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Traumatic spinal cord injury: a review of the current state of art and future directions – what do we know and where are we going?

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ABSTRACT

Background: Traumatic spinal cord injury (SCI) remains a devastating condition, with limited functional recovery despite advancements in clinical management and understanding of its mechanisms. SCI pathophysiology involves primary mechanical trauma and secondary neuroimmune and structural changes, leading to neuronal death and chronic functional deficits.

Methods: Through a comprehensive literature review of articles published in the PubMed, MEDLINE, Embase, and Cochrane Reviews Library databases, this article provides an update on the current management of traumatic SCI with a focus on these emerging therapeutic strategies that hold potential for future advancements in the field.

Results: Current management strategies include pre-hospital care, acute clinical interventions, surgical decompression and spine destabilization, and neurorehabilitation. Despite these interventions, SCI patients often fail to fully restore lost functions. Emerging therapies focus on neuroprotection, neuroregeneration, and neuromodulation, leveraging advances in molecular biomarkers, imaging techniques, and cell-based treatments. Neuroprotective agents, including the sodium-glutamate antagonist riluzole, aim to keep cells alive through the secondary injury phase, while regenerative strategies utilize neurotrophic factors and stem cell transplantation or approaches to target inhibitor molecules such as NOGO or RGMa to regenerate new cells, axons, and neural circuits. Neuromodulation techniques, such as electrical and magnetic field stimulation, offer promising avenues for functional recovery. Combining these novel therapies with traditional neurorehabilitation holds potential for improved outcomes.

Conclusions: While significant strides have been made in understanding the mechanisms underlying SCI and in developing novel therapeutic approaches, the challenge and opportunity will be to tailor treatments to fit the heterogenous clinical presentation of patients with SCI and to better understand the heterogeneity in clinical trajectories.

Introduction

Traumatic spinal cord injury (SCI) remains one of the most devastating conditions, affecting approximately 27 million people globally, with an incidence of 930,000 new cases each year according to recent studies [1,2]. This traumatic disorder leads to severe motor and sensory disabilities, significantly impacting the quality of life for affected individuals [3]. Despite advances in understanding the mechanisms of SCI and improvements in clinical management, such as surgical decompression and

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supportive rehabilitation protocols, functional recovery remains limited for many patients [4,5].

Recent research has shifted towards exploring advanced therapeutic approaches aimed at not only mitigating the damage but also promoting regeneration and functional recovery [6,7]. There is a clear need for continued research and development of novel interventions to improve outcomes for SCI patients, as current approaches are unfortunately unable to fully restore lost functions. This paper aims to provide a state-of-the-art overview of the current state of SCI treatment and discuss emerging therapies that hold potential for future advancements in the field.

Pathophysiology of SCI

The pathophysiological process of SCI is divided into primary and secondary phases. Primary SCI involves the initial mechanical trauma to the spinal cord, causing immediate vascular and structural damage [8,9]. Secondary SCI is further categorized into acute (within 24 hours), subacute (2–14 days), and chronic (up to 6 months) stages (Fig. 1) [10].

In the acute phase, hemorrhage leads to ischemia, necrosis, and edema, triggering pro-apoptotic signaling and exacerbating neuronal ischemia [11–13]. Disruption of the blood-spinal cord barrier (BSCB) results in the release of free radicals [14–16], myelin sheath decomposition material (myelin-associated glycoprotein [MAG], neurite outgrowth inhibitor protein [Nogo-A], chondroitin sulfate proteoglycans [CSPGs]) [17–19], and inflammatory cells that releases TNF-α, IL-1β, and IL-6 [15].

During the subacute phase, further vascular injury occurs, causing neuronal death due to a toxic microenvironment created by lipid peroxidation, glutamate excitotoxicity, mitochondrial dysfunction, and ionic dysregulation [20–23]. The chronic phase is characterized by impaired neurovascular remodeling, ECM remodeling, demyelination, Wallerian degeneration, and glial scar formation [24,25]. Microglia clear damage-associated molecular patterns (DAMPs), forming cystic cavities surrounded by the glial scar [24]. Cystic cavities coalesce to create barriers that hinder axonal regrowth, neuronal cell migration, and myelin regeneration, leading to irreversible neural damage [6,25,26].

Methods

This review was conducted through a comprehensive literature review of English articles published from January 2000 to October 1, 2024. Four different databases, PubMed, MEDLINE, Embase, and Cochrane Reviews Library, were queried with a combination of the following search terms: “spinal cord injury,” “traumatic spinal cord injury,” “neuroprotection,” “anti-inflammatory agents,” “biologics,” “biomarkers,” “neuroregeneration,” “neurotrophic factors,” “stem cells,” “stem cell therapy,” “neuromodulation,” “brain computer interface,” “rehabilitation,” “spinal cord stimulation,” “exoskeleton,” “nanoparticles,” “robot,” “scaffolds,” and “advances.” Studies were selected based on their relevance to SCI pathophysiology, current treatment, emerging therapeutics, and clinical outcomes.

Given the large volume of published literature on the topic, priority was given to systematic reviews, meta-analyses, randomized controlled trials, and high-quality observational studies. Key guidelines, expert consensus treatments, and recent findings from preclinical studies were also incorporated for a holistic overview of our review. Additionally, relevant references from identified literature were reviewed for inclusion.

Current management landscape in SCI management

Management of acute SCI

Pre-hospital first-line care

Care of SCI patients begins at the injury scene with rapid recognition and appropriate triage to ensure timely and safe treatment. Immediate management focuses on securing the airway, breathing, and circulation, and immobilizing the spine to prevent further injury while allowing cardiopulmonary resuscitation [27]. Immobilization techniques include a cervical collar for cervical spine injuries and a backboard for thoracic and lumbosacral injuries [28]. However, spinal immobilization carries certain risks, such as raised intracranial pressure (ICP) with rigid cervical collars, pressure ulcers, and higher mortality in patients with penetrating trauma [29–31].

After initial assessment, resuscitation and immobilization, SCI patients should be promptly transferred to a hospital with intensive care facilities for cardiopulmonary and hemodynamic monitoring [32]. Early transfer (within 24 hours) is linked to improved neurological recovery, reduced complication rates, and better long-term outcomes [33,34].

Assessment and prognostication of SCI

Following stabilization and resuscitation, a rapid assessment of traumatic SCI patients is essential. Current guidelines recommend the American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (ISNCSCI) to determine injury level, baseline neurological status, and prognosis [32,35].

The ASIA classification uses a 5-point scale (grades A to E) to classify sensorimotor impairment [36]. However, the ASIA score’s prognostic potential is limited due to varying neurologic improvement of patients with the same grade [37,38]. Additionally, the presence of other traumatic injuries and varying levels of consciousness can complicate its use [39,40]. Therefore, a multimodal approach, including neuromonitoring, imaging, electrophysiology, and emerging biomarkers, is necessary for accurate SCI prognosis [38,41,42]. Moreover, advances in machine learning approaches, including group-based trajectory modeling hold promise in more accurately defining the clinical trajectory of patients with SCI [43,44].

Radiological evaluation is crucial for assessing injury severity, detecting missed injuries, determining spinal instability, and guiding treatment [45,46]. Computed tomography (CT) is preferred for acute SCI, having largely replaced plain x-rays in larger tertiary care settings [47].

While MRI is the gold standard for SCI diagnosis,[48]. it is not routinely recommended in the acute phase due to increased time to acquire the image, limited availability, potential delays in extubation, and prolonged hospital stays [45,46]. However, MRI has prognostic value; patients with a greater degree of injury-spared cord tissue based on imaging findings is predictive clinical improvement while spinal cord hemorrhage or significant cord edema (seen as T2 hyperintensity) tend to have poorer outcomes [49–51]. Additionally, MRI can identify coexisting injuries such as epidural hematomas, large disc herniations, ligamentous injuries, and tissue bridges, all of which guide treatment planning [52]. Moreover, emerging evidence suggests that microstructural MRI techniques can identify “tissue bridges”, which assist in prognosticating outcomes after SCI [53,54].

Cardiopulmonary management

Cardiopulmonary compromise is common in acute SCI, particularly in patients with higher AIS grades or higher injury levels due to damage to the upper cervical spinal cord, sympathetic tracts, the diaphragm, intercostal muscles, and abdominal muscles [45]. Cardiovascular complications include neurogenic shock, bradycardia, and hypotension. A systolic blood pressure below 90 mmHg is associated with poorer neurological outcomes due to worsened ischemia and systemic hypoperfusion from trauma-related hemorrhage and neurogenic shock [32,45]. Intravenous crystalloids (either normal saline or Ringer’s lactate) are the first-line treatment for blood pressure augmentation in acute SCI. In cases of neurogenic shock, alpha-adrenergic vasopressors like norepinephrine, dopamine, and phenylephrine may be used with crystalloids [55,56].

Maintaining a mean arterial pressure (MAP) above 85 to 90 mm Hg has been shown to improve ASIA grades in SCI patients [57,58], and observational studies have indicated that maintaining this MAP target may

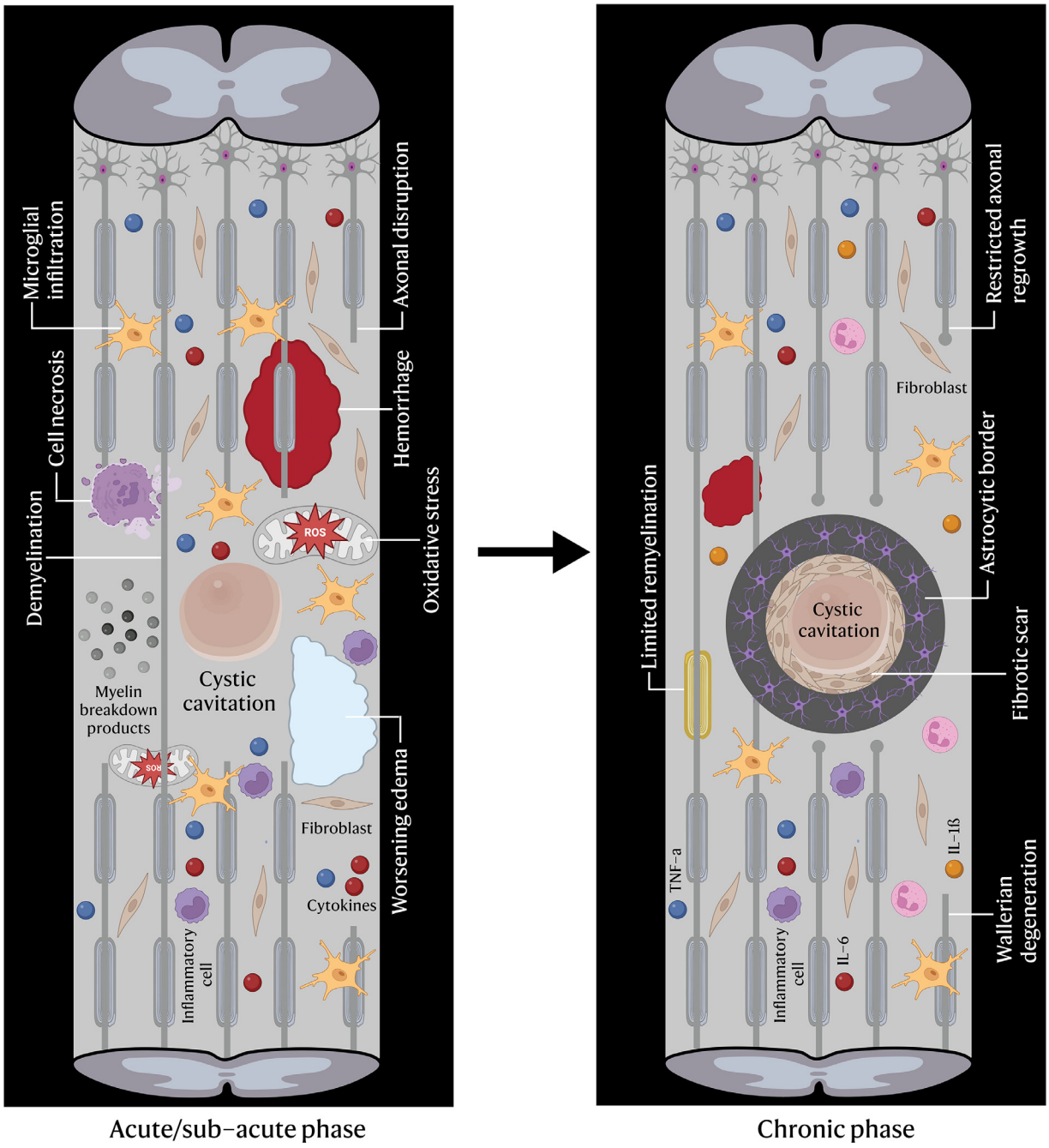

Fig. 1. Pathophysiology of spinal cord injury (SCI). SCI involves primary mechanical trauma and secondary (acute, subacute, and chronic) phases. Subacute phase includes hemorrhage and ischemia; acute phase, neuronal death from toxic microenvironment; chronic phase, impaired neurovascular and extracellular matrix remodeling with glial scar formation, hindering axonal regrowth and leading to irreversible damage.

correlate with neurological improvement [59–61]. This led to the 2013 AANS/CNS recommendation of sustaining MAP ≥85 to 90 mm Hg for 7 days post-injury [62]. However, more recent evidence has suggested that primarily avoiding hypotension by implementing wider MAP goals (75–95 mm Hg), and over shorter durations of MAP augmentation (3–7 days) may offer similar benefit, which is reflected by the most recent AO Spine guidelines [61,63].

Respiratory complications of SCI include increased risk of respiratory infections due to impaired cough and secretion clearance, reduced forced vital capacity, hypoxemia, predisposition to atelectasis, and impaired gas exchange [64–66]. Initial airway management involves establishing a definitive airway while maintaining immobilization. The American College of Surgeons Advanced Trauma Life Support guidelines recommend direct laryngoscopy with orotracheal intubation for trauma patients with known or suspected SCI [67]. Chronic mechanical ventilation and tracheostomy may be required for patients with persistent respiratory compromise, respiratory infections, respiratory failure exacerbations [66].

