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ORIGINAL RESEARCH

A Bibliometric Analysis of Mesenchymal Stem Cell-Derived Exosomes in Acute Lung Injury/Acute Respiratory Distress Syndrome from 2013 to 2022

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Background: Mesenchymal stem cell-derived exosomes (MSC-exosomes) have been found to effectively improve the systemic inflammatory response caused by acute lung injury and acute respiratory distress syndrome (ALI/ARDS), regulate systemic immune disorders, and help injured cells repair. The purpose of this study was to take a holistic view of the current status and trends of MSC-exosomes research in ALI/ARDS.

Methods: Bibliometrix, Citespace and VOSviewer software were used for bibliometric analysis of the data. We analysed the world trends, country distribution, institution contribution, most relevant journals and authors, research hotspots, and research hotspots related to Coronavirus Disease 2019 (COVID-19) based on the data collected.

Results: China possessed the largest number of publications, while the USA had the highest H-index and the number of citations. Both China and the USA had a high influence in this research field. The largest number of publications in the field of MSC-exosomes and ALI/ARDS were mainly from the University of California system. Stem Cell Research & Therapy published the largest number of papers in this scope. The author with the greatest contribution was LEE JW, and ZHU YG published an article in Stem Cell with the highest local citation score. The most frequent keyword and the latest research hotspot were "NF-κB" and "Coronavirus Disease 2019". Furthermore, our bibliometric analysis results demonstrated that MSC-exosomes intervention and treatment can effectively alleviate the inflammatory response caused by ALI/ARDS.

Conclusion: Our bibliometric study suggested the USA and China have a strong influence in this field. COVID-19-induced ALI/ARDS had become a hot topic of research.

Keywords: acute respiratory distress syndrome, mesenchymal stem cells, exosome, bibliometrix, Citespace, VOSviewer

Introduction

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) are common clinical syndromes in critically ill patients with high morbidity and mortality. ALI/ARDS is characterized by diffuse damage to alveolar epithelial cells and capillary endothelial cells.[1,2] ALI/ARDS can be caused by sepsis, trauma, inhalation of gastric contents and intrapulmonary and extrapulmonary pathogenic factors in addition to cardiogenic factors.[3,4] In recent years, mesenchymal stem cells (MSCs) have been found to effectively improve the systemic inflammatory response caused by ALI/ARDS, regulate systemic immune disorders, and help injured cells repair.[5,6] MSCs-derived exosomes (MSC-exosomes) are membranous vesicles with a diameter of 30–150 nm, that play a key role in regulating inflammation and immune response and repairing damaged cells.[7–9] In a number of basic experiments, MSC-exosomes has already made progress in studies of heart, liver, lung and bone diseases.[10–13] In addition, a number of clinical trials are underway, for example, using

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exosomal nebulised inhalation to treat patients with COVID-19 and using exosomes to treat scars.[14–16] Therefore, it is of great significance to quantitatively analyze the research progress, development findings and future prospects of MSC-exosomes in ALI/ARDS.

Bibliometrics is one of the active professional fields in current international library intelligence research and information management.[17] It can conveniently analyze the distribution structure, quantitative relationship, change rule and quantitative management of publication based on the literature in the database.[18,19] Citespace and VOSviewer are computer software that can be used to view and construct bibliometric analysis network maps.[20] At present, bibliometric analysis has been widely applied in various medical research fields.[21] However, bibliometric studies on MSC-exosomes in ALI/ARDS are still scarce. Therefore, this study focused on the research status and hotspot of MSC-exosomes in ALI/ARDS.

Materials and Methods

Data Source and Search Method

Science Citation Index Expanded of Web of Science Core Collection, developed by Thomson Scientific, was used for data collection and data analysis. In order to avoid any deviation due to time, the data collection was set as June 8, 2023 and all data collection was completed on this day. The keywords searched were TS= ((mesenchymal stem cells) OR (mesenchymal stem cell)) AND TS= (exosomes OR exosome OR (extracellular vesicles) OR (extracellular vesicle) OR EVs) AND TS= ((ALI) OR (ARDS) OR (acute lung injury) OR (acute respiratory distress syndrome) OR (respiratory distress syndrome)). The period of publication was 2013–2022. The publication types were articles and reviews. The language of publication is English. These keywords were reasonably translated from Web of Science. Two researchers each performed data search and cleaning, and discussed the controversial document. We excluded documents where the search terms did not all appeared in the title, abstract, or author keywords. In addition, studies not related to the research topic after browsing the titles and abstracts were also excluded. Through the above search, we finally identified 181 articles (Figure 1).

Data Collection and Cleaning

First, we exported the collected database data. The exported information was the full record and referenced references (including title, keyword, author, institution, country, source, reference, etc.). The format was TXT. We then manually reviewed the exported files to eliminate possible factors that might lead to inaccurate analysis in order to make sure that most of the raw dates are reliable. Finally, we imported the original data into the Bibliometrix package from R (Version X64 4.0.5), Citespace (Version 5.8.R3) and VOSviewer (Version 1.6.16). It was worth noting that, before using VOSviewer for co-citation analysis and keyword analysis of data, we combined partial words with repeated or similar meanings in the original data through VOSviewer thesaurus file, and removed the words with no actual meaning but repeated with high frequency (a, The, etc.).

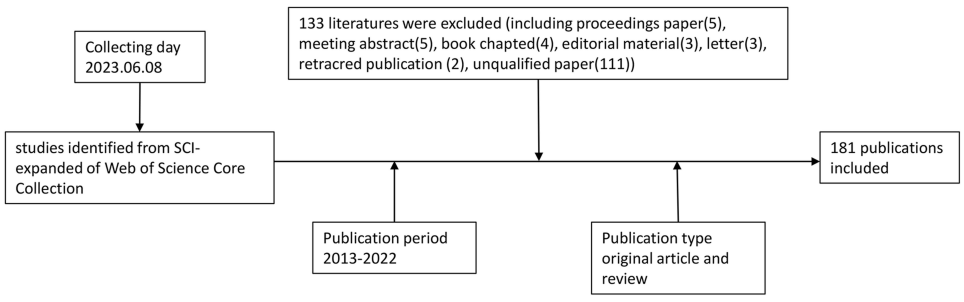


Figure 1 Data Collection Process.

Data Analysis

The Impact Factor (IF) is a measure used to evaluate scientific journals and represents the average number of times that a journal has published articles in the Science Citation Index. With the development of science, it cannot well reflect the academic achievements of a researcher.[22,23] Bibliometric analysis is a quantitative analysis method, the main two indicators are the number of publication (Np) and the number of no self-citation (Nc). Np represents the total number of published literatures, while Nc indicates the influence of published literatures.[24,25] As an indicator to evaluate the innovation degree of a publication in a certain field, local citation score (LCS) can also represents its Nc value.[26] The LCS is the number of times a collected article has been cited by other literature in the collected literature. H-index plays an increasingly important role in evaluating the academic achievements of a scientific researcher in recent years. It is defined as when an author has published H articles that have been cited at least H times, the author's H-index is H. H-index also now more and more be used to evaluate a journal, an institution, or the level of a country or a region scientific research.[27,28] Most of these values can be obtained from the analytical search results and citation analysis provided by Web of Science.

