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RESEARCH ARTICLE

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The research landscape of immunology research in spinal cord injury from 2012 to 2022

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Abstract

Background: Spinal cord injury (SCI) is defined as traumatic damage to the spinal cord, affecting over three million patients worldwide, and there is still no treatment for the injured spinal cord itself. In recent years, immunology research on SCI has been published in various journals.

Methods: To systematically analyze the research hotspots and dynamic scientific developments of immunology research in SCI, we conducted a bibliometric and knowledge map analysis to help researchers gain a global perspective in this research field.

Results: The bibliometric study we completed included 1788 English-language papers published in 553 journals by 8861 authors from 1901 institutions in 66 countries/regions. Based on the references and keyword analysis, researchers in the past 10 years have mainly focused on the research directions of "monocyte chemoattractor protein 1," "nitric oxide," "pain," and "nitric oxide synthase" related to immunological research in SCI. However, with the development of other new directions such as "extracellular vesicles" (2019–2022), "Regenerative medicine" (2019–2022), "stromal cells" (2018–2022), "motor recovery" (2019–2022), and "glial activation" (2019–2022). Researchers prefer to study the application of regenerative strategies in SCI, the mechanism of extracellular vesicles in the development of SCI, the activation of spinal glial cells in SCI, and the pathways of motor recovery. This bibliometric analysis of immunology research in SCI summarizes the current status of this research field. The relationship between extracellular vesicles, regenerative medicine, stromal cells, motor recovery, and glial activation is currently a major research frontier. Further research and cooperation worldwide need to be enhanced.

Conclusion: We believe that our research can help researchers quickly grasp the current hotspot of immunology research in SCI and determine a new direction for future research.

KEYWORDS

bibliometric analysis, CiteSpace, immunology, spinal cord injury, VOSviewer

Yirui Kuang and Songlin Liu contributed equally to this study.

1 | INTRODUCTION

Spinal cord injury (SCI) results from direct trauma and remains a serious disease resulting in loss of motor, sensory, and autonomic functions caudal to the injury site. There are 250 000 to 500 000 people eventually suffering from SCI in a single year around the world, and SCI most often occurs in young and middle-aged adults.[1] In the United States, it is estimated that more than 250 000 people with SCI suffer from this disease, with cumulative lifetime treatment costs of 1.1–4.6 million USD per patient.[2] SCI can be divided into acute, subacute, and intermediate-chronic injury phases. The subacute phase, following the initial injury, is characterized by worsening pathology including ischemia, inflammation, and cytotoxic microenvironment leading to cell death and scarring around cystic cavities.[2] SCI may have some endogenous regenerative potential due to CNS neuron plasticity, contributing to functional recovery for years after injury.[3] Therefore, effective therapeutic intervention should understand the inflammation and tissue repair process in SCI and improve prognosis and treatment by addressing the underlying pathophysiology.

Inflammatory response in SCI mediates tissue injury and repair, drawing significant attention due to dynamic changes causing immune cell/regulator imbalances, and involving immune cell infiltration, activation, proliferation of resident immune cells, and secretion of cytokines, chemokines, and reactive oxygen species.[4–7] In the acute injury phase, damage to the BSCB leads to severe bleeding and spinal cord exposure to inflammatory cells (neutrophils and monocytes) and proinflammatory cytokines (TNF-α and IL-1β), which further exacerbate mechanical compression and aggravate injury.[8–10] During subacute injury, microglia and inflammatory cells (macrophages, polymorphonuclear cells, and lymphocytes) infiltrate and activate, causing inflammation and neuronal/oligodendrocyte apoptosis. Phagocytic cells can remove myelin debris, but also cause further injury, worsened by cytotoxic byproducts' release (free radicals, etc.) leading to necrosis and delayed apoptotic cell death.[11,12] Intermediate-chronic injury sees immune cells participate in glial scar formation via ECM proteins that inhibit axonal growth, coagulating with astrocytes to hinder neurite outgrowth, axonal regeneration, and anatomical plasticity.[13,14]

Inflammation in SCI has a complex nature; for example, macrophage and potentially microglial phenotypes can be separated into neurotoxic, proinflammatory M1, and immunomodulatory M2 subsets, which secrete factors that promote axonal outgrowth and enhance remyelination.[15,16] There are several emerging treatments for SCI, including cell-based therapies, gene therapies, and neurostimulation. Cell-based therapies involve the transplantation of stem cells, such as mesenchymal stem cells (MSCs), neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs), to promote regeneration and repair. Gene therapies use viral vectors to deliver therapeutic genes to the site of injury, aiming to enhance axonal regeneration, neuroprotection, and remyelination. Neurostimulation techniques, such as epidural stimulation, transcutaneous electrical stimulation, and magnetic stimulation, aim to activate spared neural circuits and promote functional recovery. Additionally, pharmacological interventions targeting inflammation, oxidative stress, and demyelination are also being developed. Despite these promising approaches, more research is needed to fully understand their safety and efficacy in humans. For instance, cell transplantation may benefit by reducing harmful inflammation or stimulating beneficial inflammation. MSCs have also been shown to achieve anti-inflammatory effects by elevating anti-inflammatory responses after injury.[17,18] A study has demonstrated that intravenous delivery of MSCs at 1 day after traumatic SCI can increase forelimb–hindlimb coordination and improve urination, and M2 markers have been found to be increased.[19] This information indicates the importance of regulating immune reactions to achieve SCI regeneration and repair. Despite advances in immunology research in SCI, there is still a need for comprehensive analysis and meaningful summaries of publication trends in this field.

In recent years, bibliometric analysis has been widely used to analyze a specific topic, influential and practical areas, knowledge bases, and emerging hotspots.[20–24] It has advantages that review, meta-

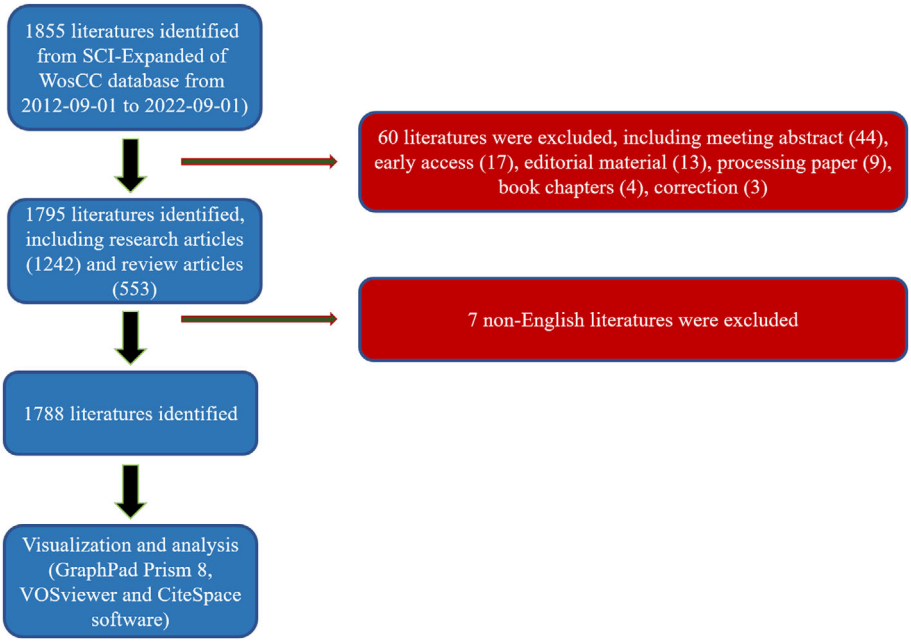


FIGURE 1 Flowchart depicting the article selection process.

analysis, or experimental studies do not have. The citation network can summarize publishing developments, predict research hotspots, and further evaluate the frontiers of specific fields.[25–28] To the best of our knowledge, although related academic researchers have published bibliometric studies of stem cell therapy in SCI,[29] no similar analysis of immunology studies in SCI has been reported. Therefore, in this study, we used CiteSpace bibliometrics with VOSviewer to fill this knowledge gap. This paper comprehensively analyzed and visualized the relevant literature in the past decade (2012–2022) to identify its salient features and predict future research directions.

2 | MATERIALS AND METHODS

2.1 | Data source and search strategy

The literature was retrieved and obtained from the Science Citation Index Expanded of Web of Science Core Collection (WoSCC) database because it is considered one of the most authoritative and comprehensive databases.[30] Therefore, the time frame was determined to be from September 1, 2012, to September 1, 2022, and all published literature was extracted and downloaded from WoSCC and

