ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
DOI:

Dynamics of Key Proteins and Systemic Inflammatory Profiles during Neuro-immune Modulation after Spinal Cord Injury

Junfeng Niu[1], Qiaoyi Cui[1], Ming Li[2], and Yubin Liu[1]

[1] Department of Rehabilitation, Yantaishan Hospital, Yantai, Shandong, China
[2] Department of Rehabilitation, Jinan Central Hospital, Jinan, Shandong, China

Received: 17 October 2025; Received in revised form: 9 May 2026; Accepted: 19 June 2026

ABSTRACT

Spinal cord injury (SCI) is a serious neurological trauma causing permanent functional impairments. This retrospective study (2022-2024) of 80 SCI patients examined dynamic protein changes during neural repair and their link to peripheral inflammatory mediators.

Before and at 2 and 4 weeks after treatment, patients' spinal cord function was assessed with the American Spinal Injury Association (ASIA) impairment scale. Motor nerve conduction velocities (MCV) and sensory nerve conduction velocities (SCV) were measured. Enzyme-linked immunosorbent assay (ELISA) was used to quantify serum levels of pro-inflammatory cytokines interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α), alongside neurotrophic factors basic fibroblast growth factor (bFGF), mature brain-derived neurotrophic factor (mBDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Patients' self-care abilities were evaluated with the Functional Independence Measure (FIM) scale and quality of life with the World Health Organization Quality of Life-Brief Version (WHO-QOL-BREF) scale.

During treatment, ASIA sensory and motor scores improved significantly. MCV and SCV of median, ulnar, tibial, and common peroneal nerves increased significantly. The levels of pro-inflammatory cytokines IL-6, IL-17, and TNF-α decreased significantly, while the serum levels of neurotrophic factors bFGF, mBDNF, NT-3, and NT-4 increased significantly. There was a significant negative correlation between pro-inflammatory cytokines and neurotrophic factors at 2 and 4 weeks after treatment, which was stronger at 4 weeks. FIM and WHO-QOL-BREF scores also improved significantly with treatment time.

These findings suggest a close interaction between the dynamic changes in key proteins and systemic inflammatory profiles during neural repair after SCI.

Keywords: Inflammation mediators; Neural conduction; Neuroimmunomodulation; Spinal cord injuries

INTRODUCTION

While the general interplay between neurotrophic factors and cytokines after spinal cord injury (SCI) is well recognized, the existing literature largely relies on cross-sectional designs, single-factor analyses, or preclinical animal models. Consequently, the time-dependent, quantitative relationship between the dynamic changes of multiple key proteins and the evolving peripheral inflammatory response—and how this relationship directly correlates with measurable functional recovery in patients—remains poorly

Corresponding Author: Yubin Liu, MD;
Department of Rehabilitation, Yantaishan Hospital, Yantai, Shandong, China. Tel: (+86 136) 4645 0037. Fax: (+86 53) 5686 1030, Email: 13646450037@163.com

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

defined. This study provides three specific innovations: (1) it is the first to simultaneously track the longitudinal changes (baseline, 2 weeks, 4 weeks) of four neurotrophic factors (BDNF, bFGF, NT-3, NT-4) and three pro-inflammatory cytokines (IL-6, IL-17, TNF-α) in a relatively large (N=80), homogeneous cohort of SCI patients receiving standardized treatment; (2) it quantifies a progressively strengthening negative correlation between cytokine and neurotrophic factor levels from 2 to 4 weeks; and (3) it establishes a time-resolved, quantitative framework that links these systemic biomarkers directly to clinically meaningful improvements in ASIA scores, nerve conduction velocities, functional independence, and quality of life (WHO-QOL-BREF). These findings advance the field by providing clinical evidence for neuro-immune modulation, thereby offering a more precise theoretical foundation for future targeted interventions.

Spinal cord injury (SCI) is a condition caused by trauma, tumors, or inflammation that damages the integrity and continuity of the spinal cord, leading to the dysfunction of motor, sensory, and autonomic systems.[1] Currently, millions of people worldwide are suffering from the pain inflicted by SCI.[2] The incidence of SCI continues to rise globally, imposing immeasurable losses on individual patients and society.[3] SCI can be divided into two stages: the acute phase and the subacute phase. During the acute phase, due to physical injury, cells at the injured site undergo disintegration, necrosis, and apoptosis, accompanied by vascular rupture and tissue edema.[4] In the subacute stage, secondary tissue damage follows the initial acute phase. Meanwhile, a notable infiltration of macrophages, T lymphocytes, microglial cells, and neutrophils into the lesion site takes place. This cellular influx compromises the blood-spinal cord barrier's integrity, induces substantial release of inflammatory mediators, and initiates a series of inflammatory cascades that contribute to secondary damage.[5] Secondary SCI further impedes synaptic remodeling and neural circuit regeneration, becoming one of the major obstacles to SCI repair.[6] In addition, SCI patients not only face challenges related to motor and sensory dysfunction but are also highly susceptible to severe complications such as respiratory system infections, urinary system infections, and deep vein thrombosis.[7] These complications significantly shorten the patients' average lifespan and drastically reduce their quality of life.

At present, the main treatment strategies for SCI involve pharmacological treatments, surgical operations, rehabilitation therapy, and cell therapy, among others. In terms of pharmacological treatment, neuroprotective agents and anti-inflammatory drugs are used to mitigate inflammation and protect neural tissue.[8] Surgical interventions primarily involve spinal decompression surgery to remove bone fragments or intervertebral disks that compress the spinal cord, maintaining spinal stability and preventing further injury.[9] Rehabilitation therapy aims to help patients restore function through methods such as physical therapy and functional electrical stimulation.[10] Additionally, cell therapy, as an emerging treatment approach, involves transplanting stem cells to promote neural regeneration and functional recovery.[11] Despite the numerous breakthroughs in neuroscience achieved by modern medicine, the issue of neural repair following SCI remains a major challenge. The core obstacle lies in the extremely limited inherent regenerative capacity of the central nervous system.[12] Although current clinical treatment methods for SCI can alleviate patients' symptoms to a certain extent, the recovery of neural function in patients is still far from satisfactory.

Delving into the pathophysiological mechanisms following SCI is essential for identifying effective treatment strategies. In this process, key proteins involved in neural repair and the immune microenvironment play crucial roles. Key neural repair proteins, such as brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4), are indispensable regulators in processes such as the survival, differentiation, migration, axonal growth, and synapse formation of neural cells.[13–15] The immune microenvironment also exerts a dual role in the pathophysiological process after SCI. Following SCI, the body's immune system is rapidly activated, with a large influx of immune cells into the injured area, leading to drastic changes in the immune microenvironment.[16] In the initial phase of injury, pro-inflammatory cells, primarily neutrophils and M1-type macrophages, rapidly accumulate. They participate in clearing damaged tissues and pathogens by releasing pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α), as well as reactive oxygen species. However, an excessive inflammatory response can result in secondary injury, exacerbating neural cell death and

loss of neural function.[17] Over time, the increasing number of M2-type macrophages, which secrete anti-inflammatory cytokines, can mitigate the inflammatory response and promote tissue repair and neural regeneration.[18] Nevertheless, our current understanding of how the immune microenvironment collaborates with key proteins to regulate the neural repair process remains relatively limited. The dynamic changes in neurotrophic factors are not independent of the immune microenvironment; instead, they exhibit a complex and intricate interrelationship. Inflammatory factors within the immune microenvironment can modulate the expression and function of key neural repair proteins through various signaling pathways. Conversely, alterations in neurotrophic factors can influence the activity, differentiation, and migration of immune cells, thereby changing the state of the immune microenvironment.[19–21] This interaction permeates the entire pathophysiological process after SCI, presenting distinct characteristics and roles at different stages, jointly determining the progression and outcome of neural repair. Elucidating the interplay mechanisms between the fluctuations of key proteins and the immune microenvironment not only aids in obtaining a more thorough and profound comprehension of the pathophysiological mechanisms subsequent to SCI, but also offers a theoretical foundation for pinpointing novel therapeutic targets and devising groundbreaking treatment approaches.

