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ARTICLE

Predictive factors for irreversible motor paralysis following cervical spinal cord injury

Tsunehiko Konomi[1,2] · Kota Suda[1] · Masahiro Ozaki[1,3] · Satoko Matsumoto Harmon[1] · Miki Komatsu[1] · Seiji Iimoto[1,4] · Osahiko Tsuji[1,5] · Akio Minami[1] · Masahiko Takahata[6] · Norimasa Iwasaki[6] · Morio Matsumoto[5] · Masaya Nakamura[5]

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Abstract

Study design A retrospective observational study.

Objectives To elucidate predictive clinical factors associated with irreversible complete motor paralysis following traumatic cervical spinal cord injury (CSCI).

Setting Hokkaido Spinal Cord Injury Center, Japan.

Methods A consecutive series of 447 traumatic CSCI persons were eligible for this study. Individuals with complete motor paralysis at admission were selected and divided into two groups according to the motor functional outcomes at discharge. Initial findings in magnetic resonance imaging (MRI) and other clinical factors that could affect functional outcomes were compared between two groups of participants: those with and those without motor recovery below the level of injury at the time of discharge.

Results Of the 73 consecutive participants with total motor paralysis at initial examination, 28 showed some recovery of motor function, whereas 45 remained complete motor paralysis at discharge, respectively. Multivariate logistic regression analysis showed that the presence of intramedullary hemorrhage manifested as a confined low intensity changes in diffuse high-intensity area and more than 50% of cord compression on MRI were significant predictors of irreversible complete motor paralysis (odds ratio [OR]: 8.4; 95% confidence interval [CI]: 1.2–58.2 and OR: 14.4; 95% CI: 2.5–82.8, respectively).

Conclusion The presence of intramedullary hemorrhage and/or severe cord compression on initial MRI were closely associated with irreversible paralysis in persons with motor complete paralysis following CSCI. Conversely, subjects with a negligible potential for recovery could be identified by referring to these negative findings.

Introduction

Spinal cord injury (SCI) can cause a severe physical problem, resulting in motor and sensory deterioration. Nowadays, several clinical trials of novel therapeutics have been widely launched for treatment of SCI, and the inclusion criteria are mostly persons with motor complete paralysis at baseline to ensure a more homogeneous study cohort [1–8]. One of the

✉ Tsunehiko Konomi
konomitsunehiko@gmail.com

1 Department of Orthopaedic Surgery, Hokkaido Spinal Cord Injury Center, 3-1 Higashi 4 Minami 1, Bibai, Hokkaido 072-0015, Japan

2 Department of Orthopaedic Surgery, Murayama Medical Center, National Hospital Organization, 2-37-1 Gakuen, Musashimurayama, Tokyo 208-0011, Japan

3 Department of Orthopaedic Surgery, Saiseikai Yokohamashi Tobu Hospital, 3-6-1 Shimosueyoshi, Tsurumi, Yokohama, Kanagawa 230-8765, Japan

4 Department of Orthopaedic Surgery, Ehime Prefectural Central Hospital, 83 Kasugamachi, Matsuyama, Ehime 790-0024, Japan

5 Department of Orthopaedic Surgery, Graduate School of Medicine, Keio University, 35 Shinanomachi, Shinjyuku-ku, Tokyo 160-8582, Japan

6 Department of Orthopaedic Surgery, Graduate School of Medicine, Hokkaido University, Kita 8, Nishi 5, Kita-ku, Sapporo, Hokkaido 060-0808, Japan

problems related to treatment of SCI is difficulties in distinguishing between treatment effect and spontaneous functional improvement [9].