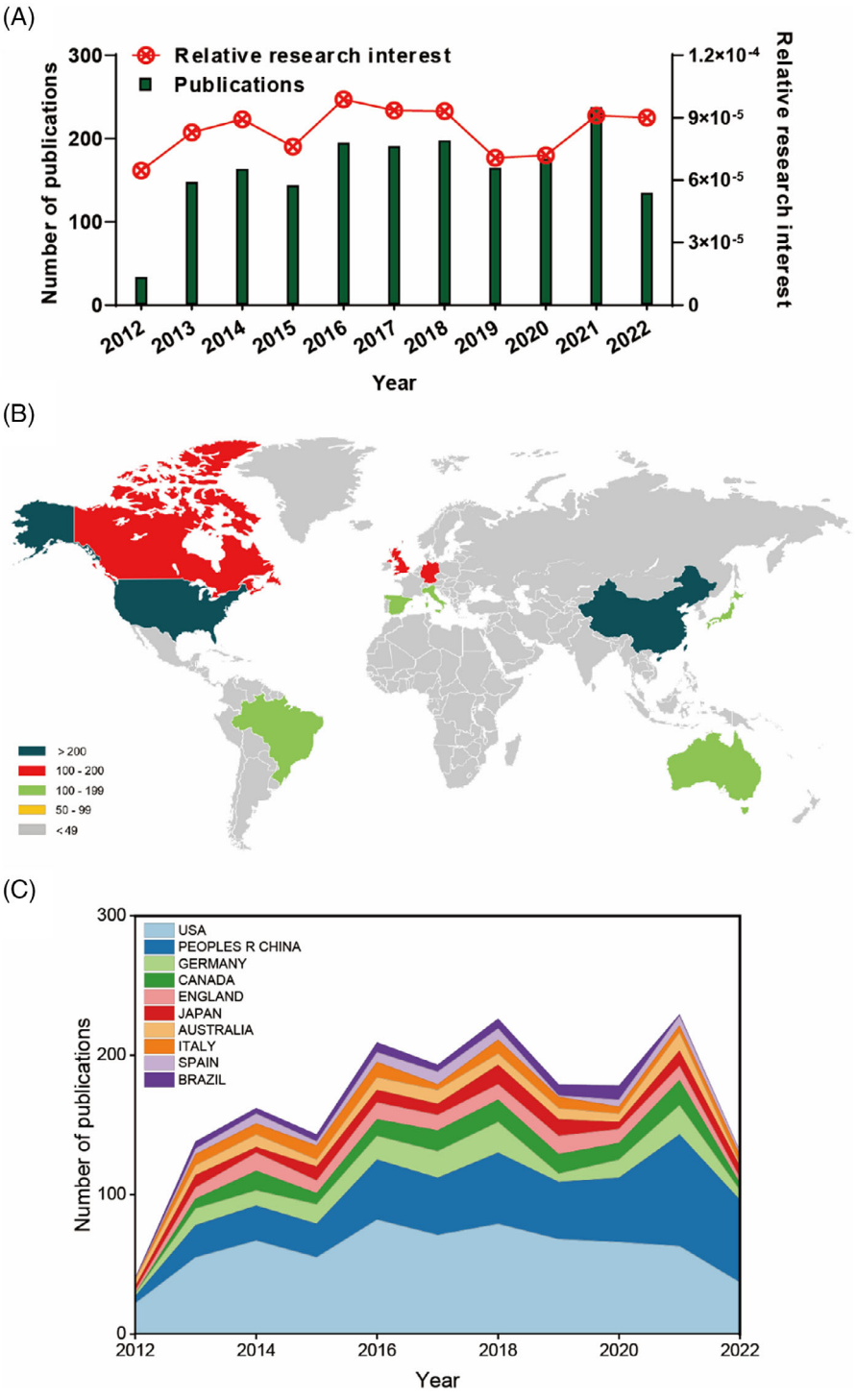


FIGURE 2 Global trends and countries/regions contributing to the research field regarding immunology in spinal cord injury (SCI) from 2012 to 2022. (A) The annual number of publications related to immunology research in SCI. (B) A world map depicting the distribution of immunology research in SCI. (C) The annual number of publications in the 10 most productive countries from 2012 to 2022.

independently verified by the two authors (YRK and SLL). The search terms were as follows: theme = spinal cord injury or spinal cord injuries *AND theme = immune or immunology or immunity or immunization or immunotherapy or immunotherapeutic or immune regulation or immunomodulation. The following selection criteria were used: (1) publications mainly focused on the theme of immunology research in SCI; (2) document type: article or review; and (3) language: English. The exclusion criteria were as follows: (1) the themes were not related to immunology research in SCI; (2) publications were meeting abstracts, proceedings paper, correction book chapter letter, news, and so on (Figure 1). For these included publications, all valid data, including publishing year, title, author, nationalities, affiliations, abstract, keywords, and journals, were exported and saved in the format of download.txt files for further analysis. Coauthors (YRK and SLL) independently searched and extracted all data from these studies. Any disagreement was resolved by consulting with experts to reach the final consensus. Finally, all the documents were imported into CiteSpace and VOSviewer separately for visualization analysis.

2.2 | Bibliometric analysis and visualization

First, the annual trend publications and relative research interest (RRI) over years were analyzed and visualized by the curve-fitting function of GraphPad Prism 8. The world map was created by R software, including python + numpy + scipy + matplotlib.[31] The time curve of publications was drawn according to a previous article.[31] Second, we chose VOSviewer (1.6.17) software to construct and visualize (1) the collaboration analysis of countries/regions and institutions; (2) the cocitation analysis of journals, authors and references; and (3) the co-occurrence analysis of keywords. Third, CiteSpace (6.1. R2), which was developed by Professor Chen C,[32] was used to construct and visualize (1) a dual-map overlay for journals; (2) cluster analysis of cocited keywords and references; and (3) the detection of authors, references and keywords with intense citation bursts. The CiteSpace parameters were set as follows: time span (2012–2022), years per slice = 1, link retaining factor (LRF = 3), look back years (LBY = 5), e for top N ($e = 1$), links (strength: cosine, scope: within slices), and selection criteria (g-index: $k = 25$).

3 | RESULTS

3.1 | Overall performance of global literature

A total of 1855 studies were collected from 2012 to 2022 according to the selection criteria. Then, 1795 studies were identified by excluding meeting abstracts (44), early access (17), editorial material (13), proceedings papers (9), book chapters (4), and corrections (3). Subsequently, 1788 studies were identified by excluding 7 non-English studies (Figure 1). As shown in Figure 2A, the trend of global literature shows an increasing tendency year by year, while the amount of literature increased from 34 (2012) to 238 (2021). Most research was published in 2021 (238, 13.31%) (Figure 2A). In addition, the relative interest in this field has also increased steadily over the past decade (Figure 2A).

TABLE 1 The top 10 productive countries/regions related to immunology research in spinal cord injury.

Rank	Country/region	Article counts	Percentage
1	United States	665	37.19
2	China	438	24.50
3	Germany	144	8.05
4	Canada	121	6.77
5	England	103	5.76
6	Japan	93	5.20
7	Australia	82	4.59
8	Italy	75	4.20
9	Spain	54	3.02
10	Brazil	53	2.96

Regarding countries or regions, a total of 65 countries/regions were contributors. As shown in Figure 2B and Table 1, the top five countries/regions were the United States (665, 37.19%), China (438, 24.50%), Germany (144, 8.05%), Canada (121, 6.77%), and England (103, 5.76%). Figure 2C shows the distribution of publication number by year, indicating steady publication growth in this field. In conclusion, we found that research on immunology in SCI has attracted increasing attention and has reached a stage of rapid development.

3.2 | Analysis of countries and institutions

As illustrated in Figure 3A, the top five countries with the highest total citation frequencies were the United States (33 475), followed by China (10 179), Canada (7175), England (5019) and Germany (4327). Regarding the H index, Figure 3B shows that the United States exhibited the highest H index (87), followed by China (46), England (39) and Germany (38). Additionally, Canada (59.30) dominated in this field in the average citations, followed by Israel (58.80), Scotland (53.50), the United States (50.34) and England (48.73) (Figure 3C). In addition, as shown in Figure 4A,B, we find extensive cooperation among different countries/regions with varying intensity, with the strongest being between China and the United States. It is worth noting that the total link strength of the United States is significantly higher than that of other countries, which illustrates the centrality of the relationship of the United States in this field of academic cooperation.

When restricting the institutions to the top 10, the top 10 institutions contributed a total of 406 articles, accounting for 22.71% of the total (Table 2). As shown in Table 2, the top 3 institutions with the most documents were the University of California System ($n = 78$), Ohio State University ($n = 52$) and University of Miami ($n = 40$). According to the number of citations, the order from highest to lowest was the University of California System (citations = 4382), Ohio State

