JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/nwkemy57

Original Article

Cerebrospinal Fluid Neurofilament Light Chain Levels as an Early Marker of Secondary Injury After Acute Spinal Cord Trauma

Irfan Adil[1], Sana Iqbal[2], Muhammad Zain Ul Islam[3], Aliza Kanwal[4], Shaikh Khalid Muhammad[5], Umar Aslam Shah[6]

[1] Department of Neurosurgery, Bolan Medical College, Quetta, Pakistan
[2] PNS Shifa Hospital, Karachi, Pakistan
[3] Punjab Institute of Neurosciences, Lahore, Pakistan
[4] Pakistan Institute of Medical Sciences, Islamabad, Pakistan
[5] CMC Teaching Hospital, SMBBMU, Larkana, Pakistan
[6] Fauji Foundation Hospital, Rawalpindi, Pakistan

*** Corresponding author: Irfan Adil, doctorirfan777@gmail.com**

ABSTRACT

Background: Traumatic spinal cord injury is a major cause of long-term neurological disability worldwide. Early identification of injury severity and prediction of neurological deterioration remain challenging during the acute phase of trauma. Neurofilament light chain (NfL), a structural protein released during axonal injury, has emerged as a potential biomarker reflecting neuronal damage in various neurological disorders. Objective: To evaluate cerebrospinal fluid neurofilament light chain levels in patients with acute spinal cord trauma and examine their association with neurological severity, radiological injury characteristics, and early neurological deterioration. Methods: This prospective observational study included 60 adult patients presenting within 24 hours of acute traumatic spinal cord injury at a tertiary care hospital. Neurological status was assessed using the American Spinal Injury Association (ASIA) impairment scale, and radiological severity was evaluated using magnetic resonance imaging. Cerebrospinal fluid samples were obtained via lumbar puncture and analyzed for NfL concentration using enzyme-linked immunosorbent assay. Patients were monitored for early neurological deterioration during the first 72 hours. Statistical analysis was performed using SPSS version 26. Results: Mean CSF NfL concentration was 4120 ± 1850 pg/mL. Higher NfL levels were observed in patients with severe neurological impairment, with mean concentrations increasing from 1800 pg/mL in ASIA grade D to 6200 pg/mL in ASIA grade A ($p < 0.001$). Radiological injury severity also correlated with biomarker levels, increasing from 2100 pg/mL in mild MRI injury to 6100 pg/mL in severe injury ($p < 0.001$). Patients with early neurological deterioration had significantly higher NfL concentrations compared with stable patients (5800 vs 2900 pg/mL, $p < 0.001$). Conclusion: Cerebrospinal fluid neurofilament light chain levels are strongly associated with neurological severity, radiological injury characteristics, and early neurological deterioration in acute spinal cord trauma. These findings support the potential role of NfL as an early biomarker of axonal injury and secondary spinal cord damage. Keywords: spinal cord injury; neurofilament light chain; cerebrospinal fluid biomarkers; axonal injury; neurological deterioration; trauma research.

"Cite this Article" | Received: 18 October 2025; Accepted: 23 February 2026; Published: 12 March 2026.

Author Contributions: Concept: IA; Design: SI; Data Collection: MZUI, AK; Analysis: SKM; Drafting: UAS. **Ethical Approval**: Ethical Approval was obtained by respective Institute. Informed Consent: Written informed consent was obtained from all participants; Conflict of Interest: The authors declare no conflict of interest; Funding: No external funding; Data Availability: Available from the corresponding author on reasonable request; Acknowledgments: N/A.

INTRODUCTION

Traumatic spinal cord injury (SCI) is a severe neurological condition associated with substantial morbidity, long-term disability, and socioeconomic burden. Globally, the incidence of SCI is estimated to range between approximately 10 and 80 cases per million people annually, with the highest rates occurring among young adults involved in high-energy trauma such as road traffic accidents and falls from height. These injuries frequently affect individuals during their most productive years, resulting in permanent neurological deficits, reduced independence, and significant economic consequences for patients, families, and healthcare systems. Despite advances in surgical techniques, intensive care management, and rehabilitation strategies, the neurological recovery of patients with severe spinal cord

ISSN 3007-0570 | © 2026 The Authors | CC BY 4.0

injury remains limited, largely because the initial mechanical damage is followed by complex biological processes that further exacerbate neural tissue destruction (1).

The pathophysiology of spinal cord injury involves two major phases: primary injury and secondary injury. The primary injury occurs at the moment of trauma and involves direct mechanical damage to neural tissue, including axonal disruption, vascular injury, and cellular membrane destruction. However, a considerable portion of neurological deterioration occurs during the secondary injury phase, which unfolds over hours to days following the initial trauma. Secondary injury is characterized by a cascade of pathological processes such as inflammation, ischemia, oxidative stress, excitotoxicity, disruption of the blood–spinal cord barrier, and apoptosis. These processes contribute to progressive axonal degeneration and expansion of the lesion site, ultimately worsening neurological outcomes. Because secondary injury evolves over time, early identification of ongoing neuronal damage is considered a critical opportunity for therapeutic intervention aimed at limiting irreversible neurological loss (2).

