to apoptosis, autophagy, inflammation, and mesenchymal stem cells. Fig. 9B shows the frequency distribution of the top 20 most frequently occurring keywords, in which, except for intervertebral disc degeneration (frequency = 776), which was the most frequently occurring keyword, the remaining top 4 keywords were: nucleus pulposus cells (frequency = 205), apoptosis (frequency = 93), mesenchymal stem cells (frequency = 79), and inflammation (frequency = 71). However, the frequency distribution of keywords does not show well the trend characteristics of keyword distribution with year, so we used the R package “bibliometrix” to plot the trend theme analysis of keywords (Fig. 9C), and we can see that between 2007 and 2019, the research in this period mainly focused on molecular therapy mechanisms, with the main keywords being tissue engineering, regenerative medicine, gene therapy, growth factors, and histology. Since 2019, researchers have gradually transitioned to cellular regenerative therapy, with the main keywords being autophagy, senescence, exosomes, apoptosis, nucleus pulposus cells, inflammation, mesenchymal stem cells. In addition, autophagy, senescence, and exosomes are three keywords that have appeared more frequently in recent years (2020–2022). They may

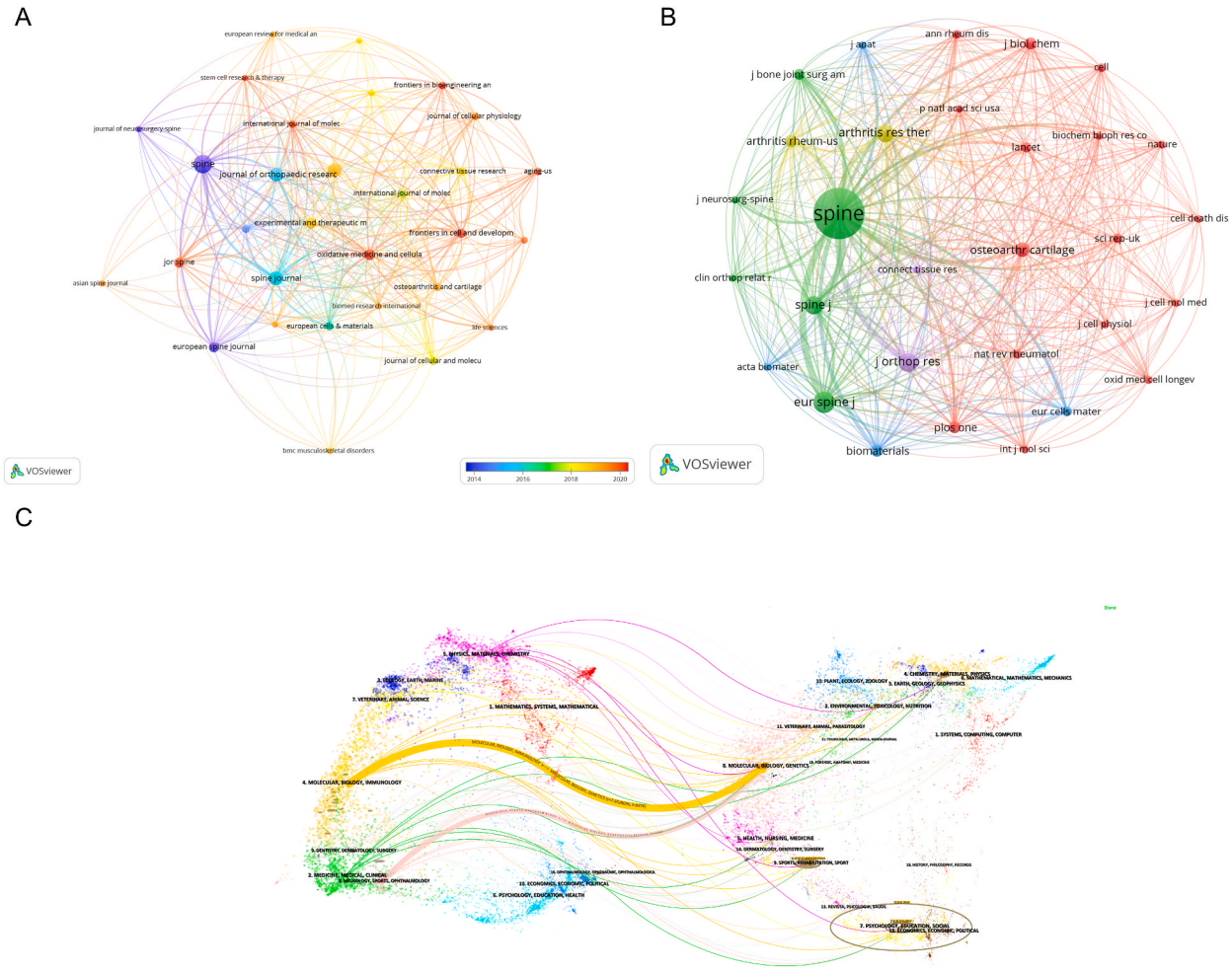

Fig. 6. (A) Visual network of journals in the field of non-surgical treatment of intervertebral disc degeneration research, node size is proportional to the number of publications, colours correspond to different years (B) Visual network of co-citations of journals in the field of non-surgical treatment of intervertebral disc degeneration research, a node represents a journal, the size of the node is proportional to the number of citations, the line segments between them indicate citation relationships, the smaller the distance between the nodes the higher the relevance, and are classified in the same colour (C) The dual-map overlay of journals on research of non-surgical treatment in intervertebral disc degeneration.

become a research hotspot in the non-surgical treatment of intervertebral disc degeneration. In addition, we mapped the top 15 critical genes in the non-surgical treatment of disc degeneration, as shown in Fig. 9D.

