Prognostic Factors for the Postoperative Improvement of Spinal Cord-Related Neuropathic Pain in Patients with Degenerative Cervical Myelopathy

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Abstract:

Introduction: The number of patients with degenerative cervical myelopathy (DCM) requiring surgical treatment has markedly increased in today's aging society. Such patients often exhibit impaired activities of daily living because of motor dysfunction as well as neuropathic pain (NeP). Although many studies have demonstrated the safety and efficacy of surgical treatment for DCM, residual postoperative NeP has not been well described. Therefore, this study aimed to identify the predictors of postoperative NeP improvement in patients with DCM.

Methods: This retrospective study included 92 outpatients with postoperative chronic NeP (≥3 months) related to DCM. Data were obtained from clinical information, magnetic resonance imaging (MRI) findings, and patient-based questionnaires using the Neuropathic Pain Symptom Inventory (NPSI) and the Brief Scale for Psychiatric Problems in Orthopaedic Patients. Univariate and multivariate analyses were performed for patients with NPSI improvement rates <30% and ≥30% to identify prognostic factors.

Results: Among 92 patients, 61 (66.3%) had residual NeP, with a low improvement rate even after surgery. The independent negative prognostic factors for NeP improvement after surgery were older age at operation (odds ratio (OR): 0.932), longer symptom duration before surgery (OR: 0.589), and higher preoperative NPSI score (OR: 0.932). The cut-off value of symptom duration before surgery for postoperative NeP improvement was 1 year. By contrast, the preoperative Japanese Orthopaedic Association score and MRI findings, including signal intensity change and the degree of spinal cord compression, were not associated with postoperative NeP improvement. Moreover, even in patients with an NPSI improvement rate ≥30%, the NPSI subscores for deep pain and paresthesia/dysesthesia remained high.

Conclusions: Discrepancies between physician- and image-based assessments and patient-based assessments were identified as factors associated with improvement in postoperative NeP. Our findings are important for both spine surgeons and patients to manage patient expectations with respect to recovery during the postoperative course.

Keywords:
degenerative cervical myelopathy, neuropathic pain, spinal cord-related pain, prognostic factors, postoperative improvement, patient-based questionnaires

Introduction

Degenerative cervical myelopathy (DCM), such as cervical spondylotic myelopathy (CSM), ossification of the posterior longitudinal ligament (OPLL), and cervical disc herniation, is common and is proportionately increasing with the aging population[1]. Patients with this disease often exhibit impaired activities of daily living because of motor dysfunction as well as neuropathic pain (NeP), accompanied by an abnormal sensation and numbness. A cross-sectional study of patients with spinal disorders in Japan reported a high incidence of NeP in patients with CSM (77.3%) and OPLL (75.7%)[2]. In another nationwide cross-sectional study of patients with spinal cord-related NeP (chronic NeP in patients

with spinal cord-associated disease) in Japan, 62.5% of the patients exhibited pain at the spinal segment, whereas 38.7% had below-level lesions. Furthermore, 43.0% of patients in this cohort presented with allodynia[3]. Surgical treatment is recommended for patients with progressive myelopathy; nevertheless, NeP often persists after surgery. Previous studies have indicated that 41% of patients with CSM and 60% of patients with OPLL exhibit postoperative residual NeP[4], which is associated with low satisfaction with surgery as well as significantly reduced health-related quality-of-life and increased economic costs[5-7].

A previous study indicated that the response rate to pharmacotherapy is lower in patients with spinal cord-related pain than in those with radicular pain and cauda equina syndrome, despite the development of NeP medications[8]. In addition, many studies have demonstrated the safety and efficacy of surgical treatment for DCM; however, residual postoperative NeP has not been well described. To understand the risk factors for postoperative residual NeP, treatment strategies for increased NeP recovery after surgery should be considered. Therefore, this study aimed to review the clinical and imaging findings in patients with DCM and postoperative residual NeP and to identify the predictors of postoperative NeP recovery in this population.

