

Epidural Electrical Stimulation Promotes Motor Recovery in Severe Acute Cervical Spinal Cord Injury: A Nonrandomized Clinical Trial

Author List:

Li Wenbo* , MD Candidate ;Wang Qingyuan*, MS Student; Wang Siming, PhD Candidate;
Li Cong, PhD; Ge Tongfei, MD Candidate; Deng Mingyang,MS Student; Xiong Wu, PhD
Candidate; Cai Bowen,MD Candidate; Wu Jiayang, MS Student; Qin Tao, MD Candidate;
Yao Li, BS; Zhou Yan, BS; Yin Guoyong‡, PhD; Fan Jin‡, PhD.

*Li Wenbo and Wang Qingyuan contributed equally as first authors

‡ Fan Jin and Yin Guoyong contributed equally as corresponding authors

Affiliations

1. Department of Orthopedics, The First Affiliated Hospital of Nanjing Medical University
(Yao Li, BS; Zhou Yan, BS; Yin Guoyong, PhD; Fan Jin, PhD.)

2. Nanjing Medical University (Li wenbo , MD Candidate ;Wang Qingyuan, MS Student;
Wang Siming, PhD Candidate; Li Cong, PhD; Ge Tongfei, MD Candidate; Deng
Mingyang,MS Student; Xiong Wu, PhD Candidate; Cai Bowen,MD Candidate; Wu
Jiayang, MS Student; Qin Tao, MD Candidate)

Corresponding Author:

Fan Jin, MD, PhD
300 Guangzhou Road, Nanjing, Jiangsu 210000, China
Email: fanjin@njmu.edu.cn; Tel: +86 13645182875

Yin Guoyong, MD, PhD
Department of Orthopedics, The First Affiliated Hospital of Nanjing Medical University
300 Guangzhou Road, Nanjing, Jiangsu 210000, China
Email: guoyong_yin@sina.com; Tel: +86 13675185445

Manuscript word count: 2564

Key Points

Question: Is epidural electrical stimulation associated with improved outcomes in patients with acute traumatic cervical spinal cord injury?

Findings: In this prospective-retrospective hybrid cohort study including 141 patients with acute cervical spinal cord injury (AIS grade A), those who received epidural electrical stimulation with standard care demonstrated significantly greater improvement in sensory function at 1 month, motor function at 3 months, and functional independence at 6 months compared to historical controls who received standard care alone.

Meaning: Epidural electrical stimulation in acute cervical spinal cord injury was associated with enhanced sensorimotor recovery and functional independence, with non-response potentially linked to impaired glycan metabolism, suggesting a biomarker for patient stratification.

Abstract

Importance: Epidural electrical stimulation may improve motor recovery after spinal cord injury, but its efficacy in acute cervical injury and mechanisms of non-response are unclear.

Objective: To evaluate efficacy and safety of epidural electrical stimulation in acute traumatic cervical spinal cord injury and identify proteomic biomarkers of treatment response.

Design: Nonrandomized clinical trial with prospective intervention group and mixed control group (historical and concurrent non-intervention patients).

Setting: Conducted from January 2022 to August 2025 in Jiangsu Province Hospital.

Participants: 141 consecutive patients with acute traumatic cervical spinal cord injury (American Spinal Injury Association Impairment Scale grade A) were enrolled: 51 received epidural electrical stimulation plus standard care, 90 received standard care alone.

Intervention: Intervention group underwent posterior decompression, implantation of high-density epidural electrode array, and active stimulation optimized by intraoperative free-run electromyography. Controls received conventional surgery and standard care alone.

Main Outcomes and Measures: Primary outcomes were motor (AIS motor score, Upper Extremity Motor Score) and sensory function, and functional independence (Spinal Cord Independence Measure) at 1, 3, 6 months. Safety outcomes included acute/chronic complications. Cerebrospinal fluid proteomics identified differential pathways between responders and non-responders.

Results: At 1 month, stimulation group had greater sensory improvement (AIS sensory: 56.67 vs 52.67, $P=0.005$). At 3 months, motor scores improved more (AIS motor: 28.49 vs 24.12, $P<0.001$; Upper Extremity Motor Score: 27.92 vs 23.76, $P<0.001$). At 6 months, functional independence was higher (Spinal Cord Independence Measure: 45.30 vs 40.35, $P=0.011$). Stimulation increased ventilator weaning (90.2% vs 65.6%, odds ratio=0.19, $P=0.0018$) and reduced muscle spasms (2.0% vs 20.0%, odds ratio=9.19, $P=0.0344$). Proteomics linked non-response to downregulated glycan metabolism pathways (glycosaminoglycan and N-glycan biosynthesis).

Conclusions and Relevance: Epidural electrical stimulation was associated with enhanced sensorimotor recovery, functional independence, and fewer complications in acute cervical spinal cord injury. Non-response linked to impaired glycan metabolism offers a potential stratification biomarker.

89 **Trial Registration:** Prospectively registered with Chinese Clinical Trial
90 Registry (ChiCTR2500095515) on January 15, 2025. The study protocol is
91 available at: <https://www.chictr.org.cn/showproj.html?proj=257000>.

92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110

Introduction

Spinal cord injury (SCI) is a devastating neurological disorder lacking disease-modifying therapy currently exists to restore lost function¹⁻⁵, particularly in severe cervical spinal cord injuries. Patients experience persistent sensorimotor impairments including spasticity (affecting up to 70%), hyperreflexia, and clonus, substantially diminishing quality of life^{6,7}. These sequelae arise from complex cellular cascades that perpetuate damage and impede neural repair through incompletely understood mechanisms^{2,8,9}. Despite urgent need, current therapeutic strategies demonstrate limited efficacy, especially in severe structural disruption^{10,11}.

Epidural electrical stimulation (EES) has emerged as a promising neuromodulatory intervention for SCI^{1,12-16}. Preclinical studies indicate EES can reactivate residual spinal circuits and restore locomotion through spatiotemporal stimulation protocols reducing pathological hyperexcitability^{12,17-19}. Clinical reports suggest targeted cervical or lumbosacral EES, combined with rehabilitation, improves motor control and upper-extremity function^{20,21}. However, these findings derive largely from small studies or heterogeneous case series, limiting generalizability²². Evidence quality from large cohorts remains scarce²⁰, with key challenges including parameter optimization and variable treatment responses due to individual neuroanatomical differences²³.

This investigation represents the largest cohort study comprehensively

evaluating EES efficacy and safety in severe acute cervical SCI. Using a prospective-retrospective hybrid design with historical controls, we systematically assess EES-mediated functional improvements, detail surgical methodology with high-density electrode arrays and optimized stimulation paradigms, and analyze procedural risks. This study aims to bridge critical evidence gaps for EES application in cervical SCI.

Methods

Study Design and Population

This nonrandomized clinical trial used a prospective intervention group and a mixed control group comprising both historical patients and concurrent non-intervention patients (Figure 1). The protocol received IRB approval (IRB No. 2024-SR-915), with written informed consent obtained from all participants. We enrolled 141 consecutive patients with acute traumatic cervical SCI (C1-C7). The intervention group (n=51) received EES plus standard care, while historical controls (n=90) underwent conventional surgery alone. The trial was registered with chictr.org.cn (Identifier: ChiCTR2500095515).

Inclusion criteria: (1) age 18-75 years with acute traumatic SCI; (2) ASIA grade A; (3) posterior decompression/fixation within 7 days post-injury; (4) ≥3 months postoperative rehabilitation; (5) ability to cooperate with ISNCSCI examination and complete ≥6 months follow-up.

Exclusion criteria included spinal infections/tumors, surgical site skin

infections, immune deficiencies, surgical contraindications, blood count abnormalities, severe chronic conditions (diabetes, epilepsy, Parkinson's), active hemorrhage, severe hypertension, thrombocytopenia, hyperkalemia, concurrent severe craniocerebral injury (GCS ≤ 8), pre-existing neurological disorders affecting limb movement, or traumatic peripheral nerve injuries interfering with functional assessment.