In routine clinical practice, we refer to physical assessments to evaluate the severity of an injured spinal cord and predict the reasonable outcome in order to design an appropriate rehabilitation program. American Spinal Injury Association (ASIA) impairment scale (AIS) grade conversion is generally considered the basis for prediction of the possibility of achieving neurological recovery following traumatic SCI [10–12]. Individuals with AIS grade A at their initial examination have a lower chance of neurological recovery, with ~80% of them remaining at AIS grade A at the 1-year follow-up [13]. In contrast, AIS grade B persons usually show some recovery of motor function, with ~50–60% of them converting to AIS grade C or D [12–14]. These facts indicate that there are differences in recovery potential between individuals with complete and incomplete injury. Conversely, approximately 0–13% of persons with AIS grade A changed to AIS grade C or D, suggesting that patterns of spontaneous recovery vary widely, even for the same degree of paralysis in AIS grade at initial examination [13–17]. Furthermore, the use of neurologic examination in the acute phase after injury for purpose of prediction has proved to problematic owing to the confounding effects of injury-related factors and extraneous individuals, which exclude accurate assessment [18, 19]. The presence of concomitant brain injury, musculoskeletal injuries, spinal shock, pain, pharmacologic sedation, and poor personal effort are several of the factors that can result in a discordant and unreliable neurologic examination [16, 20, 21], indicating difficulties in predicting a functional prognosis based only on a single AIS assessment. Therefore, further objective evaluation should be taken into consideration in addition to the AIS assessment to give a more accurate prospect of the future function and appropriate selection of possible candidates for a novel therapy, especially in regard to whether the injured spinal cord has a negligible chance of recovering meaningful motor function.

In this study, we investigated the clinical and imaging findings associated with the future prognosis following traumatic cervical SCI (CSCI). Furthermore, we conducted a multivariate stepwise regression analysis among the clinical findings, which were obtained at an early stage after injury to identify predictive factors relating irreversible complete motor paralysis in the chronic phase with statistical adjustment for confounding.

Methods

This study is a retrospective imaging and clinical observational study. A total of 447 consecutive persons with traumatic CSCI, who were hospitalized at our institution between April 2011 and March 2015 and underwent initial assessment of neurological impairment within 96 h after injury, were potentially eligible for this study. Neurological classification was measured at admission and discharge with the International Standards for Neurological Classification of Spinal Cord Injury [22], including neurological severity (ASIA Impairment Scale; A/B/C/D), neurological level of injury, total motor index score (MIS; out of 100), and pin and light touch sensory testing. A total MIS was defined as the sum of scores in the upper and lower extremity and a percent recovery was evaluated by the following formula [23]: Percent recovery (%) = (score at discharge − score at initial evaluation)/(100 − score at initial evaluation) × 100. Clinical assessments were performed by two physicians with at least 3 months of experience and one of them (senior physician) had more than 5 years of experience in examination of patients with spinal cord injury. Of 447 study participants, 73 (16.3%) who met the following criteria: (1) persons with AIS grade A or B (no motor function below the injured level including the sacral segments S4–5) at initial examination, (2) duration of hospitalization was more than 180 days, and (3) persons without disturbed consciousness such as brain injury or a severe mental disorder that could influence rehabilitation, were retrospectively included in this study and divided into two groups according to their motor functional recovery more than three levels below the neurological level of injury at the time of discharge. Persons who remained complete motor paralysis below the injured level (AIS grade B or lower) were categorized as the motor complete group and persons whose motor function was preserved at the most caudal sacral segments for voluntary anal contraction or the persons who met the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4–S5) by light touch, pin or deep anal pressure), and have some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body (AIS grade C or higher) as the motor incomplete group. Differences in radiological characteristics, MIS and related physical factors (diabetes mellitus (DM), age, sex, body mass index (BMI), surgical treatment, surgical timing, hospital stay and complications (use of ventilator, deep venous thrombosis, and death)), which were obtained from a medical database in a single institution (Hokkaido Spinal Cord Injury Center) were assessed statistically. In cases involving displacement of a vertebral body, instability or cord compression, reduction and stabilization and/or decompression surgeries were performed. Management of treatment was decided by individual faculties based on their experiences. When the physicians made different decisions regarding assessment and management, a final decision was made after discussion.