Pharmacological management

Methylprednisolone, a synthetic corticosteroid, is the only widespread pharmacological option that has been studied and employed for the management of SCI. It purportedly promotes neural cell survival by releasing anti-inflammatory cytokines, restoring the BSCB, reducing oxidative stress, and secreting neurotrophic factors [68,69].

Table 1
The SLIC and TLIC scales

	SLIC		TLIC	
Morphologic features	Compression fracture	1	Compression fracture	1
	Burst fracture	2	Burst fracture	2
	Distraction	3	Distraction	3
	Rotational and/or translational	4	Rotational and/or translational	4
Posterior discoligamentous complex	Intact	0	Intact	0
	Indeterminate	1	Injury suspected/indeterminate	2
	Disrupted	2	Injured	3
Neurologic involvement	Intact	0	Intact	0
	Nerve root injury	1	Nerve root	2
	Complete	2	Cord, conus medullaris	
	Incomplete	3	Incomplete	3
	Persistent cord compression	+1	Complete	2
			Cauda equina	3
Total score		0–10		0–10

≤3: nonoperative management.
4: either nonoperative or operative, depending on clinical picture.
≥5: operative management.
SLIC, subaxial cervical spine injury classification scale; TLIC, thoracolumbar injury classification and severity scale.

The initial National Spinal Cord Injury Study (NASCIS) highlighted severe side effects, but subgroup analyses in NASCIS II showed significant motor recovery when administered within 8 hours post-SCI [70–72]. A subsequent Cochrane review confirmed this, reporting a 4-point improvement in ASIA motor score for patients treated within this timeframe [73]. However, severe side effects including hyperglycemia, peripheral edema, increased infection risk, myopathy, and gastritis have led to ongoing debate on its use [74].

While the AOSpine 2017 guidelines recommend methylprednisolone administration within 8 hours post-injury for acute SCI, the AANS/CNS spine section has a level 1 recommendation against the use of high-dose methylprednisolone for the acute management of SCI patients [75,76]. The conflicting nature of these recommendations further justifies the necessity for additional research to clarify the risks and benefits of methylprednisolone and other steroids in SCI treatment.

Operative management

Surgical decompression. Surgery for acute SCI focuses on spinal decompression, spinal realignment and stabilization, and reducing intraspinal pressure from edema and hemorrhage. Surgery is recommended for patients scoring ≥5 on the Subaxial Cervical Spine Injury Classification (SLIC) and Thoracolumbar Injury Classification and Severity (TLIC) scales (Table 1) [77,78]. The primary technique is surgical decompression, which varies based on injury characteristics and includes laminectomy/laminotomy, possibly durotomy/duroplasty, and rarely myelotomy.

Local spinal compression with laminectomy usually treats localized edema from spinal cord compression well, while extensive edema may require a combination laminectomy and durotomy/duroplasty [79]. Durotomy involves incising the dura to reduce intraspinal pressure and improve perfusion. Perkins et al. [80] reported neurological recovery in a small case series of 6 patients following durotomy and decompression. Duroplasty, which uses a dural patch after durotomy to permanently increase the intradural space, provides similar benefits with fewer complications [81]. Zhu et al. [82] found that posterior laminectomy and durotomy with duroplasty improved cerebrospinal fluid (CSF) circulation and AIS scores in severe SCI without radiological abnormalities (SCIWORA).

Myelotomy, used for hematoma and tissue necrosis removal, has shown positive outcomes in case reports. Koyanagi et al. reported motor function and sensory improvements in patients with cervical injury treated by posterior midline myelotomy, with less effect in a patient treated 18 hours post-SCI [83]. Fox et al. also documented rapid improvement in a patient with central cervical SCI following myelotomy [84].

The timing of surgery for SCI significantly affects long-term neurological outcomes, as emphasized by the phrase "*time is spine*" [85]. The multicenter, international, prospective Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) by Fehlings et al. demonstrated that early decompression (≤ 24 hours) is associated with an improvement of ≥2 AIS grades at 6 months [86]. Early surgical decompression also leads to shorter hospitalization for patients with ASIA grades A and B, reduced care costs, and earlier engagement in neurorehabilitation [32,87]. However, guideline recommendations for early decompression for SCI vary across SCI types.

Despite the AANS/CNS and AO Spine/Praxis recommendations for early decompression in acute SCI [32,88], there is variability in guidelines for central cord syndrome (CCS). CCS is an incomplete cervical SCI without fracture or dislocation, typically in older adults with preexisting cervical stenosis after low-energy trauma, and is characterized by greater weakness in the upper extremities, variable sensory loss below the level of lesion, and variable lesion bladder, bowel, and sexual dysfunction [89,90]. Although there is no consensus on timing for CCS surgery, emerging data suggest early timing may be beneficial, especially for patients with ASIA C injury [91–93].

Neuromonitoring and CSF diversion. Inspired by ICP monitoring in traumatic brain injury [94], studies continue to explore optimization strategies for the use intrathecal pressure probes to monitor intraspinal pressure and the utility of CSF drainage to improve spinal cord perfusion pressure [95–97]. Lumbar intrathecal catheters for CSF drainage have been shown to be safe and capable of identifying changes in intrathecal pressure that would be otherwise unrecognized by routine MAP measurements [98]. A recent multicenter randomized control trial confirmed the safety and efficacy of intraspinal pressure monitoring and CSF diversion [99]. Future research should aim to identify which patients are best suited for CSF diversion, determine the optimal goals for CSF drainage, and establish the appropriate timing for initiating CSF diversion.

Management of Chronic SCI

Neurorehabilitation

Physical therapy post-SCI is critical for improved outcomes. Conventional neurorehabilitation options include strengthening, stretching,

transferring exercises, modified activities, and assistive devices through occupational therapy, along with continued medical and nursing care [56]. These strategies aim to achieve functional independence, optimize residual function, and minimize complications associated with chronic SCI [56,100].

Activity-based neurorehabilitation techniques, such as assistive treadmill training and overground gait training, promote neurophysiological, release neurotrophic factors, and encourage axonal regeneration [101–103]. Combining conventional and locomotor regimens has shown efficacy through neuroprotection and neuroregeneration mechanisms [104]. While early mobilization post-SCI is beneficial, consistent neurorehabilitation is critical to recovery [100]. Müller et al. [105] demonstrated that consistent gastrocnemius EMG activity during assisted walking was present in a patient undergoing an 18-month weekly locomotor training regimen. A 6-week, moderate-intensity, home-based program with 45-minute upper-body exercise sessions significantly improved perceived physical functioning and quality of life chronic SCI patients [106]. A systematic review confirmed the efficacy of body weight supported treadmill training (BWSTT) in improving functional ambulation in chronic SCI patients [107].

Advances in SCI management

Advances in SCI prognostication

Neuroimaging biomarkers of SCI

Advances in MRI imaging have enabled detailed tissue microstructural and functional analyses, providing prognostic indicators for SCI (Table 2). These advanced protocols include T2*-weighted imaging (T2WI), diffusion tensor imaging (DTI), magnetization transfer (MT), myelin water fraction (MWS), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI). Poor neurological outcomes are associated with several markers on T2WI, including white to gray matter signal hyperintensity, high Brain and Spinal Injury Center (BASIC) scores, facet dislocation, intramedullary edema over 36 mm, and ligamentum flavum injury, narrower mid-sagittal tissue bridges, large injury area volumes, and the presence of Wallerian degeneration [108–112].

DTI enables 3D modeling of neural tracts to assess axonal integrity, known as tractography [113]. The primary quantitative metric used in DTI is factional anisotropy (FA), which measures the degree water molecule diffusion restriction in a region of interest. Severe SCI is characterized by increased diffusion due to neural tract damage. Axial diffusivity (AD), the rate of water diffusion parallel to white fiber tracts, also indicates neuronal tract damage [114]. FA values correlate significantly with baseline and 1-year ASIA scores and the Frankel grade (Pearson correlation, R^2=0.86) following cervical SCI [115,116]. AD also correlates significantly with ASIA motor scores (R^2=0.76) and Spinal Cord Independence Measure (SCIMM III) scores (R^2=0.77) 1 year postcervical SCI [117]. Machine learning using FA indices, trained and validated K Nearest Neighbor (KNN) and Support Vector Machine (SVM) classifiers, showed high predictive power in detecting SCI with 95.2% sensitivity and 91.2% specificity [118].

Additional MRI-based techniques, such as fMRI, MT, MWF, and MRS, are being studied to visualize neuronal activity and connectivity, quantify myelin content, and measure molecular biomarkers of neuronal injury and neurodegeneration, providing further prognostic insights [119].

Molecular biomarkers of SCI

CSF biomarkers of acute SCI include inflammatory cytokines (eg, IL-6, IL-8, monocyte chemotactic protein [MCP]-1, and tumor necrosis factor [TNF]-α), structural proteins (eg, calcium binding protein B [S100-β], glial fibrillary acidic protein [GFAP], high molecular-weight neurofilament subunit [pNF-H], myelin basic protein [MBP], spectrin breakdown product [SBDP], and Tau), enzymes (eg, neuron-specific enolase (NSE), ubiquitin carboxy-terminal hydrolase-[UCH]-L1, matrix metalloproteinases [MMP]), and microRNA [120–123]. Levels of IL-6, IL-8, MCP-1, Tau, S100-β, and GFAP sampled at 24 hours post-SCI can accurately predict baseline and 6-month AIS grades [120,121], with low levels of Tau, GFAP, and S100-β correlating with better motor outcomes [124]. Transient increases MBP, SBDP, and UCH-L1 concentrations are also observed in acute SCI [122]. Recent studies identified microRNA-9 and microRNA-219 as biomarkers of myelin disruption and spinal cord parenchyma destruction, respectively [123].

Serum biomarkers for acute and chronic SCI have been identified. Elevated serum levels of structural neuronal proteins (GFAP, NSE, pNF-H, and neurofilament light chain) are associated with poor motor outcomes following acute SCI [125–128]. Biomarkers like pNF-H peak at 3 days post-SCI and decrease over 3 months [129]. The use of insulin growth factor 1 (IGF-1) as a serum biomarker of acute SCI has yielded inconsistent results, with studies reporting the association of high IGF-1 levels with both poorer and better neurological outcomes [130,131]. High levels of zinc and low levels of copper and selenium are good prognostic indicators of acute SCI [132,133] In chronic SCI patients, elevated serum levels of IL-6, IL-2 receptor (IL-2R), intercellular adhesion molecule (ICAM)-1, and TNF-α are common and may predict complications such as neuropathic pain, pressure ulcers, and urinary tract infections [134,135]

Advances in neuroprotection

Neuroprotective therapies target the secondary phase of SCI, addressing excitotoxicity, ionic dysregulation, mitochondrial dysfunction, lipid peroxidation, inflammation, and cell death (Table 3). Anti-excitotoxic agents include NMDA and non-NMDA receptor antagonists.

Magnesium, which may be PEGylated to enhance bioavailability, is a noncompetitive NMDA receptor antagonist showed neuroprotective effects in preclinical studies but failed in clinical settings [136,137]. Non-NMDA receptor antagonists with reported efficacy include riluzole (sodium channel blocker),[138]. levetiracetam (calcium channel blocker) [139], and nimodipine (calcium channel blocker) [140]. The RISCIS trial evaluated the efficacy of riluzole in patients with cervical SCI and while it did not meet its primary endpoint for efficacy in the study population, additional sub-group analyses for ASIA C participants demonstrated significant improvements in motor recovery with considerable benefits in functional and quality-of-life indices particularly among ASIA B & C patients [141]. Moreover, a biomarker study revealed riluzole reduced axonal degradation, as indicated by serum phosphorylated neurofilament levels [142]. Secondary analyses are ongoing, and clinicians may consider riluzole for acute SCI patients. Treatments for mitochondrial dysfunction have explored mitochondrial biogenesis (acetyl-L-carnitine, *N*-acetylcysteine, and formoterol) [143–145], inhibition of mitochondrial pore formation (cyclosporin and its derivative NIM811) [146,147], and ATP production (ketogenic diet and mitochondrial division inhibitor 1 [Mdivi-1]) [148,149].

Anti-inflammatory approaches, balancing between pro-inflammatory and anti-inflammatory responses, have highlighted minocycline, micro-RNAs, and therapeutic hypothermia for improving neuronal integrity and neurological outcomes [150–152]. Targeting cell death processes such apoptosis, necrosis, necroptosis, ferroptosis, and autophagy has also been explored. A noteworthy contributor to the neuroimmunologic milleu after SCI is the regulatory T cell (Treg cells). As a key subset of the CD4+ T cells, the Treg role in regulating astrocytes, macrophage/microglia and stem cell responses to neurologic injury, the development of new therapeutic strategies to target this subpopulation represents a critical unmet need in the neuroprotective armamentarium against SCI [153]. Stimulating autophagy (eg, metformin, atorvastatin) and inhibiting autophagy (valproate) have both shown potential in preventing apoptosis and improving functional recovery in rodent models of SCI [154–156].