4. Discussion

4.1. General information

4.1.1. Global publication trends

As can be seen from the line graph of the number of publications, the overall number of publications showed a rapid increase yearly. From 1998 to 2007, the number of publications was tiny and did not attract the attention of researchers. More basic research in the non-surgical treatment of intervertebral disc degeneration needed to be done, which was at an early stage of overall research. From 2008 to 2012, the average number of publications was 13, an increase in the number of publications compared to the first phase, but still at the initial stage of development of the field. Interestingly, since 2013, the number of publications has increased rapidly, with an average of 86.1 publications per year and 89.6 % of the total publications in this phase. The substantial increase in the literature in this field in the last decade indicates that the research on non-surgical treatment modalities in intervertebral disc degeneration is in an explosive phase and that this field will receive more and more attention from researchers. The number of publications is expected to continue to grow.

Table 2
Top 15 journals and co-cited journals on research of nonsurgical treatment in IDD.

Rank	Journal	Counts	IF	Q (JCR quartile 2021)	Co-cited Journal	Co-citation	IF	Q (JCR quartile 2021)
1	*Spine*	54 (5.6 %)	3.269	Q2	*Spine*	7374	3.269	Q2
2	*Spine Journal*	33 (3.4 %)	4.297	Q1	*European Spine Journal*	1649	2.721	Q2
3	*Journal of Orthopaedic Research*	32 (3.3 %)	3.103	Q2	*Journal of Orthopaedic Research*	1322	3.103	Q2
4	*Molecular Medicine Reports*	32 (3.3 %)	3.423	Q3	*Spine Journal*	1317	4.297	Q1
5	*Experimental and Therapeutic Medicine*	22 (2.3 %)	2.751	Q4	*Arthritis Research & Therapy*	1221	5.606	Q1
6	*Oxidative Medicine and Cellular Longevity*	22 (2.3 %)	7.310	Q2	*Osteoarthritis and Cartilage*	891	7.507	Q1
7	*European Spine Journal*	19 (2.0 %)	2.721	Q2	*Arthritis and Rheumatism*	640	8.955	Q1
8	*Jor Spine*	19 (2.0 %)	3.757	Q1	*Plos One*	615	3.752	Q2
9	*Frontiers in Cell and Developmental Biology*	17 (1.8 %)	6.081	Q2	*Journal of Biological Chemistry*	603	5.485	Q2
10	*Arthritis Research & Therapy*	14 (1.5 %)	5.606	Q1	*Biomaterials*	601	15.304	Q1
11	*Journal of Cellular and Molecular Medicine*	14 (1.5 %)	5.295	Q2	*Journal of Bone and Joint Surgery-American Volume*	499	6.558	Q1
12	*European Cells & Materials*	13 (1.4 %)	4.325	Q2	*Lancet*	481	202.731	Q1
13	*Connective Tissue Research*	12 (1.2 %)	3.342	Q2	*Sci Rep-Uk*	427	4.997	Q2
14	*International Journal of Molecular Sciences*	12 (1.2 %)	6.208	Q1	*European Cells & Materials*	420	4.325	Q2
15	*Osteoarthritis and Cartilage*	12 (1.2 %)	7.507	Q1	*Nature Reviews Rheumatology*	396	32.286	Q1

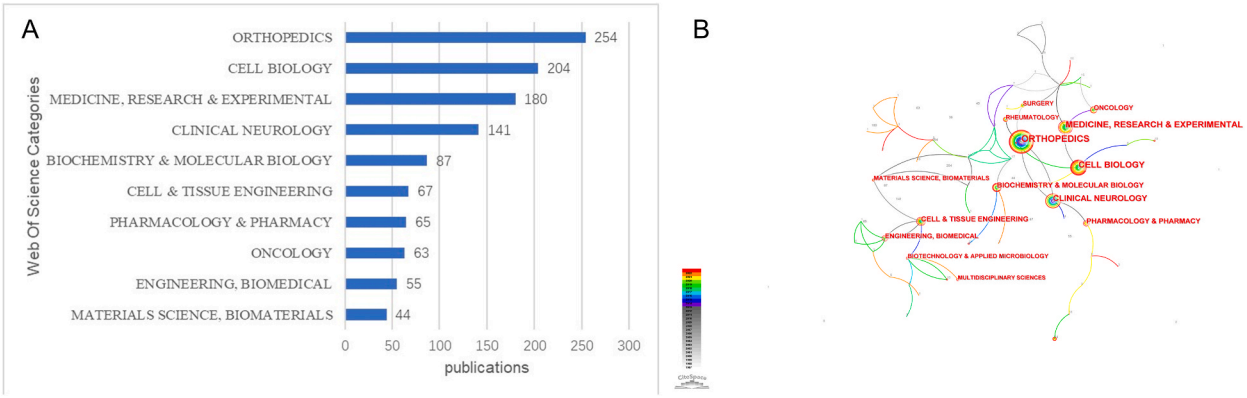

Fig. 7. (A) Top 10 subject categories by number of publications (B) Network of subject categories generated by CiteSpace.

4.1.2. Countries and institutions

As seen in Table 1, Europe and Asia account for most of the top 15 countries in number of publications. Among them, China, the United States, Japan, and the United Kingdom are the major countries studying the non-surgical treatment of disc degeneration, with China being the first in the number of publications. Although China and the United States have a close H-index, the ACI of the United States is much higher than that of China, indicating that the United States is in the leading position in terms of scientific influence in this field, and China still needs to strengthen the depth of scientific research. In terms of national cooperation, it can be seen from Fig. 3C that there is close cooperation between the US and China, Japan, and the UK. At the level of institutional cooperation, it can be seen from Fig. 4A and **B** that there is more cooperation between Huazhong Univ Sci & Technol and Zhengzhou Univ, Shanghai Jiao Tong Univ, Tongji Univ, and Wenzhou Med Univ and Zhejiang Univ. However, it is limited to domestic, and there is very little collaborative research between institutions in different countries. Univ Manchester, although it has the highest ACI in the top 15 institutions in terms of publication volume, has almost no cooperation with other institutions, which will be detrimental to the long-term development of research and scholarship and will increase the worldwide research expenditures in the field. Therefore, to make