Computed tomography (CT) and magnetic resonance imaging (MRI) data were obtained at admission before any treatment with a fiberglass cervical collar when appropriate. For MRI evaluation, we qualitatively assessed three types of characteristic changes on sagittal view of initial T1- and T2-weighted spin-echo images determined by reference to previous studies [24, 25]: (a) intramedullary-confined low intensity changes within diffuse high-intensity areas, which represents an intramedullary hemorrhage surrounded by edema on T2-weighted spin-echo sagittal images (intramedullary hemorrhage), (b) alterations in cord caliber as defined by loss of subdural space, which spans in both directions more than the height of one vertebra and adjacent disk to the lesion epicenter on T2-weighted spin-echo sagittal images (cord swelling), and (c) vertebral displacement or cord compression of at least 50% of the lesion epicenter (cord compression), which was calculated using T1-weighted midsagittal spin-echo images as follows: (diameter of the cervical cord at the non-compression level—diameter of the cervical cord at the injured level) × 100/diameter of the cervical cord at the non-compression level [25] (Fig. 1). For CT, we assessed the presence of diffuse idiopathic skeletal hyperostosis (DISH) [26] and ossification of the posterior longitudinal ligament (OPLL). The pattern of traumatic cervical spine injury was classified into one of four types based on AO subaxial classification (compression injury: failure of the anterior structures under compression or mechanically insignificant fractures of the spinal processes, tension band injury: injuries with either the anterior or posterior tension band, and translation injury: injuries with displacement or translation of one vertebral body relative to another in any direction) [27] and CSCI without radiological abnormality (CSCIWORA), which is a spinal cord injury without evidence of fracture or dislocation of the spine on plain radiographs or CT studies [28, 29].

Possible associations of each obtainable clinical factors between CSCI persons with motor complete and incomplete groups were assessed by *t* test for continuous variables or by Fisher's exact test for other categorical variables (DM, age (≤ 60 years, 61–75 years or ≥ 76 years), sex, BMI > 30, symptoms at initial evaluation (complete loss of motor and sensory below the injured level or any touch and/or pin sensation retained on either side of the lower extremity (L/E)), MRI findings at initial evaluation (intramedullary hemorrhage, cord compression and/or cord swelling), CT findings at initial evaluation (CSCIWORA, OPLL and/or DISH) and surgical timing (<8 h and/or, <24 h)) using Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA). To compare among these relative potential risk factors for complete motor paralysis at discharge, multivariate stepwise logistic regression analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [30]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Odds ratios (OR) for enduring motor paralysis and their 95% confidence intervals (CI) were calculated as an approximation of the relative risk estimates. The factors included in the multivariate model were age, sex, OPLL, DISH and those with a value of $P < 0.1$ in the univariate analyses (cord compression, cord swelling, intramedullary hemorrhage, CSCIWORA, DM, complete loss of motor and sensory (AIS A) and retaining pin sensation in L/E at initial examination). A value of $P < 0.05$ was considered as statistically significant.

Fig. 1 Representative features on T2-weighted spin-echo sagittal MRI following CSCI. Intramedullary-confined low intensity changes in diffuse high-intensity area (intramedullary hemorrhage: white arrow), alterations in cord caliber as defined by loss of subdural space, which spans in both directions more than the height of one vertebral and adjacent disk to the lesion epicenter (cord swelling: arrow head) and at least 50% of vertebral displacement (cord compression) were demonstrated.

Results

The 73 participants consisted of 68 males and five females, with a mean age of 60.3 years (range 22–83).

Table 1 Demographic characteristics and clinical features of the subjects.