Table 2
Diagnostic and prognostic factors of SCI

Author	Country	Type of study	No. of patients	Injury level	Key findings
T2–weighted MRI Imaging (T2*WI)					
Talbott [109]	USA	Retrospective case series	60	Cervical SCI	The BASIC score, a 5-point ordinal MRI score for classifying acute SCI based on axial T2*WI correlates with neurological symptoms at time of hospital admission and discharge.
Martin [108]	Canada	Case-cohort	98 (58 cases, 40 controls)	Cervical SCI	Rostral T2*WI strongly correlates with focal motor and sensory deficits and is the strongest predictor of the mJOA score.
Martinez-Perez [110]	Canada	Retrospective case series	86	Cervical SCI	Ligamentum flavum injury, intramedullary edema >36 mm, and face dislocation are associated with no neurologic improvement. Edema >36 mm and facet dislocation are strong predictors of poor outcome.
Mummaneni [111]	USA	Prospective cohort study	60	Cervical SCI	The volume of total injury and of injured spinal cord motor regions on T2*WI are significantly and independently associated with neurologic outcome at discharge.
Fischer [112]	Switzerland	Retrospective case series	35	Cervical SCI	Wallerian degeneration in the dorsal column, lateral corticospinal tract, and lateral spinothalamic tract on T2*WI is associated with a higher degree of impairment.
Diffuse tensor imaging (DTI)					
D'souza [115]	India	Case-cohort	50 (20 cases, 30 age- and sex-matched controls)	Cervical SCI	Mean FA at the level of injury was less than in controls, whereas mean MD at the level of injury was higher than in controls. FA values show a statistically significant positive correlation with the Frankel grade.
Diffuse tensor imaging (DTI)					
Shanmuganathan [101]	USA	Prospective case-cohort	30	Cervical SCI	AD strongly correlates with 1-year SCIM III and ISNCSCI scores. AD is a more specific parameter for axonal injury than radial diffusivity, indicating that axonal injury in the cord is the main factor affecting patient recovery.
Shabani [100]	USA	Prospective cohort	23	Cervical (n=19) and Thoracic (n=4)	FA value at the cervical spine significantly correlates with ASIA score at the time of arrival as well as at 1-year follow-up. In the high cervical cord (C1–C2), FA correlates with injury severity and long-term follow up. This correlation is not seen in patients with thoracic SCI.
CSF biomarkers					
Kwon [104]	Canada	Prospective cohort	50	Cervical (n=32) and Thoracic (n=18)	IL-6, tau, S100β, and GFAP correlate with baseline AIS grades. IL-6, IL-8, MCP-1, tau, S100β, and GFAP levels correlate with 6-month neurologic improvement. IL-6 and S100β levels correlate with AIS A to B or C conversion, and 24-hour post-injury levels of all 6 biomarkers correlate with motor score improvement.
Dalkilic [105]	Canada	Prospective cohort	36	Cervical SCI	CSF biomarkers correlate with baseline injury grade. IL-6, IL-8, and MCP-1 best predict AIS score conversion, while GFAP, tau, and S100β best predict motor score improvement. CSF biomarkers outperform MRI in distinguishing injury severity and predicting neurological outcomes.
Tigchelaar [107]	Canada	Prospective case-cohort	44 (39 cases, 5 controls)	Cervical (n=22), thoracic (n=12), and lumbar (n=5)	204 microRNAs are significantly associated with injury severity at 24h post-injury, with 139 microRNAs increasing in expression with increasing injury severity, and 65 microRNAs decreasing in expression with increasing injury severity.

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Table 2 (*continued*)

Author	Country	Type of study	No. of patients	Injury level	Key findings
Serum biomarkers					
Segal [119]	USA	Case-control	90 (70 cases, 20 controls)	Cervical, Thoracic, and Lumbar	IL-6, IL-2R, and ICAM-1 levels are significantly elevated in patients with SCI, with greatest increase seen in patients with pressure ulcers compared to healthy controls.
Davies [118]	Canada	Cross-sectional study	91 (56 cases, 35 controls)	Cervical and Thoracic	Serum IL-6, TNF-alpha, IL-1RA, and anti-GM(1) (IgG) levels are elevated in SCI patients, and further elevated in SCI subjects with neuropathic pain, UTI, or pressure ulcers, compared to healthy controls.
Ahadi [110]	Iran	Case-control	35 (26 cases, 9 controls)	Cervical (n=8), Thoracic (n=8), and Lumbar (n=10)	Serum GFAP, NSE, and pNF-H levels at 24-48 hours post-injury correlate with degree of SCI severity.
Ferbert [115]	Germany	Prospective cohort	23	Cervical (n=7), Thoracic (n=10), and Lumbar (n=6)	Serum levels of IGF-1, TGF-β1, and sCD95L are significantly higher in patients without neurological improvement 12 weeks post-injury.
Moghaddam [111]	Germany	Prospective cohort	115	N/A	Serum MMP-8 and MMP-9 levels significantly correlate with neurological improvement after SCI.
Singh [113]	India	Prospective case-control	40 (28 cases, 12 controls)	Thoracic and Lumbar	Plasma pNF-H is positively correlated with SCI severity.
Du [112]	China	Prospective cohort	60	Cervical (n=15), Thoracic (n=16), and Lumbar (n=29)	Serum NSE and S100β levels can reflect the degree of spinal cord injury, with cutoff values of 29.07 μg/L and 1.67 μg/L, respectively.
Serum biomarkers					
Kijima [116]	Japan	Prospective cohort	64	Cervical SCI	Serum zinc concentrations in the acute phase accurately predicts long-term functional outcome (R^2=0·84).
Tigchelaar [107]	Canada	Prospective case-cohort	44 (39 cases, 5 controls)	Cervical (n=22), Thoracic (n=12), and Lumbar (n=5)	83 microRNAs are significantly associated with injury severity at 24 h post-injury, with 46 microRNAs increasing in expression with increasing injury severity and 37 microRNAs decreasing in expression with increasing injury severity.
Seelig [117]	Germany	Prospective case-control	62 (52 cases, 10 controls)	Thoracic SCI	Temporal changes in serum selenium and copper levels are strongly associated with clinical outcome after TSC.

AD, axial diffusivity; ASIA, American Spinal Injury Association scale; AIS, ASIA impairment scale; BASIC, the Brain and Spinal Injury Center score; FA, functional anisotropy; GFAP, glial fibrillary acidic protein; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; MCP-1, monocyte chemotactic protein-1; MD, mean diffusivity; mJOA, modified Japanese orthopedic association scale; MMP, matrix metalloproteinase; pNF-H, high molecular-weight neurofilament subunit; SCIM III, Spinal Cord Independence Measure; NSE, neuron specific enolase; UTI, urinary tract infection.

Advances in neuroregeneration

Advanced neuroregenerative strategies for SCI focus on molecular and cellular approaches, and methods enhancing their delivery to the injury site. Molecular approaches improve the SCI microenvironment by stimulating trophic effects and targeting inhibitory components of neuronal survival.

Neurotrophic factors that stimulate neuroregeneration include brain-derived growth factor (BDNF) [157], ciliary neurotrophic factor (CNTF) [158], connective tissue growth factor (CTGF) [159], neurotrophin 3 (NT3) [160], fibroblast-derived factor (FGF), glial cell-derived neurotrophic factor (GDNF) [161], and nerve growth factor inducible (VGF) [162]. Inhibitory myelin decomposition products include CSPGs, Nogo-A, and MAG. Chondroitinase ABC (ChABC), an enzyme that catabolizes CSPGs, reduces glial scar formation, and when combined exogenous NPCs, promotes neuroregeneration by allowing extensive NSPC distribution at the injury site [163]. Inhibiting NOGO or downstream targets (eg, RhoA-ROCK, which is also activated by CSPGs) improves axonal sprouting and corticospinal tract regeneration [164–166]. Recent trials, including the Nogo-A Inhibition in acute Spinal Cord Injury (NISCI) trial shows promise in targeting these pathways. Additionally, industry-funded trials targeting the repulsive guidance molecule A (RGMa), which is upregulated in SCI, presents additional avenues for therapeutic intervention [167–170].

Pharmacological and gene therapy approaches to neutralize myelin-associated inhibitors fosters a conducive environment for axonal regeneration and functional recovery post-SCI [171].

Cell transplantation using stem and neural cells promotes tissue repair and regeneration. Mechanisms of neuroregeneration by stem cells in animal SCI models include axonal remodeling by embryonic stem cells (ESCs) [172], synaptogenesis by induced pluripotent stem cells and neural progenitor/stem (NPCs/NSCs) [173,174], neuroprotection by mesenchymal stem cells (MSCs) [175–177], and myelin sheath formation by oligodendrocyte progenitor cells (OPCs) [178]. Neurally-derived therapies like astrocyte progenitors, olfactory ensheathing cells (OECs), and Schwann cells, show promise in improving motor and respiratory function [179], promoting axonal growth and survival [180], and providing neurotrophic support [181].

Delivery of bioactive molecules and cell-based therapies is enhanced by biomaterials, such as nanoparticles, exosomes, and scaffolds [182–184], which also support axonal growth and survival [185] An emerging surgical technique, nerve and tendon transfers, supports axonal regeneration by providing a favorable microenvironment [186,187]. Animal SCI models have shown that axon growth into and through peripheral nerve grafts is enhanced, especially when combined with exogenous BDNF, ChABC, and GDNF [188,189]. Clinical studies also demonstrate that nerve and tendon transfers improve functional restoration in SCI patients [190].

Table 3
Neuroprotective agents studied for SCI treatment

Agent	Injury model	Effects
Anti-excitotoxicity approaches		
Magnesium [120,121]	Hemicontusion and contusion injuries	• Lowered forelimb errors compared to control. • Reduced secondary damage and improved behavioral recovery. • Improved number of perfused microvessels, but did not reduce acute microvessel, motor neuron or oligodendrocyte loss, and did not affect functional recovery or spared epicenter white matter.
Riluzole [122]	Clip compression injury	• Recovered coordinated hindlimb function and strength. • Enhanced residual tissue area at the injury epicenter. • Reduced tissue loss in rostrocaudal regions surrounding the epicenter, with overall sparing of gray matter and selective sparing of white matter. • Increased counts of red nuclei neurons at the injury site
Levetiracetam [123]	Contusion injury	• Improved gross and fine motor functions. • Reduced cavity size and increased neuronal and oligodendrocyte survival. • Stabilized astrocytes, increasing effective excess glutamate uptake from the extracellular space.
Nimodipine [124]	Clip compression injury	• Increased spinal cord blood flow, which is related to improvements in axonal function. • Improved motor (MEP) and somatosensory (SSEP) evoked potentials.
Mitochondrial enhancing approaches		
Acetyl-L-carnitine [125]	Spinal lesion	• Maintained mitochondrial length, reduced number of damaged mitochondria, and reversed mitochondrial score. • Maintained mitochondrial membrane potential and Na^+-K^+-ATPase activity. • Reversed downregulation of mitofusin 1 (Mfn1), Mfn2, Bcl-2, and upregulation of dynamin-related protein 1 (Drp1), mitochondrial fission 1 (Fis1), Bcl-2-associated X protein (Bax) and cytosol cytochrome C. • Reduced percentage of apoptotic cells.
N-acetylcysteine [126]	Upper lumbar contusion	• Improved mitochondrial bioenergetics in a dose-dependent manner. • Normalized mitochondrial glutathione levels. • Improved hindlimb function and increased tissue sparing at the injury site.
Formoterol [127]	Force-controlled impactor-induced contusion model	• Enhanced mitochondrial biogenetics and restored downstream protein expression. • Reduced histological damage and lesion volume. • Increased white and gray matter sparing in regions rostral and caudal to the injury epicenter. • Improved locomotor capability.
Mdivi–1 [130]	Ischemia-reperfusion injury (descending thoracic aorta occlusion)	• Attenuated glutamate induced neuronal injury and apoptosis in spinal cord neurons. • Reduced oxidative stress, mitochondrial dysfunction, and preserved activities of antioxidant enzymes. • Increased expression of large-conductance Ca^{2+}- and voltage-activated K^+ channels.
Anti-inflammatory approaches		
Minocycline with BMSCs [132]		• Reduced inflammation factors • Upregulated vascular endothelial growth factor and brain-derived neurotrophic factor expression. • Suppressed caspase-3 activation
microRNA 155-5p deletion [133]	Dorsal column crush or contusion injury	• Improved locomotor function. • Decreased accumulation of inflammatory macrophages. • Enhanced spontaneous axon growth.
Agents directed at autophagy		
Valproic acid [135]	Weight-drop contusion injury	• Markedly reduced autophagy. • Improved the Basso-Beattie-Bresnahan locomotor rating scale. • Increased number of ventral horn motoneurons. • Reduced myelin sheath damage.
Atorvastatin [136]	Allen weight-drop contusion injury	• Increased Beclin-1 and light chain 3B gene and protein expressions. • Reduced caspase-9 and caspase-3 expression. • Improved the Basso, Beattie, and Bresnahan locomotor rating scale.

Research into intracellular signaling pathways has revealed the PTEN/mTOR and SOCS3/STAT pathways as promising targets for promoting axonal regeneration following SCI [191]. PTEN inhibition or deletion enhances mTOR signaling, promoting axon regrowth, and improving locomotor and respiratory functions [192–194]. These effects are enhanced with combined neurorehabilitation, which additionally promotes neuronal plasticity [195]. Similarly, SOCS3 deletion amplifies JAK/STAT signaling, driving transcription of regeneration-associated genes with resultant CST axon sprouting [196]. Studies show that co-deleting PTEN and SOCS3 leads to synergistic effects, markedly enhancing axonal regeneration and recovery of locomotor function [197–199].