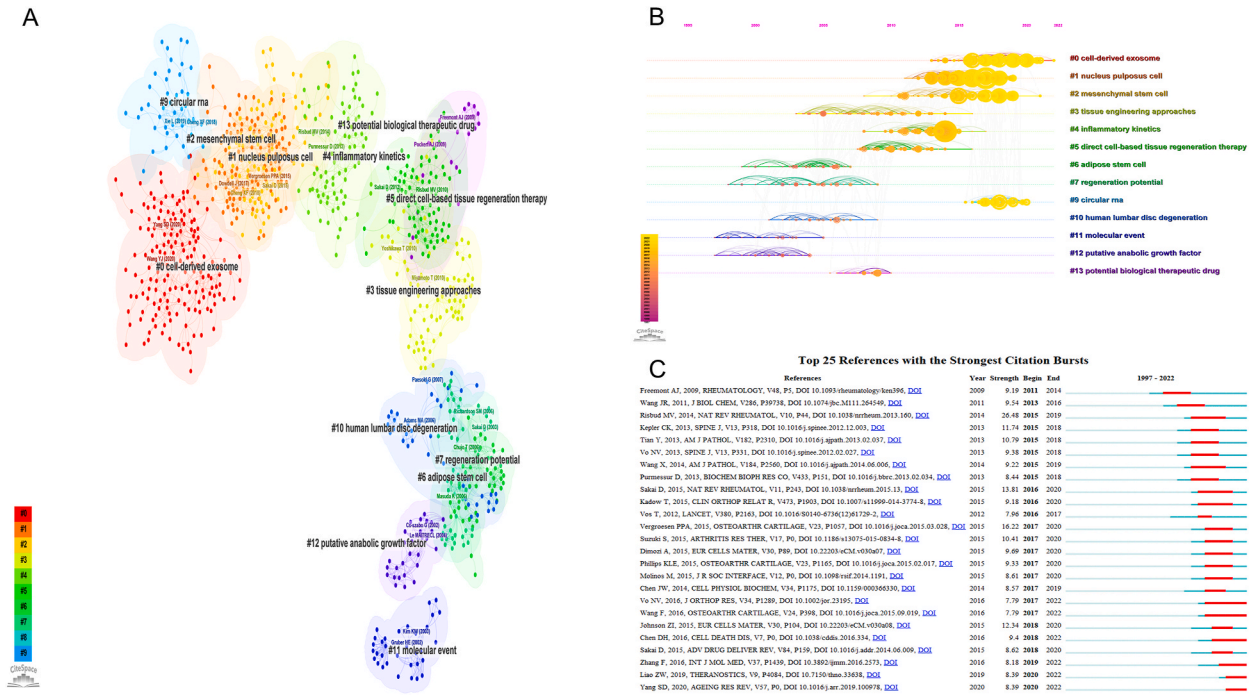

Fig. 8. (A) Clustering plot of references co-cited generated by CiteSpace, with a dot indicating a reference and different colours indicating different clusters (B) Timeline plot of the main clusters generated by CiteSpace (C) The top 25 references with the strongest citation bursts, with red bars representing the duration of the citation bursts.

Table 3
Top 10 co-cited references on research of nonsurgical treatment in IDD.

Rank	Co-cited reference	Citations
1	Risbud MV, 2014, NAT REV RHEUMATOL, V10, P44, DOI 10.1038/nrrheum.2013.160	71
2	Dowdell J, 2017, NEUROSURGERY, V80, P0, DOI 10.1093/neuros/nyw078	62
3	Vergroesen PPA, 2015, OSTEOARTHR CARTILAGE, V23, P1057, DOI 10.1016/j.joca.2015.03.028	45
4	Ji ML, 2018, NAT COMMUN, V9, P0, DOI 10.1038/s41467-018-07360-1	45
5	Vo NV, 2016, J ORTHOP RES, V34, P1289, DOI 10.1002/jor.23195	44
6	Wang F, 2016, OSTEOARTHR CARTILAGE, V24, P398, DOI 10.1016/j.joca.2015.09.019	44
7	Sakai D, 2015, NAT REV RHEUMATOL, V11, P243, DOI 10.1038/nrrheum.2015.13	42
8	Chen DH, 2016, CELL DEATH DIS, V7, P0, DOI 10.1038/cddis.2016.334	41
9	Wang YJ, 2020, BIOMED PHARMACOTHER, V131, P0, DOI 10.1016/j.biopha.2020.110660	41
10	Liao ZW, 2019, THERANOSTICS, V9, P4084, DOI 10.7150/thno.33638	40

an all-out attack on the non-surgical treatment of disc degeneration, we suggest that institutions in different countries jointly eliminate academic barriers and develop extensive academic cooperation to promote scientific research in this field.

4.1.3. Authors

At the author level, WANG K published the most articles, followed by YANG C and ZHANG Y. All three authors are from China. Fig. 5A, B shows that WANG K is also the author with the highest H-index and has a strong academic influence from 2017 to 2021. WANG K et al. in 2018 found that Sirtuin3 in mitochondria can mitigate apoptosis induced by advanced glycation end products (AGEs), confirming the protective effect of Sirtuin3 on intervertebral disc degeneration as a potential therapeutic tool [43]. In addition, another highly cited paper described that circRNA-CIDN, in combination with miR-34a-5p, could reduce stress-induced myeloid cell damage by targeting the silent mating type information regulation two homolog 1 (SIRT1). At the same time, CircRNA-CIDN has also been shown to similarly inhibit the progression of disc degeneration in IDD models [44]. The above studies illustrate that small molecules can be crucial in inhibiting disc degeneration as anti-apoptotic, antioxidant, and synthetic promoting substances to prevent further degeneration of disc cells, which is essential for the inspiration of subsequent studies [45].