	Motor complete ($n = 45$)	Motor incomplete ($n = 28$)	*P*
Participant characteristics			
Age (year; mean [SD])	60.4 (16.4)	60.1 (13.1)	0.94
Sex (male: female)	42:3	26:2	0.95
Body Mass Index (mean [SD])	23.6 (3.8)	23.9 (4.4)	0.79
Hospital Stay (day; mean [SD])	263.1 (130.6)	256.4 (80.9)	0.81
Initial Evaluation (hour; mean [SD])	10.9 (14.1)	13.3 (11.8)	0.38
Surgical Treatment (no. of Pts. [%])	43 (95.6)	26 (92.9)	0.64
Motor Index Score (mean [SD])			
U/E at Admission	13.2 (12.0)	9.6 (10.2)	0.19
L/E at Admission	0 (0)	0 (0)	1
Total Score at Admission	13.2 (12.0)	9.6 (10.2)	0.19
U/E at Discharge	17.6 (15.2)	22.1 (16.9)	0.39
L/E at Discharge	0 (0)	18.1 (19.1)	**<0.001**
Total Score at Discharge	17.6 (15.2)	44.3 (33.2)	**<0.001**
Percent Recovery (%: mean [SD])			
U/E	16.9 (26.5)	34.2 (43.4)	0.12
L/E	0 (0)	39.1 (38.2)	**<0.001**
Total Score	5.6 (9.2)	38.3 (35.7)	**<0.001**
Complications (no. of Pts. [%])			
Use of Ventilator	12 (26.7)	8 (28.6)	0.87
Deep Vein Thrombosis	21 (46.7)	11 (39.3)	0.63
Death	0 (0)	0 (0)	1

U/E upper extremity, *L/E* lower extremity.

Bold values indicate statistical significance.

The mean timing of initial and final evaluation was 11.5 h (range 2–72) and 260.5 days (range 184–828) post injury. Of the 73 persons with complete loss of motor function at admission, 28 were categorized as motor incomplete group with a mean total MIS of 9.6 at admission and of 44.3 at discharge. Recovery rates of upper extremity (U/E), L/E and total score were 34.2, 39.1, and 38.3%, respectively. Forty-five were categorized as motor complete group with a mean total MIS of 13.2 at admission and 17.6 at discharge, respectively. Percent recovery of U/E, L/E, and total score were 16.9, 0, and 5.6%, respectively. As shown in Table 1, apart from MIS at discharge and percent recovery of total and L/E, there were no significant differences between the two groups regarding participant demographics and complications (Table 1).

Changes in neurological status of AIS are shown in Table 2 and the distribution of the neurological levels of injury and types of injury are shown in Fig. 2. Most neurological levels of injury were at C4 or C5 (Fig. 2a) and types of injury were translation injury (Fig. 2b). CSCI-WORA was recognized in seven participants (25.0%) of motor incomplete group and in three (6.7%) of motor complete group. There were no substantial patterns of differences between the two groups.

Table 2 Changes in neurological status (ASIA impairment scale).

	Neurological status at discharge			
	A	B	C	D
Initial neurological status				
A	30 (54.6)	7 (12.3)	15 (27.3)	3 (5.5)
B	1 (5.6)	7 (38.9)	6 (33.3)	4 (22.2)

Values are presented as number (%).

ASIA American Spinal Injury Association.

According to univariate analyses, intramedullary hemorrhage, cord compression, cord swelling, and CSCI-WORA were identified as potential factors affecting functional outcomes at the time of discharge (Table 3). As shown in Table 4, multivariate regression analysis revealed that intramedullary hemorrhage and cord compression on MRI at first examination were significant prognostic factors for complete motor paralysis following CSCI (OR = 8.4, 95% CI = 1.2–58.2, $P < 0.05$ and OR = 14.4, 95% CI = 2.5–82.8, $P < 0.01$, respectively). In contrast, multivariate analyses found no significant differences in the variables related to the presence of DM and complete loss of motor and sensory function (AIS grade A) at initial examination. Furthermore, CSCIWORA and retention of pin sensation in

Fig. 2 Neurological levels of injury (a) and types of injury (b). Most neurological levels of injury were at C4 or C5 and types of injury was translation injury.