Much current effort is also devoted towards temporarily opening the blood-spinal cord barrier in order to enable delivery of neuroprotective and/or neuroregenerative agents. Specifically, low intensity focused ultrasound (LIFU) can modulate the permeability of the BSCB through mechanisms such as microbubble cavitation [200]. This enhanced permeability facilitates the targeted delivery of therapeutic agents directly to the injury site, promoting neuroprotection and regeneration. Animal

Table 4
Exoskeletons for rehabilitation following SCI

Device	Assisted functions	Limitations
Upper extremity exoskeletons		
ASIBOT (University Carlos III of Madrid, Spain) [237]	• Drinking. • Brushing teeth. • Washing the face.	• Ergonomic design in terms of size and appearance • Requires improved mobility
Armeo Spring [238]	• Reaching movements • Pronation/supination at the radio-ulnar joint • Handgrip strength	• Limited functional improvements with device • Not typically preferred by users over conventional therapy
Systemic Autonomous Majordomo (SAM) [239]	• Grasping movements • Object handling	• Experiences of failures during various stages of task completion • Technical, financial, and human obstacles to uptake
RiceWrist-S [240]	• Forearm pronation/supination • Forearm flexion/extension • Radial/ulnar deviation of the wrist	• Subject fatigue affects device performance. • Cumbersome setup and donning process.
Haptic Master (HM) [241]	• Eating with a fork and knife • Taking money out of a purse • Moving a cap	• Requires a larger workspace requirement. • Orthosis restricts fluent movement. • Requires therapist intervention to start different activities. • Some programming sequences activities not yet possible. • Too complex for use outside laboratory conditions.
Handexos (HX) [242]	• Hand grasps. • Precision grips.	• Mechanical complexity. • Low adaptability to different hand sizes. • Limited control of the range of motion at the finger joints.
Adaptative head Motion Control for User-friendly Support (AMiCUS) [243]	• Head motion-controlled robot arm with a gripper to perform pick and place tasks, such as stacking cubes.	• Requires multiple trials for correct head gesture recognition. • Difficult to use in some tetraplegics due to requirement for head gestures. • Higher spatial ability required for rotations. • Requires additional feedback to achieve precise grasping
Hand Extension Robot Orthosis grip glove (HERO) [244]	• Hand opening and grasping. • Five-finger flexion. • Five-finger extension. • Thumb abduction, adduction, and opposition.	• Donning difficulty. • Inconsistent assistance in hand movements. • Insufficient grip strength for some tasks. • Short batter life. • Heavy device weight.
SEM Glove [245]	• Provides additional finger flexion strength to support grasp function.	• Variable usability due to part placed on palmar side. • May cause pain on the involved limb after long periods of use. • Heavy and cumbersome control unit. • Requires a longer period for effects on muscle hypertonia. • Not water-resistant and does not cover all digits.
RELab tenoexo [246]	• Four main grasping tasks: palmar pinch, medium wrap, parallel extension, and lateral pinch. • Ensures functional ROM for fingers, thumb, and wrist movement.	• Long and cumbersome donning process. • Variable usability among users. • Difficult to execute dextrous grasping tasks. • Need complex and heavier design to actuate wrist and thumb abduction/adduction.
FLEXotendon glove III [247]	• Grasping and manipulating objects	• Can be difficult and cumbersome in manipulating small objects.
Lower extremity exoskeletons		
ReWalk [248]	• Walking. • Sit-to-stand. • Stand-to-sit. • Up steps and down steps. • Gait training.	• Requires significant training. • High energy demands for functional walking may limit long-term use. • Moderate fatigue after using device. • Not simple to wear and adjust. • Difficult to achieve proficiency needed for daily use.
Hybrid assistive limb (HAL) [249]	• BWSTT to assist in improving walking capabilities, including speed, distance, and time	• Requires several training sessions. • Progress in speed decreases over time.
Locomat [250]	• BWSTT. • Skilled walking tasks such as obstacle crossing, walking on different surfaces, and various walking activities.	• Pain and soreness associated with use. • Associated with a more intense and strenuous training experience.

(*continued on next page*)

Table 4 (*continued*)

Device	Assisted functions	Limitations
Indego [251]	• Standing, walking, and sitting. • Overground walking. • Sit-to-stand. • Stand-to-sit. • Walk-to-stand. • Stand-to-walk.	• Requires several training sessions. • Requires assistance with use. • Device performance affected by type of surface and environmental conditions, such as weather. • Associated with bruising and skin redness. • Donning and doffing difficulties.
Ekso [253]	• Standing. • Voluntary over-ground stepping with weight-bearing and alternating gait. • Standing balance, weight shifting, walking, turning, sit-to-stand, and stand-to-sit.	• Requires upper extremity supports, such as crutches, which impacts performance of functional tasks. • Limitations in range of movement beyond walking in a straight line. • High cost. • High weight, which affects assembly and transport.
Rex [254]	• Sit-to-stand. • Walking forward, backward, and sideways. • Turning in both directions.	• Does not have the capability to ascend and descend stairs. • Requires improvements in ease of transferring in and out of the device. • Slower speed compared to other exoskeletons that require walking aids like crutches.
Mobile, patient-adapted, robot-assisted gait rehabilitation system (MOPASS)[255]	• Overground walking (walking freely in space), • Body weight support (BWS). • Falls prevention with built-in walker system.	• Time-consuming setup and tight leg shells. • Issues with wearing comfort. • Physically straining for some patients.
G-Exos [256]	• Gait assistance with ankle movements, especially with dorsiflexion, plantarflexion, and ankle stability.	• Designed to assist one limb, which may cause gait compensation for users with conditions affecting both limbs

models have demonstrated the efficacy of ultrasound in SCI research. For instance, studies using rhesus monkeys and rodents have shown that contrast-enhanced ultrasound (CEUS) can visualize spinal cord blood flow (SCBF) and identify perfusion abnormalities following acute SCI [201,202]. Additionally, in rodent models, LIFU has been used to successfully deliver neurotrophic genes, resulting in improved neuronal survival, reduced injury severity, and better motor function [203].

Advances in neuromodulation

Neuromodulation techniques offer promising avenues for SCI treatment. These approaches primarily involve electric stimulation, magnetic field stimulation, and ultrasound stimulation, sometimes in conjunction with brain-computer interfaces (BCIs) to enhance their effectiveness.

Electric stimulation, including functional electrical stimulation (FES), transcutaneous electrical stimulation (TES) and epidural electrical stimulation (EES), has shown significant potential in SCI treatment [204–206]. FES utilizes surface electrical stimuli to activate peripheral nerves, enhancing muscle contractions and improving motor functions in incomplete SCI patients, especially when combined with exercise [204] EES, on the other hand, involves surgically implanted electrodes delivering rhythmic currents to the spinal cord, which has been effective in restoring motor control, improving bladder, bowel, cardiovascular, respiratory, and sexual functions, and alleviating neuropathic pain [206].

Magnetic field stimulation, particularly repetitive transcranial magnetic stimulation (rTMS), which involves non-invasive magnetic pulses that modulate cortical activity, has demonstrated benefits in motor recovery and pain management post-SCI [207,208]. Ultrasound stimulation, particularly LIFU, offers a non-invasive method to modulate neural activity. LIFU can activate spinal neurocircuits, reduce spasticity, and promote axonal regeneration [209]. Integrating neuromodulation techniques with BCIs enables real-time feedback and precise control over the neuromodulatory process, directs brain control of the electrical stimulation, and provides a more targeted and responsive treatment approach, facilitating more precise and volitional movements [210,211].

Recent research has explored selective manipulation of the intraspinal propriospinal network, which maintains inter-segmental communication below the lesion after complete SCI, to restore locomotor function without brain-derived inputs [212,213]. Recent studies have documented injury-triggered KCC2 downregulation contributes to the diminished excitability of the injured spinal cord. Activation of KCC2 either pharmacologically or via gene therapy could restore the excitability levels and improve functional recovery in an incomplete SCI [213].

Exploiting the compromised BSCB post-SCI, AAV9 vectors have been administered via the tail vein to effectively transduce neurons in lesion-adjacent spinal segments in thoracic crush injury mouse models. Chemogenetic actuators were used to modulate propriospinal neuron excitability, leading to significant hindlimb stepping improvements [212]. Furthermore, systemic injection of mutant-AAV9 vectors expressing liver kinase (LK)-B1, promote extensive CST fiber regeneration and enhancing locomotor function [214]. Complementarily, delivery of BDNF mRNA with cationic polymers improved motor recovery in contusive SCI models [215], while retrograde AAV-NT3 (neurotrophin-3) and AAV-DREADD delivery reinforced propriospino-motor neuron circuit reorganization and activation [216,217]. These findings suggest that combining genetic, chemogenetic, and neuromodulation approaches can optimize functional recovery post-SCI.

Advances in neurorehabilitation

Combined neurorehabilitation with neuromodulation and cell-based therapies

The beneficial effects of neurorehabilitation techniques are well documented, but their positive impact often plateaus over time [218]. For sustained recovery of function, combining neurorehabilitation with neuromodulation and cell-based therapies has shown promising results. Neurorehabilitation, when used as alongside eSCS, tSCS, and FES, either before, after, on in combination, has demonstrating clinical efficacy in locomotor and autonomic functions (Fig. 2) [219–229].

Co-transplantation of NPCs, MSCs, OECs, and Schwann cells with neurorehabilitation has shown synergistic effects in preclinical studies. NPCs combined with treadmill training have improved functional recovery and reduce neuropathic pain in rat contusion and clip compression SCI models [230–232]. This effect has been inconsistent with MSC transplantation and exercise training in rats [233,234]. Combinatorial OECs

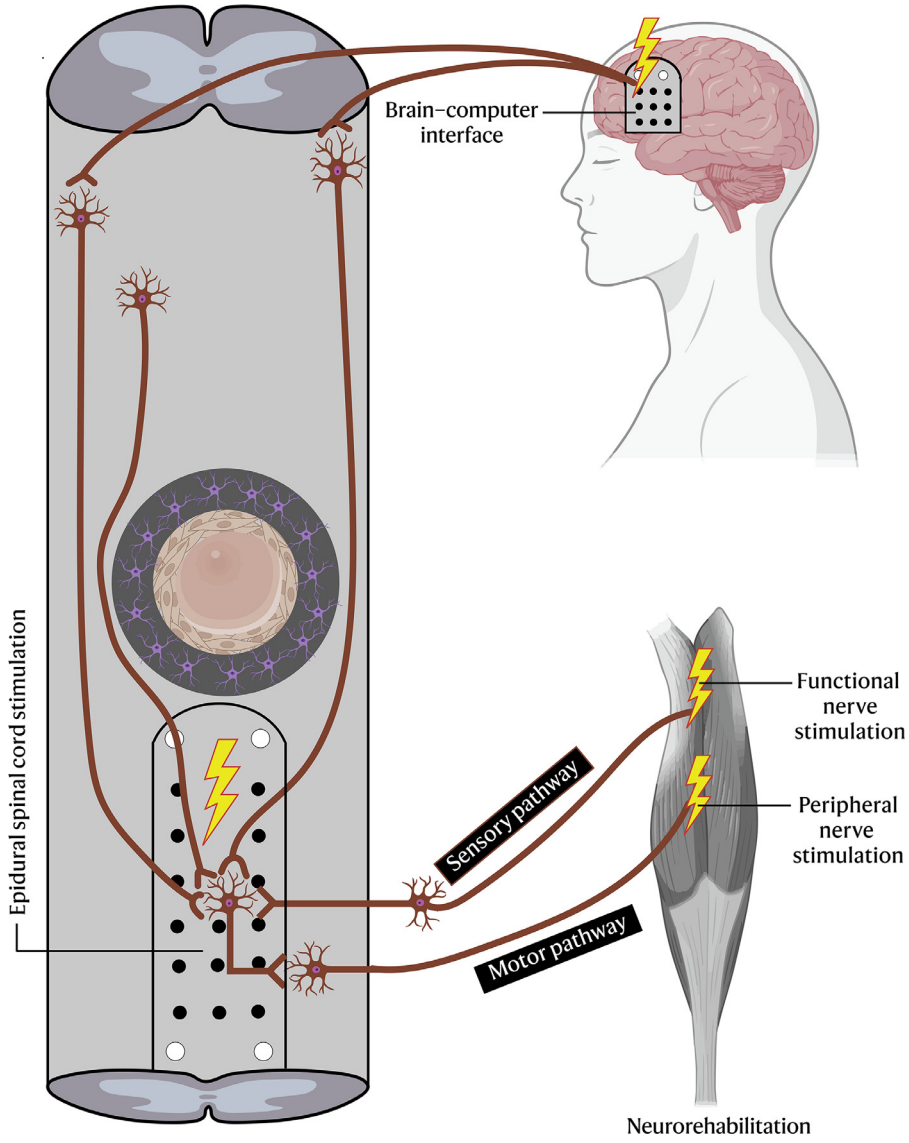

Fig. 2. Combined neuromodulation and neurorehabilitation therapy. Neuromodulation when used with neurorehabilitation post-SCI activates sensorimotor circuits, facilitating immediate and long-term motor function recovery. This multimodal approach reorganizes spared circuits for functional recovery. Integration with BCIs offers precise control and feedback, enhancing volitional movements and adaptive plasticity.

and Schwann cells in rat contusion models with treadmill training has also demonstrated synergistic effects for functional recovery [235].

Advances in assistive technologies

Physical therapy for SCI requires sufficient residual strength, posing limitations for those with varying degrees of SCI in participating in gait and locomotion training. Body weight support devices, either mobile or ceiling-fixed, help by supporting the individual's weight for overground and treadmill walking activities [236].

To further aid functional independence and restoration, external robotic orthoses, or exoskeletons, have been developed (Table 4) [237–256]. Lower extremity exoskeletons improve gait training providing a seamless user interface, better walking kinematics, reduced energy costs, less therapist assistance, improved training efficiency, and high user acceptance [257–260]. They also reduce spasticity and pain, improve bowel function, and improves body composition (eg, reducing fat, increasing muscle mass, and bone mineral density) [252,261,262]. However, they are costly, can restrict daily activities, offer variable user experiences, and show no significant improvement in walking speed over conventional therapy [263–266]. Upper extremity exoskeletons assist with goal-oriented hand movements but face challenges with usability, accessibility, and ergonomic design.

Combining exoskeletons with neuromodulation techniques enhances functional recovery in SCI patients. Robotic-driven gait orthosis assisted-BWSTT with 30-Hz tSCS in 4 complete SCI patients, has demonstrated increase in muscle activation, muscular response, and suppression of clonus [267]. In another study, combining of tSCS with an EKSO technology-assisted overground stepping program enabled a chronically complete SCI patient to achieve coordinated stepping movements and improved autonomic function [253]. Additionally, the potential for BCI-enabled prostheses such as neurally-controlled robotic arms to restore grasp and reach functions in tetraplegic patients has proven to be effective and continues to be a field of exciting research and development [268,269].