Based on the aforementioned background, this study hypothesizes that there is a close association between the dynamic changes in key proteins and systemic inflammatory mediator levels during the neural repair process following SCI. This interaction is expected to influence patients' neural function recovery, self-care abilities, and quality of life. The study enrolled 80 patients with SCI who received conventional treatment and rehabilitation. It is anticipated that during the treatment process, indicators such as patients' spinal cord function and nerve conduction velocity will significantly improve. Additionally, the levels of pro-inflammatory cytokines are expected to decrease and show a significant negative correlation with neurotrophic factors. Patients' self-care abilities and quality of life are also anticipated to enhance. This will provide a theoretical basis for developing targeted intervention strategies targeting key proteins and the immune microenvironment. It holds promise for improving the neural function recovery outcomes of SCI patients, enhancing their self-care abilities and quality of life, and offering a new direction for the clinical treatment and rehabilitation of SCI.

MATERIALS AND METHODS

The research is a retrospective clinical study. This retrospective design was chosen as an initial, exploratory approach to identify dynamic patterns and correlations between key proteins and immune markers in a real-world clinical cohort receiving standardized treatment. While prospective studies are better suited for mechanistic inference, retrospective analysis of existing clinical data allows for the generation of hypotheses regarding potential interactions that can be tested in future prospective trials. Data collection and analysis were performed by researchers who did not participate in the treatment of the patients. A total of 80 patients with SCI admitted to our hospital's SCI Rehabilitation Department from January 2022 to December 2024 were included. Conventional treatment and rehabilitation were given to all the patients. Nerve potential-related indicators were examined using an electromyography-evoked potential instrument. Serum levels of inflammatory cytokines and neurotrophic factors were measured. Additionally, the patients' self-care abilities and quality of life were evaluated. The study flowchart is shown in Figure 1.

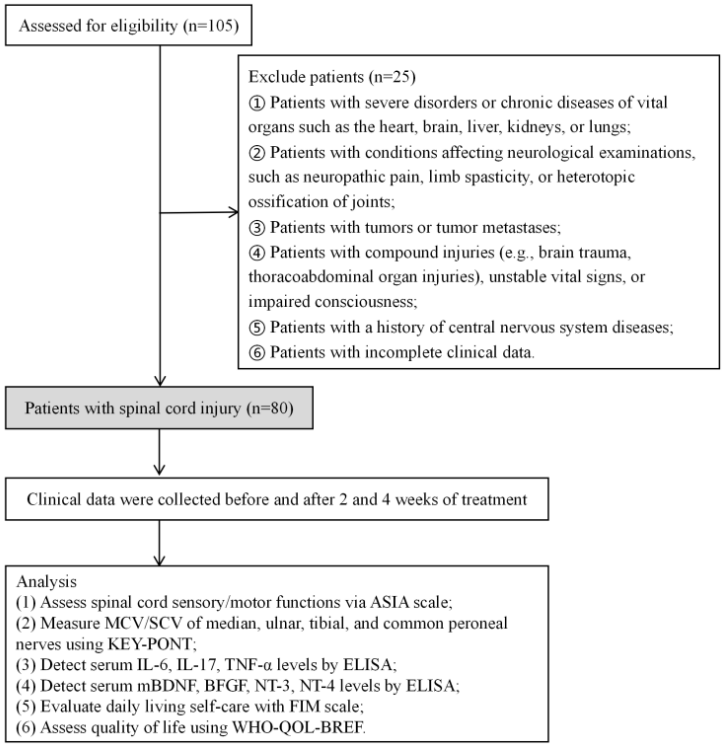

Figure 1. Retrospective study design flowchart. ASIA: American Spinal Injury Association; MCV: motor nerve conduction velocity; SCV: sensory nerve conduction velocity; IL-6: interleukin-6; IL-17: interleukin-17; TNF-α: tumor necrosis factor-α; ELISA: enzyme-linked immunosorbent assay; mBDNF: mature brain-derived neurotrophic factor; bFGF: basic fibroblast growth factor; NT-3: neurotrophin-3; NT-4: neurotrophin-4; FIM: Functional Independence Measure; WHO-QOL-BREF: World Health Organization Quality of Life-Brief Version.

Inclusion Criteria

The inclusion criteria were: (1) age ≥ 18 years; (2) time from injury to hospital visit < 24 hours; (3) physical examination reveals forced posture, tenderness over spinous processes, and abnormal sensory and motor functions in the trunk and limbs, or the presence of pathological reflexes, and imaging examinations show spinal cord compression, edema, hematoma around the spinal cord, accompanied by spinal fractures or dislocations, narrowing of the intervertebral space, etc., confirming the diagnosis of SCI; and (4) no history of spinal surgery or fractures within the past 2 years.

Exclusion Criteria

The exclusion criteria were: (1) patients with severe dysfunction or chronic diseases of vital organs such as the heart, brain, liver, kidneys, or lungs; (2) patients with conditions affecting neural function examination, such as neuropathic pain, limb spasticity, or heterotopic ossification around joints; (3) patients with tumors or tumor metastases; (4) patients with compound injuries such as traumatic brain injury, thoracoabdominal organ injuries, unstable vital signs, or altered consciousness; (5) patients with a previous history of central nervous system diseases; and (6) patients with incomplete clinical data.

Ethical Statement

This study is a retrospective clinical research project that strictly adheres to the ethical principles outlined in the Declaration of Helsinki.[22] The research plan has gained the endorsement of the Jinan Central Hospital ethics review board (approval No. KY-20200551). During the study, only de-identified, anonymous historical clinical data were used, and no additional interventions were imposed on the patients. All data were stored and managed in an encrypted database, accessible only to authorized researchers. Considering the characteristics of this research and the data protection measures put in place, this research poses no

additional risks to the participating patients or risks of privacy breaches.

Sample Size Calculation

In this study, a repeated measures analysis of variance (ANOVA) design was employed to compare differences in neural function recovery across three time points. Based on sample size estimation using G*Power 3.1 software,[23] with a medium effect size (effect size f=0.25), a significance level (α=0.05, two-tailed), and a test power (power=0.95) set for a single-group repeated measures design (with 3 time points and an intraclass correlation coefficient ICC=0.3), the minimum theoretical sample size was calculated to be 60 cases. However, this ideal estimate does not account for missing data, interpatient variability, or biomarker noise. After inflating the sample size by 20% to 25% to accommodate these factors, the required sample size increased to approximately 75 to 80 participants. This study ultimately included 80 subjects, which meets this more conservative requirement and ensures adequate statistical power.

