

# Circulating Ubiquitin Carboxyl Terminal Hydrolase L1 and Neuroglobin Levels in Traumatic Spinal Cord Injuries: Relation to Severity and Outcomes

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**Introduction:** Traumatic spinal cord injury (TSCI) is a life-threatening neurological disorder and there is a lack of biomarker research, particularly human studies that could help to categorize the severity and predict the outcome. We aimed to assess the role of serum Ubiquitin C-terminal hydrolase L1 (UCH-L1) and Neuroglobin (NGB) in predicting severity and outcome of TSCI.

**Methods:** This prospective study included 63 participants categorized into 33 patients with various types of TSCI and 30 unrelated healthy volunteers. Neurosurgical [American spinal injury association (ASIA) impairment score (AIS)] and radiological [using spine computed tomography (CT) and magnetic resonance imaging (MRI)] assessments were performed on the included patients to determine the severity and the level of injury with neurological follow-up of patients within 6 months post-injury. Serum UCH-L1 and NGB were measured for all participants using commercially available ELISA assay kits.

**Results:** Of the included patients, 20 (60.60%) had partial SCI and the remaining 13 patients (39.39%) had complete SCI. On follow-up, 19 patients (57.57%) showed improved AIS, while 14 cases (42.42%) did not show any improvement in their AIS scores. There was significantly higher median serum UCHL1 value among cases compared to controls (1723 pg/mL and 657 pg/mL, respectively),  $p < 0.05$ . There was an insignificant rise of serum NGB levels among cases in comparison with the controls (15.2pg/mL and 7.52pg/mL, respectively,  $p > 0.05$ ). Significantly lower initial median serum UCHL1 levels (pg/mL) were observed in patients with improved AIS during the neurological follow-up compared with those who did not show any improvement in their AIS score (1723, and 4700 respectively,  $p < 0.05$ ), with lack of significant difference in the initial median serum NGB levels,  $p > 0.05$ .

**Conclusion:** Initial serum UCHL1 assay could be a helpful marker in reflecting the degree of TSCI and predicting its outcome, though NGB needs further assessment.

**Keywords:** traumatic spinal cord injury, Ubiquitin C-terminal hydrolase L1, neuroglobin, diagnostic and prognostic markers

## Introduction

Traumatic spinal cord injury (TSCI) is a type of injury to the spinal cord that causes loss of function. It can be either a complete or incomplete injury, depending on the extent of the damage. SCI has the potential to cause serious cellular and physiological disruption.<sup>1</sup> Symptoms include loss of motor, sensory, and autonomic nervous system functioning soon after the damage, as well as subsequent complications such as muscular atrophy and chronic pain (in regions of the body below the lesion level) and urinary infection.<sup>2,3</sup> SCI has been linked to both primary and secondary damage mechanisms.<sup>4</sup> Primary SCI has been shown to be irreversible, whereas secondary SCI affects a variety of cellular and metabolic processes, including free radical generation, vascular disturbances, lipid peroxidation, apoptosis, and mitochondrial damage.<sup>5</sup>

Ubiquitin C-terminal hydrolase L1 (UCH-L1) is a small 27-kDa deubiquitinating enzyme that belongs to the UCH family (DUBs).<sup>6</sup> CH-L1 has a strong affinity for ubiquitin, which it effectively proteolyzes from short C-terminal amino acids and diubiquitins *in vitro*.<sup>7</sup> UCH-L1 is a CNS enzyme that plays a critical function in neuronal health. It is one of the most abundant and perplexing enzymes. Because of its high expression in neurons, UCH-L1 is assumed to be essential for the maintenance of axonal integrity based on previous UCH-L1 deletion models.<sup>8</sup> In neurons, UCH-L1 is thought to have an antioxidant effect.<sup>9</sup>

Neuroglobin (NGB) was the first nerve globin discovered in human neural tissues.<sup>10</sup> It has been suggested that neuroglobin is involved in the mitochondrial release of cytochrome c and, as a result, the apoptotic pathway, and it has been prescribed to treat pathologies caused by reactive oxygen species (ROS).<sup>5,11</sup>

The lack of biomarkers that can objectively stratify injury severity and predict outcome is a major barrier to translational research in acute TSCI.<sup>12</sup> Therefore, the present study aimed to investigate the circulating NGB and UCH-L1 expressions in various TSCI and correlate their initial levels with the severity and outcomes of these injuries.