Materials and Methods

Study design

We performed a retrospective study involving 92 outpatients with postoperative residual chronic cervical spinal cord-related NeP who visited our hospital between 2020 and 2021 and had received a fixed dose of pregabalin, mirogabalin, duloxetine, or neurotropin for ≥3 months. Diagnosis of chronic spinal cord-related NeP was based on the following criteria: (1) persistent pain and/or numbness for ≥3 months above, at, or below the level of the affected spinal cord segment, identified by using magnetic resonance imaging (MRI); (2) sensory disturbance at or around the pain region; (3) compressive lesions, signal intensity areas, intumescences, or spinal cord atrophy, confirmed by using imaging studies consistent with neurological findings; (4) poor response to nonsteroidal anti-inflammatory drugs; and (5) clinically confirmed absence of neurodegenerative diseases, brain diseases, and peripheral nerve disorders (e.g., diabetic neuropathy and strangulated neuropathy), as described previously[3]. Patients who had no pain (only residual numbness and/or hyper-/hypoesthesia) were excluded from this study. The following data were also obtained: basic information (age, sex, body mass index [BMI], duration of pain before surgery, and symptom duration at follow-up), onset pattern (slowly progressive [>3 months], acute progressive [within a few months], and deterioration after minor trauma), diabetes as a comorbidity, underlying disorders, surgical procedures (anterior or posterior decompression), preoperative Japanese Orthopaedic Association (JOA) scores, and drug informa-

tion. Three senior spine surgeons performed all the neurological evaluations. The study protocol was approved by the Human Ethics Review Committee of our University Medical Faculty and strictly followed the Clinical Research Guidelines of the Ministry of Health, Labor, and Welfare of the Japanese Government.

MRI findings

We evaluated the presence of a significant signal intensity change in the spinal cord on a T2-weighted MRI. Based on the morphologic classification on MRI, the MRI signal intensity was also classified as isointense, mildly/severely hyperintense, and cystic formation (Fig. 1A)[9-11]. A high-intensity area and/or the largest compression lesion on T2-weighted MRI was considered as the affected segment of the cervical spinal cord (upper [C1-C5]/lower [C6-C8] cervical spinal cord). In addition, the spinal cord diameter was measured at both the non-compression lesion (a) and the largest compression lesion (b) on T1-weighted MRI, and the extent of the spinal cord compression was calculated using the following equation: $[(a-b)/a\times100]$ (Fig. 1B)[12,13]. All measurements were performed by two observers. Each measurement was performed thrice, and the average value was calculated.

Patient-based questionnaires

Two patient-based questionnaires were used in this study. The first was the Japanese version of the Neuropathic Pain Symptom Inventory (NPSI), which was regarding pain before surgery and at follow-up[14,15]. Subscores were evaluated for burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia within this scoring system (10 possible points for each subscale, with a possible total of 50). The pain reduction rate (%) was calculated as (baseline NPSI score − follow-up NPSI score)×100/baseline NPSI score. Nonresponders were identified as the proportion of patients with a <30% reduction in the NPSI score from baseline to follow-up. The second questionnaire was the Brief Scale for Psychiatric Problems in Orthopaedic Patients (BS-POP), which was used to evaluate psychiatric problems at follow-up[16]. The BS-POP has doctor and patient versions, with cut-off values of ≥10 and ≥15, respectively, as indicators of psychiatric problems.