Intervention Protocol

EES group patients received standardized surgery within 48 hours after admission. The procedure involved posterior cervical laminectomy and decompression, followed by implantation of a designated epidural electrode (PINS Medical, L3213). Under direct visualization, an introducer needle was percutaneously advanced into the epidural space from the caudal incision end. The electrode array was positioned midline along the dorsal spinal cord, targeting C3-T1 or directly covering the injury epicenter.

Intraoperative neurophysiological monitoring used continuous free-run electromyography (free-EMG) to detect stimulus-induced neurotonic discharges. Bipolar stimulation testing identified optimal electrode contacts and established baseline parameters. After electrophysiological confirmation, porcine fibrin sealant stabilized the electrode. Externalized lead extensions were secured with sutures.

Stimulation began 24 hours postoperatively with initial parameters: pulse width 200-300 μ s, frequency 5-30 Hz, amplitude 3-10 mA. Amplitude

adjustments were guided by intraoperative motor thresholds and patient feedback, with further optimization during daily rehabilitation.

Baseline information

Comprehensive baseline characteristics were collected across five domains: (1) demographics (age, sex, height, weight, BMI); (2) comorbidities (hypertension, diabetes, coronary disease, ankylosing spondylitis, chronic lung disease, prior cerebral infarction); (3) injury characteristics (vertebral level, facet dislocation, BASIC grade 1-4 on preoperative MRI assessing T2 hyperintensity, cord compression, intramedullary hemorrhage¹¹); (4) concomitant injuries (craniocerebral trauma, rib fractures, pleural effusion, pulmonary contusion, pneumothorax); (5) surgical parameters (operative time, blood loss).

Outcome Measurements

Neurological and functional assessments were conducted preoperatively and at 1, 3, and 6 months postoperatively. Primary efficacy endpoints included AIS motor and sensory scores, Upper Extremity Motor Score (UEMS), and Lower Extremity Motor Score (LEMS). Functional independence was evaluated using the Spinal Cord Independence Measure (SCIM, 0-100), Barthel Index (0-100), and EMS functional grading scale (5-18). Structural injury severity was classified preoperatively using BASIC grading (1-4) by two blinded neuroradiologists (inter-rater $\kappa=0.85$).

Safety outcomes were categorized by Clavien-Dindo criteria: acute complications (≤ 14 days: hyponatremia, pneumonia, DVT, hypotension); chronic complications (> 1 month: pathological spasticity with Modified Ashworth Scale ≥ 2 , neuropathic pain with VAS ≥ 4); device-related events (electrode migration, lead fracture, surgical site infection); ventilator weaning success; and mortality. Functional assessments were performed by blinded rehabilitation specialists.

Radiological Assessment and Measurement

Quantitative MRI parameters were evaluated preoperatively, postoperatively, and at 1, 3, and 6 months by two blinded neuroradiologists using standardized PACS. Primary imaging outcomes included spinal canal compromise (SCC), spinal cord compression ratio (SCCR), T2 hyperintensity length (T2HL), syrinx sagittal diameter (SSD), and syrinx length (SL).

Changes from Protocol

The trial was registered (ChiCTR2500095515) with prespecified criteria: enrollment of AIS A-C, use of JOA and WISCI-II, and 12-month follow-up. During enrollment, patients with AIS B/C were predominantly unwilling to undergo electrode implantation, restricting the study population to AIS grade A. Consequently, outcome measures were revised to ASIA motor/sensory scores and Barthel Index, replacing JOA and WISCI-II. These changes were made prior to data analysis. Interim analysis at 6 months revealed most neurological

recovery occurred within this period, so primary analysis focused on 6-month outcomes; 12-month follow-up continues for long-term safety monitoring.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD or median (IQR); categorical variables as frequencies. Group comparisons employed ANCOVA adjusted for age, injury level, and baseline scores, with non-parametric alternatives where appropriate. Inverse probability of treatment weighting (IPTW) balanced baseline characteristics. For longitudinal outcomes (AIS scores, UEMS, SCIM) at 1, 3, and 6 months, generalized estimating equations (GEE) with exchangeable correlation structure were fitted. To handle missing data, particularly non-ignorable missingness due to death, mixed-effects model for repeated measures (MMRM) was applied as primary analysis. Sensitivity analyses examined prospective versus retrospective subgroups. Statistical significance was set at $\alpha=0.05$ (two-tailed), with analyses in R 4.1.0.

Results

Patient Characteristics and Surgical Parameters

A total of 141 patients with acute traumatic cervical SCI (ASIA grade A) were included: 51 receiving EES plus standard care and 90 historical controls receiving standard care alone. After IPTW application (eFigure 1), all measured demographic and injury characteristics were well-balanced between groups (all absolute standardized mean differences <0.10).

All surgical procedures were completed successfully. In the EES group, mean operative time was 230.00 (200.00, 280.00) minutes, and mean intraoperative blood loss was 400.00 (200.00, 600.00) ml (Table 1). No serious procedure-related adverse events (surgical site infection, hematoma, neurological deterioration) occurred in the immediate postoperative period.

Neurological and Functional Outcomes

Longitudinal analysis adjusted with IPTW revealed significant between-group differences over 6 months. The EES group demonstrated significantly greater sensory improvement at 1 month (AIS light touch: 56.67 ± 8.62 vs. 52.67 ± 9.65 , $P=0.005$). By 3 months, EES showed superior motor recovery (AIS motor: 28.49 ± 7.48 vs. 24.12 ± 7.74 , $P<0.001$; UEMS: 27.92 ± 7.17 vs. 23.76 ± 7.15 , $P<0.001$).

SCIM score at 3 months was higher in EES group but not statistically significant (36.52 ± 10.31 vs. 33.64 ± 8.82 , $P=0.165$). However, significant functional independence differences emerged by 6 months (45.30 ± 10.08 vs. 40.35 ± 7.64 , $P=0.011$). This sensory-preceding-motor pattern suggests a potential sequence of EES-facilitated neurological recovery.

Radiological Parameters

Longitudinal imaging (eTable 1) showed no statistically significant between-group differences at any time point across all assessed parameters (SCC, SCCR, T2HL, SSD, SL; all $P>0.05$), indicating that functional

improvements with EES were not reflected in conventional structural MRI measures.

Safety and Complications

Acute complication profiles were comparable (respiratory failure $P=0.614$; infection rates similar). However, EES conferred significant protection against chronic sequelae, reducing pathological spasticity (2.0% vs. 20.0%, $OR=9.19$, $P=0.0344$) and neuropathic pain by 59.4% (11.8% vs. 17.8%, $OR=1.47$, $P=0.4450$). Clinically meaningful advantages included 24.6% absolute increase in ventilator weaning success (90.2% vs. 65.6%, $OR=0.19$, $P=0.0018$) and non-significant mortality reduction trend (5.9% vs. 11.1%, $OR=2.01$, $P=0.3183$). Device-related complications were infrequent (electrode migration: 3.9%; lead infection: 2.0%) (Table 2).

Proteomics Analysis

Principal component analysis revealed that the largest source of variation (PC1, 26.66%) distinguished normal controls from SCI cohorts (eFigure 2). While EES responders and non-responders showed a trend toward separation along PC2 (12.29%), substantial overlap indicated that SCI-induced proteomic alterations dominate inter-individual variance. Direct comparison yielded no significantly differentially abundant proteins between responders and non-responders at $FDR<0.05$ (eFigure 2B).

Functional enrichment analysis of proteins downregulated in responders highlighted impairments in "Cell adhesion molecules" and "Axon guidance"

pathways (eFigure 2C). Crucially, non-responders exhibited specific and significant downregulation of glycan metabolism pathways—"Glycosaminoglycan biosynthesis" and "N-Glycan biosynthesis"—not enriched in responders (eFigure 2D).