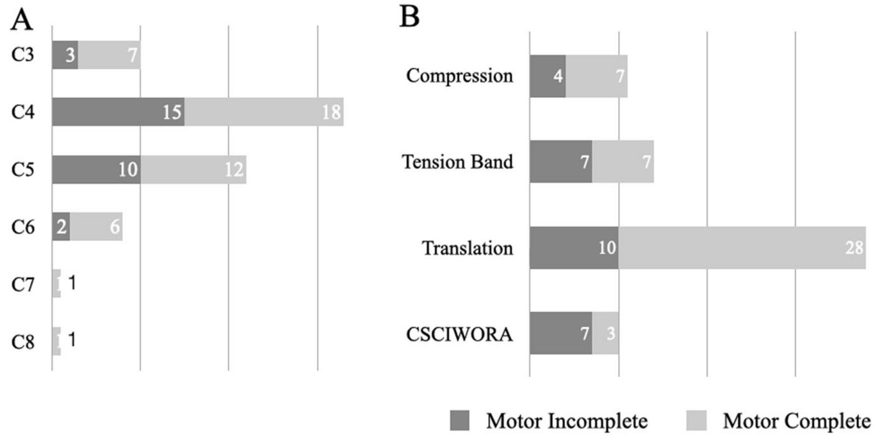

Table 3 Distributions of functional outcomes according to initial clinical factors.

	Motor Complete ($n = 45$)	Motor Incomplete ($n = 28$)	*P*
Participant characteristics			
≤60 years	16 (35.6)	3 (10.7)	0.24
61–75 years	21 (46.7)	11 (39.3)	0.63
≥76 years	8 (17.8)	14 (50.0)	0.51
BMI ≥ 30	2 (4.4)	4 (14.3)	0.20
DM	12 (26.7)	2 (7.1)	0.06
Symptom at Initial Evaluation			
Complete Loss of Motor & Sensory (AIS A)	37 (82.2)	16 (57.1)	0.10
Touch Sensation retained in L/E	4 (8.9)	8 (28.6)	0.17
Pin Sensation retained in L/E	0 (0)	3 (10.7)	0.05
MRI & CT			
Intramedullary Hemorrhage	25 (55.6)	4 (14.3)	**<0.001**
Cord Compression	31 (68.9)	6 (21.4)	**<0.001**
Cord Swelling	17 (37.8)	1 (3.6)	**<0.001**
CSCIWORA	3 (6.7)	7 (25.0)	**<0.05**
OPLL	20 (44.4)	9 (32.1)	0.33
DISH	5 (11.1)	1 (3.6)	0.40
Surgery	**($n = 43$)**	**($n = 26$)**	
<8 h post injury	20 (46.5)	7 (26.9)	0.14
<24 h post injury	38 (88.4)	21 (80.8)	0.37

Values are presented as number (%).

BMI body mass index, *DM* diabetes mellitus, *AIS* American Spinal Injury Association impairment scale, *L/E* lower extremity, *MRI* magnetic resonance imaging, *CT* computer tomography, *CSCIWORA* cervical spinal cord injury without radiological abnormality, *OPLL* ossification of posterior longitudinal ligament, *DISH* diffuse idiopathic skeletal hyperostosis.

Bold values indicate statistical significance.

L/E also did not positively affect clinical outcomes (Table 4).

The overall sensitivity, specificity, positive predictive value and negative predictive value of the presence of intramedullary hemorrhage and/or cord compression in predicting the functional outcomes were 88.9% (40/45), 67.9% (19/28), 81.6% (40/49), and 79.2% (19/23), respectively (Table 5). The diagnostic accuracy was 80.8% (59/73).

Discussion

In this study, we demonstrate potential clinical factors that could predict prognosis following traumatic CSCI by multivariate stepwise regression analyses with statistical adjustment for confounding. The presence of MRI features such as intramedullary hemorrhage and/or severe cord compression in persons with complete motor paralysis at the initial examination are associated with a higher likelihood of irreversible motor paralysis in the chronic phase.