Research Design

Symptomatic treatment was administered based on the patients' symptoms, physical signs, and examination results. For patients experiencing difficulty or labored breathing, routine oxygen inhalation was provided. Those with cervical spinal cord injuries at the mid-to-upper cervical levels received endotracheal intubation and mechanical ventilation. Dehydrating agents such as mannitol or furosemide were used to treat spinal cord edema, and steroidal hormones like methylprednisolone were employed for the treatment of acute SCI. For spinal fractures and dislocations, surgical intervention was considered based on imaging examination findings. Antibiotics were used as appropriate for anti-infective treatment. Additionally, hyperbaric oxygen therapy (HBOT) was administered using a medical air hyperbaric oxygen chamber (Model: YC320J-X; Manufacturer: Yantai Moon Hyperbaric Oxygen Chamber Co., Ltd.). Patients undergoing hyperbaric oxygen therapy were accompanied and monitored by physiotherapists. The chamber pressure was set at 0.2 MPa. All patients receiving hyperbaric oxygen therapy wore masks and inhaled pure oxygen in two 30-minute sessions, with a 5-minute break in between. The treatment was administered once daily for a duration of 4 weeks.[24] In addition to hyperbaric oxygen therapy, all patients received a standardized, multimodal rehabilitation program. The program included: (1) physical therapy (range of motion exercises, trunk and limb strengthening, balance and transfer training); (2) occupational therapy (training in activities of daily living, self-care, and fine motor skills); and (3) functional electrical stimulation (applied to affected limb muscles to maintain muscle mass and promote motor recovery). Rehabilitation sessions were conducted once daily, 5 days per week, for 4 weeks, each session lasting 45 to 60 minutes at moderate intensity. The same rehabilitation protocol was applied to all enrolled patients to ensure consistency. All baseline measurements were performed upon admission to the rehabilitation department after initial acute-phase management, not within 24 hours post-injury.

Observation Indicators

(1) American Spinal Injury Association (ASIA) Impairment Scale:[25] The ASIA Impairment Scale was used to evaluate patients' spinal cord function, including sensory function scores and motor function scores. The sensory function score has a maximum of 112 points, and the motor function score has a maximum of 100 points. Higher scores indicate better spinal cord function in patients.

(2) Nerve potential-related indicators: Before and after treatment, patients were examined using the KEY-PONT electromyography-evoked potential instrument (Medtronic, USA) to measure motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the median nerve, ulnar nerve, tibial nerve, and common peroneal nerve.[26] Limb skin temperature was maintained at 32°C to 34°C using a warm blanket or infrared lamp, and monitored with a surface thermometer, as temperature variations can significantly affect nerve conduction parameters. Limb positioning was standardized for each nerve tested, with the limb fixed in a neutral position to avoid artificial nerve elongation or compression. All electrophysiological examinations were performed by the same two trained technicians, who were blinded to the patients' clinical status and treatment time points. Inter-examiner variability was minimized through pre-study training and a standardized testing protocol. The KEY-PONT electromyography-evoked potential instrument was calibrated weekly using a built-in calibration function and validated with a biological signal simulator (Natus Neurology, USA).

(3) Serum inflammatory cytokine levels: Before and after the treatment, 5 mL of fasting venous blood was drawn from each patient. The blood underwent centrifugation at 3000 r/min for 10 minutes, and the supernatant was retained. Enzyme-linked immunosorbent assay (ELISA) kits produced by Shanghai Enzyme-linked Biotechnology Co., Ltd. were used to detect the levels of IL-6, IL-17, and TNF-α. The operations strictly followed the kit instructions. The detection instrument was the iMark fully automated microplate reader from Bio-Rad, USA. The detection sensitivities of the IL-6, IL-17, and TNF-α kits were all <1 pg/mL.

(4) Serum neurotrophic factor levels: The levels of mature brain-derived neurotrophic factor (mBDNF), basic fibroblast growth factor (bFGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) in peripheral blood were detected using the ELISA method, and the kit has no significant cross-reactivity with pro-BDNF (<0.1% as reported by the manufacturer). The mBDNF and bFGF ELISA kits were purchased from Shanghai Sangon Biotech Co., Ltd., with sensitivities both less than 1 μg/L. The NT-3 and NT-4 ELISA kits were from Shanghai Yeasen Biotechnology Co., Ltd., with sensitivities of 22.17 ng/L each. Data reading and analysis were performed using the fully automated microplate reader (Model: iMark) produced by Bio-Rad, USA.

(5) Self-care ability: The Functional Independence Measure (FIM) scale[27] was used to assess patients' self-care ability, with a total score ranging from 0 to 126 points.

(6) Quality of life: The World Health Organization Quality of Life-Brief Version (WHO-QOL-BREF)[28] was used to assess patients' quality of life, with a total score ranging from 0 to 100 points. The score is positively correlated with patients' quality of life.

Quality Control for ELISA Measurements

To ensure the reliability and reproducibility of the ELISA results, strict quality control procedures were implemented. Standard curves for IL-6, IL-17, TNF-α, bFGF, mBDNF, NT-3, and NT-4 were generated using serial dilutions of recombinant proteins provided in each kit. All calibration curves yielded a coefficient of determination (R^2)>0.99. Intra-assay coefficients of variation (CVs) were determined by analyzing each sample in triplicate, and inter-assay CVs were assessed by measuring the same control samples across three independent runs. Intra-assay CVs were <8% for all analytes, and inter-assay CVs were <10%. Before centrifugation, all blood samples were inspected for visible hemolysis; no visibly hemolyzed samples were included. Serum samples were immediately separated, aliquoted, and stored at −80°C until analysis, and all samples underwent no more than one freeze-thaw cycle. These procedures ensure the reproducibility of the cytokine and neurotrophic factor measurements reported in this study. Manufacturer-validated cross-reactivity among mBDNF, NT-3, and NT-4 kits was all <0.5%, confirming assay specificity.

Statistical Analysis

Data analysis was conducted using SPSS 25.0 statistical software (IBM, USA). Measurement data, such as ASIA scores, nerve potential-related indicators, serum inflammatory cytokine levels, and serum neurotrophic factor levels, were confirmed to follow a normal distribution through the Shapiro-Wilk test and were expressed as mean±standard deviation. Repeated measures ANOVA was used for comparisons across time points, with the Greenhouse-Geisser correction applied if sphericity was violated. Pearson correlation analysis was conducted to assess the relationship between serum inflammatory cytokine and neurotrophic factor levels. All tests were two-tailed, with p<0.05 indicating statistical significance.

RESULTS

Baseline Data of Patients

Baseline characteristics of patients with SCI are outlined. Among the patients, there were 48 males (60.00%) and 32 females (40.00%). The mean age was 45.36 years, the average body mass index (BMI) was 22.44 kg/m², and the mean time from injury to hospital presentation was 6.25 hours. The main causes of injury were traffic accidents (32.50%) and falls from heights (26.25%). Patients with underlying medical conditions such as hypertension, hyperlipidemia, and diabetes accounted for 10.00%, 11.25%, and 7.50% of the cohort, respectively, while 36.25% of the patients were smokers. The distribution of injury segments was as follows: cervical spine (30.00%), thoracic spine (27.50%), lumbar spine (23.75%), and sacral spine (18.75%). These characteristics are summarized in Table 1.

Dynamic Changes of Patients' ASIA Scores

Spinal injury scale outcomes before and after intervention are compared. Before treatment, the patients' ASIA sensory score was 45.66±4.85, and the motor score was 35.46±4.20. After 2 weeks of treatment, the sensory score increased to 53.44±6.09, and the motor score increased to 42.15±4.12. After 4 weeks of treatment, the sensory score further improved to 66.75±8.19, and the motor score increased to 48.66±4.41. Repeated measures ANOVA revealed that the effect of time on both the ASIA sensory score (F=226.241; p<0.001) and motor score (F=185.523; p<0.001) was significant, indicating a significant improvement in the patients' sensory and motor functions over time. The scores are detailed in Table 2.

Table 1. Baseline characteristics of patients with spinal cord injury

Variables	Patients with SCI (N=80)
Gender, n (%)	
Male	48 (60.00)
Female	32 (40.00)
Age, mean±SD, y	45.36±6.24
BMI, mean±SD, kg/m²	22.44±2.12
Time from injury to presentation, mean±SD, h	6.25±2.44
Causes of injury, n (%)	
Car accidents	26 (32.50)
Falls from heights	21 (26.25)
Heavy object injuries	16 (20.00)
Sports injuries	17 (21.25)
Underlying medical condition, n (%)	
Hypertension	8 (10.00)
High blood lipids	9 (11.25)
Diabetes	6 (7.50)
Smoking history, n (%)	
Yes	29 (36.25)
No	51 (63.75)
SCI segment, n (%)	
Cervical segment	24 (30.00)
Thoracic segment	22 (27.50)
Lumbar segment	19 (23.75)
Sacral segment	15 (18.75)

BMI: body mass index; SCI: spinal cord injury.