Discussion

This nonrandomized trial with mixed control group provides the largest evidence that acute-phase cervical SCI EES is associated with accelerated sensorimotor recovery, improved functional independence, and reduced complications. The observed sensory-preceding-motor recovery pattern suggests distinct neurophysiological mechanisms in the acute setting, extending findings from chronic SCI cohorts. Compared with previous small-scale studies, our larger sample size and multidimensional assessment offer more robust efficacy and safety estimates. However, the nonrandomized design and retrospective registration introduce potential bias, mitigated through IPTW and transparent reporting. The exploratory proteomic finding linking non-response to impaired glycan metabolism generates a testable hypothesis for patient stratification, though validation in animal models and independent cohorts is warranted.

Motor Recovery

This study provides novel evidence that EES promotes multidimensional recovery in acute cervical SCI. We observed a distinct spatiotemporal pattern:

sensory improvements occurred first, with AIS sensory scores increasing by 6.45 points more in the EES group at 1 month $P = 0.004$. Motor recovery progressively accelerated, becoming significant at 3 months ($P < 0.001$) and reaching 48.1% greater improvement than controls at 6 months (44.43 ± 16.58 vs. 30.00 ± 11.48 , $P < 0.001$). This sequential recovery—sensory preceding motor—aligns with EES first reactivating dorsal column sensory pathways before supporting corticospinal reorganization for voluntary control^{12,24}.

The recovery trajectory extends previous reports of EES-mediated motor restoration in chronic SCI¹² to the acute phase. Notably, the 48.1% motor improvement exceeds the 30-40% range reported in chronic studies^{12,25}, suggesting greater neuroplastic potential during the acute post-injury window. Functional relevance is reinforced by SCIM scores, consistent with earlier reports^{26,27}.

In contrast to thoracic/lumbar SCI studies reporting motor-dominant effects²⁴, the sensory-first pattern observed here may reflect anatomical distinctions in cervical circuitry or better sensory pathway preservation. The gradually accelerating motor recovery supports the hypothesis that EES promotes gradual corticospinal reorganization, enhancing understanding of EES-mediated mechanisms and underscoring clinical translatability across injury stages^{28,29}.

Complications

EES demonstrated a biphasic therapeutic profile in mitigating SCI complications. During the acute phase (≤ 14 days), EES significantly enhanced ventilator weaning success (absolute increase 20.4%, 80.4% vs. 60.0%, $P=0.022$), likely mediated through cervical cord facilitation of phrenic nerve output. In the chronic phase (>1 month), EES substantially reduced debilitating sequelae, including $>60\%$ decrease in pathological spasticity (9.8% vs. 25.5%, $P=0.041$) and neuropathic pain (11.8% vs. 29.1%, $P=0.031$), highlighting long-term symptom management potential.

These findings align with accumulating evidence that EES modulates spinal networks to restore motor and autonomic functions. The acute respiratory benefits parallel studies demonstrating EES improves trunk stability and cardiovascular regulation through residual spinal circuit neuromodulation. Spasticity reduction corresponds to reports that EES combined with rehabilitation reduces pathological co-contraction and hyperreflexia in chronic SCI³⁰. Neuropathic pain alleviation reflects EES's established ability to modulate spinal interneuronal activity and suppress maladaptive signaling¹⁶. The effect sizes exceed those in prior small-scale trials³¹, possibly reflecting optimized stimulation parameters or patient selection. The dual-phase efficacy extends beyond locomotion-focused outcomes^{15,32}, highlighting EES's broader therapeutic potential and reinforcing that EES engages both segmental and supraspinal pathways to address multifaceted SCI pathophysiology^{18,33}.

The Parameter of Stimulation

Optimal parameter selection for cervical EES remains critically challenging. Conventional approaches rely on empirical trial-and-error, often yielding variable outcomes due to absence of neurophysiological guidance. Since EES-induced motor recovery is not immediate, surgeons depend on subjective parameter adjustments without objective accuracy verification. This clinician-driven titration fails to account for individual neuroanatomical and physiological variability. Programming often lacks standardized algorithms or closed-loop feedback, leading to inconsistent recovery and extended optimization periods³⁴⁻⁴⁰.

In contrast, our method leverages intraoperative free-EMG to determine optimal initial parameters by monitoring real-time EMG waveform changes, offering significant advantages over trial-and-error. This technique enables patient-specific customization using physiological activity to guide stimulation, enhancing precision and efficacy. Preclinical evidence demonstrates activity-dependent EMG systems can trigger stimulation, promoting targeted neuromodulation and improving motor outcomes by aligning parameters with individual neural dynamics⁴¹⁻⁴³. This approach reduces empirical adjustment burden, leading to more consistent therapeutic effects^{34,44,45}. However, substantial improvement remains possible: future research should develop advanced closed-loop algorithms integrating multiple neurophysiological signals, as current EMG-based systems require refinement to address parameter complexity and ensure translatability across injury severities^{14,25,39}.

Radiological and Proteomics Analysis

Notably, despite significant functional improvements, no between-group differences were found across any radiological parameters at any time point. This dissociation suggests EES effects are mediated through functional neuromodulation and network-level reorganization rather than macroscopic anatomical changes detectable by conventional MRI. These findings align with emerging evidence that neuromodulatory interventions facilitate recovery by enhancing residual neural circuit function, not by reversing structural damage.

Our integrated proteomic analysis establishes that severe SCI pathophysiological alterations dominate the CSF proteome landscape, diminishing more nuanced variations directly associated with EES response. The absence of significantly differentially abundant proteins between responders and non-responders (eFigure 2B), coupled with substantial PCA overlap (eFigure 2A), provides robust evidence for this conclusion.

The critical mechanistic finding from this study is the specific downregulation of glycan metabolism pathways exclusively in patients who were non-responsive to EES (eFigure 2D). Glycosaminoglycans and N-glycans constitute essential elements of the extracellular matrix and play a pivotal role in cellular signaling, axonal pathfinding, and synaptic plasticity, which are fundamental to neural repair processes after SCI ⁴⁶⁻⁴⁸. Specifically, N-glycans undergo dynamic alterations in the injured spinal cord, with changes such as reduced complex glycans and increased oligomannose structures

potentially impeding regeneration^{46,47,49}. Biosynthesis of these glycans is vital for fostering a permissive environment conducive to functional reorganization and neuroplasticity^{50,51}. We propose that an intact glycan biosynthetic capacity represents a prerequisite for enabling the beneficial neuroplastic adaptations promoted by EES, such as those involving spinal cord circuitry reactivation and sensorimotor recovery^{12,52}. In non-responders, deficiencies in this supportive metabolic function may render the spinal cord circuitry incapable of adequately responding to neuromodulatory stimuli like EES, leading to poor therapeutic outcomes^{12,14,53}. This discovery underscores the potential of pre-therapeutic assessment of glycan metabolism status or targeted interventions, such as modulating glycosylation pathways, to enhance EES efficacy in a subset of patients.

Limitations

This study has several limitations. First, despite IPTW, residual confounding may persist due to non-randomized design and evolving standards of care in historical controls. Second, postoperative stimulation titration relied partially on subjective patient feedback, introducing heterogeneity that future closed-loop systems may address. Third, 6-month follow-up precludes assessment of long-term efficacy durability. Fourth, proteomic findings are exploratory and hypothesis-generating, lacking functional validation. Finally, protocol modifications (restriction to AIS grade A, revised outcome measures) necessitated by enrollment realities and made

prior to analysis may introduce potential bias. Multi-center randomized trials with longer follow-up are warranted.

