Research article

Worldwide productivity and research trend of publications concerning extracellular vesicles role in fibrosis: A bibliometric study from 2013 to 2022

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ABSTRACT

Background: Fibrosis is a heavy burden on the global healthcare system. Recently, an increasing number of studies have demonstrated that Extracellular vesicles play an important role in intercellular communication under both physiological and pathological conditions. This study aimed to explore the role of extracellular vesicles' in fibrosis using bibliometric methods.

Methods: Original articles and reviews related to extracellular vesicles and fibrosis were obtained from the Web of Science Core Collection database on November 9, 2022. VOSviewer was used to obtain general information, including co-institution, co-authorship, and co-occurrence visualization maps. The CiteSpace software was used to analyze citation bursts of keywords and references, a timeline view of the top clusters of keywords and cited articles, and the dual map. R package "bibliometrix" was used to analyze annual production, citation per year, collaboration network between countries/regions, thematic evolution map, and historiography network.

Results: In total, 3376 articles related to extracellular vesicles and fibrosis published from 2013 to 2022 were included in this study, with China and the United States being the top contributors. Shanghai Jiao Tong University has the highest number of publications. The main collaborators were Giovanni Camussi, Stefania Bruno, Marta Tepparo, and Cristina Grange. Journals related to molecular, biology, genetics, health, immunology, and medicine tended to publish literature on extracellular vesicles and fibrosis. "Recovery," "heterogeneity," "degradation," "inflammation," and "mesenchymal stem cells" are the keywords in this research field. Literature on extracellular vesicles and fibrosis associated with several diseases, including "kidney disease," "rheumatoid arthritis," and "skin regeneration" may be the latest hot research field.

Conclusions: This study provides a comprehensive perspective on extracellular vesicles and fibrosis through a bibliometric analysis of articles published between 2013 and 2022. We identified the most influential countries, institutions, authors, and journals. We provide information on recent research frontiers and trends for scholars interested in the field of extracellular vesicles and fibrosis. Their role in biological processes has great potential to initiate a new upsurge in future research.

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1. Introduction

Fibrosis is an outcome of the tissue repair response, which becomes dysfunctional following various types of tissue injury, especially chronic inflammation. When tissue damage is minor, local tissue fibroblasts are activated and increase the secretion of inflammatory mediators and the synthesis of extracellular matrix (ECM) components. These changes initiate a wound healing response. The formation of fibrotic tissue, which is defined by the unnecessary accumulation of ECM components, such as fibronectin and collagen, is a basic and critical phase of tissue repair in all organs. However, when the damage is severe or repetitive, ECM components continue to accumulate, resulting in disruption of tissue construction, organ dysfunction, and eventually organ failure [1,2]. Fibrosis is a heavy burden on the global healthcare system. After the coronavirus disease 2019 (COVID-19) epidemic, approximately one-third of patients experienced fibrotic lung abnormalities [3,4]. Fibrosis has long been considered progressive and permanent; however, preclinical models and clinical trials of various organ systems have demonstrated it as a complicated and dynamic process [5–7]. This has strong implications for therapeutic interventions aimed at exploiting inherent plasticity. Therefore, the discovery of key therapeutic targets with high relevance to human fibrotic disease and the subsequent development of effective treatments for fibrotic disease are a research priority.

Currently, extracellular vesicles (EVs) are referred to as heterogeneously secreted membrane-bound structures that play an important role in intercellular communication under both physiological and pathological conditions. Based on their features, EVs are classified into six categories: oncosomes, apoptotic bodies, exosomes, ectosomes, exomeres, and migrasomes [8]. These EVs have been reported to carry micro ribonucleic acid (microRNA), messenger RNA (mRNA), and proteins and transfer genetic information between cells [9]. Extensive research has indicated that EVs have a critical biological significance in the fibrotic process. Previous studies have reported that mesenchymal stem cell-derived extracellular vesicles are a promising therapy for cardiac repair to improve cardiac remodeling [10]. In addition, EVs from the serum of healthy individuals have antifibrogenic and antifibrotic effects, and EVs containing miRNAs have therapeutic effects in liver fibrosis [11]. A growing body of research has revealed that EVs containing microRNAs secreted by mesenchymal stem cells can attenuate the development of organ fibrosis, including liver, renal, and lung fibroses [10, 12–14]. In recent years, EVs have also played an essential role in cancer-associated fibroblasts, contributing to tumor development and chemoresistance [15,16]. EVs have emerged as important cell-derived particles in fibrosis progression. However, a comprehensive overview and dynamic analysis of the literature on EVs function and fibrosis remains lacking.

Bibliometric analysis is a mathematical and statistical research method that provides quantitative and qualitative results
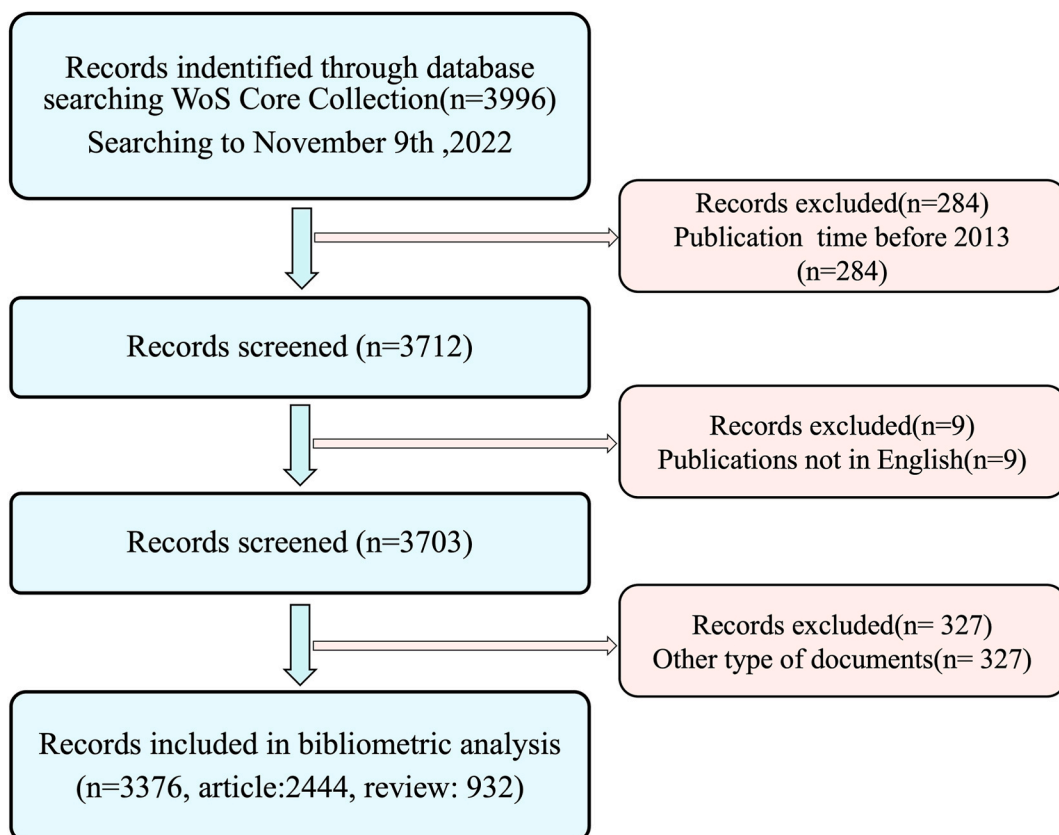

