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REVIEW ARTICLE

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A bibliometric analysis of global research on spinal cord injury: 1999–2019

Yongbo Li[1], Baixing Wei[1], Yihan Zhong[1], Hao Feng[1] and Han Wu[1]✉

STUDY DESIGN: Bibliometric review.
OBJECTIVE: The spatial structure of the global spinal cord injury (SCI) research field has not been summarized or analyzed. The objective of this study was to understand the current status and global trends of SCI research, and provide scholars knowledge to integrate into their plans for future research.
SETTING: Not applicable.
METHODS: The Web of Science database was searched for articles related to SCI published between 1999 and 2019. Metrics based on publication data, including publication counts, H indices, countries, institutions, authors, and journals were extracted. Co-citation analysis, collaboration analysis, and co-occurrence analysis of keywords were conducted using CiteSpace.
RESULTS: The search identified a total of 41,012 articles related to SCI. Overall, the number of publications increased annually. The United States was the top ranked country by publication count, H index, and citation count. Harvard University and the University of Toronto made the most contributions. M.G. Fehlings was the top ranked author. *Spinal Cord* published the largest number of articles, and was the most frequently cited journal. The top 5 ranked keywords that appeared most frequently were spinal cord injury, functional recovery, adult rat rehabilitation, and paraplegia. Twelve major clusters of keywords and 15 clusters of co-cited references were generated.
CONCLUSIONS: This study comprehensively analyzed and summarized the trends in SCI research during the past 20 years. Findings should provide scholars information on the countries, institutions, authors, and journals that are active in the field of SCI research, and a knowledge base for future projects.

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INTRODUCTION

Spinal cord injury (SCI) may result in damage to the central nervous system and cause motor and sensory dysfunction. In severe cases, SCI can lead to lifelong disability or death. Between 2006 and 2016, the global incidence of SCI was 10.5 cases per 100,000 persons, resulting in an estimated 768,473 new cases of SCI each year [1, 2].

SCI places a heavy economic burden on families and society. Globally, the incidence of economically impactful SCI is estimated at 13 cases per 100,000 per year [3]. Direct costs are highest in the first year after SCI onset, decrease over time, and are influenced by the level and severity of the injury. In the United States, mean annual costs (health care and living expenses) directly attributable to SCI for the first year and each subsequent year are estimated at $347,896 and $42,256 for patients with motor dysfunction at any level, $519,520 and $68,821 for paraplegia, $771,264 and $113,557 for low tetreplegia (C5–C8), and $1,065,980 and $185,111 for high tetreplegia (C1–C4) (2015 USD), respectively [4].

Extensive medical research has been conducted on SCI. In recent years, the main research topics included the pathology of SCI [5] and therapeutic rehabilitation [6], which led to a growing network of researchers joining the field and a concomitant increase in publications. To date, the spatial structure of the global SCI research field has not been summarized or analyzed.

Bibliometrics is a method of objective measurement that is commonly used to analyze research topics, research status, and publication quality. It can evaluate influential and groundbreaking research and is used in many fields of medical science [7–9]. CiteSpace is a popular bibliometric and visual analysis tool based on the theory of co-citation analysis and path-finding algorithms. CiteSpace analyzes literature in specific fields to explore the critical paths and inflection points of knowledge in the evolution of a subject area. Through a series of visualization techniques, CiteSpace evaluates global research hotspots and detects research trends [10].

This study used the Web of Science and CiteSpace software to perform a bibliometric and visual exploration of articles related to SCI published between 1999 and 2019. The objective was to understand the current status and global trends of SCI research, and provide scholars knowledge to integrate into their plans for future research.

MATERIALS AND METHODS

Data sources and search strategy

On December 10, 2019, the Web of Science database was searched for publications related to SCI, using the following search

[1]Department of Orthopedics, China-Japan Union Hospital of Jilin University, Jilin University, Changchun, China. ✉email: wu_han@jlu.edu.cn

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strategy: (TS = ("spinal injur *" OR "spinal cord injur *" OR "spinal traum *" OR "spinal cord traum *" OR tetraplegia OR paraplegia)). The time period was 1999–2019, and the document type was article.