Bibliometrix is a workflow for bibliometric analysis written on the basis of R.[29] It can carry out automatic analysis of data source information such as author, country or region, institution and journal, and is compatible with other operations based on R.[30]

Citespace and VOSviewer are free software that can build visual maps for bibliometric analysis,[20] which can well show the strength of the internal connection between original data and divide it into different clusters.[31] In this study, the software were used to analyze and visualize the co-citation and keyword co-occurrence of references, so as to illustrate the current situation and hotspot of ALI/ARDS and MSCs-exosomes research.

Results

Analysis of Annual Publication Quantity and Growth Trend

Figure 2 shows the annual publication of MSC-exosomes and ALI/ARDS. Generally, the annual publication increased steadily with fluctuations in the past decade, rising from 0 papers in 2013 to 54 papers in 2021. The number of annual studies published was at a high level in the last four years, and the growth rate increased significantly. These results suggested that MSC-exosomes in ALI/ARDS has received attention, and an amount of researchers are conducting related studies.

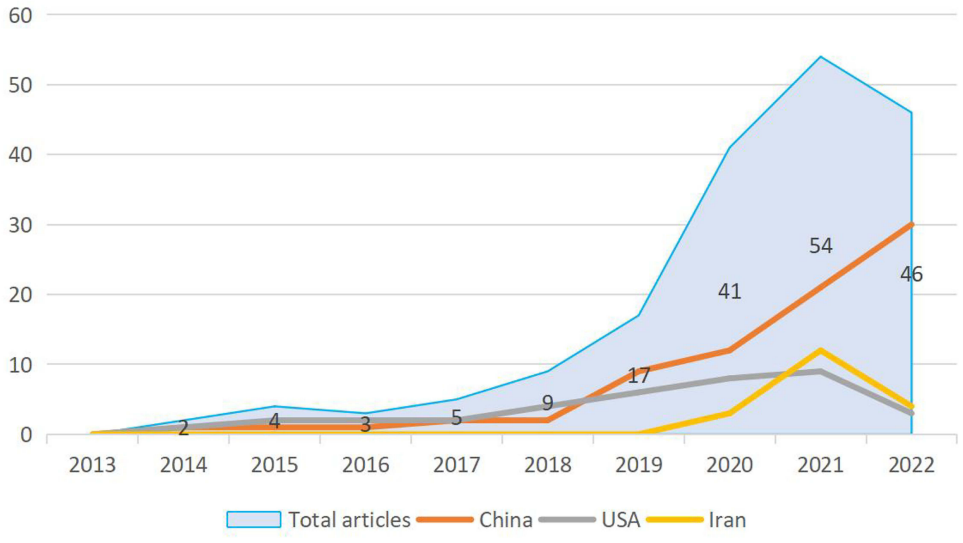


Figure 2 Publication published per year in the last ten years.
Abbreviation: Np, number of publications.

Countries/Regions Distribution Analysis

We ranked the total number of publications in the author's country or region. As shown in Table 1, China had the largest number of articles (79), followed by the USA (39) and Iran (19). China, a developing country in these top 10 countries, ranked first, indicating its great progress in medicine and life sciences during the past decade. The distribution is illustrated on the world map (Figure 3A). The darker the color indicates a greater number of articles published. The map showed that two regions, North America and East Asia, published most of the articles. In addition, India had 10 articles, Canada had 8 articles, and North Ireland, Italy and Spain all had 7 articles. Based on the bibliographic data collected from Web of Science, all articles related to MSC-exosomes and ALI/ARDS were cited 5327 times. Specifically, papers from the USA were cited 2626 times, followed by China (2110) and North Ireland (607).

At the same time, the H-index of the USA was the highest (24), followed by China (23) and Iran (11) ranks third (Table 1). The H-index of the USA was approximately 6 times higher than that of Italy and England. This result indicated that the USA was a country with relatively high quality and high output in this research field. Vosviewer automatically analysed the cooperation between countries (Figure 3B). China cooperated with 10 countries in this field, while the United States cooperated with 24 countries in this field. And the cooperation between China and the USA is the most numerous. The articles from the USA were obviously of higher quality and more innovative than those from other countries. This may be attributed to the close cooperation between the USA and other countries.

Institution Analysis

Table 2 listed the top 10 institutions with the largest number of publications in the field of MSC-exosomes and ALI/ARDS. The University of California System had the highest Np (14), followed by Shahid Beheshti University of Medical Sciences (8) and Queen's University Belfast (7). Similarly, the Nc and H-index of the University of California System ranked first, with 1473 and 12, respectively. China had 7 institutions in the top 10 institutions. This means that China is innovating in this field, but more effort is needed.

Author Analysis

We ranked the top 10 most productive authors in MSC-exosomes and ALI/ARDS research scope. In Table 3, all the top 10 authors contributed a total of 28 publications, making for 15.47% of the total. LEE JW was the leading productive author in this research field (11), followed by HAO Q with 6 articles. LEE JW and MATTHAY MA came from the USA, and HAO Q came from China, while their H-index ranked in the top 3. Meanwhile, the position was the same in terms of Nc, with LEE JW (1340) ranking first, followed by MATTHAY MA (1045) and HAO Q (1026). Meanwhile almost half of the top 10 most productive authors were from China. But they ranked relatively low.

In addition, we used Vosviewer to investigate the mutual cooperation between authors (Figure 4). The software automatically classified the authors into 9 clusters. Apparently excluding the red and green clusters, the other clusters exhibited a relative state of isolation from each other. Of the authors appearing in Table 3, 7 authors were in the red and

Table 1 The Top 10 Most Productive Country/Region

Rank	Country/Region	Np	Nc	H-Index
1	China	79	2110	23
2	USA	39	2626	24
3	Iran	19	312	11
4	India	10	212	5
5	Canada	8	241	6
6	North Ireland	7	607	7
7	Italy	7	96	4
8	Spain	7	68	5
9	Brazil	6	187	5
10	England	6	94	4