## Materials and Methods

### Study Design and Participants

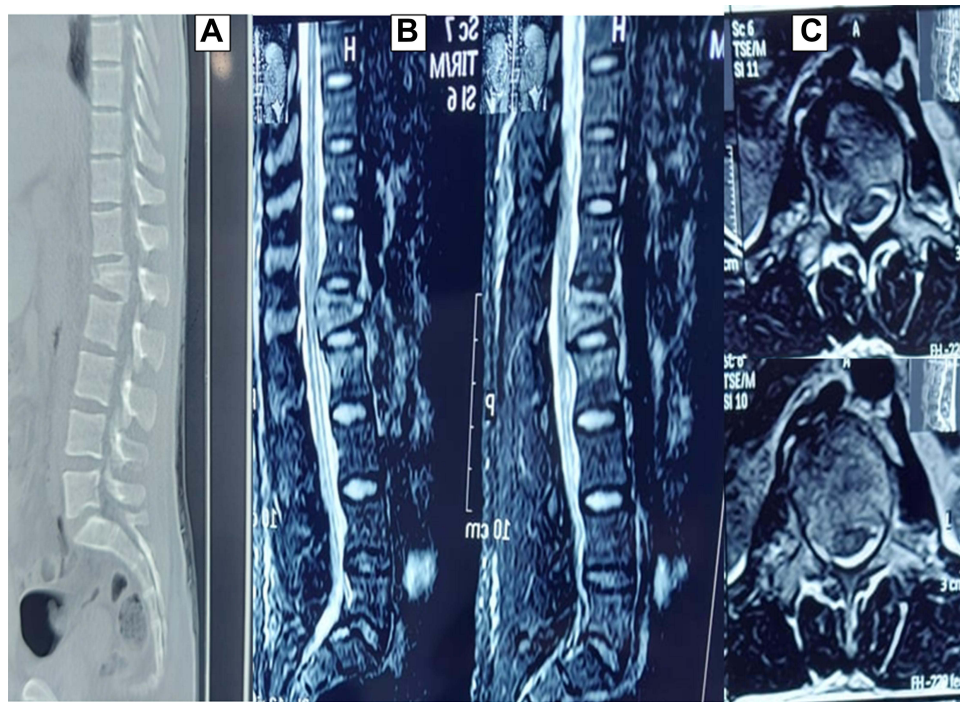
A total of 33 patients with various types of traumatic spinal cord injuries were enrolled in this prospective case-control, hospital-based study. They were recruited from the University Hospitals' outpatient clinics and inpatient Neurosurgery Department at South Valley University in Qena, Egypt, a major tertiary referral center in Upper Egypt. The included patients were comparable with 30 unrelated healthy, age- and sex-matched volunteers selected as controls. The recruitment of patients and controls in the present study was done in accordance with the guidelines laid down in the Declaration of Helsinki, and all participants were informed about the aim of the study and their written informed consent was obtained, after approval of the local Ethics Committee of Faculty of Medicine, South Valley University, Qena, Egypt. The total duration of the study was one year, from December 1st, 2020 to November 30th, 2021. We adjusted the sample size to attain 80% power and a 5% confidence level of significance (type I error).

### Neurosurgical and Radiological Evaluation of the Included Patients

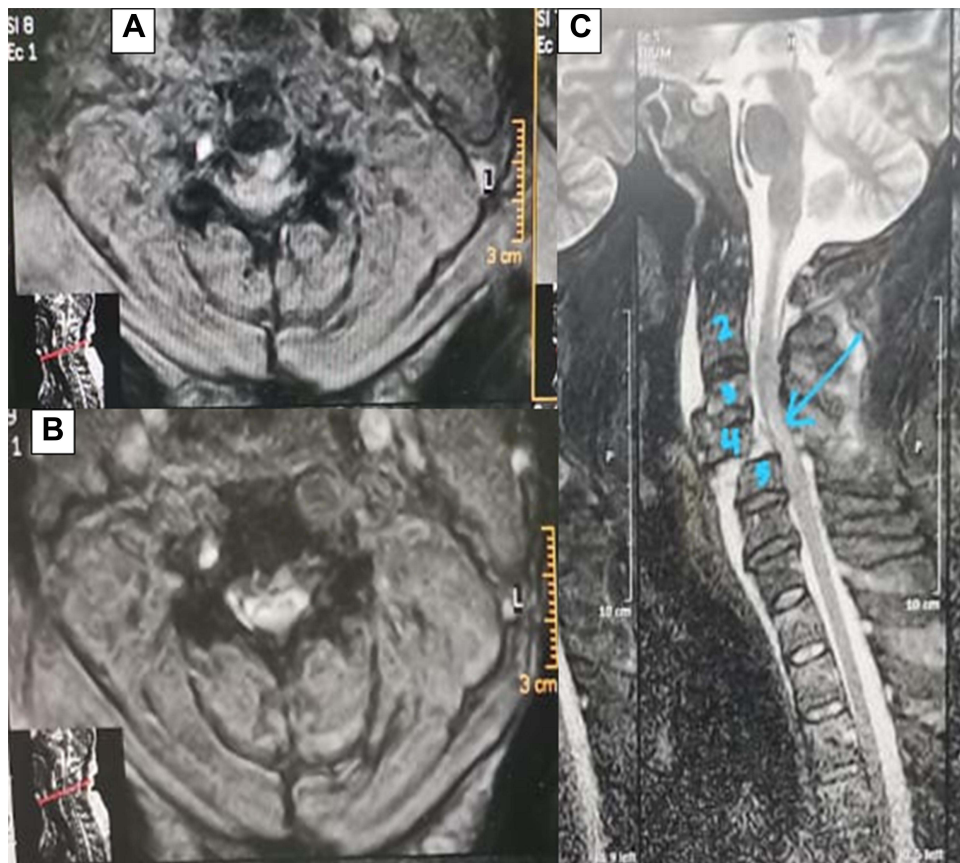
Full history (age, sex, and etiology of the spinal cord injury) and thorough clinical examination of the included cases were performed using American spinal injury association (ASIA) impairment score (AIS) to assess the sensory and motor levels which were affected by spinal cord injury.<sup>13</sup>

