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RESEARCH

50 years of methylprednisolone application in spinal cord injury: a bibliometric analysis

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Abstract

Purpose Methylprednisolone (MP) is a synthetic glucocorticoid known for its anti-inflammatory and immunosuppressive effects, yet its application in global spinal cord injury (SCI) research has not been thoroughly summarized. This study aims to assess the current status and trends of methylprednisolone research in SCI, providing insights for future scholarly work.

Methods Articles on methylprednisolone in SCI published from 1975 to 2023 were retrieved from the Web of Science database. Metrics such as publication counts, H-index values, and data on countries, institutions, authors, and journals were analyzed. Co-citation, collaboration, and co-occurrence analyses of keywords were performed using CiteSpace.

Results A total of 1,651 articles were identified, and publication numbers showed a consistent annual increase. The United States and Canada led in publication counts, H-index values, and citations, with the University of Toronto and the Veterans Health Administration being significant contributors. Bracken M.B. was the leading author. The most frequent keywords included 'trauma,' 'lipid peroxidation,' 'dose response,' 'ischemia,' and 'methylprednisolone.' A co-occurrence analysis classified 225 keywords into three clusters, highlighting key research areas in SCI.

Conclusions These findings offer valuable insights into authors, countries, institutions, keywords, and research hotspots in SCI over the past 50 years, guiding future research directions in this field.

Keywords Spinal cord injury · Methylprednisolone · Bibliometrics · Trauma · Lipid peroxidation

Introduction

Methylprednisolone (MP) is a synthetic glucocorticoid medication that shares a similar chemical structure with the endogenously secreted glucocorticoid cortisol (Timmermans, Souffriau, & Libert [41]), . Glucocorticoids are a class of drugs with broad anti-inflammatory(Vandewalle, Luypaert, De Bosscher, & Libert [43]), and immunosuppressive properties [8], which are utilized in clinical settings to treat a variety of inflammatory diseases [30], allergic reactions [42], and immune system-related disorders [20].

The condition of spinal cord injury (SCI), which can result in lifelong disability for patients [50], is a significant burden for those involved, their families, and society as a whole(Fan, Wei, & Feng [13]), . SCI affected approximately 0.9 million people annually worldwide in 2019 [48]. The incidence of SCI was estimated at 20.6 million people in 2019. Among these individuals with spinal cord injury (SCI), 90% of the cases are due to trauma. In 2019, falls and road injuries were identified as the two leading causes of SCI [22, 49].

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During the initial stage of spinal cord injury, a strong primary inflammation frequently occurs in the spinal cord. Early research reports suggested that high-dose glucocorticoids may alleviate the inflammatory response following SCI and possibly promote neural recovery. It is believed that the early administration of high-dose methylprednisolone in the acute phase of spinal cord injury can rescue damaged cells of the spinal cord, reduce the release of inflammatory mediators, mitigate secondary injury to the spinal cord, facilitate spinal cord recovery, and decrease the degree and rate of disability [4, 5].

With the deepening of related research, the mechanism of methylprednisolone in the treatment of spinal cord injury has been greatly elucidated. In animal experiments, it can be observed that following the initiation of methylprednisolone administration, continuous application of methylprednisolone sodium succinateis Associated with fewer pyknotic nuclei and more oligodendrocytes and astrocytes surviving in ventral white matter [35]. As demonstrated by Zou and colleagues(Zou, Guo, Zhu, Xu, & Liu [51]), , methylprednisolone can suppress A1 neurotoxic reactive astrocyte activation and decrease levels of Iba1, Il-1, TNF, and C3., thereby inhibiting A1-type astrocyte activation and promoting functional recovery in rats. Through high-throughput sequencing, it was found that after treatment with Methylprednisolone, 316 genes exhibited differential expression, and in addition to nerve recovery genes, anti-oxidative, anti-inflammatory, and anti-apoptotic genes were also upregulated [27].

The current dilemmas surrounding the use of methylprednisolone (MPSS) include: the perception that there is insufficient evidence supporting the beneficial effects of MPSS for acute spinal cord injury, and the belief that the evidence for harmful effects of MPSS administration outweighs any suggestions of benefit(Bowers, Kundu, & Hawryluk [3]), .

A great deal of controversy surrounds the use of high-dose shock therapy in the early treatment of spinal cord injuries. It was reported in 1990 that Methylprednisolone could prove beneficial in the early treatment of spinal cord injury, but this was quickly followed by a great deal of controversy. Subsequent clinical trials did not observe similar clinical achievements as the initial studies and identified many serious side effects, such as infections. In the meta-analysis conducted by Liu and colleagues, which included three randomized controlled trials and 13 observational studies. At the final follow-up, there were no significant differences between the Methylprednisolone group and the control group in terms of combined motor and sensory scores(Fehlings, Wilson, & Cho [14]), . In addition, the glucocorticoid group experienced significantly more adverse events than the control group, primarily due to gastrointestinal bleeding and respiratory infections [28].

Therefore, in recent years, many researchers have focused on Methylprednisolone in spinal cord injury, and to date, the spatial structure of global SCI research has not been analyzed or summarized.

Methylprednisolone application in Spinal Cord Injury (SCI) from 1975 to 2023 was examined using Web of Science and CiteSpace software. It provided scholars with valuable knowledge for incorporating into their future research plans, by offering insights into the current landscape and global trends of SCI research.

Methods

Literature sources and search strategy

This study conducted a search in the Web of science Core Collection (WoSCC) database. The search terms used were as follows: TS = (Spinal Cord Trauma* OR Traumatic Myelopath* OR Spinal Cord Injur* OR Spinal Cord Transection* OR Spinal Cord Laceration* OR Post-Traumatic Myelopath* OR Post Traumatic Myelopath* OR Spinal Cord Contusion*)) AND TS = (Steroid* OR Catatoxic Steroids OR Steroids, Catatoxic OR Corticoid* OR Adrenal Cortex Hormone OR Corticosteroid* OR 6-Methylprednisolone OR 6 Methylprednisolone OR Metipred OR Medrol OR Urbason OR Methylprednisolone Hemisuccinate OR Methylprednisolone Succinate OR Methylprednisolone Sodium Succinate OR Methylprednisolone Sodium Hemisuccinate OR Methylprednisolone Hemisuccinate Monosodium Salt OR 6 alpha-Methylprednisolone Sodium Hemisuccinate OR A-MethaPred OR Solu-Medrol OR Solumedrol. The time period was 1975 to 2023, the document type was article. 1509 articles were accepted with complete author, country, institution, journal, publication year, and citation information, excluding review articles, meeting abstracts, corrections, and non-English literature. (Figure 1).

Data collection and statistics

We conducted publication volume statistics and journal source analysis using Bibliometrix in R version 4.2.1 as well as VOSviewer version 1.6.18 and Scimago Graphica for international cooperation analysis. A CiteSpace version 6.2.R2 was used for analyzing author and institutional collaborations, clustering, and burst detection of keywords.

Results

Publishing trend

A distribution of publication times and trends can be determined by analyzing all the literature data on "*Methylprednisolone therapy for spinal cord injuries*" to determine how the topic has developed and how much academic attention it has received. In total, 1255 studies have been published related to

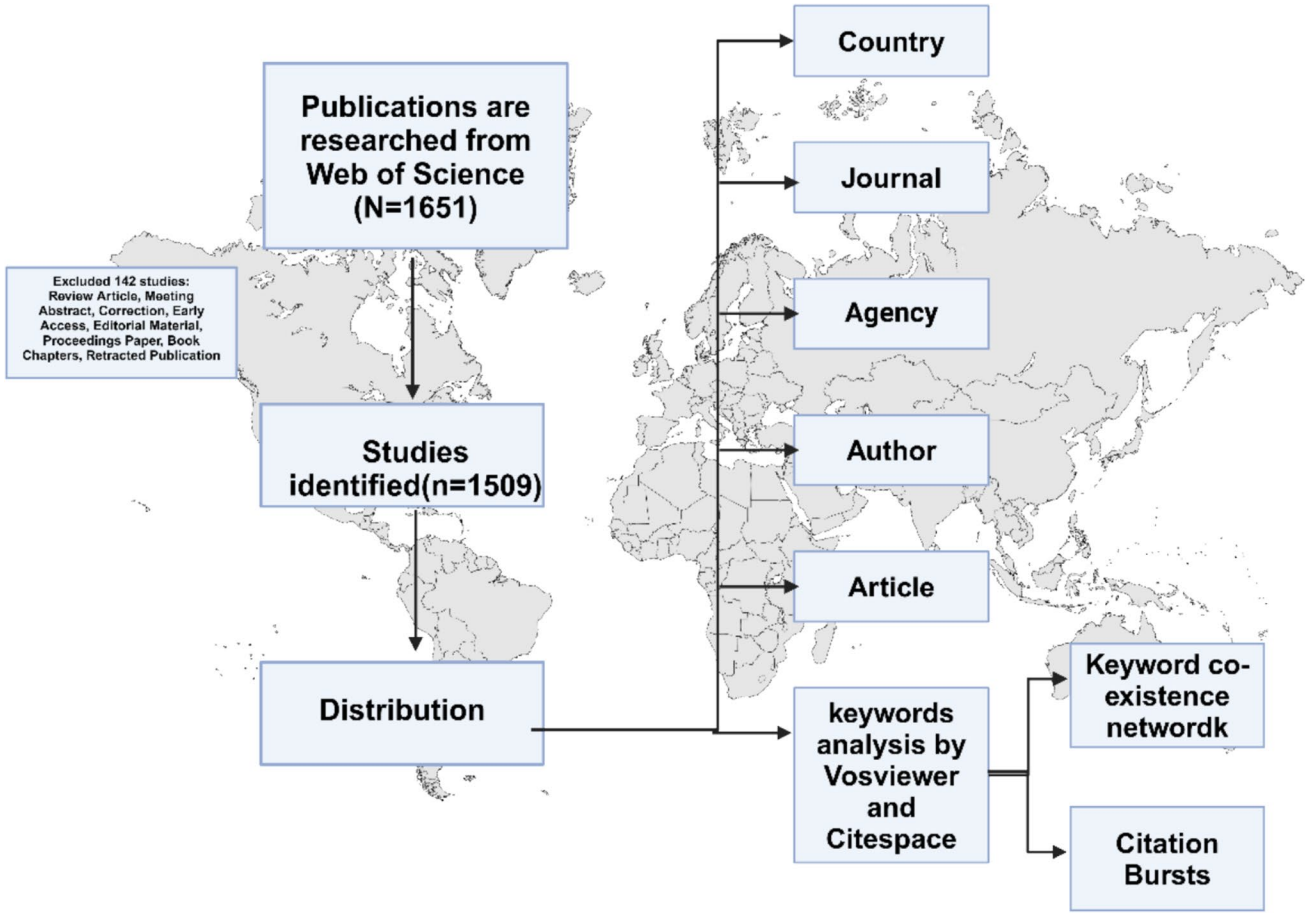

Fig. 1 Flow chart of bibliometric research

Methylprednisolone therapy for spinal cord injuries from 2000 to 2023, and the cumulative publication volumes are on the rise. However, since 2000, it is noteworthy that the number of publications annually has not consistently increased, with some years showing slight decreases and fluctuations. The publication volume reached its peak in the year 2021, reached at 70.