Conclusion and perspectives

Traumatic SCI presents significant challenges due to its complex pathophysiology and limited treatment options. Despite advances in acute management, surgical techniques, and rehabilitation, full func-

tional recovery remains inadequate for many patients. The challenges of translating advanced clinical approaches into improved neurological outcomes are reflected by evolving of clinical practice guidelines that provide context-specific validation and updates in the care of patients with SCI. These guidelines are developed using rigorous methodologies, including systematic reviews on best available evidence adhering to AMSTAR 2 and the use of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework [63,270]. Additionally, Guideline Development Groups comprise a diverse group of stakeholder representation, including clinicians involved in the care of patients with SCI, patient advocacy groups, and individuals living with SCI, ensuring comprehensive perspectives [270].

Recent research into secondary injury mechanisms has led to the development of neuroprotective therapies targeting excitotoxicity, inflammation, and mitochondrial dysfunction, though further validation in clinical settings is still needed. Advances in molecular and imaging biomarkers have enhanced the ability to predict outcomes and tailor treatments, contributing to more personalized and effective care.

Neuroregenerative strategies, including neurotrophic factors, stem cell transplantation, and gene therapy have made significant strides, creating a conducive microenvironment for axonal regeneration and functional recovery. Biomaterials, such as nanoparticles and scaffolds, have improved the delivery and efficacy of these regenerative therapies, facilitating better integration and repair at the injury site.

Neuromodulation techniques like electrical and magnetic stimulation have demonstrated substantial potential in restoring motor functions and alleviating complications such as pain and spasticity. However, the effects of these approaches are often limited and variable, requiring research into their functional mechanisms. The integration of these techniques with BCIs offers a promising avenue for enhancing the precision and effectiveness of neuromodulation, enabling more targeted and responsive treatments. Emerging therapies combined with traditional neurorehabilitation approaches, along with assistive technologies like exoskeletons, show synergistic benefits for mobility and independence.

While significant progress has been made in preclinical studies of neuroprotective and neuroregenerative biologics, continuous research and clinical trials are essential to validate and translate these therapies into routine clinical practice. Most current therapies are in early-phase clinical trials, with some, such as riluzole and stem cell transplantation, showing promise for broader adoption within the next decade. Advancements in biomaterials and targeted delivery systems are expected to accelerate this timeline, requiring large-scale, multicenter randomized controlled trials to validate safety and efficacy. Through sustained innovation and collaborative efforts between multidisciplinary teams, we can anticipate the clinical integration of these novel treatments within the next 5–10 years.

Declaration of competing interest

No conflicts of interest.

References

[1] Lee BB, Cripps RA, Fitzharris M, Wing PC. The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate. Spinal Cord 2014;52:110–16.

[2] James SL, Theadom A, Ellenbogenet RG, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:56–87.

[3] Ong B, Wilson JR, Henzel MK. Management of the patient with chronic spinal cord injury. Med Clin North Am 2020;104:263–78.

[4] Ahuja CS, Wilson JR, Nori S. Traumatic spinal cord injury. Nat Rev Dis Primers 2017;3:17018.

[5] Izzy S. Traumatic spinal cord injury. CONTINUUM: Lifelong Learning Neurol 2024;30:53–72.

[6] Ahuja CS, Nori S, Tetreault L, et al. Traumatic spinal cord injury-repair and regeneration. Neurosurgery 2017;80:S9–S22.

[7] Kim HN, McCrea MR, Li S. Advances in molecular therapies for targeting pathophysiology in spinal cord injury. Expert Opin Ther Targets 2023;27:171–87.

[8] Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 1991;75:15–26.

[9] Kumar H, Ropper AE, Lee S-H, Han I. Propitious therapeutic modulators to prevent blood-spinal cord barrier disruption in spinal cord injury. Mol Neurobiol 2017;54:3578–90.

[10] He X, Li Y, Deng,et B, et al. The PI3K/AKT signalling pathway in inflammation, cell death and glial scar formation after traumatic spinal cord injury: mechanisms and therapeutic opportunities. Cell Prolif 2022;55:e13275.

[11] LaPlaca MC, Simon CM, Prado GR, Cullen DK. CNS injury biomechanics and experimental models. Prog Brain Res 2007;161:13–26.

[12] Cristante AF, Filho Barros, de TEP, Marcon RM, Letaif OB, Rocha IDda. Therapeutic approaches for spinal cord injury. Clinics (Sao Paulo) 2012;67:1219–24.

[13] Kjell J, Olson L. Rat models of spinal cord injury: from pathology to potential therapies. Dis Model Mech 2016;9:1125–37.

[14] Trivedi A, Olivas AD, Noble-Haeusslein LJ. Inflammation and spinal cord injury: infiltrating leukocytes as determinants of injury and repair processes. Clin Neurosci Res 2006;6:283–92.

[15] Rowland JW, Hawryluk GWJ, Kwon B, Fehlings MG. Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. Neurosurg Focus 2008;25:E2.

[16] Taylor, E. C., Fitzpatrick, C. E., Thompson, S. E. & Justice, S. B. Acute traumatic spinal cord injury. *Adv Emerg Nurs J* 44, 272–280.

[17] Butt AM, Duncan A, Hornby MF, et al. Cells expressing the NG2 antigen contact nodes of Ranvier in adult CNS white matter. Glia 1999;26:84–91.

[18] Geoffroy CG, Zheng B. Myelin-associated inhibitors in axonal growth after CNS injury. Curr Opin Neurobiol 2014;27:31–8.

[19] Beller JA, Snow DM. Proteoglycans: road signs for neurite outgrowth. Neural Regen Res 2014;9:343–55.

[20] Li S, Stys PK. Mechanisms of ionotropic glutamate receptor-mediated excitotoxicity in isolated spinal cord white matter. J Neurosci 2000;20:1190–8.

[21] Festoff BW, Ameenuddin S, Arnold PM, et al. Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression early after spinal cord injury. J Neurochem 2006;97:1314–26.

[22] Ibarra A, García E, Flores N, et al. Immunization with neural-derived antigens inhibits lipid peroxidation after spinal cord injury. Neurosci Lett 2010;476:62–5.

[23] Liu M, Wu W, L H, et al. Necroptosis, a novel type of programmed cell death, contributes to early neural cells damage after spinal cord injury in adult mice. J Spinal Cord Med 2015;38:745–53.

[24] Sofroniew MV. Dissecting spinal cord regeneration. Nature 2018;557:343–50.

[25] Liddelow SA, Barres BA. Regeneration: not everything is scary about a glial scar. Nature 2016;532:182–3.

[26] Nagoshi N, Khazaei M, Ahlfors J-E, et al. Human spinal oligodendrogenic neural progenitor cells promote functional recovery after spinal cord injury by axonal remyelination and tissue sparing. Stem Cells Transl Med 2018;7:806–18.

[27] Theodore N, Hadley MN, Aarabi B, et al. Prehospital cervical spinal immobilization after trauma. Neurosurgery 2013;72(Suppl 2):22–34.

[28] Kang DG, Lehman RA. Spine immobilization: prehospitalization to final destination. J Surg Orthop Adv 2011;20:2–7.

[29] Kolb JC, Summers RL, Galli RL. Cervical collar-induced changes in intracranial pressure. Am J Emerg Med 1999;17:135–7.

[30] Haut ER, Kalish BT, Efron DT, et al. Spine immobilization in penetrating trauma: more harm than good? J Trauma 2010;68:115–20 discussion 120-1.

[31] Ham W, Schoonhoven L, Schuurmans MJ, Leenen LPH. Pressure ulcers from spinal immobilization in trauma patients: a systematic review. J Trauma Acute Care Surg 2014;76:1131–41.

[32] Resnick DK. Updated guidelines for the management of acute cervical spine and spinal cord injury. Neurosurgery 2013;72(Suppl 2):1.

[33] DeVivo MJ, Go BK, Jackson AB. Overview of the national spinal cord injury statistical center database. J Spinal Cord Med 2002;25:335–8.

[34] Ahn H, Singh J, Nathens A, et al. Pre-hospital care management of a potential spinal cord injured patient: a systematic review of the literature and evidence-based guidelines. J Neurotrauma 2011;28:1341–61.

[35] Walters BC, Hadley MN, Hurlbert RJ, et al. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. Neurosurgery 2013;60:82–91.

[36] ASIA and ISCoS International Standards CommitteeThe 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)-what's new? Spinal Cord 2019;57:815–17.

[37] McDonald JW, Belegu V. Demyelination and remyelination after spinal cord injury. J Neurotrauma 2006;23:345–59.

[38] Tsehay Y, Weber-Levine C, Kim T, et al. Advances in monitoring for acute spinal cord injury: a narrative review of current literature. Spine J 2022;22:1372–87.

[39] Burns AS, Lee BS, Ditunno JF, Tessler A. Patient selection for clinical trials: the reliability of the early spinal cord injury examination. J Neurotrauma 2003;20:477–82.

[40] Yue JK, Winkler EA, Rick JW, et al. Update on critical care for acute spinal cord injury in the setting of polytrauma. Neurosurg Focus 2017;43:E19.

[41] Furlan JC, Fehlings MG, Tator CH, Davis AM. Motor and sensory assessment of patients in clinical trials for pharmacological therapy of acute spinal cord injury: psychometric properties of the ASIA Standards. J Neurotrauma 2008;25:1273–301.

[42] Kirshblum S, Snider B, Rupp R, Read MS. International Standards Committee of ASIA and ISCoS. Updates of the International Standards for Neurologic Classification of Spinal Cord Injury: 2015 and 2019. Phys Med Rehabil Clin N Am 2020;31:319–30.

[43] Jaja BNR, Badhiwala J, Guest J, et al. Trajectory-based classification of recovery in sensorimotor complete traumatic cervical spinal cord injury. Neurology 2021;96:e2736–48.

[44] Badhiwala JH, Wilson JR, Kulkarni AV, et al. A novel method to classify cervical incomplete spinal cord injury based on potential for recovery: a group-based trajectory analysis. J Neurotrauma 2022;39:1654–64.

[45] Hachem LD, Ahuja CS, Fehlings MG. Assessment and management of acute spinal cord injury: from point of injury to rehabilitation. J Spinal Cord Med 2017;40:665–75.

[46] Shank CD, Walters BC, Hadley MN. Current topics in the management of acute traumatic spinal cord injury. Neurocrit Care 2019;30:261–71.

[47] Hadley MN, Walters BC, Aarabi B, et al. Clinical assessment following acute cervical spinal cord injury. Neurosurgery 2013;72(Suppl 2):40–53.

[48] Smith AC, Albin SR, O'Dell DR, et al. Axial MRI biomarkers of spinal cord damage to predict future walking and motor function: a retrospective study. Spinal Cord 2021;59:693–9.

[49] Iaconis Campbell J, Coppola F, Volpe E, Salas Lopez E. Thoracic spinal cord injury without radiologic abnormality in a pediatric patient case report. J Surg Case Rep 2018;2018:rjy250.

[50] Pfyffer D, Smith AC, Weber KA, et al. Prognostic value of tissue bridges in cervical spinal cord injury: a longitudinal, multicentre, retrospective cohort study. Lancet Neurol 2024;23:816–25.

[51] Talbott JF, Whetstone WD, Readdy WJ, et al. The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. J Neurosurg Spine 2015;23:495–504.

[52] Bozzo A, Marcoux J, Radhakrishna M, Pelletier J, Goulet B. The role of magnetic resonance imaging in the management of acute spinal cord injury. J Neurotrauma 2011;28:1401–11.

[53] Freund P, Seif M, Weiskopf N, et al. MRI in traumatic spinal cord injury: from clinical assessment to neuroimaging biomarkers. Lancet Neurol 2019;18:1123–35.

[54] Pfyffer D, Huber E, Sutter R, Curt A, Freund P. Tissue bridges predict recovery after traumatic and ischemic thoracic spinal cord injury. Neurology 2019;93:e1550–60.

[55] Consortium for Spinal Cord MedicineEarly acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2008;31:403–79.

[56] Ahuja CS, Martin AR, Fehlings M. Recent advances in managing a spinal cord injury secondary to trauma. F1000Res 2016;5.

[57] Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. J Neurosurg 1997;87:239–46.

[58] Levi L, Wolf A, Belzberg H. Hemodynamic parameters in patients with acute cervical cord trauma: description, intervention, and prediction of outcome. Neurosurgery 1993;33:1007–16 discussion 1016-7.

[59] Wilson JR, Forgione N, Fehlings MG. Emerging therapies for acute traumatic spinal cord injury. CMAJ 2013;185:485–92.

[60] Weinberg JA, Farber SH, Kalamachi LD, et al. Mean arterial pressure maintenance following spinal cord injury: does meeting the target matter? J Trauma Acute Care Surg 2021;90:97–106.

[61] Hawryluk G, Whetstone W, Saigal R, et al. Mean arterial blood pressure correlates with neurological recovery after Human spinal cord injury: analysis of high frequency physiologic data. J Neurotrauma 2015;32:1958–67.

[62] Ryken TC, Hulbert RJ, Hadley MN, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery 2013;72(Suppl 2):84–92.

[63] Kwon BK, Tetreault LA, Evaniew N, Skelly AC, Fehlings MG. AO Spine/Praxis Clinical Practice Guidelines for the management of acute spinal cord injury: an introduction to a focus issue. Global Spine J 2024;14:5S–9S.

[64] Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. Am Rev Respir Dis 1981;124:41–4.

[65] Berney S, Bragge P, Granger C, Opdam H, Denehy L. The acute respiratory management of cervical spinal cord injury in the first 6 weeks after injury: a systematic review. Spinal Cord 2011;49:17–29.

[66] Arora S, Flower O, Murray NPS, Lee BB. Respiratory care of patients with cervical spinal cord injury: a review. Crit Care Resusc 2012;14:64–73.

[67] ATLS SubcommitteeAmerican College of Surgeons' Committee on Trauma & International ATLS working group. Advanced trauma life support (ATLS®): the ninth edition. J Trauma Acute Care Surg 2013;74:1363–6.