All included patients were evaluated radiologically by using spine computed tomography (CT) and magnetic resonance imaging (MRI) to determine the degree and the level of injury. The vertebrae were assessed using an MDCT scanner with 64 detectors, a detector configuration of 64×0.625, an interval of 0.5 mm, a pitch of 0.98:1, a rotation period of 0.8 seconds, and a peak voltage of 120 kVp. In terms of axial, sagittal, and coronal views, CT gives reformatted pictures. After excluding MRI contraindications such as claustrophobia, implanted coils, clips, or pacemaker, an MRI examination was performed with a superconducting Philips scanner (Achieva, 1.5 Tesla Philips, Health care, Best, The Netherlands). Sagittal T1-weighted, sagittal T2-weighted, sagittal STIR, axial T2-weighted, and axial T1-weighted images with 3 mm slice thickness are typical unenhanced lumbar spine MRI protocols.<sup>14</sup> On a typical high-field MRI machine, this treatment takes about 20 minutes. Anxiety, metallic implant, and claustrophobia are all problems with MRI (Figures 1A–C and 2A–C).

Fixation and fusion were done for spinal instability with or without decompression in patients who needed surgery. Surgical options for cervical fractures were as follows: anterior fixation using H plate with or without corpectomy and pyramesh insertion. Posterior decompression with lateral mass fixation or combined anterior and posterior approach, or posterior fixation using pedicular screw with or without decompression was done for thoracolumbar fractures. The included patients were followed prospectively to determine neurological outcomes within 6 months post-injury.



**Figure 1** Male patient aged 36 years old with history of road traffic accident, lower limb paraparesis [L1 (lumbar vertebra 1) compressed fracture] more at the right side, AIS grade D, operated on for decompression and fixation, improved after 2 wks to AIS grade E. ((A) sagittal CT scan, (B) sagittal MRI, (C) axial MRI).



**Figure 2** Male patient aged 43 years old with history of road traffic accident, patient was quadriplegic at time of examination, AIS grade A, MRI showed C4–5 (cervical vertebrae 4–5) fracture dislocation with corresponding cord contusion seen in the form of hyperintense signal in T2, and patient was operated on for reduction, fixation, and fusion. Patient was followed-up for 6 months with no improvement in his neurological state ((A and B) MRI axial view, (C) MRI sagittal view).

## Blood Samples and Biochemical Assays

A total of 5 mL peripheral venous blood samples were drawn from an antecubital vein from both cases (collected over the first 24h post-injury) and controls, and were evacuated into serum separator gel tubes, where the samples were allowed to clot for 30 minutes at 37°C before centrifugation for 15 minutes at 3500 rpm. Separated sera were aliquoted into 1 mL cryotubes and stored at -80°C until time of biochemical analysis in the form of NGB and UCH-L1 via commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits [supplied by Chongqing biospes, China, Catalog No: BYEK3249, and BYEK3256, respectively], using microplate ELISA reader (EMR 500, USA), according to manufacturers' protocols and the calculation of NGB and UCH-L results was performed using standard curves (see supplementary figures: [Figures S1](#) and [S2](#)).

## Statistical Analysis

For statistical assessments we utilized Statistical Package for Social Sciences (SPSS) for Windows version 28.0 (Armonk, NY: IBM Corp). Kolmogorov–Smirnov test was used to check for data normality. Categorical variables were described by number and percent (N, %), where continuous data were expressed as mean + standard deviation (SD) or median (interquartile range). Differences between the two groups were detected using independent-samples *t*-test for parametric data (age) and Mann–Whitney test for non-parametric data between two groups (UCHL1 and NGB). Nominal data were expressed as percentage; differences between the two groups were detected using Chi-square test. Correlations were analyzed using Spearman correlation among quantitative variables in the case of non-parametric data. The sensitivity, specificity, positive and negative predictive values were calculated using Medcalc Program, P-value < 0.05 was considered significant.