Prognostic factors after SCI

Diagnostic MRI findings can provide us with additional objective information about the neurological condition of the damaged cord. MRI features of hemorrhage and degree of edema were modestly associated with motor recovery post injury [24, 31, 32]. Hemorrhagic changes were described as a hypointensity region surrounded by an area of hyperintensity on T2-weighted MRI [33]. Previous studies showed that cord hemorrhage on early MRI was associated with AIS grade A persons, and thus indicative of poor prognosis for motor recovery [24, 34–36]. Boldin et al. reported that the presence of intramedullary extensive hemorrhage (length of 10.5 mm or more) was found to be associated with poorer prognosis at long-term follow-up [37]. The pattern and degree of signal intensity changes on T1- and T2-weighted MRI were well correlated with functional prognosis [31, 38–40]. Moreover, prevertebral hyperintensity changes and segmental instability were also some of the factors that affect the severity of paralysis [29, 41]. Apart from MRI characteristics, serum

Table 4 Prognostic factors for the complete loss of motor function at the time of discharge.

	Univariate		Multivariate[a]	
	OR (95%CI)	*P*	OR (95%CI)	*P*
MRI & CT				
Cord Compression	7.9 (2.4–29.3)	**<0.001**	14.4 (2.5–82.8)	**<0.01**
Cord Swelling	15.9 (2.2–707.4)	**<0.001**	4.7 (0.4–63.9)	0.24
Intramedullary Hemorrhage	7.3 (2.0–33.7)	**<0.001**	8.4 (1.2–58.2)	**<0.05**
DISH	3.3 (0.3–165.3)	0.40	0.2 (0.0–5.1)	0.31
CSCIWORA	0.2 (0.0–1.1)	**<0.05**	0.8 (0.1–5.6)	0.83
OPLL	1.7 (0.6–5.2)	0.33	1.0 (0.2–6.0)	0.96
Others				
DM	4.6 (0.9–46.4)	0.06	6.2 (0.4–89.2)	0.18
Complete Loss of Motor & Sensory (AIS A)	2.5 (0.8–8.8)	0.10	0.4 (0.1–2.3)	0.28
Pin Sensation retained in L/E	0.0 (0.0–1.5)	0.05	0.0 (0.0-Inf.)	0.99

MRI magnetic resonance imaging, *CT* computer tomography, *DISH* diffuse idiopathic skeletal hyperostosis, *CSCIWORA* cervical spinal cord injury without radiological abnormality, *OPLL* ossification of posterior longitudinal ligament, *DM* diabetes mellitus, *AIS* American Spinal Injury Association impairment scale, *L/E* lower extremity.

[a]The multivariate model included age, gender, and all the variables listed in the table.

Bold values indicate statistical significance.

Table 5 Significant prognostic factors and clinical outcomes at the time of discharge.

	Motor complete	Motor incomplete	Total
Prognostic Factor (+)	40 (true positive)	9 (false positive)	49
Prognostic Factor (−)	5 (false negative)	19 (true negative)	24
Total	45	28	73

Sensitivity: 88.9% (40/45); Specificity: 67.9% (19/28); Positive Predictive Value: 81.6% (40/49); Negative Predictive Value: 79.2% (19/23); Diagnostic Accuracy: 80.8% (59/73).

hyperglycemia during acute SCI impaired functional improvement [42]. In contrast, early surgical reduction of dislocation and younger age (<50) at injury were found to be associated with better prognosis in cases with incomplete SCI [43–46]. Although these previous studies have evaluated the effect of individual risk factors on future functional prognosis, the influence of confounding factors were not well considered from the statistical viewpoint, indicating the necessity of investigating not only MRI findings but also among MRI features and other multiple clinical factors simultaneously.