Fig. 1. Flowchart of this study.

demonstrating scientific production and effectiveness [17]. Through a bibliometric analysis, we can analyze and visualize different gradations of co-authorship, document co-citation, co-occurrence, emerging topics, thematic evolution, category assignment, and other bibliographic parameters [18]. Bibliometric analyses provide a general overview of a specific field, highlight the landscape of historical research, and provide recommendations for future studies.

Therefore, this study aimed to apply a bibliometric analysis of the literature published from 2013 to 2022 on the role of extracellular vesicles in fibrosis to provide new insights to guide the direction of future research and applications for fibrosis studies.

2. Materials and methods

2.1. Data source and search strategy

We conducted a literature search for Web of Science Core Collection (WoSCC) on November 9, 2022. The data collection and filtering processes are illustrated in Fig. 1. The main search formulas are as described below: TS = ("fibro*") AND TS = ("EVs" or "extracell*vesic*" or "exoso*" or "migrasome" or "exomere*" or "ectosome*" or "apoptotic bodies" or "apoptotic body" or "oncosome*"). The publication time span was set from 2013 to 2022, and the article language was filtered in English. Articles and reviews were the main publication types. Meeting abstracts, editorial materials, and proceedings papers were excluded. A total of 3376 refined literature were included in the bibliometric analysis. All information, including the number of papers and citations, keywords, titles, authors, journals, publication years, affiliations, countries, and references, were collected.

2.2. Bibliometric analysis

In this study, the VOSviewer (v.1.6.10), CiteSpace (v.6.1. R3), and the Bibliometrix Package (http://www.bibliometrix.org) based on R language (v.4.2.1) were used to conduct the bibliometric analyses. VOSviewer is a widely used software for constructing and visualizing bibliometric networks, developed by van Eck and Waltman of the Science and Technology Research Center of Leiden University in the Netherlands. VOSviewer can build three different types of visualization maps: network, density, and overlay visualization maps [19]. In this bibliometric analysis, VOSviewer was used to build co-institution, co-authorship, and co-occurrence visualization maps to determine general information on the extracellular vesicles in fibrosis. In the network visualization maps, nodes represent the items, and node size represents the occurrence of authors, institutions, and keywords. The larger the node, the greater the occurrence of the items. The distance between the nodes in the visualization indicates the relatedness of the items. The different colored points and lines represent different clusters, wherein the nodes and links in that cluster can be used to explain the theme's (cluster's) coverage of topics (nodes) and the relationships (links) between the topics (nodes) manifesting under that theme (cluster). The lines between the nodes represent the co-occurrence between items, and the line thickness between the nodes represents the linkage strength of co-institution, co-authorship, and co-occurrence of keywords. Additionally, an author keyword overlay visualization map was generated to understand the research hotspots and development trends of extracellular vesicles in the field of fibrosis. In the overlay visualization maps, the node colors represent the average publication dates of the words. Purple indicates the former publication date, and yellow indicates a later publication date.

The CiteSpace software, a mathematical analysis tool, was used to generate interactive visualizations of structural and temporal patterns and trends in the scientific field [20]. In this study, the CiteSpace software was used to analyze the citation burst of keywords and references, a timeline view of the top clusters of keywords, cited articles, and dual-map in the field of extracellular vesicles and fibrosis. Burst detection determines whether and when burstiness occurs, indicating emerging trends. The timeline view of the clusters presents the cited articles and keywords more clearly. The bold timeline indicates that the clustering topic was a popular topic during this period. The sizes of the tree rings on the timeline represent important references and keywords with high citation rates. Dual-map thematic overlays on a global map of science are a visual analytical method for analyzing, comparing, and contrasting the characteristics of publications. Each publication portfolio can be added as one layer of dual-map overlays over two related but distinct global maps of science: one for citing journals and the other for cited journals [21].

The online bibliometric analysis platform was applied to generate annual production and citations from 2013 to 2022 and a collaboration analysis of countries/regions. Biblioshiny was also applied to process a thematic evolution map and historiographic network in this work. Historiography path analysis analyzes topics and core authors/documents. Each article symbolizes a node which is cited by other papers. Each edge stands for a direct citation. Nodes and edges are plotted on an oriented graph, where the horizontal axis represents the year of publication.

3. Results

In this study, the research strategy of bibliometrix is presented in Fig. 1. In total, 3996 articles were retrieved, and 284 articles published before 2013 were excluded, followed by 9 non-English articles, and 317 articles whose article type was neither an article nor a review. Finally, 3376 refined studies were included in the bibliometric analysis.

3.1. Annual publication growth trend and social structure (relevant countries, institutions, and authors)

The number of articles retrieved from the WoSCC database was 3376, which were related to extracellular vesicles in the fibrosis data selection criteria from 2013 to November 9, 2022. As demonstrated in Fig. 2A, the number of publications on extracellular