Clinical evaluation of spinal cord injury severity traditionally relies on neurological examination and imaging studies. The International Standards for Neurological Classification of Spinal Cord Injury developed by the American Spinal Injury Association (ASIA) is the most widely used clinical tool for assessing motor and sensory deficits and classifying injury severity. This scale categorizes patients into grades ranging from complete injury (ASIA A) to normal neurological function (ASIA E). Although the ASIA scale provides a standardized framework for neurological assessment, it has limitations in the acute trauma setting. Early neurological examination can be challenging due to factors such as sedation, associated injuries, altered consciousness, or patient instability. Moreover, early clinical assessment may not always accurately reflect the underlying extent of axonal damage or predict subsequent neurological deterioration (3).

Magnetic resonance imaging (MRI) has become the primary imaging modality for evaluating spinal cord injury because it allows visualization of cord edema, hemorrhage, compression, and structural disruption. Radiological findings such as lesion length, hemorrhagic components, and degree of spinal cord compression have been associated with injury severity and neurological outcome. However, imaging primarily reflects structural changes and may not fully capture ongoing molecular and cellular processes occurring during secondary injury. As a result, there has been increasing interest in identifying biological markers that can objectively reflect neuronal damage and provide additional prognostic information beyond clinical examination and imaging (4).

In recent years, several biochemical markers have been investigated in patients with spinal cord injury. These include neuron-specific enolase (NSE), S100B protein, glial fibrillary acidic protein (GFAP), and phosphorylated neurofilament heavy chain (pNF-H). These proteins are released into cerebrospinal fluid (CSF) or blood following neuronal or glial cell damage and have been studied as potential indicators of injury severity and prognosis. Although some of these markers have demonstrated associations with neurological outcome, their diagnostic accuracy and clinical applicability remain inconsistent across studies, and no single biomarker has yet been established as a reliable indicator of early secondary spinal cord injury (5).

Neurofilament light chain (NfL) has emerged as one of the most promising biomarkers of axonal injury in neurological diseases. Neurofilaments are structural proteins that form a major component of the neuronal cytoskeleton, particularly within axons where they maintain structural integrity and contribute to axonal transport and signal conduction. When axons are damaged due to trauma or neurodegeneration, neurofilament proteins are released into extracellular spaces and subsequently enter the cerebrospinal fluid and bloodstream. Elevated concentrations of NfL therefore reflect axonal damage and neuronal degeneration. Advances in laboratory techniques such as enzyme-linked immunosorbent assay (ELISA) and highly sensitive single-molecule array (SIMOA) assays have enabled accurate detection of neurofilament levels in biological fluids, further expanding their potential role as biomarkers in neurological research (12).

Growing evidence indicates that neurofilament light chain levels increase significantly in various neurological disorders characterized by axonal injury, including multiple sclerosis, traumatic brain injury, Alzheimer's disease, and other neurodegenerative conditions. In these contexts, elevated NfL concentrations have been shown to correlate with disease severity, progression, and neurological outcomes. Because of its strong association with axonal damage, NfL has been proposed as a sensitive and relatively specific biomarker of neuronal injury across multiple neurological conditions (13,14).

Within the field of spinal cord injury, emerging studies suggest that NfL may provide valuable information regarding injury severity and prognosis. Investigations measuring neurofilament levels in cerebrospinal fluid during the acute phase of spinal trauma have demonstrated significantly higher concentrations in patients with severe neurological impairment compared with those with milder injuries. In addition, elevated NfL levels have been associated with larger lesion size and structural damage observed on MRI. These findings suggest that neurofilament light chain may reflect the degree of axonal disruption occurring after traumatic spinal cord injury and may potentially serve as a biomarker for monitoring neuronal damage during the early post-traumatic period (2,11).

Another potential clinical application of neurofilament light chain is the detection of ongoing secondary injury processes. During the early phase after trauma, progressive axonal degeneration may continue to release neurofilament proteins into the cerebrospinal fluid. Measurement of NfL levels during this acute period may therefore provide insight into the extent of ongoing neuronal damage and the risk of early neurological deterioration. Identifying patients at higher risk of deterioration could have important clinical implications, including closer monitoring, earlier therapeutic interventions, and improved prognostic counseling (15).

