A bibliometric analysis of autophagy in prostate cancer from 2003 to 2023

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Abstract: *Autophagy can regulate the occurrence and development of prostate cancer. In recent years, research on autophagy in prostate cancer has received widespread attention. However, there has been no bibliometric analysis in this field. Inorder to study the research status and hotspot of autophagy in prostate cancer in recent 20 years. We searched the literature on prostate cancer in the field of autophagy published in the Web of Science Core Database (WoSCC) between January 1, 2003 and April 1, 2023. We used CiteSpace 6.1R software to draw visual knowledge maps such as document publication trend chart, authors, research institutions, national and regional cooperation networks and keywords, and conduct bibliometric analysis. Resultly, a total of 770 papers were included, and the overall number of published papers showed an increasing trend. A total of 291 authors were included in the author collaboration Atlas, including 167 core authors. There are 231 institutions included in the Institutional Collaboration Map, of which only the University of California System has a centrality greater than 0.1. The authors are distributed in 58 countries, of which the largest number of articles published by PEOPLES R CHINA is 282. A total of 238 keywords were included, forming 12 clusters, 30 of which had a keyword frequency ≥30 times. Thus, the molecular mechanism of autophagy regulating the proliferation, apoptosis and metastasis of prostate cancer is a hot topic in current research. Drug resistance therapy of prostate cancer and development of new drugs targeting autophagy are the research trends.*

Keywords: *Prostate Cancer; Autophagy; CiteSpace; Visualization Analysis; Bibliometrics*

1. Introduction

In recent years, the incidence of malignant tumors is still on the rise, seriously threatening human health and life. The incidence of prostate cancer ranks second and the mortality ranks fifth among male malignant tumors [1]. There are no obvious symptoms in early prostate cancer, and most patients have progressed to middle and advanced stages when diagnosed, and the optimal surgical treatment time is missed. Androgen deprivation therapy and chemotherapy are the main treatment methods for patients with advanced prostate cancer. However, drug side effects and drug resistance and other problems greatly limit the clinical benefits of patients. The 5-year survival rate was 30% [2]. Therefore, further in-depth study of the pathogenesis of prostate cancer and search for potential sensitive targets are the fundamental methods for the treatment of prostate cancer. Autophagy is a highly conservative process of self-digestion and degradation of self-destroyed organelles and abnormally folded proteins as substrates, and then reuse of digestive components to maintain a stable state of cells [3]. Autophagy is widely involved in the physiological and pathological processes of cells in the body, and plays a role in promoting or inhibiting the progression of prostate cancer [4], providing new ideas for the treatment of prostate cancer.

Bibliometrics is a scientific quantitative analysis method integrating philology, mathematics and statistics to analyze the distribution structure, quantitative relationship and change law of scientific literature information [5]. CiteSpac e is a visual literature analysis software developed by Professor Chen Chaomei based on JAVA language, which can search and analyze the published literature in this research field by keyword, and explore the research hot spots and frontier trends in this field [6]. At present, the literature information on prostate cancer in the field of autophagy is increasing year by year. In this paper, CiteSpace 6.1R document metrology software is used to search the literature related to prostate cancer in the field of autophagy, and a visual knowledge map is drawn for the authors, research institutions,

national and regional cooperation networks and keywords of the literature, so as to visually display the research status and research hotspots in this field. The research trend is analyzed in order to provide reference for the subsequent research.

2. Methods and materials

2.1. Data sources and search strategy

The data were obtained from the Web of Science Core Database (WoSCC) from January 1, 2003 to April 1, 2023. The search terms included: TS=(prostate OR prostatic) NEAR/1 (cancer* OR tumor* OR tumour* OR oncology OR neoplasm* OR carcinoma*) AND TS=(autophagy OR autophage OR autophagocytosis), the Language is set to English, and the Document Types are article and review.

2.2. Literature screening and data cleaning

According to the above retrieval strategy, a total of 1571 literatures were retrieved from WoSCC, the search results were manually reviewed again, the title, abstract and content of the literatures were read, and the literatures unrelated to the research topic were excluded, including 801 conference papers, newspapers, notices, popular science, incomplete information and repeated publications. Finally, 770 articles were included in this study.

