

# Risk Factor Analysis of Perioperative Complications in Patients with Rheumatoid Arthritis Undergoing Primary Cervical Spine Surgery

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## Research Article

**Keywords:** three to ten, rheumatoid arthritis, cervical spine surgery, perioperative complications, occipito-cervical/thoracic fusion, occipito-cervical fusion, cervical spine lesion, subaxial subluxation ASA-PS, prednisolone

**Posted Date:** December 29th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-1196439/v1>

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**Version of Record:** A version of this preprint was published at Arthritis Research & Therapy on March 31st, 2022. See the published version at <https://doi.org/10.1186/s13075-022-02767-0>.

# Abstract

**Background:** Rheumatoid arthritis (RA) often causes cervical spine lesions as the disease condition progresses, which induce occipital neuralgia or cervical myelopathy requiring surgical interventions. Meanwhile, patients with RA are susceptible to infection or other complications in the perioperative period because they frequently have comorbidities and use immunosuppressive medications. However, the risk factors or characteristics of patients with RA who experience perioperative complications after cervical spine surgery remain unknown. A risk factor analysis of perioperative complications in patients with RA who underwent primary cervical spine surgery was conducted in the present study.

**Methods:** A total of 139 patients with RA who underwent primary cervical spine surgery from January 2001 to March 2020 were retrospectively investigated. Age and height, weight, serum albumin, serum C-reactive protein, American Society of Anesthesiologists Physical Status (ASA-PS), Charlson comorbidity index, medications used, cervical spine lesion, surgery time, bleeding volume, and procedures were collected from medical records to compare the patients with complications to those without complications after surgery. The risk factors for perioperative complications were assessed by univariate and multivariate logistic regression analysis.

**Results:** Twenty-eight patients (20.1%) had perioperative complications. Perioperative complications were significantly associated with the following factors [data presented as odds ratio (confidence interval)]: lower height [0.928 (0.880-0.980),  $p=0.007$ ], higher ASA-PS [2.296 (1.007-5.235),  $p=0.048$ ], longer operation time [1.013 (1.004-1.021),  $p=0.003$ ], more bleeding volume [1.004 (1.000-1.007),  $p=0.04$ ], higher rates of vertical subluxation [2.914 (1.229-6.911),  $p=0.015$ ] and subaxial subluxation (SAS) [2.507 (1.063-5.913),  $p=0.036$ ], occipito-cervical (OC) fusion [3.438 (1.189-9.934),  $p=0.023$ ], and occipito-cervical/thoracic (long) fusion [8.021 (2.145-29.99),  $p=0.002$ ] in univariate analyses. In multivariate analyses, lower height [0.915 (0.860-0.974),  $p=0.005$ ], higher ASA-PS [2.622 (1.023-6.717),  $p=0.045$ ] and long fusion [7.289 (1.694-31.36),  $p=0.008$ ] remained risk factors. High-dose prednisolone use [1.247 (1.024-1.519),  $p=0.028$ ], SAS [6.413 (1.381-29.79),  $p=0.018$ ], OC fusion [17.93 (1.242-258.8),  $p=0.034$ ] and long fusion [108.1 (6.876-1699),  $p<0.001$ ] were associated with severe complications.

**Conclusions:** ASA-PS and long fusion could be indicators predicting perioperative complications in patients with RA after cervical spine surgery. In addition, cervical spine lesions requiring OC fusion or long fusion and high-dose prednisolone use were suggested to be risk factors for increasing severe complications.

## Background

Rheumatoid arthritis (RA) is a systemic inflammatory disease that induces not only destructive arthritis in the systemic joint but also distinct spine lesions (1–3). Surgical interventions are often required as these musculoskeletal disabilities progress (3–6). In the cervical spine, RA-related spine lesions can cause occipital neuralgia and myelopathy, which are major issues that interfere with activities of

daily living (7,8). Surgical interventions are mandatory to relieve neck pain, to improve physical function, and to decrease the risk of mortality when patients are treated conservatively (9–11).

RA-derived systemic inflammation leads to spinal pathology through bony erosion and ligamentous laxity (12–16). The prevalence of cervical spine lesions has been reported across a wide range, 9% to 88%, of patients with RA who have neck pain (3,8,15). In addition, five percent of patients with cervical spine lesions because of RA had observable neurological deficits (7). Although surgical intervention has been the mainstay of treatment to resolve robust occipital pain and neurological deficits, perioperative complications, including infections, are of concern because patients with RA are more likely to have comorbidities and take immunosuppressive agents, such as biologics and JAK inhibitors. In various retrospective cohort series, the incidence of perioperative complications was reported to range from 8 to 30% (17–20). However, the risk of perioperative complications after cervical spine surgery in patients with RA has not been well established.