Despite these promising findings, the clinical application of neurofilament light chain as a biomarker in spinal cord injury remains under investigation. Many existing studies have been conducted in high-income healthcare settings and often involve relatively small patient cohorts or heterogeneous injury populations. Furthermore, there is limited evidence from low- and middle-income countries, where patterns of trauma, healthcare resources, and diagnostic infrastructure may differ substantially. In countries such as Pakistan, spinal cord injuries frequently result from road traffic accidents and falls, particularly in rural and underserved regions. Limited access to advanced diagnostic tools and specialized neurotrauma care may hinder early prognostic assessment in these settings. Consequently, identifying reliable and accessible biomarkers that can complement clinical and radiological evaluation may improve early risk stratification and management of patients with spinal cord injury in resource-limited environments (10).

Given these considerations, further clinical studies are needed to evaluate the relationship between neurofilament light chain levels and injury severity, radiological findings, and early neurological outcomes in patients with acute spinal cord trauma. Understanding whether CSF NfL concentrations reflect the extent of axonal damage and are associated with early neurological deterioration could provide valuable insight into the biological processes underlying secondary spinal cord injury and may contribute to improved prognostic assessment.

Therefore, the present prospective clinical study was conducted to investigate cerebrospinal fluid neurofilament light chain levels in patients presenting with acute traumatic spinal cord injury within 24 hours of trauma. Specifically, the study aimed to evaluate the association between CSF NfL concentrations and neurological severity assessed by the ASIA impairment scale, radiological injury characteristics identified on magnetic resonance imaging, and the occurrence of early neurological deterioration during the first 72 hours after injury. We hypothesized that higher CSF neurofilament light chain levels measured in the acute phase of spinal cord trauma would be associated with greater neurological impairment, more severe radiological damage, and an increased risk of early neurological deterioration.

METHODS

This prospective biomarker-based observational study was conducted to evaluate the relationship between cerebrospinal fluid neurofilament light chain (NfL) concentrations and early clinical and radiological indicators of injury severity in patients with acute traumatic spinal cord injury. The prospective design was selected to allow standardized measurement of biomarkers within the acute post-trauma period and to permit short-term follow-up for early neurological deterioration. The study was performed at a tertiary care referral hospital in Balochistan, Pakistan, which serves as a major regional center for neurotrauma management and receives patients from both urban and rural districts. The study period extended from January 2023 to June 2024. During this period, all patients presenting to the emergency department with suspected spinal cord trauma were screened for eligibility.

Participants were selected using a consecutive sampling strategy to minimize selection bias. Adult patients aged between 18 and 65 years who presented within 24 hours of acute traumatic spinal cord injury and had radiological evidence of spinal cord involvement on computed tomography or magnetic resonance imaging were considered eligible. Both male and female patients were included. Patients were excluded if they had a prior history of spinal cord injury, pre-existing neurodegenerative disease, central nervous system infection, chronic neurological disorders such as multiple sclerosis, severe traumatic brain injury that could interfere with neurological assessment, or current use of immunosuppressive therapy. These exclusion criteria were implemented to reduce confounding factors that could independently influence neurofilament concentrations in cerebrospinal fluid. Eligibility screening was performed by the neurosurgical team at the time of admission.

Eligible patients or their legally authorized representatives were approached for study participation after stabilization in the emergency department. The study purpose, procedures, potential risks, and confidentiality safeguards were explained in detail. Written informed consent was obtained prior to enrollment. After consent, baseline demographic and clinical information including age, sex, mechanism of injury, and time from trauma to hospital presentation were recorded using a standardized data collection form. Neurological status was assessed by trained neurosurgery residents using the International Standards for Neurological Classification of Spinal Cord Injury developed by the American Spinal Injury Association. The ASIA impairment scale categorizes neurological function from grade A (complete injury) to grade E (normal neurological function) based on standardized motor and sensory examination (8). Baseline neurological assessment was performed immediately after enrollment and repeated during the first 72 hours following injury to detect early neurological deterioration. Early neurological deterioration was operationally defined as a decline in ASIA impairment grade or a measurable reduction in motor or sensory scores compared with the initial examination during the 72-hour observation period.

Radiological evaluation of spinal cord injury was performed as part of routine clinical management. All participants underwent computed tomography scanning to identify vertebral fractures or dislocations and magnetic resonance imaging of the affected spinal region to assess the extent of spinal cord damage. MRI findings were evaluated by an experienced radiologist who was blinded to biomarker measurements. Injury severity was categorized according to radiological characteristics including the presence of cord edema, hemorrhage, degree of spinal canal compromise, and extent of cord compression. Radiological injury patterns were grouped into mild, moderate, and severe categories based on the extent of structural damage observed on MRI. These imaging variables were recorded for subsequent correlation with biomarker levels and clinical outcomes.