Table 2. Dynamic changes of patient ASIA scores

Time	ASIA sensory score	ASIA motor score
Pretreatment	45.66±4.85	35.46±4.20
2 weeks posttreatment	53.44±6.09	42.15±4.12
4 weeks posttreatment	66.75±8.19	48.66±4.41
Test	Repeated-measures ANOVA	Repeated-measures ANOVA
F	226.241	185.523
p	<0.001	<0.001
partial η^2	0.741	0.701

ANOVA: analysis of variance; ASIA: American Spinal Injury Association.

Dynamic Changes of Nerve Potential Related Indicators in Patients

Motor nerve potential changes are detailed. For the median nerve, the MCV values were 36.87±2.83 m/s, 42.55±3.65 m/s, and 47.77±4.12 m/s respectively; for the ulnar nerve, they were 36.57±2.49 m/s, 42.35±3.78 m/s, and 46.81±4.22 m/s; for the tibial nerve, the values were 29.86±3.85 m/s, 37.65±4.29 m/s, and 45.55±5.38 m/s; and for the common peroneal nerve, they were 30.83±3.45 m/s, 41.55±5.01 m/s, and 49.89±5.42 m/s. Repeated-measures ANOVA revealed that time had a significant effect on the MCV of the median nerve (F=166.686; p<0.001), ulnar nerve (F=157.291; p<0.001), tibial nerve (F=267.777; p<0.001), and common peroneal nerve (F=350.439; p<0.001), indicating a significant improvement in the patients' motor nerves during the treatment process. These findings are presented in Table 3.

Sensory nerve potential changes are detailed. For the median nerve, the SCV values were 37.63±2.68 m/s, 42.02±4.21 m/s, and 48.67±5.32 m/s respectively; for the ulnar nerve, they were 36.81±2.75 m/s, 44.77±3.95 m/s, and 51.65±4.78 m/s; for the tibial nerve, the values were 32.33±3.57 m/s, 41.66±5.74 m/s, and 47.56±5.77 m/s; and for the common peroneal nerve, they were 35.62±4.25 m/s, 45.72±5.21 m/s, and 52.21±6.12 m/s. Repeated-measures ANOVA demonstrated that time had a significant effect on the SCV of the median nerve (F=136.187; p<0.001), ulnar nerve (F=292.665; p<0.001), tibial nerve (F=162.332; p<0.001), and common peroneal nerve (F=199.866; p<0.001), indicating a noticeable recovery in the patients' sensory nerves during the treatment. These findings are presented in Table 4.

Dynamic Changes of Serum Inflammatory Factor Levels in Patients

Inflammatory cytokine levels over time are compared. Before treatment, the serum levels of IL-6, IL-17, and TNF-α in patients were 18.19±3.21 pg/mL, 28.88±3.56 pg/mL, and 23.45±3.51 pg/mL, respectively. After 2 weeks of treatment, the levels of IL-6 decreased to 13.34±2.15 pg/mL, IL-17 decreased to 21.35±1.65 pg/mL, and TNF-α decreased to 17.66±2.15 pg/mL. By the 4th week of treatment, IL-6 further declined to 8.78±2.62 pg/mL, IL-17 decreased to 13.07±2.21 pg/mL, and TNF-α decreased to 11.23±2.75 pg/mL. Repeated-measures ANOVA demonstrated that time had a statistically significant effect on the levels of IL-6 (F=232.770; p<0.001), IL-17 (F=761.306; p<0.001), and TNF-α (F=387.465; p<0.001). This indicates that the treatment can significantly reduce the levels of pro-inflammatory cytokines such as IL-6, IL-17, and TNF-α, thereby alleviating the inflammatory cascade reaction following nerve injury and creating a favorable microenvironment for nerve repair. These profiles are shown in Table 5.

Table 3. Dynamic changes of patient motor nerve conduction velocity (MCV)

Time	Median nerve, m/s	Ulnar nerve, m/s	Tibial nerve, m/s	Common peroneal nerve, m/s
Pretreatment	36.87±2.83	36.57±2.49	29.86±3.85	30.83±3.45
2 weeks posttreatment	42.55±3.65	42.35±3.78	37.65±4.29	41.55±5.01
4 weeks posttreatment	47.77±4.12	46.81±4.22	45.55±5.38	49.89±5.42
Test	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA
F	166.686	157.291	267.777	350.439
p	<0.001	<0.001	<0.001	<0.001
partial η^2	0.678	0.666	0.772	0.816

ANOVA: analysis of variance; MCV: motor nerve conduction velocity.

Table 4. Dynamic changes of patient sensory nerve conduction velocity (SCV)

Time	Median nerve, m/s	Ulnar nerve, m/s	Tibial nerve, m/s	Common peroneal nerve, m/s
Pretreatment	37.63±2.68	36.81±2.75	32.33±3.57	35.62±4.25
2 weeks posttreatment	42.02±4.21	44.77±3.95	41.66±5.74	45.72±5.21
4 weeks posttreatment	48.67±5.32	51.65±4.78	47.56±5.77	52.21±6.12
Test	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA
F	136.187	292.665	162.332	199.866
p	<0.001	<0.001	<0.001	<0.001
partial η^2	0.633	0.787	0.673	0.717

ANOVA: analysis of variance; SCV: sensory nerve conduction velocity.

Table 5. Dynamic changes of patient serum inflammatory factor levels

Time	IL-6, pg/mL	IL-17, pg/mL	TNF-α, pg/mL
Pretreatment	18.19±3.21	28.88±3.56	23.45±3.51
2 weeks posttreatment	13.34±2.15	21.35±1.65	17.66±2.15
4 weeks posttreatment	8.78±2.62	13.07±2.21	11.23±2.75
Test	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA
F	232.770	761.306	387.465
p	<0.001	<0.001	<0.001
partial η^2	0.746	0.906	0.831

ANOVA: analysis of variance; IL-6: interleukin-6; IL-17: interleukin-17; TNF-α: tumor necrosis factor-α.

Dynamic Changes of Serum Neurotrophic Factor Levels in Patients

Neurotrophic factor changes are examined. The results indicate that before treatment, the serum levels of bFGF, mBDNF, NT-3, and NT-4 in patients were 8.22±0.75 μg/L, 3.52±0.75 μg/L, 3522.45±185.63 ng/L, and 6033.43±175.22 ng/L, respectively. After 2 weeks of treatment, the levels of bFGF increased to 11.17±1.11 μg/L, mBDNF increased to 6.25±1.03 μg/L, NT-3 increased to 4223.44±246.74 ng/L, and NT-4 increased to 7144.25±188.65 ng/L. By the 4th week of treatment, bFGF further rose to 16.33±1.76 μg/L, mBDNF rose to 8.33±1.24 μg/L, NT-3 rose to 5612.66±278.44 ng/L, and NT-4 rose to 8964.33±222.44 ng/L. Repeated-measures ANOVA demonstrated that time had a statistically significant effect on the levels of bFGF (F=889.575; p<0.001), mBDNF (F=436.161; p<0.001), NT-3 (F=1739.837; p<0.001), and NT-4 (F=4521.282; p<0.001). This indicates that the serum neurotrophic factor levels of patients significantly increased during the treatment process, suggesting that the treatment may promote the synthesis and release of neurotrophic factors by glial cells or neurons through activating relevant signaling pathways, thereby accelerating the growth of nerve axons and the reconstruction of synaptic connections. This potentially forms a relationship with the improvement in patients' ASIA scores. These changes are shown in Table 6.