At the level of co-cited authors, as shown in Fig. 5D and 35 authors were filtered by citations greater than or equal to 90, and the most cited authors were Le Maitre CL, followed by Risbud MV, Sakai D, and Gruber HE, respectively. Le Maitre CL et al. investigated the role of interleukin-1 (IL-1) in intervertebral disc degeneration. It confirmed that IL-1 is produced by degenerating discs and that IL-1 becomes an essential target for treating or delaying disc degeneration [46]. A 2014 review by Risbud MV and colleagues entitled

Table 4
The main research contents of the 25 references with strong citations bursts.

Rank	Strength	Main research content
1	9.19	Cytopathological process of lower back pain due to disc degeneration caused by disruption of cytokine biology, cellular dysfunction, and altered load response
2	9.54	In nucleus pulposus tissue, the pro-inflammatory cytokines TNF-α and IL-1β play an important role in intervertebral disc degeneration
3	26.48	Role of pro-inflammatory cytokines, neurogenic factors produced by immune cells in the process of intervertebral disc degeneration
4	11.74	Molecular basis of disc degeneration: decreased production of extracellular matrix, increased production of degradative enzymes and increased inflammatory cytokines leading to loss of structural integrity and accelerated disc degeneration
5	10.79	Pro-inflammatory cytokines TNF-α and IL-1β lead to reduced degradation of TNF-α-dependent aggregated proteoglycans in myeloid cells
6	9.38	The regulation of metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) expression and enzymatic activity plays a crucial role in future disc degeneration-related diseases
7	9.22	Regulation of TNF-α-dependent expression of MMP-3 in nucleus pulposus cells reduces intervertebral disc degeneration and matrix catabolism
8	8.44	In addition to limiting inflammation, anabolic and cellular proliferation must be promoted in the treatment of disc degeneration
9	13.81	Barriers to survival and adaptation of stem cell transplantation in the avascular environment of disc degeneration and solutions
10	9.18	The pathological process of disc degeneration is the upregulation of pro-inflammatory cytokines, an increase in degradative enzymes and a loss of matrix proteins
11	7.96	The main specific causes of the number of years of disability for people with sequelae in 2010 were essentially the same as in 1990: low back pain, major depression, iron deficiency anaemia, neck pain, chronic obstructive pulmonary disease, anxiety disorders, migraines, diabetes and falls
12	16.22	Interplay of mechanics and biology in disc degeneration: a vicious cycle of mechanical overload, catabolic cellular responses and degeneration of the water-bound extracellular matrix
13	10.41	Oxidative stress contributes to the progression of disc degeneration, and the oral antioxidant N-acetylcysteine (NAC) eliminates the catabolic effects of excess reactive oxygen species and TNF-α in vitro
14	9.69	Oxidative stress inhibits proliferation, induces premature aging and promotes a catabolic phenotype in human nucleus pulposus intervertebral disc cells
15	9.33	Myeloid cells express many cytokines and chemokine receptors, with IL-1 being the main regulator in IVD
16	8.61	The role of inflammatory factors in intervertebral disc degeneration and regeneration and the treatment of key inflammatory factors
17	8.57	Controlling the autophagic response of nucleus pulposus cells under oxidative stress will facilitate cell survival and may slow down the process of disc degeneration
18	7.79	The biochemical process of disc ageing can be divided into three distinct stages: firstly, exposure to inflammation and oxidative stress causes damage to biomolecules such as DNA and proteins. Secondly, tissue damage is exacerbated when the abnormal cellular response to damage is dysregulated. Thirdly, cumulative damage leads to the loss of biological structure and function of the disc tissue
19	7.79	In intervertebral disc degeneration, the accumulation of cellular senescence is associated with reduced cell proliferation, impaired self-repair, increased inflammatory response and enhanced catabolism
20	12.34	TNF-α and IL-1β have key roles in intervertebral disc degeneration at the cellular and tissue levels
21	9.4	Metformin protects nucleus pulposus cells against apoptosis and senescence through autophagy stimulation and improves disc degeneration in vivo, demonstrating its potential as a therapeutic agent for intervertebral disc degeneration
22	8.62	Advances in intervertebral disc cell and molecular therapy, including mobilization and activation of endogenous progenitor cells, progenitor cell homing and targeted delivery of cells, genes or bioactive factors
23	8.18	Molecular mechanisms of cell death in intervertebral disc degeneration include activation of apoptotic pathways and regulation of autophagy in response to nutrient deprivation and multiple stresses
24	8.39	MSC-derived exosomes attenuate endoplasmic reticulum stress-induced apoptosis through activation of AKT and ERK signaling pathways
25	8.39	Estrogen reduces disc cell apoptosis through a variety of pathways, including inhibition of the inflammatory cytokines IL-1β and TNF-α, and inhibition of matrix metalloproteinases to reduce catabolism

"Role of cytokines in intervertebral disc degeneration: pain and disc content" summarized the mechanisms by which the pro-inflammatory cytokines TNF, IL-1α, IL-1β, IL-6, and IL-17 are involved in intervertebral disc degeneration and pain, with blockade of the relevant cytokines being the key to preventing all stages of disc degeneration. The key to blocking the relevant cytokines is to stop the ongoing degeneration of the disc at all stages [40]. In 2015, Sakai, d et al. published advances for cellular and molecular therapies related to disc degeneration [47]. The co-cited author system formed in the above studies centered on Le Maitre, CL and Risbud, MV, which made disc-associated cytokines the main center of research and laid the experimental and theoretical foundations for non-surgical treatment modalities for the intervertebral disc.