Bibliometrics and visual exploration

Metrics based on publication data, including publication counts, H indices, countries, institutions, authors, journals, and language of publication were extracted from the Web of Science search results. Then, CiteSpace software (5.5.R2) was used for visual exploration of the literature identified by the search. The visual knowledge network created by CiteSpace consists of nodes and lines. Nodes in the network represent items, such as authors, countries, institutions, and cited references, and lines between nodes represent co-operative, co-occurring, or co-citation relationships. The size of each node indicates how often the item appears or is referenced. Node and line colors represent different years. A purple ring indicates a node with a high degree of centrality, which is considered a key node in a collaborative or co-citation network.

RESULTS

Publication output

A total of 41,012 articles related to SCI were indexed in Web of Science between 1999 and 2019. The number of articles per year increased steadily from 995 in 1999 to 3159 in 2018, and then decreased to 2496 in 2019. Approximately 96% (39,755/41,012) of the articles were written in English (Fig. 1).

Country analysis

Research teams in 152 countries published articles related to SCI between 1999 and 2019. The top 10 ranked countries producing the most publications, with H indices and citation frequencies, are listed in Table 1. The top 3 ranked countries by publication count were the United States ($n = 15,850$), China ($n = 4328$), and Canada ($n = 3315$). The United States had the highest H index and total citation frequency. Figure 2A shows the top 10 ranked national cooperation networks by co-occurrence. The top 3 ranked networks were the United States ($n = 15,766$), China ($n = 4326$), and Canada ($n = 3299$).The top 3 ranked countries by centrality were France (0.15), Switzerland (0.1), and Belgium (0.1) (Fig. 2B). The top 3 ranked countries by sudden publication increases were China (2015–2019), Iran (2015–2019), and Russia (2016–2019) (Fig. 2C). This may be related to the increasing number of motor vehicles with the economic development of these countries, which has led to an increase in the incidence of SCI and the large amounts of funds invested in this field by these countries. There were collaborations between the United States, Japan, South Korea, China, and Canada; between China, Russia, Australia, and Singapore; and between Canada, Hungary, Morocco, the United States, Russia, and Mexico (Fig. 2D).

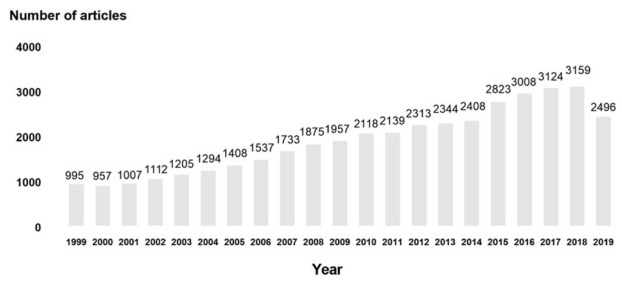

Fig. 1 Number of publications per year 1999–2019.

Institutional analysis

Research teams from 21,239 institutions published articles related to SCI. The top 3 ranked institutions by publication count were the University of Toronto ($n = 792$), the University of British Columbia ($n = 752$), and the University of Miami ($n = 734$) (Table 2). The top 5 ranked institutions by H index and citation count were Harvard University, the University of Toronto, the University of California Los Angeles, the University of Miami, and the University of British Columbia (Table 2). A visual exploration of institutions that published articles on SCI between 1999 and 2019 is shown in Fig. 3.

Author analysis

Approximately 100,000 authors published articles related to SCI. The top 3 ranked authors by publication count were M.G. Fehlings ($n = 271$), J. Liu ($n = 174$), and A. Curt ($n = 156$) (Table S1). The top 3 ranked authors by H index and citation count were M.G. Fehlings, M.H. Tuszynski, and M.E. Schwab (Table S1). A visual exploration of authors that published articles on SCI between 1999 and 2019 is shown in Fig. S1.