[68] Fehlings MG, Wilson JR, Harrop JS, et al. Efficacy and safety of methylprednisolone sodium succinate in acute spinal cord injury: A systematic review. Global Spine J 2017;7:116S–137S.

[69] Liu Z, Yang Y, He L, et al. High-dose methylprednisolone for acute traumatic spinal cord injury: A meta-analysis. Neurology 2019;93:e841–50.

[70] Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. JAMA 1984;251:45–52.

[71] Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National acute spinal Cord Injury Study. N Engl J Med 1990;322:1405–11.

[72] Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998;89:699–706.

[73] Bracken MB. Steroids for acute spinal cord injury. Cochrane Database Syst Rev 2012;1:CD001046.

[74] Canseco JA, Karamian BA, Bowles DR, et al. Updated review: the steroid controversy for management of spinal cord injury. World Neurosurg 2021;150:1–8.

[75] Fehlings MG, Wilson JR, Tetreault LA, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. Global Spine J 2017;7:203S–211S.

[76] Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery 2013;72(Suppl 2):93–105.

[77] Spitnale MJ, Grabowski G. Classification in brief: subaxial cervical spine injury classification and severity score system. Clin Orthop Relat Res 2020;478:2390–8.

[78] Lee JY, Vaccaro AR, Lim,et MR, et al. Thoracolumbar injury classification and severity score: a new paradigm for the treatment of thoracolumbar spine trauma. J Orthop Sci 2005;10:671–5.

[79] Wang J-Z, Yang M, Meng M, Li Z-H. Clinical characteristics and treatment of spinal cord injury in children and adolescents. Chin J Traumatol 2023;26:8–13.

[80] Perkins PG, Deane RH. Long-term follow-up of six patients with acute spinal injury following dural decompression. Injury 1988;19:397–401.

[81] Phang I, Werndle MC, Saadoun S, et al. Expansion duroplasty improves intraspinal pressure, spinal cord perfusion pressure, and vascular pressure reactivity index in patients with traumatic spinal cord injury: injured spinal cord pressure evaluation study. J Neurotrauma 2015;32:865–74.

[82] Zhu F, Yao S, Ren Z, et al. Early durotomy with duroplasty for severe adult spinal cord injury without radiographic abnormality: a novel concept and method of surgical decompression. Eur Spine J 2019;28:2275–82.

[83] Koyanagi I, Iwasaki Y, Isu T, et al. Myelotomy for acute cervical cord injury, report of four cases. Neurol Med Chir (Tokyo) 1989;29:302–6.

[84] Fox JL, Wener L, Drennan DC, et al. Central spinal cord injury: magnetic resonance imaging confirmation and operative considerations. Neurosurgery 1988;22:340–7.

[85] Quddusi A, Pedro KM, Alvi MA, Hejrati N, Fehlings MG. Early surgical intervention for acute spinal cord injury: time is spine. Acta Neurochir (Wien) 2023;165:2665–74.

[86] Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical timing in acute spinal cord injury study (STASCIS). PLoS One 2012;7:e32037.

[87] Dvorak MF, Noonan VK, Fallah N, et al. The influence of time from injury to surgery on motor recovery and length of hospital stay in acute traumatic spinal cord injury: an observational Canadian cohort study. J Neurotrauma 2015;32:645–54.

[88] Fehlings MG, Tetreault LA, Hachem L, et al. An update of a clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the role and timing of decompressive surgery. Global Spine J 2024;14:174S–186S.

[89] Schneider RC, Cherry G, Pantek H. The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. J Neurosurg 1954;11:546–77.

[90] Ahuja CS, Schroeder GD, Vaccaro AR, Fehlings MG. Spinal cord injury-what are the controversies? J Orthop Trauma 2017;31(Suppl 4):S7–S13.

[91] Anderson KK, Tetreault L, Shamji MF, et al. Optimal timing of surgical decompression for acute traumatic central cord syndrome: a systematic review of the literature. Neurosurgery 2015;77(Suppl 4):S15–32.

[92] OSCIS investigatorsEffect of early vs delayed surgical treatment on motor recovery in incomplete cervical spinal cord injury with preexisting cervical stenosis: A randomized clinical trial. JAMA Netw Open 2021;4:e2133604.

[93] Badhiwala JH, Wilson JR, Harrop JS, et al. Early vs late surgical decompression for central cord syndrome. JAMA Surg 2022;157:1024–32.

[94] Czosnyka M, Hutchinson PJ, Balestreri M, et al. Monitoring and interpretation of intracranial pressure after head injury. Acta Neurochir Suppl 2006;96:114–18.

[95] Werndle MC, Saadoun S, Phang I, et al. Monitoring of spinal cord perfusion pressure in acute spinal cord injury: initial findings of the injured spinal cord pressure evaluation study*. Crit Care Med 2014;42:646–55.

[96] Aucoin VJ, Eagleton MJ, Farber MA, et al. Spinal cord protection practices used during endovascular repair of complex aortic aneurysms by the U.S. Aortic Research Consortium. J Vasc Surg 2021;73:323–30.

[97] Lavadi RS, Johnson BR, Chalif JI, et al. Comparing reactive versus empiric cerebrospinal fluid drainage strategies for spinal perfusion pressure optimization in patients with acute traumatic spinal cord injuries. J Clin Neurosci 2024;127:110757.

[98] Kwon BK, Curt A, Belanger LM, et al. Intrathecal pressure monitoring and cerebrospinal fluid drainage in acute spinal cord injury: a prospective randomized trial. J Neurosurg Spine 2009;10:181–93.

[99] Theodore N, Martirosyan N, Hersh AM, et al. Cerebrospinal fluid drainage in patients with acute spinal cord injury: A multi-center randomized controlled trial. World Neurosurg 2023. doi:10.1016/j.wneu.2023.06.078.

[100] Snyder R, Verla T, Ropper AE. Practical application of recent advances in diagnostic, prognostic, and therapeutic modalities for spinal cord injury. World Neurosurg 2020;136:330–6.

[101] Houle JD, Côté M-P. Axon regeneration and exercise-dependent plasticity after spinal cord injury. Ann N Y Acad Sci 2013;1279:154–63.

[102] Theisen CC, Sachdeva R, Austin S, et al. Exercise and peripheral nerve grafts as a strategy to promote regeneration after acute or chronic spinal cord injury. J Neurotrauma 2017;34:1909–14.

[103] Rejc E, Angeli CA, Atkinson D, Harkema SJ. Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. Sci Rep 2017;7:13476.

[104] Gaspar R, Padula N, Freitas TB, de Oliveira JPJ, Torriani-Pasin C. Physical exercise for individuals with spinal cord injury: systematic review based on the International classification of functioning, disability, and health. J Sport Rehabil 2019;28:505–16.

[105] Müller R, Dietz V. Neuronal function in chronic spinal cord injury: divergence between locomotor and flexion- and H-reflex activity. Clin Neurophysiol 2006;117:1499–507.
[106] Nightingale TE, Rouse PC, Walhin J-P, Thompson D, Bilzon JLJ. Home-based exercise enhances health-related quality of life in persons with spinal cord injury: A randomized controlled trial. Arch Phys Med Rehabil 2018;99:1998–2006 e1.
[107] Lam T, Eng JJ, Wolfe DL, et al. A systematic review of the efficacy of gait rehabilitation strategies for spinal cord injury. Top Spinal Cord Inj Rehabil 2007;13:32–57.
[108] Martin AR, De Leener B, Cohen-Adad J, et al. A novel MRI biomarker of spinal cord white matter injury: T2*-weighted white matter to gray matter signal intensity ratio. AJNR Am J Neuroradiol 2017;38:1266–73.
[109] Talbott JF, Whetstone WD, Readdy WJ, et al. The Brain and Spinal Injury Center score: a novel, simple, and reproducible method for assessing the severity of acute cervical spinal cord injury with axial T2-weighted MRI findings. J Neurosurg Spine 2015;23:495–504.
[110] Martínez-Pérez R, Cepeda S, Paredes I, Alen JF, Lagares A. MRI prognostication factors in the setting of cervical spinal cord injury secondary to trauma. World Neurosurg 2017;101:623–32.
[111] Mummaneni N, Burke JF, DiGiorgio AM, et al. Injury volume extracted from MRI predicts neurologic outcome in acute spinal cord injury: a prospective TRACK-SCI pilot study. J Clin Neurosci 2020;82:231–6.
[112] Fischer T, Stern C, Freund P, Schubert M, Sutter R. Wallerian degeneration in cervical spinal cord tracts is commonly seen in routine T2-weighted MRI after traumatic spinal cord injury and is associated with impairment in a retrospective study. Eur Radiol 2021;31:2923–32.
[113] Wheeler-Kingshott CAM, Hickman SJ, Parker GJM, et al. Investigating cervical spinal cord structure using axial diffusion tensor imaging. Neuroimage 2002;16:93–102.
[114] Loy DN, Kim JH, Xie M, et al. Diffusion tensor imaging predicts hyperacute spinal cord injury severity. J Neurotrauma 2007;24:979–90.
[115] D'souza MM, Choudhary A, Poonia M, Kumar P, Khushu S. Diffusion tensor MR imaging in spinal cord injury. Injury 2017;48:880–4.
[116] Shabani S, Kaushal M, Budde M, Kurpad SN. Correlation of magnetic resonance diffusion tensor imaging parameters with American Spinal Injury Association score for prognostication and long-term outcomes. Neurosurg Focus 2019;46:E2.
[117] Shanmuganathan K, Zhuo J, Chen HH, et al. Diffusion tensor imaging parameter obtained during acute blunt cervical spinal cord injury in predicting long-term outcome. J Neurotrauma 2017;34:2964–71.
[118] Tay B, Hyun JK, Oh S. A machine learning approach for specification of spinal cord injuries using fractional anisotropy values obtained from diffusion tensor images. Comput Math Methods Med 2014;2014:276589.
[119] Martin AR, Aleksanderek I, Cohen-Adad J, et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: a systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. Neuroimage Clin 2016;10:192–238.
[120] Kwon BK, Streijger F, Fallah N, et al. Cerebrospinal fluid biomarkers to stratify injury severity and predict outcome in Human traumatic spinal cord injury. J Neurotrauma 2017;34:567–80.
[121] Dalkilic T, Fallah N, Noonan VK, et al. Predicting injury severity and neurological recovery after acute cervical spinal cord injury: a comparison of cerebrospinal fluid and magnetic resonance imaging biomarkers. J Neurotrauma 2018;35:435–45.
[122] Yokobori S, Zhang Z, Moghieb A, et al. Acute diagnostic biomarkers for spinal cord injury: review of the literature and preliminary research report. World Neurosurg 2015;83:867–78.
[123] Tigchelaar S, Gupta R, Shannon CP, et al. MicroRNA biomarkers in cerebrospinal fluid and serum reflect injury severity in Human acute traumatic spinal cord injury. J Neurotrauma 2019;36:2358–71.
[124] Capirossi R, Piunti B, Fernández M, et al. Early CSF biomarkers and late functional outcomes in spinal cord injury. A pilot study. Int J Mol Sci 2020;21.
[125] Kuhle J, Gaiottino J, Leppert D, et al. Serum neurofilament light chain is a biomarker of human spinal cord injury severity and outcome. J Neurol Neurosurg Psychiatry 2015;86:273–9.
[126] Ahadi R, Khodagholi F, Daneshi A, et al. Diagnostic value of serum levels of GFAP, pNF-H, and NSE compared with clinical findings in severity assessment of Human traumatic spinal cord injury. Spine (Phila Pa 1976) 2015;40:E823–30.
[127] Moghaddam A, Heller R, Daniel V, et al. Exploratory study to suggest the possibility of MMP-8 and MMP-9 serum levels as early markers for remission after traumatic spinal cord injury. Spinal Cord 2017;55:8–15.
[128] Du W, Li H, Sun J, et al. The prognostic value of serum neuron specific enolase (NSE) and S100B level in patients of acute spinal cord injury. Med Sci Monit 2018;24:4510–15.
[129] Singh A, Kumar V, Ali S, Mahdi AA, Srivastava RN. Phosphorylated neurofilament heavy: A potential blood biomarker to evaluate the severity of acute spinal cord injuries in adults. Int J Crit Illn Inj Sci 2017;7:212–17.
[130] Moghaddam A, Sperl A, Heller R, et al. Elevated serum insulin-like growth factor 1 levels in patients with neurological remission after traumatic spinal cord injury. PLoS One 2016;11:e0159764.
[131] Ferbert T, Child C, Graeser V, et al. Tracking spinal cord injury: differences in cytokine expression of IGF-1, TGF- B1, and sCD95l can Be measured in blood samples and correspond to neurological remission in a 12-week follow-up. J Neurotrauma 2017;34:607–14.
[132] Kijima K, Kubota K, Hara M, et al. The acute phase serum zinc concentration is a reliable biomarker for predicting the functional outcome after spinal cord injury. EBioMedicine 2019;41:659–69.
[133] Seelig J, Heller RA, Hackler J, et al. Selenium and copper status - potential signposts for neurological remission after traumatic spinal cord injury. J Trace Elem Med Biol 2020;57:126415.
[134] Davies AL, Hayes KC, Dekaban GA. Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. Arch Phys Med Rehabil 2007;88:1384–93.
[135] Segal JL, Gonzales E, Yousefi S, Jamshidipour L, Brunnemann SR. Circulating levels of IL-2R, ICAM-1, and IL-6 in spinal cord injuries. Arch Phys Med Rehabil 1997;78:44–7.
[136] Lee JHT, Lee JHT, Roy J, et al. Magnesium in a polyethylene glycol formulation provides neuroprotection after unilateral cervical spinal cord injury. Spine (Phila Pa 1976) 2010;35:2041–8.
[137] Muradov JM, Hagg T. Intravenous infusion of magnesium chloride improves epicenter blood flow during the acute stage of contusive spinal cord injury in rats. J Neurotrauma 2013;30:840–52.
[138] Schwartz G, Fehlings MG. Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole. J Neurosurg 2001;94:245–56.
[139] Lima R, Gomes ED, Cibrão JR, et al. Levetiracetam treatment leads to functional recovery after thoracic or cervical injuries of the spinal cord. NPJ Regen Med 2021;6:11.
[140] Fehlings MG, Tator CH, Linden RD. The effect of nimodipine and dextran on axonal function and blood flow following experimental spinal cord injury. J Neurosurg 1989;71:403–16.
[141] Fehlings MG, Moghaddamjou A, Harrop JS, et al. Safety and efficacy of riluzole in acute spinal cord injury study (RISCIS): a multi-center, randomized, placebo-controlled, double-blinded trial. J Neurotrauma 2023;40:1878–88.
[142] Chow DS-L, Nguyen A, Park J, et al. Riluzole in spinal cord injury study (RISCIS)-pharmacokinetic (PK) sub-study: an analysis of pharmacokinetics, pharmacodynamics, and impact on axonal degradation of Riluzole in patients with traumatic cervical spinal cord injury enrolled in the RISCIS phase III randomized controlled trial. J Neurotrauma 2023;40:1889–906.
[143] Zhang Z, Fan Z, Cao Y, et al. Acetyl-L-carnitineameliorates mitochondrial damage and apoptosis following spinal cord injury in rats. Neurosci Lett 2015;604:18–23.
[144] Patel SP, Sullivan PG, Pandya JD, et al. N-acetylcysteine amide preserves mitochondrial bioenergetics and improves functional recovery following spinal trauma. Exp Neurol 2014;257:95–105.
[145] Scholpa NE, Williams H, Wang W, et al. Pharmacological stimulation of mitochondrial biogenesis using the Food and Drug Administration-approved β2-adrenoreceptor agonist formoterol for the treatment of spinal cord injury. J Neurotrauma 2019;36:962–72.
[146] Sullivan PG, Thompson M, Scheff SW. Continuous infusion of cyclosporin A postinjury significantly ameliorates cortical damage following traumatic brain injury. Exp Neurol 2000;161:631–7.
[147] McEwen ML, Sullivan PG, Springer JE. Pretreatment with the cyclosporin derivative, NIM811, improves the function of synaptic mitochondria following spinal cord contusion in rats. J Neurotrauma 2007;24:613–24.
[148] Liu J-M, Yi Z, Liu S-Z, et al. The mitochondrial division inhibitor mdivi-1 attenuates spinal cord ischemia-reperfusion injury both in vitro and in vivo: involvement of BK channels. Brain Res 2015;1619:155–65.
[149] Gasior M, Rogawski MA, Hartman AL. Neuroprotective and disease-modifying effects of the ketogenic diet. Behavioural pharmacology 2006;17:431–9.
[150] Chen D, Zeng W, Fu Y, Gao M, Lv G. Bone marrow mesenchymal stem cells combined with minocycline improve spinal cord injury in a rat model. Int J Clin Exp Pathol 2015;8:11957–69.
[151] Gaudet AD, Mandrekar-Colucci S, Hall JCE, et al. miR-155 deletion in mice overcomes neuron-intrinsic and neuron-extrinsic barriers to spinal cord repair. J Neurosci 2016;36:8516–32.
[152] Levi AD, Green BA, Wang MY, et al. Clinical application of modest hypothermia after spinal cord injury. J Neurotrauma 2009;26:407–15.
[153] Chen H, Peng H, Wang P-C, et al. Role of regulatory T cells in spinal cord injury. Eur J Med Res 2023;28:163.
[154] Hao H-H, Wang L, Guo Z-J, et al. Valproic acid reduces autophagy and promotes functional recovery after spinal cord injury in rats. Neurosci Bull 2013;29:484–92.
[155] Gao S, Zhang Z-M, Shen Z-L, et al. Atorvastatin activates autophagy and promotes neurological function recovery after spinal cord injury. Neural Regen Res 2016;11:977–82.
[156] Liao H-Y, Wang Z-Q, Ran R, et al. Biological functions and therapeutic potential of autophagy in spinal cord injury. Front Cell Dev Biol 2021;9:761273.
[157] Sieck GC, Gransee HM, Zhan W-Z, Mantilla CB. Acute intrathecal BDNF enhances functional recovery after cervical spinal cord injury in rats. J Neurophysiol 2021;125:2158–65.
[158] Xie Y, Song W, Zhao W, et al. Application of the sodium hyaluronate-CNTF scaffolds in repairing adult rat spinal cord injury and facilitating neural network formation. Sci China Life Sci 2018;61:559–68.
[159] Mokalled MH, Patra C, Dickson AL, et al. Injury-induced *ctgfa* directs glial bridging and spinal cord regeneration in zebrafish. Science (1979) 2016;354:630–4.
[160] Rao J-S, Zhao C, Zhang A, et al. NT3-chitosan enables de novo regeneration and functional recovery in monkeys after spinal cord injury. Proc Natl Acad Sci U S A 2018;115:E5595–604.
[161] Khazaei M, Ahuja CS, Nakashima H, et al. GDNF rescues the fate of neural progenitor grafts by attenuating notch signals in the injured spinal cord in rodents. Sci Transl Med 2020;12.
[162] Gao X, Cheng W, Zhang X, et al. Nerve growth factor-Laden anisotropic silk nanofiber hydrogels to regulate neuronal/astroglial differentiation for scarless spinal cord repair. ACS Appl Mater Interfaces 2022;14:3701–15.
[163] Bradbury EJ, Moon LDF, Popat RJ, et al. Chondroitinase ABC promotes functional recovery after spinal cord injury. Nature 2002;416:636–40.