vesicles in fibrosis increased steadily and gradually, with an annual growth rate of approximately 36.77 %. Moreover, the frequency of citations of these publications from 2013 to 2022 indicated a continuous upward trend during this period, and the number of citations of published articles peaked in 2015, illustrating that articles published in 2015 remarkably influenced the field of fibrosis and EVs. The production of the top five countries over time is illustrated in Fig. 2B. The most productive country in 2022 was China (n = 4131), followed by the United States of America (USA) (n = 2511), Italy (n = 874), Japan (n = 535), and Korea (n = 527). The USA demonstrated a greater growth rate until 2020 than China, although China surpassed the USA in terms of number of publications.
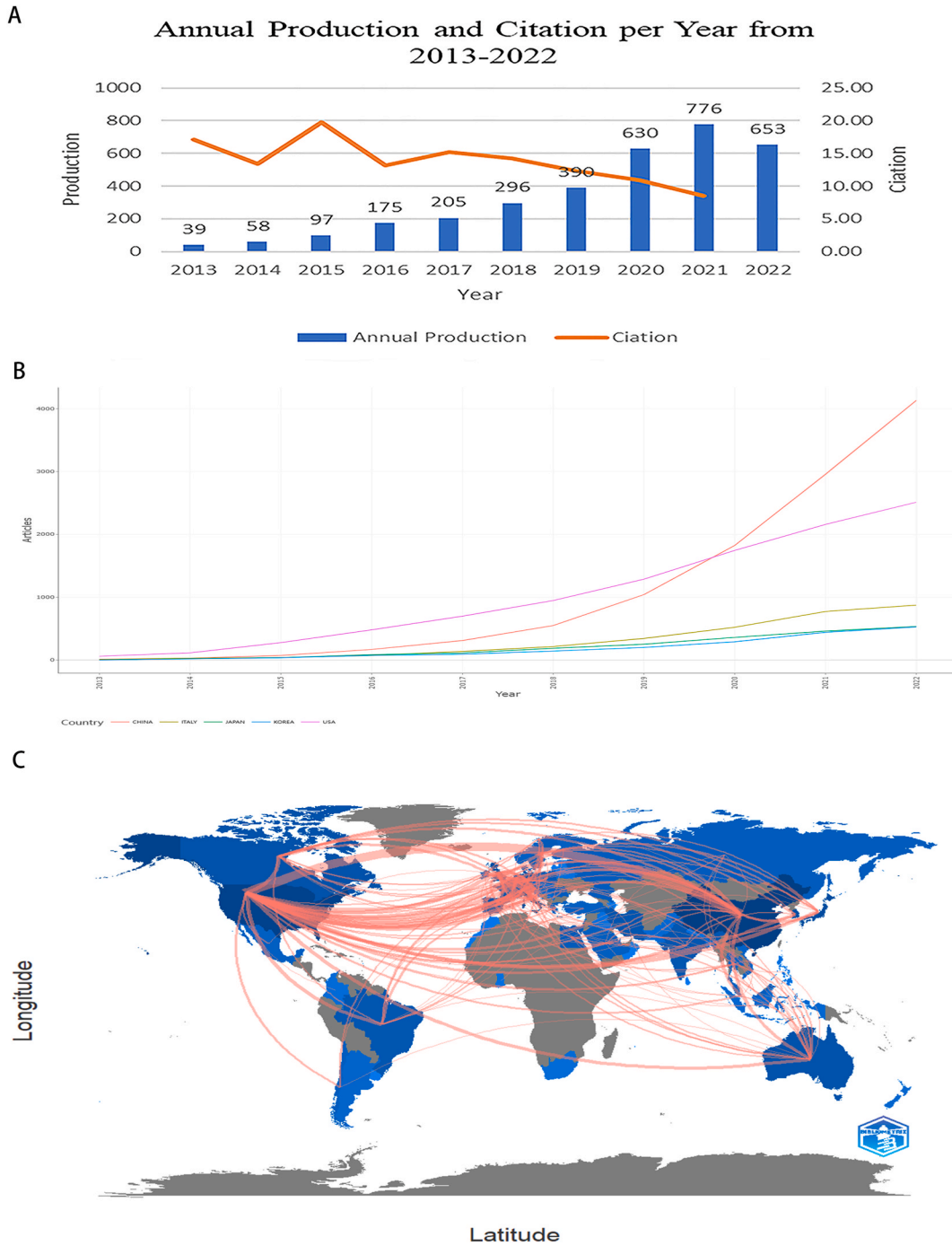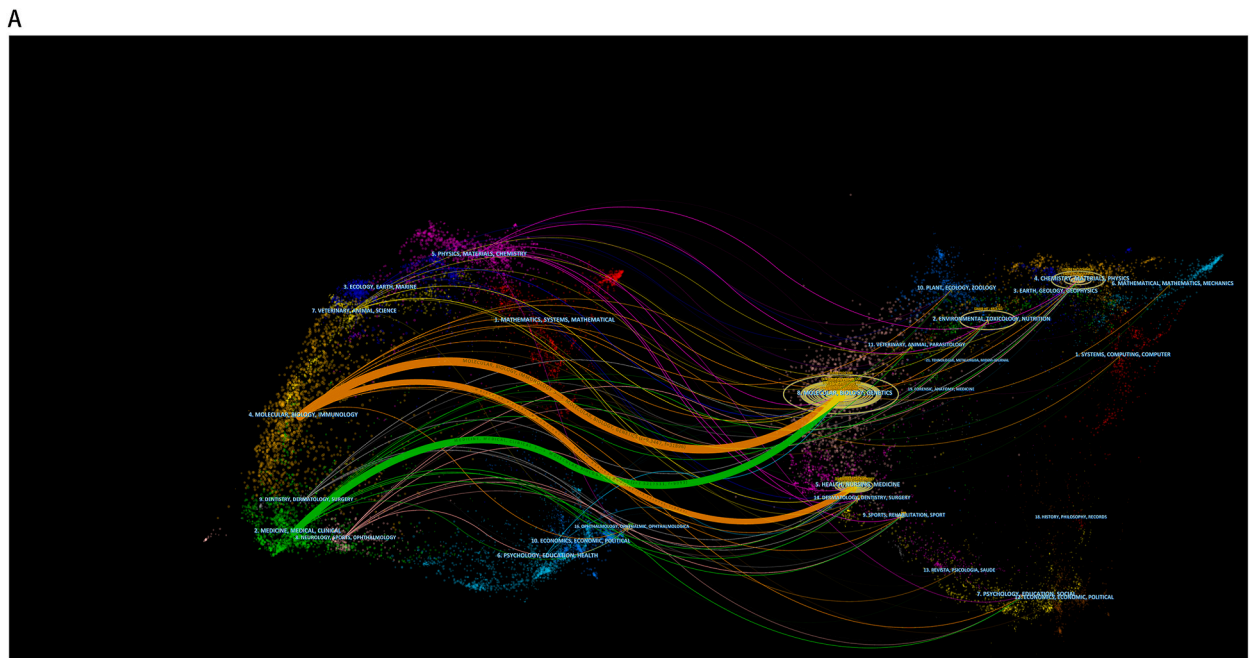