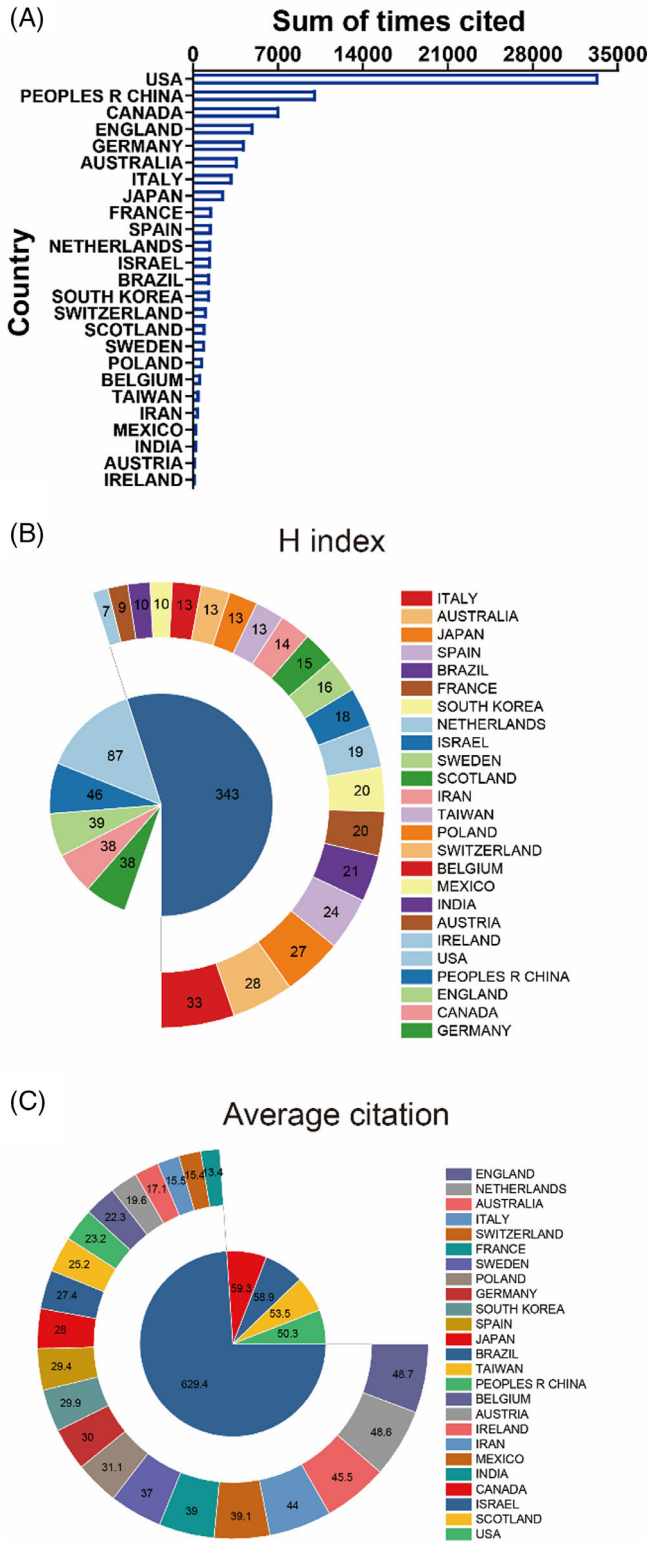


FIGURE 3 (A) The top 25 countries/regions of total citations related to immunology research in spinal cord injury (SCI). (B) The top 25 countries/regions of the publication H-index related to immunology research in SCI. (C) The top 25 countries/regions of the average citations per publication related to immunology research in SCI.

University (citations = 3305) and Harvard University (citations = 2538). Remarkably, seven of the top 10 institutions are from the United States. They are the University of California System, Ohio State University, University of Miami, Harvard University, University of Texas System, Us Department of Veterans Affairs, and Veterans Health Administration Vha. The intensity of cooperation between institutions in the

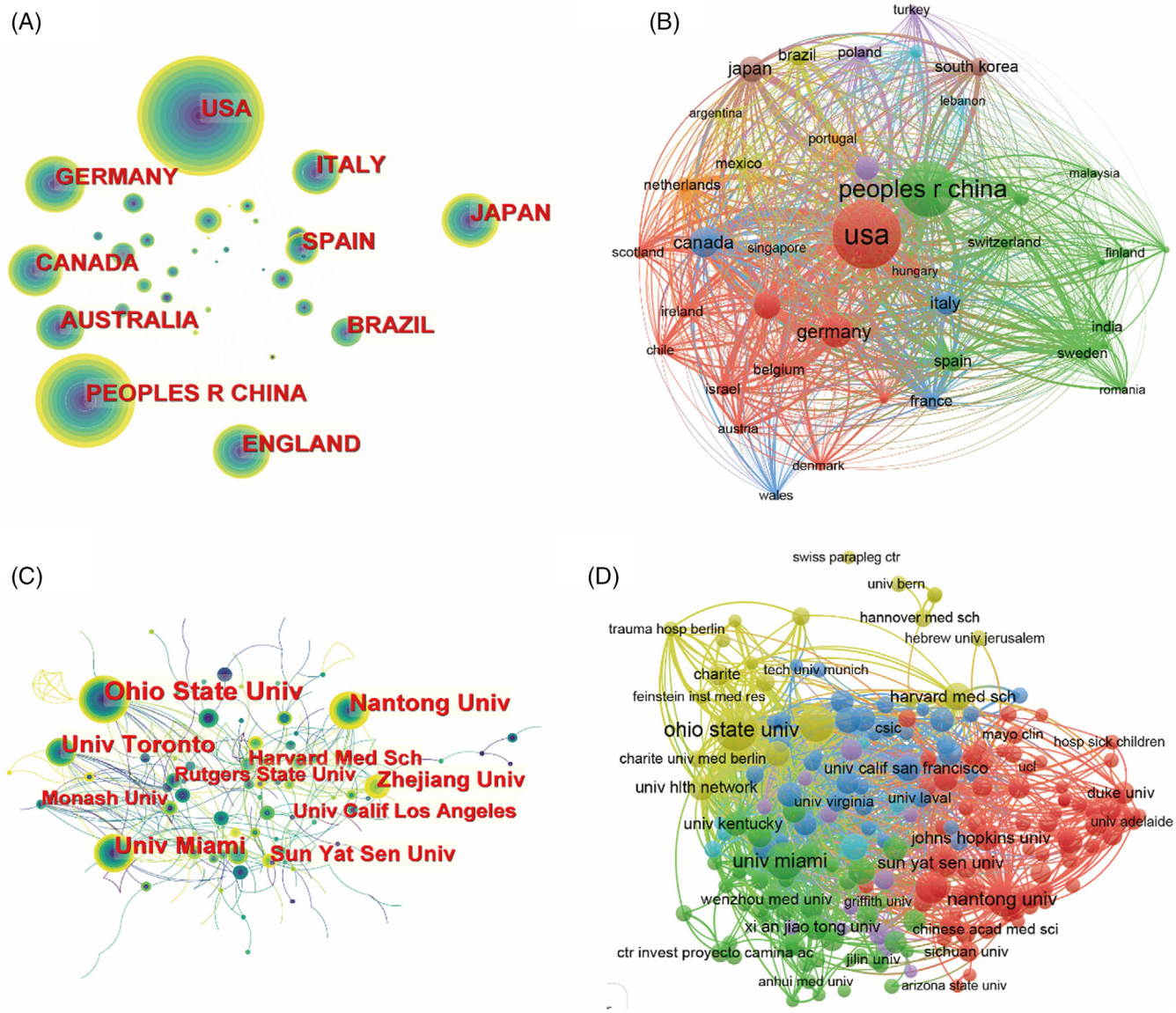


FIGURE 4 Mapping of countries/regions and institutions associated with immunology research in spinal cord injury. Country/regional collaboration analysis derived based on CiteSpace (A) and Vosviewer (B). Institutional collaboration analysis based on CiteSpace (C) and Vosviewer (D). The nodes represent countries/regions or institutions, and the lines connect them. The number of publications grows proportionally to the size of the nodes. The lines between the nodes represent the cooperation relationship, and the thickness of the connecting lines represents the strength of their cooperation; the closer the cooperation is, the thicker the connecting lines. The nodes with the outermost purple circles have higher centrality.

United States is significantly higher than that in other countries, which suggests that institutions in other countries should strengthen cooperation and communication (Figure 4C,D).

3.3 | Analysis of journals and research areas

As shown in Figure 5A, the dual-map overlay of journals shows the topic distribution of academic journals. One primary citation path marked in orange shows that papers published in molecular/biology/genetics were primarily cited by researchers published in molecular/biology/immunology. Specific to the kinds of journals and contributions, the top 10 productive journals involved in this field are presented in Table 3. The *Journal of Neuroinflammation* published the most, with 83 publications. There were 49 publications in *Plos One*, 47 publications in *Experimental Neurology*, 37 publications in *Frontiers in Immunology* and 36 articles in *Brain Behavior and Immunity*. We used VOSviewer to perform a network map co-citation analysis of journals, and journals with more than 50 citations were defined and are plotted in Figure 5A. More specifically, the top 5 journals with the strongest total link strength were as follows: *J Neurosci* (total link strength = 326 447 times), *Proc Natl Acad Sci USA* (total link strength =351 830 times), *Exp Neurol* (total link strength = 135 410 times), *Nature* (total link strength = 294 913 times), and *Glia* (total link

TABLE 2 The top 10 institutions published literature related to immunology research in spinal cord injury.

Rank	Institution	Article counts	Percentage	Country	Total citations	Average citation
1	University of California System	78	4.36	United States	4382	56.18
2	Ohio State University	52	2.91	United States	3305	63.56
3	University of Miami	40	2.24	United States	1813	45.33
4	Harvard University	39	2.18	United States	2538	65.08
5	Nantong University	38	2.13	China	1335	35.13
6	University of Toronto	37	2.07	Canada	1110	30
7	University of London	32	1.79	England	2275	71.09
8	University of Texas System	30	1.68	United States	1004	33.47
9	Us Department of Veterans Affairs	30	1.68	United States	911	30.37
10	Veterans Health Administration Vha	30	1.68	United States	911	30.37