Pearson correlation analysis between serum inflammatory cytokine levels and neurotrophic factor levels in patients after 2 weeks of treatment was performed. The results show that IL-6 is significantly negatively correlated with bFGF, mBDNF, NT-3, and NT-4 (Pearson r values are −0.567, −0.609, −0.585, and −0.597 respectively, all p values<0.001). Similarly, IL-17 is significantly negatively correlated with bFGF, mBDNF, NT-3, and NT-4 (Pearson r values are −0.732, −0.733, −0.729, and −0.697 respectively, all P values<0.001), as is TNF-α (Pearson r values are −0.723, −0.718, −0.707, and −0.700 respectively, all P

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

values<0.001). These correlations are presented in Table 7.

Pearson correlation analysis between serum inflammatory cytokine levels and neurotrophic factor levels in patients after 4 weeks of treatment was performed. The results reveal that IL-6 is significantly negatively correlated with bFGF, mBDNF, NT-3, and NT-4 (Pearson *r* values are −0.723, −0.738, −0.822, and −0.764 respectively, all P values<0.001). Likewise, IL-17 is significantly negatively correlated with bFGF, mBDNF, NT-3, and NT-4 (Pearson *r* values are −0.756, −0.742, −0.676, and −0.734 respectively, all P values<0.001), as is TNF-α (Pearson *r* values are −0.775, −0.779, −0.830, and −0.789 respectively, all P values<0.001). These correlations are presented in Table 8.

Patient capacity to carry out daily activities is evaluated. The results reveal that before treatment, the patients' FIM score was 62.36±4.68. After 2 weeks of treatment, the FIM score increased to 72.23±6.22, and by the 4th week of treatment, it further improved to 81.44±5.63. Repeated-measures ANOVA demonstrated that time had a statistically significant effect on the FIM score (F=240.492; p<0.001), suggesting a remarkable enhancement in the patients' capacity to carry out daily activities throughout the treatment. These scores are presented in Table 9.

Quality of life outcomes over time are presented. The results indicate that the pre-treatment WHO-QOL-BREF score was 54.33±8.55. After 2 weeks of treatment, the score increased to 62.45±5.45, and further rose to 69.33±6.64 at 4 weeks of treatment. Repeated measures ANOVA revealed that the effect of time on the WHO-QOL-BREF score was statistically significant (F=85.056; p<0.001), suggesting that the therapeutic effect gradually emerged over time, leading to a continuous improvement in the patients' quality of life. These data are summarized in Table 10.

Table 6. Dynamic changes of patient serum neurotrophic factor levels

Time	bFGF, μg/L	mBDNF, μg/L	NT-3, ng/L	NT-4, ng/L
Pretreatment	8.22±0.75	3.52±0.75	3522.45±185.63	6033.43±175.22
2 weeks posttreatment	11.17±1.11	6.25±1.03	4223.44±246.74	7144.25±188.65
4 weeks posttreatment	16.33±1.76	8.33±1.24	5612.66±278.44	8964.33±222.44
Test	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA	Repeated-measures ANOVA
F	889.575	436.161	1739.837	4521.282
p	<0.001	<0.001	<0.001	<0.001
partial η^2	0.918	0.847	0.957 0.983	

ANOVA: analysis of variance; bFGF: basic fibroblast growth factor; mBDNF: mature brain-derived neurotrophic factor; NT-3: neurotrophin-3; NT-4: neurotrophin-4.

Table 7. Pearson correlation analysis of patient serum inflammatory cytokines and neurotrophic factors at 2 weeks posttreatment

Cytokine	Statistical metric	bFGF	mBDNF	NT-3	NT-4
IL-6	Pearson *r*	−0.567	−0.609	−0.585	−0.597
	p	<0.001	<0.001	<0.001	<0.001
IL-17	Pearson *r*	−0.732	−0.733	−0.729	−0.697
	p	<0.001	<0.001	<0.001	<0.001
TNF-α	Pearson *r*	−0.723	−0.718	−0.707	−0.700
	p	<0.001	<0.001	<0.001	<0.001

bFGF: basic fibroblast growth factor; IL-6: interleukin-6; IL-17: interleukin-17; mBDNF: mature brain-derived neurotrophic factor; NT-3: neurotrophin-3; NT-4: neurotrophin-4; TNF-α: tumor necrosis factor-α.

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

Table 8. Pearson correlation analysis of patient serum inflammatory cytokines and neurotrophic factors at 4 weeks posttreatment

Cytokine		Statistical metric	bFGF	mBDNF	NT-3	NT-4
IL-6	Pearson *r*	−0.723		−0.738	−0.822	−0.764
	p	<0.001		<0.001	<0.001	<0.001
IL-17	Pearson *r*	−0.756		−0.742	−0.676	−0.734
	p	<0.001		<0.001	<0.001	<0.001
TNF-α	Pearson *r*	−0.775		−0.779	−0.830	−0.789
	p	<0.001		<0.001	<0.001	<0.001

bFGF: basic fibroblast growth factor; IL-6: interleukin-6; IL-17: interleukin-17; mBDNF: mature brain-derived neurotrophic factor; NT-3: neurotrophin-3; NT-4: neurotrophin-4; TNF-α: tumor necrosis factor-α.

Table 9. Dynamic changes of patient FIM scores

Time	FIM score
Pretreatment	62.36±4.68
2 weeks posttreatment	72.23±6.22
4 weeks posttreatment	81.44±5.63
Test	Repeated-measures ANOVA
F	240.492
p	<0.001
partial η^2	0.753

ANOVA: analysis of variance; FIM: functional independence measure.

Table 10. Dynamic changes of patient WHO-QOL-BREF scores

Time	WHO-QOL-BREF score
Pretreatment	54.33±8.55
2 weeks posttreatment	62.45±5.45
4 weeks posttreatment	69.33±6.64
Test	Repeated-measures ANOVA
F	85.056
p	<0.001
partial η^2	0.518

ANOVA: analysis of variance; WHO-QOL-BREF: World Health Organization Quality of Life-Brief Version.

DISCUSSION

SCI is a serious neurological injury that usually leads to sensory and motor dysfunction in patients, severely impacting their quality of life and self-care abilities.[29] With in-depth research into the mechanisms of SCI, scholars have gradually come to recognize the significance of inflammatory responses and the immune microenvironment in the process of neural repair. The repair following SCI not only involves the regeneration of neurons and functional restoration but is also closely linked to complex immune reactions. This study unveiled the dynamic changes in key proteins and their interactions with the immune microenvironment, thereby providing a theoretical basis for targeted intervention strategies.

In the initial phase following SCI, the inflammatory response is mainly triggered by tissue destruction and cell death caused by the injury, encompassing a series of processes such as vasodilation and leukocyte

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

infiltration.[30] Leukocyte infiltration is the core mechanism of the inflammatory response, with neutrophils being the first immune cells to arrive at the site of inflammation following tissue damage.[31] Neutrophils clear pathogens through phagocytosis while simultaneously releasing enzymes like myeloperoxidase and lysozyme, as well as reactive oxygen species, forming neutrophil extracellular traps to capture bacteria.[32] However, in the context of SCI, the excessive activation of neutrophils and the release of harmful substances may also damage adjacent neurons, leading to axonal injury and blood flow disturbances.[33] Subsequently, monocytes and macrophages infiltrate the injured area, clearing cellular debris and pathogens through phagocytosis and secreting various cytokines to regulate the severity and duration of the inflammatory response. The spontaneous apoptosis of neutrophils and their subsequent phagocytosis by macrophages are crucial for the resolution of inflammation. If neutrophils survive excessively or are not cleared promptly, they may continue to release pro-inflammatory factors, leading to uncontrolled inflammation.[34]