Fig. 2. general information (a) Annual Publication growth trend around the world. (b) Countries' Production over Time. (c) Collaboration WorldMap, countries' color represents their number of publications, thickness of the line revealed linkage strength between countries. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Fig. 3. (a) Co-institution in the field of extracellular vesicles associated fibrosis. (b) Co-authorship. Each color represents a thematic cluster, bubble size indicated occurrence of the entity, and thickness of the line revealed linkage strength between entities. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Moreover, the world map of collaboration among the 31 countries was also reflected in the country of production. In Fig. 2C, which an international collaboration map, collaborations between different countries are indicated by red lines. The thickness of the red line between the two countries indicates the extent of collaboration between the researchers from these two nations. Country colors represent the number of publications. The darker the blue, the more publications have been contributed by researchers in a specific country. Several countries have published articles on extracellular vesicles in fibrosis; however, most of the published articles were concentrated in a few countries. The largest number of works published in collaboration was between the USA and China (n = 172), Italy (n = 45), Japan (n = 30), the United Kingdom (n = 28), and Germany (n = 24).

Overall, 3447 organizations published papers in the area of extracellular vesicles in fibrosis, and 155 organizations published more than 10 documents. As demonstrated in Fig. 3A, the size of a bubble signifies the number of publications, and institutions with more published articles tend to present larger bubbles. The links between the two institutions indicate that they have published articles jointly. The bold lines indicate the strength of cooperation. Shanghai Jiao Tong University won first rank, publishing 101 papers, followed by Nanjing Medical University with 82 papers, Fudan University with 66 papers, Mayo Clinic with 63 papers, and Southern Medical University with 58 papers. In terms of collaboration, the Nanjing Medical University had a total link strength of 97. It is closely

Fig. 4. (a) Dual-map overlay of articles citing on extracellular vesicles in fibrosis research indicating the major research disciplines. (b) The top 25 references with the strongest citation bursts. References marked in red indicate a sharp increase in citation frequency during this period. Blue represents periods of relative unpopularity. (c) Historiographic parameters. Showing the historical evolution of the most-cited work. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

tied to Shanghai Jiao Tong University, with the highest link strength of 92.

To present the most productive authors, an individualized author-wise collaboration is demonstrated in Fig. 3B, which was analyzed using the VOSviewer software. Some useful insights emerged from this bibliometric analysis. In total, 161 authors were selected from 20274 authors by setting the baseline of the minimum number of documents of an author to five. Giovanni, who published 22 articles from the University of Torino, Italy, studied platelet-activating factors, stem cells, and EVs associated with liver fibrosis and inflammation, and had the strongest total link strength of 67. The primary collaborators were Bruno Stefania,(link strength with Camussi Giovanni, 12; total link strength, 45), Tepparo Marta (link strength with Camussi Giovanni, 11; total link strength, 38), and Grange Cristina (link strength with Camussi Giovanni, 11; total link strength, 28).

3.2. Co-cited references and the bursts citation of the reference

To analyze, compare, and contrast the characteristics of the publications, a dual-map overlay was generated using the CitesSpace software (Fig. 4A). The left side demonstrates the citing journal, the right side indicates the cited journal, and the line path demonstrates the citation relationships. In the field of extracellular vesicles of fibrosis, there are three main links: academic research results were mainly published in molecular, biology, and immunology journals, which are generally cited by molecular, biological, and genetic, journals and health, nursing, and medicine journals, and studies published in molecular, biological, and genetic journals were affected by references related to medicine, medical, and clinical field journals. Fig. 4B demonstrates the top 25 references that were the most productive and influential on extracellular vesicles in the fibrosis field. Among these references, we pay special attention to the highest strength reference "Extracellular vesicles: exosomes, microvesicles, and friends. – 2013" (strength 47.03) [22], which was an important indicator of extracellular vesicles fibrosis in 2013. Moreover, an article indicating that circulating tumor-derived exosomal integrins could be used to predict organ-specific metastasis and has been cited consistently for 4 years since 2015 [23]. In recent years, burst references have demonstrated that Tkach M et al. [24] and Yanez-Mo Mal et al. [25] have high citation strength, which both comprehensively summarized the function of EVs and demonstrated clear directions for future research.

The chronological tables highlight the most-cited works in and outside the collection. A historiographic analysis was performed to help scholars quickly identify the most significant work on this topic and trace its year-by-year historical development [26]. As presented in Fig. 4C, two research paths were identified. One path is around the authors Costa-Silva B et al. (2015), Hoshino A et al. (2015), Zhao HY et al. (2016), Yeung CLA et al. (2016), Richards Ke et al. (2017), Fang T et al. (2018) and Ren J et al. (2018) [15,16,23, 27–30], which is approximately extracellular vesicles and its role and impact on different diseases related to the fibrotic process. Another pathway is around Zhou Y (2013), Borges FT (2013), Li TF (2013), Zhang JY (2015), Fang S (2016), Hu L (2016), Wang B (2016), Qu Y (2017) [12,13,31–36], with publications on exosomes released from stem cell contributing to fibrosis in various pathophysiological processes.

To identify the clusters of cited articles more clearly, a timeline view of these twelve clusters is presented in Fig. 5. The axis represents the time span of the clustered references, the size of the bubble indicates the reference frequency, and the clustering topic is a hotspot during this period. The earlier study concerns were mainly devoted to "stroma," (cluster 0), "telocytes," (cluster 8), "paracrine factors," (cluster 9), "kidney disease," (cluster 10), and "non-coding RNA." (cluster 12). "Tumor microenvironment"
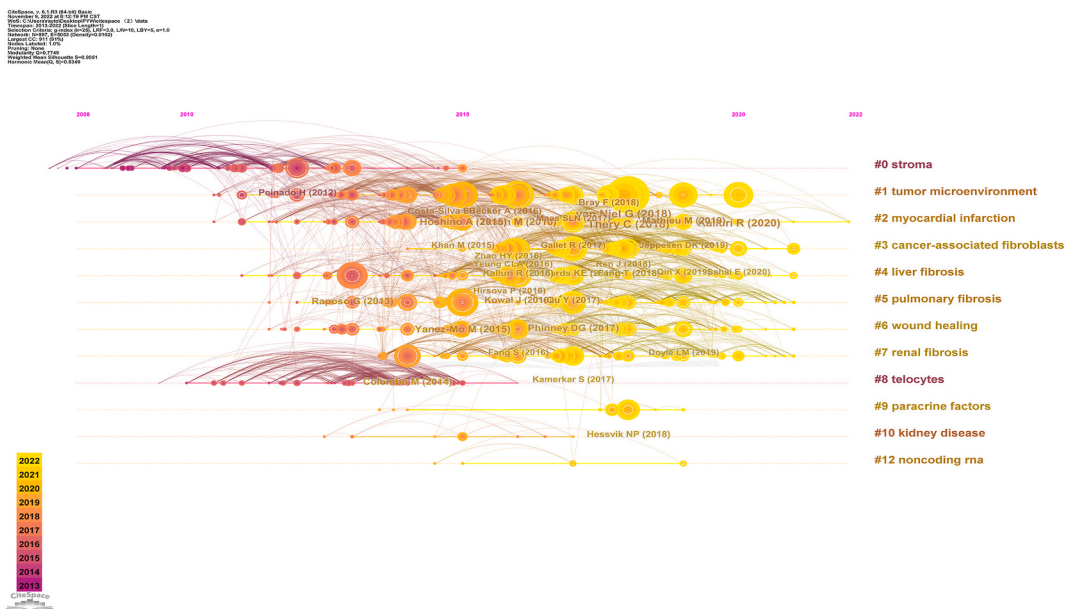
Fig. 5. Timeline view of the top 12 largest clusters of reference co-citation. Labels of clusters and main references were automatically generated by CiteSpace. Citation tree-rings of different sizes on the timeline represent key references with high citation rates. Right side = cluster labels.