The growing interest in research indicates that the topic is attracting scholars' attention and that it is garnering increasing attention from scholars (Fig. 2). This indicates a growing attention from scholars on research in this area, and this relatively classic treatment method continues to receive significant attention from the research community.

Author publication volume and most relevant affiliation

The top ten authors in terms of number of 226 publications are DE Nicola AF (33 publications), Fehlings MG (31 publications), Schumacher M (28.

publications), Labombarda F (27 publications), Guennoun R(24 publications), Deniselle MCG (22 publications), Young W(16 publications), Bracken MB (15 publications), Garcia-Segura LM (15 publications), Hall ED (15 publications). The most cited author is Young W (5430). Bracken MB is the second most cited author (5018). Labombarda F, Guennoun R, Deniselle MCG, Garcia-Segura LM, and Hall ED have articles cited around 1000 (Fig. 3). The details of the top 10 productive affiliations are shown in Fig. 4. University of Toronto is ranked first, with 90 papers, followed by University of California (69 publications) and US Veterans health administration (VHA) (69 publications). Furthermore, the top 10 affiliations locate in North America. (Tables 1 and 2).

Country analysis

At the national level (Fig. 5), the United States and China are the most prominent countries in terms of publications with international corresponding authors. The United States boasts the highest number of publications, followed closely by China and Canada. In terms of highly cited publications, the United States exerts the greatest influence in the field, with a total citation count of 33,910. Canada follows with a citation count of 5,860, and the United Kingdom has a citation count of 2,272. Furthermore, the graph depicting the

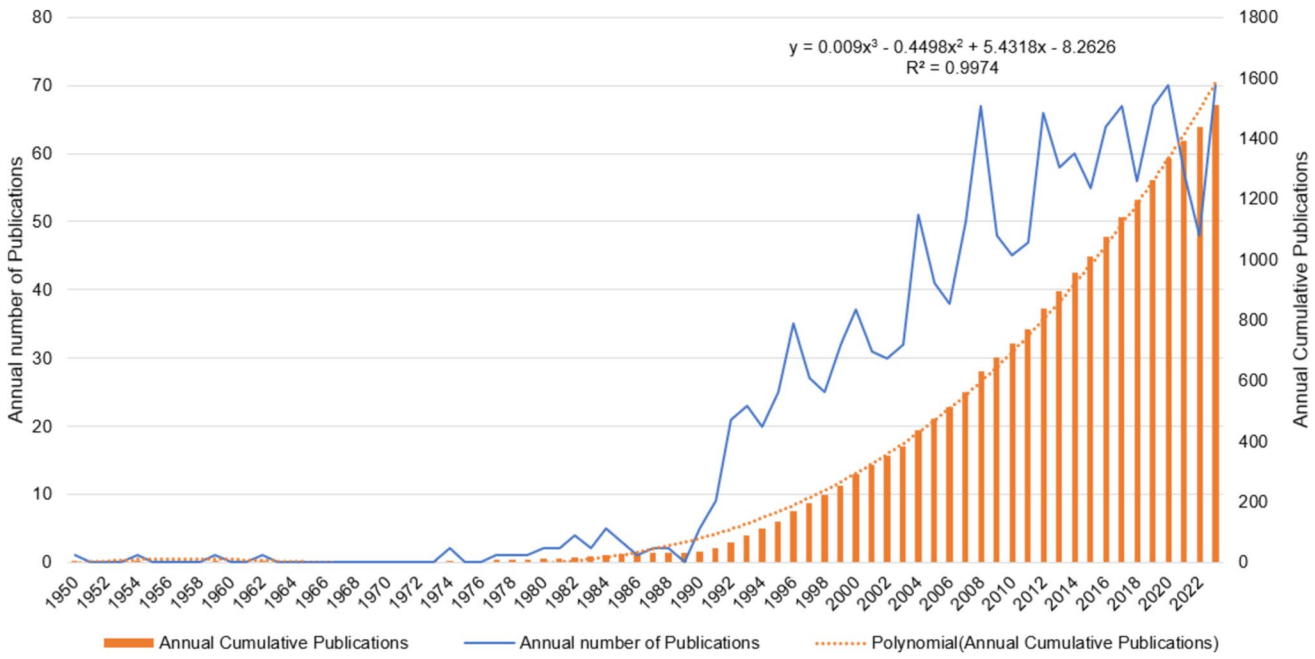

Fig. 2 Annual publication statistics and cumulative annual publication statistics for literature on steroid medications and spinal cord injury, with the dashed line representing the curve fitting for the cumulative annual publication volume

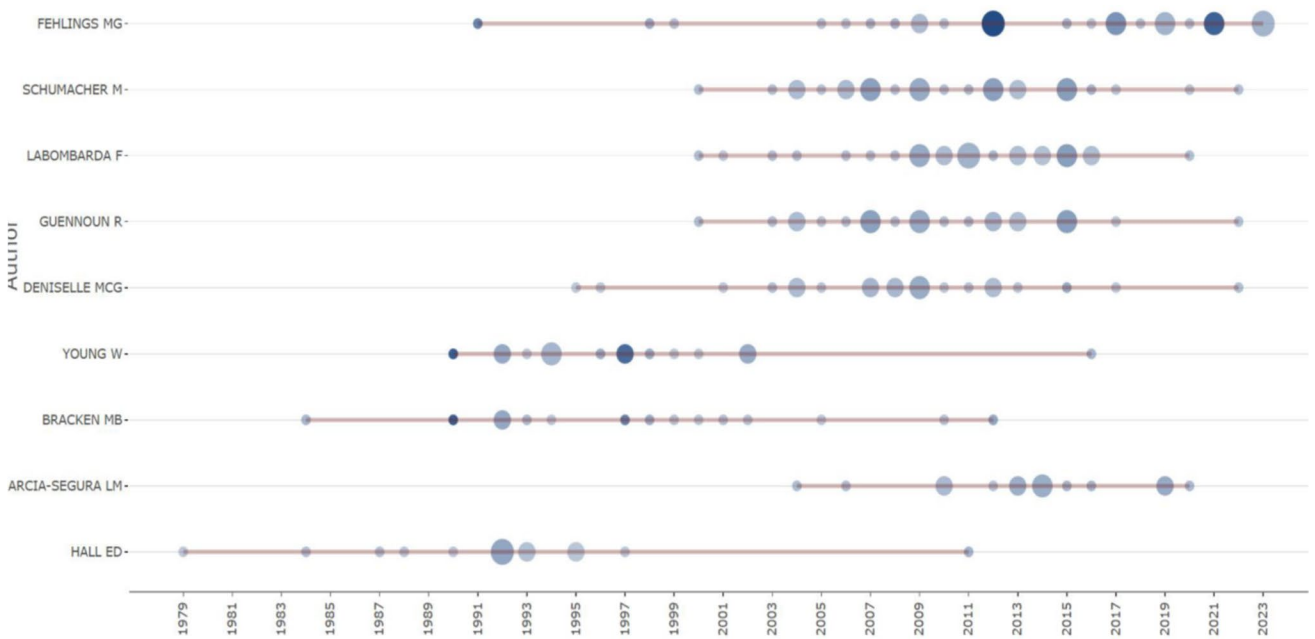

Fig. 3 The top ten most prolific and highly cited authors, along with their H-indexes. A chart of the most prolific author in recent years is displayed, with circles representing publications and colors representing citations

annual publication volume by the most productive countries reveals that the United States has consistently maintained a leading position in publications, followed by China. The publication volumes of other countries are relatively similar and do not differ significantly.