[164] Fry EJ, Chagnon MJ, López-Vales R, Tremblay ML, David S. Corticospinal tract regeneration after spinal cord injury in receptor protein tyrosine phosphatase sigma deficient mice. Glia 2010;58:423–33.
[165] Forgione N, Fehlings MG. Rho-ROCK inhibition in the treatment of spinal cord injury. World Neurosurg 2014;82:e535–9.
[166] Bradbury EJ, Burnside ER. Moving beyond the glial scar for spinal cord repair. Nat Commun 2019;10:3879.
[167] Mothe AJ, Tassew NG, Shabanzadeh AP, et al. RGMa inhibition with human monoclonal antibodies promotes regeneration, plasticity and repair, and attenuates neuropathic pain after spinal cord injury. Sci Rep 2017;7:10529.
[168] Jacobson PB, Goody R, Lawrence M, et al. Elezanumab, a human anti-RGMa monoclonal antibody, promotes neuroprotection, neuroplasticity, and neurorecovery following a thoracic hemicompression spinal cord injury in non-human primates. Neurobiol Dis 2021;155:105385.
[169] Mothe AJ, Jacobson PB, Caprelli M, et al. Delayed administration of elezanumab, a human anti-RGMa neutralizing monoclonal antibody, promotes recovery following cervical spinal cord injury. Neurobiol Dis 2022;172:105812.
[170] Hirata T, Itokazu T, Sasaki A, Sugihara F, Yamashita T. Humanized anti-RGMa antibody treatment promotes repair of blood-spinal cord barrier under autoimmune encephalomyelitis in mice. Front Immunol 2022;13:870126.
[171] Tian T, Zhang S, Yang M. Recent progress and challenges in the treatment of spinal cord injury. Protein Cell 2023;14:635–52.
[172] Jones I, Novikova LN, Wiberg M, Carlsson L, Novikov LN. Human embryonic stem cell–derived neural crest cells promote sprouting and motor recovery following spinal cord injury in adult rats. Cell Transplant 2021;30:096368972098824.
[173] Ceto S, Sekiguchi KJ, Takashima Y, Nimmerjahn A, Tuszynski MH. Neural stem cell grafts form extensive synaptic networks that integrate with host circuits after spinal cord injury. Cell Stem Cell 2020;27:430–40 e5.
[174] Lin W, Shiomoto S, Yamada S, et al. Dendritic spine formation and synapse maturation in transcription factor-induced human iPSC-derived neurons. iScience 2023;26:106285.
[175] Wang S, Jia Y, Cao X, et al. HUCMSCs transplantation combined with ultrashort wave therapy attenuates neuroinflammation in spinal cord injury through NUR77/NF-κb pathway. Life Sci 2021;267:118958.
[176] Fu Q, Liu Y, Liu X, et al. Engrafted peripheral blood-derived mesenchymal stem cells promote locomotive recovery in adult rats after spinal cord injury. Am J Transl Res 2017;9:3950–66.
[177] Li H, Wang C, He T, et al. Mitochondrial transfer from bone marrow mesenchymal stem cells to motor neurons in spinal cord injury rats via gap junction. Theranostics 2019;9:2017–35.
[178] Jeffery ND, Crang AJ, O'Leary MT, Hodge SJ, Blakemore WF. Behavioural consequences of oligodendrocyte progenitor cell transplantation into experimental demyelinating lesions in the rat spinal cord. Eur J Neurosci 1999;11:1508–14.
[179] Goulão M, Ghosh B, Urban MW, et al. Astrocyte progenitor transplantation promotes regeneration of bulbospinal respiratory axons, recovery of diaphragm function, and a reduced macrophage response following cervical spinal cord injury. Glia 2019;67:452–66.
[180] Ursavas S, Darici H, Karaoz E. Olfactory ensheathing cells: unique glial cells promising for treatments of spinal cord injury. J Neurosci Res 2021;99:1579–97.
[181] Gaudet AD, Fonken LK. Glial cells shape pathology and repair after spinal cord injury. Neurotherapeutics 2018;15:554–77.
[182] Rahmanian M, Ghahremani A, Kesharwani P, Oroojalian F, Sahebkar A. Nanomedicine innovations in spinal cord injury management: bridging the gap. Environ Res 2023;235:116563.
[183] Afsartala Z, Hadjighassem M, Shirian S, et al. Advances in management of spinal cord injury using stem cell-derived extracellular vesicles: a review study. Basic Clin Neurosci 2023;14:443–51.
[184] Zhao C, Rao J-S, Duan H, et al. Chronic spinal cord injury repair by NT3-chitosan only occurs after clearance of the lesion scar. Signal Transduct Target Ther 2022;7.
[185] Ashammakhi N, Kim H-J, Ehsanipour A, et al. Regenerative therapies for spinal cord injury. Tissue Eng Part B Rev 2019;25:471–91.
[186] David S, Aguayo AJ. Axonal elongation into peripheral nervous system 'bridges' after central nervous system injury in adult rats. Science 1981;214:931–3.
[187] Richardson PM, McGuinness UM, Aguayo AJ. Axons from CNS neurons regenerate into PNS grafts. Nature 1980;284:264–5.
[188] Tom VJ, Sandrow-Feinberg HR, Miller K, et al. Combining peripheral nerve grafts and chondroitinase promotes functional axonal regeneration in the chronically injured spinal cord. J Neurosci 2009;29:14881–90.
[189] Tom VJ, Sandrow-Feinberg HR, Miller K, et al. Exogenous BDNF enhances the integration of chronically injured axons that regenerate through a peripheral nerve grafted into a chondroitinase-treated spinal cord injury site. Exp Neurol 2013;239:91–100.
[190] van Zyl N, Hill B, Cooper C, Hahn J, Galea MP. Expanding traditional tendon-based techniques with nerve transfers for the restoration of upper limb function in tetraplegia: a prospective case series. Lancet 2019;394:565–75.
[191] Winter CC, He Z, Jacobi A. Axon regeneration: a subcellular extension in multiple dimensions. Cold Spring Harb Perspect Biol 2022;14:1–19.
[192] Park KK, Liu K, Hu Y, et al. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science 2008;322:963–6.
[193] Liu K, Lu Y, Lee JK, et al. PTEN deletion enhances the regenerative ability of adult corticospinal neurons. Nat Neurosci 2010;13:1075–81.
[194] Urban MW, Ghosh B, Block CG, et al. Long-distance axon regeneration promotes recovery of diaphragmatic respiratory function after spinal cord injury. eNeuro 2019;6.
[195] Pan L, Tan B, Tang W, et al. Combining task-based rehabilitative training with PTEN inhibition promotes axon regeneration and upper extremity skilled motor function recovery after cervical spinal cord injury in adult mice. Behavioural brain research 2021;405:113197.
[196] Liu X, Williams PR, He Z. SOCS3: a common target for neuronal protection and axon regeneration after spinal cord injury. Exp Neurol 2015;263:364–7.
[197] Sun F, Park KK, Belin S, et al. Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. Nature 2011;480:372–5.
[198] Belin S, Nawabi H, Wang C, et al. Injury-induced decline of intrinsic regenerative ability revealed by quantitative proteomics. Neuron 2015;86:1000–14.
[199] Jin D, Liu Y, Sun F, et al. Restoration of skilled locomotion by sprouting corticospinal axons induced by co-deletion of PTEN and SOCS3. Nat Commun 2015;6:8074.
[200] Chu P-C, Liu H-L, Lai H-Y, et al. Neuromodulation accompanying focused ultrasound-induced blood-brain barrier opening. Sci Rep 2015;5:15477.
[201] Huang L, Chen K, Chen F-C, et al. Intraoperative contrast-enhanced ultrasonography for microcirculatory evaluation in rhesus monkey with spinal cord injury. Oncotarget 2017;8:40756–64.
[202] Khaing ZZ, Cates LN, DeWees DM, et al. Contrast-enhanced ultrasound to visualize hemodynamic changes after rodent spinal cord injury. J Neurosurg Spine 2018;29:306–13.
[203] Song Z, Ye Y, Zhang Z, et al. Noninvasive, targeted gene therapy for acute spinal cord injury using LIFU-mediated BDNF-loaded cationic nanobubble destruction. Biochem Biophys Res Commun 2018;496:911–20.
[204] Rahimi M, Torkaman G, Ghabaee M, Ghasem-Zadeh A. Advanced weight-bearing mat exercises combined with functional electrical stimulation to improve the ability of wheelchair-dependent people with spinal cord injury to transfer and attain independence in activities of daily living: a randomized controlled trial. Spinal Cord 2020;58:78–85.
[205] Benavides FD, Jo HJ, Lundell H, et al. Cortical and subcortical effects of transcutaneous spinal cord stimulation in humans with tetraplegia. J Neurosci 2020;40:2633–43.
[206] Chalif JI, Chavarro VS, Mensah E, et al. Epidural spinal cord stimulation for spinal cord injury in humans: a systematic review. J Clin Med 2024;13.
[207] Zhao C-G, Sun W, Ju F, et al. Analgesic effects of directed repetitive transcranial magnetic stimulation in acute neuropathic pain after spinal cord injury. Pain Med 2020;21:1216–23.
[208] Krogh S, Aagaard P, Jønsson AB, Figlewski K, Kasch H. Effects of repetitive transcranial magnetic stimulation on recovery in lower limb muscle strength and gait function following spinal cord injury: a randomized controlled trial. Spinal Cord 2022;60:135–41.
[209] Liao Y-H, Chen M-X, Chen S-C, et al. Low-intensity focused ultrasound alleviates spasticity and increases expression of the neuronal K-Cl cotransporter in the L4-L5 sections of rats following spinal cord injury. Front Cell Neurosci 2022;16:882127.
[210] Osuagwu BCA, Wallace L, Fraser M, Vuckovic A. Rehabilitation of hand in subacute tetraplegic patients based on brain computer interface and functional electrical stimulation: a randomised pilot study. J Neural Eng 2016;13:065002.
[211] Ajiboye AB, Willett FR, Young DR, et al. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. Lancet 2017;389:1821–30.
[212] Brommer B, He M, Zhang Z, et al. Improving hindlimb locomotor function by non-invasive AAV-mediated manipulations of propriospinal neurons in mice with complete spinal cord injury. Nat Commun 2021;12:781.
[213] Chen B, Yu B, Zhang Z, et al. Reactivation of dormant relay pathways in injured spinal cord by KCC2 manipulations. Cell 2018;174:1599.
[214] Ohtake Y, Sami A, Jiang X, et al. Promoting axon regeneration in adult CNS by targeting liver kinase B1. Mol Ther 2019;27:102–17.
[215] Crowley ST, Fukushima Y, Uchida S, Kataoka K, Itaka K. Enhancement of motor function recovery after spinal cord injury in mice by delivery of brain-derived neurotrophic factor mRNA. Mol Ther Nucleic Acids 2019;17:465–76.
[216] Han Q, Ordaz JD, Liu N-K, et al. Descending motor circuitry required for NT-3 mediated locomotor recovery after spinal cord injury in mice. Nat Commun 2019;10:5815.
[217] Gao Z, Yang Y, Feng Z, et al. Chemogenetic stimulation of proprioceptors remodels lumbar interneuron excitability and promotes motor recovery after SCI. Mol Ther 2021;29:2483–98.
[218] Truchon C, Fallah N, Santos A, et al. Impact of therapy on recovery during rehabilitation in patients with traumatic spinal cord injury. J Neurotrauma 2017;34:2901–9.
[219] 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 2019;36:1451–60.
[220] Cheng R, Sui Y, Sayenko D, Burdick JW. Motor control after Human SCI through activation of muscle synergies under spinal cord stimulation. IEEE Trans Neural Syst Rehabil Eng 2019;27:1331–40.
[221] Boakye M, Ball T, Dietz N, et al. Spinal cord epidural stimulation for motor and autonomic function recovery after chronic spinal cord injury: a case series and technical note. Surg Neurol Int 2023;14:87.
[222] Rowald A, Komi S, Demesmaeker R, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Med 2022;28:260–71.
[223] Linde MB, Thoreson AR, Lopez C, et al. Quantitative assessment of clinician assistance during dynamic rehabilitation using force sensitive resistors. Front Rehabil Sci 2021;2:757828.
[224] Kandhari S, Sharma D, Samuel S, et al. Epidural spinal stimulation enables global sensorimotor and autonomic function recovery after complete paralysis: 1st study from India. IEEE Trans Neural Syst Rehabil Eng 2022;30:2052–9.