(cluster 1) has been a hot topic since 2012, reaching its peak moment in 2018. Studies on "myocardial infarction," (cluster 2) first appeared in 2011 and made a robust comeback in 2018, "liver fibrosis," (cluster 4) and "pulmonary fibrosis," (cluster 5) have been an attention hotspot in academic research for a long time, while "wound healing," (cluster 6), "cancer-associated fibroblasts," (cluster 3), and "renal fibrosis" (cluster 7) were three emerging research fields in 2015 and has attracted increasing attention recently.

Fig. 6. (a) Co-occurrence. Each color represents a thematic cluster, bubble size indicated occurrence of the keyword, and thickness of the line revealed linkage strength between keywords. (b) Overlay visualization of thematic terms. The bubble colors indicated the average publication date of keywords. The purple color indicated the former publication date. The yellow color indicated later publication date. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. Keywords co-occurrence and burst citation of keywords

Keyword co-occurrence analysis examines the actual content of the publication itself. In the network map generated by VOSviewer divided into three clusters (Fig. 6A), larger nodes representing the keywords appeared more frequently, including "exosomes," "expression," "extracellular vesicles," "microRNA," "stem-cells," and "therapy" in the field of "extracellular vesicles and fibrosis" appeared more frequently. In addition, the keywords are overlaid with the timeline indicated by different colors in Fig. 6B; yellow indicates a more recent appearance, and blue represents the earlier emergence of keywords. The keywords "diagnosis," "survival," "circulating microRNA," "skin," "fibronectin," "tumor," and "colorectal cancer" were frequently appeared in approximately 2020. The keyword timeline map displays the evolution of high-frequency keywords in each cluster produced by CiteSpace, which considers time while clustering the keywords. As demonstrated in Fig. 7, the foci of "extracellular vesicles and fibrosis" at each stage and the evolution track are clearly displayed. The chronological order of keyword occurrences in each cluster can be observed. The smaller the number, the more nodes the cluster contains. Nine clusters were identified, including "cancer-associated fibroblast," "myocardial infarction," "mesenchymal stem cell," "cellular senescence," "skin regeneration," "rheumatoid arthritis," and "intervertebral disc." Fig. 8A illustrates a burst detection of the top 25 keywords in the recent decade, organized by the years of occurrence: the delicate blue grid from left to right represents the years from 2013 to 2022, and the bold red grid represents the years of the emergence of this keyword. The keywords of "membrane vesicles," "protein," "circulating microRNA," "microvesicles," "messenger RNA," "cancer cell," "exosome mediated transfer," "vesicles," and "lung telocyte" had been studied deeply from 2013 to 2019. Recently, some new keywords such as "recovery," "heterogeneity," "degradation," and "kidney disease" have drawn great interest from researchers, which can be extrapolated and may also become the hot keywords of these fields in the future. Moreover, similar to the burst results of keywords, Fig. 8B presents the evolution of the "extracellular vesicles" and "fibrosis" themes over time. Between 2014 and 2016, "cajal-like cells" and "interstitial cells" were associated with dominant themes such as the human heart and cardiac telocytes. Since 2016, another relevant component of exosome-mediated miRNA communication has been highlighted. Researchers' enthusiasm for gemcitabine, an important medicine related to EVs and fibrosis, began in 2017 and continuesto date. From 2020 to 2022, new themes were explored that were directly related to the extracellular vesical role in "pathogenesis," "injury," "inflammation," and "degeneration" procedures.

4. Discussion

This study provides a bibliometric analysis of "extracellular vesicles and fibrosis" from the publications from 2013 to 2022. Fibrosis has become a heavy burden on the global healthcare system, and the importance of EV-mediated intercellular communication under both physiological and pathological conditions is rapidly developing. Comprehending the extent of the "fibrosis and EVs" enables us to trail patterns and identify gaps, while also conferring a sense of membership to individuals who identify with the field. Therefore, understanding the relationship between EVs development and fibrosis is important. This study collected 3376 articles on EVs and fibrosis, analyzing all these studies through three multifunctional software programs, providing the researchers with an overview of the research field of EVs and fibrosis over the past decade and indicating the emerging trends in this research in the future.