Statistical analyses

Patients with NPSI improvement rates <30% and ≥30% were compared. Categorical variables were compared using the chi-squared test or the nonparametric Mann-Whitney U test. Significant factors in the univariate analysis were included in the multivariate regression model. For measurement of radiological parameters, the inter- and intra-observer reliabilities were assessed by calculating intraclass correlation coefficients (ICCs). ICC (1,3) and ICC (2,3) values >0.75 were considered to represent good to excellent reliability. Odds ratios (ORs) and 95% confidence intervals
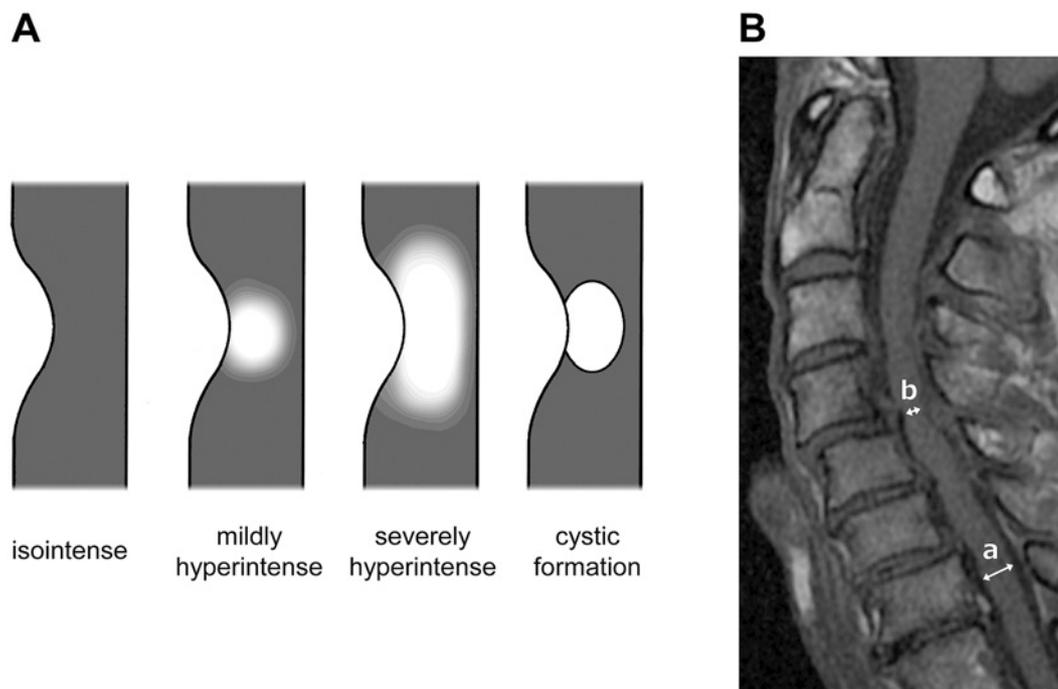
Figure 1. (A) Morphological classification of signal intensity changes on T2-weighted magnetic resonance imaging (MRI). (B) The rate of spinal cord compression was calculated using the T-1 weighted image with the formula [(a−b)/a] ×100.

were calculated to identify independent predictors for NPSI improvement ≥30% of spinal cord-related NeP after surgery. Statistical significance was set at P<0.05. The appropriate cut-off was defined as the point on the curve nearest to the upper-left corner of the receiver operating characteristic (ROC) graph. Then, we used the area under the curve (AUC) to assess how accurate the parameter is as a predictor. All 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).

Results

Patients' background and clinical characteristics

Among the 92 patients with spinal cord-related NeP, 61 (66.3%) had poor pain reduction after surgery (nonresponders; NPSI improvement rate <30%). A comparison of the background and clinical characteristics of patients with and without postoperative NPSI improvement rates ≥30% is shown in Table 1. In the univariate analysis, age at operation (P=0.003) and symptom duration before surgery (P=0.001) were significantly higher and longer in patients with poor postoperative pain reduction. However, no differences were observed in terms of sex, BMI, diabetes as a comorbidity, symptom onset pattern, symptom duration at follow-up, underlying disorders, surgical procedures, preoperative JOA scores, and types of drugs.

Differences in preoperative MRI findings

In the univariate analysis, no significant differences in preoperative MRI findings (the presence of signal intensity change, morphological classification of signal intensity change, affected segment, and spinal cord compression ratio) were observed (Table 2). The inter- and intra-observer reliabilities for these imaging findings were both good to excellent (ICC (1,3)=0.974-0.986, ICC (2,3)=0.896-0.909).

Association of patient-based questionnaires with residual NeP

A comparison of patient-based questionnaires with and without postoperative NPSI improvement rates ≥30% is shown in Table 3. In the univariate analysis, the preoperative total NPSI score was significantly higher in patients with poor postoperative pain reduction. Furthermore, with respect to the NPSI subscores, we observed that deep pain and paresthesia/dysesthesia remained at high levels even among responders. Changes in the total NPSI score were significantly higher in responders. Among the 92 patients, 42 (45.7%) had psychiatric problems (with BS-POP ≥15 for patients and ≥10 for doctor versions). Nevertheless, no significant difference in BS-POP was identified between responders and nonresponders.

Prognostic factors for residual postoperative spinal cord-related NeP

We performed a multivariate logistic regression analysis including significant variables from the univariate analysis to identify the independent prognostic factors for residual post-

Table 1. Comparison of Patients' Background and Clinical Characteristics According to the NPSI Score Improvement Rate.