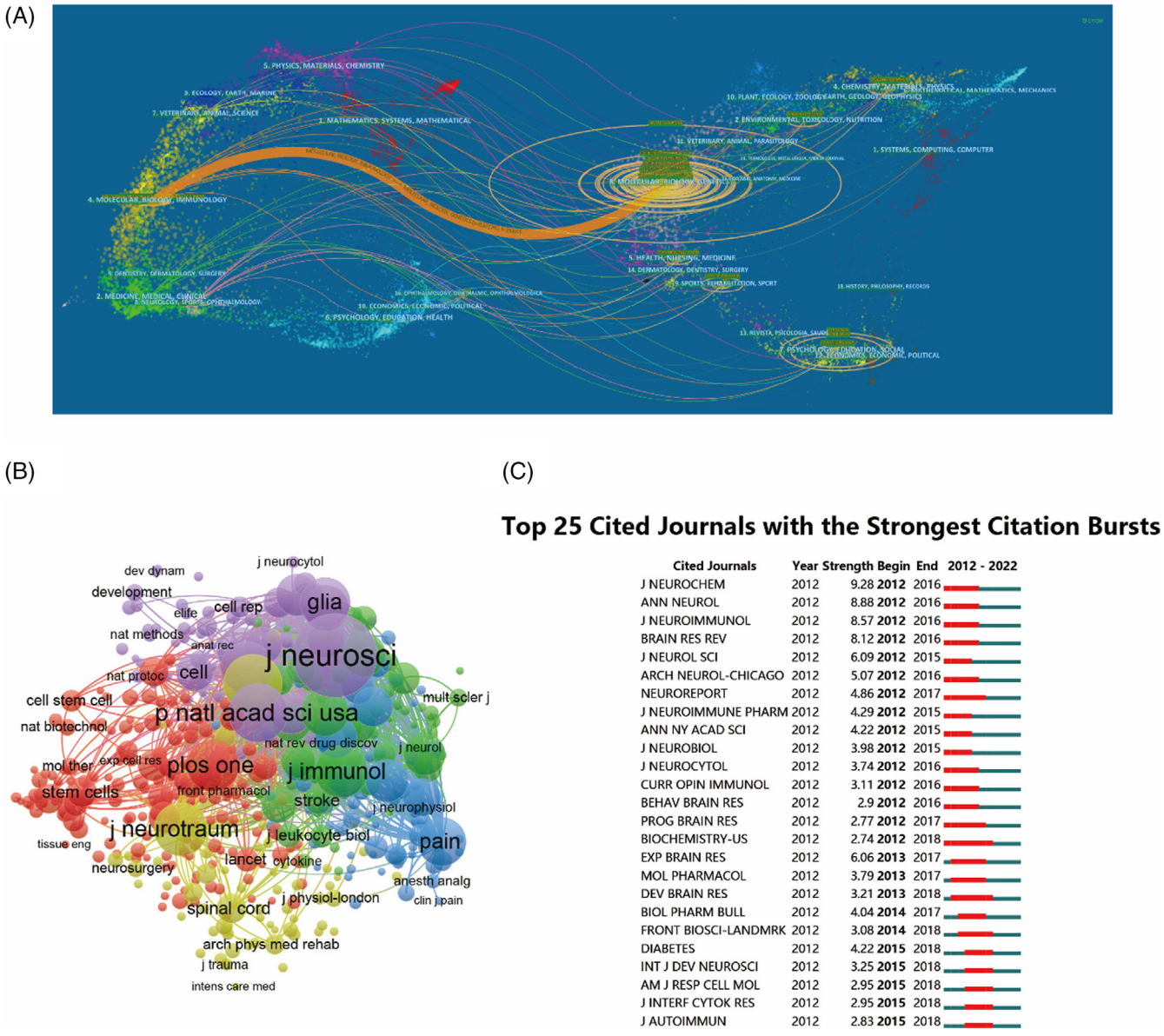


FIGURE 5 Articles published in different journals on immunology research in spinal cord injury (SCI). (A) The dual-map overlay of journals related to immunology research in SCI. (B) Network map of journals that were cocited in more than 50 citations based on Vosviewer. (C) Top 25 cited journals with the strongest citation bursts of publications related to immunology research in SCI.

TABLE 3 The top 10 productive journals related to immunology research in spinal cord injury.

Rank	Journal	Article counts	Percentage
1	*Journal of Neuroinflammation*	83	4.64
2	*Plos One*	49	2.74
3	*Experimental Neurology*	47	2.63
4	*Frontiers in Immunology*	37	2.07
5	*Brain Behavior and Immunity*	36	2.01
6	*International Journal of Molecular Sciences*	35	1.96
7	*Glia*	32	1.79
8	*Journal of Neurotrauma*	29	1.62
7	*Frontiers in Cellular Neuroscience*	28	1.57
10	*Scientific Reports*	27	1.51

TABLE 4 The top 10 co-cited journals related to immunology research in spinal cord injury.

Rank	Cited journal	Citations	Total link strength
1	*J Neurosci*	6584	755 002
2	*Proc Natl Acad Sci USA*	3241	383 955
3	*Exp Neurol*	3185	352 385
4	*Nature*	2610	319 550
5	*Glia*	2327	284 134
6	*J Neurotraum*	2617	284 015
7	*J Immunol*	2531	282 779
8	*Plos One*	2482	279 344
9	*Science*	1978	252 017
10	*Pain*	2159	241 156

TABLE 5 The top 10 well-represented research areas.

Rank	Research areas	Records	Percentage
1	Neurosciences Neurology	801	44.80
2	Immunology	295	16.50
3	Cell Biology	260	14.54
4	Biochemistry Molecular Biology	183	10.24
5	Pharmacology Pharmacy	173	9.67
6	Research Experimental Medicine	157	8.78
7	Science Technology Other Topics	137	7.66
8	General Internal Medicine	68	3.80
9	Chemistry	53	2.96
10	Materials Science	42	2.35

strength = 266 069 times) (Table 4). For burst monitoring of journals (Figure 5C), the top three ranked journals were *J Neurochem*, *Ann Neurol*, and *J Neuroimmunol*, all of which burst from 2012 to 2016. Table 5 includes the research orientations, and the most prevalent research fields were neurosciences neurology, immunology, cell biology, biochemistry molecular biology, and pharmacology pharmacy.

3.4 | Analysis of authors

The top 10 authors contributed 170 publications, which accounted for approximately 9.50% of all publications in this field. As shown in Table 6, the most productive author is Popovich PG, with 31 publications, followed by Wang Y with 23 publications and Fehlings MG with 19 publications. From Figure 6A, we can see that authors from the same country cooperate more closely, while the strength of connection between authors from different countries is still insufficient. A total of 166 authors with a minimum of 50 publications were analyzed using VOSviewer (Figure 6B). The top five authors with the largest total link strength were as follows: Kigerl, KA (total link strength = 6909 times), Popovich, PG (total link strength = 6466 times), Shechter, R (total link strength = 5063 times), Ji, RR (total link strength = 4556 times), and David, S (total link strength = 4064 times). As shown in the top 25 authors with the strongest citation bursts (Figure 6C), Bethea J showed the highest burst strength (5.61) since 2012, and Chen H exhibited the most recent burst strength from 2017 to 2020, indicating that there were many scholars studying during this period.

3.5 | Citation and co-citation analysis

We used VOSviewer to construct a network map of references, and 198 articles in this field with more than 25 citations were analyzed (Figure 7A). The top 5 most cited publications are also listed in Table 7. There were 1575 citations for "Macrophages in Tissue Repair, Regeneration, and Fibrosis," followed by "New tools for studying microglia in the mouse and human CNS," with 925 citations. The third-ranked article with the largest number of citations was "Reactive Astrocytes: Production, Function, and Therapeutic Potential," with 913 citations. Moreover, cocited references showing the most influential literature (Figure 7B and Table 8) are also presented. The top 17 cocitation clusters are shown in Figure 7C. The clusters were listed as follows: "chronic pain" (Cluster 0), "dieback" (Cluster 1), "NLRP3 inflammasome" (Cluster 2), "amyotrophic lateral sclerosis" (Cluster 3), "leukocyte" (Cluster 4), "mesenchymal stem cells" (Cluster 5), "immune" (Cluster 6), "priming" (Cluster 7), "autonomic dysreflexia" (Cluster 8), "rolipram" (Cluster 9), "neurodegenerative diseases"

TABLE 6 The top 10 authors with the most publications on immunology research in spinal cord injury.

Rank	High published authors	Country	Article counts	Percentage
1	Popovich PG	United States	31	1.73
2	Wang Y	China	23	1.29
3	Fehlings MG	Canada	19	1.06
4	Ibarra A	Mexico	18	1.00
5	Schwartz M	United States	14	0.78
6	Wang YJ	China	14	0.78
7	Ruitenberg MJ	Australia	13	0.73
8	Wang J	Japan	13	0.73
9	Zhang Y	United States	13	0.73
10	Flores-romero A	Canada	12	0.67

(Cluster 10), "neurogenesis" (Cluster 11), "chondroitinase abc" (Cluster 12), "cord blood" (Cluster 13), "mouse models" (Cluster 14), "controlled cortical impact" (Cluster 15), and "immune depression syndrome" (Cluster 16).

In addition, citation bursts reflect the references that researchers in a particular field are interested in over a period of time and are valuable for determining the direction of research development.[33] In our study, CiteSpace was further applied to identify the top 25 articles with the strongest citation outbreak, and the intensity and duration were annotated (Figure 8). The article titled "Repertoire of microglial and macrophage responses after spinal cord injury," published in 2011, ranked first (strength = 8.41). Meanwhile, Kroner A published articles with the longest citation duration, from 2015 to 2019.

3.6 | Analysis of keywords and hotspots

We used VOSviewer to conduct keyword co-occurrence analysis to understand the research hotspots and directions in this field. We extracted a total of 522 keywords (minimum number of occurrences of a keyword ≥5), of which the five with the highest occurrences were SCI (491), spinal cord (245), expression (237), central nervous system (223), and activation (213) (Figure 9A). We also perform a network map analysis on keywords to visualize the distribution of keywords according to the average publication year (dark blue: earlier, yellow: later). In Figure 9B, the majority of the keywords were published from 2016 to 2019, while recovery, transplantation, and stromal cells were relatively new keywords that recently emerged. We also conducted a network map to visualize keyword clusters (Figure 9C), and we found that "multiple sclerosis" (Cluster0), "neuropathic pain" (Cluster2), "mesenchymal stem cells" (Cluster4), "schwann cell" (Cluster5), "methylprednisolone" (Cluster7), "machine learning" (Cluster8), and "inflammasome" (Cluster9) were the hotspots of research since 2012.