## Results

### Demographic Data of the Participants

The current study was conducted on 63 participants, categorized into two groups; 33 patients with different types of TSCI (with mean age 31.36 years  $\pm$ 11.58 SD, 24 males and 9 females) and 30 healthy controls (with mean age 32.06 years  $\pm$ 10.63 SD, 21 males and 9 females). The two groups were matched regarding age and sex as evidenced by insignificant differences between them ( $p>0.05$ ).

### Clinical Data of the Included Patients with Traumatic Spinal Cord Injury

The included patients with partial SCI were 20 (60.60%) cases and the remaining 13 patients (39.39%) had complete SCI. Lumbar SCI was present in 15 patients (45.45%) while the remaining cases had cervical or thoracic SCI (9 cases [27.27%] each), with various AIS scores as presented in ([Table 1](#)). 6 patients presented with quadriplegia (18.18%), 8

**Table 1** Clinical Data of the Included Cases

Variables	Number (Total=33)	%
<b>Level of the spinal cord injury</b>		
• Cervical	9	27.27
• Thoracic	9	27.27
• Lumbar	15	45.45
<b>AIS</b>		
• A	13	39.39
• B	2	6.06
• C	8	24.24

(Continued)

**Table 1** (Continued).

Variables	Number (Total=33)	%
• D	10	30.30
<b>Type of spinal cord injury</b>		
• Partial	20	60.60
• Complete	13	39.39
<b>Neurological affection</b>		
• Quadriplegia	6	18.18
• Quadraparesis	3	9.09
• Paraplegia	8	24.24
• Paraparesis	16	48.48
<b>Etiology</b>		
• Motor car accident	12	36.36
• Falling from height	18	54.45
• Falling from stairs	3	9.09
<b>Outcome</b>		
• Improved	19	57.57
• Not improved	14	42.42

patients presented with paraplegia (24.24%), 3 patients had quadriplegia (9.09%), and 16 cases (48.48%) presented with paraparesis.

With neurological follow-up, 19 patients (57.57%) showed improved AIS, while 14 cases (42.42%) did not show any neurological improvement in their AIS scores within the 6 months of follow-up as presented in (Table 1).

## Circulating UCHL1 and NGB Levels in Traumatic Spinal Cord Injuries of Various Severities and Outcomes

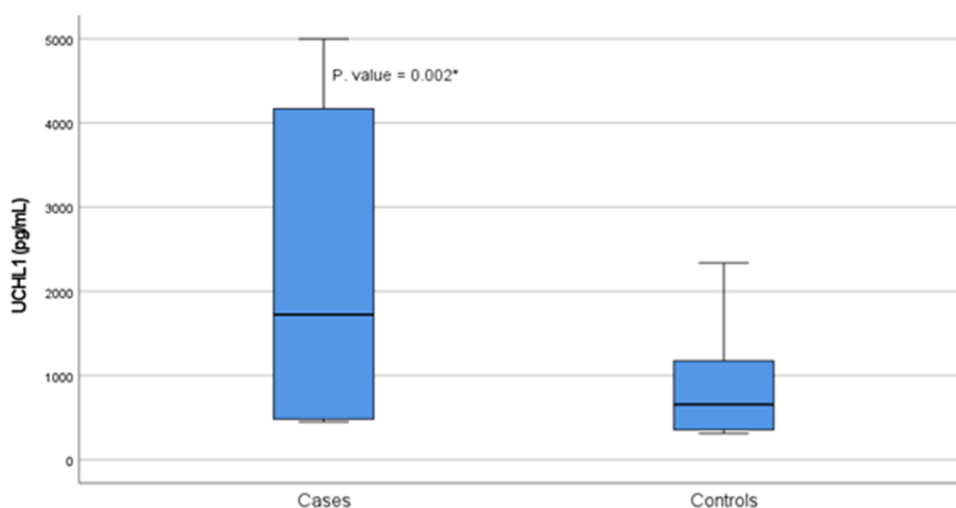
The median serum UCHL1 value was significantly higher among cases with traumatic SCI compared to the healthy controls (1723 pg/mL and 657 pg/mL, respectively),  $p < 0.05$ , (Table 2 and Figure 3). Although there were higher serum NGB levels among the included cases in comparison with the controls (15.2pg/mL and 7.52pg/mL, respectively) it did not reach a significant level,  $p > 0.05$ , (Table 2).