Variable	NPSI improvement rate <30% (nonresponders; n=61)	NPSI improvement rate ≥30% (responders; n=31)	P value
Age at operation, median [IQR], years	69.00 [61.00–74.00]	62.00 [52.00–68.00]	**0.003**
Male/female, n (%)	26 (42.6)/35 (57.4)	16 (51.6)/15 (48.4)	0.551
BMI, median [IQR]	23.12 [22.12–25.80]	23.60 [21.65–25.48]	0.967
Diabetes as comorbidity, n (%)	20 (32.8)	9 (29.0)	0.897
Duration before surgery, median [IQR], years	2.00 [1.00–3.00]	1.00 [0.50–2.00]	**0.001**
Symptom onset pattern, n (%)			
Slowly progressive	49 (80.3)	23 (74.2)	0.712
Acute progressive	10 (16.4)	6 (19.4)	
Deterioration after minor trauma	2 (3.3)	2 (6.5)	
Symptom duration at follow-up, median [IQR], years	6.00 [3.20–9.00]	6.00 [2.75–9.60]	0.951
Underlying disorders, n (%)			
CSM	35 (57.4)	14 (45.2)	0.302
OPLL	23 (37.7)	13 (41.9)	
CDH	3 (4.9)	4 (12.9)	
Operative procedures, n (%)			
Anterior	12 (19.7)	10 (32.3)	0.281
Posterior	49 (80.3)	21 (67.7)	
Preoperative JOA, median [IQR]	12.00 [11.00–13.00]	13.00 [11.50–13.00]	0.378
Drug, n (%)			
Pregabalin	30 (49.2)	12 (38.7)	0.288
Mirogabalin	15 (24.6)	12 (38.7)	
Duloxetine	9 (14.8)	6 (19.4)	
Neurotropin	7 (11.5)	1 (3.2)	

NPSI: Neuropathic Pain Symptom Inventory; IQR: interquartile range; BMI: body mass index; CSM: cervical spondylotic myelopathy; OPLL: ossification of posterior longitudinal ligament; CDH: cervical disc herniation; JOA: Japanese Orthopaedic Association

Table 2. Differences in the MRI Findings According to the NPSI Score Improvement Rate.

Variable	NPSI improvement rate <30% (nonresponders; n=61)	NPSI improvement rate ≥30% (responders; n=31)	P value
Signal change on MRI, n (%)	52 (85.2)	29 (93.5)	0.412
Classification of signal changes on MRI, n (%)			
1 (isointense)	11 (18.0)	3 (9.7)	0.304
2 (mildly hyperintense)	27 (44.3)	10 (32.3)	
3 (severely hyperintense)	16 (26.2)	12 (38.7)	
4 (cystic formation)	7 (11.5)	6 (19.4)	
Affected segment, n (%)			
Upper (C1–C5)	36 (59.0)	20 (64.5)	0.776
Lower (C6–C8)	25 (41.0)	11 (35.5)	
Spinal cord compression ratio, median [IQR]	45.36 [32.11–56.37]	39.39 [27.05–50.00]	0.267

NPSI: Neuropathic Pain Symptom Inventory; MRI: magnetic resonance imaging; IQR: interquartile range

operative spinal cord-related NeP (Table 4). In this analysis, older age at operation, longer duration before surgery, and higher preoperative NPSI total score were identified as independent negative prognostic factors.

The prediction of the duration before surgery was calculated using the ROC curve (Fig. 2). The AUC for the duration before surgery was 0.712. The cut-off value for postoperative NeP improvement derived from the AUC data was a 1-year duration before surgery (sensitivity, 71.0%; specificity, 68.9%).

Discussion

A review article estimated the incidence and prevalence of DCM to be at a minimum of 41 and 605 per million in North America, respectively, with increasing surgical rates[1]. A meta-analysis also estimated the prevalence of CSM to be 16 per million[17]. A cohort study in Japan reported that the prevalence of a narrow cervical canal (diameter of cervical spinal canal <13 mm) was 13.5%, and 10.1% of such patients had clinical cervical myelopathy[18]. These reports suggest that the prevalence of cervical spinal canal stenosis is

Table 3. Differences in Data from the Patient-Based Questionnaires According to the NPSI Score Improvement Rate.

Variable	NPSI improvement rate <30% (nonresponders; n=61)	NPSI improvement rate ≥30% (responders; n=31)	P value
Preoperative total NPSI score, median [IQR]	23.00 [13.00–28.33]	14.00 [8.75–20.92]	**0.002**
Preoperative NPSI subscore			
Superficial pain	5.00 [3.00–7.50]	3.50 [0.00–5.25]	**0.006**
Deep pain	5.00 [0.0–7.00]	4.00 [0.00–6.00]	0.262
Paroxysmal pain	3.50 [0.00–5.00]	0.00 [0.00–2.50]	**0.007**
Evoked pain	4.33 [1.33–7.00]	1.67 [0.00–4.00]	**0.022**
Paresthesia/dysesthesia	5.00 [3.00–7.50]	4.00 [2.50–6.25]	0.060
Changes in total NPSI score	3.00 [1.25–4.00]	7.00 [4.50–10.42]	**<0.001**
BS-POP			
Scores for patient ≥15 and for doctor ≥10	32 (52.5)	10 (32.3)	0.106
Score for patients	16.00 [13.00–19.00]	14.00 [11.50–17.50]	0.127