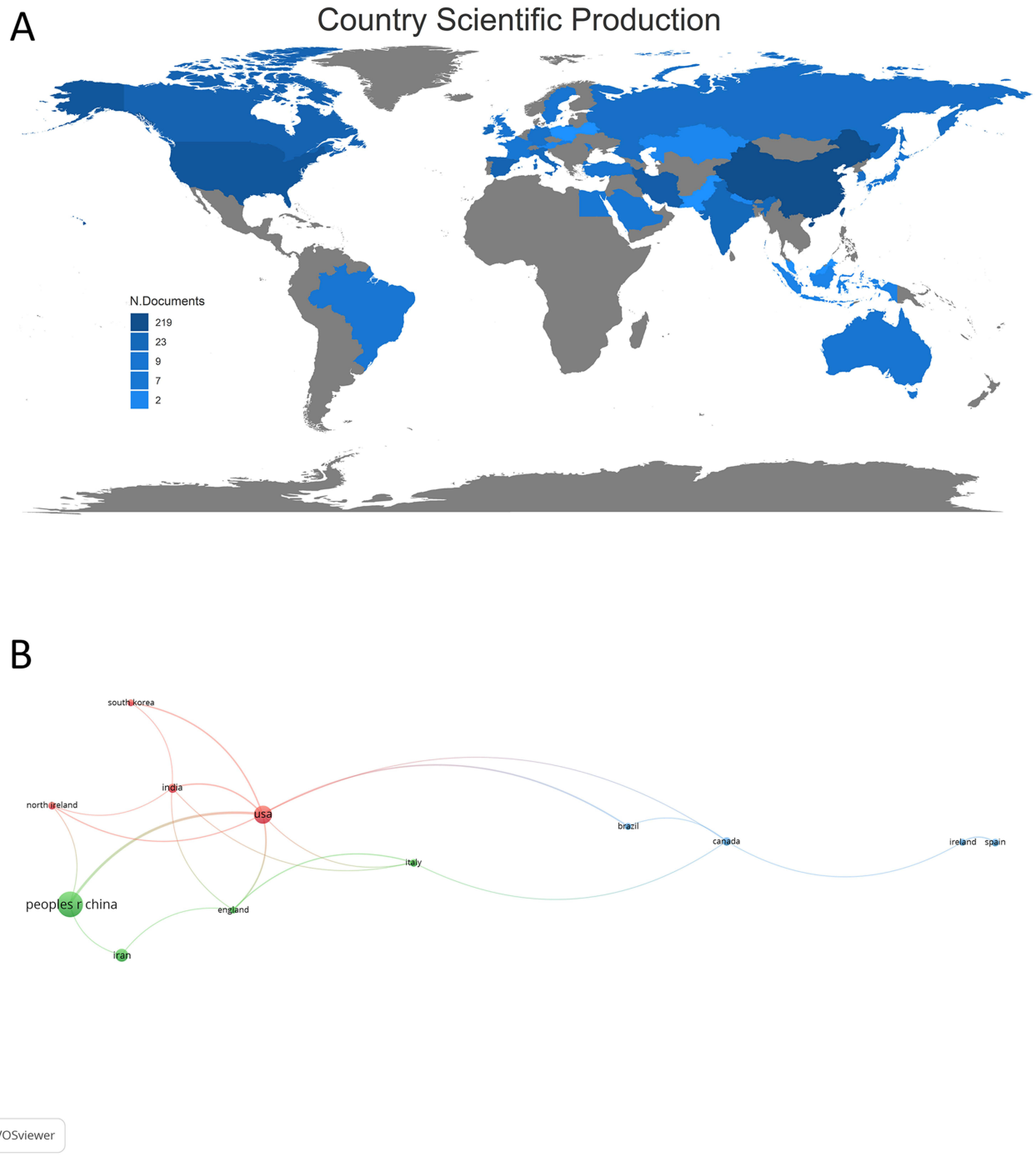


Figure 3 Relationship between publications and countries. (**A**) Geographical map of total publications in different countries or regions. (**B**) Visual network analysis of country relations. N. Documents: Number of Documents published (multiple authors of the same article are counted by author).

green clusters. They worked collaboratively and contributed a large number of high quality scientific articles. It also showed that China and the United States are working more intensively together in this area than other countries.

Journal Analysis

Approximately 53 papers within the scope of MSC-exosomes and ALI/ARDS were published in the top 10 journals (Table 4). The number of papers published on Stem Cell Research & Therapy (IF: 8.088) was the highest with 12 articles in this field, followed by Cells (7 articles, IF: 7.666) and Stem Cell Reviews and Reports (7 articles, IF: 6.692). In addition,

Table 2 The Top 10 Most Productive Institutions

Rank	Institution	Country/Region	Np	Nc	H-Index
1	University of California System	USA	14	1473	12
2	Shahid Beheshti Univ Med Sci	Iran	8	121	7
3	Queens University Belfast	North Iceland	7	607	7
4	Shanghai Jiao Tong University	China	7	569	65
5	China Med Univ	China	7	29	2
6	Fudan Univ	China	6	682	5
7	Anhui Med Univ	China	6	115	5
8	Sun Yat Sen University	China	5	308	5
9	Zhejiang Univ	China	5	187	4
10	Cent South Univ	China	5	75	3

Table 3 The Top 10 Most Productive Authors

Rank	Author	Country/Region	Np	Nc	H-index
1	Lee JW	USA	11	1340	9
2	Hao Q	China	6	1026	6
3	Matthay MA	USA	5	1045	5
4	Monsel A	France	5	969	5
5	laffey jg	Ireland	5	116	4
6	Zhu Yg	China	4	907	4
7	Hu SL	China	4	496	3
8	Zhou L	China	4	114	3
9	Xiao K	China	4	85	3
10	Nie HG	China	4	3	1

Stem Cells showed the highest Nc (861), even though it was ranked sixth. The journal Stem Cell Research & Therapy ranked first based on the Nc (476). Although the journal CELLS ranked third in Np, its Nc was only 73. It is worth noting that Stem Cell Research & Therapy also had the highest H-index (8), followed by Stem Cell Reviews and Reports (6).

In the dual-map overlay on the topic of MSCs-exosomes in ALI/ARDS (Figure 5), each dot on the map represented a journal. The map was divided into two sections, with the citing journals on the left and the cited journals on the right. The two most prominent lines represent the most significant citation routes. Studies published in Molecular, Biology, Clinical Medicine and immunology tended to be cited in Molecular, Biology and Genetics.

Local Citations Analysis

Figure 6 lists the top 10 most cited local papers. Zhu YG published an article in Stem Cells with the highest LCS (78). By constructing an Escherichia coli endotoxin-induced ALI/ARDS model of mice, he confirmed that exosomes derived from human MSCs could play a therapeutic role in injured alveoli by expressing keratinocyte growth factor (KGF).[32] Morrison, T.J,[33] Monsel, A.[34] and Khatri M.[35] further studied the possibility of using MSC-exosomes to treat ALI/ARDS caused by different pathogenic factors, thus obtaining a higher LCS. Song, Y.[36] and Park, J.[37] explored and confirmed that pretreatment with MSC-exosomes could attenuate ALI/ARDS. Cruz, F.F.[38] found that human-derived and mouse-derived MSCs-exosomes differ in the mechanisms that reduce lung inflammation. These studies, taken together, build on previous pioneering research and, despite their different directions, all succeed in enriching the research on MSC-exosomes in the field of ALI/ARDS.

Sources of MSCs Analysis

MSCs are adult stem cells isolated from different sources, and we manually compiled these data from 63 original articles. Because 2 articles analyzed MSCs from two different sources simultaneously, our final total number of articles was 65.

Figure 4 Visual network analysis of author relationships.