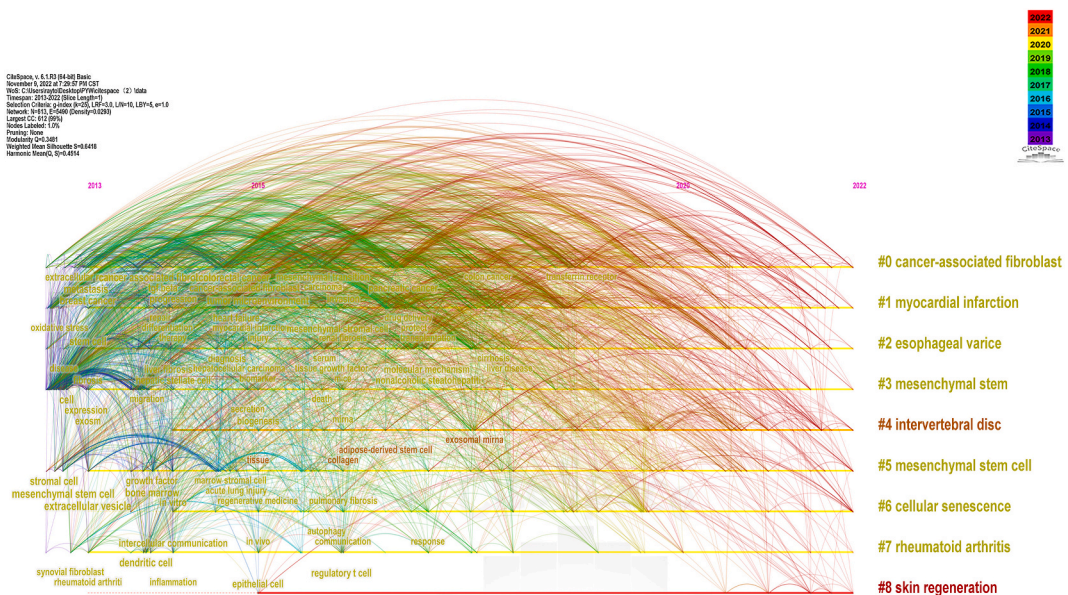**Fig. 7.** Timeline view of the top 12 largest clusters of keywords. Labels of clusters and keywords were automatically generated by CiteSpace. The chronological order of occurrence of keywords in each cluster can be found. The smaller the number, the more nodes the cluster contains. Right side = cluster labels.
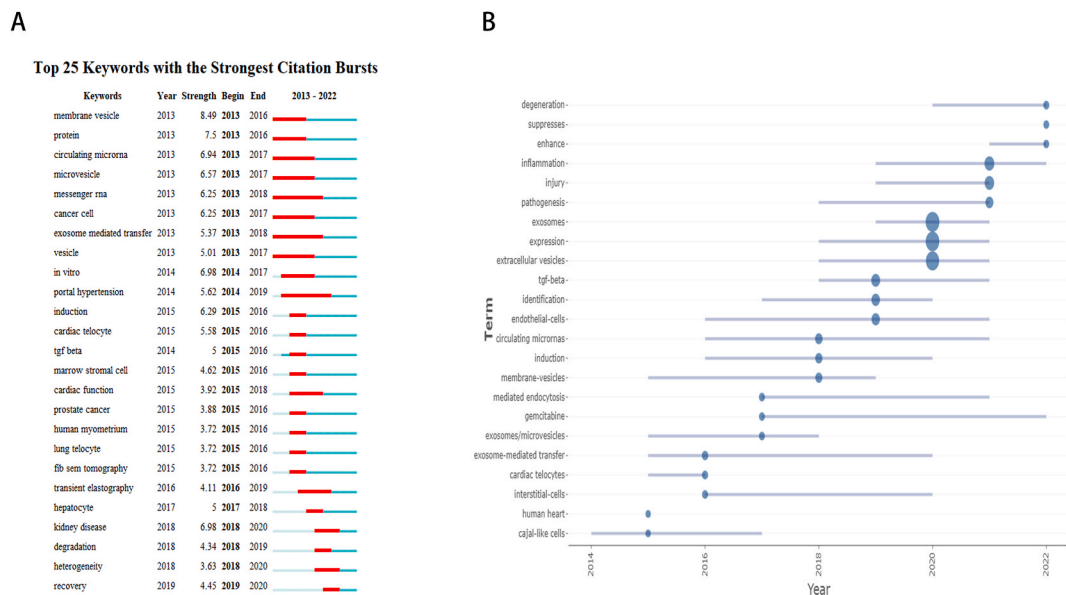
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Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2022
membrane vesicle	2013	8.49	2013	2016	
protein	2013	7.5	2013	2016	
circulating microrna	2013	6.94	2013	2017	
microvesicle	2013	6.57	2013	2017	
messenger rna	2013	6.25	2013	2018	
cancer cell	2013	6.25	2013	2017	
exosome mediated transfer	2013	5.37	2013	2018	
vesicle	2013	5.01	2013	2017	
in vitro	2014	6.98	2014	2017	
portal hypertension	2014	5.62	2014	2019	
induction	2015	6.29	2015	2016	
cardiac telocyte	2015	5.58	2015	2016	
tgf beta	2014	5	2015	2016	
marrow stromal cell	2015	4.62	2015	2016	
cardiac function	2015	3.92	2015	2018	
prostate cancer	2015	3.88	2015	2016	
human myometrium	2015	3.72	2015	2016	
lung telocyte	2015	3.72	2015	2016	
fib sem tomography	2015	3.72	2015	2016	
transient elastography	2016	4.11	2016	2019	
hepatocyte	2017	5	2017	2018	
kidney disease	2018	6.98	2018	2020	
degradation	2018	4.34	2018	2020	
heterogeneity	2018	3.63	2018	2020	
recovery	2019	4.45	2019	2020	

B

Fig. 8. (a) Top 25 keywords with the strongest citation bursts. Keywords marked in red indicates a sharp increase in the usage frequency of this keyword during that period. Blue represents a relatively unpopular time period. (b) Trend topics. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.1. General information

Our in-depth bibliometric analysis focused on extracellular vesicles and fibrosis research streams. This study aimed to investigate qualitative and quantitative variables, such as authors, citations, landmark publications, and trends in this field. From 2013 to 2022, in the WoSCC database, 3996 studies associated with EVs and fibrosis were published by 20274 authors from 3447 institutions. Several interesting insights emerged. For instance, the number of publications on extracellular vesicles in fibrosis increased steadily and gradually year by year with a 36.77 % growth rate, whereas the number of literatures in 2022 was lower than that in 2021, which may be caused by the search time, which was processed on November 9. Cooperation among countries plays an important role in analyzing the progression of EVs and fibrosis. The results revealed that China has the closest cooperative relationship with the United States, and the organization that published the most articles was Shanghai Jiao Tong University with 101 published papers, suggesting that researchers from the USA and China have the strongest financial support in terms of EVs and fibrosis, and these two countries are the most powerful countries in this academic research. This information can be helpful to scholars interested in determining suitable research platforms and experienced researchers in the field. The co-occurrence map of the authors revealed that Camussi Giovanni from the University of Torino, Italy, maintained a good and long-term cooperative relationship with his main collaborator, Bruno Stefania, indicating that this research team has great potential in this field and has received increasing attention. This information enables collaboration across periods, allowing researchers to revisit trajectories of intellectual development based on collaborative networks, while equipping prospective scholars with valuable information to connect and collaborate with established and emerging scholars in specific research fields.