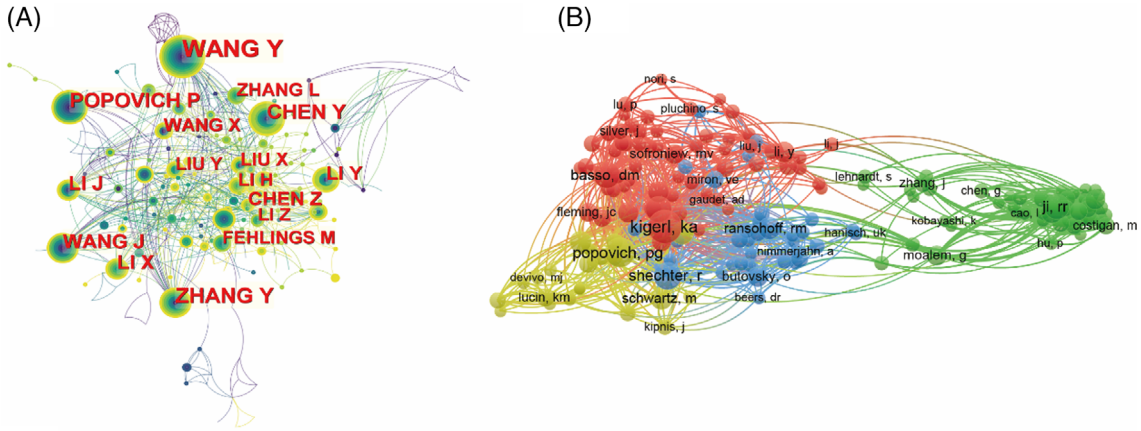
We also used CiteSpace's algorithm to obtain the burst of keywords based on burst detection. Figure 9C shows the top 25 keywords among them with the highest burst strength. The top 3 keywords with the highest citation outbreaks were monocyte chemoattractant protein 1 (strength = 4.48), followed by nitric oxide (3.3) and pain (3.05). The keyword with the longest burst time was focal cerebral ischemia, which lasted 5 years from 2014 to 2018. More meaningfully, the keywords "extracellular vesicle," "regenerative medicine," "stromal cells," "locomotor recovery" and "glial activation" had outbreak citations most recently (2019–2022), which means that the link between regenerative medicine strategies related to SCI and the rehabilitation of locomotor capacity may be the focus and direction of future research.

4 | DISCUSSION

Despite numerous clinical and research advances, effective and standardized treatments for SCI remain lacking.[34] Pathological inflammatory responses involving various cell populations and mediators contribute to SCI pathogenesis.[5,35,36] The immediate phase involves microglial activation and neutrophil infiltration, resulting in tissue damage, neuronal apoptosis, and mitochondrial blockade. The acute phase involves macrophage and T cell-mediated proinflammatory and proregenerative responses, highlighting the need for effective therapies to modulate specific inflammatory processes.[37] In the present investigation, a bibliometric analysis of immunological research in SCI was initially conducted to delineate the prevailing status of this field of research. In the past decade, research in immunology for SCI has mainly focused on "monocyte chemoattractor protein 1," "nitric oxide," "pain," and "nitric oxide synthase"; however, recent research has shifted toward "extracellular vesicles," "regenerative medicine," "stromal cells," "motor recovery," and "glial activation" as new directions for investigation, with a preference toward studying regenerative strategies, the mechanism of extracellular vesicles in SCI, activation of spinal glial cells, and pathways for motor recovery.

4.1 | The trend overview of the development of immunology research in SCI

For social network analysis including countries, journals, authors, and studies, our results provide a comprehensive description of these field for the first time. As shown in this study, a continuously increasing number of publications were found from September 1, 2012 to September 1, 2022. For national contributions, we can see that the



(C)

Top 25 Cited Authors with the Strongest Citation Bursts

Cited Authors	Year	Strength	Begin	End	2012 - 2022
BETHEA J	2012	5.61	2012	2015	
COSTIGAN M	2012	4.71	2012	2017	
STREIT W	2012	3.84	2012	2018	
CROWE M	2012	3.29	2012	2015	
JONES L	2012	3.12	2012	2018	
TSUDA M	2012	7.52	2013	2018	
FITCH M	2012	5.57	2013	2016	
GINHOUX F	2012	5.06	2013	2016	
NIMMERJAHN A	2012	5.04	2013	2016	
MOALEM G	2012	4.44	2013	2017	
SILVER J	2012	3.94	2013	2017	
AJAMI B	2012	3.08	2013	2016	
KARIMI-ABDOLREZAEE S	2012	2.94	2013	2018	
SHECHTER R	2012	3.94	2014	2017	
BUTOVSKY O	2012	3.52	2014	2017	
MIRON V	2012	4.76	2015	2019	
BEGGS S	2012	4.11	2015	2018	
LIVAK K	2012	3.79	2015	2018	
DIDANGELOS A	2012	3.79	2015	2018	
ZHUANG Z	2012	3.48	2015	2018	
PERRY V	2012	3.48	2015	2018	
BARTUS K	2012	3.48	2015	2018	
DE B	2012	2.97	2015	2018	
SCHOLZ J	2012	4.78	2016	2019	
CHEN H	2012	3.22	2017	2020	

FIGURE 6 CiteSpace network visualization of author collaboration analysis and co-cited authors regarding immunology research in spinal cord injury (SCI). (A) Author publishing analysis. (B) Network visualization diagram of the co-cited authors of the publications associated with immunology research in SCI. (C) Top 25 cited authors with the strongest citation bursts of publications related to immunology research in SCI. Author collaboration or co-cited authors are indicated by the node. The co-citation relationship is indicated by the line connecting the nodes. The node area grows as the number of co-citations increases. The colors represent different years in which the color changes from green to yellow from 2012 to 2022.

United States contributed the most papers, total citations, and the largest H-index, suggesting that it played a central role in this field. Besides, China ranks second in total publications and citations but performs weakly in average citations, suggesting that China should catch up with the United States in terms of paper quality. Meanwhile, the University of California System ranked first as an institution with 78 publications, followed by Ohio State University (52 publications) and the University of Miami (40 publications). The journal *Journal of Neuroinflammation*, *Plos One*, and *Experimental Neurology* were the most published papers. More specifically, the results of Figure 5A reflect the concentration of research in molecular, biology, and immunology studies. The top-ranked authors are listed in Table 1. As shown in Table 6, Popovich PG, Wang Y, and Fehlings MG might be the top authors with the highest numbers of publications, which represents their essential role in international recognition and cooperation in this field. The impact of published papers was evaluated in citation analysis (Figure 7A) and co-citation network analysis (Figure 7B). Table 7 shows that the most cited article was "Macrophages in Tissue Repair,

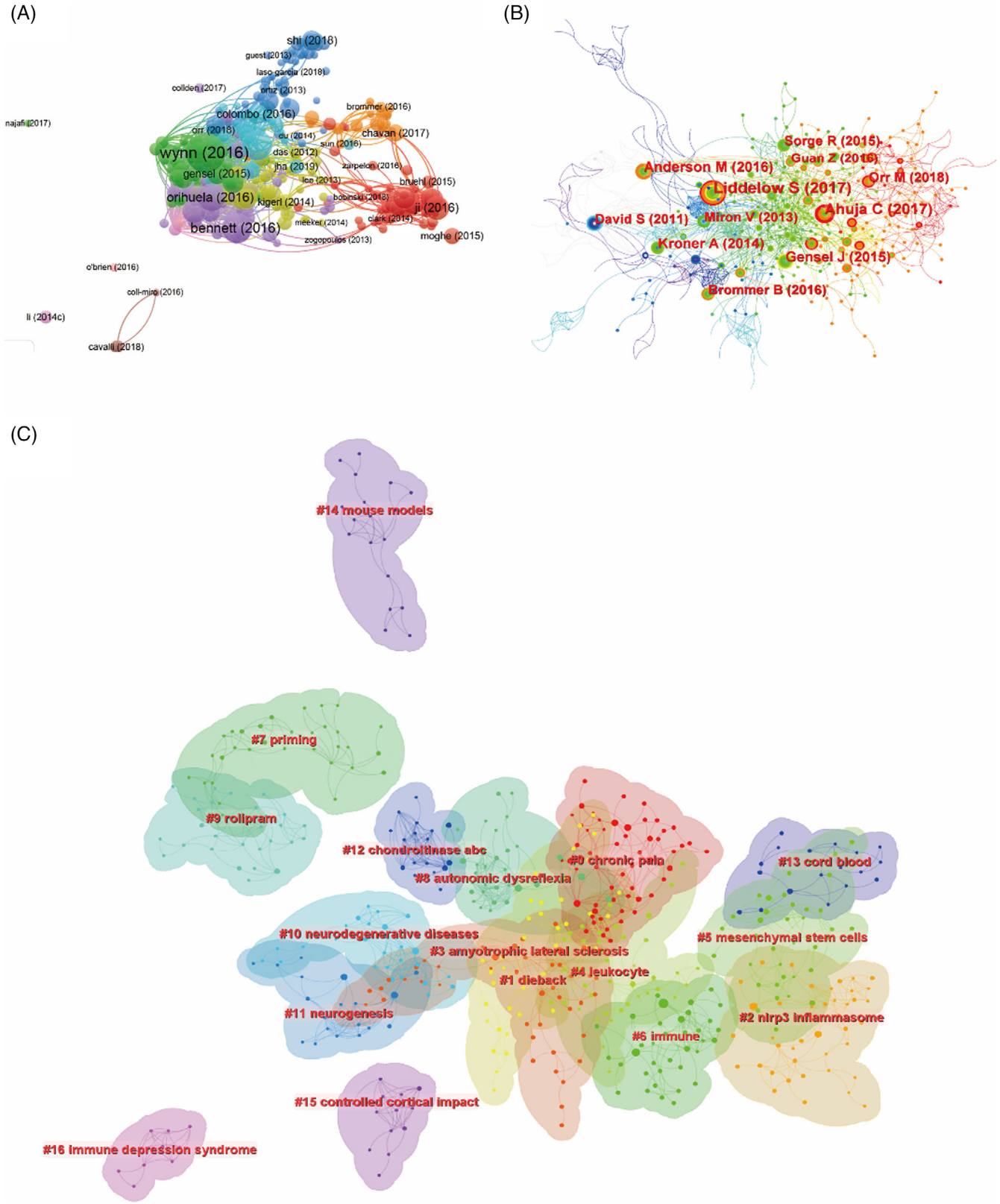


FIGURE 7 Mapping of documents and references in studies on immunology research in spinal cord injury. (A) Network map of the citation analysis of documents with more than 50 citations based on Vosviewer. (B) Network map of co-citation analysis of references based on CiteSpace. (C) Clustering analysis of the co-citation network based on CiteSpace.