Journal analysis

A total of 3848 journals published articles related to SCI. The top 10 ranked journals by publication count contributed 20% of those articles. The top 3 ranked journals by publication count were *Spinal Cord* ($n = 2231$), *Archives of Physical Medicine and Rehabilitation* ($n = 1092$), and the *Journal of Neurotrauma* ($n = 1058$) (Table S2). A visual exploration of journals that published articles on SCI between 1999 and 2019 is shown in Fig. S2. The top 3 ranked journals by co-occurrence frequency were *Spinal Cord*, the *Journal of Neuroscience*, and *Archives of Physical Medicine and Rehabilitation*. The top 3 ranked journals by centrality were the *Journal of Neuroscience*, the *Journal of Neurotrauma*, and *Spinal Cord*.

Table 1. Top 10 countries by publication count, H index, and citation count.

Rank	Publications	Country	H index	Country	Sum of times cited	Country
1	15,850	United States	196	United States	477,829	United States
2	4328	China	123	Canada	98,396	Canada
3	3315	Canada	112	England	71,048	England
4	2582	Japan	109	Germany	69,700	Germany
5	2492	Germany	94	Japan	55,872	Japan
6	2455	England	93	Switzerland	47,124	China
7	1635	Australia	89	Italy	43,997	Italy
8	1622	France	85	France	41,477	Switzerland
9	1616	Italy	84	Australia	38,557	France
10	1315	Switzerland	82	The Netherlands	38,002	Australia