Conclusion

In this study, EES was associated with enhanced sensorimotor recovery, improved functional independence, and reduced complications in acute cervical SCI. Recovery followed a characteristic sensory-then-motor sequence, suggesting EES facilitates neural reorganization through distinct physiological mechanisms. Furthermore, identification of glycan metabolism as a potential biomarker for non-response offers a novel patient stratification strategy. These findings support EES as a promising therapeutic intervention in acute cervical SCI. Future efforts should focus on developing closed-loop stimulation systems, validating long-term efficacy, and integrating biomarker-guided patient selection to optimize outcomes.

Reference

1. Chalif JI, Chavarro VS, Mensah E, et al. Epidural Spinal Cord Stimulation for Spinal Cord Injury in Humans: A Systematic Review. *J Clin Med*. Feb 14 2024;13(4)doi:10.3390/jcm13041090
2. Tang H, Gu Y, Jiang L, Zheng G, Pan Z, Jiang X. The role of immune cells and associated immunological factors in the immune response to spinal cord injury. *Front Immunol*. 2022;13:1070540. doi:10.3389/fimmu.2022.1070540
3. Cheng RD, Ren W, Luo BY, Ye XM. The role of purinergic receptors in neural repair and regeneration after spinal cord injury. *Neural Regen Res*. Aug 2023;18(8):1684–1690. doi:10.4103/1673-5374.363186
4. Lu ZJ, Pan QL, Lin FX. Epigenetic modifications of inflammation in spinal cord injury. *Biomed Pharmacother*. Oct 2024;179:117306. doi:10.1016/j.biopha.2024.117306
5. Abbas WA, Ibrahim ME, El-Naggar M, et al. Recent Advances in the Regenerative Approaches for Traumatic Spinal Cord Injury: Materials Perspective. *ACS Biomater Sci Eng*. Dec 14 2020;6(12):6490–6509. doi:10.1021/acsbiomaterials.0c01074
6. Wenqiang L, Zhian C, Hua L, Yang L, Yi C, Zhijun C. Neuromodulation techniques for the treatment of spinal cord injury: current progress, challenges, and future prospects. *Eur J Med Res*. Jun 19 2025;30(1):495. doi:10.1186/s40001-025-02689-y
7. Chopra M, Kumar H. Navigating the complexities of spinal cord injury: an overview of pathology, treatment strategies and clinical trials. *Drug Discov Today*. Jun 2025;30(6):104387. doi:10.1016/j.drudis.2025.104387
8. Abd-Elsayed A, Robinson CL, Shehata P, Koh Y, Patel M, Fiala KJ. Neuromodulation's Role in Functional Restoration in Paraplegic and Quadriplegic Patients. *Biomedicines*. Mar 24 2024;12(4)doi:10.3390/biomedicines12040720
9. Xie T, Xu J, Liu X, et al. Mechanistic insights into Nrf2-driven pathogenesis and therapeutic targeting in spinal cord injury. *Front Immunol*. 2025;16:1574834. doi:10.3389/fimmu.2025.1574834
10. Sousa CS, Monteiro A, Salgado AJ, Silva NA. Combinatorial therapies for spinal cord injury repair. *Neural Regen Res*. May 1 2025;20(5):1293–1308. doi:10.4103/nrr.Nrr-d-24-00061
11. Fan B, Wei Z, Feng S. Progression in translational research on spinal cord injury based on microenvironment imbalance. *Bone Res*. Apr 8 2022;10(1):35. doi:10.1038/s41413-022-00199-9
12. Kathe C, Skinnider MA, Hutson TH, et al. The neurons that restore walking after paralysis. *Nature*. Nov 2022;611(7936):540–547. doi:10.1038/s41586-022-05385-7
13. Elkholy MAE, Nagaty A, Abdelbar AE, Simry HAM, Raslan AM. Effect of spinal cord stimulation on quality of life and opioid consumption in patients with failed back surgery syndrome. *Pain Pract*. Feb 2024;24(2):261–269. doi:10.1111/papr.13300
14. Choi EH, Gattas S, Brown NJ, et al. Epidural electrical stimulation for spinal cord injury. *Neural Regen Res*. Dec 2021;16(12):2367–2375. doi:10.4103/1673-5374.313017
15. Hofstoetter US, Freundl B, Binder H, Minassian K. Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: Elicitation of posterior root-muscle reflexes. *PLoS One*. 2018;13(1):e0192013. doi:10.1371/journal.pone.0192013
16. Mu Z, Qin J, Zhou X, Wang K. Synergistic effects of human umbilical cord mesenchymal stem cells/neural stem cells and epidural electrical stimulation on spinal cord injury rehabilitation. *Sci Rep*. Oct 30 2024;14(1):26090. doi:10.1038/s41598-024-75754-x
17. Alcantar-Garibay OV, Incontri-Abraham D, Ibarra A. Spinal cord injury-induced cognitive

impairment: a narrative review. *Neural Regen Res.* Dec 2022;17(12):2649–2654. doi:10.4103/1673-5374.339475

18. Audet J, Lecomte CG. Epidural electrical stimulation to facilitate locomotor recovery after spinal cord injury. *J Neurophysiol.* Nov 1 2021;126(5):1751–1755. doi:10.1152/jn.00261.2021
19. Yan D, Guo Z, Liu H, et al. Comparison of activation and selectivity in dorsal and ventral epidural spinal cord stimulation in rats: a computational modeling study. *Sci Rep.* Oct 13 2025;15(1):35711. doi:10.1038/s41598-025-19555-w
20. Forouzan EJ, Rashid MY, Nasr NF, Abd-Elseyed A, Knezevic NN. The Potential of Spinal Cord Stimulation in Treating Spinal Cord Injury. *Curr Pain Headache Rep.* Jan 27 2025;29(1):35. doi:10.1007/s11916-024-01311-w
21. Suarez M, Gallacher DM, Jevotovsky DS, Chopra H, Broachwala M, Castellanos JP. Improved Motor Function in Cervical Spinal Cord Injury Following Spinal Cord Stimulation. *Clin Case Rep.* Feb 2025;13(2):e70032. doi:10.1002/ccr3.70032
22. Laskin JJ, Waheed Z, Thorogood NP, Nightingale TE, Noonan VK. Spinal Cord Stimulation Research in the Restoration of Motor, Sensory, and Autonomic Function for Individuals Living With Spinal Cord Injuries: A Scoping Review. *Arch Phys Med Rehabil.* Jul 2022;103(7):1387–1397. doi:10.1016/j.apmr.2022.01.161
23. Rodas R. Spinal Cord Stimulation Using High Frequency Electromagnetic Coupling (HF-EMC) Technology to Power an Implanted Neurostimulator With a Separate Receiver for Treating Chronic Back and Leg Pain: A Retrospective Study. *Pain Physician.* Jan 2025;28(1):E43–e47.
24. Calvert JS, Grahn PJ, Strommen JA, et al. Electrophysiological Guidance of Epidural Electrode Array Implantation over the Human Lumbosacral Spinal Cord to Enable Motor Function after Chronic Paralysis. *J Neurotrauma.* May 1 2019;36(9):1451–1460. doi:10.1089/neu.2018.5921
25. Greiner N, Barra B, Schiavone G, et al. Recruitment of upper-limb motoneurons with epidural electrical stimulation of the cervical spinal cord. *Nat Commun.* Jan 19 2021;12(1):435. doi:10.1038/s41467-020-20703-1
26. Martinez M. A bi-cortical neuroprosthesis to modulate locomotion after incomplete spinal cord injury. *Sci Prog.* Oct–Dec 2023;106(4):368504231212788. doi:10.1177/00368504231212788
27. Chu J, Glinsky JV, Liu H, et al. Early and Intensive Motor Training for people with spinal cord injuries (the SCI-MT Trial): protocol of the process evaluation. *BMJ Open.* Aug 29 2023;13(8):e072219. doi:10.1136/bmjopen-2023-072219
28. Udoekwere UI, Oza CS, Giszter SF. Teaching Adult Rats Spinalized as Neonates to Walk Using Trunk Robotic Rehabilitation: Elements of Success, Failure, and Dependence. *J Neurosci.* Aug 10 2016;36(32):8341–55. doi:10.1523/jneurosci.2435-14.2016
29. Samejima S, Henderson R, Pradarelli J, Mondello SE, Moritz CT. Activity-dependent plasticity and spinal cord stimulation for motor recovery following spinal cord injury. *Exp Neurol.* Nov 2022;357:114178. doi:10.1016/j.expneurol.2022.114178
30. Romeni S, Losanno E, Emedoli D, et al. High-frequency epidural electrical stimulation reduces spasticity and facilitates walking recovery in patients with spinal cord injury. *Sci Transl Med.* Jan 8 2025;17(780):eadp9607. doi:10.1126/scitranslmed.adp9607
31. Ren Y, Mo L, Lu J, et al. Epidural Electrical Stimulation for Functional Recovery in Incomplete Spinal Cord Injury. *Cyborg Bionic Syst.* 2025;6:0314. doi:10.34133/cbsystems.0314
32. Hofstoetter US, Minassian K. Transcutaneous Spinal Cord Stimulation: Advances in an Emerging Non-Invasive Strategy for Neuromodulation. *J Clin Med.* Jul 1 2022;11(13)doi:10.3390/jcm11133836