As shown in Figure 7A, we counted the different sources of species. Human-derived MSCs accounted for 57% (37), ranking first, followed by mouse-derived MSCs (26%, 17). In terms of tissue sources results (Figure 7B), bone marrow-MSCs accounted for 62% (40), which was far above umbilical cord-MSCs (18%, 12). Finally, we combined the results of Figure 7A and B. Human bone marrow-MSCs (18), mouse bone marrow-MSCs (14) and human umbilical cord-MSCs (12) were the top three most popular sources of cells (Figure 7C). Morrison[33] demonstrated that human bone marrow-MSCs promoted anti-inflammatory effects and strengthened the expression of M2 macrophage markers through

Table 4 The Top 10 Journals Publishing Research on MSCs-Exosomes and ALI/ARDS

Rank	Journal	Np	Nc	H-Index	IF (2021)
1	Stem Cell Research & Therapy	12	476	8	8.088
2	Stem cell reviews and reports	7	207	6	6.692
3	Cells	7	73	5	7.666
4	Stem Cells International	6	151	5	5.131
5	International Journal of Molecular Sciences	5	86	4	6.208
6	Stem Cells	4	861	3	5.845
7	Expert Opinion on Biological Therapy	4	199	3	5.589
8	Stem Cells Translational Medicine	3	171	3	7.655
9	Journal of Clinical Medicine	3	158	3	4.964
10	Clinical and Translational Medicine	3	90	3	8.554

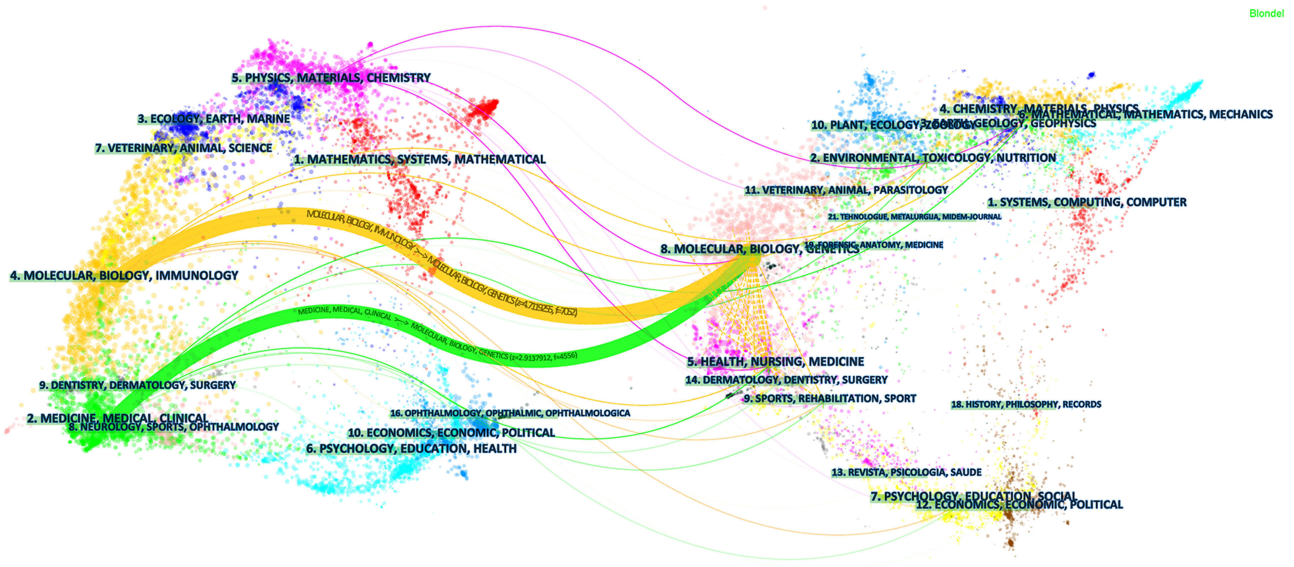


Figure 5 The dual-map overlay of citing of citation relationship of articles, with citing journal on the left, and the cited journal on the right. The colored path represented the citation relationship.

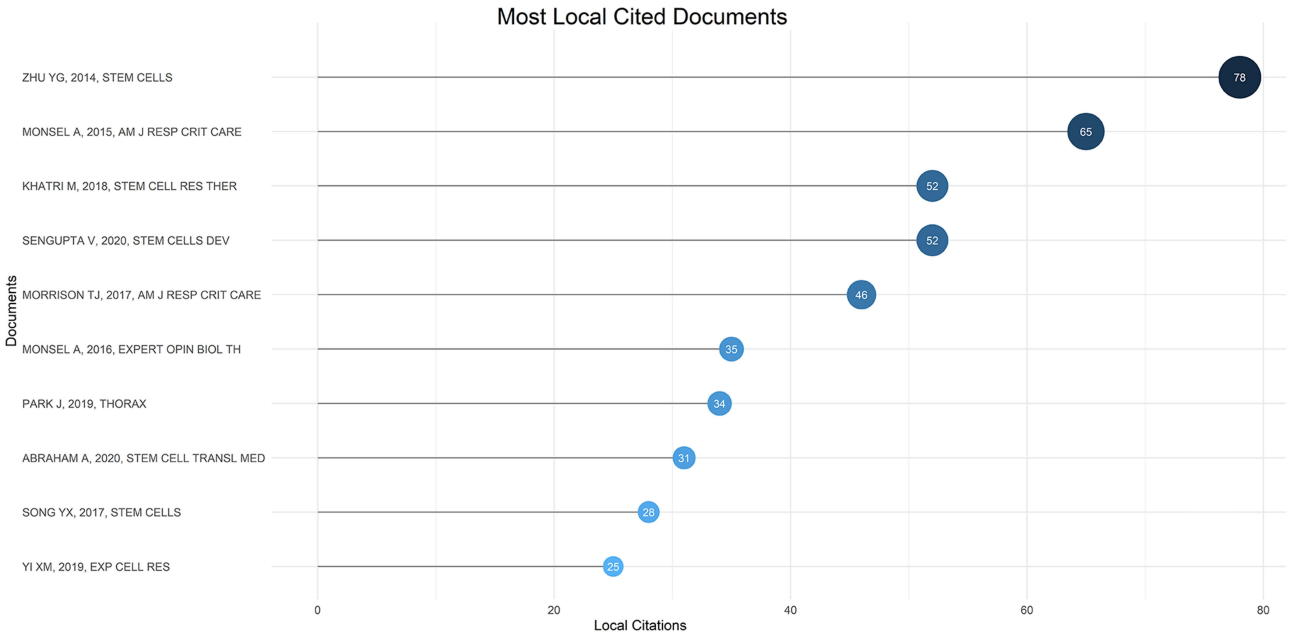


Figure 6 Top 10 most cited local articles.

exosome-mediated mitochondrial transfer. Therefore, this article received high attention, and most researchers had accepted the author's views.

Co-Cited References Analysis

Publication co-citation analysis aims to determine publications that have a great influence on a specific field. When two papers are both cited as references in another article, those two papers have a co-citation relationship. We set the minimum citation threshold to 22 and selected 46 references from 9628 cited papers for analysis (Figure 8A). Each node represents a paper. When two papers are both cited in another article, a line will connect them. The shorter line means