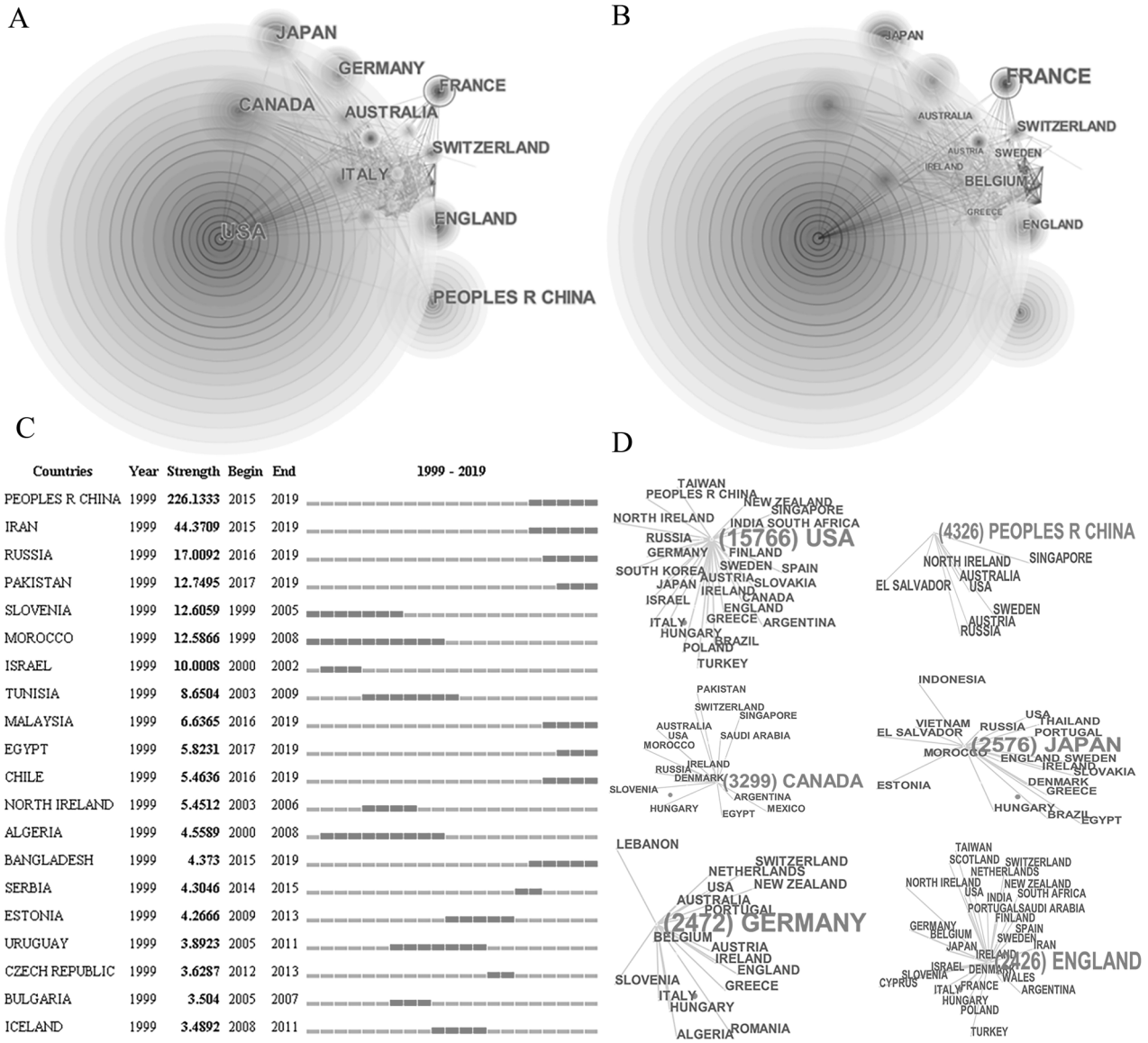

Fig. 2 Country analysis: **A** co-occurrence counts, **B** centrality, **C** publication bursts, **D** collaboration network.

Keyword analysis

An analysis of keywords used in articles on SCI between 1999 and 2019 is shown in Fig. S3. The top 5 ranked keywords were spinal cord injury, functional recovery, adult rat rehabilitation, and paraplegia (Fig. S3A). The keyword co-occurrence cluster map revealed 12 clusters (Fig. S3B and Table S3); for example, keywords that occurred most often with "neuroprotection" were stroke, rat, axonal regeneration, neuroogenesis, and neurore-generation, and keywords that occurred most often with "differentiation" were stem cell, transplantation, and clinical trial. Keywords with an increased number of occurrences in recent years were methylprednisolone (1999–2006), electrical stimulation (1999–2008), and oxidative stress (2014–2019) (Fig. S3C). Other keywords that appeared more often in recent years were health, people, and epidemiology, which have become research hotspots in the SCI field (Fig. S3D). Trends in keyword changes as time progressed are shown in Fig. S4 and Table S4. Taken together, the data generated by the keyword analysis revealed the research hotspots that have developed in the SCI field over time (Fig. S4 and Tables S3 and S4).

Co-citation analysis

Co-citation analysis of the 41,012 articles yielded co-citation of 449 articles; these form the knowledge base of the SCI field (Tables S5 and S6). A visual exploration of co-cited articles on SCI between 1999 and 2019 is shown in Fig. S5. A total of 15 clusters were generated, including "inflammation", "myeloperoxidase", and "induced pluripotent stem cells" (Fig. S5B). These represent research frontiers in the SCI field in the past 20 years.

DISCUSSION

Research status and quality of global publications

Between 1999 and 2019, there was an annual increase in the number of articles published in the SCI field. The number of articles in 2019 decreased slightly, possibly because our search did not include the complete year; however, the overall trend showed a rise. This implies that research in the SCI field is in a progressive state of growth and development.

The H index and citation count reflect the quality and academic impact of publications by country, institution, or author [11]. The

Table 2. Top 10 institutions by publication count, H index, and citation count.

Rank	Publications	Institution	H index	Institution	Sum of times cited	Institution
1	792	University of Toronto	91	Harvard University	34,539	Harvard University
2	752	University of British Columbia	81	University of Toronto	28,434	University of Toronto
3	734	University of Miami	80	University of California Los Angeles	25,521	University of Miami
4	616	Northwestern University	79	University of Miami	22,565	University of California Los Angeles
5	581	University of Pittsburgh	74	University of British Columbia	22,346	University of British Columbia
6	577	University of Washington	74	University of Zurich	22,202	University of Zurich
7	458	Harvard University	74	University of California San Diego	22,143	University of London
8	421	Case Western Reserve University	71	University of London	17,245	University of California San Diego
9	421	University of Michigan	70	Northwestern University	15,649	Northwestern University
10	393	University of California Los Angeles	69	University of Washington	14,382	University of Washington