2.3. Data analysis

The selected literature data was exported from WoSCC and other file formats were selected. Each data piece of WoSCC literature was downloaded as a full record and referenced reference, and the output format was plain text download_**.txt, which was imported into CiteSpac e 6.1R for conversion and analysis. Time Slicing is set to 2003-2023, years per slice is set to 1 year, and Selection Criteria is set to Top N to 50. Keyword Pruning items Select Pathfinder, Pathfinder, and Pruning Networks. According to different research contents, different node types are set, visual knowledge maps are drawn for Author, Institution, Country, Keyword, and corresponding cooperative network analysis and co-occurrence analysis. The LLR algorithm is used for weighted calculation of cluster analysis. Different nodes in the graph represent authors, institutions, keywords and other elements; the connections between nodes represent cooperative relationships; the size of nodes represents their number; and the thickness of connections between nodes represents the degree of connection between them [7].

3. Results

3.1. Annual publications

The number of published papers annually can reflect the research status of the field to a certain extent. A statistical analysis was made on the number of published papers on autophagy in prostate cancer from 2003 to 2023. Figure 1 shows that although the number of published papers in this field fluctuated in the past 20 years, it showed an overall upward trend. From 2003 to 2014, the number of published papers increased slightly, with an annual average of less than 50 papers, which belonged to the primary research stage of autophagy in prostate cancer. The number of published papers from 2015 to 2022 exceeded 50, among which the number of published papers in 2022 reached the highest, reaching 86, indicating that autophagy of prostate cancer has gradually become a research hotspot of scholars at this time. Since the literature in 2023 has not been fully included and there are analytical biases, it is expected that the number of its papers will continue to grow. The results show that the study of autophagy in prostate cancer is in a period of rapid development and will receive more attention from researchers in the future.
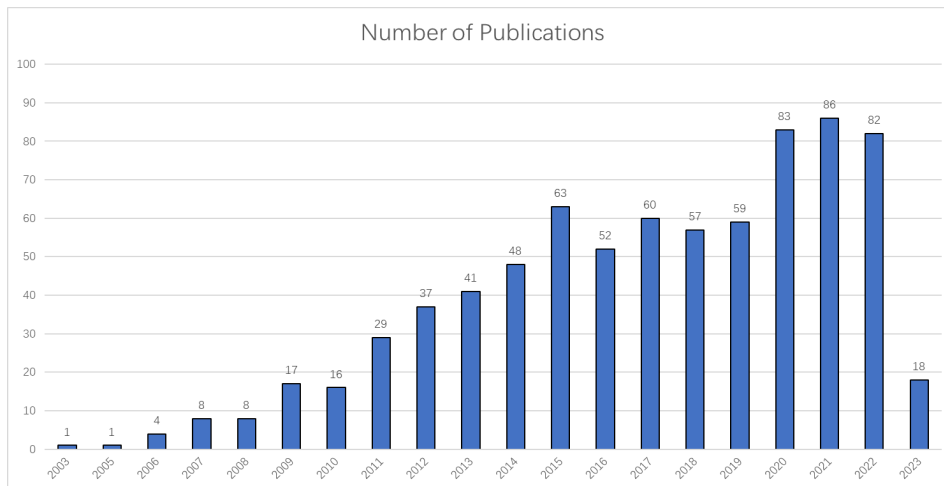
Figure 1: Annual trend of publications