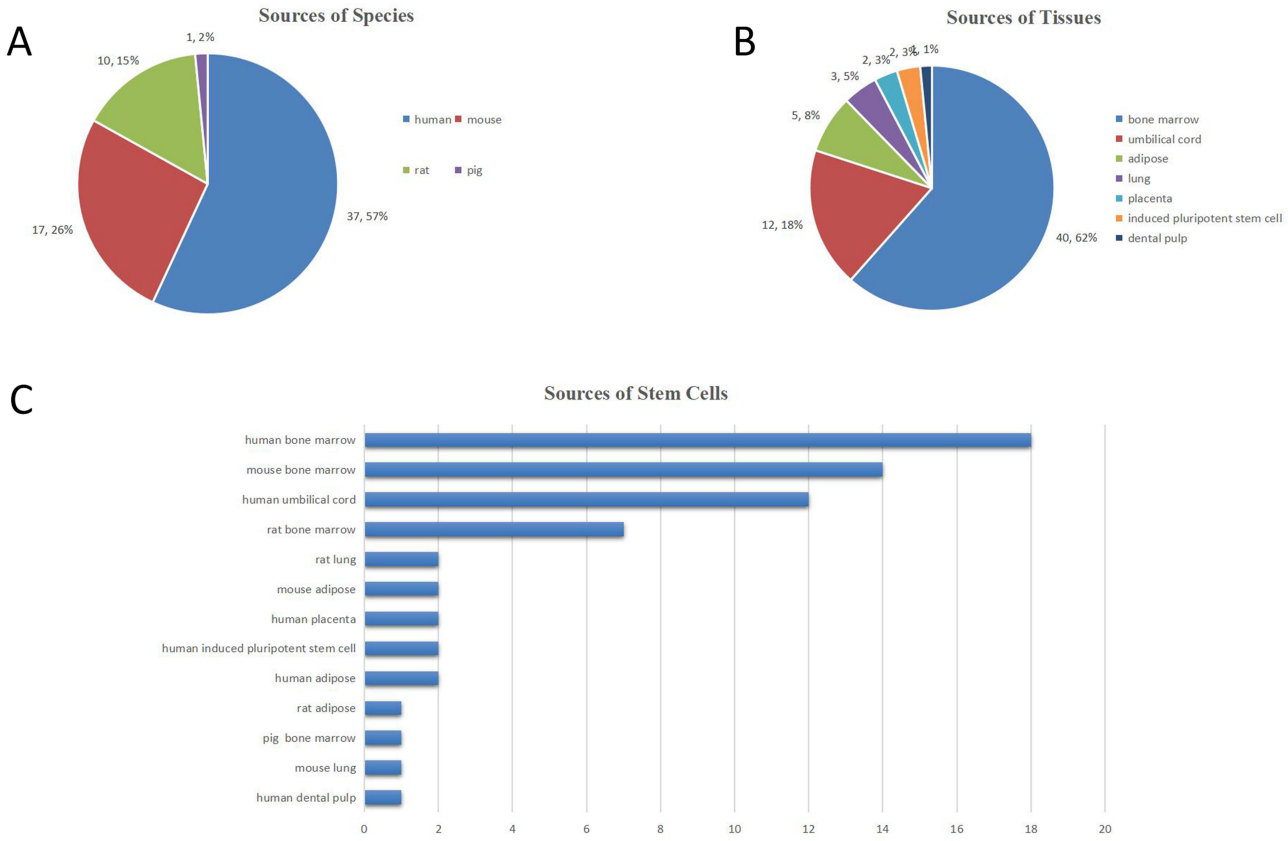


Figure 7 Source analysis of MSCs. (**A**) Pie charts of different species derived Stem Cells. (**B**) Pie charts of different tissue derived Stem Cells. (**C**) The bar chart of sources that Stem Cells derived from.

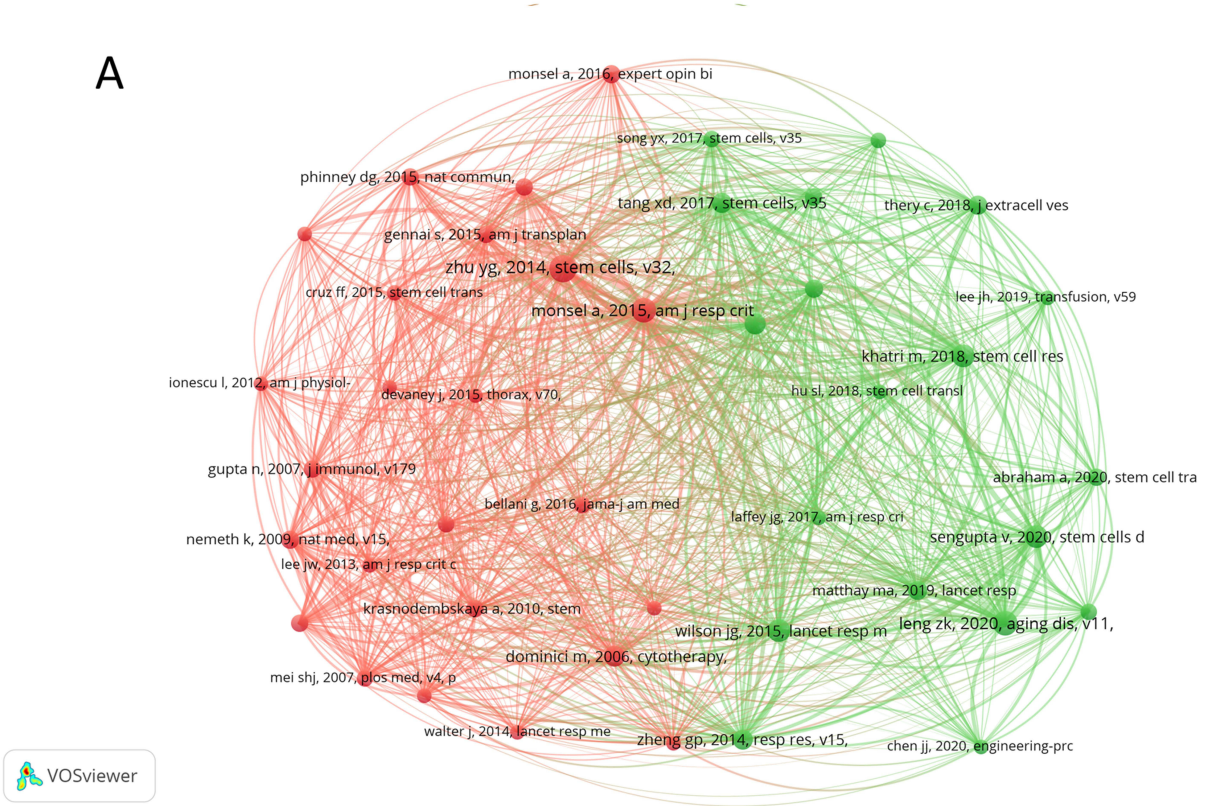
a stronger relationship and the larger node represents the more co-citation of the document. In addition, these papers were divided into different clusters according to nodes of different colors. Cluster 1 (red) consisted of 26 articles focusing on the therapeutic effects of MSC-exosomes. Cluster 2 (green) consisted of 20 articles that paid more attention to the role of MSC-exosomes in immune regulation.

In Figure 8B, we listed the top 15 references with the strongest citation bursts. The timeline is represented by the blue line segment. The duration is indicated by the red line segment. A sudden explosion in the number of citations to certain literature over a period of time may indicate that a new research hotspot may be emerging in the field. Zhu YG published an article in Stem Cells with the strongest strength (13.66). Although MSCs-exosomes have been shown to have anti-inflammatory effects in a variety of inflammatory diseases, their relationship with ARDS is unclear. In this article, the authors demonstrate that treatment with MSCs-exosomes has the same alleviating effect on ARDS as treatment with stem cells. Their research laid the foundation for subsequent trials.