United States was ahead of other countries in terms of publication count, H index, and citation count, and is at the core of SCI research. China was the only developing country in the top 10 ranked countries by publication count, coming in second; however, China was not among the top 10 ranked countries by H index or citation count. An estimated 21,239 institutions were active in SCI research. The top 10 ranked institutions were in developed countries, specifically the United States [8] and Canada [2]. The top 2 ranked institutions by H index and citation count were Harvard University in the United States and the University of Toronto in Canada. These are first-class institutions that have an international impact in the SCI field. M.G. Fehlings from Canada was the top ranked author of articles relevant to SCI by publication count, H index and citation count. Publications by top ranked authors reflect research trends and future directions.

Co-occurrence analysis showed extensive cooperation between countries, with the United States having the most collaborations and China ranked second. China's academic influence is currently small, but researchers in this country are eager to collaborate and the research environment in China is flourishing. France played a key intermediary role in academic exchanges between scholars in various research institutions.

Research hotspots and trends

Research hotspots are topics examined by researchers in a particular field over a certain period of time. Research hotspots can be identified by keyword co-occurrence and cluster analysis. Analysis of co-occurring keywords used in articles on SCI published between 1999 and 2019 yielded 12 clusters: neuroprotection, differentiation, apoptosis, family, paraplegia, response, quality of life, methylprednisolone, tetraplegia, microglia, cervical spine, and disease (Table S3). Further examination of the co-occurring key works and clusters revealed interesting information. For example, research on neuroprotection, involving axons and other nerve regeneration, was mainly carried out in mice; many studies on stem cell differentiation and transplantation have entered clinical trials; some paralysis is caused by family inheritance, with studies focused on genetic loci and proteins; and methylprednisolone has important side effects.

During 1999–2019, research hotspots and trends in the SCI field varied (Fig. S4 and Table S4). Between 1999 and 2002, there were 12 clusters, covering diverse research topics and based on collaborative innovation. Between 2003 and 2008, the number of clusters and amount of influential research decreased. Research hotspots included stem cells, differentiation, neuropathic pain, activation, neuron outgrowth, and mortality. Between 2009 and 2019, research topics became more varied, with research hotspots focused on people, adults, health, and epidemiology, and clusters in apoptosis, quality of life, microglia, cervical spine, and disease.

In general, researchers have focused on the pathology (rat models), natural history, and treatment (electrical stimulation, stem cell therapy, pharmacological intervention, rehabilitation programs) of SCI; more recently, epidemiology has become a research hotspot. Collecting "big data" on SCI allows estimates of the incidence and prevalence of SCI, which reflect the global burden of these injuries, informing a future research trend in the SCI field.

Research frontiers and knowledge base

A knowledge base is composed of a collection of co-cited articles, while a research front is cluster of articles that is actively cited by researchers. In Citespace, clusters of knowledge bases are named according to nouns extracted from the citing documents; this name can be considered a research frontier. In the present study, a total of 15 clusters were generated (Fig. S5B). Here, we summarize the most cited and central articles in each cluster, which constitute the knowledge base of each research frontier in the SCI field.