3.2. Contribution of authors

Through the analysis of the number of authors' papers and cooperation relationship, we can understand the results distribution in the whole research field and the cooperation status of the team. Among the 770 literatures, a total of 291 authors were included, and Ahn Soon-Cheol, who published the highest number of papers, published 5 articles. According to Lyps' law $N=0.749\sqrt{Mmax}$ (Mmax is the number of papers published by the most prolific author) [8], the minimum number of papers published by core authors in this field was calculated, and it was obtained that N=1.67. The core authors in this field are those who have published more than or equal to 1.67 papers, and a total of 167 authors meet this condition, accounting for 57% of the total number of authors. According to the author cooperation diagram in Figure 2, it can be seen that there are multiple research teams in this research field, and a research team represented by Ahn, Soon-Cheol, Hahm, Eun-Ryeong, Yu, Ying, Wang, Ying-yu, Murtola, Teemu J, etc. is formed among the core authors. The overall research team has reached its initial size with close internal connections, but there is no obvious cooperation outside the teams, the research force is relatively dispersed, no leader appears, the utilization rate of advantageous resources is low, and relevant academic exchanges need to be further strengthened.
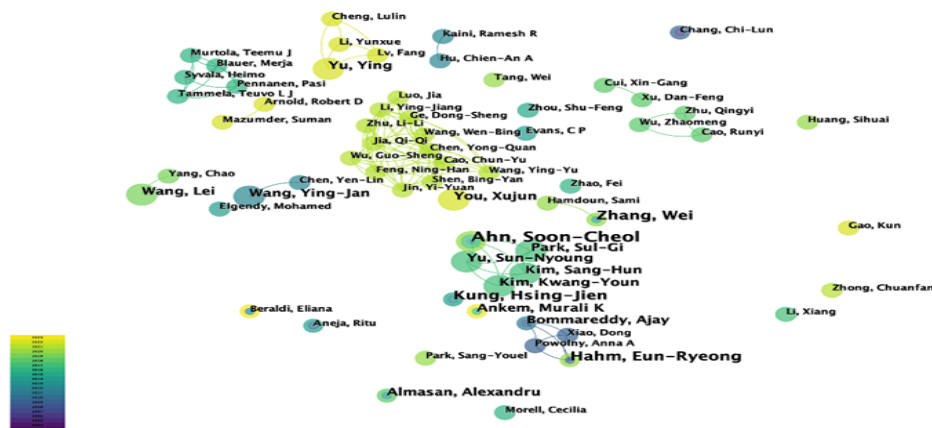

Figure 2: Contribution of authors

3.3. Contribution of Institution / Countries

The institutional/country collaboration map can clearly show the research degree and cooperation intensity of different institutions/countries in the same field. The information of the included institutions was combined and sorted out, and a visual map of the institutions was drawn (Figure 3). A total of 231

institutions were included in the map. The top 3 institutions in terms of publication volume were University of California System (19 articles), University of Texas System (15 articles) and Shanghai Jiao Tong University (11 articles). Nodes with centrality greater than 0.1 represent key hubs at the core that connect different domains [9]. In addition, from the perspective of centrality, only the University of California System (0.11) cooperated closely with other institutions, indicating that although there are many research institutions on prostate cancer autophagy, the current research is relatively scattered, with less inter-institutional cooperation and weak links, and most of them are independent studies within institutions. In the future, inter-agency exchanges and cooperation need to be further strengthened.
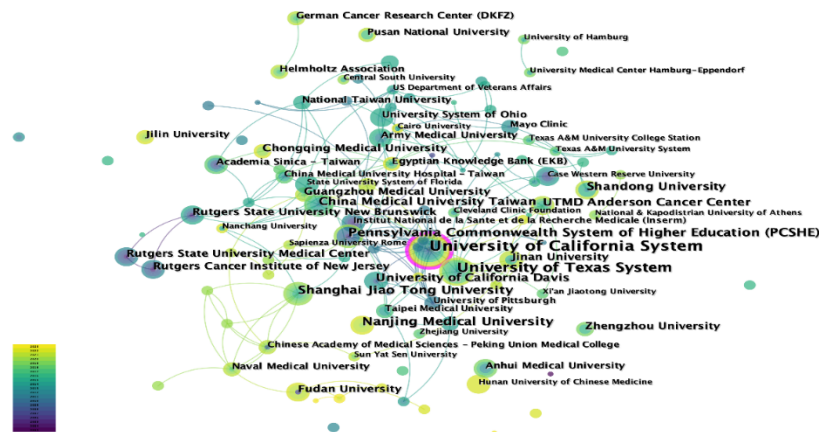