Citation analysis

Among our findings, we discovered that articles from the United States have the highest total citation count, reaching 33,910, which accounts for approximately 38.70% of the

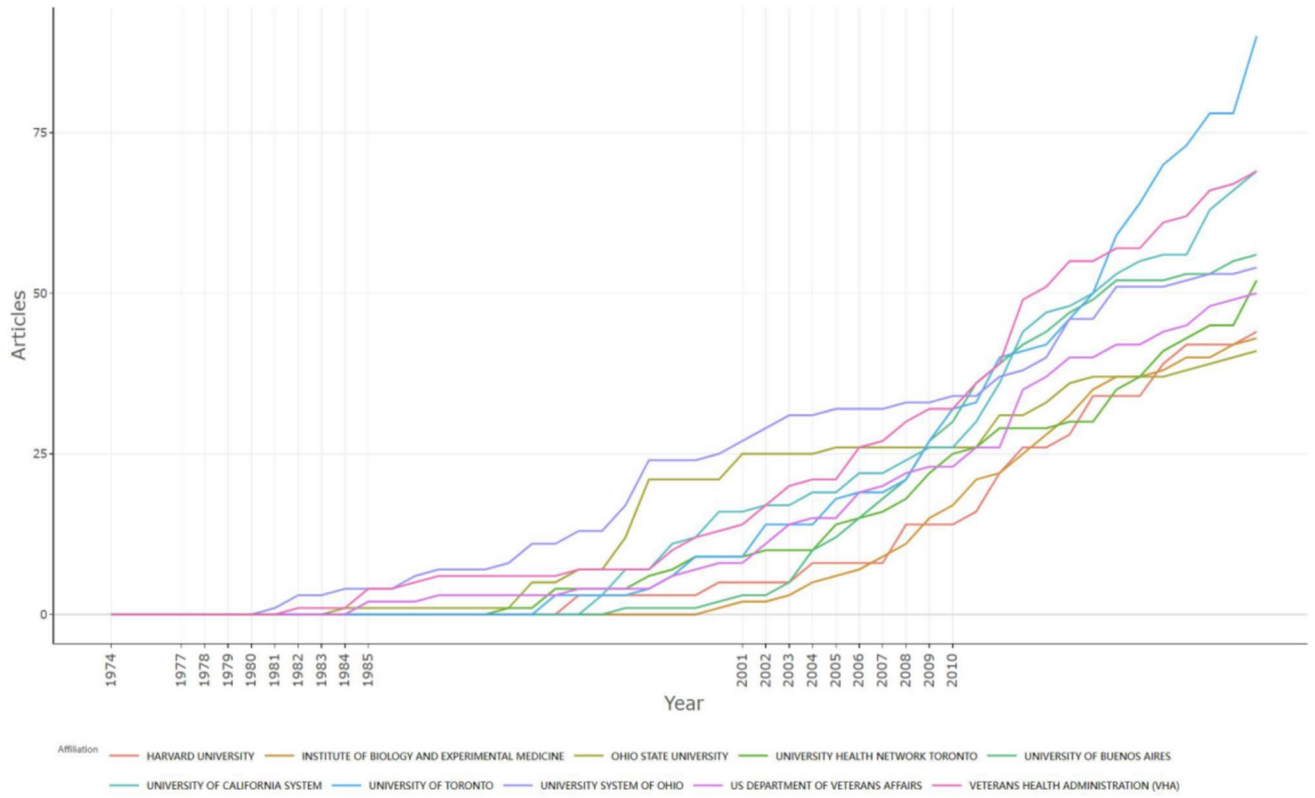

Fig. 4 **A**: The top ten most productive institutions and their recent publications. **B**: Most productive institutions in recent publications

Table 1 Authors

Authors	Articles	Articles fractionalized	Total cited	H-index
DE NICOLA AF	33	4.88	2064	25
FEHLINGS MG	31	6.22	3774	22
SCHUMACHER M	28	4.07	2135	24
LABOMBARDA F	27	4.32	1645	22
GUENNOUN R	24	3.29	1835	22
DENISELLE MCG	22	3.43	1261	17
YOUNG W	16	3.77	5430	16
BRACKEN MB	15	6.19	5018	14
GARCIA-SEGURA LM	15	2.82	1040	15
HALL ED	15	8.48	1336	13

Table 2 Most relevant affiliations

Affiliation	Articles
UNIVERSITY OF TORONTO	90
UNIVERSITY OF CALIFORNIA SYSTEM	69
VETERANS HEALTH ADMINISTRATION (VHA)	69
UNIVERSITY OF BUENOS AIRES	56
UNIVERSITY SYSTEM OF OHIO	54
UNIVERSITY HEALTH NETWORK TORONTO	52
US DEPARTMENT OF VETERANS AFFAIRS	50
HARVARD UNIVERSITY	44
INSTITUTE OF BIOLOGY AND EXPERIMENTAL MEDICINE	43

total citations, with an H-index of 67.00 (Table 3). Following this, articles from Canada have 5,860 citation counts, with an H-index of approximately 45.00. The most cited article is from Bracken MB, published in the New England Journal of Medicine in 1990, with a total of 1,919 citations. Following this, the article by Basso DM, published in Experimental Neurology, has received 1,227 citations. Next is the article by Tator CH, published in the Journal of Neurosurgery in 1991, with a total of 1,197 citations (Table 4).

Collaboration network analysis

Through in-depth analysis of the collaborative relationships among different countries, research institutions, and scholars (Fig. 6), we can not only clearly observe the disparities in publication numbers among the various participants but also uncover their interconnections

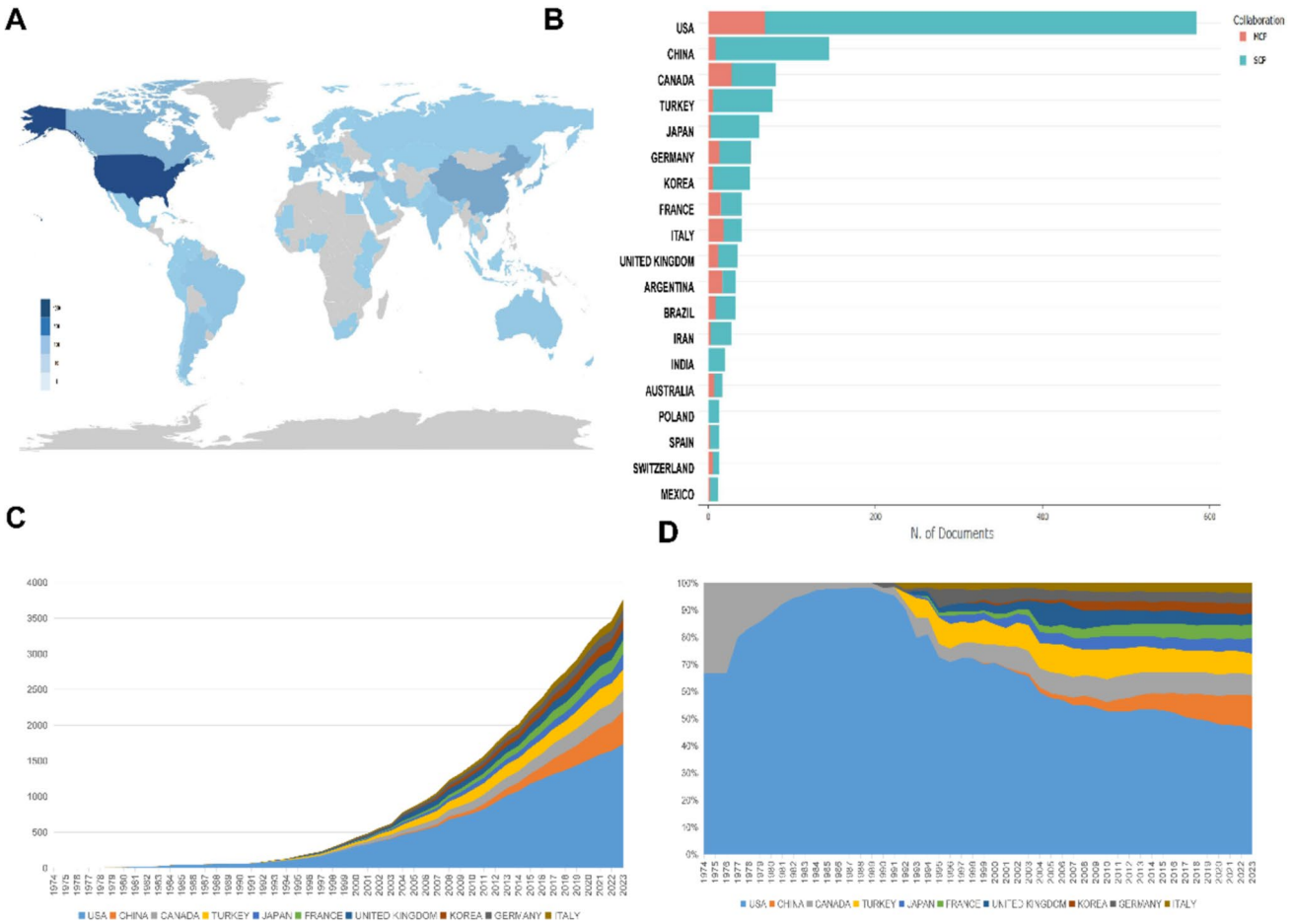

Fig. 5 **A**: The number of publications from various countries. **B**: MCP stands for papers co-authored with authors from other countries; SCP stands for papers co-authored with authors of the same nationality. **C**: Cumulative annual publication volume of the top 10 most productive countries (stacked area chart). **D**: Cumulative annual publication volume of the top 10 most productive countries (percentage stacked chart)

Table 3 Most cited countries

Country	NP	%	TC	H-index
USA	584	38.70	33,910	67
CHINA	145	9.61	2212	33
CANADA	81	5.37	5860	45
TURKEY	77	5.10	1725	16
JAPAN	61	4.04	1649	25
GERMANY	51	3.38	1235	21
KOREA	50	3.31	1400	18
FRANCE	40	2.65	2163	30
ITALY	40	2.65	1373	25
UNITED KINGDOM	35	2.32	2277	15

and respective positions within the broader research field. This kind of analysis provides us with a comprehensive perspective to understand the research structure and evolutionary process of the field.

Research groups within each of the six major research groups collaborate closely, but cross-group collaboration, especially across national borders, has not yet been established. By analyzing the collaboration between various institutions, we can also observe that the connectivity among research institutions in North America tends to be higher than that of institutions in other regions.

Similarly, when analyzing the connectivity between countries, a similar phenomenon can be observed, with the collaboration between China, the United States, and Canada being notably closer. Similarly, the connections between some other European countries are also relatively close.

Furthermore, by analyzing the collaboration within different time periods, we can observe the research structure and evolutionary process within the field. Over time, some research institutions and scholars may emerge while others may fade away. This evolutionary process reflects the shift in research interests and hotspots within the field, which aids in predicting future research directions and potential opportunities.