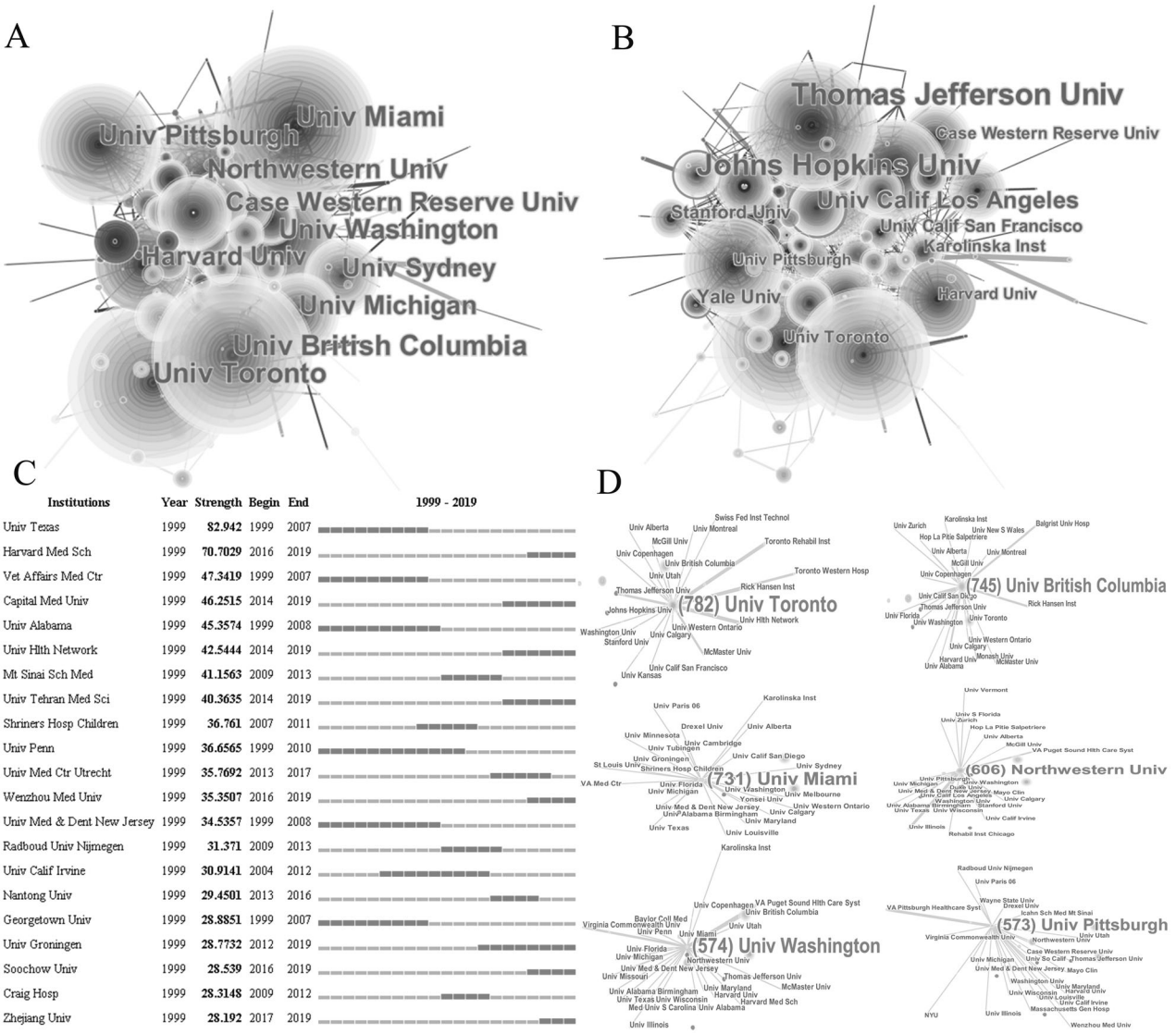

Fig. 3 Institution analysis: **A** co-occurrence counts, **B** centrality, **C** publication bursts, **D** cooperation network.

Inflammatory response. After a SCI, the body produces an inflammatory response, and the blood-brain spinal cord barrier may be destroyed. Cells and other components of the immune system invade, which can exacerbate SCI and affect its repair and regeneration. Kigerl et al. showed that an M1 macrophage response was rapidly induced and maintained at sites of traumatic SCI, while a comparatively smaller and transient M2 macrophage response promoted the regeneration of sensory axons in adult mice [12]. Donnelly et al. reviewed the literature describing the complexities and controversies of post-traumatic neuroinflammation in the spinal cord, concluding that inflammation is a pathogenic component of SCI, but crucial for tissue repair. The authors highlighted the need to control the crosstalk between the nervous system and the immune system to minimize delayed neurodegeneration while promoting axon plasticity and regeneration [13]. David et al. reviewed the literature describing the activation of macrophages and microglia following SCI and their effects on repair, proposing that novel therapeutic approaches should focus on promoting M2 polarization in the injured spinal cord [14]. Beck et al. provided new insight into cellular inflammation in SCI and identified an extended multiphasic response [15]. Fleming et al. suggested that potentially destructive neutrophils and activated microglia, replete with oxidative and proteolytic enzymes, appear within the first few days of SCI. They proposed that anti-inflammatory "neuroprotective" strategies should be directed at preventing early neutrophil influx and modifying microglial activation [16].