The purpose of this study was to clarify the risk factors for perioperative complications in consecutive patients with RA who underwent cervical spine surgery at one institution. Demographic status, RA medication, type of cervical spine lesion, and surgery-related factors were retrospectively investigated. In addition, we evaluated comorbidities at the time of surgery that might affect the occurrence of complications using the Charlson comorbidity index (CCI) (21–23) and American Society of Anesthesiologists Physical Status (ASA-PS) (24,25) to assess preoperative physical condition.

## Patients And Methods

From January 2001 to March 2020, 139 patients with RA underwent primary cervical spine surgery in our institution because of cervical myelopathy or occipital neuralgia. We reviewed medical records during a series of hospitalizations that underwent surgery and confirmed any perioperative complications. Physical information (sex, age, height, and weight), disease history of RA including medication used, laboratory data (serum albumin and serum C-reactive protein), comorbidities, radiographs to clarify the cervical spine lesion with RA before surgery, and surgical procedure were collected. In accordance with Common Terminology Criteria for Adverse Event (CTCAE) version 5, which displays grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on the general guidelines, severe complications were defined as grade 3, which is severe or medically significant but not immediately life threatening (hospitalization or prolongation of hospitalization indicated, disabling, or limiting selfcare ADLs) or higher grades. All patients fulfilled the American Rheumatism Association 1987 revised criteria or the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA.

## Evaluation of comorbidities

Comorbidities were evaluated by the CCI and ASA-PS. The CCI is a weighted index to predict short-term and long-term outcomes, including mortality rates, by assessing comorbidity levels by taking

into account both the number and severity of 19 predefined comorbid conditions and age (21–23). The score can range from 0 to 37. The ASA-PS classification system was used to assess and communicate patients' preanesthesia medical comorbidities; patients are classified into six classes based on the type of comorbidities, lifestyle factors such as smoking and alcohol consumption, and physical condition, including body mass index and the status of respiration and circulation: class I: normal health; class II: mild systemic disease; class III: severe systemic disease; class IV: severe systemic disease that is a constant threat to life; class V: moribund patients who are not expected to survive without the operation; and class VI: a declared brain-dead patient (24,25).

## Cervical spine lesion

Cervical spine lesions with RA were classified into three types by radiographic imaging (Fig. 1). Atlantoaxial subluxation (AAS) was defined as an expansion of the atlantodental interval (ADI) of more than 3 mm in the flexed position (Fig. 1A) (3). The ADI was measured from the posterior edge of the anterior arch of the atlas to the anterior edge of the axis dens in the lateral view. Vertical subluxation (VS) was assessed by the Ranawat C1-C2 index (3,16). The measurement of the Ranawat index was made from the centre of the pedicles of the axis to a line connecting the midpoint of the anterior and posterior arches of the atlas. Anything less than 15 mm for men and 13 mm for women confirmed VS (Fig. 1B). Subaxial subluxation (SAS) was diagnosed as migration of more than 3 mm from the superior vertebra compared to the inferior vertebra (3). Migration distance was measured between posterior walls of adjacent vertebrae (Fig. 1C).

## Procedure

The patients who had prolonged robust occipital pain and progressive neurological deficits even with conservative treatment underwent cervical spine surgery. All surgical treatments were performed by two spine surgeons. Fixative procedures were performed due to occipital neuralgia and/or myelopathy based on the unstable alignment of the cervical spine. Unstable alignment was defined by deterioration of subluxation in the flexed position or reduceable cases in the extended position. VS with robust neck pain was also defined as unstable. The types of fixative procedures were chosen depending on the affected levels of the cervical spine. Atlantoaxial fusion (C1-2 fusion) was performed for unstable AAS (Fig. 1E). After reducing AAS under general anaesthesia, a Magerl screw (Medtronic Sofamor Danek, USA) was inserted from the inferior articular process of C2 to the lateral mass of C1 (Magerl procedure) (26). In addition to stabilization of the bilateral facet joint between C1 and C2, monocortical autograft bone from the ilium was transplanted on the decorticated arch of the C1 and C2 vertebrae before fixing it on the backside of both arches with sublaminar taping or wiring (Brooks procedure) (27). VS was stabilized in situ through posterior spine fixation with an occipito-cervical fusion (OC fusion) system (DePuy Synthes, USA) (Fig. 1F). Monocortical autograft bone from the ilium was also transplanted on the backside from the lower edge of the occipital bone to the lamina of the C2 vertebra. Since SAS was

usually accompanied by AAS and VS, occipito-cervical/thoracic fusion (long fusion) was conducted (Fig. 1 G). OC fusion was extended downwards to the thoracic level after correcting the malalignment of SAS under general anaesthesia. Laminoplasty was performed for myelopathy that was not associated with an unstable alignment of the cervical spine (Fig. 1D).