Table 4 Most cited document

Document	Total citations	TC per year	Normalized TC	DOI
BRACKEN MB, 1990, NEW ENGL J MED	1919	54.83	4.83	https://doi.org/10.1056/NEJM199005173222001
BASSO DM, 1996, EXP NEUROL	1227	42.31	12.51	https://doi.org/10.1006/exnr.1996.0098
TATOR CH, 1991, J NEUROSURG	1197	35.21	6.54	https://doi.org/10.3171/jns.1991.75.1.0015
BRACKEN MB, 1997, JAMA-J AM MED ASSOC	1027	36.68	6.62	https://doi.org/10.1001/jama.277.20.1597
CROWE MJ, 1997, NAT MED	952	34.00	6.13	https://doi.org/10.1038/nm0197-73
FITCH MT, 2008, EXP NEUROL	777	45.71	15.30	https://doi.org/10.1016/j.expneurol.2007.05.014
POPOVICH PG, 1997, J COMP NEUROL	748	26.71	4.82	https://doi.org/10.1002/(SICI)1096-9861(19970120)
FEHLINGS MG, 2012, PLOS ONE	704	54.15	13.52	https://doi.org/10.1371/journal.pone.0032037
MUZHA I, 2004, LANCET	703	33.48	10.97	https://doi.org/10.1016/s0140-6736(04)17188-2
BRACKEN MB, 1992, J NEUROSURG	529	16.03	5.87	https://doi.org/10.3171/jns.1992.76.1.0023

Trend topic analysis and thematic evaluation

The research trend has transitioned from exploring therapeutic mechanisms and targets to focusing on stem cell therapy and drug delivery from 1993 to 2023 (Fig. 7). The analysis reveals that the most frequently used terms over the past 30 years include growth-factor receptor, compression injury, high-dose methylprednisolone sodium succinate, and follow-up, among others. In the year 2000, the term "intravenous methyprednisolone" saw widespread use. Between 2005 and 2017, the most prevalent terms were therapeutic evaluation, clinical-practice guideline, perfusion-pressure, computed-tomography, regeneration, and functional recovery. This shift indicates a move from investigating the therapeutic targets of methylprednisolone to a more detailed assessment of its specific efficacy. The thematic evolution graph illustrates how these themes have evolved over the past three decades.

A thematic map provides a visual representation of significant themes within a research field, constructed based on author-provided keywords. This analysis clusters keywords and identifies the predominant themes in the field. In the upper left quadrant of the thematic map, we find the most discussed topics in the field, which are related to motor themes. The map indicates that these themes include infarction, radiculopathy, and steroid injections. In the lower right quadrant, we identify themes that are considered fundamental and cross-cutting. As depicted on the map, these encompass functional recovery and spinal cord injury.

Summary from relevant research keywords

A co-occurrence network analysis of keywords was performed using VOS viewer, resulting in the division of 225 keywords into 3 clusters (Fig. 8). The largest red cluster, comprising 82 keywords, predominantly focuses on the therapeutic targets of methylprednisolone, with "neuroprotection" and "inflammation" being the most emphasized terms. The green cluster, representing the clinical applications of methylprednisolone, includes keywords such as "steroids," "surgery," "trauma," and "randomized controlled trial." The blue cluster centers on the advancements of methylprednisolone in various other aspects, including contusion, focal cerebral ischemia, and subarachnoid hemorrhage. We discovered that "Lipid peroxidation" exhibited the strongest citation burst (intensity = 20.50), followed by "blood flow" (intensity = 14.03) and "naloxone" (intensity = 11.74). The keywords "trauma," "lipid peroxidation," "dose response," and "ischemia" garnered earlier and sustained attention throughout the study period. Furthermore, "regeneration," "epidemiology," "stem cells," and "transplantation" are among the keywords that remained in a state of high emergence in 2011. This suggests that these keywords have recently garnered significant interest and may emerge as future research hotspots (Fig. 8C).

Distribution of journals and co-cited journals

Figure 9 shows a dual- map of journals. In the double map overlay of the journal, the left side is the citing map, and the right side is the cited map. Citing generally correlates with the cutting edge of knowledge, while being cited generally correlates with the knowledge foundation. The curves represent citation links, showing the complete context of the citations. The longer the vertical axis of the ellipse, the more papers the journal publishes; the longer the horizontal axis, the more authors. Publications in the neurology, sports, ophthalmology (pink trajectory) domain are clearly influenced by publications in the molecular biology, genetics, and social sciences (z = 3.24, f = 3,356) domains. Furthermore, the molecular, biology, and immunology domains (orange trajectory) were influenced by publications in the genetics domain (z = 7.87, f = 7,728). Subsequently, in our domain overlay analysis, we examined the distribution and proportion of journals from this

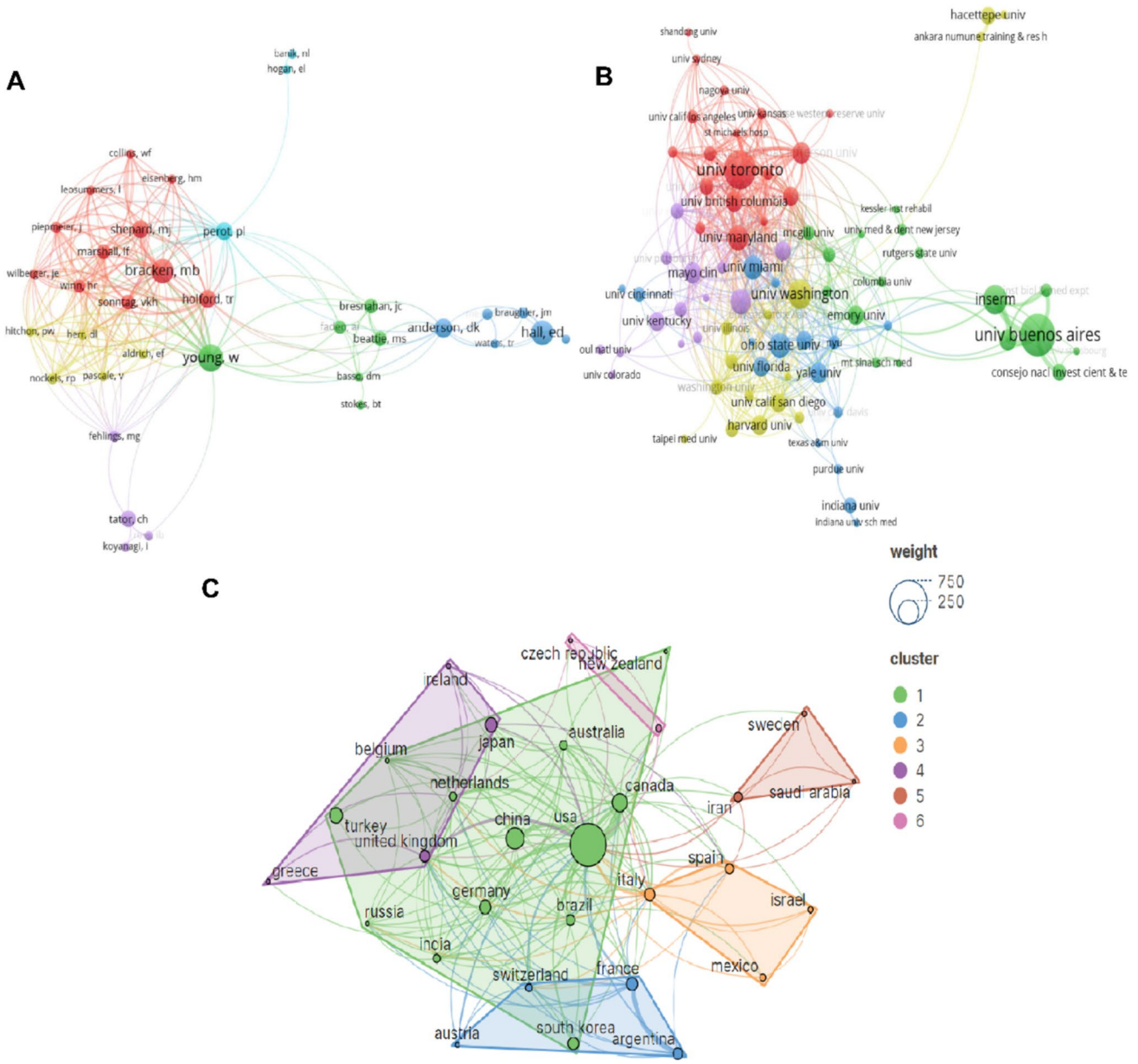

Fig. 6 Author, institutional, and national collaboration networks

database across five fixed domains: Biology and Medicine, Chemistry and Physics, Psychology and Social Sciences, Engineering and Mathematics, and Ecology and Environmental Science and Technology. It was found that the literature is mainly concentrated in Biology and Medicine.