**Table 2** Serum UCHL1 and NGB Among the Study Groups

Biochemical Biomarkers	Cases (n=33)	Controls (n=30)	P value
UCHL1 (median, IQR; pg/mL)	1723(481–4185)	657(356–1175)	0.002*
NGB (median, IQR; pg/mL)	15.2(2.23–27.86)	7.52(5.05–25.3)	0.452

**Note:** \*Significant p value  $< 0.05$ .

**Abbreviations:** UCHL1, Ubiquitin carboxyl terminal hydrolase L1; NGB, neuroglobin; IQR, Interquartile range.



**Figure 3** Comparison of the serum levels of UCHL1 (pg/mL) among patients with traumatic spinal cord injury and controls. \*Significant (p value <0.05).

Regarding the AIS, the included TSCI patients with A score showed significantly higher median serum UCHL1 levels compared with those who had other AIS scores (B, C, D, or E), [3161.5 pg/mL, and 833 pg/mL, respectively],  $p < 0.05$ , (Table 3 and Figure 4), with lack of significant difference regarding serum NGB levels,  $p > 0.05$ , (Table 3).

Regarding the level of spinal cord injury, there were significantly higher median serum UCHL1 levels (pg/mL) among patients with either cervical or thoracic TSCI compared to those with lumbar TSCI (4700, 4200, and 575 respectively),  $p < 0.05$ , (Table 4 and Figure 5), with lack of significant difference in the median serum NGB levels,  $p > 0.05$ , (Table 4).

In terms of outcome, TSCI patients with improved AIS during the neurological follow-up showed significantly lower initial median serum UCHL1 levels (pg/mL) compared with those who did not show any improvement in their AIS score (1723, and 4700 respectively),  $p < 0.05$ , (Table 5 and Figure 6). While the median serum NGB levels did not show significant difference,  $p > 0.05$ , (Table 5).

The profile of the serum levels of the measured biomarkers in relation to gender revealed insignificant differences in the serum levels of UCHL1 and NGB between control males and females,  $p > 0.05$ , (Table 6). Among patients with TSCI, there was a significantly higher median serum level (pg/mL) of NGB among females than males (27.86 vs 9.1),  $p < 0.05$ , with non-significant differences in the serum UCHL1 levels among males compared to females with TSCI,  $p > 0.05$ , (Table 6).

There was no significant correlation between the measured serum biochemical markers UCHL1 and NGB among patients with TSCI ( $r = -0.019$ ,  $p = 0.918$ ).

## Characteristic Performance of UCHL1 in Predicting Severity and Outcome of TSCI

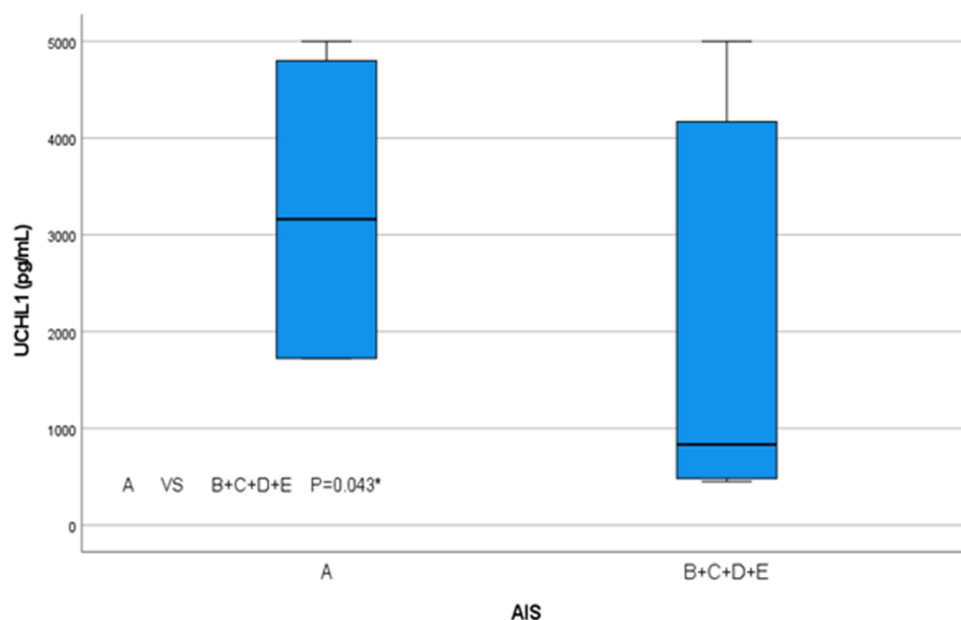
The area under the curve (AUC) for serum UCHL1 was calculated using receiver operative characteristic (ROC) curve to determine the cut-off value for predicting the severity (partial vs complete injury) and outcome (improved vs not improved) of traumatic spinal cord injury. The cut-off value could be considered when the parameter's area under curve

**Table 3** Serum UCHL1 and NGB Among the Included Patients with TSCI According to AIS

Biochemical Biomarkers	A (n= 13)	(B+C+D+E) (n= 20)	P value
UCHL1 (median, IQR; pg/mL)	3161.5(1723–4900)	833(481–4170)	0.043*
NGB (median, IQR; pg/mL)	8.01(0.82–23.8)	15.2(2.39–27.86)	0.279

**Note:** \*Significant p value <0.05.

**Abbreviations:** UCHL1, Ubiquitin carboxyl terminal hydrolase L1; NGB, neuroglobin; IQR, interquartile range; TSCI, traumatic spinal cord injury; AIS, American spinal injury association (ASIA) impairment score (from A to E).