Behavioral assessments. Several animal models have been developed to study the neurobiological and behavioral consequences of SCI. Basso et al. stated that the Basso, Beattie, Bresnahan Locomotor Rating Scale for rats does not accurately reflect locomotor recovery after SCI in mice. They developed the Basso Mouse Scale for Locomotion as a valid locomotor rating scale for mice and to identify strain differences in locomotor recovery after SCI [17]. Keirstead et al. transplanted human embryonic stem cells (hESC)-derived oligodendrocyte progenitor cells (OPC) into adult rat SCIs. Predifferentiating hESCs into functional OPCs enhanced myelin sheath regeneration and improved motor function, demonstrating the therapeutic potential of OPCs at early time points after SCI [18]. Scheff et al. designed a novel SCI device to produce graded morphological and behavioral changes in adult rats following an injury at thoracic level 10 (T10). This SCI rodent model reduced the

variability associated with existing devices by defining injury with a constant preset force [19].

Induced pluripotent stem cells. Multipotent stem cells can indefinitely self-renew and differentiate into any cell type. These cells may promote functional recovery after SCI by rebuilding damaged circuits, remyelinating the myelin sheath, and increasing plasticity and/or axonal regeneration; however, the survival, integration, and differentiation of transplanted cells must be controlled [20]. Lu et al. embedded neural stem cells expressing GFP into a fibrin matrix containing a mixture of growth factors, and transplanted them to the site of severe SCI in adult rats. Grafted cells differentiated into a variety of cell phenotypes, including neurons, which extended large numbers of axons over long distances. The extended axons formed abundant synapses with host cells, thereby creating new relay circuits and significantly improving function [21]. Karimi-abdolrezaee et al. transplanted adult brain-derived neural precursor cells (NPCs) isolated from transgenic mice into the spinal cord of adult rats after injury. NPCs integrated along white matter tracts, and NPC-derived oligodendrocytes expressed myelin basic protein, ensheathed axons, and promoted functional recovery [22]. Cummings et al. demonstrated that human central nervous system stem cells grown as neurospheres and engrafted in NOD-scid mice with SCI, survived, implanted, differentiated into neurons and oligodendrocytes, and promoted locomotor recovery [23].

Plasticity. Inhibitory components in the glial environment can affect axon regeneration and remodeling after SCI. Treatments should support growth across the lesion cavity, intrinsically augment the ability of neurons to elongate, and influence the extrinsic inhibitors that block growth at the site of the glial scar. Chondroitinase ABC can promote regeneration, plasticity, and functional recovery in various experimental models [24]. Garcia-alias et al. combined chondroitinase-induced plasticity with physical rehabilitation to promote recovery of manual dexterity in rats with cervical SCI [25]. Bareyre et al. revealed that axonal sprout formation and removal caused spontaneous extensive remodeling after incomplete SCI in adult rats. They postulated this remodeling may be crucial for human rehabilitation [26].

Astrogliosis. The glial environment of the adult central nervous system, including inhibitory molecules in the central nervous system, myelin, and proteoglycans associated with astrological scars, may be the main obstacles to successful axonal regeneration. Fitch et al. reviewed the literature describing the role of inflammatory cell activation, reactive astrogliosis, and the production of growth promoting and inhibitory extracellular molecules during abortive attempts at neuronal regeneration after SCI [27]. Sofroniew et al. reviewed the literature describing the molecular mechanisms of reactive astrocytes and highlighted the potential for identifying novel therapeutic targets for various neurological diseases [28]. Faulkner et al. used a transgenic mouse model to show that reactive astrocytes have protective functions after mild or moderate SCI. They speculated that preserving reactive astrocytes, augmenting their protective functions, or both, may lead to novel approaches to reducing secondary tissue degeneration and improving functional outcomes after SCI [29].