Possible implications

Although we assessed several possible explanatory factors such as cord swelling on MRI, presence of DM, OPLL, or DISH, which have been reported to be predictive of prognosis [20, 42, 47], no significant associations were identified by multivariate stepwise regression analyses. Furthermore, CSCIWORA, early surgical intervention (<8 h) or younger age at injury also did not positively affect clinical outcomes at final follow-up. Indeed, previous studies about surgical timing reported by Fehlings et al. demonstrated the effectiveness of early decompression surgery [48], but our study does not prove the efficacy of early surgical intervention in persons with complete motor paralysis. The possible reason for such differences is due not to the surgical timing and surgical treatment itself, but to differences in the proportion of included study participants with recovery potential. Furthermore, Kawano et al. reported that despite early surgical intervention, the recovery rates of persons with AIS grade A with bone injury was significantly worse than that of without bone injury [49], suggesting that consideration whether or not a CSCI person with complete motor paralysis at the initial examination has a negligible chance of recovering meaningful motor function before invasive treatment, is important for achieving maximum therapeutic benefits.

In this study, the presence of intramedullary hemorrhage change and/or more than 50% of cord compression at initial MRI were statistically demonstrated to be significant risk factors for complete paralysis in the chronic phase. Although, our results were supportive confirmation of previous studies, a qualitative prediction could be possible by combining initial AIS grade with these MRI findings.

Limitations

This study has several limitations. First, the timing of initial and final assessment is different for each person. It is known that the severity of paralysis dramatically alters within the first 2 weeks post-SCI [50], whereas the neurological recovery after injury reaches a plateau after 6 months post injury [25, 51, 52], leading to difficulties in unifying baseline neurologic status for research purposes. Indeed, the median timing of initial assessment was much earlier in average (11.5 h) than 72 h that was considered as more reliable prognostic values following SCI [50]. We attribute this to necessities for surgical treatments for minimization of the secondary damage as soon after arriving hospital as possible, if indicated. Thus, we conducted a retrospective cohort design to estimate clinical factors affecting outcomes, which could be obtainable in the initial evaluation before any invasive intervention. Early identification of subjects with a negligible potential for recovery is particularly important for invasive interventions such as neural stem-cell transplantations and intrathecal administrations of neuro-protective drugs.

Second, the overall sensitivity of either of the MRI characteristics or both in predicting the functional outcomes is 88.9% (40/45), whereas specificity is 67.9% (19/28), indicating that these findings are not always robust clinical prognostic factors (Table 5). In general, previous experimental animal studies revealed that if ~5–25% of the axons in the injured spinal cord were spared, motor function would be retained [53–56]. Consequently, our speculated pathology underlying the intramedullary hemorrhage and severe cord deviation on MRI findings could be a large cavity formation or transection of the spinal cord itself. Indeed, conventional MRI could detect pathological changes after SCI [57], but the information provided by T1- and T2-weighted MRI of the spinal cord is essentially limited and we believe that quantitative assessments of the injured spinal cord could provide further beneficial information in the future [58–60].

Third, the sample size and selection of the clinical variables for analysis are small and somewhat arbitrary. Indeed, ambulatory function is reasonable and comprehensive outcome to define, but only four out of 73 participants with complete motor paralysis at baseline had acquired the ability. We, therefore, defined the good clinical outcome as any and all motor functional recovery below the level of injury, regardless of ambulatory status. Moreover, although pinprick preservation was considered more reliable than light touch sensation in predicting the recovery of ambulatory function after SCI [61], it failed to reach statistical significance as a predictor among these population, possibly because there were only three persons who had retained pin sensation in L/E at baseline. Furthermore, this study is a retrospective cohort largely based on a SCI database at a single institution. So, we could not include a myriad of other diseases and factors into multivariance analyses, which needs to be confirmed in future prospective studies with a larger sample size.

Conclusion

This study shows the relationships between the presence of intramedullary hemorrhage and/or severe cord compression on initial MRI following CSCI and enduring motor paralysis at the time of discharge. Such negative MRI findings are useful early predictors of irreversible complete motor paralysis in the chronic phase. Conversely, early identification of subjects with a negligible potential for recovery could be possible by referring to these negative findings.

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Author contributions TK and KS designed the research; TK, KS, SMH, SI, OT, MK, and MO analyzed the data; TK and KS wrote the paper; MT, NI, MN, MM, and AM supervised the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by our institution's review board. We certify this all applicable institutional regulations concerning the ethical use of human volunteers were followed during the course of this research.

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