NPSI: Neuropathic Pain Symptom Inventory; IQR: interquartile range; BS-POP: Brief Scale for Psychiatric Problems in Orthopaedic Patients

Table 4. Multivariate Logistic Regression Analysis of Predictors for NPSI Improvement ≥30% of Spinal Cord–Related Neuropathic Pain after Surgery.

Variables	OR	95% CI	P value
Age at operation	0.932	0.882–0.985	0.0122
Duration before operation	0.589	0.378–0.918	0.0195
Preoperative NPSI total score	0.932	0.880–0.986	0.0145

NPSI: Neuropathic Pain Symptom Inventory; OR: odds ratio; CI: confidence interval
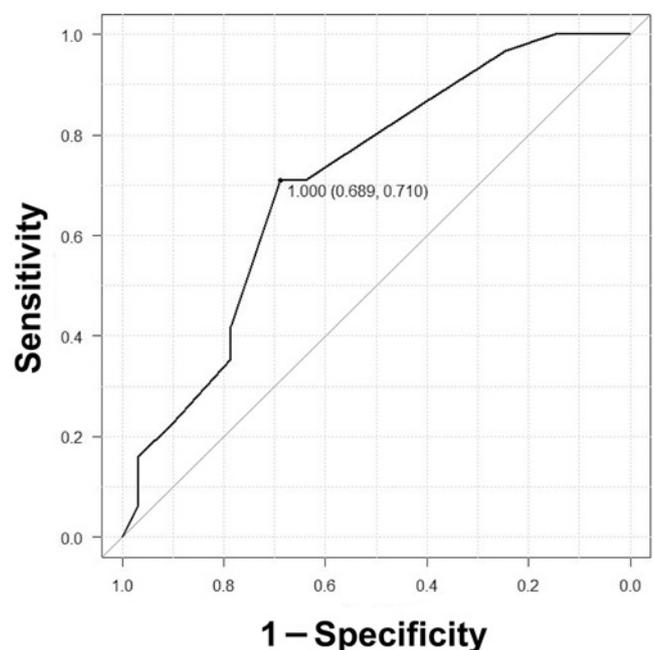

Figure 2. Receiver operating characteristic (ROC) curve of the symptom duration before surgery for postoperative neuropathic pain (NeP) improvement and determination of the cut-off value.

higher in Japan, and therefore, the patient population presenting with myelopathy could likewise be higher. Furthermore, the prevalence of OPLL is reportedly higher in Asian countries than in Western countries: 3.7% using the lateral view of cervical radiography and 6.3% using computed tomography in Japan[19,20]. The cervical spinal canal diameter is a significant risk factor for the development of cervical myelopathy[18,21], and spinal cord-related NeP in such patients should receive greater attention in Asian countries.

A previous study indicated that 74.8% of patients with spinal cord-related pain had NeP with an NPSI score >10 (moderate to severe pain) prior to treatment; moreover, patients with a history of spine surgery had significantly higher NPSI scores than those without (17.2 vs. 13.4). Additionally, the average NPSI score after pharmacotherapy ≥3 months with or without surgery was 12.5[8]. Therefore, this study aimed to investigate the preoperative predictors of NeP improvement in patients with spinal cord-related NeP. Among the patient background information, age at surgery and symptom duration before surgery were identified as independent predictors for NeP improvement after surgery and pharmacotherapy. In addition, a symptom duration before surgery ≥1 year was one of the risk factors for poor improvement of NeP after surgery. Several studies have reported that older age and symptom duration are associated with worse functional, disability, and quality-of-life outcomes after surgery for DCM[22-24]. Interestingly, the preoperative JOA score was not a significant predictor of NeP im-

provement in this study, despite many studies indicating that the preoperative severity of neurological symptoms affects the surgical outcome[22-24]. A multicenter study reported a discrepancy between functional outcomes and self-reported health status after surgery for DCM[25]. This study suggested that older age, increased body pain, and reduced upper extremity motor function improvement were associated with worsened or unchanged general health, despite clinically significant improvements in overall postoperative function. It is possible that the degree of NeP could not be captured by the JOA score. Furthermore, a discrepancy can be observed between physician- and patient-based assessments, with the patient's expectations on NeP improvement being directly related to postoperative patient satisfaction. Therefore, the lack of preoperative assessments for NeP could lead to a disso-

ciation between postoperative functional improvement and patient satisfaction. Our results can be used by spine surgeons to manage patient expectations with respect to recovery across the postoperative course and aid preoperative patient education.