Cerebrospinal fluid samples were collected within 24 hours of injury using a standardized lumbar puncture procedure performed under sterile conditions by experienced physicians. Approximately 3 to 5 mL of CSF was obtained from each participant and immediately transferred to sterile polypropylene tubes. Samples were transported to the hospital laboratory on ice and centrifuged at 2000 rpm for 10

minutes to remove cellular components. The resulting supernatant was aliquoted and stored at −80°C until analysis to prevent protein degradation. All samples were processed using identical protocols to ensure consistency. Laboratory personnel responsible for biomarker measurement were blinded to patients' clinical and radiological information in order to minimize measurement bias.

The concentration of neurofilament light chain in cerebrospinal fluid was measured using a commercially available enzyme-linked immunosorbent assay. Each sample was analyzed in duplicate according to the manufacturer's instructions, and the mean value of duplicate measurements was used for statistical analysis. ELISA-based detection of NfL has been widely used in neurotrauma research and has demonstrated reliable sensitivity and specificity for identifying axonal injury (22). Laboratory procedures were conducted in a controlled environment to ensure analytical reproducibility. Calibration standards and quality-control samples were included in each assay batch to monitor assay performance and reduce analytical variability.

The primary study variable was the concentration of cerebrospinal fluid neurofilament light chain measured within 24 hours of injury. Secondary variables included neurological injury severity based on the ASIA impairment scale, radiological severity of spinal cord damage observed on MRI, and the occurrence of early neurological deterioration within 72 hours of admission. Additional variables such as age, sex, mechanism of injury, and time from trauma to sampling were recorded to allow assessment of potential confounding factors. Standardized clinical examination protocols and blinded laboratory measurements were used to minimize information bias. Consecutive patient recruitment and predefined eligibility criteria were implemented to reduce selection bias.

The target sample size was determined based on previous biomarker studies in spinal cord injury that demonstrated meaningful associations between cerebrospinal fluid biomarkers and injury severity with sample sizes ranging from 40 to 80 participants (3). Considering the expected incidence of eligible patients during the study period and the feasibility of performing early CSF sampling, a total of 60 participants were enrolled. This sample size was considered sufficient to detect clinically relevant differences in biomarker levels across neurological severity groups while maintaining feasibility within the single-center setting.

All collected data were entered into a secure electronic database and analyzed using the Statistical Package for Social Sciences (SPSS) software, version 26. Continuous variables were summarized as mean values with standard deviation, whereas categorical variables were presented as frequencies and percentages. Normality of distribution for continuous variables was assessed using the Shapiro–Wilk test. Differences in neurofilament light chain concentrations across ASIA severity categories and MRI injury groups were evaluated using analysis of variance or independent sample t-tests where appropriate. Correlation analysis was performed to assess the relationship between biomarker levels and neurological severity scores. Logistic regression analysis was used to evaluate the association between elevated NfL concentrations and early neurological deterioration while adjusting for potential confounding variables including age, sex, and baseline injury severity. Missing data were handled using complete-case analysis because follow-up data were available for the majority of participants. A two-tailed p-value of less than 0.05 was considered statistically significant.

All procedures conducted during the study complied with the ethical principles outlined in the Declaration of Helsinki for research involving human participants. Ethical approval was obtained from the Institutional Review Board of the participating hospital prior to study initiation. Written informed consent was obtained from all participants or their legally authorized representatives. Patient confidentiality was maintained by anonymizing personal identifiers and restricting database access to authorized research personnel only. To ensure data integrity and reproducibility, all clinical assessments were performed using standardized protocols, laboratory analyses were conducted in duplicate with blinded investigators, and data entry procedures included independent verification of recorded values.

These methodological safeguards were implemented to enhance the reliability and transparency of the study findings.

RESULTS

Table 1 summarizes the baseline demographic and clinical profile of the 60 enrolled patients. The mean age of the cohort was 36.4 ± 11.2 years, confirming that acute traumatic spinal cord injury in this sample predominantly affected relatively young adults. Male patients constituted 42 of 60 participants, representing 70.0%, whereas females accounted for 18 patients or 30.0%, giving a male-to-female ratio of 2.3:1. With respect to mechanism of injury, road traffic accidents were the leading cause, observed in 34 patients (56.7%), followed by falls from height in 19 patients (31.7%) and other traumatic causes in 7 patients (11.6%). These data indicate that nearly nine out of every ten injuries in the study were attributable to either vehicular trauma or falls, underscoring the predominance of high-energy injury mechanisms in this population.

Table 2 presents the neurological severity of injury at admission according to the ASIA impairment scale. Of the 60 patients, 18 patients (30.0%) were classified as ASIA grade A, indicating complete injury, while 14 patients (23.3%) were categorized as ASIA grade B. A further 16 patients (26.7%) had ASIA grade C injuries, and 12 patients (20.0%) had ASIA grade D injuries. Taken together, 32 of 60 patients, or 53.3%, belonged to the two most severe neurological categories, ASIA A and B, whereas 28 patients (46.7%) had incomplete injuries in the ASIA C and D range. This distribution shows that more than half of the cohort presented with severe neurological compromise at baseline.