TABLE 7 The top five documents with the most citations in the field of immunology research in spinal cord injury.

Rank	Title	Corresponding author	Journal	IF (2021)	Publication year	Total citations
1	Macrophages in Tissue Repair, Regeneration, and Fibrosis	Vannella, KM	*Immunity*	43.474	2016	1575
2	New tools for studying microglia in the mouse and human CNS	Barres, BA	*PNAS*	12.779	2016	925
3	Reactive Astrocytes: Production, Function, and Therapeutic Potential	Barres, Ba	*Immunity*	43.474	2017	913
4	Microglial M1/M2 polarization and metabolic states	Harry, GJ	*British Journal of Pharmacology*	9.473	2016	779
5	Pain regulation by non-neuronal cells and inflammation	Zhang, YQ	*Science*	63.714	2016	562

TABLE 8 The top five co-citation analysis of cited reference on immunology research in spinal cord injury.

Rank	Title	Corresponding author	Journal	IF (2021)	Publication year	Total citations
1	Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord	Popovich, P. G.	*The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*	6.709	2009	227
2	Repertoire of microglial and macrophage responses after spinal cord injury	Kroner, A.	*Nature Reviews. Neuroscience*	38.755	2011	158
3	Basso Mouse Scale for locomotion detects differences in recovery after spinal cord injury in five common mouse strains	Popovich, P. G.	*Journal of Neurotrauma*	4.869	2006	109
4	Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment	Anderson, A. J.	*Brain: A Journal of Neurology*	15.255	2010	109
5	Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury	Popovich, P. G.	*Experimental Neurology*	5.620	2008	108

Regeneration, and Fibrosis."[38] Of the five most cited articles, most types of literature are of the basic research type, focusing on macrophages, microglia, astrocytes, and inflammation-related cells in SCI. In Figure 7C, we can see that most of the top 17 clusters with the strongest citations were related to SCI pathophysiology, diagnosis, and therapy, indicating that these directions are hot topics in immunology research in the SCI field.

4.2 | Research hotspots and frontiers

The co-occurrence analysis of keywords and bursts can reflect the research development directions and hotspots in the immunology-related SCI research field. From Figure 9D, "monocyte chemoattractant protein 1" is the keyword with the highest citation outbreaks, while "extracellular vesicles" (2019–2022), "Regenerative medicine" (2019–2022), "stromal cells" (2018–2022), "motor recovery" (2019–2022), and "glial activation" (2019–2022) represent the most recent representative keywords in SCI research. As shown in Figure 9C, we noticed that the primary research clusters mainly referred to "multiple sclerosis," "neuropathic pain," "mesenchymal stem cells," "schwann cell," and "inflammasome," indicating that molecular biology exploration in SCI disease is a major hotspot.

In our study, we summarize and visualize the keyword co-occurrence network based on the determination of keywords in the titles/abstracts of all included publications. Figure 9D shows four main research trends: (1) mesenchymal stem cells and SCI; (2) extracellular vesicles and SCI; (3) glial activation and SCI; (4) Inflammatory factors and SCI and (5) locomotor recovery and SCI. Presently, these four research areas could not only comply with current hotspots in this field of immunology research in SCI but also forecast the directions of future studies, as follows.

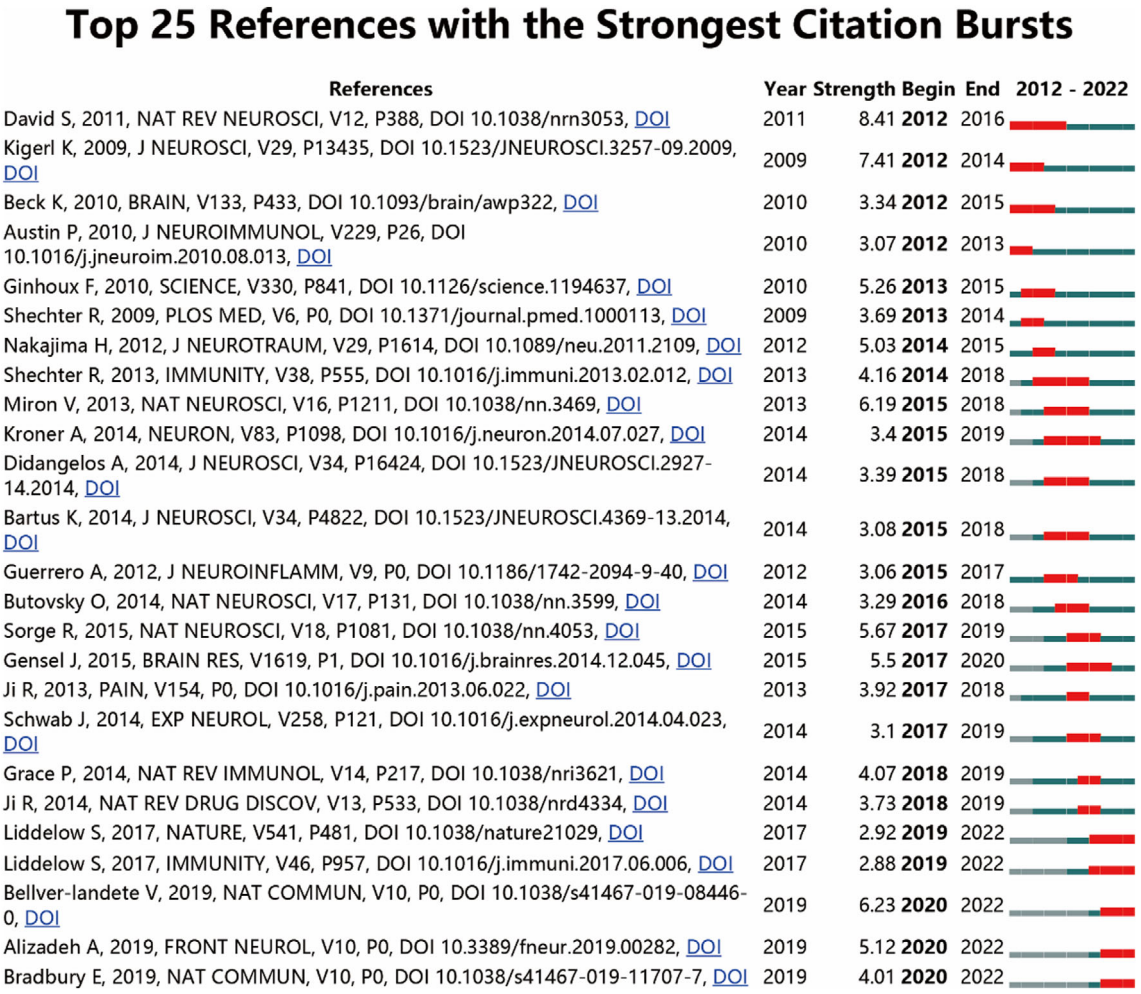


FIGURE 8 Top 25 references with the strongest citation bursts of publications related to immunology research in spinal cord injury.

1. Mesenchymal stem cells and SCI: Co-occurrence analysis of keywords identified "mesenchymal stem cells" as a research hotspot that deserves further attention. With the rapid development of regenerative medicine, scientists have isolated various MSCs from different tissues, such as peripheral blood, bone marrow, placenta, umbilical cord, and amniotic fluid.[39–41] Numerous studies have shown that these pluripotent stem cells can effectively improve various functional parameters of tissue regeneration and functional recovery after SCI.[42] Mechanistically, MSCs were found to exert therapeutic effects by inhibiting the inflammatory response mainly through cell–cell interactions and the secretion of various cytokines.[43] For example, studies have shown that transplantation of bone marrow mesenchymal stem cells into an SCI mouse model can significantly upregulate the number of M2 and M1 macrophages at the injury site, accompanied by increased levels of IL-4 and IL-13 and decreased levels of TNF-A and IL-6. These cellular and molecular changes may contribute to the recovery of motor function, increased retention of axons and myelin sheaths after injury and reduced glial scar formation.[17] MSCs can also play an inflammatory regulatory role by regulating T cells. Transplantation of peripheral blood mesenchymal stem cells into SCI rats also inhibited the expression of Th17-related genes and promoted the expression of Treg-related genes, which may contribute to the recovery of spinal cord function.[44] In addition, MSCs also play an essential role in the inhibition of glial scar formation after SCI and further promote functional recovery.[45] For example, Okuda et al. demonstrated that transplantation of bone marrow stromal cell sheets into SCI rats not only inhibited glial scar formation but also provided a favorable microenvironment for axonal regeneration and functional recovery by affecting the morphology of reactive astrocytes.[46] To maintain the beneficial properties of MSCs, Deng et al. found that MSCs derived from human placenta in 3D culture showed a significant increase in the secretion of anti-inflammatory factors and nutritional factors such as VEGF, PDGF, and FGF and showed great potential in angiogenesis and neurites.[47] When transplanted into the injured spinal cord, these 3D cultured MSCs survived the entire experimental period and retained their secretory advantage to exert significant neuroprotective effects by minimizing the injured cavity, inhibiting inflammation and astrogliosis, and promoting angiogenesis.[47] This study provides a new scheme for the treatment of SCI with different culture patterns of stem cells.