4.1.4. Journals

Journals are an essential tool for scholarly communication among researchers from all countries, and quality journal publications can lead to the convergence of the academic achievements of global researchers and guide research in various fields. However, not all researchers know all the journals in their field of study, and a metric visualization of journals relevant to the non-surgical treatment of disc degeneration will help researchers select the relevant journals in the field for their article submission. Most of the top 15 journals in terms of publications were published in Q1 or Q2 journals, with *Spine* (IF = 3.269, Q2) being the most popular journal, followed by *Spine Journal* (IF = 4.297, Q1), *Journal of Orthopaedic Research* (IF = 3.103, Q2), and *Molecular Medicine Reports* (IF = 3.423, Q3). Regarding co-cited journals, it can be seen that they are all Q1 or Q2 journals, and most of them are Q1 journals, while *Spine* (n = 7374) has far more citations than the others, probably related to its high publication volume, followed by *European Spine Journal*, *Journal of Orthopaedic Research*, *Spine Journal,* and *Arthritis Research & Therapy*. Of these, *Spine*, *European Spine Journal*, *Journal of Orthopaedic Research,* and *Spine* Journal focus on the molecular mechanisms of spinal and orthopedic-related diseases. In contrast, *Arthritis Research & Therapy* focuses on the molecular treatment of osteoarthritis and other orthopedic diseases. As a result, it is easier to access the latest research in the non-surgical treatment of disc degeneration by following the articles in these journals.

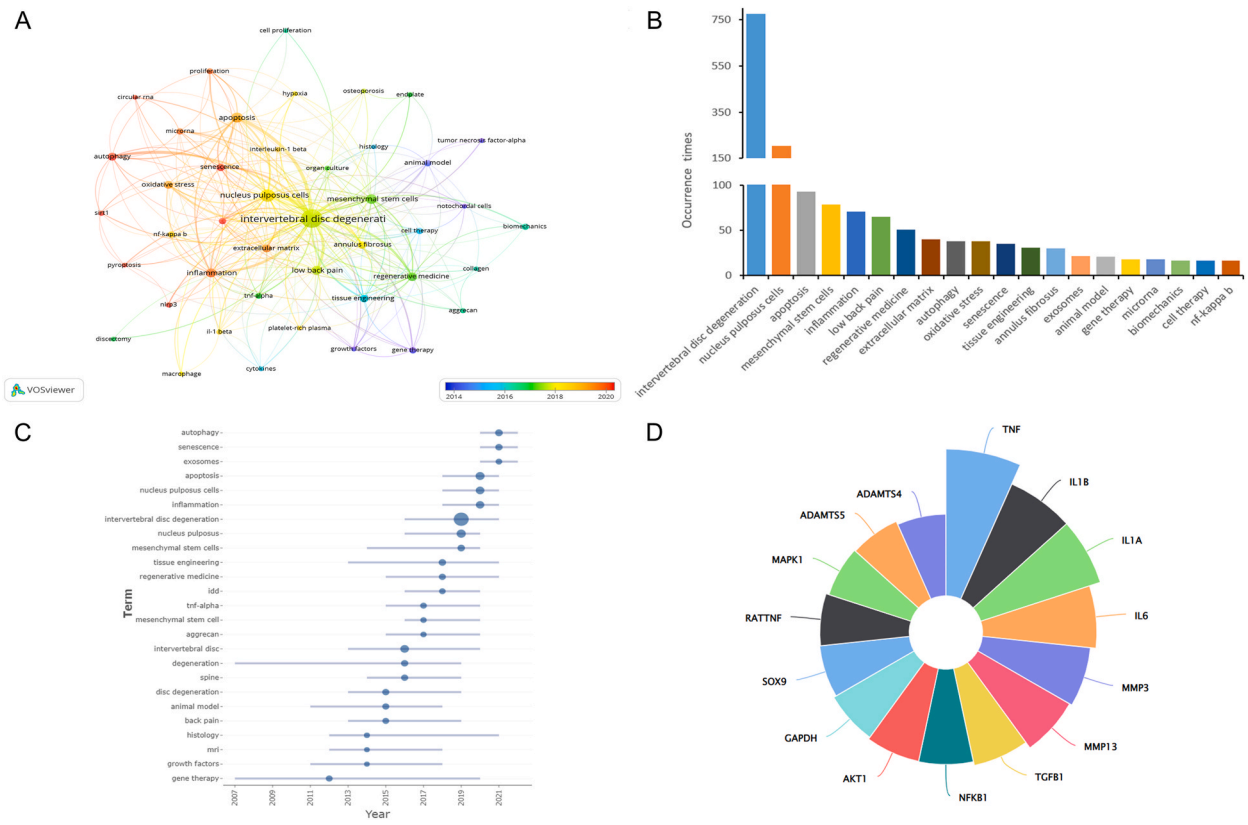

Fig. 9. (A) Co-occurrence network plot of the keywords generated by VOSviewer (B) Frequency distribution of the top 20 keywords (C) Thematic distribution of keywords by year (D) Top 15 genes studied most in the field of non-surgical treatment of intervertebral disc degeneration.

4.1.5. Hotspots and frontiers

The subject categories are based on the Web of Science database and reflect the current research priorities and hotspots [48]. The analysis of references and keywords is the most critical method of bibliometrics, which is the basis, hot spot, and future research direction in a particular field [49,50].

As can be seen from Fig. 7A, the top five subject categories are Orthopedics, Cell Biology, Medicine Research Experimental, Clinical Neurology, and Biochemistry & Molecular Biology. Other subjects, aside from orthopedics, focus on cell, molecular, and clinical experimental research. Fig. 7B shows the cross-disciplinary research on each topic, and the research combining cell, molecular, and clinical experiments may become the hot topic of future research.