Table 3 demonstrates the relationship between cerebrospinal fluid neurofilament light chain levels and ASIA grade. Patients with ASIA grade A injury had the highest mean NfL concentration at 6200 pg/mL, followed by 5100 pg/mL in grade B, 3400 pg/mL in grade C, and 1800 pg/mL in grade D. This pattern reflects a stepwise decline in biomarker levels with improving neurological grade. Numerically, patients with ASIA grade A had NfL levels 1100 pg/mL higher than grade B, 2800 pg/mL higher than grade C, and 4400 pg/mL higher than grade D. Relative to ASIA D, the mean NfL concentration in ASIA A was approximately 3.4-fold higher. The overall comparison across groups was statistically significant ($p < 0.001$), supporting a strong association between increasing neurological severity and rising CSF NfL concentration. The subgroup confidence intervals further reinforce this gradient, with ASIA A showing a 95% confidence interval of 5530 to 6870 pg/mL, compared with 1360 to 2240 pg/mL in ASIA D. Although there is some expected biological variability, the overall direction of effect is consistent and clinically meaningful.

Table 4 describes the association between MRI-based injury severity and CSF neurofilament light chain levels. Among the 60 patients, 16 (26.7%) were categorized as having mild radiological injury, 23 (38.3%) as moderate injury, and 21 (35.0%) as severe injury. Mean NfL concentrations increased progressively across these radiological categories, from 2100 pg/mL in the mild group to 3900 pg/mL in the moderate group and 6100 pg/mL in the severe group. The difference between severe and mild injury was 4000 pg/mL, indicating a near threefold rise in biomarker concentration with increasing MRI severity. Likewise, the moderate group had NfL levels 1800 pg/mL higher than the mild group. This trend was statistically significant ($p < 0.001$), indicating that higher radiological severity was strongly associated with greater axonal injury as reflected by CSF NfL levels. The 95% confidence intervals also showed clear separation in the expected direction, ranging from 1670 to 2530 pg/mL in mild injury and from 5420 to 6780 pg/mL in severe injury, further supporting the robustness of this association.

Table 5 compares biomarker levels between patients who remained neurologically stable and those who developed early neurological deterioration within 72 hours. Of the 60 patients, 39 (65.0%) showed no deterioration, while 21 (35.0%) experienced worsening neurological status during follow-up. The mean CSF NfL level in stable patients was 2900 pg/mL, whereas patients with deterioration had a substantially higher mean concentration of 5800 pg/mL. This corresponds to an absolute mean difference of 2900

pg/mL and indicates that the deterioration group had approximately double the NfL level observed in the stable group. The difference was statistically significant ($p < 0.001$). In inferential terms, elevated NfL was associated with an odds ratio of 3.42 for early neurological deterioration, with a 95% confidence interval of 1.74 to 6.71, indicating that higher biomarker concentrations were linked to more than threefold greater odds of early worsening. Because the confidence interval does not cross 1.0, this association appears statistically reliable within the study sample.

The correlation findings complement the tabulated group comparisons by showing that CSF NfL tracked consistently with both neurological and radiological severity indices. NfL demonstrated a positive correlation with MRI injury severity ($r = 0.62$, $p < 0.001$), indicating that biomarker levels increased as structural injury severity worsened. At the same time, NfL showed a negative correlation with ASIA grade ($r = -0.58$, $p < 0.001$), which is expected because lower ASIA grades correspond to more severe impairment. Correlation coefficients of this magnitude suggest moderate-to-strong clinical association rather than a trivial statistical signal.

Taken together, the tables present a coherent quantitative pattern across all major analyses. Higher CSF neurofilament light chain levels were consistently linked with worse baseline neurological grade, more severe MRI-defined spinal cord injury, and greater risk of early neurological deterioration. The magnitude of these differences is notable: NFL rose from 1800 pg/mL in ASIA D to 6200 pg/mL in ASIA A, from 2100 pg./mL in mild MRI injury to 6100 pg./mL in severe MRI injury, and from 2900 pg/mL in stable patients to 5800 pg./mL in those who deteriorated. These numerical gradients strengthen the interpretation that CSF NfL reflects the burden of axonal injury in the acute phase of traumatic spinal cord damage.