Figure 3: Contribution of Institution

At the same time, we conducted a statistical analysis on the author distribution, and found that since 2003, the authors of articles were distributed in 58 countries, among which the number of articles published by PEOPLES R CHINA was the largest 282, followed by the USA with 251, indicating that PEOPLES R CHINA and USA have made greater contributions to this field (Figure 4). In terms of centrality, the top five are USA (0.51), AUSTRALIA (0.45), SPAIN (0.42), INDIA (0.4) and GERMANY (0.36), which cooperate closely with other countries and whose research results are more recognized by other countries. From this we can see that countries such as the USA, AUSTRALIA and PEOPLES R CHINA have played a key role in scientific output and national cooperation.
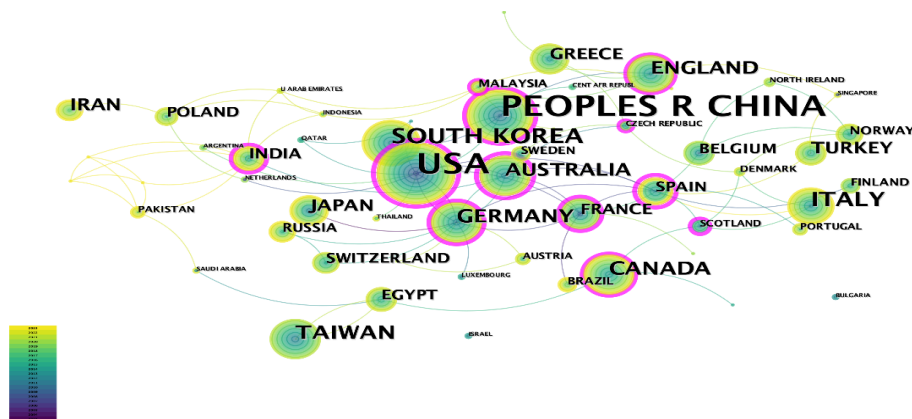

Figure 4: Contribution of Countries

4. Keywords analysis

4.1. Keyword co-occurrence analysis

Keywords are highly refined and summarized the research content of a literature, and to a certain extent, they represent the research hotspots in this field. Through keyword analysis, we can explore the evolution of knowledge, hot spots and future research directions. In order to improve the accuracy of statistics, keywords with the same or similar meanings but different expressions are combined and the

keyword co-occurrence map is drawn (Figure 5). A total of 238 keywords are obtained, of which 30 have frequency ≥30 times, among which the keyword with the highest frequency is "prostate cancer". Through the analysis of high-frequency keywords, it can be seen that the current research in this field mainly focuses on cell-based experiments, mostly from the direction of androgen receptors, to study the mechanism of autophagy in prostate cancer, so as to explore new treatment schemes.

Figure 5: Keyword co-occurrence

4.2. Key words cluster analysis

Keywords as the embodiment of research hotspots and frontiers, cluster analysis can clarify the research theme and its development process in this field, which is conducive to in-depth exploration of research hotspots in this field. The LLR algorithm in CiteSpace software will be used for keyword cluster analysis, and the keyword cluster analysis map will be generated (Figure 6). Modularity Q=0.7213 > 0.3 and Mean Silhouette=0.8816 > 0.5 indicate that the keyword clustering in this field is significant and the clustering results are reasonable. The same color in the figure represents a cluster, and a total of 12 cluster labels have been obtained. #4 is the main research object of Castra-resistant prostate cancer, and the main treatment program is anti-male therapy. #0, #1, #3, #5, #6 and #9 indicate that autophagy can regulate the biological behavior of prostate cancer cells. Including cell death, migration, endoplasmic reticulum stress, epithelial-mesenchymal transition, etc. #2, #7, #8, #10 and #11 are studies on the internal molecular mechanism and gene expression of autophagy affecting the progression of prostate cancer, and androgen receptor is a hot topic in this field.

Figure 6: Key words cluster

4.3. Key words Time zone diagram analysis

The keyword time zone chart can visually show the evolution path of each cluster keyword, which is conducive to understanding the research hotspots and research trends in different time periods in this field. The year 2003-2023 is divided into one year as a time zone, and the key word co-current area map is drawn (Figure 7). Currently, the research methods of autophagy in prostate cancer are mainly animal experiments and cell experiments, and the research contents have been established before 2009, mainly focusing on the growth, proliferation and apoptosis of autophagy and prostate cancer. From 2010 to 2013, we began to explore the occurrence process of autophagy at the molecular level, and discovered a new treatment plan for prostate cancer through autophagy. Since 2014, we have studied the metastasis and drug resistance of castration-resistant prostate cancer with autophagy and androgen receptor as the starting point. MAPK and NF-κB signaling pathways are popular research pathways.