**Figure 4** Comparison of the serum levels of UCHL1 (pg/mL) among patients with traumatic spinal cord injury with AIS grade A and those with others AIS grades (B–E). \*Significant (p value <0.05).

(AUC) is close to one. Regarding the performance characteristics of UCHL1 in predicting complete TSCI, at cut-off point >4500 pg/mL it showed 50% sensitivity, 100% specificity, positive predictive value (PPV)=100%, negative predictive value (NPP)= 77.8% with AUC=0.643 (Figure 7A). While, in predicting improved outcome, at cut-off point ≤4600 pg/mL it showed 80% sensitivity, 57.14% specificity, positive predictive value (PPV)= 57.1%, negative predictive value (NPP)= 80% with AUC=0.557 (Figure 7B).

## Discussion

Traumatic SCI has a diverse and complicated pathogenesis. Although SCI research has made significant progress, more work has to be done to adapt what has been learned in animal studies to clinical applications in humans.<sup>15</sup> The World Health Organization (WHO) estimates that between 250,000 and 500,000 new cases are recorded each year. Trauma, such as car accidents, falls, or violence, is the leading cause of spinal cord damage. A spinal cord injury increases the risk of mortality prematurely by two to five times. Low- and middle-income countries have the lowest survival rates. In addition to societal expenses, spinal cord damage is linked to decreased rates of economic involvement and school enrollment.<sup>16</sup>

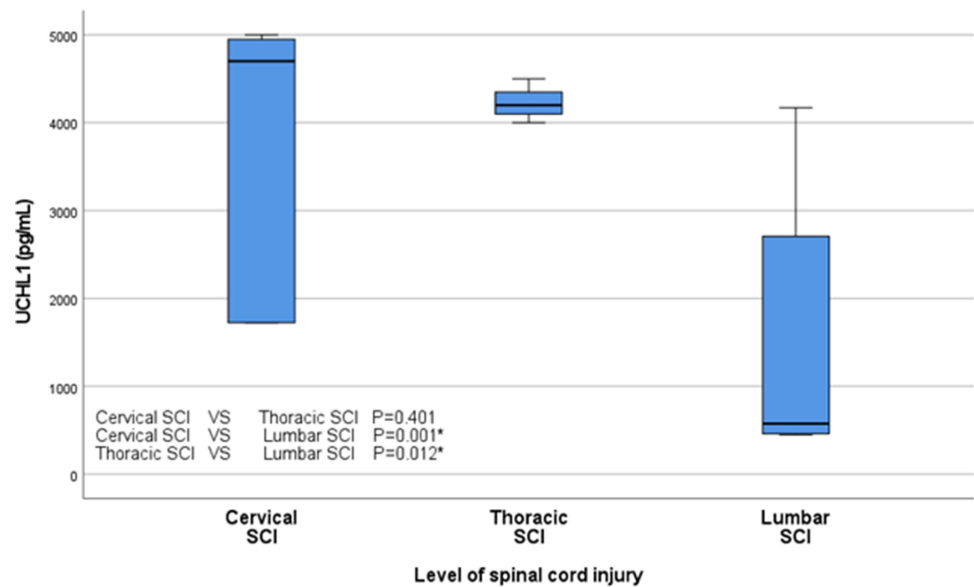
Traumatic damage to the spinal cord is the most common cause of SCI. Multiple secondary sequelae, including ischemia, inward calcium flux, infiltration of inflammatory cells, and liberation of high amounts of ROS, quickly exacerbate the original mechanical disruption of white matter pathways, resulting in a chronic state of inflammation. In neurons, UCH-L1 is thought to have an antioxidant effect.<sup>17,18</sup>

**Table 4** Serum UCHL1 and NGB Among the Included Patients with TSCI According to the Level of the Spinal Cord Injury

Biochemical Biomarkers	Cervical SCI (N= 9)	Thoracic SCI (N= 9)	Lumbar SCI (N= 15)	P value	P1	P2	P3
UCHL1 (median, IQR; pg/mL)	4700(1723–4975)	4200(4000–4500)	575(462–2707)	<0.001**	0.401	0.001**	0.012*
NGB (median, IQR; pg/mL)	15.2(0.82–26.66)	2.94(2.54–3)	26.66(2.23–30.66)	0.270	0.395	0.218	0.236

**Notes:** \*Significant p value <0.05. \*\*Significant p value <0.001. P1= cervical vs thoracic. P2= cervical vs lumbar. P3= thoracic vs lumbar.