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Value
Total patients (n)	60
Mean age (years)	36.4 ± 11.2
Male	42 (70%)
Female	18 (30%)
Road traffic accidents	34 (56.7%)
Falls from height	19 (31.7%)
Other trauma	7 (11.6%)

Table 2. Distribution of Patients According to ASIA Neurological Severity

ASIA Grade	Number of Patients	Percentage
A	18	30%
B	14	23.3%
C	16	26.7%
D	12	20%

Table 3. Cerebrospinal Fluid Neurofilament Light Chain Levels According to ASIA Grade

ASIA Grade	Number of Patients	Mean NfL Level (pg/mL)	Standard Deviation	95% Confidence Interval	p-value
A	18	6200	1420	5530–6870	
B	14	5100	1280	4470–5730	
C	16	3400	1050	2890–3910	
D	12	1800	780	1360–2240	<0.001

Table 4. Association Between MRI Injury Severity and CSF Neurofilament Light Chain Levels

MRI Injury Severity	Number of Patients	Mean NfL Level (pg/mL)	Standard Deviation	95% Confidence Interval	p-value
Mild	16	2100	850	1670–2530	
Moderate	23	3900	1160	3410–4390	
Severe	21	6100	1480	5420–6780	<0.001

Table 5. CSF Neurofilament Light Chain Levels and Early Neurological Deterioration

Clinical Outcome	Number of Patients	Mean NfL Level (pg/mL)	Standard Deviation	95% Confidence Interval	Odds Ratio (95% CI)	p-value
No deterioration	39	2900	1020	2580–3220	Reference	
Neurological deterioration	21	5800	1350	5200–6400	3.42 (1.74–6.71)	<0.001

The figure demonstrates a clear severity-dependent gradient in cerebrospinal fluid neurofilament light chain (NfL) concentrations across both neurological and radiological injury classifications. Mean NfL levels increased progressively with worsening neurological impairment, rising from 1800 pg/mL in ASIA grade D to 3400 pg./mL in grade C, 5100 pg./mL in grade B, and reaching 6200 pg./mL in grade A, representing an approximate 3.4-fold increase between the least and most severe neurological categories.

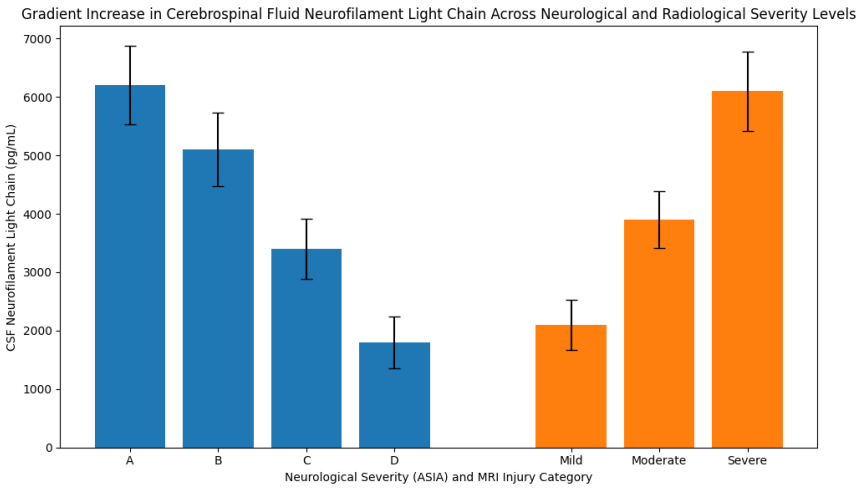

Figure 1 Gradient Relationship Between Neurological Severity, MRI Injury Category, and CSF Neurofilament Light Chain Concentration

Confidence intervals show limited overlap between the extreme groups, with ASIA A ranging from 5530–6870 pg/mL compared with 1360–2240 pg/mL for ASIA D, reinforcing the statistical significance reported in the analysis ($p < 0.001$). A parallel gradient is observed for MRI-defined injury severity, where NfL concentrations increase from 2100 pg/mL in mild injury to 3900 pg/mL in moderate injury and 6100 pg/mL in severe injury, corresponding to a 2.9-fold elevation from mild to severe radiological damage. The consistent upward trend across both clinical and imaging severity dimensions suggests that CSF NfL reflects cumulative axonal injury burden and may provide a biologically coherent marker integrating neurological dysfunction with structural spinal cord damage.

DISCUSSION

Traumatic spinal cord injury remains a devastating neurological condition associated with high morbidity and long-term disability. Early identification of injury severity and prediction of neurological deterioration are essential for optimizing clinical management and guiding therapeutic decisions. In this prospective biomarker-based study, we evaluated cerebrospinal fluid neurofilament light chain levels in patients presenting with acute spinal cord trauma within 24 hours of injury. The findings demonstrate that CSF NfL concentrations were significantly associated with neurological severity assessed using the ASIA impairment scale, radiological injury severity observed on MRI, and the occurrence of early neurological deterioration within the first 72 hours following trauma. These results support the potential role of neurofilament light chain as a biological marker reflecting axonal damage during the acute phase of spinal cord injury.