Figure 7: Key words Time zone diagram

4.4. Keyword Burst analysis

Figure 8: Keyword Burst

Keyword Burst means that the occurrence frequency of keywords increases significantly in a short period of time. Through keyword Burst analysis, the research hotspots in a certain period of time can be clearly understood and the development direction of the research can be judged. From 2003 to 2023, a total of 24 intentional emergent words were detected (Figure 8). In the figure, Begin represents the time when emergent keywords appear, End represents the time when emergent keywords end, and Strength represents the intensity of emergent words. The key words beclin1, phosphorylation, reactive oxygen species and induced apoptosis with high pre-2016 intensity are the molecular markers and pathological processes closely related to autophagy. After 2016, metastasis, invasion, epithelial mesenchymal transition, drug resistance and other prostate cancer etiology mechanism and treatment plan have obvious emergence and outbreak. It can be inferred that the research hotspot of prostate cancer autophagy has gradually transiited from basic experimental research to clinical application, and the development of

effective prostate cancer therapy targeting autophagy will continue to exist as a hot spot and trend.

5. Discussion

In this study, the bibliometric method and CiteSpace 6.1R software were used to analyze 770 literatures in the core database of Web of Science, and visually present the basic situation of research literatures in the field of prostate cancer autophagy in the past 20 years in the form of knowledge graph. Including the trend of publication, author, institutional/national cooperation network, keywords, etc., to provide reference and ideas for in-depth research in this field.

5.1. State of the Research

The number of literature related to autophagy in prostate cancer is generally increasing, and the number of published papers in the next few years will continue to grow, indicating that autophagy research is gradually attracting wide attention from everyone. However, compared with the rapidly increasing incidence of prostate cancer, the overall number of literature is small, and the highest annual number of published papers is only 86, reflecting the lag of research in this field to some extent. Further in-depth exploration is needed. From the analysis of the existing research results, the author team represented by Ahn, Soon-Cheol, Zhang, Wei, Hahm, Eun-Ryeong, etc. has published a large number of papers. University of California System, University of Texas System and Shanghai Jiao Tong University are the main research institutions. USA, AUSTRALIA and PEOPLES R CHINA are the high-influence countries in this research field. Although there are cooperative relations among these authors, institutions and countries, the research content is scattered and there is a lack of high-frequency cooperation. On the one hand, there are differences in scientific research level with various regions. On the other hand, it is also closely related to the incidence of prostate cancer. With the improvement of living standards and the change of living environment, the incidence of prostate cancer has continued to rise in recent years. According to statistics, in developed countries, the incidence of prostate cancer is three times that of developing countries. The incidence is relatively high in European and American countries, whereas the incidence is low in Asian and North African countries [10]. These high incidence areas provide researchers with more reliable experimental samples and data, which is essential to drive the progress of research and make breakthroughs. It is suggested that those countries that are in the leading position in research output should actively shoulder their corresponding responsibilities, give full play to their own advantages, and cooperate with other countries to complement each other's advantages, improve the quality of research and the efficiency of resource utilization, and promote the comprehensive development of this field. At the same time, as the main publishing institutions of research results, research institutions should pay attention to interdisciplinary and scientific and technological innovation, strengthen cooperation and communication, further promote the research of autophagy in all stages of prostate cancer, and provide strong scientific evidence for the clinical application of autophagy in prostate cancer.

5.2. Research Focus Areas

Based on the keyword frequency and cluster analysis results, it can be speculated that the molecular mechanism by which autophagy regulates prostate cancer proliferation, apoptosis and metastasis is a current research hotspot. Although autophagy has been extensively studied in cancer, its complex mechanism of action remains controversial [11]. Prostate cancer is a disease caused by the malignant proliferation of prostate epithelial cells. In the early stage of prostate cancer, autophagy protects cells from malignant transformation by removing abnormal organelles, misfolded proteins and reducing the level of reactive oxygen species to maintain intracellular environmental stability and genomic stability. However, with tumor growth, autophagy can not only meet the high metabolic demands of tumor cells, but also initiate a cellular survival response to ensure the survival of tumor cells under various stress conditions, which in turn promotes tumor cell survival and drug resistance [12]. Lin et al. [13] found that AR-CAMK2-AMPK signaling cascade can initiate autophagy by inducing the activation of ULK1 complex to promote the growth and metastasis of prostate cancer cells. However, it has also been reported that autophagy can promote the death of prostate cancer cells. The results of Han et al. [14] showed that fibroblast growth factor 21 can induce autophagy by inhibiting the PI3K/Akt/mTOR axis, leading to increased apoptosis of prostate cancer cells. It can be seen that the effect of autophagy on the survival of prostate cancer cells depends on the specific stage and environmental background, and the progression of prostate cancer may have two sides. Therefore, it is necessary to further study the specific role of autophagy in prostate cancer to provide more treatment options for patients.