Pro-inflammatory cytokines, specifically IL-6, IL-17, and TNF-α, can further promote the development of the inflammatory response, recruiting more inflammatory cells to the injured area and amplifying inflammatory signals. Studies by Shipman et al[35] and Boehl et al[36] have both demonstrated that individuals with SCI exhibit higher levels of IL-6. As a cytokine that plays a crucial role in the immune system, the abnormal elevation of IL-6 following SCI may indicate the activation of the body's inflammatory response. This inflammatory response could be one of the significant factors contributing to secondary injury after SCI, potentially adversely affecting neural tissue through various pathways, such as exacerbating neuronal damage and inhibiting nerve regeneration. Tang et al[37] discovered that the IL-17 signaling pathway is highly activated post-SCI and is involved in the inflammatory cascade. Bone marrow mesenchymal stem cell-derived exosomes (BMMSC-exos) can inhibit this pathway, downregulate acyl-CoA synthetase long-chain family member 4 (*ACSL4*) expression, and upregulate the antioxidant enzymes glutathione peroxidase 4 (*GPX4*) and *xCT* expression. This mechanism reduces lipid peroxidation, elevates glutathione levels, ultimately alleviates spinal cord pathological damage, and promotes functional recovery. This finding reveals the dual protective effects of BMMSC-exos in achieving anti-inflammatory and anti-ferroptosis outcomes through the regulation of the IL-17 pathway, providing a theoretical basis for its use as an alternative treatment for SCI and suggesting that the IL-17 pathway may be a key target for SCI intervention. Bai et al[38] utilized a multi-omics method to investigate the impact of zinc ions on the immune response in damaged spinal cord tissue. Zinc ions were found to significantly regulate TNF-α signaling molecules, reducing cell apoptosis and inflammation after SCI by inhibiting the TNF-α pathway. The study also constructed an immune atlas of spinal cord tissue treated with zinc ions, revealing that microglia exert anti-inflammatory effects through suppressed TNF-α signaling. During the comprehensive treatment of SCI patients, we kept a close eye on the fluctuations of crucial pro-inflammatory factors within their bodies. It was observed that the levels of three pro-inflammatory cytokines, namely IL-6, IL-17, and TNF-α, significantly decreased over the course of treatment. This finding is in line with previous studies, highlighting the essential role of inflammatory factors in SCI. The abnormal elevation of inflammatory factors may be one of the important factors contributing to a series of pathophysiological changes after SCI, and effective regulation of these factors through comprehensive treatment holds positive significance for improving the condition of SCI patients and promoting neural functional recovery.

During the neural repair process subsequent to SCI, the dynamic alterations of key proteins are of vital significance to neuronal regeneration and functional recovery.[39] Neurotrophic factors are a category of proteins that have the ability to boost the survival, growth, and differentiation of neurons, and they are of great significance in neural repair following SCI.[40] In this study, the neurotrophic factors identified encompass mBDNF, bFGF, NT-3, and NT-4. The primary mode of action of mBDNF is through its binding to the tyrosine kinase receptor B (TrkB), which triggers the activation of downstream signaling pathways.[41] bFGF is a growth factor with diverse biological functions. It not only boosts neural stem cell proliferation and differentiation but also facilitates angiogenesis, providing nutritional support for neural regeneration.[42] NT-3 and NT-4 are also important neurotrophic factors that regulate neuronal growth, differentiation, survival, as well as the regeneration and myelination of nerve fibers by binding to specific receptors.[43] Muheremu et al[44] demonstrated that through the use of various cellular carriers, viral

vectors, and tissue engineering scaffold technologies, these crucial neurotrophic factors can be safely and continuously delivered precisely to the injured site, achieving satisfactory neural repair outcomes and functional recovery in many cases. In our study, as the treatment duration increased, the levels of mBDNF, bFGF, NT-3, and NT-4 significantly rose, indicating their active roles in neural repair after SCI. The synergistic effects of these neurotrophic factors provide a powerful driving force and material basis for neural repair, thereby facilitating axonal growth and synaptic reconstruction.

The dynamic changes in neurotrophic factors are not independent of the immune microenvironment; instead, they exhibit a complex and intricate interrelationship. Inflammatory factors within the immune microenvironment can modulate the expression and function of key neural repair proteins through various signaling pathways. Conversely, alterations in neurotrophic factors can influence the activity, differentiation, and migration of immune cells.[19–21] This interaction is reflected in the progressive strengthening of the negative correlations observed over time between pro-inflammatory cytokines (IL-6, IL-17, TNF-α) and neurotrophic factors (bFGF, mBDNF, NT-3, NT-4) from 2 to 4 weeks posttreatment. This reduction in pro-inflammatory cytokine levels likely alleviates the damage caused by chronic inflammation to neural tissue, establishing a favorable microenvironment to support endogenous neural regeneration and functional recuperation, while the concurrent elevation in neurotrophic factors directly supports the survival and growth of regenerated axons.[45]

In parallel with our correlational findings, several experimental therapeutic strategies have been developed to directly modulate the post-SCI immune microenvironment. Interleukin-10 (IL-10), a classic anti-inflammatory cytokine, has shown neuroprotective effects by polarizing microglia and macrophages toward an M2 phenotype, reducing pro-inflammatory cytokine release, and promoting axonal sparing.[46,47] However, the short half-life and potential systemic side effects of exogenous IL-10 have prompted the development of immune-modulating biomaterials. For example, injectable hydrogels or porous scaffolds functionalized with IL-10, or with surface chemistry designed to adsorb endogenous inflammatory mediators, can sustain local delivery and create a pro-regenerative niche.[48,49] Separately, exosome-based treatments—particularly those derived from mesenchymal stem cells (MSC-exos)—have gained attention for their ability to transfer anti-inflammatory microRNAs (miRs) and proteins to injured spinal cord tissues, suppress IL-6, IL-17, and TNF-α, and simultaneously upregulate neurotrophic factors such as BDNF and NT-3.[50,51] While our study did not test these interventions, the progressively strengthening negative correlations we observed between pro-inflammatory cytokines and neurotrophic factors provide a quantitative rationale for such approaches: interventions that reduce IL-6, IL-17, or TNF-α might indirectly permit or amplify endogenous neurotrophic support.

Our findings align with and provide clinical support for several modern therapeutic strategies in SCI. First, the progressive reduction of pro-inflammatory cytokines (IL-6, IL-17, TNF-α) over time suggests that immunomodulatory therapies—such as blocking IL-17 or TNF-α signaling, or promoting M2 macrophage polarization—could enhance neural repair by suppressing secondary inflammation. Second, the simultaneous and sustained elevation of multiple neurotrophic factors (BDNF, bFGF, NT-3, NT-4) supports the rationale for combinatorial neurotrophic factor delivery strategies using biomaterial scaffolds, viral vectors, or cell-based platforms. Third, the time-dependent strengthening of negative correlations between cytokine and neurotrophic factor levels (from 2 to 4 weeks) implies that early control of inflammation may be a prerequisite for optimal neurotrophic support, a concept directly relevant to staged rehabilitation protocols. Thus, our findings not only describe neuro-immune dynamics but also provide a quantitative, time-resolved framework for designing and monitoring targeted interventions that modulate the immune microenvironment to enhance endogenous neurotrophic responses after SCI.

It is important to acknowledge that spinal cord injury induces systemic inflammation and immune suppression (SCI-IDS), a well-recognized phenomenon involving altered circulating cytokine profiles and peripheral immune cell dysfunction. In this study, all serum inflammatory markers (IL-6, IL-17, TNF-α) and neurotrophic factors were measured in peripheral blood. Therefore, these biomarkers reflect systemic, rather than spinal cord-specific, immune and neurotrophic dynamics. We cannot definitively attribute the observed changes exclusively to local neuro-immune interactions within the injured spinal cord. Systemic inflammatory

responses originating from secondary infections, autonomic dysreflexia, or other SCI-related complications may also contribute to the serum levels reported here. This distinction is critical because the immune microenvironment directly at the lesion site—including microglial polarization, resident macrophage phenotypes, and perilesional astrocyte responses—cannot be directly inferred from peripheral blood measurements. Future studies should combine cerebrospinal fluid analysis or intrathecal biomarker sampling with postmortem tissue validation to disentangle local versus systemic neuro-immune dynamics.