**Abbreviations:** UCHL1, Ubiquitin carboxyl terminal hydrolase L1; NGB, neuroglobin; IQR, interquartile range; TSCI, traumatic spinal cord injury; AIS, American spinal injury association (ASIA) impairment score.



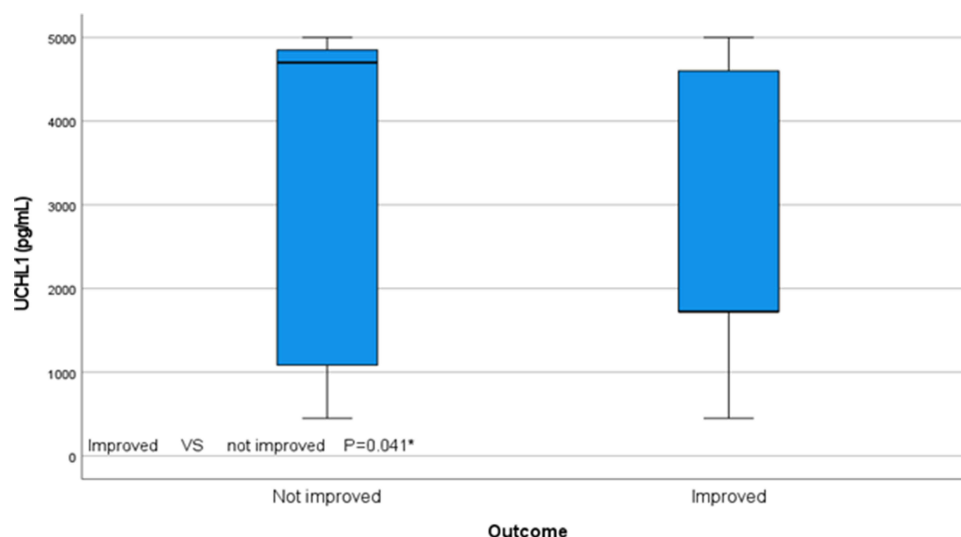
**Figure 5** Serum levels of UCHL1 (pg/mL) among patients with traumatic spinal cord injury according to the level of injury. \*Significant (p value <0.05).

Our findings revealed significantly higher UCH-L1 among cases with TSCI compared to the controls. UCH-L1 was significantly higher in cases with AIS score A than cases with score B, C, D or E. Also, UCH-L1 serum levels were significantly higher among patients with cervical or thoracic TSCI in comparison to those with lumbar TSCI. The included TSCI patients with improved AIS during the neurological follow-up showed significantly lower initial median serum UCHL1 levels compared with those who did not show any improvement in their AIS score. Additionally, our results showed that the characteristic performance of UCHL1 in predicting complete TSCI, at cut-off point >4500 pg/mL, showed 50% sensitivity, 100% specificity, with AUC=0.643. While, in predicting improved outcome, at cut-off point ≤4600 pg/mL, it showed 80% sensitivity, 57.14% specificity, with AUC=0.557. Very few human studies could be traced in literature regarding the expression profile of serum UCH-L1 in various TSCI and its role in predicting the outcome of such patients. In a rat SCI model, Yang et al<sup>19</sup> found that CSF and serum UCH-L1 levels increased quickly at 4 hours after damage. Additionally, Stukas et al<sup>12</sup> reported that in an injury severity and time-dependent manner, CSF UCH-L1 was considerably higher compared to controls, but failed to show such a difference in serum UCH-L1 levels and mentioned that technique may not be sufficiently sensitive. Patients’ selection criteria, sampling time, and ethnic differences may be additional factors. In the acute context, CSF UCH-L1 concentrations differentiated between AIS A and AIS B, as well as AIS A and AIS C patients, and predicted who would stay “motor complete” (AIS A/B) at 6 months with a sensitivity of 100% and a specificity of 86%, concluding that in acute SCI, CSF UCH-L1 showed promise as a biomarker for assessing injury severity and predicting outcome. Wang et al<sup>20</sup> reported the promising role of UCH-L1 and other biomarkers as indicators in AIS classification and their prognostic utility in patients with TSCI.