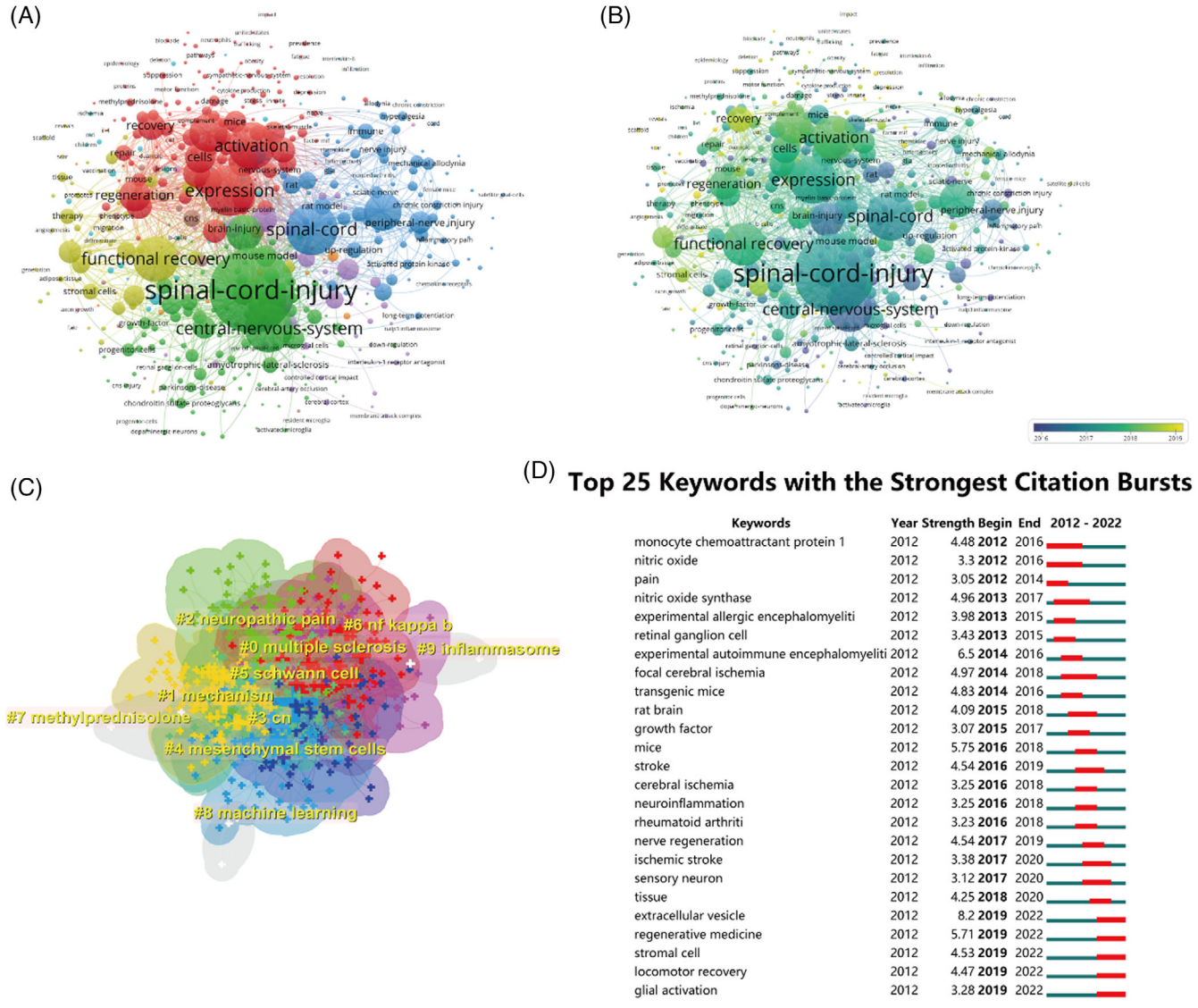


FIGURE 9 Mapping of keywords in studies on immunology research in spinal cord injury (SCI). (A) Network visualization of keywords. (B) Distribution of keywords according to average publication year (blue: earlier, yellow: later). (C) Keyword clustering visualization from 2012 to 2022. (D) Top 25 keywords with the strongest citation bursts of publications related to immunology research in SCI.

2. Extracellular vesicles and SCI: Extracellular vesicles, also known as exosomes, are important mediators of cell–cell communication and are involved in many pathological processes. In recent years, the therapeutic potential of exosomes in SCI has attracted increasing attention. Modulating the formation of a proinflammatory environment is the main strategy for the treatment of SCI, and inhibiting the activation of the NLRP3 inflammasome is expected to promote the functional recovery of rats after SCI.[48,49] For example, Huang et al. found that exosomes derived from epidural adipose-derived mesenchymal stem cells (EFMSCs) promoted the recovery of neural function and reduced the injury degree by significantly inhibiting the activation of the NLRP3 inflammasome and decreasing the expression of inflammatory cytokines.[50] In addition, several miRNAs have recently been identified as potential new targets for the treatment of SCI, including miRNA-486, miRNA-21, and miRNA-126.[51–53] Increasing evidence suggests that exosomes with bilayer structures can be used as valuable vectors for delivering miRNAs at SCI sites. Furthermore, exosomes can penetrate the blood–brain barrier, enhancing the therapeutic effect of miRNA.[54] For example, injection of miRNA-133b-modified exosomes into the tail vein of SCI rats can significantly improve the functional recovery of the hind limb, reduce the volume of injured lesions and preserve neuronal cells to further promote the regeneration of axons.[55] On the other hand, extracellular vesicles can be engineered to load multiple bifactors, which can achieve more targeted and efficient SCI treatment. For example, in view of their natural inflammatory targeting ability, M2 type macrophage exosomes are designed to be used as drug carriers for berberine, and effectively target the injured spinal cord, ultimately achieving significant improvement in the motor function of SCI mice.[56] Another study

prepared a scaffold based on autologous plasma exosomes (AP-EXOs), in which AP-EXOs are loaded with neuron targeting peptides (RVGs) and growth promoting peptides (ILPs and ISPs), which can target neurons in the injured area and cause robust axon regeneration in the lesion core.[57] In general, exosomes have great therapeutic potential in SCI. The next step is to optimize MSC-derived exosomes and adopt various strategies to improve their therapeutic effects in SCI.

3. Glial activation and SCI: Microglia are strongly activated and secrete numerous inflammatory mediators after SCI, which is closely related to the pathophysiological process of SCI.[58] In the subacute phase of SCI, activated M1 microglia trigger a cascade of neurotoxic reactions and cause apoptosis and necrosis of endothelial cells, neurons, axons, and oligodendrocytes.[59] Activated macrophages/microglia are major sources of cytotoxic substances such as TNF-α, inducible nitric oxide synthase (iNOS), hypochlorous acid (HOCl) and reactive oxygen species (ROS).[60] Therefore, the regulation of microglial overactivation may improve SCI repair. For example, Georgieva et al. demonstrated that intravenous docosahexaenoic acid (DHA) effectively alleviated central neuropathic pain after SCI by inhibiting microglial and astrocyte activation in a clinically relevant mouse spinal contusion model.[61] Another study found that 2-(nicotinamide)-1,3,4-thiadiazole (TGN-020), a potent selective inhibitor of aquaporin 4 (AQP4), attenuates edema and inhibits astrocyte activation and glial scar formation after spinal cord compression injury.[62] Indeed, the status and functional phenotype of microglia/macrophages are much more complex in vivo. An increasing number of studies have identified polymorphisms in M2 phenotypic subgroups, such as M2a, M2b and M2c phenotypes.[63] Each phenotype has unique physiological characteristics and unique biological functions. In general, activated M2 microglia/macrophages can increase anti-inflammatory molecules (such as IL-10, TGF-β，IGF-1 and BNDF) and exert neuroprotective effects.[64] For example, Jessica Y Chen et al. loaded IL-10 onto a poly (lactate co glycolide) (PLG) scaffold and delivered it to a mouse SCI model. The results showed that IL-10 could significantly reduce tissue damage and improve subsequent motion recovery.[65] In addition, the proper modulation of glial activation may be of significance for SCI repair, and the findings of Li et al. confirmed the critical role of microglia in coordinating the inflammatory response and scar-less healing after SCI in neonatal mice.[66] Therefore, future studies should emphasize the tissue repair effect and specific time window of microglia after SCI to better regulate their repair potential.
4. Inflammatory factors and SCI: In the whole process of SCI, there are numerous inflammatory factors. Based on the above results, we can identify several of the most popular inflammatory factors, including "chondroitinase ABC," "NLRP3 inflammasome," "monocyte chemoattractant protein 1 (MCP-1)," and "nitric oxide". In fact, these inflammatory factors play an important role in neuroinflammation and tissue repair and may be potential therapeutic targets in the future. Chondroitinase ABC is a bacterial enzyme that can remove sugar sidechains from extracellular matrix molecules (including chondroitin sulfate proteoglycan). They exist in the intact and damaged nervous system and are effective inhibitors of axon growth.[67] To prolong the activity of the enzyme, a study incorporated it in trehalose (which stabilized the protein and helped to maintain the activity of the enzyme) and embedded it in lipid microtubules (to achieve continuous release). Animal experiments found that during the 6-month follow-up period, the coordination between the steps of the forelimb and hind limb of chondroitinase treated animals was improved by an average of 23%, and the three dogs (10%) in the chondroitinase group also recovered their walking ability without help. This study provides strong evidence for a starting chondroitinase ABC clinical trial in patients with chronic SCI.[68] The NLRP3 inflammasome is another key therapeutic target. A study has shown that the pharmacological inhibitors BAY 11-7082 and A438079 inhibit the activation of the NLRP3 inflammasome, which can alleviate neuroinflammation, reduce mitochondrial dysfunction, reduce the severity of SCI, and improve the recovery of neural function after SCI.[69] In addition, after the occurrence of secondary SCI, the mRNA expression level of MCP-1 can be observed to increase.[70] After RNAi is used to inhibit the expression of MCP-1, the expression level of caspase-3 and the damage to neurons and astrocytes can be reduced, indicating that the reduction in MCP-1 expression inhibits the aggravation of apoptosis, which is expected to play a neuroprotective role in the process of secondary SCI.[71] Similarly, a review published by Tardivo V et al. summarized that excessive NO production after SCI promotes oxidative injury, makes the injury permanent, and leads to the loss of neurons in the injured site and surrounding areas. The use of compounds including nitric oxide synthase inhibitors, compounds that interfere with the expression of inducible nitric oxide synthase and molecules that act as antioxidants is expected to be an early and effective SCI intervention.[72] These findings indicate that the regulation of inflammatory factors may be a potential therapeutic strategy to intervene in the malignant inflammatory microenvironment after SCI and promote tissue regeneration and repair.
5. Locomotor recovery and SCI: SCI, especially complete transection SCI with spinal cord tissue defects, usually results in severe irreversible neurological dysfunction below the injured segment, including permanent sensory and motor function loss.[73] However, it has been shown that a limited degree of spontaneous plasticity and motor improvement can be observed after SCI and even after complete transection.[74] The specific mechanism by which this spontaneous motor recovery occurs is largely unknown. It has been shown that lentivirus-mediated Gsx1 expression improved the number of endogenous neural stem cells and progenitor cells in a mouse model of laterally cut SCI in the acute phase. Subsequently, Gsx1 expression stimulated the production of glutamatergic and cholinergic interneurons and attenuated the production of GABAergic interneurons in the SCI chronic phase. In addition, Gsx1 reduces reactive astrogliosis and glial scarring, enhances serotonin (5-HT) neuronal activity, and ultimately restores motor function in injured mice.[75] Rehabilitation training can also exert