Discussion

Research status and quality of global publications

This study provides a bibliometric analysis of the application of methylprednisolone in spinal cord injury research over the past 50 years. Following the year 2000, we observed an increase each year in the number of publications on methylprednisolone's use in spinal cord injury research. Specifically, during the period from 2000 to 2010, the number of annual publications rose from 30 to 60 articles. However, after 2010 and into the 2020s, the number of published papers experienced considerable fluctuations, but the peak values no longer exceeded 70 articles. At the country, institutional, or author level, the H index and citation count are indicators of the quality and academic impact of publications. At the author level, DE Nicola AF from the Instituto de Biología y Medicina Experimental in Buenos Aires, Argentina, is the most

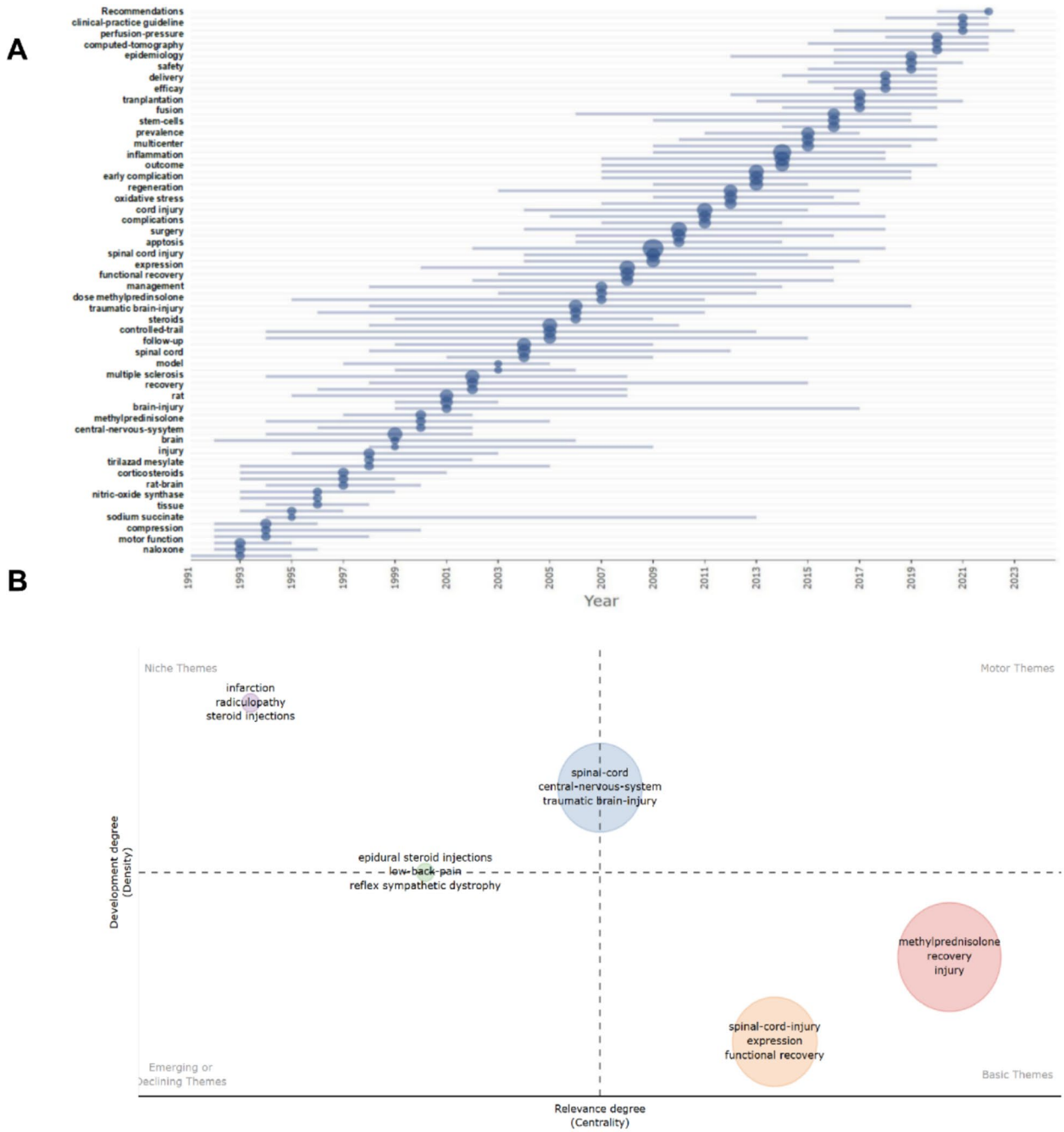

Fig. 7 **A**: Thematic evolution; **B**: Thematic map (X-axis: Centrality; Y-axis: Density). First quadrant (top right): motor themes. Second quadrant (top left): well-developed and isolated themes. Third quadrant (bottom left): emerging or fading themes. Fourth quadrant (lower right corner): basic and transversal themes

prolific author, having published a total of 33 articles. Young W from Rutgers University has accumulated a total of 5,430 citations, with an H-Index reaching 16. The most highly cited publication is the article by Bracken MB, published in The New England Journal of Medicine in 1990, which has accumulated approximately 1,919 citations in total. Among the top ten most productive institutions in terms of publication output, the majority are concentrated in North America. The University of Toronto stands out as the most productive institution, having published 90 articles. The only institution outside of the North American region is the University of Buenos Aires. Subsequently, the thematic words have also undergone a shift, evolving from the initial focus on mechanism and targets to the

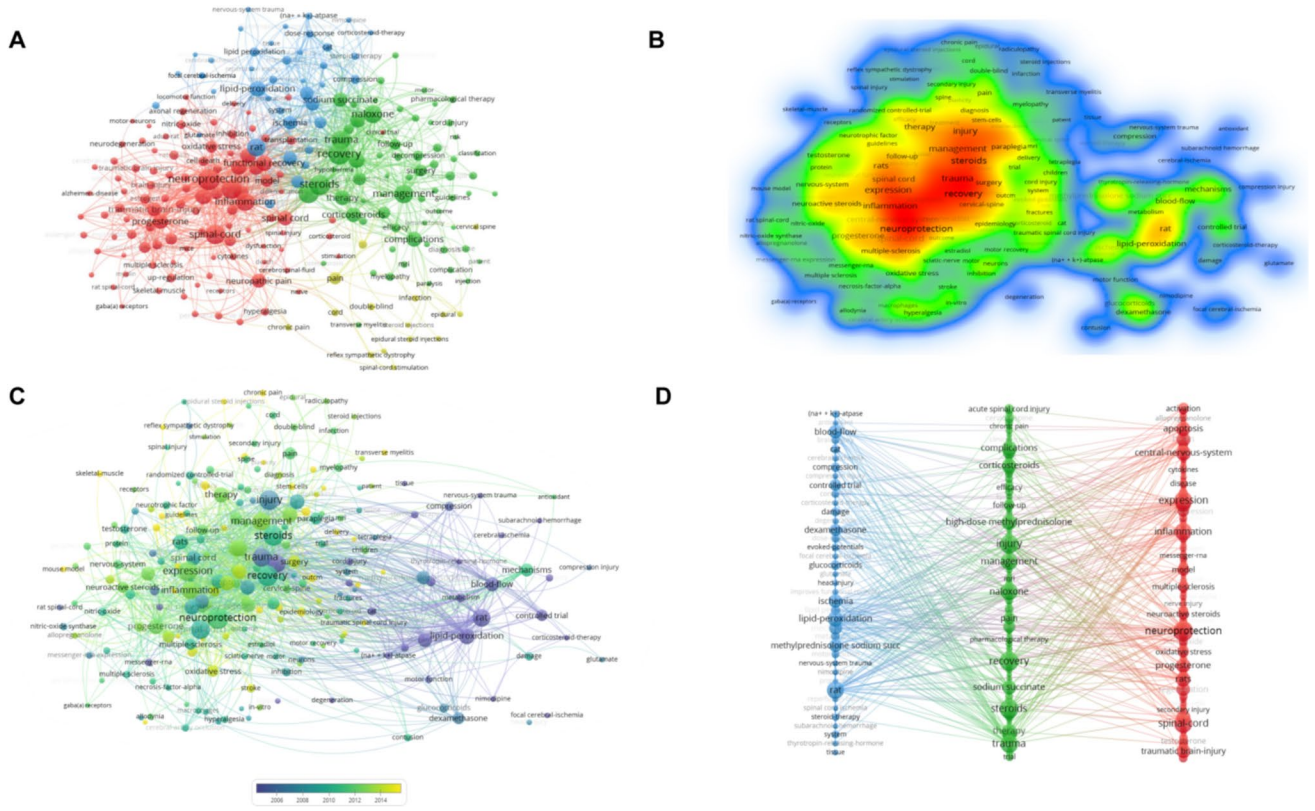

Fig. 8 Keyword co-occurrence network, density map, and clustering diagram

current emphasis on the refinement of evaluation systems. It can be found that currently some scholars believe that the controversy over the efficacy of methylprednisolone is due to the imperfection of its evaluation system. The use of a more scientific evaluation system can better verify its effectiveness. For example, Evaniew et al. [12] adopted statistical methods including Propensity Score Matching, Multivariate Model, and Negative Binomial Regression in statistics to conduct evaluation with more scientific strategies. And the large-scale clinical experiment conducted by Fehlings's team that further investigated the temporal changes in the use of steroids at North American Clinical Trials Network (NACTN) centers. The primary outcome was the change in the rate of steroid use per year between 2008 and 2018. Secondary outcomes included cardiac, gastrointestinal and genitourinary (GIGU), pulmonary, and dermatological complications. It can be seen from this that the improvement of the evaluation of the specific efficacy of methylprednisolone is an important research focus at present [19].

Research hotspots and trends

Through keyword co-occurrence and cluster analysis, hotspots in the field can be identified. Keywords such as trauma, lipid peroxidation, dose response, ischemia, blood flow, and tirilazad mesylate were the main focuses of research from 1990 to 2000. Between 2010 and 2020, transplantation, epidemiology, and stem cells emerged as the primary keywords.

Research frontiers and knowledge base

A knowledge base is comprised of a collection of co-cited articles. In this study, keywords were divided into 3 clusters (see Fig. 9A). A summary of the most frequently cited and pivotal articles within each cluster, which constitute the knowledge base for each research frontier, is presented.

Lipid peroxidation

In spinal cord injury (SCI), lipid peroxidation encompasses the process where an overabundance of free radicals induces oxidative damage to lipid molecules within the spinal cord [23]. Reactive species include hydroxyl radical, superoxide anion, peroxide anion, hydrogen peroxide, nitric oxide, peroxynitrite, lipid peroxyl, and lipid alkoxyl [33]. The pathophysiological consequences of oxidative stress arise from the interaction of these reactive species with lipids, proteins, DNA, cell organelles, and mitochondria. This interaction leads to membrane peroxidation, DNA damage, and mitochondrial dysfunction, ultimately initiating a cascade of inflammatory responses and cell death, exacerbating the degree of injury in SCI.