4.2. References with citation burst

This study provides references and citation-related information in various ways. The benefit of using citation-related analysis is that in addition to identifying the most influential publications, scholars can also discover thematic clusters. In the field of extracellular vesicles in fibrosis, academic research results have mainly been published in the molecular, biological, genetic, health, immunology, and medical fields, and this information may help authors make better choices in selecting appropriate journals to publish their studies on EVs and fibrosis. Among these literatures, the highest strength reference is "Extracellular vesicles: exosomes, microvesicles, and friends. – 2013" (strength 47.03) which has an important influence on the extracellular vesicle research field from 2013 to 2018. In this review, the authors discussed and highlighted the experimental limitations that need to be resolved and characterize EVs and their possible functions, illustrating two ways of EVs' intercellular delivery of RNA and proteins by fusion or endocytosis [22]. In addition, EVs have diverse biological functions in intercellular communication, including promoting the differentiation of regulatory T lymphocytes [37], increasing proinflammatory cytokine secretion by pulmonary epithelial cells [38], and are involved in several types of central nervous system diseases [22]. Understanding the mechanisms underlying EVs is crucial for developing effective therapies for fibrotic diseases; therefore, many researchers have devoted considerable time and effort to studying and synthesizing advances in this field. In recent years, burst references have demonstrated that Tkach M et al. [24] and Yanez-Mo Mal et al. [25] had high citation strength. Tkach M et al. updated the most outstanding functions of EVs and highlighted the limitations of their physiological roles in

2016. Tkach M et al. reviewed the literatures demonstrating that tumor- and stroma-derived EVs promote cancer progression and metastasis in different stages and designed an in vivo visualization system, such as an intracellular probe to label mRNA secreted in EVs and tools to measure EV-borne mRNA, and EVs as a new container to transport miRNA and other non-coding RNA messages to target cells. These documents not only comprehensively summarize the current research status in this field but also inspire other scholars. Researchers hope to acquire more advanced technical knowledge and comprehend the various fundamental roles of each type of EVs in the near future.

A historiographic analysis was performed to help scholars quickly identify the most significant work on this topic and trace it. Historiography has several aspects, and it is particularly valuable for researchers who wish to seek a place for their studies in the context of other historians' research on a particular topic. One path was around author Costa-Silva B et al. (2015), Hoshino A et al. (2015), Zhao HY et al. (2016), Yeung CLA et al. (2016), Richards Ke et al. (2017), Fang T et al. (2018), and Ren J et al. (2018). Previous studies have reported that pancreatic ductal adenocarcinoma-derived exosomes containing macrophage migration inhibitory factors may be prognostic markers for the development of pancreatic ductal adenocarcinoma liver metastasis [27]. Two years later, Richards Ke et al. demonstrated that cancer-associated fibroblasts (CAF) exosomes played an essential role in chemotherapeutic drug resistance in pancreatic ductal adenocarcinoma [29]. Meanwhile, Hoshino A et al. discovered that exosomal integrins α6β1 and α6β4 were linked to lung metastasis, whereas exosomal integrin αvβ5 was associated with liver metastasis. Moreover, clinical data suggest that exosomal integrins could be prognostic markers for organ-specific metastasis [23]. Subsequently, the Zhao HY et al. study provided convincing evidence that cancer-associated fibroblasts-derived exosomes (CDEs) contain intact metabolites, including lipids, amino acids, and tricarboxylic acid cycle (TCAcycle) intermediates, which are utilized by cancer cells for central carbon metabolism and promote tumor growth under malnutrition conditions [30]. Furthermore, Yeung CLA et al. revealed that microRNA-21 in exosomes derived from cancer-associated adipocytes (CAAs) and cancer-associated fibroblasts (CAFs) could be transferred to cancer cells, where it suppresses ovarian cancer apoptosis and confers chemoresistance through APAF1 in advanced ovarian cancer [28]. In 2018, both Fang T et al. and Ren J et al. demonstrated that the intercellular crosstalk between tumor cells and fibroblasts is mediated by tumor-derived exosomes, which contribute to tumor development and chemoresistance [15,16]. All these significant works were on extracellular vesicles and their role and impact on different disease processes. EVs secreted by CAFs act as cargo molecules carrier for intercellular communication and play a crucial role in tumor metastasis and resistance to chemotherapeutic drugs. Researchers are currently investigating the underlying mechanisms associated with integrins and APAF1. These studies hold significant clinical value for identifying biomarkers for the early detection and diagnosis of tumor diseases. The other path was approximately Zhou Y et al. (2013), Borges FT et al. (2013), Li TF et al. (2013), Zhang JY et al. (2015), Fang S et al. (2016), Hu L et al. (2016), Wang B et al. (2016), Qu Y et al. (2017) [7,8,26–31]. Borges FT et al. published an article on fibroblast being activated by TGF-β1 mRNA transported by exosomes which contributed to tissue repair/regenerative responses in a kidney resident parenchyma injury model [31], and Wang B et al. results are further proof of exosomes as an important carrier to attenuate renal fibrosis [13]. Other researchers have also demonstrated that mesenchymal stem cell-secreted exosomes can heal cisplatin-induced acute kidney injury by ameliorating oxidative stress and cell apoptosis [32], suggesting that transferring miR-181-5p via exosomes secreted by adipose-derived mesenchymal stem cells could be a potential clinical application in liver disease [35]. In addition, human adipose-derived mesenchymal stem cells could also promote collagen synthesis and angiogenesis to aid cutaneous wound healing [33,34]. However, mesenchymal stem cells secreted exosomal microRNA could suppress myofibroblast formation through negativing the transforming growth factor-β2/SMAD2 pathway to prevent scarring [36]. All the above-mentioned publications demonstrate that exosomes released from stem cells contribute to fibrosis in various pathophysiological conditions and could be an impending clinical treatment method. Transformative experimental strategies are being leveraged to dissect the key cellular and molecular mechanisms by which EVs regulate fibrosis, enabling translational approaches to deliver precise medical treatments to patients with fibrosis.