Disability and health. An understanding of the global epidemiology and clinical and economic burden of SCI is essential to implement appropriate preventative and management strategies.

Rehabilitation. Effective and reliable walking tests can quantify gait performance, and therapists can assess changes in a patient's walking ability throughout the rehabilitation process. Dobkin et al. compared the efficacy of step training with body weight support on a treadmill with over-ground practice to a defined over-ground mobility therapy (CONT) in patients with incomplete SCI and found the strategies did not produce different results. These findings provided new insights into disability after incomplete SCI and confirmed the need for multicenter, randomized clinical trials to test rehabilitation strategies [30]. Van Hede et al. evaluated the effectiveness and reliability of three timed walking tests (Timed Up and Go, 10-meter walk test, 6-minute walk test) in patients with SCI, and concluded that the three timed tests were valid and reliable measures for assessing walking function in these patients [31].

Brain-computer interface. Hochberg et al. directly translated neural activity into control signals for assistive devices to restore mobility and independence in paralyzed patients. They demonstrated the ability of two people with long-standing tetraplegia to perform three-dimensional reach and grasp movements using neural interface system-based control of a robotic arm [32]. van den Brand et al. described an electrochemical neuroprosthesis and a robotic postural interface designed to encourage supraspinally mediated movements in rats with paralyzing lesions. By encouraging active participation under functional states, this training paradigm triggered a cortex-dependent recovery with potential to improve function in humans after similar injuries [33].

Transplantation. Ramon-Cueto et al. revealed that olfactory ensheathing glial (OEG) transplants restored the structure and function of the spinal cord after complete transection in adult rats. Rats exhibited voluntary hind limb movements, supported their weight, and their hind limbs responded to mild skin contact and proprioceptive stimuli. Findings suggested that OEG transplantation provides a useful repair strategy for adult mammals with SCI [34]. In another study, Ramon-Cueto et al. showed that transplanted OEG moved through white matter bundles, gray matter and glial scars, overcoming the inhibitory effects of the central nervous system environment in adult rats. Transplanted OEG appeared to provide damaged spinal axons with appropriate factors for long-distance elongation, and offer new possibilities for the treatment of CNS conditions that require axonal regeneration [35].

Nogo. Myelin-derived axon growth inhibitors, such as Nogo, may be responsible for the lack of regeneration of CNS axons after injury in adult mammals. Wang et al. reported that oligodendrocyte-myelin glycoprotein was an inhibitor of neurite outgrowth like Nogo-A that acts through the Nogo receptor (NgR) and its associated receptor complex [36]. Grandpre et al. showed that Nogo-66 (1–40) antagonist peptide (NEP1-40) blocked Nogo-66 or CNS myelin inhibition of axonal outgrowth in vitro, indicating that the NgR mediates a substantial portion of axonal outgrowth inhibition by myelin [37].

Limitations

This study has certain limitations. First, the inclusion of a single database (vs. Pubmed Embase, and Cochrane) may have influenced our findings. Second, bibliometric analysis may not accurately track research impact. For example, the individual prominence of recently published high-quality papers may not be captured due to low citation counts. Thus, future research should not be based a single database, and should focus on recently published articles.

CONCLUSION

This study comprehensively analyzed and summarized the trends in SCI research during the past 20 years. Findings should provide scholars information on the countries, institutions, authors, and journals that are active in the field of SCI research, and a knowledge base for future projects.

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AUTHOR CONTRIBUTIONS

YL designed the study; BW and YZ performed data collection; YZ and HF analyzed the data and performed the statistical analysis. HF and YL drafted the initial manuscript. HW critically reviewed and revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Han Wu

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