[225] Hofstoetter US, Krenn M, Danner SM, et al. Augmentation of voluntary locomotor activity by transcutaneous spinal cord stimulation in motor-incomplete spinal cord-injured individuals. Artif Organs 2015;39:E176–86.
[226] Gad P, Lee S, Terrafranca N, et al. Non-invasive activation of cervical spinal networks after severe paralysis. J Neurotrauma 2018;35:2145–58.
[227] Sayenko DG, Rath M, Ferguson AR, et al. Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. J Neurotrauma 2019;36:1435–50.
[228] Estes S, Zarkou A, Hope JM, Suri C, Field-Fote EC. Combined transcutaneous spinal stimulation and locomotor training to improve walking function and reduce spasticity in subacute spinal cord injury: a randomized study of clinical feasibility and efficacy. J Clin Med 2021;10.
[229] Wiesener C, Spieker L, Axelgaard J, et al. Supporting front crawl swimming in paraplegics using electrical stimulation: a feasibility study. J Neuroeng Rehabil 2020;17:51.
[230] Hwang DH, Shin HY, Kwon MJ, et al. Survival of neural stem cell grafts in the lesioned spinal cord is enhanced by a combination of treadmill locomotor training via insulin-like growth factor-1 signaling. J Neurosci 2014;34:12788–800.
[231] Dugan EA, Jergova S, Sagen J. Mutually beneficial effects of intensive exercise and GABAergic neural progenitor cell transplants in reducing neuropathic pain and spinal pathology in rats with spinal cord injury. Exp Neurol 2020;327:113208.
[232] Younsi A, Zheng G, Scherer M, et al. Treadmill training improves survival and differentiation of transplanted neural precursor cells after cervical spinal cord injury. Stem Cell Res 2020;45:101812.
[233] Yoshihara H, Shumsky JS, Neuhuber B, et al. Combining motor training with transplantation of rat bone marrow stromal cells does not improve repair or recovery in rats with thoracic contusion injuries. Brain Res 2006;1119:65–75.
[234] Carvalho KAT, Cunha RC, Vialle EN, et al. Functional outcome of bone marrow stem cells (CD45(+)/CD34(-)) after cell therapy in acute spinal cord injury: in exercise training and in sedentary rats. Transplant Proc 2008;40:847–9.
[235] Sun T, Ye C, Zhang Z, Wu J, Huang H. Cotransplantation of olfactory ensheathing cells and Schwann cells combined with treadmill training promotes functional recovery in rats with contused spinal cords. Cell Transplant 2013;22(Suppl 1):S27–38.
[236] Field-Fote EC. Therapeutic interventions to improve mobility with spinal cord injury related upper motor neuron syndromes. Phys Med Rehabil Clin N Am 2020;31:437–53.
[237] Jardón A, Gil ÁM, de la Peña AI, Monje CA, Balaguer C. Usability assessment of ASIBOT: a portable robot to aid patients with spinal cord injury. Disabil Rehabil Assist Technol 2011;6:320–30.
[238] Zariffa J, Kapadia N, Kramer JLK, et al. Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population. Spinal Cord 2012;50:220–6.
[239] Coignard P, Departe JP, Neris OR, et al. ANSO study: evaluation in an indoor environment of a mobile assistance robotic grasping arm. Ann Phys Rehabil Med 2013;56:621–33.
[240] Pehlivan A, Sergi F, Erwin A, Yozbatiran N. Design and validation of the RiceWrist-S exoskeleton for robotic rehabilitation after incomplete spinal cord injury. Rehabil Robot Human-Robot Interaction 2014;32:1415–31.
[241] Vanmulken DAMM, Spooren AIF, Bongers HMH, Seelen HAM. Robot-assisted task-oriented upper extremity skill training in cervical spinal cord injury: a feasibility study. Spinal Cord 2015;53:547–51.
[242] Almenara M, Cempini M, Gómez C, et al. Usability test of a hand exoskeleton for activities of daily living: an example of user-centered design. Disabil Rehabil Assist Technol 2017;12:84–96.
[243] Jackowski A, Gebhard M, Thietje R. Head motion and head gesture-based robot control: a usability study. IEEE Trans Neural Syst Rehabil Eng 2018;26:161–70.
[244] Yurkewich A, Hebert D, Wang RH, Mihailidis A. Hand extension robot orthosis (HERO) glove: development and testing with stroke survivors with severe Hand impairment. IEEE Trans Neural Syst Rehabil Eng 2019;27:916–26.
[245] Osuagwu BAC, Timms S, Peachment R, et al. Home-based rehabilitation using a soft robotic hand glove device leads to improvement in hand function in people with chronic spinal cord injury:a pilot study. J Neuroeng Rehabil 2020;17:40.
[246] Bützer T, Lambercy O, Arata J, Gassert R. Fully wearable actuated soft exoskeleton for grasping assistance in everyday activities. Soft Robot 2021;8:128–43.
[247] Tran P, Elliott D, Herrin K, Bhatia S, Desai JP. Evaluation of the FLEXotendon glove-III through a human subject case study. Biomed Eng Lett 2023;13:153–63.
[248] Zeilig G, Weingarden H, Zwecker M, et al. Safety and tolerance of the ReWalk™ exoskeleton suit for ambulation by people with complete spinal cord injury: a pilot study. J Spinal Cord Med 2012;35:96–101.
[249] Aach M, Cruciger O, Sczesny-Kaiser M, et al. Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord injury: a pilot study. Spine J 2014;14:2847–53.
[250] Lam T, Pauhl K, Ferguson A, et al. Training with robot-applied resistance in people with motor-incomplete spinal cord injury: pilot study. J Rehabil Res Dev 2015;52:113–29.
[251] Hartigan C, Kandilakis C, Dalley S, et al. Mobility outcomes following five training sessions with a powered exoskeleton. Top Spinal Cord Inj Rehabil 2015;21:93–9.
[252] Stampacchia G, Rustici A, Bigazzi S, et al. Walking with a powered robotic exoskeleton: subjective experience, spasticity and pain in spinal cord injured persons. NeuroRehabilitation 2016;39:277–83.
[253] Gad P, Gerasimenko Y, Zdunowski S, et al. Weight bearing over-ground stepping in an exoskeleton with non-invasive spinal cord neuromodulation after motor complete paraplegia. Front Neurosci 2017;11:333.
[254] Birch N, Graham J, Priestley T, et al. Results of the first interim analysis of the RAPPER II trial in patients with spinal cord injury: ambulation and functional exercise programs in the REX powered walking aid. J Neuroeng Rehabil 2017;14:60.
[255] Eicher C, Haesner M, Spranger M, et al. Usability and acceptability by a younger and older user group regarding a mobile robot-supported gait rehabilitation system. Assist Technol 2019;31:25–33.
[256] Zorkot M, Dac LH, Morya E, Brasil FL. G-Exos: a wearable gait exoskeleton for walk assistance. Front Neurorobot 2022;16:939241.
[257] Veale AJ, Xie SQ. Towards compliant and wearable robotic orthoses: a review of current and emerging actuator technologies. Med Eng Phys 2016;38:317–25.
[258] Gagnon DH, Vermette M, Duclos C, et al. Satisfaction and perceptions of long-term manual wheelchair users with a spinal cord injury upon completion of a locomotor training program with an overground robotic exoskeleton. Disabil Rehabil Assist Technol 2019;14:138–45.
[259] Gagnon DH, Escalona MJ, Vermette M, et al. Locomotor training using an overground robotic exoskeleton in long-term manual wheelchair users with a chronic spinal cord injury living in the community: lessons learned from a feasibility study in terms of recruitment, attendance, learnability, performance and safety. J Neuroeng Rehabil 2018;15:12.
[260] Quinlivan BT, Lee S, Malcolm P, et al. Assistance magnitude versus metabolic cost reductions for a tethered multiarticular soft exosuit. Sci Robot 2017;2.
[261] Miller LE, Zimmermann AK, Herbert WG. Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: systematic review with meta-analysis. Med Devices (Auckl) 2016;9:455–66.
[262] Karelis AD, Carvalho LP, Castillo MJ, Gagnon DH, Aubertin-Leheudre M. Effect on body composition and bone mineral density of walking with a robotic exoskeleton in adults with chronic spinal cord injury. J Rehabil Med 2017;49:84–7.
[263] Fisahn C, Aach M, Jansen O, et al. The effectiveness and safety of exoskeletons as assistive and rehabilitation devices in the treatment of neurologic gait disorders in patients with spinal cord injury: a systematic review. Global Spine J 2016;6:822–41.
[264] Aguirre-Güemez AV, Pérez-Sanpablo AI, Quinzaños-Fresnedo J, Pérez-Zavala R, Barrera-Ortiz A. Walking speed is not the best outcome to evaluate the effect of robotic assisted gait training in people with motor incomplete spinal cord injury: a systematic review with meta-analysis. J Spinal Cord Med 2019;42:142–54.
[265] Kressler J, Wymer T, Domingo A. Respiratory, cardiovascular and metabolic responses during different modes of overground bionic ambulation in persons with motor-incomplete spinal cord injury: a case series. J Rehabil Med 2018;50:173–80.
[266] Heinemann AW, Jayaraman A, Mummidisetty CK, et al. Experience of robotic exoskeleton use at four spinal cord injury model systems centers. J Neurol Phys Ther 2018;42:256–67.
[267] Minassian K, Hofstoetter US, Danner SM, et al. Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. Neurorehabil Neural Repair 2016;30:233–43.
[268] Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature 2012;485:372–5.
[269] Flesher SN, Downey JE, Weiss JM, et al. A brain-computer interface that evokes tactile sensations improves robotic arm control. Science 2021;372:831–6.
[270] Tetreault LA, Skelly AC, Alvi MA, et al. An overview of the methodology used to develop clinical practice guidelines for the management of acute and intraoperative spinal cord injury. Global Spine J 2024;14:25S–37S.