Research Limitations

This study has several important limitations. All patients received hyperbaric oxygen therapy as part of a combined treatment protocol, and no non-HBO control group was included. Consequently, the specific contribution of hyperbaric oxygen to the observed reductions in pro-inflammatory cytokines or increases in neurotrophic factors cannot be determined. The findings should therefore be interpreted as the net effect of multimodal rehabilitation, rather than as a single-agent analysis. This study measured only serum cytokine levels and did not perform any immune cell phenotyping. Therefore, it is not possible to characterize the local immune microenvironment at the cellular level, including T-lymphocyte subsets ($CD4^+/CD8^+$ ratio, T_H17/T_{reg} balance), macrophage polarization (M1 vs. M2 phenotypes), neutrophil activation status, or microglial responses. Serum cytokines reflect systemic inflammatory states but do not directly capture the complex cellular interactions within the injured spinal cord. Addressing these questions would require cerebrospinal fluid analysis, flow cytometry, or immunohistochemistry in prospective studies or animal models.

The absence of a healthy control group or a non-rehabilitation SCI control group limits causal inference regarding treatment specificity. The retrospective design is inherently susceptible to selection bias and unmeasured confounding variables. Because this study relied solely on serum samples from a retrospective cohort, it was not possible to measure local immune cell phenotypes, which require invasive cerebrospinal fluid sampling or tissue immunohistochemistry and were not feasible in this clinical setting. Future prospective studies using animal models or cerebrospinal fluid analysis are needed to fully characterize the local immune microenvironment. Blood samples were collected during routine clinical hours without standardization for circadian timing or interval from hyperbaric oxygen therapy, both of which may affect cytokine and neurotrophic factor levels. Furthermore, the FIM and the WHO-QOL-BREF are subjective assessment tools that may be influenced by psychosocial factors such as patients' mood, motivation, social support, and cultural expectations. Without concurrent objective functional measures or adjustment for psychological confounders, the observed improvements in self-care ability and quality of life may carry potential measurement bias.

Due to the limited sample size and exploratory design, this study did not perform subgroup analyses by injury level, completeness, or etiology. Future stratified studies are needed. Some patients received methylprednisolone for acute SCI per clinical indication. Because steroid treatment was not randomized and was confounded by injury severity, valid statistical adjustment was not feasible in this retrospective cohort. Thus, the observed reductions in pro-inflammatory cytokines may partly reflect steroid effects rather than spontaneous neuro-immune dynamics. Future prospective studies with standardized protocols are needed to isolate these effects. Although signaling pathways such as TrkB (downstream of neurotrophic factors) and the TNF-α/IL-17 cascades are discussed, this retrospective clinical study does not provide direct mechanistic validation of these pathways, and the reported correlations do not establish causality. The Pearson correlation coefficients (approximately 0.7 to 0.8) observed between pro-inflammatory cytokines and neurotrophic factors, although strong, do not establish causality or the direction of interaction. Experimental studies (e.g., blockade of IL-6 or BDNF signaling in animal models or cell cultures) are required to determine whether these relationships are causal and, if so, in which direction they operate.

Through a retrospective clinical study, this research dynamically monitored and analyzed multiple indicators in patients with SCI, systematically revealing associations between key proteins and systemic inflammatory profiles during the neural repair process. This interaction is vital for the recovery of neurological function, improvement of nerve conduction velocities, and enhancement of quality of life. These findings not only provides a new perspective for understanding the

biological mechanisms following SCI but also lays a theoretical foundation for future targeted intervention strategies.

STATEMENT OF ETHICS

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Jinan Central Hospital (approval No. KY-20200551), which granted a waiver of written informed consent for all participants.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

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

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Hu X, Xu W, Ren Y, Wang Z, He X, Huang R, et al. Spinal cord injury: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2023;8(1):245.
2. Izzy S. Traumatic spinal cord injury. Continuum (Minneap Minn). 2024;30(1):53-72.
3. Sterner RC, Sterner RM. Immune response following traumatic spinal cord injury: Pathophysiology and therapies. Front Immunol. 2022;13:1084101.
4. Adegeest CY, Ter Wengel PV, Peul WC. Traumatic spinal cord injury: acute phase treatment in critical care. Curr Opin Crit Care. 2023;29(6):659-65.
5. Sunshine MD, Bindi VE, Nguyen BL, Doerr V, Boeno FP, Chandran V, et al. Oxygen therapy attenuates neuroinflammation after spinal cord injury. J Neuroinflammation. 2023;20(1):303.
6. Zhang Q, Yu B, Zhang Y, Tian Y, Yang S, Chen Y, et al. Combination of single-cell and bulk RNA seq reveals the immune infiltration landscape and targeted therapeutic drugs in spinal cord injury. Front Immunol. 2023;14:1068359.
7. Baroudi M, Rezk A, Daher M, Balmaceno-Criss M, Gregoryczyk JG, Sharma Y, et al. Management of traumatic spinal cord injury: A current concepts review of contemporary and future treatment. Injury. 2024;55(6):111472.
8. Wang JZ, Yang M, Meng M, Li ZH. Clinical characteristics and treatment of spinal cord injury in children and adolescents. Chin J Traumatol. 2023;26(1):8-13.
9. Rose Hill EJ, Bertelli JA. Spinal cord injury: Epidemiology, spontaneous recovery, and hand therapy for the reconstructive hand surgeon. J Hand Surg Am. 2023;48(7):711-8.
10. Guo J, Cao J, Wu J, Gao J. Electrical stimulation and conductive materials: electrophysiology-based treatment for spinal cord injury. Biomater Sci. 2024.
11. Yu T, Yang LL, Zhou Y, Wu MF, Jiao JH. Exosome-mediated repair of spinal cord injury: a promising therapeutic strategy. Stem Cell Res Ther. 2024;15(1):6.
12. Song Q, Cui Q, Sun S, Wang Y, Yuan Y, Zhang L. Crosstalk between cell death and spinal cord injury: Neurology and therapy. Mol Neurobiol. 2024.
13. Wang Y, Liang J, Xu B, Yang J, Wu Z, Cheng L. TrkB/BDNF signaling pathway and its small molecular agonists in CNS injury. Life Sci. 2023;336:122282.
14. Zou Z, Liu R, Wang Y, Tan H, An G, Zhang B, et al. Protein arginine methyltransferase 8 regulates ferroptosis and macrophage polarization in spinal cord injury via glial cell-derived neurotrophic factor. CNS Neurosci Ther. 2023;29(8):2145-61.
15. Shamsnia HS, Peyrovinasab A, Amirlou D, Sirouskabiri S, Rostamian F, Basiri N, et al. BDNF-TrkB signaling pathway in spinal cord injury: Insights and implications. Mol Neurobiol. 2024.
16. DiSabato DJ, Marion CM, Mifflin KA, Alfredo AN, Rodgers KA, Kigerl KA, et al. System failure: Systemic inflammation following spinal cord injury. Eur J Immunol. 2023;e2250274.
17. Jerome AD, Sas AR, Wang Y, Hammond LA, Wen J, Atkinson JR, et al. Cytokine polarized, alternatively