528 33. Sharma P, Shah PK. In vivo electrophysiological mechanisms underlying cervical epidural
529 stimulation in adult rats. *J Physiol.* Jun 2021;599(12):3121–3150. doi:10.1113/jp281146

530 34. Levy RM, Mekhail NA, Kapural L, et al. Maximal Analgesic Effect Attained by the Use of Objective
531 Neurophysiological Measurements With Closed-Loop Spinal Cord Stimulation. *Neuromodulation.* Dec
532 2024;27(8):1393–1405. doi:10.1016/j.neurom.2024.07.003

533 35. Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderroth B. Parameters of Spinal Cord
534 Stimulation and Their Role in Electrical Charge Delivery: A Review. *Neuromodulation.* Jun
535 2016;19(4):373–84. doi:10.1111/ner.12438

536 36. Chakravarthy K, Reddy R, Al-Kaisy A, Yearwood T, Grider J. A Call to Action Toward Optimizing the
537 Electrical Dose Received by Neural Targets in Spinal Cord Stimulation Therapy for Neuropathic Pain. *J*
538 *Pain Res.* 2021;14:2767–2776. doi:10.2147/jpr.S323372

539 37. Mesbah S, Gonnelli F, Angeli CA, El-Baz A, Harkema SJ, Rejc E. Neurophysiological markers
540 predicting recovery of standing in humans with chronic motor complete spinal cord injury. *Sci Rep.* Oct
541 9 2019;9(1):14474. doi:10.1038/s41598-019-50938-y

542 38. Zhao Z, Ahmadi A, Hoover C, et al. Optimization of Spinal Cord Stimulation Using Bayesian
543 Preference Learning and Its Validation. *IEEE Trans Neural Syst Rehabil Eng.* 2021;29:1987–1997.
544 doi:10.1109/tnsre.2021.3113636

545 39. Govindarajan LN, Calvert JS, Parker SR, et al. Fast inference of spinal neuromodulation for motor
546 control using amortized neural networks. *J Neural Eng.* Oct 18
547 2022;19(5)doi:10.1088/1741-2552/ac9646

548 40. Sheldon B, Staudt MD, Williams L, Harland TA, Pilitsis JG. Spinal cord stimulation programming: a
549 crash course. *Neurosurg Rev.* Apr 2021;44(2):709–720. doi:10.1007/s10143-020-01299-y

550 41. Rascoe A, Sharma P, Shah PK. Development of an Activity-Dependent Epidural Stimulation
551 System in Freely Moving Spinal Cord Injured Rats: A Proof of Concept Study. *Front Neurosci.*
552 2018;12:472. doi:10.3389/fnins.2018.00472

553 42. Tang S, Cuellar CA, Song P, et al. Changes in spinal cord hemodynamics reflect modulation of
554 spinal network with different parameters of epidural stimulation. *Neuroimage.* Nov 1
555 2020;221:117183. doi:10.1016/j.neuroimage.2020.117183

556 43. Milosevic M, Masugi Y, Sasaki A, Sayenko DG, Nakazawa K. On the reflex mechanisms of cervical
557 transcutaneous spinal cord stimulation in human subjects. *J Neurophysiol.* May 1 2019;121(5):1672–
558 1679. doi:10.1152/jn.00802.2018

559 44. Mekhail NA, Levy RM, Deer TR, et al. Neurophysiological outcomes that sustained clinically
560 significant improvements over 3 years of physiologic ECAP-controlled closed-loop spinal cord
561 stimulation for the treatment of chronic pain. *Reg Anesth Pain Med.* Jun 10 2025;50(6):495–502.
562 doi:10.1136/rapm-2024-105370

563 45. McIntosh JR, Joiner EF, Goldberg JL, et al. Intraoperative electrical stimulation of the human
564 dorsal spinal cord reveals a map of arm and hand muscle responses. *J Neurophysiol.* Jan 1
565 2023;129(1):66–82. doi:10.1152/jn.00235.2022

566 46. Osimanjiang W, Roballo KCS, Houck BD, et al. Analysis of N- and O-Linked Glycosylation:
567 Differential Glycosylation after Rat Spinal Cord Injury. *J Neurotrauma.* Sep 15 2020;37(18):1954–1962.
568 doi:10.1089/neu.2019.6974

569 47. Ronan R, Kshirsagar A, Rebelo AL, et al. Distinct Glycosylation Responses to Spinal Cord Injury in
570 Regenerative and Nonregenerative Models. *J Proteome Res.* Jun 3 2022;21(6):1449–1466.
571 doi:10.1021/acs.jproteome.2c00043

48. Rebelo AL, Bizeau J, Russo L, Pandit A. Glycan-Functionalized Collagen Hydrogels Modulate the Glycoenvironment of a Neuronal Primary Culture. *Biomacromolecules*. Jul 13 2020;21(7):2681–2694. doi:10.1021/acs.biomac.0c00387
49. Hatchett CJ, Hall MK, Messer AR, Schwalbe RA. Lowered GnT-I Activity Decreases Complex-Type N-Glycan Amounts and Results in an Aberrant Primary Motor Neuron Structure in the Spinal Cord. *J Dev Biol*. Aug 16 2024;12(3)doi:10.3390/jdb12030021
50. Nogueira-Rodrigues J, Leite SC, Pinto-Costa R, et al. Rewired glycosylation activity promotes scarless regeneration and functional recovery in spiny mice after complete spinal cord transection. *Dev Cell*. Feb 28 2022;57(4):440–450.e7. doi:10.1016/j.devcel.2021.12.008
51. Dyck S, Kataria H, Alizadeh A, et al. Perturbing chondroitin sulfate proteoglycan signaling through LAR and PTPsigma receptors promotes a beneficial inflammatory response following spinal cord injury. *J Neuroinflammation*. Mar 20 2018;15(1):90. doi:10.1186/s12974-018-1128-2
52. Francos-Quijorna I, Sanchez-Petidier M, Burnside ER, et al. Chondroitin sulfate proteoglycans prevent immune cell phenotypic conversion and inflammation resolution via TLR4 in rodent models of spinal cord injury. *Nat Commun*. May 25 2022;13(1):2933. doi:10.1038/s41467-022-30467-5
53. Kilcoyne M, Patil V, O'Grady C, Bradley C, McMahon SS. Differential Glycosylation Expression in Injured Rat Spinal Cord Treated with Immunosuppressive Drug Cyclosporin-A. *ACS Omega*. Feb 28 2019;4(2):3083–3097. doi:10.1021/acsomega.8b02524