Keyword Analysis

Keywords are the research themes and core contents of the articles. To explore the research hotspots in the scope of MSC-exosomes and ALI/ARDS, we conducted keyword co-occurrence analysis. We analyzed keywords extracted from 181 publications by applying VOSviewer. As shown in Figure 9A, we constructed the keyword co-occurrence network and classified these keywords into 3 clusters. Cluster 1 (red, 20) was mainly concentrated on the therapeutic effect and potential mechanisms of MSC-exosomes in ALI/ARDS treatment. Cluster 2 (green, 10) focused on MSC-exosome nanosized extracellular vesicles participating in immune function and the inflammatory response. Cluster 3 (blue, 26) focused on the regulatory role of miRNAs in MSC-exosomes on intercellular communication and disease. In Figure 9B, we colored these keywords in accordance with the average time of the word's appearance. The blue color means the word

A



B

Top 15 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2022
Zhu YG, 2014, STEM CELLS, V32, P116, DOI 10.1002/stem.1504, DOI	2014	**13.66**	2015	2019	
Monsel A, 2015, AM J RESP CRIT CARE, V192, P324, DOI 10.1164/rccm.201410-1765OC, DOI	2015	**9.4**	2016	2020	
Wilson JG, 2015, LANCET RESP MED, V3, P24	2015	**7.34**	2015	2020	
Phinney DG, 2015, NAT COMMUN, V6, P0, DOI 10.1038/ncomms9472, DOI	2015	**6.33**	2016	2020	
Cruz FF, 2015, STEM CELL TRANSL MED, V4, P1302, DOI 10.5966/sctm.2014-0280, DOI	2015	**4.93**	2016	2019	
Lee C, 2012, CIRCULATION, V126, P2601, DOI 10.1161/CIRCULATIONAHA.112.114173, DOI	2012	**4.77**	2014	2017	
Devaney J, 2015, THORAX, V70, P625, DOI 10.1136/thoraxjnl-2015-206813, DOI	2015	**4.76**	2018	2020	
Monsel A, 2016, EXPERT OPIN BIOL TH, V16, P859, DOI 10.1517/14712598.2016.1170804, DOI	2016	**4.73**	2018	2019	
Gennai S, 2015, AM J TRANSPLANT, V15, P2404, DOI 10.1111/ajt.13271, DOI	2015	**3.99**	2017	2020	
Bellani G, 2016, JAMA-J AM MED ASSOC, V315, P788, DOI 10.1001/jama.2016.0291, DOI	2016	**3.61**	2016	2019	
Zheng GP, 2014, RESP RES, V15, P0, DOI 10.1186/1465-9921-15-39, DOI	2014	**3.23**	2016	2019	
Islam MN, 2012, NAT MED, V18, P759, DOI 10.1038/nm.2736, DOI	2012	**2.98**	2014	2017	
Arslan F, 2013, STEM CELL RES, V10, P301, DOI 10.1016/j.scr.2013.01.002, DOI	2013	**2.87**	2015	2018	
Le Blanc K, 2012, NAT REV IMMUNOL, V12, P383, DOI 10.1038/nri3209, DOI	2012	**2.57**	2015	2016	
Lee JW, 2011, STEM CELLS, V29, P913, DOI 10.1002/stem.643, DOI	2011	**2.57**	2015	2016	

Figure 8 Visual analysis of references. (**A**) Network map of co-cited references related to MSCs-exosomes in ALI/ARDS. 46 references were collected from 9682 cited papers for analysis, with at least 22 times cited. (**B**) The top 15 references with the strongest citation bursts.

appeared earlier, while keywords in yellow indicated a recent appearance. The average publication year (APY) showed that the latest keywords were "NF-κB" (Cluster 2, APY: 2021.20), "Coronavirus Disease 2019" (COVID-19) (Cluster 3, APY: 2020.90) and "cytokine storm" (Cluster 3, APY: 2020.79), which are closely linked to MSC-exosomes for treating COVID-19 patients. Moreover, increasing attention has been given to the function of exosomal miRNA, compared with exosomal proteins, lipids, and DNA.

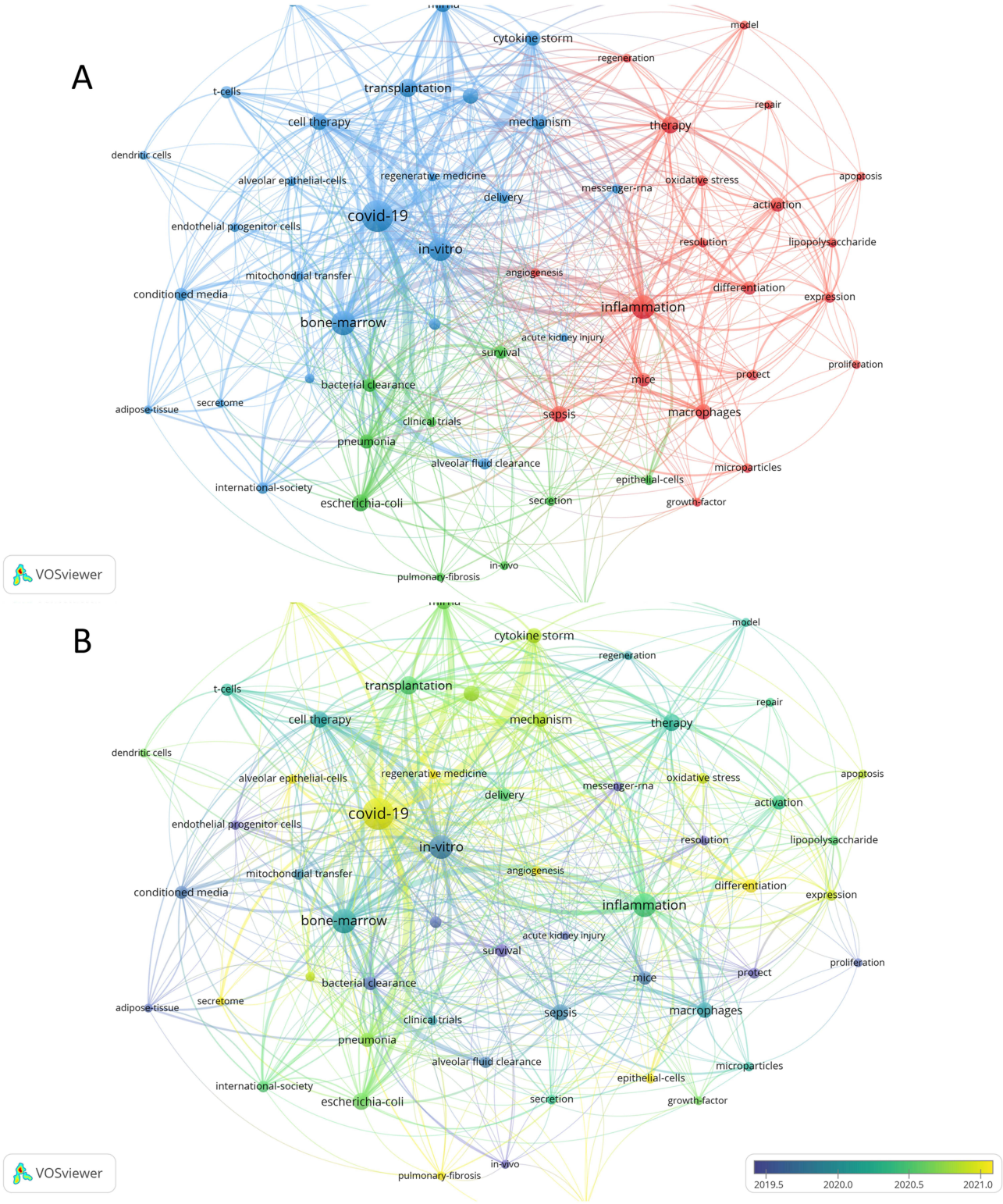


Figure 9 Keywords co-occurrence analysis of MSCs-exosomes in ALI/ARDS. (**A**) Keywords co-occurrence network. (The 56 keywords that appeared more than 5 times were selected. Cluster 1: red, cluster 2: green, cluster 3: blue). (**B**) Keywords Visual analysis according to the APY. (The color of the dot represented the time when the keyword appeared. The more recent the keyword, the more yellow the dot color).