**Table 5** Serum UCHL1 and NGB Among the Included Patients with TSCI According to the Outcome

Biochemical Markers	Improved (n= 19)	Not Improved (n= 14)	P value
UCHL1 (median, IQR; pg/mL)	1723 (1086.5–4800)	4700 (450–4950)	0.041*
NGB (median, IQR; pg/mL)	15.2 (2.23–26.66)	12.23 (0.82–20.93)	0.452

**Note:** \*Significant p value <0.05.  
**Abbreviations:** UCHL1, Ubiquitin carboxyl terminal hydrolase L1; NGB, neuroglobin; IQR, interquartile range; TSCI, traumatic spinal cord injury.



**Figure 6** Serum levels of UCHL1 (pg/mL) among patients with traumatic spinal cord injury in terms of the outcome. \*Significant (p value <0.05).

Necrosis and apoptosis were originally identified as two major cell death mechanisms following SCI.<sup>21</sup> More direct evidence has been developing to support the role of neuroglobin in protecting cells from a range of apoptotic challenges, in addition to population-based genetic association studies and findings that specific forms of neuronal injury are related to higher expression of NGB.<sup>22,23</sup> In the current research, we observed higher serum NGB levels among patients with TSCI compared to the healthy controls, but this difference did not reach a significant level. Additionally, we found lack of significant association of NGB serum levels with AIS, levels or outcome of TSCI among the included patients. Although this could be explained by the segregation of NGB expression in brain neurons especially in the hypothalamus,<sup>24</sup> rather than spinal cord, but further larger scale research is required to confirm our findings.

## Conclusion

The initial serum Ubiquitin C-terminal hydrolase L1 assay, but not the neuroglobin assay, may be useful in defining the severity of traumatic spinal cord injuries and predicting their prognosis. Circulating UCH-L1 levels were higher in cases with AIS score A than those with score B, C, D or E and among patients with cervical or thoracic TSCI compared to those with lumbar injury, while UCH-L1 serum levels were lower in patients with improved AIS compared with those who did not show any improvement in their AIS score.

## Study Limitations

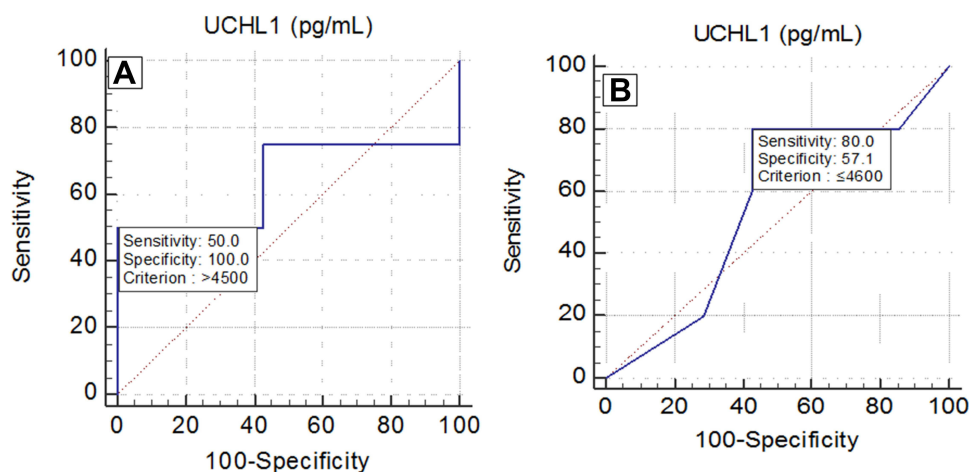
Sample size was rather small considering the heterogeneity of SCI presentation. But more importantly, external validation of the findings (at least with temporal validation in the same center) would be necessary. Lack of serial

**Table 6** Serum UCHL1 and NGB Levels Among the Study Groups in Terms of Gender

Biochemical Markers	Cases (n=33)		P value	Controls (n=30)		P value
	Males (n=24)	Females (n=9)		Males (n=21)	Females (n=9)	
<b>UCHL1</b> (median, IQR; pg/mL)	2861.5 (569–4575)	575 (462–2707)	0.072	657 (393.5–1175)	544 (356–1050)	0.449
<b>NGB</b> (median, IQR; pg/mL)	9.1 (1.17–26.66)	27.86 (9.17–30.66)	0.029*	7.52 (5.05–25.3)	18.8 (5.11–25.3)	0.782

**Note:** \*Significant p value <0.05.

**Abbreviations:** UCHL1, Ubiquitin carboxyl terminal hydrolase L1; NGB, neuroglobin; IQR, interquartile range.



**Figure 7** Receiver operative characteristic (ROC) curves for serum UCHL1 (pg/mL) in predicting severity (A) and outcome (B) of traumatic spinal cord injury.

biomarker assays to more accurately explore the marker expression profile was another limitation. Additionally, the lack of markers' assays in the CSF that was not available in all included patients was also an additional limitation.

## Data Sharing Statement

The datasets used and analyzed in this study are available upon reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in relation to this work.

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