surprising effects on the recovery of motor function. A study of intrathecal ChABC therapy combined with artificial dexterity or motor training rehabilitation in rats. Both combinations resulted in an increase in axonal buds in CST, but only rats receiving task-specific rehabilitation showed an increase in manual dexterity. The mice that received the exercise capacity rehabilitation did better on the ladder, but they had worse skill arrival than the mice that did not receive the treatment.[76] Subsequent studies further found that rehabilitation treadmill training in combination with chondroitinase abc and anti-Nogoa antibody treatment was shown to significantly increase axon germination and functional recovery after partial cervical SCI.[77]

4.3 | Future research directions

Based on the aforementioned analysis, it is paramount to prognosticate the forthcoming trends and potential future ramifications on immunology research stemming from SCI. This can be succinctly summarized as follows:

1. In recent years, significant progress has been made in the study of tissue regeneration for SCI treatment. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic tool due to their ability to differentiate into various cell types and their capacity to secrete a range of bioactive molecules that can promote tissue repair and modulate immune responses. Extracellular vesicles (EVs), which are small membrane-bound structures released by cells, have also garnered attention for their potential in promoting tissue regeneration through their ability to transport and deliver bioactive molecules to target cells. Moreover, the study of neurogenesis, the process of generating new neurons in the brain and spinal cord, has shown promising results for SCI treatment. Researchers have identified a variety of signaling pathways and molecules that play a crucial role in regulating neurogenesis and promoting axonal regrowth after SCI. As such, the exploration of advanced tissue engineering strategies, including the use of MSCs, EVs, and neurogenesis, has become a major hotspot and future direction in SCI research. These strategies hold great promise for improving the treatment and management of SCI, with the potential to lead to significant advancements in the field of immunology.
2. Microglia activation has been identified as a crucial pathogenic mechanism in the development and progression of SCI. These specialized immune cells are the resident macrophages of the central nervous system and play a critical role in maintaining homeostasis in the nervous system. Following SCI, microglia become activated and release proinflammatory cytokines and chemokines, leading to the recruitment of peripheral immune cells and exacerbating tissue damage. As such, targeting microglia activation has become an important research direction in the field of SCI. Several studies have shown that inhibiting microglia activation can reduce inflammation and promote tissue repair, highlighting the potential therapeutic value of this approach. However, the underlying mechanisms of microglia activation in SCI remain poorly understood, and further investigation is required to identify potential therapeutic targets and develop effective treatments. In summary, the activation of microglia represents a significant pathogenic mechanism in SCI and is a promising research direction for the development of novel therapeutic strategies. Further research is needed to elucidate the underlying mechanisms and identify potential therapeutic targets for this complex process.
3. SCI is a complex pathophysiological process that involves a cascade of events, including inflammation that can lead to secondary damage and worsen outcomes. A number of inflammatory factors have been identified as key players in the progression of SCI, including chondroitinase ABC, leukocytes, the NLRP3 inflammasome, monocyte chemoattractant protein 1 (MCP-1), and nitric oxide (NO). Chondroitinase ABC, an enzyme that degrades chondroitin sulfate proteoglycans (CSPGs), has been shown to promote axonal regeneration and functional recovery following SCI. Leukocytes, particularly neutrophils and monocytes, play a crucial role in the early stages of SCI by mediating the inflammatory response and promoting the recruitment of immune cells to the injury site. The NLRP3 inflammasome, a multiprotein complex that plays a key role in the innate immune response, has also been implicated in the progression of SCI through its activation of proinflammatory cytokines. MCP-1, a chemokine that mediates the recruitment of monocytes and macrophages, has been shown to play a role in the development of SCI-induced neuropathic pain. Finally, NO, a free radical gas produced by immune cells, has been implicated in SCI-induced apoptosis and tissue damage. Overall, these inflammatory factors are closely associated with the progression of SCI and represent important targets for the development of novel therapeutic strategies aimed at modulating the immune response and promoting tissue repair. Further research is needed to fully elucidate the complex interplay between these factors and to identify potential therapeutic targets for SCI.
4. In addition to tissue regeneration and inflammation, research in the field of SCI has also focused on improving locomotor recovery and managing clinical symptoms related to patients. These symptoms include neuropathic pain, immune depression syndrome, autonomic dysreflexia, and amyotrophic lateral sclerosis (ALS). Advances in these areas have the potential to significantly improve patient outcomes and quality of life. For example, studies have shown that early rehabilitation and activity-based therapies can promote locomotor recovery and improve functional outcomes in SCI patients. Additionally, pharmacological interventions targeting neuropathic pain, such as gabapentin and pregabalin, have been shown to reduce pain and improve quality of life in these patients. Other interventions, such as immunomodulatory therapies and bladder management strategies, have also been explored as potential approaches for managing immune depression syndrome, autonomic dysreflexia, and other clinical symptoms related to SCI. The future direction predictions discussed earlier, including the exploration of advanced tissue engineering strategies and the targeting of inflammatory factors, are in line with current research hotspots

and keywords related to SCI. Further research in these areas has the potential to not only advance our understanding of the pathophysiology of SCI but also assist clinicians in better managing patients' symptoms and improving their overall quality of life.

4.4 | Strengths and limitations

SCI places a heavy burden on patients and society. The main motivation of this study is to analyze the progress in the literature over the last 10 years and summarize the main directions in the future to provide the latest comprehensive information for clinicians and medical researchers. Based on the above analysis, our contribution is reflected in the fact that this study is the first systematic and objective data analysis of the dynamic evolution of immunology research in SCI by using relevant software (CiteSpace and VOSviewer), which has positive reference value for the future research and development of related fields.

However, there are some limitations in the research design. First, because of the limitations of CiteSpace and VOSviewer, our bibliometric software cannot wholly replace the function of system retrieval. Furthermore, the entirety of the literary material was procured and amassed solely from WoSCC, a methodology that potentially overlooked relevant data obtainable from alternative databases, such as PubMed, Cochrane, CINAHL and Scopus; therefore, some measurements and alternative software, such the R package "bibliometrix," Histcite, and Citexs software, can be used. Second, all extracted research and review articles were written in English, which might result in bias, as non-English or nonresearch/review articles were not included. In addition, we did not provide timeline maps and more specific topic analysis, which might result in follow-up prediction bias.

5 | CONCLUSION

This study employed bibliometric analysis software, namely CiteSpace and VOSviewer, to scrutinize the global landscape of immunology research in the SCI field from 2012 to 2022. Our inquiry unraveled a steady yearly escalation in publications within this research domain, with a pronounced focus on regenerative medicine, mesenchymal stem cells, extracellular vesicles, neuroimmune cells, and motor function recovery. Moreover, our investigation revealed that the United States reigns supreme in terms of publication output, citation count, and h-index in the realm of immunology research related to SCI. Among the institutions with the most prolific publication output, the University of California System, Ohio State University, and University of Miami took the top three spots. By discerning the interconnections and rudimentary scientific knowledge in immunology-linked SCI research, this study furnishes invaluable insights into research trends and frontiers. These findings can furnish researchers with a roadmap for navigating the current overarching directions of this field and pinpointing potential avenues for future exploration.

AUTHOR CONTRIBUTIONS

Bowen Zheng, Yirui Kuang and Songlin Liu conceived and designed the study. Dun Yuan, Yirui Kuang analyzed the data. Haoxuan Huang, Yirui Kuang wrote the manuscript. Bowen Zheng, Dun Yuan and Haoxuan Huang contributed to revise the manuscript. Bowen Zheng, Songlin Liu supervised the study. All authors approved the final manuscript as submitted.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available through the corresponding author on reasonable request.

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