Figure 1. Flowchart of Cohort Selection

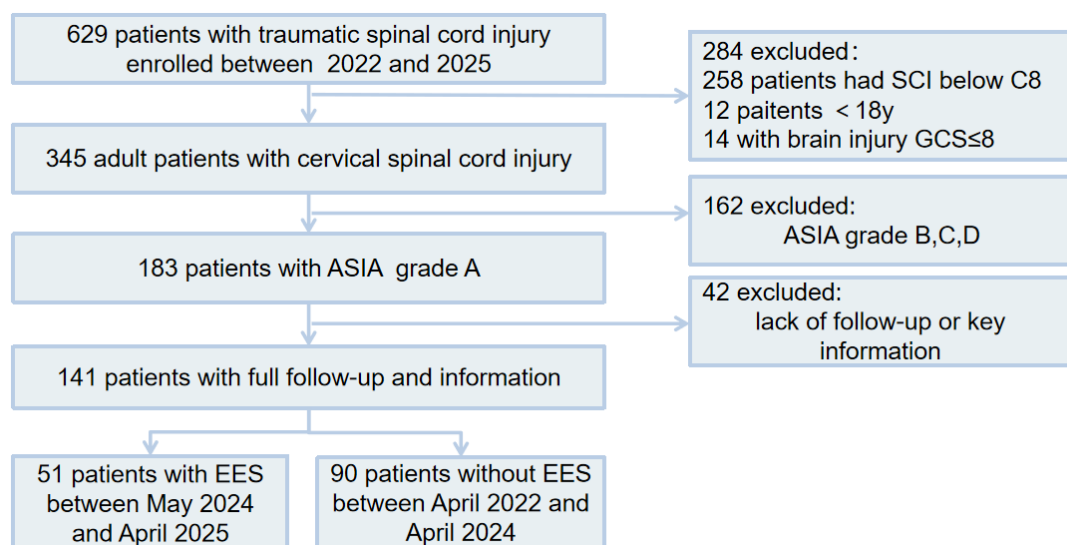


Table 1: Baseline factors by treatment group Articles

Variables	Total (N = 141)	EES (N = 51)	Control (N = 90)	P
Sex				0.989
Female	23 (16.3)	8 (15.7)	15 (16.7)	
Male	118 (83.7)	43 (84.3)	75 (83.3)	
Age	56.72 ± 9.85	56.76 ± 10.63	56.70 ± 9.44	0.769
BMI	24.10 ± 3.75	24.11 ± 3.65	24.10 ± 3.82	0.879
Basic Diseases				
Hypertension	48 (34)	15 (29)	33 (37)	0.339
Diabetes mellitus	19 (13)	5 (9.8)	14 (15)	0.370
Coronary disease	9 (6.4)	3 (5.2)	6 (7.1)	0.645
Ankylosing spondylitis	20 (14)	7 (13)	13 (15)	0.829
Chronic lung disease	3 (2.2)	1 (2.6)	2 (1.9)	0.793
Cerebral infarction	5 (3.4)	2 (3.2)	3 (3.5)	0.936
Injury level(%)				0.858
C0-3	62 (44)	21 (42)	40 (45)	
C3-5	73 (52)	28 (55)	45 (50)	
C5-7	6 (4.4)	2 (3.5)	4 (4.8)	

GCS score	13.00 (11.00, 14.00)	13.00 (11.00, 15.00)	13.00 (11.00, 14.00)	0.932
BASIC score				0.904
1	16 (11)	6 (13)	9 (10)	
2	32 (22)	13 (25)	19 (21)	
3	63 (45)	22 (42)	41 (46)	
4	31 (22)	10 (20)	20 (23)	
		230.00	222.00	
Operation time(min)	225.00 (195.00, 280.00)	(200.00, 280.00)	(194.00, 285.00)	0.406
		400.00	375.00	
Blood loss (ml)	380.00 (190.00, 560.00)	(200.00, 600.00)	(185.00, 550.00)	0.348
Combined injuries				
Craniocerebral injury	36 (25)	11 (22)	25 (27)	0.459
Rib fracture	47 (33)	14 (28)	32 (36)	0.320
Pleural effusion	25 (18)	8 (16)	17 (19)	0.639
Lung contusion	27 (19)	8 (16)	19 (22)	0.380
Aerothorax	12 (8.6)	4 (7.0)	9 (9.6)	0.608
Hyponatremia	30 (21)	10 (19)	20 (22)	0.714

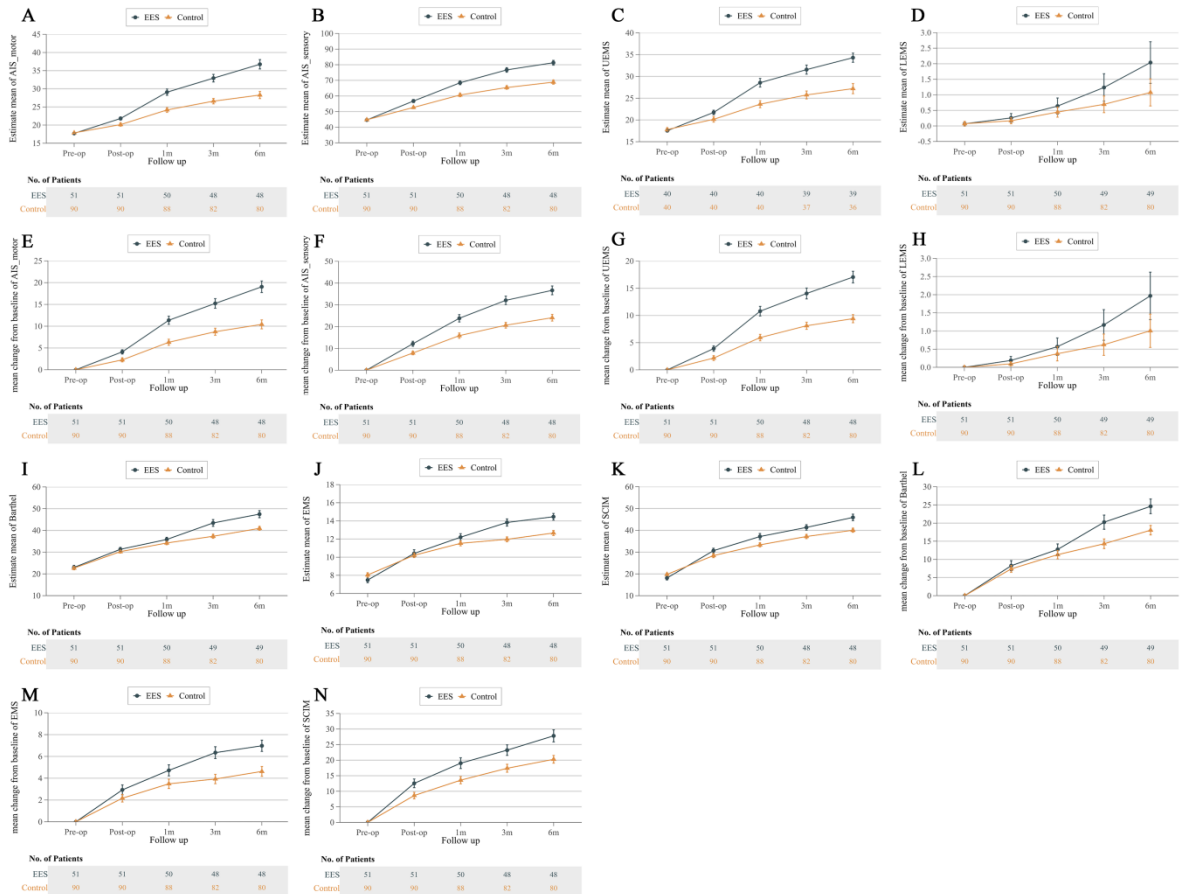
611

612

613

614

Figure 2. Neurological Scores and Functional score



A-D:The estimate mean of AIS motor score, AIS sensory socre,UEMS and LEMS; **E-H:** The mean change from baseline of AIS motor score, AIS sensory socre,UEMS and LEMS; **I-K:**The estimate mean of Barthel index, EMS and SCIM; **L-N:** The mean change from baseline of Barthel index, EMS and SCIM.