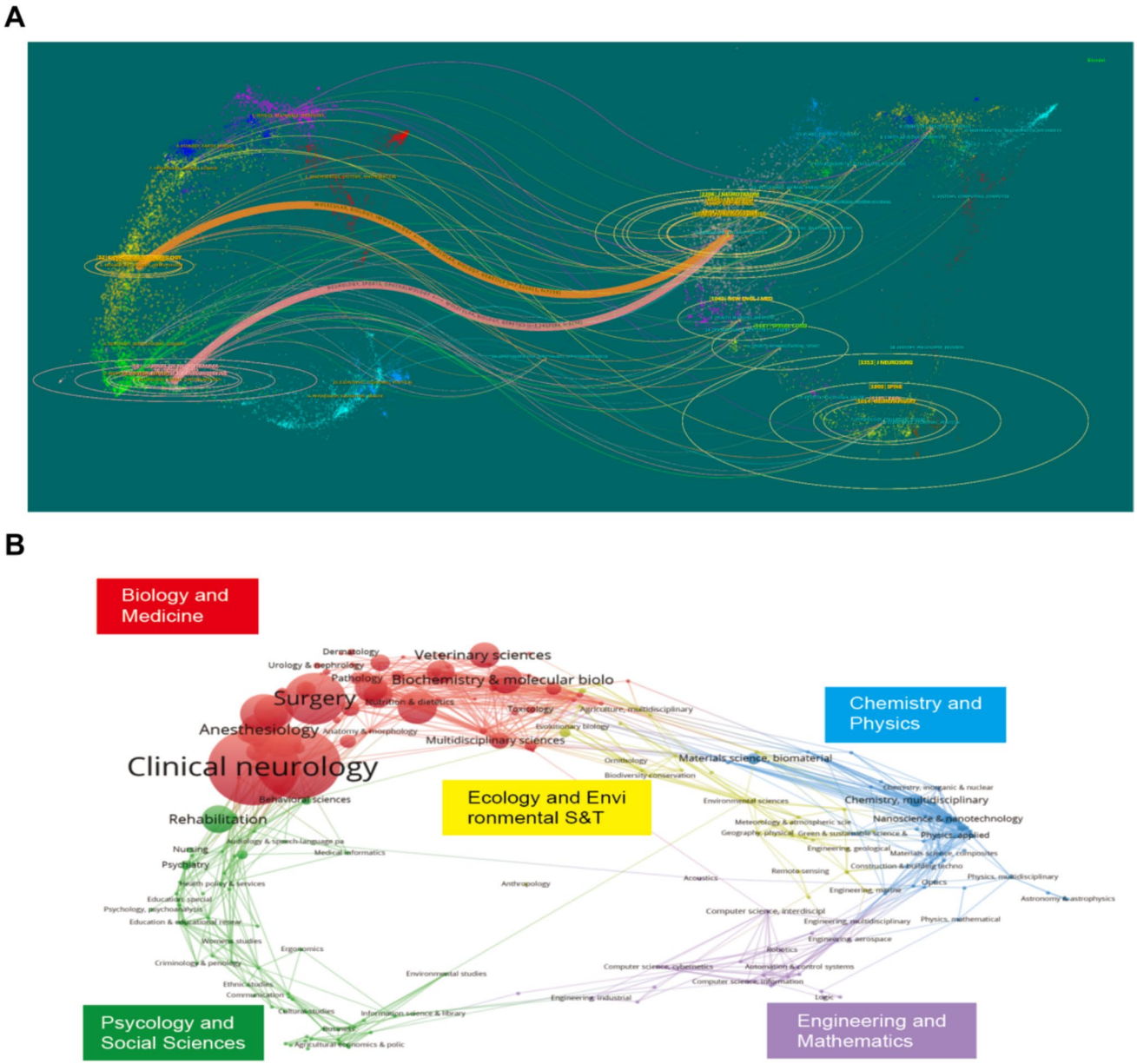

Fig. 9 **A**: domain overlay analysis showing the distribution and proportion of journals from this database across various fields; **B**: dual-graph overlay of journal representation

Methylprednisolone, a glucocorticoid, functions by inhibiting inflammatory reactions and reducing the production of free radicals. During secondary spinal cord injury, it stabilizes cell membranes and diminishes lipid peroxidation products.

According to research reports, methylprednisolone has been shown to inhibit the peroxidation of lipids under in vitro conditions [51]. In addition, high-dose methylprednisolone (30 mg/kg, intravenous injection) has also demonstrated supportive effects on energy metabolism, prevention of the progression of ischemia following trauma, inhibition of membrane lipid hydrolysis, reversal of intracellular calcium accumulation, and improvement in neurofilament degradation [10]. The combination therapy with hyperbaric oxygen (HBO) has also been demonstrated to significantly decrease malondialdehyde levels and increase ferric reducing ability of serum ferric reducing antioxidant power levels compared to other treatment groups. Concurrently, the HBO + MP group exhibited a significant reduction in the expression of TNF-α and Caspase-3(Ahmadi, Zargari, Nasiry, & Khalatbary [2]), . Recent research has established a single-nucleus transcriptome atlas to compare the effects of different drugs, including methylprednisolone, minocycline, and chondroitinase ABC (ChABC), on spinal cord injury

(SCI). Single-cell sequencing analysis indicates that both methylprednisolone and minocycline modulate the immune response to SCI. Specifically, the surviving neurons revert to their baseline transcriptional state following treatment with methylprednisolone. Moreover, methylprednisolone treatment enables the surviving neurons to downregulate transcriptional programs associated with stress responses in both innate and adaptive immune reaction cells [38].

Controlled trial

In animal studies, methylprednisolone may be beneficial in acute spinal cord injury, but whether it is clinically effective remains to be determined [7]. A randomized, double-blind, placebo-controlled multicenter trial evaluating the efficacy and safety of methylprednisolone was conducted in patients with acute spinal cord injury as part of the National Acute Spinal Cord Injury Study. However, in this study published in 1984, the researchers did not find any significant differences in the recovery of relevant indicators at the six-week follow-up. Instead, an increased incidence of wound infections was observed [4]. A randomized, double-blind, placebo-controlled study of patients with acute spinal cord injury (treated within 14 h) found that, after six months, Patients administered methylprednisolone within eight hours of their injury showed notable improvements in motor function, pinprick sensation, and touch compared to those who received a placebo [5]. In a subsequent large-scale randomized controlled trial conducted in 1997, the primary focus was on the duration of methylprednisolone administration, either for 24–48 h. At 6 weeks, patients treated with methylprednisolone for 48 h demonstrated enhanced motor recovery compared to those treated for 24 h. Acute spinal cord injury patients who receive methylprednisolone within 3 h of the injury should continue the treatment regimen for 24 h. Patients should be maintained on steroid therapy for 48 h after methylprednisolone is initiated between 3 and 8 h post-injury [6]. Three large-scale clinical controlled trials have demonstrated the efficacy of methylprednisolone in treating acute spinal cord injuries. However, in subsequent clinical controlled trials, similar experimental results have not been observed. For instance, in a retrospective nonrandomized study by Levy et al. [26] in 1996, it was indicated that the administration of methylprednisolone did not significantly enhance functional outcomes in patients with gunshot wound injuries to the spine. Additionally, it did not increase the number of complications patients experienced during hospitalization. Several studies have investigated whether high-dose methylprednisolone (MP) can induce acute corticosteroid myopathy (ACM). In a prospective cohort study, they found that MP at the dose recommended by the North American Spine Cord Injury Consortium (NASCIS) may indeed lead to the development of ACM [31]. From the aforementioned large-scale controlled trials, it is evident that future studies on the treatment of spinal cord injury with methylprednisolone require more rigorous design in several aspects. This includes the establishment of a well-structured trial design encompassing appropriate sample selection, randomization methods, and intervention strategies. Additionally, stricter inclusion and exclusion criteria should be implemented to enhance the reliability and validity of the findings.

Corticosteroids

Other types of steroid hormones have been used in the treatment of spinal cord injuries in addition to methylprednisolone. For instance, dexamethasone, being a more long-acting glucocorticoid, has also been experimented with in the acute phase treatment of spinal cord injury, in comparison to methylprednisolone. In contrast to dexamethasone, methylprednisolone (MP) is distinguished by its additional capacity to bind to the mineralocorticoid receptor, thereby eliciting sodium-retaining effects [45]. The results of a randomized trial by Srensen et al. have found that among patients suffering from metastatic spinal cord compression due to solid tumors. Treatment success, defined as gait function after treatment, was achieved in 81% of patients who received dexamethasone, compared to 63% who did not(Sørensen, Helweg-Larsen, Mouridsen, & Hansen [39]), . However, some studies have pointed out that dexamethasone faces similar issues to those of methylprednisolone, which is the risk of complications such as gastrointestinal bleeding and wound infection under the high-dose steroid shock therapy. Consequently, low-dose dexamethasone may also be more effective in treating spinal cord injuries than high-dose dexamethasone [25].

Neuroprotection

With the implementation of large-scale clinical trials, in vitro experiments have also been conducted to validate the neuroprotective effects of methylprednisolone. Using an in vitro model of the rat spinal cord, Samanos et al.(Sámano, Kaur, & Nistri [34]), investigated whether methylprednisolone sodium succinate (MPSS) could record reflexes, fictive locomotion, and perform morphological analysis of damage to the spinal cord neurons and glial cells. The results revealed that the application of MPSS (6–10 μM) for 24 h after a 1-hour exposure to a pathological medium protected astrocytes and oligodendrocytes, particularly in the ventrolateral white matter. In a similar study, Sámano utilized a simplified in vitro model of the rat spinal cord to simulate the process of neuronal damage due to excessive activation of glutamate receptors. The findings demonstrated that MPSS could protect glial cells from the insults of hypoxia and metabolic dysfunction, yet it was

insufficient in preventing neuronal death. Furthermore, the study showed that the combined administration of MPSS with riluzole did not confer additional benefits [35]. Using the N2a cell line, it was discovered that methylprednisolone treatment for 30 min followed by exposure to 100 μM H_2O_2 for 24 h significantly reduced the percentage of apoptotic cells, maintained a healthy morphology, and demonstrated downregulation of the autophagic protein. By suppressing autophagy and apoptosis, pretreatment with methylprednisolone confers neuroprotective effects against oxidative damage [16]. Based on the above research findings, some scholars have proposed the study of a targeted delivery nano N-(2-hydroxypropyl) methacrylamide copolymer-based MP prodrug nanomedicine (Nano-MP), envisioning the delivery of MP to the spinal cord injury (SCI) segment to avoid the systemic side effects associated with the use of high-dose methylprednisolone [47]. The relevant experiments have demonstrated the effective prevention of glucocorticoid-induced muscle atrophy and osteoporosis [32].