Co-cited references refer to standard references cited by other documents, which can be used as a common basis for further research in this field. It is of great significance to analyze and summarize them [51]. As can be seen from Fig. 8A and B, the research base has rapidly developed into a “cell-derived exosome” (#0), “nucleus pulposus cell” (#1), “mesenchymal stem cell” (#2), and “circular RNA” (#9). Among the ten most cited articles, the article published by Prof. Risbud MV has been described above and will not be repeated here. In a 2017 article, Dowdell J et al. described a variety of non-surgical treatments, such as protein injection, stem cell injection, gene therapy, and tissue engineering. They achieved good results in animal models [41]. The article published by Ji ML and colleagues in *Nature Communications* revealed that miR-141 promotes the development of IDD by targeting the inhibition of SIRT1, and inhibition of miR-141 becomes a potential therapeutic strategy for IDD [52]. Sakai D et al. described that the current surgical methods could not reverse or restore the pathological state of IDD. Stem cell injection therapy has become a promising treatment method. However, stem cells do not survive well in avascular intervertebral disc tissues, so it is imperative to screen its indications and patients [53]. The article published by Chen DH proposed that metformin can protect nucleus pulposus cells from apoptosis through autophagy, which provides a reasonable basis for small-molecule drugs to act on IDD [54]. Liao ZW et al. confirmed in a study published in 2019 that mesenchymal stem cell-derived exosomes (MSC-exos) can effectively inhibit apoptosis of nucleus pulposus cells caused by endoplasmic reticulum stress during IDD, which was confirmed in an in vivo model of rat intervertebral disc degeneration. Overall, the top 10 co-cited references focus their research on stem cells, small molecule drugs, and exosomes, forming a vital research base in this field.

Reference citation burst refers to the frequently cited literature in a specific research field in a certain period, representing the novel topics and research hotspots in this field. It can be seen in the primary research contents of the first 25 reference citation burst (Table 4) that both mechanics and biology are the leading causes of intervertebral disc degeneration. In contrast, the biological causes are mainly caused by pro-inflammatory cytokines (such as TNF-α and IL-1β), oxidative stress, extracellular matrix reduction, nucleus

pulposus cell apoptosis, and other factors, while the corresponding stem cell transplantation, exosomes, small molecule drugs, and other means can inhibit the above factors and inhibit the re-progression of intervertebral disc degeneration.

In addition to the citation burst of references, keyword analysis is a crucial bibliometric index to quickly obtain research topics and hot prospects in a particular field. In this study, we created a keyword visualization network using VOSviewer after combining keywords with the same meaning (Fig. 9A). In Fig. 9B, besides the essential keywords such as intervertebral disc degeneration, nucleus pulposus cells, apoptosis, and low back pain, the keywords mainly focus on mesenchymal stem cells, inflammation, and regenerative medicine. It is known from the burst of references cited that inflammatory factors are mainly caused by pro-inflammatory cytokines, which play an indelible role in accelerating disc degeneration. In addition, Fig. 9C shows that the evolution process of the topic trend of the keyword, which can be divided into three stages: 2007–2011, 2012–2019, and 2020–2022. It can be seen from the first stage that there is less research on keywords in this stage, only degeneration and gene therapy. In the second stage, 16 keyword topics are mentioned, among which the most significant ones are tissue engineering, regenerative medicine, gene therapy, growth factors, and histology. In the third stage, the keyword topics are mainly autophagy, senescence, exosomes, apoptosis, nucleus pulposus cells, inflammation, and mesenchymal stem cells.

From the above, we can see that gene therapy is important in disc degeneration. We also screened the top 15 genes reported in the literature through an online data analysis website. As shown in Fig. 9D, the top 5 most studied genes are TNF, IL1B, IL1A, IL6, and MMP3. It can be seen that the first four genes are all pro-inflammatory cytokines. Many studies have reported that TNF - α, IL - 1 β, IL - 1 α, and IL - 6 are related to various pathological processes of the intervertebral disc, such as extracellular matrix degradation, nucleus pulposus cell apoptosis, and various clinical manifestations such as intervertebral disc protrusion and nerve root pain [40,46]. Johnson ZI discussed that TNF-α, IL-1β, and IL-1α aggravate the inflammatory process in disc degeneration and symptoms such as low back pain, and inhibition of this process is beneficial to reduce disc inflammation and low back pain [55]. Wang YJ et al. believe that TNF-α and IL-1β are closely related to various pathological processes of IDD, such as inflammatory reaction, matrix destruction, cell aging, autophagy, cell apoptosis, pyrosis and proliferation, and further research on TNF-α and IL-1β may develop effective therapeutic methods [56]. Ji ML et al. found that miR-98 can target IL-6 to promote the expression of type II collagen in nucleus pulposus cells, and IL-6 has become a promising target [57]. MMP3 is matrix metalloproteinase 3, which is generally induced by TNF-α in myeloid cells, leading to the degradation of the extracellular matrix. Yang, H et al. found that TGF-β1 could antagonize these processes [58]. These results suggest that various pro-inflammatory cytokines accelerate the progression of disc degeneration and that various non-surgical treatments targeting pro-inflammatory cytokines will greatly benefit disc relief. To sum up, in the analysis of co-cited references (Fig. 8A and B), the research base has rapidly evolved toward the exosomes and mesenchymal stem cells areas. A reading and analysis of the top 10 cited literatures shows that they are mainly focused on miRNAs, stem cells, small molecule drugs, and exosomes. In addition, in the top 25 literatures with reference citation outbreaks (Table 4), means such as stem cell transplantation, exosomes, and small molecule drugs were found to inhibit a variety of biological factors that cause IDD. The results of the keyword analysis (Fig. 9A, B, and C) again highlight the importance of the elements of mesenchymal stem cells, degenerative drugs, and exosomes. Considering these results together, the authors concluded that the aspects of MSCs, exosomes, and drugs have potential means for a nonsurgical approach to treating IDD.