activated bone marrow neutrophils drive axon regeneration. Nat Immunol. 2024.
18. Li J, Wang P, Zhou T, Jiang W, Wu H, Zhang S, et al. Neuroprotective effects of interleukin 10 in spinal cord injury. Front Mol Neurosci. 2023;16:1214294.
19. Kayagaki N, Webster JD, Newton K. Control of cell death in health and disease. Annu Rev Pathol. 2024;19:157-80.
20. Kedia-Mehta N, Finlay DK. Competition for nutrients and its role in controlling immune responses. Nat Commun. 2019;10(1):2123.
21. Palasz E, Wilkaniec A, Stanaszek L, Andrzejewska A, Adamczyk A. Glia-neurotrophic factor relationships: Possible role in pathobiology of neuroinflammation-related brain disorders. Int J Mol Sci. 2023;24(7).
22. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. JAMA. 2025;333(1):71-4.
23. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.
24. Zhang Z, Li Q, Yang X, Li B, Zhou Y, Hu T, et al. Effects of hyperbaric oxygen therapy on postoperative recovery after incomplete cervical spinal cord injury. Spinal Cord. 2022;60(2):129-34.
25. Kirshblum S, Botticello A, Benedetto J, Donovan J, Marino R, Hsieh S, et al. A comparison of diagnostic stability of the ASIA Impairment Scale versus Frankel classification systems for traumatic spinal cord injury. Arch Phys Med Rehabil. 2020;101(9):1556-62.
26. Li Z, Gao Y, Jia Y, Chen S. Correlation between hemoglobin glycosylation index and nerve conduction velocity in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2021;14:4757-65.
27. Kobayashi T, Kodama A, Okazaki T, Honma T, Yamada T, Ishibashi H, et al. Prognostic significance of preoperative functional independence measure (FIM) on long-term outcomes in patients with chronic limb-threatening ischemia (CLTI). Ann Vasc Surg. 2022;83:275-83.
28. Kumar V, Malhotra V, Sinha V. Evaluation of individual quality of life (QOL) among patients with tracheostomy using WHO-QOL BREF questionnaire. Indian J Otolaryngol Head Neck Surg. 2022;74(Suppl 3):5207-16.
29. Sargent L, Smitherman J, Sorenson M, Brown R, Starkweather A. Cognitive and physical impairment in spinal cord injury: A scoping review and call for new understanding. J Spinal Cord Med. 2023;46(3):343-66.
30. Freyermuth-Trujillo X, Segura-Uribe JJ, Salgado-Ceballos H, Orozco-Barrios CE, Coyoy-Salgado A. Inflammation: A target for treatment in spinal cord injury. Cells. 2022;11(17).
31. Ren J. Advances in combination therapy for gastric cancer: integrating targeted agents and immunotherapy. Adv Clin Pharmacol Ther. 2024;1(1):1-15.
32. Michel-Flutot P, Bourcier CH, Emam L, Gasser A, Glatigny S, Vinit S, et al. Extracellular traps formation following cervical spinal cord injury. Eur J Neurosci. 2023;57(4):692-704.
33. de Sena-Tomás C, Rebola Lameira L, Rebocho da Costa M, Naique Taborda P, Laborde A, Orger M, et al. Neutrophil immune profile guides spinal cord regeneration in zebrafish. Brain Behav Immun. 2024;120:514-31.
34. Seo YK. Modulation of inflammatory responses to enhance nerve recovery after spinal cord injury. Tissue Eng Regen Med. 2024;21(3):367-8.
35. Shipman H, Monsour M, Foley MM, Marbacher S, Croci DM, Bisson EF. Interleukin-6 in spinal cord injury: Could immunomodulation replace immunosuppression in the management of acute traumatic spinal cord injuries? J Neurol Surg A Cent Eur Neurosurg. 2024;85(6):602-9.
36. Boehl G, Raguindin PF, Valido E, Bertolo A, Itodo OA, Minder B, et al. Endocrinological and inflammatory markers in individuals with spinal cord injury: A systematic review and meta-analysis. Rev Endocr Metab Disord. 2022;23(5):1035-50.
37. Tang W, Zhao K, Li X, Zhou X, Liao P. Bone marrow mesenchymal stem cell-derived exosomes promote the recovery of spinal cord injury and inhibit ferroptosis by inactivating IL-17 pathway. J Mol Neurosci. 2024;74(2):33.
38. Bai M, Sang Z, Cui Y, Feng H, Liu Y, Dai Z, et al. Multi-omics analysis identified and confirmed TNF-α as a key initiator of the inflammatory response following spinal cord injury. Int J Biol Macromol. 2025;311(Pt 2):143866.
39. Martínez-Moreno CG, Calderón-Vallejo D, Díaz-Galindo C, Hernández-Jasso I, Olivares-Hernández JD, Ávila-Mendoza J, et al. Neurotrophic and synaptic effects of GnRH and/or GH upon motor function after spinal cord injury in rats. Sci Rep. 2024;14(1):26420.
40. Sanati M, Manavi MA, Noruzi M, Behmadi H, Akbari T, Jalali S, et al. Carbohydrates and neurotrophic factors: A promising partnership for spinal cord injury rehabilitation. Biomater Adv. 2024;166:214054.
41. Li Y, Tran A, Graham L, Brock J, Tuszynski MH, Lu P. BDNF guides neural stem cell-derived axons to ventral

interneurons and motor neurons after spinal cord injury. Exp Neurol. 2023;359:114259.
42. Ardizzone A, Bova V, Casili G, Filippone A, Lanza M, Repici A, et al. bFGF-like activity supported tissue regeneration, modulated neuroinflammation, and rebalanced Ca2+ homeostasis following spinal cord injury. Int J Mol Sci. 2023;24(19):Article number unavailable.
43. Stepanova OV, Voronova AD, Chadin AV, Fursa GA, Karsuntseva EK, Valikhov MP, et al. Neurotrophin-3 enhances the effectiveness of cell therapy in chronic spinal cord injuries. Bull Exp Biol Med. 2022;173(1):114-118.
44. Muheremu A, Shu L, Liang J, Aili A, Jiang K. Sustained delivery of neurotrophic factors to treat spinal cord injury. Transl Neurosci. 2021;12(1):494-511.
45. Khan AW, Farooq M, Hwang MJ, Haseeb M, Choi S. Autoimmune neuroinflammatory diseases: Role of interleukins. Int J Mol Sci. 2023;24(9):Article number unavailable.
46. Li J, Wang P, Zhou T, Jiang W, Wu H, Zhang S, et al. Neuroprotective effects of interleukin 10 in spinal cord injury. Front Mol Neurosci. 2023;16:1214294.
47. Thompson CD, Zurko JC, Hanna BF, Hellenbrand DJ, Hanna A. The therapeutic role of interleukin-10 after spinal cord injury. J Neurotrauma. 2013;30(15):1311-24.
48. Beskid NM, Kolawole EM, Coronel MM, Nguyen B, Evavold B, García AJ, et al. IL-10-functionalized hydrogels support immunosuppressive dendritic cell phenotype and function. ACS Biomater Sci Eng. 2022;8(10):4341-53.
49. Wang C, Li T, Zeng X, Wu L, Gao M, Tong N, et al. Sustained delivery of IL-10 by self-assembling peptide hydrogel to reprogram macrophages and promote diabetic alveolar bone defect healing. Dent Mater. 2023;39(4):418-29.
50. Li D, Zhang P, Yao X, Li H, Shen H, Li X, et al. Exosomes derived from miR-133b-modified mesenchymal stem cells promote recovery after spinal cord injury. Front Neurosci. 2018;12:845.
51. Yari H, Mikhailova MV, Mardasi M, Jafarzadehgharehziaaddin M, Shahrokh S, Thangavelu L, et al. Emerging role of mesenchymal stromal cells (MSCs)-derived exosome in neurodegeneration-associated conditions: A groundbreaking cell-free approach. Stem Cell Res Ther. 2022;13(1):423.