Table 2.Safety Profile: Complications

Outcome	EES	Control	adj.OR	adj.p.valu e	adj.RR	adj.p.valu e	adj.RD	adj.p.valu e
Pulmonary infection	19/51 (37.3%)	25/90 (27.8%)	0.64 (0.30 to 1.34)	0.2315	0.74 (0.53 to 1.04)	0.0792	-9.99 (-27.21 to 7.23)	0.2555
Deep vein thrombosis	22/51 (43.1%)	23/90 (25.6%)	0.46 (0.22 to 0.97)	0.0406	0.60 (0.43 to 0.83)	0.0026	-17.26 (-34.79 to 0.27)	0.0537
Pulmonary embolism	2/51 (3.9%)	1/90 (1.1%)	0.32 (0.03 to 3.61)	0.3536	0.32 (0.03 to 3.02)	0.3216	-2.29 (-6.86 to 2.29)	0.3271
Failure of respiration	18/51 (35.3%)	20/90 (22.2%)	0.53 (0.25 to 1.16)	0.1131	0.64 (0.42 to 0.96)	0.0300	-12.57 (-29.12 to 3.98)	0.1365
Infection of incisional wound	4/51 (7.8%)	3/90 (3.3%)	0.33 (0.07 to 1.57)	0.1630	0.35 (0.09 to 1.32)	0.1215	-5.28 (-14.10 to 3.54)	0.2410
Central infection	5/51 (9.8%)	0/90 (0.0%)	0.00 (0.00 to 0.00)	< 0.0001	0.00 (0.00 to 0.00)	< 0.0001	-9.38 (-17.41 to -1.35)	0.0221
Leakage of cerebrospinal	15/51 (29.4%)	12/90 (13.3%)	0.38 (0.16 to 0.92)	0.0319	0.47 (0.26 to 0.84)	0.0104	-15.62 (-31.29 to 0.05)	0.0508
Hypoplasia	9/51 (17.6%)	6/90 (6.7%)	0.37 (0.12 to 1.16)	0.0895	0.42 (0.16 to 1.11)	0.0791	-9.89 (-23.60 to 3.83)	0.1577
Epidural hematoma	3/51 (5.9%)	2/90 (2.2%)	0.39 (0.06 to 2.52)	0.3225	0.40 (0.08 to 2.09)	0.2797	-3.07 (-9.38 to 3.25)	0.3415
Urinary infection	18/51 (35.3%)	20/90 (22.2%)	0.53 (0.24 to 1.15)	0.1094	0.64 (0.43 to 0.95)	0.0268	-12.91 (-30.11 to 4.29)	0.1414
Pathologic al muscle spasms	1/51 (2.0%)	18/90 (20.0%)	9.19 (1.18 to 71.74)	0.0344	7.55 (0.58 to 97.94)	0.1220	17.34 (6.40 to 28.28)	0.0019
Pathologic al pain	6/51 (11.8%)	16/90 (17.8%)	1.47 (0.55 to 3.96)	0.4450	1.39 (0.67 to 2.88)	0.3781	4.89 (-7.15 to 16.94)	0.4256
Ventilator weaning successfully	46/51 (90.2%)	59/90 (65.6%)	0.19 (0.07 to 0.54)	0.0018	0.72 (0.68 to 0.76)	< 0.0001	-25.70 (-38.46 to -12.95)	< 0.0001
dead	3/51 (5.9%)	10/90 (11.1%)	2.01 (0.51 to 7.92)	0.3183	1.90 (0.54 to 6.61)	0.3150	5.31 (-4.49 to 15.10)	0.2886
Electrodetachment shift	4/51 (7.8%)							
Infection at puncture site	1/51 (2.0%)							

633

634

635

636

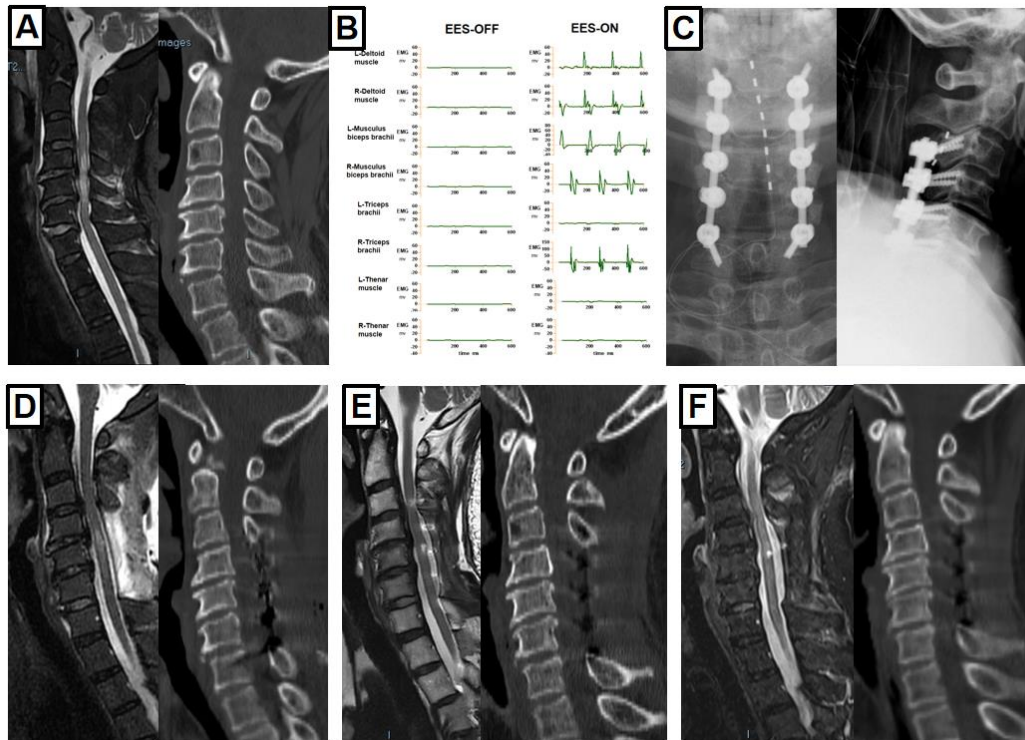


Figure 3. Demo case of the epidural stimulation.

A 60-year-old female was admitted to the hospital due to "limb motor impairment for more than one day after a fall from height." On October 31, 2024, at approximately 07:00, the patient accidentally fell from a height of 2 meters onto the ground, landing face first. She subsequently experienced neck pain accompanied by quadriparesis.

Preoperative physical examination revealed muscle strength graded at 2/5 in the biceps and triceps brachii, as well as forearm muscle groups, with grip strength assessed as 0/5. In the lower extremities, muscle strength was 0/5. A loss of superficial sensation was observed below the umbilical level. The patient presented to the emergency department on November 1, 2024. An emergency surgical procedure was performed that same noon, during which an epidural electrical stimulation (EES) device was implanted.

(A): Preoperative MRI of the patient demonstrated extensive spinal canal stenosis accompanied by spinal cord contusion. Preoperative CT imaging showed no significant ossification. The patient's Lower Extremity Motor Score (LEMS) was 12 prior to surgery.

(B): Intraoperative electrode configuration was set with contacts 3 and 4 as anodes, and contacts 5–8 as cathodes. Stimulation parameters were set at an amplitude of 6 V, a pulse width of 210 μ s, and a frequency of 5 Hz. Intraoperative electrophysiological monitoring showed significant signal changes upon activation of the stimulator in the bilateral deltoids, bilateral biceps brachii, and the right triceps brachii.