4.3. Emerging topics

Our analyses also highlighted the importance of the pathophysiological and differentiation states of EVs, which affect downstream treatment reactions and therapeutic consequences. EVs play significant roles in various biological processes, including immune responses, oxidative stress, migration, cancer progression, cardiovascular diseases, and tumor metastasis. These small vesicles transport proteins, metabolites, and nucleic acids to recipient cells, leading to significant changes in their biological response [39–41]. In accordance with the historiographic analysis results, the timeline view of the largest clusters of citing articles and keyword citation bursts can reflect the evolution and emerging trends in the academic field.Previous understanding of the biological activities of EVs has primarily been based on tissue cultures generated from stromal cells, endothelial cells, and mesenchymal stem cells. EV research remains restricted by current experimental limitations in single-particle isolation and detection and the lack of reliable resolution for imaging and tracking EVs in vivo [42]. Recently, EVs derived from cancer-associated fibroblasts have received much attention because of their distinctive role in early detection and diagnosis, and accumulating evidence suggests that the cargo molecules carried by EVs facilitate the identification of specific biomarkers for diagnosing cancer and improving treatment outcomes [43,44]. More co-cited references were transferred from EV microstructure to EV-associated fibrotic disease and finally to EV-related treatment functions in clinics from 2013 to 2022. For example, the combination of nanotechnology and EVs may offer tremendous opportunities to develop new nanomaterials that will change the way we live, particularly in the field of next-generation theranostic nanoplatforms [45]. These academic advances have promoted studies onEVs and fibrosis and provided new directions for researchers.

Keywords reflect the core themes and main content of publications and a keywords timeline map displays the evolution of high-frequency keywords in each cluster. Therefore, they can provide an appropriate description of the research focus, which could help us easily identify the period of a particular topic and the evolution track of our research field. interest.For instance, the keywords

timeline map "#2 esophageal varice" cluster is associated with "cirrhosis," "hepatocellular carcinoma biomarker," and "diagnosis," suggesting that EVs may be a potential biomarker for early diagnosis of cirrhosis, and may be beneficial in reducing the incidence of complications of esophageal varices. Most studies have focused on mesenchymal stem cell-derived extracellular vesicles, and the efficient communication of cellular components through EVs implies their practical use in designing EV-based therapeutics. Previously, proteomic data demonstrated that exosomes have positive effects against autoimmunity and perform immunosuppressive functions in rheumatoid arthritis [46]. Exosome-based detection methods have potential value in the diagnosis and prognosis of patients with cancer and other diseases [45].For instance, many recent studies have implied that extracellular vesicles can be used as an emerging treatment method for intervertebral disc degeneration [47–49]. The viewer can easily determine the period of a particular topic and the evolutionary track of the research field of interest.

Trends in different key areas of research can be identified to make better research choices. A burst term refers to keywords cited more frequently than the average value of a period, which can indicate the frontier of the research field. The keywords "recovery," "heterogeneity," "degradation," and "kidney disease" have drawn great interest from researchers in recent years, indicating that the important role of EVs in degenerative and inflammatory diseases is emerging, which can be extrapolated and may also become the popular keywords of these fields in the future. For instance, accumulating evidences demonstrated great interest in the application potential of MSC-derived EVs in the field of skin regeneration. Recent studies have suggested that treatment with MSC-derived EVs can significantly inhibit scar formation by affecting angiogenesis-related and antifibrotic pathways; promoting macrophage polarization, wound angiogenesis, cell proliferation, and cell migration; and inhibiting excessive extracellular matrix production [50–52]. Moreover, trend topics demonstrate the evolution of the "extracellular vesicles" and "fibrosis" theme over time. From 2020 to 2022, new themes directly related to the extracellular vesical role in "pathogenesis," "injury," "inflammation," and "degeneration" procedures were explored. Therefore, the change in the knowledge structure of EVs and fibrosis research is clearly demonstrated; emerging topics are concentrated on the extracellular vesicles as a promising next-generation clinical treatment strategy for various diseases such as cancer, degenerative diseases, and fibrosis because of their ability to weaken chronic inflammation, attenuate apoptosis, and stimulate proliferation in multiple tissue systems. Although impressive progress has been made in our understanding of the pathogenesis of fibrosis in recent years, several challenges must be overcome to translate this information into effective antifibrotic therapies. The decisive advantage of EVs is that their natural release remains stable and retains their full binding effect [53,54]. For successful clinical applications, cell-derived therapeutic EVs should maintain high standards of quality control, including sufficiently high purity and containing appropriate cargo and surface molecules, to guarantee effectiveness for the intended patients. Therefore, research has focused on the discovery of highly relevant therapeutic targets for human fibrotic diseases, and the development of effective antifibrotic therapies targeting these targets remains a priority.

4.4. Strengths and limitations

To the best of our knowledge, this study is the first to review the literature of extracellular vesicles and fibrosis from 2013 to 2022 using a bibliometric analysis. The present study provides insights into the current vital challenges and research trends that require further study in this scientific area, based on published work. Thus, scholars can better comprehend the latest developments and hot topics in a particular field. This study has the potential to substantially improve our understanding of the basic biology of exosomes and fibrosis and their use in clinical and biological technology. However, this study has some limitations. On the one hand, to ensure the quality of publications, only the database "WoSCC" was searched, and other related information may be leaked, which may result in the analysis having cognitive bias. On the other hand, the quality of documents was not considered, and hotspots were produced based on the high frequency of keywords, which may result in incomplete analysis results.

5. Conclusions

Bibliometrics allows us to define a field by identifying relevant journals, articles, authors, and topics. Comprehending the extent of the "fibrosis and EVs" field empowers scholars to observe trends and pinpoint areas that need attention. Based on the quantitative analysis of "extracellular vesicles and fibrosis" from 2013 to 2022, we identified China and Shanghai Jiao Tong University as the country and institution with the highest number of publications, respectively. The most cooperative team is Camussi Giovanni's team. Journals on molecular, biology, genetics, health, immunology, and medicine are more interested in publishing literature related to EVs and fibrosis. Finally, we thematically analyzed the publications and identified key topics and the most cited publications. We identified that "recovery," "heterogeneity," "degradation," "inflammation," and "mesenchymal stem cells," are associated with several disease fields including "kidney disease," "rheumatoid arthritis," and "skin regeneration," which may be the latest hot research field. Based on the reference with the strongest citation burst results, the articles "Tkach M [24] and Yanez-Mo M [25]" may deserve more attention. Based on these bibliometrics findings, we provide a systematic and holistic overview of the "fibrosis and EVs" field and hope to inspire researchers to further advance this exciting field.

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Data availability statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Ya-Wen Peng: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Ri Tang:** Software, Methodology, Data curation. **Qiao-Yi Xu:** Supervision, Software, Funding acquisition. **Shu-Ya Mei:** Supervision, Project administration, Methodology. **Yang Zhou:** Software, Methodology. **Jin-Hua Feng:** Software. **Shu-Yi Zhang:** Writing – review & editing, Supervision, Data curation. **Zheng-Yu He:** Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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