5.3. Research Trends

According to the keyword time zone map, burst analysis and literature review, the research trends of autophagy in prostate cancer include drug resistance treatment of prostate cancer and the development of new drugs targeting autophagy. Tumor cells can survive by degrading autologous necrotic organelles and misfolded proteins to regain nutrients, so most researchers believe that protective autophagy is an important cause of tumor drug resistance and poor prognosis [15]. Androgen receptor is the main driver to maintain prostate cancer growth and the key target of endocrine drug therapy. Most patients respond to androgen deprivation therapy, but there are still many castration-resistant prostate cancer patients with poor prognosis and short survival, and need further chemotherapy [16]. Docetaxel and cabazitaxel are first-line chemotherapy drugs, which can improve the overall survival time of patients with advanced prostate cancer [17]. However, with the increase of the course of treatment, patients often develop different degrees of chemotherapy resistance. Chemotherapy resistance of prostate cancer involves the transcription, expression and regulation of a variety of genes, such as Bcl-2, P53, etc. In addition, AMPK, NF-κB and other signaling pathways are also involved in the occurrence of drug resistance [18,19], and these genes and signaling pathways are closely related to the regulation of autophagy activation. At the same time, a number of studies have also confirmed that chemotherapy can induce protective autophagy in CRPC cells and promote docetaxel resistance, and inhibition of autophagy can increase the apoptosis rate of cancer cells and improve the sensitivity of treatment [20,21]. Therefore, the in-depth study of autophagy helps us to better understand the mechanism of chemoresistance of prostate cancer, so as to provide new ideas and strategies for the treatment of prostate cancer.

In addition, androgen receptor signaling pathway also plays an important role in CRPC resistance [22]. Androgen receptor resistance alterations are associated with amplification, polyclonal and compound mutations, rearrangements, and exon deletions, such as the androgen splice variant 7 (AR-V7) involved in enzalutamide resistance [23]. Nguyen et al. [24] have shown that enzalutamide can trigger autophagy in PCa cells or animal models, allowing androgen-sensitive prostate cancer cells to evade anti-androgen therapy, and the treatment regimen combined with autophagy inhibitors can significantly reduce tumor growth and reverse the occurrence of drug resistance. These results suggest that autophagy is an important survival mechanism of CRPC, and improving the therapeutic effect of existing therapies by regulating autophagy level has important clinical significance for improving drug resistance and prognosis of prostate cancer patients.

Autophagy inhibitors currently in clinical research include chloroquine and its derivatives hydroxychloroquine, bafilomycin A1, etc. These drugs can inhibit autophagy by preventing the fusion of autophagosomes and lysosomes [25]. In addition to autophagy inhibitors, some traditional Chinese medicine ingredients and non-coding RNA can also affect the therapeutic effect of prostate cancer by regulating autophagy. Reversal of drug resistance [26]. In conclusion, inhibition of autophagy is an effective method for the treatment of prostate cancer and has broad research prospects, but its specific mechanism of action, drug dosage and safety still need to be further studied. In the future, the clinical application of autophagy regulatory drugs such as radiotherapy, immunotherapy and targeted therapy can be further explored to make autophagy regulatory drugs play a better role.

6. Summary

In summary, this study systematically analyzed the WoSCC literature on autophagy in prostate cancer through bibliometric methods, and visualized measurement showed the research status and hotspots in this field in the past 20 years. At present, castration-resistant prostate cancer is resistant to therapeutic drugs, which greatly affects the effective survival and quality of life of patients. The combination of various treatment methods provides the possibility of precise treatment for patients. Autophagy, as an effective therapeutic target, provides new ideas for the treatment of drug resistance, but there are still insufficient clinical transformation. The evidence level of efficacy and safety is insufficient, and the multi-center and large-sample randomized controlled trials are lacking, which need to be further explored and improved in the future. This paper also has some shortcomings. Due to the limitation of CiteSpace software itself, multiple databases cannot be analyzed at the same time, and only the literature of WoSCC is comprehensively searched, which makes the research in this field cannot be fully presented and may affect the accuracy of some conclusions. It is hoped that this paper can provide a reference for researchers in this field, open up researchers' thinking to a certain extent, and promote the further development of this field.

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