Analysis of Research in MSCs-Exosomes and COVID-19

Due to the COVID-19 outbreak, much new research has appeared in this area related to COVID-19-induced ALI/ARDS and MSC-exosomes. This may be the reason for the rapid growth of Np in the research field of MSC-exosomes and ALI/

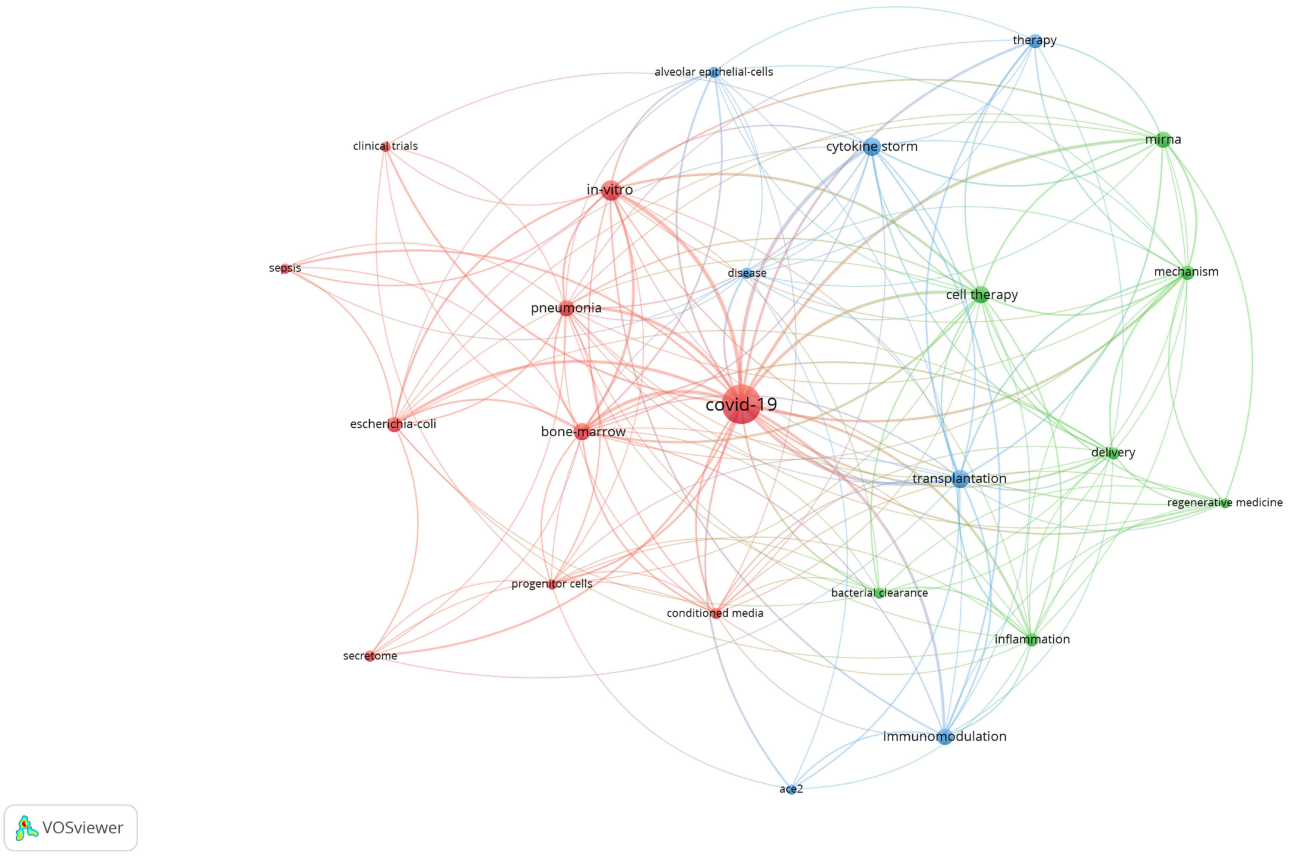


Figure 10 Keywords co-occurrence analysis of MSCs-exosomes in COVID-19-ALI/ARDS. The 35 keywords that appeared more than 3 times were selected. Cluster 1: red, cluster 2: green, cluster 3: blue.

ARDS after 2019. To further understand the relevant progress and hotspots in this scope, 72 studies related to COVID-19 were screened out based on the previous retrieval results. As shown in Figure 10, apart from COVID-19, "cytokine storm", "transplantation", "cell therapy" and "bone-marrow" appeared more frequently. This suggests that MSC- and MSC-exosome-based therapies for COVID-19-induced ALI/ARDS are being extensively explored. In addition, the mechanism by which MSC-exosome therapy affects COVID-19-induced ALI/ARDS by inhibiting the inflammatory response and regulating immune function was further revealed. More importantly, the low frequency of most keywords suggested that more discoveries are needed in this area on the mechanisms and pathways of exosome therapy for COVID-19-induced ALI/ARDS.

Discussion

In this paper, we collected 181 original articles and reviews from the SCI-Expanded database in the past 10 years after setting the search keywords. We performed a bibliometric analysis of research progress and hotspots in the field of MSC-exosomes and ALI/ARDS using Bibliometrix in R, CiteSpace and Vosviewer.

In general, the study of exosomes in ARDS was relatively new, and the total number of relevant studies published was relatively small. The annual number of articles published increased steadily and reached 54 articles in 2021. The Np after 2018 increased rapidly, with the outbreak of COVID-19 as a possible cause, indicating that research in this field is developing rapidly. Moreover, some researchers were attempting to explore the possibility of using MSCs-exosomes to treat COVID-19 induced ARDS. Research in this area is in a period of rapid development, which is and will be a potential research hotspot in the future.

Among the top 10 countries/regions, China ranked first in Np. Correspondingly, China had 7 institutions in the top 10 most productive institutions, indicating that China is developing rapidly and has strong scientific research potential in this

area. In comparison, the USA ranked second in Np, and had 1 institution in the top 10, with 2 authors in the top 10 most prolific authors. Similarly, the USA ranked first in the Nc and H-index. American scholar Johnstone et al proposed the original concept of exosomes. This may explain why the USA is playing a leading role in this research field. Although China has published the largest number of articles in this field, the quality of research needs to be further improved. It is clear that other countries, including Iran and Italy, face the same problem. China and the USA cooperated most closely of all countries and as a result they were at the forefront of research in this field. This suggested that in the background of the continuous development of science and technology, collaborative communication may be a better way to solve scientific problems. Breaking down academic barriers can facilitate academic exchanges between countries and has a positive impact on scientific development.

Among the top 10 journals in terms of Np, all of them have high IF, indicating that these journals are more innovative, groundbreaking and influential in this field. Researchers interested in ALI/ARDS and MSC-exosomes should pay more attention to these journals. They can try to publish their works in these high-scoring journals.