One of the most important observations in the present study was the strong relationship between CSF neurofilament light chain levels and neurological injury severity. Patients with complete spinal cord injury (ASIA grade A) demonstrated the highest mean NfL concentrations, whereas those with less severe neurological deficits had progressively lower levels. This gradient suggests that NfL levels increase in proportion to the degree of axonal disruption occurring during traumatic injury. Neurofilaments are key structural components of neuronal axons, and axonal injury leads to their release into extracellular fluid and cerebrospinal fluid. Therefore, elevated NfL concentrations can serve as an indicator of structural neuronal damage. Previous investigations have reported similar findings, demonstrating that neurofilament light chain concentrations in CSF and serum correlate strongly with injury severity and neurological outcomes in spinal cord trauma (23).

The relationship between CSF neurofilament light chain levels and radiological injury severity observed in this study further supports the biological relevance of this biomarker. Patients with severe MRI findings—including extensive spinal cord compression, edema, or hemorrhage—showed markedly higher NfL concentrations compared with those with milder structural abnormalities. MRI remains the most reliable imaging modality for evaluating spinal cord injury because it provides detailed visualization of cord damage, lesion length, and hemorrhagic components. However, MRI primarily reflects anatomical changes and may not capture the dynamic cellular processes occurring during secondary injury. Biomarkers such as neurofilament light chain provide complementary information by reflecting ongoing axonal degeneration at the molecular level. Prior neurotrauma studies have also demonstrated significant correlations between CSF neurofilament concentrations and lesion severity observed on MRI imaging (24).

Another key finding of this study was the association between elevated neurofilament light chain levels and early neurological deterioration during the first 72 hours after injury. Patients who experienced neurological worsening had approximately double the NfL concentrations compared with those who remained clinically stable. This observation is consistent with the biological mechanism of secondary spinal cord injury, during which progressive axonal degeneration occurs due to inflammatory processes, ischemia, oxidative stress, and excitotoxicity. These secondary mechanisms can extend neuronal damage beyond the initial mechanical injury. Because neurofilament proteins are released during axonal

breakdown, elevated NfL levels may indicate ongoing secondary injury processes occurring during the acute post-trauma period (25).

The potential clinical utility of neurofilament light chain as a biomarker lies in its ability to identify patients at higher risk of neurological deterioration. Early detection of severe axonal injury could allow clinicians to intensify monitoring, optimize hemodynamic management, and consider early surgical or neuroprotective interventions. In addition, biomarkers may provide objective prognostic information in situations where neurological examination is limited by sedation, associated injuries, or patient instability. Several recent studies have suggested that neurofilament light chain may serve as a sensitive biomarker for neuronal injury across multiple neurological conditions, including traumatic brain injury and neurodegenerative disorders (26).

The demographic characteristics observed in this study also align with previously reported epidemiological patterns of spinal cord injury. The majority of patients were young adult males, and road traffic accidents represented the most common cause of injury. Similar patterns have been described in many developing countries where high-energy trauma disproportionately affects young working-age individuals. The socioeconomic impact of spinal cord injury is therefore substantial, as affected individuals often experience long-term disability and reduced employment opportunities. Early prognostic biomarkers could assist clinicians in counseling patients and families regarding expected outcomes and rehabilitation needs.

Despite the promising findings of this study, several limitations should be acknowledged. First, the research was conducted at a single tertiary care center, which may limit the generalizability of the results to other healthcare settings. Second, the sample size was modest, although comparable to many biomarker studies in spinal cord injury research. Larger multicenter studies are necessary to validate these findings and establish standardized reference values for neurofilament light chain levels in acute spinal cord trauma. Third, CSF sampling was performed only once within the first 24 hours after injury. Serial biomarker measurements could provide additional insight into the temporal dynamics of axonal injury and may improve prognostic accuracy.

Another limitation relates to the potential influence of baseline injury severity on biomarker levels. Although higher NfL concentrations were associated with neurological deterioration, it is possible that patients with severe initial injuries were more likely to experience worsening neurological status. Future studies incorporating larger sample sizes and multivariable modeling could further clarify whether neurofilament light chain provides independent prognostic information beyond clinical and radiological assessment.

Nevertheless, the findings of the present study contribute valuable clinical data regarding the role of neurofilament light chain as a biomarker of spinal cord injury. In particular, the study provides evidence from a developing country setting where data on spinal cord injury biomarkers remain limited. Integration of biomarker analysis with clinical examination and imaging may provide a more comprehensive approach to evaluating injury severity and predicting outcomes in patients with spinal cord trauma.