4.1.6. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are pluripotent stem cells that can be derived from bone marrow, adipose tissue, synovium, placenta, human umbilical cord blood, and urine [59]. Mesenchymal stem cells can be induced and differentiated into different types of cells through self-division and continuous renewal. Early researchers co-cultured mesenchymal stem cells with nucleus pulposus cells and injected them into rabbit intervertebral discs for in vivo experiments. The results showed that mesenchymal stem cells could effectively up-regulate extracellular matrix production in nucleus pulposus cells, and the experimental animals did not have systemic disease manifestations, proving the feasibility of mesenchymal stem cells for the treatment of intervertebral disc degeneration [60]. Adipose-derived mesenchymal stem cells (ADSCs) have become the preferred source of stem cells for intervertebral disc degeneration due to their abundance, availability, and universality [61]. Compared with the nucleus pulposus cells, the mesenchymal stem cells have a better effect on promoting repair [62]. In addition, human umbilical cord-derived mesenchymal stem cells have been carried out in vivo animal and human experiments, and no adverse reactions have been found. Positive effects of intervertebral disc repair have been achieved [63,64]. More and more studies have demonstrated that mesenchymal stem cells can inhibit various pathological states of intervertebral disc degeneration, such as extracellular matrix degradation, apoptosis, inflammation, and so on [65–67]. Mesenchymal stem cell injection therapy will soon become a safe and reliable option for patients with early-stage disc degeneration [68].

4.1.7. Exosomes and biomarker

Mesenchymal stem cell injection is a promising therapy, but it has some disadvantages, such as low cell survival rate, rejection, and tumorigenicity [69]. Exosomes are nano-sized vesicles (40–120 nm in diameter) with bilayer phospholipid membrane structure secreted by cells through budding. Exosomes can be fused with target cells remotely or locally. Exosomes can be derived from various cells and are easy to store, free of immunogenicity and tumorigenicity, and easy to obtain and transform [70]. Exosomes have become a potential substitute for stem cell therapy for degenerative disc diseases because of their excellent properties [71]. Exosomes derived from mesenchymal stem cells can avoid the defects of mesenchymal stem cells and inherit their good therapeutic properties, so they are widely studied and applied. Exosomes derived from mesenchymal stem cells can inhibit disc degeneration not only by anti-inflammation and anti-oxidation [72]but also by inhibiting apoptosis and pyroptosis [73] and promoting autophagy [74]. Exosomes contain various substances, including mRNA, miRNA, and other non-coding RNAs and protein lipids [75]. In addition, exosome

miRNAs are more stable and specific than other substances, such as proteins and lipids, and play a role in cell communication and disc degeneration [76]. Exosomes from rat bone marrow mesenchymal stem cells can deliver miR-155 to degenerated nucleus pulposus cells, increase autophagy, and reduce apoptosis of degenerated nucleus pulposus cells, thereby treating intervertebral disc degeneration [77]. MSC-exos also inhibits apoptosis of nucleus pulposus cells and degradation of extracellular matrix by delivering miR125-5p [78]. In addition, MSC-exos can also delay nucleus pulposus degeneration in intervertebral discs by delivering miR-21, miR-31- 5p, and miR-142- 3p, mainly by inhibiting apoptosis of nucleus pulposus cells [79–81], Mesenchymal stem cell-derived exosomes inhibit NOD-like receptor thermal protein domain associated protein 3 (NLRP3)-mediated pyroptosis in intervertebral disc degeneration by delivering miR-410, miR-26a-5p, and miR-141-3p [82–84]. In summary, mesenchymal stem cell-derived exosomes can inhibit various pathological conditions in intervertebral disc degeneration. The miRNAs therein have good characteristics and are easier to assemble into multifunctional exosomes to exert therapeutic properties.

Exosomes can be used as therapeutic agents and diagnostic biomarkers in developing disc degeneration [85]. Nucleus pulposus cell-derived exosome miR-15a can target matrix metalloproteinase-3 (MMP3) and promote the chondrogenic differentiation of nucleus pulposus stem cells [86], exosome-derived circRNA competes for miRNA-141-5p to exacerbate disc degeneration [87]. Therefore, detecting relevant exosomes can be used as a potential biomarker for early diagnosis of intervertebral disc degeneration. However, studies on exosomes as biomarkers of intervertebral disc degeneration are still few, and their sensitivity and specificity have not been entirely determined. Further studies are needed to clarify the biomarker role of more exosomes in intervertebral disc degeneration.

Although exosomes have made significant achievements in treating and diagnosing intervertebral disc degeneration, there are still few studies on exosomes in clinical trials. Many clinical trials are needed, from clinical trials to wide clinical applications. Studies on other contents of exosomes, such as mRNA, non-coding RNA, and protein lipids, still need to be made. Exosomes' separation and purification technology have yet to reach an advanced level, which can easily cause therapeutic bias. Exosomal miRNA therapy's safety and adverse effects should be investigated in future studies. With further study and the progress of scientific research, we believe that exosomes will be widely used in degenerative disc diseases shortly.