The article published by Zhu YG in STEM CELLS had the highest LCS, indicating that his article had a great influence in this field and that most scholars agree with his views. He demonstrated that the therapeutic effect of MSC-exosomes on ALI/ARDS may be partly mediated by expressing keratinocyte growth factor (KGF) mRNA.[32] A meta-analysis by Fengyun Wang et al also confirmed this view with clinical data.[39] In Figures 6 and 7 original articles, all of which discussed the role and function of MSC-exosomes by establishing LPS- or endotoxin-induced ALI/ARDS animal models. Based on these exciting results obtained from animal experiments, subsequent cell- or cell-free therapies in human patients have been developed.

Consistent with the results of MSC sources and co-citation analysis, keyword analysis indicated that exosomes derived from human bone marrow-MSCs are currently the most widely studied. MSCs are widely used in regenerative medicine and have multidirectional differentiation ability. Exosomes derived from these cells can be used as a safe treatment method, a new breakthrough in cell-free therapy.[40] Due to the low immunogenicity and convenience of sampling, most researchers preferred human bone marrow-MSCs as the sources of exosomes. Exosomes derived from MSCs can exert anti-inflammatory effects by inhibiting proinflammatory factors and promoting the secretion of anti-inflammatory factors, thus improving the survival rate of lung injury patients.[40] Geng, et al[41] showed that human dental pulp MSC-exosomes were more effective than human umbilical cord MSC-exosomes in reducing lung inflammation, suggesting that the differential lung-protective capacity of exosomes derived from different sources of human MSCs needs to be further discovered.

As shown in Figures 8 and 9, many studies have been carried out on MSC-exosomes. Although exosomes contain many substances, research on miRNAs is obviously more enthusiastic (Figure 9). MSC-exosomes exert immunomodulatory functions by delivering different miRNAs. For example, MSC-exosomal miRNA-146a, miRNA-371b-5p and miRNA-30b-3 can reduce the expression of inflammatory genes and the production of inflammatory mediators, thus achieving a protective effect on ALI/ARDS.[42–44] In contrast, miRNA-155 can promote inflammatory responses by promoting the expression of inflammatory genes.[42] In addition, a comparison between Figure 9A and B revealed that the relationship between MSC-exosomes and the inflammatory response was a relatively new hotspot in this research field. Many researchers are currently focusing on the mechanisms by which MSC-exosomes regulate the inflammatory response and injured tissue repair.

As shown in Figure 9, nuclear factor kappa-B (NF-κB) played a key role in the mechanism by which MSC-exosomal miRNAs regulate the inflammatory response. MSC-exosomal miRNAs, such as miRNA-23a-3p and miRNA-182-5p, inhibited the NF-κB and hedgehog pathways by silencing inhibitors of nuclear factor kappa B kinase subunit beta (Ikbkb) and destroying inhibitor kappa B kinase β (IKKβ),[8,45] to reverse the progression of LPS-induced lung injury and fibrosis. In addition, transforming growth factor-β1 (TGF-β1) was a critical factor in inducing myofibroblastic differentiation. MSC-exosomes can reduce the expression of alpha-smooth muscle actin (α-SMA) in TGF-β1-induced lung fibroblasts, while the expression of fibronectin and collagen III is inhibited.[46]

It is worth noting that "COVID-19" was the latest hotspot in this field due to the COVID-19 outbreak (Figure 10). "Cytokine storm" was closely associated with COVID-19-related ALI/ARDS, probably because "cytokine storm" is one of the core mechanisms through which COVID-19 causes lung damage. Numerous studies have indicated that cytokine

storms induce the progression of COVID-19-related ALI/ARDS, and injections of MSC-exosomes can downregulate the acute phase reactant CRP without adverse reactions.[47] The use of stem cell therapy carries risks of iatrogenic tumors and other adverse outcomes.[48] MSC-exosomes have been shown to protect the lung and other tissues through immunomodulatory effects, promoting tissue repair and regeneration, and anti-fibrosis effects.[49,50] Therefore, MSC-exosomes were more suitable for COVID-19-related ALI/ARDS treatment as a cell-free therapy, either intravenous injection or inhalation.[51] Pretreatment of stem cells with LPS or inflammatory factors (IL-1) can enhance the immunomodulatory effect of the exosomes they secrete.[34,52] In addition, exosomes act as a natural nanocarrier that can carry a cocktail of suitable exogenous interfering RNAs to transport them to the cell of interest for palliation and treatment of COVID-19-related ALI/ARDS.[53] Analysis of MSC-exosomes may provide new insights into ALI/ARDS caused by COVID-19 worldwide and contribute to the recession of the epidemic. It was worth noting that with the continuous development of related research, the use of MSCs-exosomes in the treatment of COVID-19-related ALI/ARDS had also made progress. Ruijing Zhao et al[54] used MSCs-exosomes to treat COVID-19-related ARDS by aerosol inhalation in a mouse model, showing strong anti-inflammatory activity and effectively alleviated lung inflammation in mice. Human trials by Meiping Chu et al[16] also showed similar results, demonstrating the effectiveness and reliability of MSCs-exosome therapy.

The present study used bibliometric methods to analyze the research progress and hotspots of MSC-exosomes in ALI/ARDS and facilitate readers to understand the research status in this field. Recently, bibliometric analysis has become an important and effective tool in the scientific evaluation process. It allows a large body of literature in a field to be objectively analyzed at a lower cost and in less time, and the results can be presented visually. Based on these results, researchers can learn about relevant research hotspots and find high-scoring journals and articles. It also helps researchers to identify suitable potential partners and research areas. Peer review is an important process throughout a researcher's career. The process is time and cost intensive, and could be influenced by prejudices and conflicts of interest of the referee. Therefore, we believe that the use of bibliometric analysis in combination with peer review can make research evaluation more scientific and democratic.

Inevitably, there are some limitations in this study. Firstly, only English original articles and reviews were collected, some linguistic bias was introduced. Secondly, the web of science is updated continuously, there might be some new data missing, meanwhile, data from other significant databases such as PubMed, Embase were excluded. Thirdly, due to their low citation rate, some of the most recently published high quality articles cannot be included.

Conclusion

Through bibliometric analysis, we found that the study of ALI/ARDS in the direction of MSC-exosomes is in a rapid development stage in general. The USA was playing a leading role in this area, contributing many influential articles and promoting the development of this research field. China is the most prolific country. However, the quality of research needs to be improved. The underlying mechanism of MSC-exosomes in the treatment of ALI/ARDS has been a hot research topic. Currently, the regulatory role of MSC-exosomal miRNAs has received more attention. Due to the outbreak of COVID-19, the treatment of MSC-exosomes on ALI/ARDS caused by COVID-19 has already become the newest research hotspot.

Abbreviations

ALI/ARDS, acute lung injury and acute respiratory distress syndrome; MSCs, mesenchymal stem cells; IF, Impact Factor; Np, number of publication; Nc, number of no self-citation; LCS, local citation score; APY, average publication year; COVID-19, Coronavirus Disease 2019; KGF, keratinocyte growth factor; NF-κB, nuclear factor kappa-B; Ikbkb, kappa B kinase subunit beta; IKKβ, inhibitor kappa B kinase β; TGF-β1, transforming growth factor-β1; α-SMA, alpha-smooth muscle actin; IL-1, inflammatory factors.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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