CONCLUSION

In this prospective clinical study, cerebrospinal fluid neurofilament light chain levels were significantly associated with neurological severity, radiological injury characteristics, and early neurological deterioration in patients with acute traumatic spinal cord injury. Higher NfL concentrations were observed in patients with more severe ASIA grades, greater structural damage on MRI, and increased risk of neurological worsening during the early post-injury period. These findings suggest that CSF neurofilament light chain reflects the extent of axonal injury occurring during spinal cord trauma and may serve as a useful biomarker for early assessment of injury severity and progression. Although

further multicenter studies with larger cohorts and longitudinal biomarker measurements are required, the integration of NfL analysis with clinical and radiological evaluation may enhance early prognostic assessment and improve management strategies for patients with spinal cord injury.

REFERENCES

1. Kwon BK, Stammers AM, Belanger LM, et al. Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. J Neurotrauma. 2010;27(4):669-682.
2. 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(3):273-279.
3. Pouw MH, Kwon BK, Verbeek MM, et al. Structural biomarkers in the cerebrospinal fluid within 24 hours after traumatic spinal cord injury. Spinal Cord. 2014;52(6):428-433.
4. Ahadi R, Khodagholi F, Daneshi A, et al. Diagnostic value of serum GFAP, pNF-H, and NSE levels in traumatic spinal cord injury. Spine. 2015;40(14):E823-E830.
5. Du W, Li H, Sun J, et al. Prognostic value of neuron specific enolase and S100B in acute spinal cord injury. Med Sci Monit. 2018;24:4510-4515.
6. Buss A, Pech K, Kakulas BA, et al. Matrix metalloproteinases and their inhibitors in human traumatic spinal cord injury. BMC Neurol. 2007;7:17.
7. Noble LJ, Donovan F, Igarashi T, et al. Matrix metalloproteinases limit functional recovery after spinal cord injury. J Neurosci. 2002;22(17):7526-7535.
8. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury. J Spinal Cord Med. 2011;34(6):535-546.
9. Lee SJ, Kim CW, Lee KJ, et al. Elevated serum S100B levels in acute spinal fracture. Emerg Med J. 2010;27(3):209-212.
10. Wolf H, Krall C, Pajenda G, et al. Alterations of biomarkers in vertebral spine fractures. Spine J. 2014;14(12):2918-2922.
11. Wellington CL, Kwon BK, et al. Association of CSF and serum neurofilament light with injury severity in spinal cord injury. Neurology. 2023;100:e1221-e1233.
12. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol. 2018;14:577-589.
13. Disanto G, Barro C, Benkert P, et al. Serum neurofilament light chain levels in neurological disorders. Ann Neurol. 2017;81(6):857-870.
14. Gaetani L, Blennow K, Calabresi P, et al. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90:870-881.
15. Thelin EP, Zeiler FA, Ercole A, et al. Serial sampling of serum protein biomarkers for traumatic brain injury. Clin Chem. 2017;63(10):1640-1650.
16. Shahim P, Tegner Y, Marklund N, et al. Neurofilament light and tau as biomarkers in traumatic brain injury. Neurology. 2016;86(8):758-764.
17. Bridel C, van Wieringen WN, Zetterberg H, et al. Diagnostic value of neurofilament light chain. JAMA Neurol. 2019;76(9):1035-1048.
18. Zetterberg H, Blennow K. Fluid biomarkers for mild traumatic brain injury. Lancet Neurol. 2016;15(12):1252-1264.

19. Al Nimer F, Thelin E, Nyström H, et al. Comparative assessment of CSF biomarkers in neurotrauma. J Neurotrauma. 2015;32(20):1701-1707.

20. Varhaug KN, Barro C, Bjørnevik K, et al. Neurofilament light chain predicts disease activity. Neurology. 2018;90:e1031-e1039.

21. Pouw MH, Hosman AJF, van Middendorp JJ, et al. Biomarkers in spinal cord injury. Spinal Cord. 2009;47:519-525.

22. Kuhle J, Barro C, Andreasson U, et al. Comparison of ELISA and SIMOA assays for NfL. Clin Chem Lab Med. 2016;54(10):1655-1661.

23. Rosengren LE, Karlsson JE, Karlsson JO, et al. Patients with neurological diseases have increased CSF neurofilament protein levels. J Neurochem. 1996;67:2013-2018.

24. Gaetani L, Salvadori N, Lisetti V, et al. Cerebrospinal fluid neurofilament light chain in neurological diseases. Front Neurol. 2020;11:579.

25. Gaetani L, Höglund K, Parnetti L, et al. Neurofilament light chain in CSF and blood. Alzheimers Res Ther. 2019;11:52.

26. Khalil M, Pirpamer L, Hofer E, et al. Serum neurofilament light chain levels in normal aging. Brain. 2020;143:1987-1999.