4.1.8. Medication and tissue engineering

At present, the main clinical treatments for IDD are physical therapy, anti-inflammatory and analgesic drugs, surgical treatment, etc. Although they can partially solve the clinical symptoms of patients with neurological disorders, pain, etc., they can not repair intervertebral disc degeneration [88]. New drugs or drugs in other fields are also widely studied in the field of intervertebral disc degeneration and regeneration. Salmon calcitonin is used to treat osteoporosis-related intervertebral disc degeneration, which can significantly maintain the structural integrity and biological strength of intervertebral discs in rat models by increasing the expression of aggrecan and type II collagen [89], and other drugs such as alendronate [90], and parathyroid hormone [91]which are used to treat osteoporosis, may also be used to treat disc degeneration associated with osteoporosis. Andrographis paniculata, a natural compound widely used in apoptotic and inflammatory diseases, can maintain the phenotypic characteristics of nucleus pulposus cells by increasing the expression of extracellular matrix markers and inhibit the NF-κB pathway to prevent inflammation caused by the degeneration of nucleus pulposus cells [92]. Other drugs, such as Lycorine [93] and Oxymatrine [94], may enhance the anti-inflammatory activity of nucleus pulposus cells and inhibit extracellular matrix degradation by inhibiting the NF-κB pathway. In addition, Aspirin [95]and Acacetin [96] exert anti-inflammatory and anti-oxidative stress effects in rats. Apigenin [97], fexofenadine [98], and melatonin [99]target TNF-α-induced cellular inflammation and extracellular matrix degradation. Interestingly, classical antidiabetic agents such as metformin have also been used to inhibit disc inflammation [100] or to treat degenerative discs by promoting the release of extracellular vesicles from mesenchymal stem cells [101].

Tissue engineering was first introduced at the National Science Foundation in 1987. The four elements of tissue engineering are cells, growth factors, biomaterial scaffolds, and production technology [102], the core of which is the establishment of a three-dimensional spatial complex of cells and biomaterials, i.e., living tissue with vitality, to reconstruct the morphology, structure, and function of diseased tissues and achieve permanent replacement [103]. Among them, biomaterials in the field of disc degeneration, such as hydrogels, have become hot research materials in the field of disc degeneration repair because of their excellent biomechanical properties, especially their ability to retain water similar to that of the nucleus pulposus tissue [104]. The thermosensitive injectable hydrogel containing gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, increases the extracellular matrix and prevents intervertebral disc degeneration in rats [105]. The aspirin-loaded hydrogel not only inhibits inflammation but also has the effect of slow-release drugs and filling tissue defects [106]. The composite hydrogel encapsulated with MSCs improves the viability of myeloid cells and reduces the breakdown of the extracellular matrix [107,108]. Some investigators have recombined thermosensitive hydrogel with adipose mesenchymal stem cell-derived exosomes, the substance that not only replenishes the leakage of medullary tissue but also reduces cellular scorching by inhibiting the inflammatory response and becomes an alternative therapy for intervertebral disc degeneration [109], and another combination substance of cartilage endplate stem cell-derived exosomes and hydrogel can achieve similar therapeutic effects [110].

From the above, it can be seen that some therapeutic drugs in other fields can be further studied in disc degeneration repair to achieve the research innovation of new use of old drugs [111]. The combination of biomaterial scaffolds can be considered to achieve therapeutic effects while considering their biomechanical properties, slow release of drugs, and filling tissue defects. With the expansion of biologic scaffold materials, the non-surgical treatment modality of mesenchymal stem cells and exosomes combined with biologic scaffolds will have comprehensive application research value in intervertebral disc degeneration.

5. Strengths and limitation

Compared with previously published traditional reviews and Meta-analyses, this study is unique in several ways. First, we used a bibliometric approach to conduct a comprehensive analysis of the non-surgical treatment of intervertebral disc degeneration, which enriched the results and provided comprehensive information for researchers in related fields to draw on. Second, three bibliometric tools and two online platforms were used to perform bibliometric analysis and visualization, yielding richer and more objective results. Finally, we conducted a hotspot and prospect analysis based on the visualization analysis results, which is more unique and comprehensive than traditional reviews.

However, this study has some limitations. Firstly, the data in this study were obtained from the WoSCC database, and studies from other databases were ignored. However, WoSCC is the most commonly used and authoritative database for bibliometric analysis and can represent the general situation of most studies in a field to some extent. Secondly, we only used studies published in English and may have omitted publications in other languages. Although this study reveals various dynamics in the non-surgical treatment of IDD, it has some limitations, including reliance on a single data source, insufficient depth in collaboration network analysis, and inadequate reflection of the latest research trends. Future research should expand data sources by incorporating multiple databases such as Scopus and PubMed to obtain a more comprehensive dataset. Additionally, in-depth analyses of interdisciplinary and international collaboration networks are needed to understand their impact on research progress. Introducing dynamic analysis methods to track and predict changes in research hotspots and frontiers in real-time, along with combining qualitative and quantitative analyses to thoroughly evaluate the effectiveness and potential impact of various non-surgical treatment methods, will provide more reliable scientific evidence for clinical applications.

6. Conclusion

Overall, there has been a gradual increase in publications on the non-surgical treatment of intervertebral disc degeneration, with a rapid increase in the number of studies in China and the USA since 2013. Secondly, China and the United States also have the highest number of research institutions, funding agencies, and research authors. However, there is less cooperation between institutions in each country, and there is still a need to strengthen cooperation between international institutions in future research. Wang K is one of the most influential authors in this field, and the most published and influential journal is *Spine*. Based on keyword co-occurrence, we know that the research hotspots in the non-surgical treatment of disc degeneration are mesenchymal stem cells, inflammation, and regenerative medicine. At the same time, mesenchymal stem cells, exosomes, medication, and tissue engineering were identified as the latest research hotspots in this field and foreword. In conclusion, the results of the above analysis will help relevant researchers to understand the body of knowledge in the field, including countries, institutions, journals, and authors, and provide valuable references for future research.

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Data availability statement

The data used during the present study are available from the corresponding author upon reasonable request.

Ethics statement

This study did not require review and/or approval by an ethics committee because it was a literature-based analysis and did not involve human or animal experimentation.

CRediT authorship contribution statement

Yan Zhao: Writing – original draft. **Qiuqiu Xia:** Supervision. **Lu Zhu:** Supervision. **Jiyue Xia:** Supervision. **Shaojie Xiang:** Supervision. **Qiming Mao:** Supervision. **Huaize Dong:** Supervision. **Zijing Weng:** Supervision. **Wenbo Liao:** Writing – review & editing. **Zhijun Xin:** 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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