The presence of signal intensity change in the cervical spinal cord on T2-weighted MRI in patients with DCM reflects chronic spinal cord compression lesions. However, the prognostic value of these findings remains controversial, especially regarding its relationship with NeP severity. A previous meta-analysis of patients with CSM has reported a postoperative JOA recovery ratio in the T2-weighted (+) group that was lower than that in the T2-weighted (−) group[26]. A multicenter study also suggested that age and signal intensity change were significantly associated with the JOA score in patients with OPLL requiring surgery[22]. However, some studies have suggested that high signal intensity on T2-weighted MRI alone does not predict outcomes in patients with DCM[27,28]. Some studies have also suggested that the preoperative transverse area of the spinal cord is associated with postoperative neurological improvement[23,29]. In this study, preoperative MRI findings were not predictors of postoperative NeP improvement. The value of MRI findings as prognostic factors for functional and NeP recovery might be different, and the prognosis of functional impairment might not be essentially associated with that of NeP.

The NPSI used in this study was designed to evaluate different symptoms of NeP, which have been divided into five subgroups: superficial spontaneous pain, deep spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia[14,15]. Previous studies have suggested that the lower response rate observed among patients with spinal cord-related pain could be due to a lower response to paresthesia/dysesthesia[3,8,10]. In this study, even in patients with an NPSI improvement rate ≥30%, the NPSI subscores for deep pain and paresthesia/dysesthesia remained high (4.0). In addition, there were no cases of complete improvement for preoperative paresthesia/dysesthesia. It is therefore important to provide patients with information in the preoperative setting; in particular, that higher preoperative NeP and cases of paresthesia/dysesthesia are unlikely to improve even after surgery. This should help prevent low postoperative patient satisfaction due to preoperative overestimation for postoperative improvement. Postoperative residual NeP may also affect psychological conditions. Previous studies have found that compared to the national average, the scores for all short-form 36 subitems were significantly lower for patients with NeP[10]. Hence, the 45.7% of patients in our study who had psychiatric problems during follow-up was a matter of concern. Although no significant difference was observed between responders and nonresponders, the BS-POP score tended to be higher in nonresponders. As activities of daily living and quality-of-life decline due to residual NeP and are closely associated with the psychological condition, multidisciplinary support is important to control postoperative residual NeP[30].

The study has certain limitations, including the retrospective single-institution design, which included only 92 patients, as well as the possibility that the results may have been confounded by factors that we could not to adjust for. Some results lack statistical power; moreover, the results may change as the sample size increases. Thus, large, prospective, multicenter clinical studies are needed to provide further evidence to validate our results. In addition, the accuracy of the diagnosis of spinal cord-related NeP might have affected the accuracy of the study results as it would be rather difficult to definitively attribute the patient's symptoms to a spinal cord lesion. Despite these limitations, we believe that our findings provide novel insights that could support guidance on the therapeutic management of patients with spinal cord-related NeP.

In conclusion, as many as 66.3% of patients with spinal cord-related NeP who have undergone surgical treatment experience poor NeP improvement after surgery. The negative prognostic factors for NeP improvement after surgery were older age at operation, longer symptom duration before surgery, and higher preoperative NPSI scores. The cut-off value of symptom duration before surgery for postoperative NeP improvement was 1 year. The preoperative JOA score and preoperative MRI findings, including signal intensity changes and the degree of spinal cord compression, were not associated with postoperative NeP improvement. Severe postoperative residual NeP could occur, especially in cases with the paresthesia/dysesthesia NeP subtype. This information is significant for both spine surgeons and patients to recognize the importance of the therapeutic window for surgery and to manage patient expectations with respect to recovery during the postoperative course.

Medical Faculty (Approval Number 2014046), and it strictly followed the Clinical Research Guidelines of the Ministry of Health, Labor, and Welfare of the Japanese Government.

Informed Consent: Before filling out the questionnaire, written informed consent was obtained from each patient.

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