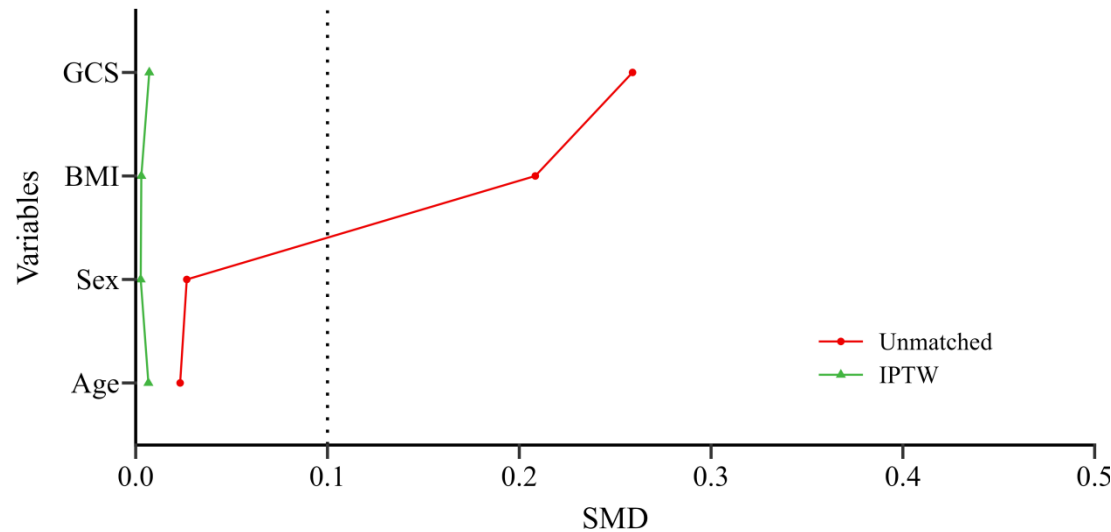
(C): Postoperative radiograph confirmed appropriate electrode positioning. The most rostral contact was designated as contact 1, and the most caudal as contact 8.

(D): Postoperative imaging indicated adequate decompression of the spinal canal and complete relief of spinal cord compression.

(E): A 3-month postoperative follow-up MRI revealed the formation of a syrinx cavity at the injury level. At this time, muscle strength in the upper limbs had improved to grade 4 (MRC scale) in the biceps brachii, triceps brachii, and forearm muscle groups, although grip strength remained at grade 0. The LEMS score improved to 24.

(F): A 6-month postoperative MRI showed no significant change in the size of the syrinx cavity. The patient's grip strength had recovered to grade 1 bilaterally, and the LEMS score further improved to 28.

eFigure 1. Evaluation of the effect of propensity score inverse probability weighted balanced baseline on confounding factors.

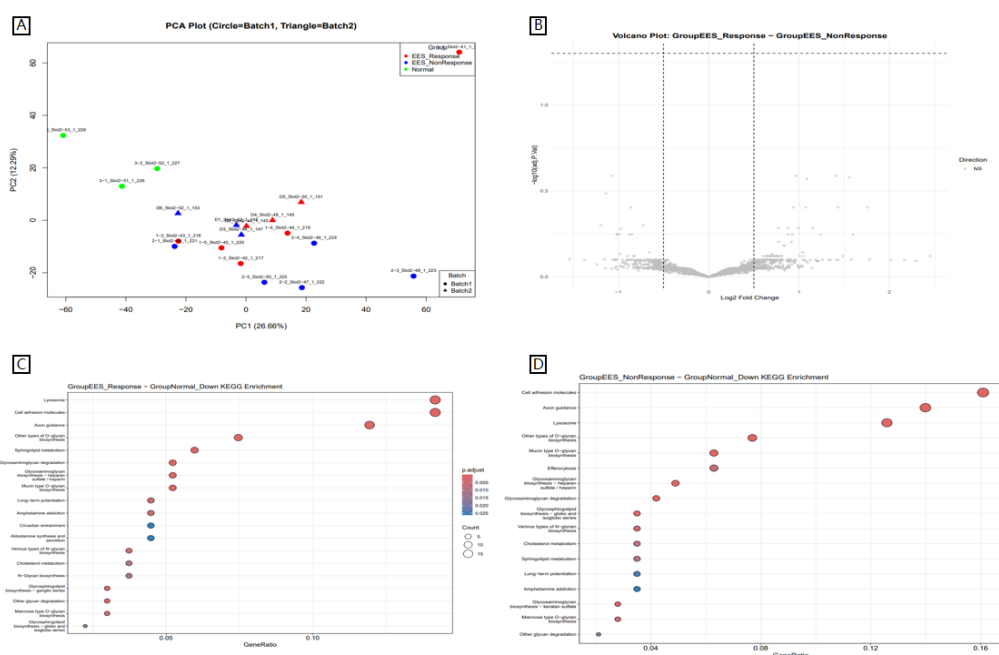


eTable 1. The imaging parameters of the patient.

Outcome	EES	Control	P
SCC			
Pre-op	49.83 (0.54)	47.69 (0.48)	0.002
Post-op	19.91 (0.77)	20.78 (0.58)	0.02
1m	18.13 (0.73)	20.01 (0.55)	0.001
3m	19.53 (0.66)	20.04 (0.52)	0.02
6m	19.60 (0.73)	19.95 (0.54)	0.06
SCCR			
Pre-op	35.00 (0.80)	36.13 (0.60)	0.25
Post-op	15.99 (0.49)	16.86 (0.53)	0.85
1m	15.41 (0.56)	16.44 (0.46)	0.94
3m	14.94 (0.63)	14.95 (0.46)	0.43
6m	14.47 (0.54)	14.30 (0.42)	0.36
T2HL			
Pre-op	18.76 (0.54)	19.89 (0.44)	0.18
Post-op	23.40 (0.72)	21.95 (0.62)	0.12
1m	21.13 (0.81)	21.88 (0.75)	0.78
3m	19.55 (1.15)	20.16 (0.86)	0.75
6m	16.40 (1.13)	18.70 (0.95)	0.50
SSD			

	1m	1.99 (0.14)	1.97 (0.12)	0.91
	3m	2.23 (0.11)	2.36 (0.10)	0.35
	6m	2.35 (0.11)	2.52 (0.10)	0.28
SL	1m	2.94 (0.21)	2.76 (0.16)	0.50
	3m	3.30 (0.16)	3.31 (0.13)	0.98
	6m	3.46 (0.17)	3.53 (0.14)	0.77

Data are mean (SD) or number (%) or median (IQR). SCC: the spinal canal compromise (SCC) ratio ; SCCR: the spinal cord compression ratio; T2HL: the Length of T2 hyperintensity ; SSD: the maximum syrinx sagittal diameter; SL: the syrinx length.



eFigure 2. Proteomic landscape and pathway enrichment analysis of cerebrospinal fluid from spinal cord injury patients with differential response to epidural electrical stimulation (EES).

(A) Principal component analysis (PCA) score plot of the first two principal components. The plot illustrates the overall separation between normal controls (Group Normal, green) and SCI patients (Groups EES Response and EES NonResponse), with considerable overlap between the two patient groups. (Circles = Batch 1, Triangles = Batch 2).

(B) Volcano plot showing the lack of significantly differentially abundant proteins (FDR < 0.05) between EES responders and non-responders. The minimal adjusted p-value was 0.089. Log2FC = log2 fold change.

(C) KEGG pathway enrichment analysis for proteins significantly downregulated in EES responders compared to normal controls. Key enriched pathways include Cell adhesion molecules, Axon guidance, and Lysosome.

(D) KEGG pathway enrichment analysis for proteins significantly downregulated in EES non-responders compared to normal controls. Note the specific and significant enrichment

of glycan metabolism-related pathways, including Glycosaminoglycan biosynthesis and N-Glycan biosynthesis (highlighted in red box), which are notably absent in the downregulated pathways of responders (Panel C). EES, epidural electrical stimulation; FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes; SCI, spinal cord injury.