Apoptosis

In spinal cord injuries, apoptosis plays a critical role in programmed cell death [37]. As a result of spinal cord injury, an inflammatory response occurs, leading to an increase in cell apoptosis, which may exacerbate neurological damage demonstrated by nuclear DNA fragmentation and caspase activation. Unlike necrosis, apoptosis is primarily mediated by free radical damage, glutamatergic excitotoxicity, and inflammatory injury [40]. Reports indicate that apoptosis can occur in oligodendrocytes(Caprariello, Mangla, Miller, & Selkirk [9]), , astrocytes(Kim, Park, & Hwang [24]), , microglia [29], and neurons(Hollville, Romero, & Deshmukh [21]), . It appears within four hours of injury and peaks eight hours later (Abbaszadeh, Fakhri, & Khan [1]), . Apoptosis can occur through mitochondrial mediated [17] and death receptor-regulated pathways [11]. In the mitochondrial pathway of apoptosis, BCL-2 is upregulated, resulting in an increase in Cyto-C release, ultimately leading to cyto-C release into the cytosol. As part of the apoptosome complex, Cyto-C binds to apoptotic protease activating factor-1 (Apaf-1) and caspase-9. Fas, TNF receptor 1, TRAMP, TRAIL-R1 and TRAIL-R2 are key death receptors belonging to the tumor necrosis factor (TNF) superfamily which induce apoptosis when bound to ligands [18].

Due to the demonstrated inhibitory effect of methylprednisolone on autophagy in other diseases models(Sauñe, Bryce-Alberti, Portmann-Baracco, & Accinelli [36]), , several researchers have thoroughly investigated how methylprednisolone inhibits cell death following spinal cord damage. MP reduced the proportion of oligodendrocytes and astrocytes positive for Apostain + cells in the rostral, caudal and lesion zone of rats following an acute spinal cord contusion injury(Vaquero, Zurita, Oya, Aguayo, & Bonilla [44]), . Meanwhile, methylprednisolone and transplantation of amniotic membrane mesenchymal stem cells (AM-MSCs) have synergistic therapeutic effects, as discovered by Gao et al. [15]. Using MP (50 mg/kg) and AM-MSCs simultaneously reduced TNF-, IL-1, IL-6, IL-17, IFN-, and TUNEL + cell expression in rats following spinal cord injury, as well as caspase-3, Bax, and Bcl-2 expression. In the future, we believe that the development of blood apoptotic markers should focus on analyzing free DNA, caspase enzymes, and apoptotic cytokines in serum, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This approach will enable a more comprehensive assessment of the apoptotic state and prognosis following spinal cord injury in clinical settings(Wimmer, Sachet, & Oehler [46]), .

Future research directions

Examining the research trends of methylprednisolone (MP) treatment in spinal cord injury (SCI) reveals that future studies will primarily focus on guidelines, clinical practices, and global standards. There are still no effective pharmacological treatments for SCI, as previously mentioned. The unclear understanding of the pathophysiology of the condition and patient heterogeneity has led to the ambiguity of drug treatment approaches in this domain. Despite these inadequacies, methylprednisolone is still widely used by physicians due to the lack of alternative treatment options. We believe that in the future, not only will the efficacy of the existing methylprednisolone therapy need to be addressed, but also the question of whether low or high doses of methylprednisolone are more effective, as well as the development of novel drug delivery systems to further reduce the systemic side effects of methylprednisolone. To establish the overall effectiveness of this treatment approach for spinal cord injury (SCI), randomized prospective clinical trials involving humans are necessary. Due to the difficulty in obtaining pathological samples in the field of spinal cord injury, the efficacy of current basic research is challenging to directly validate in clinical patients with spinal cord injury. However, in the future, the development of blood biomarkers, along with advancements in behavioral studies, functional imaging, and larger-scale controlled trials, is expected to further bridge the gap between the foundational discoveries related to methylprednisolone and the formulation of clinical application strategies.

Conclusion

Since nearly 40 years ago, methylprednisolone (MP) has been widely used in clinical settings to treat spinal cord injury (SCI). Theoretically, MP has been shown to inhibit

the secondary injury cascade following SCI, including the inflammatory response of early neurons and lipid peroxidation. However, discussions regarding the efficacy and safety of MP continue, and it is essential to consider the acceptable risk profile of the medication, as well as the autonomy that patients should be afforded, until a safer and more effective treatment method for acute spinal cord injury is identified.

In this research, we provided an overview of the countries, institutions, researchers, scientific journals, and citation data that have contributed to the scholarly work on this subject. Collaboration between different academic groups in the field needs to be strengthened, according to our research. Currently, the research on MP for spinal cord injury faces a challenge of a disconnect between clinical and basic research. Clinical teams slightly collaborate more closely with basic research teams, and there is a lack of advanced technologies and research methods such as single-cell sequencing for basic research on specific mechanisms. The exact explanations are still limited to traditional ones, such as the apoptosis of neurons and glia cells, oxidative stress at the site of injury. In addition, it appears that high-dose glucocorticoids increase the risk of adverse events in patients with acute spinal cord injury, in contrast to the relatively uncertain better neurologic recovery. Therefore, in the future, it may be necessary to further establish close connections with other materials and pharmaceutical teams to promote innovation and progress in the administration methods of methylprednisolone.

Limitations

We present the first bibliometric evaluation and systematic analysis of publications related to methylprednisolone therapy for spinal cord injuries. However, there are some drawbacks. First of all, by excluding comments and other types of literature, some popular research topics may have been missed. In addition, we omitted some research due to our use of only one database, WoSCC, while ignoring other databases such as PubMed, Scopus, and Embase. Thirdly, excluding non-English articles may affect the conclusion. Especially in our study, we found that some researchers from certain countries, such as Argentina or Brazil, might be omitted due to such inclusion criteria. Consequently, future research should not rely solely on a single database and should focus on newly published papers. Finally, it is important to note that we selected the time frame of 1975 to 2023 because only four articles were sporadically published in this field from 1950 to 1973, with the majority of significant research commencing in 1975.

Author contributions M .Z, ZY.X, L. F contributed equally to this work. M.Z, ZY X discussed the content of the manuscript including the selection of key studies, L.F wrote and edited the manuscript, and generated figure outlines and wrote the manuscript. H.Z, HJ Y, searched for articles and collected and refined relevant information. GZ.N and SQ.F reviewed and edited the manuscript before submission.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics Not applicable.

Competing interests The authors declare no competing interests.

References

1. Abbaszadeh F, Fakhri S, Khan H (2020) Targeting apoptosis and autophagy following spinal cord injury: therapeutic approaches to polyphenols and candidate phytochemicals. Pharmacol Res 160:105069. https://doi.org/10.1016/j.phrs.2020.105069
2. Ahmadi F, Zargari M, Nasiry D, Khalatbary AR (2022) Synergistic neuroprotective effects of hyperbaric oxygen and methylprednisolone following contusive spinal cord injury in rat. J Spinal Cord Med 45(6):930–939. https://doi.org/10.1080/10790268.2021.1896275
3. Bowers CA, Kundu B, Hawryluk GW (2016) Methylprednisolone for acute spinal cord injury: an increasingly philosophical debate. Neural Regen Res 11(6):882–885. https://doi.org/10.4103/1673-5374.184450
4. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, ... et al (1984) Efficacy of methylprednisolone in acute spinal cord injury. JAMA 251(1):45–52

5. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, ... et al (1990) A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the second national acute spinal cord injury study. N Engl J Med 322(20):1405–1411. https://doi.org/10.1056/nejm199005173222001
6. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, ... Young W (1997) Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. National acute spinal cord injury study. JAMA 277(20):1597–1604
7. Cabrera-Aldana EE, Ruelas F, Aranda C, Rincon-Heredia R, Martínez-Cruz A, Reyes-Sánchez A, ... Tovar-y-Romo LB (2017) Methylprednisolone administration following spinal cord injury reduces aquaporin 4 expression and exacerbates Edema. Mediat Inflamm 2017(1):4792932. https://doi.org/10.1155/2017/4792932
8. Cain DW, Cidlowski JA (2017) Immune regulation by glucocorticoids. Nat Rev Immunol 17(4):233–247. https://doi.org/10.1038/nri.2017.1
9. Caprariello AV, Mangla S, Miller RH, Selkirk SM (2012) Apoptosis of oligodendrocytes in the central nervous system results in rapid focal demyelination. Ann Neurol 72(3):395–405. https://doi.org/10.1002/ana.23606
10. Christie SD, Comeau B, Myers T, Sadi D, Purdy M, Mendez I (2008) Duration of lipid peroxidation after acute spinal cord injury in rats and the effect of methylprednisolone: Laboratory investigation. Neurosurgical Focus 25(5):E5. https://doi.org/10.3171/FOC.2008.25.11.E5
11. Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35(4):495–516. https://doi.org/10.1080/01926230701320337
12. Evaniew N, Noonan VK, Fallah N, Kwon BK, Rivers CS, Ahn H, ... Dvorak MF (2015) Methylprednisolone for the treatment of patients with acute spinal cord injuries: a propensity score-matched cohort study from a Canadian multi-center spinal cord Injury Registry. J Neurotrauma 32(21):1674–1683. https://doi.org/10.1089/neu.2015.3963
13. Fan B, Wei Z, Feng S (2022) Progression in translational research on spinal cord injury based on microenvironment imbalance. Bone Res 10(1):35. https://doi.org/10.1038/s41413-022-00199-9
14. Fehlings MG, Wilson JR, Cho N (2014) Methylprednisolone for the treatment of acute spinal cord injury: counterpoint. Neurosurgery 61(Suppl 1):36–42. https://doi.org/10.1227/neu.0000000000000412
15. Gao S, Ding J, Xiao H-J, Li Z-Q, Chen Y, Zhou X-S, ... Shi W-Z (2014) Anti-inflammatory and anti-apoptotic effect of combined treatment with methylprednisolone and amniotic membrane mesenchymal stem cells after spinal cord Injury in rats. Neurochem Res 39(8):1544–1552. https://doi.org/10.1007/s11064-014-1344-9
16. Gao W, Chen SR, Wu MY, Gao K, Li YL, Wang HY, ... Li H (2016) Methylprednisolone exerts neuroprotective effects by regulating autophagy and apoptosis. Neural Regen Res 11(5):823–828. https://doi.org/10.4103/1673-5374.182711
17. Green DR, Kroemer G (2004) The pathophysiology of mitochondrial cell death. Science 305(5684):626–629. https://doi.org/10.1126/science.1099320
18. Guicciardi ME, Gores GJ (2009) Life and death by death receptors. Faseb j 23(6):1625–1637. https://doi.org/10.1096/fj.08-111005
19. Hejrati N, Aarabi B, Neal CJ, Ugiliweneza B, Kurpad SN, Shaffrey CI, ... Fehlings MG (2023) Trends in the Use of corticosteroids in the management of Acute spinal cord Injury in North American clinical trials Network sites. J Neurotrauma 40(17–18):1938–1947. https://doi.org/10.1089/neu.2022.0409
20. Hill KD, Kannankeril PJ, Jacobs JP, Baldwin HS, Jacobs ML, O'Brien SM, Li JS (2022) Methylprednisolone for heart surgery in infants - a randomized, controlled trial. N Engl J Med 387(23):2138–2149. https://doi.org/10.1056/NEJMoa2212667
21. Hollville E, Romero SE, Deshmukh M (2019) Apoptotic cell death regulation in neurons. Febs j 286(17):3276–3298. https://doi.org/10.1111/febs.14970
22. James SL, Theadom A, Ellenbogen RG, Bannick MS, Montjoy-Venning W, Lucchesi LR, Abbasi N, Abdulkader R, Abraha HN, Adsuar JC, Afarideh M (2019) Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 18(1):56–87. https://doi.org/10.1016/s1474-4422(18)30415-0
23. Jia Z, Zhu H, Li J, Wang X, Misra H, Li Y (2012) Oxidative stress in spinal cord injury and antioxidant-based intervention. Spinal Cord 50(4):264–274. https://doi.org/10.1038/sc.2011.111
24. Kim SC, Park JY, Hwang EM (2022) Caspase-dependent apoptosis induces reactivation and gliogenesis of astrocytes in adult mice. Front Cell Neurosci 16:1054956. https://doi.org/10.3389/fncel.2022.1054956
25. Kumar A, Weber MH, Gokaslan Z, Wolinsky JP, Schmidt M, Rhines L, ... Fisher CG (2017) Metastatic spinal cord Compression and Steroid Treatment: a systematic review. Clin Spine Surg 30(4):156–163. https://doi.org/10.1097/bsd.0000000000000528
26. Levy ML, Gans W, Wijesinghe HS, SooHoo WE, Adkins RH, Stillerman CB (1996) Use of methylprednisolone as an adjunct in the management of patients with penetrating spinal cord injury: outcome analysis. Neurosurgery 39(6):1141–1148. https://doi.org/10.1097/00006123-199612000-00014. (**discussion 1148–1149.**)
27. Liu JT, Zhang S, Gu B, Li HN, Wang SY, Zhang SY (2017) Methotrexate combined with methylprednisolone for the recovery of motor function and differential gene expression in rats with spinal cord injury. Neural Regen Res 12(9):1507–1518. https://doi.org/10.4103/1673-5374.215263
28. Liu Z, Yang Y, He L, Pang M, Luo C, Liu B, Rong L (2019) High-dose methylprednisolone for acute traumatic spinal cord injury: a meta-analysis. Neurology 93(9):e841–e850. https://doi.org/10.1212/wnl.0000000000007998
29. Matsudaira T, Prinz M (2022) Life and death of microglia: mechanisms governing microglial states and fates. Immunol Lett 245:51–60. https://doi.org/10.1016/j.imlet.2022.04.001
30. Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, ... Huang GD (2022) Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med 48(8):1009–1023. https://doi.org/10.1007/s00134-022-06684-3
31. Qian T, Guo X, Levi AD, Vanni S, Shebert RT, Sipski ML (2005) High-dose methylprednisolone may cause myopathy in acute spinal cord injury patients. Spinal Cord 43(4):199–203. https://doi.org/10.1038/sj.sc.3101681
32. Qin Y, Zhao W, Jia Z, Bauman WA, Peng Y, Guo XE, ... Qin W (2024) Neuroprotective macromolecular methylprednisolone prodrug nanomedicine prevents glucocorticoid-induced muscle atrophy and osteoporosis in a rat model of spinal cord injury. Nanomed Nanotechnol Biol Med 62:102773. https://doi.org/10.1016/j.nano.2024.102773
33. Rogobete A, Bedreag O, Sarandan M, Cradigati A, Papurica M, Rosu O, Sandesc D (2014) Oxidative stress and antioxidant therapy in traumatic spinal cord injuries. Jurnalul Roman De Anestezie Terapie Intensiva 21:123–129
34. Sámano C, Kaur J, Nistri A (2016) A study of methylprednisolone neuroprotection against acute injury to the rat spinal cord in vitro. Neuroscience 315:136–149. https://doi.org/10.1016/j.neuroscience.2015.12.003
35. Sámano C, Nistri A (2019) Mechanism of neuroprotection against experimental spinal cord injury by riluzole or methylprednisolone.

Neurochem Res 44(1):200–213. https://doi.org/10.1007/s11064-017-2459-6
36. Sauñe PM, Bryce-Alberti M, Portmann-Baracco AS, Accinelli RA (2020) Methylprednisolone pulse therapy: an alternative management of severe COVID-19. Respir Med Case Rep 31:101221. https://doi.org/10.1016/j.rmcr.2020.101221
37. Shi Z, Yuan S, Shi L, Li J, Ning G, Kong X, Feng S (2021) Programmed cell death in spinal cord injury pathogenesis and therapy. Cell Prolif 54(3):e12992. https://doi.org/10.1111/cpr.12992
38. Skinnider MA, Gautier M, Teo AYY, Kathe C, Hutson TH, Laskaratos A, .., Courtine G (2024) Single-cell and spatial atlases of spinal cord injury in the Tabulae Paralytica. Nature 631(8019):150–163. https://doi.org/10.1038/s41586-024-07504-y
39. Sørensen S, Helweg-Larsen S, Mouridsen H, Hansen HH (1994) Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. Eur J Cancer 30a(1):22–27. https://doi.org/10.1016/s0959-8049(05)80011-5
40. Thornton C, Leaw B, Mallard C, Nair S, Jinnai M, Hagberg H (2017) Cell death in the developing brain after Hypoxia-Ischemia. Front Cell Neurosci 11:248. https://doi.org/10.3389/fncel.2017.00248
41. Timmermans S, Souffriau J, Libert C (2019) A General introduction to Glucocorticoid Biology. Front Immunol 10:1545. https://doi.org/10.3389/fimmu.2019.01545
42. Torrelo A (2017) Methylprednisolone aceponate for atopic dermatitis. Int J Dermatol 56(6):691–697. https://doi.org/10.1111/ijd.13485
43. Vandewalle J, Luypaert A, De Bosscher K, Libert C (2018) Therapeutic mechanisms of glucocorticoids. Trends Endocrinol Metab 29(1):42–54. https://doi.org/10.1016/j.tem.2017.10.010
44. Vaquero J, Zurita M, Oya S, Aguayo C, Bonilla C (2006) Early administration of methylprednisolone decreases apoptotic cell death after spinal cord injury. Histol Histopathol 21(10):1091–1102. https://doi.org/10.14670/hh-21.1091
45. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH (2014) Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014(9):Cd001288. https://doi.org/10.1002/14651858.CD001288.pub4
46. Wimmer K, Sachet M, Oehler R (2020) Circulating biomarkers of cell death. Clin Chim Acta 500:87–97. https://doi.org/10.1016/j.cca.2019.10.003
47. Zhao W, Jia Z, Bauman WA, Qin Y, Peng Y, Chen Z, ... Qin W (2024) Targeted-delivery of nanomedicine-enabled methylprednisolone to injured spinal cord promotes neuroprotection and functional recovery after acute spinal cord injury in rats. Nanomed Nanotechnol Biol Med 60:102761. https://doi.org/10.1016/j.nano.2024.102761
48. Zhong H, Zhang K, Zhou M, Xing C, An Y, Zhang Q, ... Ning G (2024) An implantable self-driven diaphragm pacing system based on a microvibration triboelectric nanogenerator for phrenic nerve stimulation. ACS Appl Mater Interfaces 16(33):43199–43211. https://doi.org/10.1021/acsami.4c03715
49. Zhou M, Huang M, Zhong H, Xing C, An Y, Zhu R, ... Feng S (2022) Contact separation Triboelectric Nanogenerator based neural interfacing for effective sciatic nerve restoration. Adv Funct Mater 32(22):2200269. https://doi.org/10.1002/adfm.202200269
50. Zhou M, Zhong H, Xing C, Li H, Liu S, Wang L, ... Ning G (2023) Comparison of clinical outcomes associated with spinal cord stimulation (SCS) or conventional medical management (CMM) for chronic pain: a systematic review and meta-analysis. Eur Spine J 32(6):2029–2041. https://doi.org/10.1007/s00586-023-07716-2
51. Zou HJ, Guo SW, Zhu L, Xu X, Liu JB (2021) Methylprednisolone induces neuro-protective effects via the inhibition of A1 astrocyte activation in traumatic spinal cord injury mouse models. Front Neurosci 15:628917. https://doi.org/10.3389/fnins.2021.628917