## Statistical analysis

Univariate and multivariate logistic regression analyses were performed for detecting risk factors for perioperative complications. To select the predictive variables for the multivariable analysis, stepwise regression analysis was applied. When there were variables closely related to each other, one of the variables was chosen to enter into stepwise analysis. All tests were two-tailed, and statistical significance was defined by a  $p$  value  $< 0.05$ . The analyses were conducted with JMP ver. 14 (SAS Institute Inc, NC, USA).

## Results

The baseline characteristics of the patients at the time of surgery are shown in Table 1. The mean age was 66.5 years, and the mean disease duration was 19.7 years. Regarding the evaluation of comorbidities, the mean ASA-PS score was 2.3, and the CCI score was 1.6. The proportion of patients taking oral prednisolone was high (84.9%), while that taking methotrexate was approximately 40%. Eighteen patients (13%) took biological agents or JAK inhibitors (infliximab, 1; etanercept, 6; adalimumab, 2; golimumab, 2; abatacept, 2; tocilizumab, 4; baricitinib, 1). Cervical spine lesions due to RA were found in 81.3%; AAS was observed in 66.2%; VS in 43.5%, and SAS in 30.0%. One-third of cervical spine lesions overlapped with each other.

Of the 139 patients who underwent cervical spine surgery, 28 patients (20.1%) experienced perioperative complications (Table 2). Two patients experienced two complications: one had prolonged delirium and delayed wound healing, and the other had separate instances of dural injury and SSI. One-third of the complications were defined as severe ( $n=10$ , 33%), and those were more likely to occur in patients with OC fusion and long fusion (Table 2). Infectious complications were the most common complication (40%,  $n=12$ ), and half of them were SSIs (Tables 2 and 3). There was no significant difference in the incidence of infection with or without the administration of prednisolone, methotrexate, or biologics and JAK inhibitors (Table 3). SSIs also showed no difference based on taking or not taking any particular type of medication (Table 3). There were two patients who died within 90 days after surgery: one died of acute deterioration of interstitial pneumonia at twelve weeks after laminoplasty, and the other died of pneumonia at six weeks after OC fusion.

To identify the risk factors for perioperative complications, baseline characteristics and surgery-related factors were compared between patients with complications and those without complications (Table 4). In the univariate analyses, the patients with complications had significantly shorter height [ $p=0.007$ ], higher ASA-PS [ $p=0.048$ ], and higher prevalence of VS [ $p=0.015$ ] and SAS [ $p=0.036$ ]. Regarding operative

factors, prolonged operation time [ $p=0.003$ ], heavy bleeding [ $p=0.040$ ], OC fusion [ $p=0.023$ , vs. laminoplasty] and long fusion [ $p=0.002$ , vs. laminoplasty] significantly increased the risk for complications (Table 4).

If there were multiple variables that were closely related to each other, one of those variables was selected; all selected variables were entered into stepwise regression analysis to identify candidates for the multivariate model. Although cervical spine lesions and the surgical procedures were supposed to be closely related to each other, they did not completely correspond, and therefore, we performed two kinds of multivariate analyses: one for cervical spine lesions and the other for surgical procedures. Multivariate analysis including cervical spine lesions (Model 1) revealed that short height [ $p=0.005$ ], high ASA-PS [ $p=0.045$ ], and short duration of RA [ $p=0.012$ ] were correlated with an increased risk for complications (Table 5). In the multivariate analysis including surgical procedures (Model 2), short height [ $p=0.034$ ], short duration of RA [ $p=0.017$ ] and performing long fusion [ $p=0.008$ ] were shown to increase complications (Table 5).

One-third of all complications were severe cases (Table 2). We further investigated the risk factors for severe complications. Multivariate analysis revealed that high-dose administration of prednisolone [ $p=0.028$ ], existence of SAS [ $p=0.018$ ], OC fusion [ $p=0.034$ ] and long fusion [ $p<0.001$ ] significantly increased the risk of severe complications (Table 6).

## Discussion

This study was performed to detect the risk factors for complications in patients with RA who underwent all types of cervical spine surgeries. The prevalence of complications was 20.1% in the present study. We newly found that 1) short height, 2) high ASA-PS, 3) short disease duration of RA, and 4) long fusion procedures could be risk factors for perioperative complications. In addition, when focused on severe complications, 5) high-dose prednisolone administration, 6) existence of SAS, and 7) OC fusion and long fusion were suggested to be risk factors.

Patients with RA have been shown to experience a variety of complications after spine surgery more frequently than patients without RA (18,28,29). On the other hand, there was a report that RA itself was not a risk factor for complications after cervical spine surgery (30). Comorbidities could be among the risk factors correlated with perioperative complications after spine surgery, since patients with RA have a higher incidence of not only perioperative complications but also comorbidities than patients without RA (18). Regarding cervical spine surgery, significantly higher incidences of major medical complications and postoperative infection were observed in patients with RA over 65 years old who underwent anterior cervical fusion (19). In addition, the existence of cervical spine lesions by RA was suggested to be a risk factor for SSI (17).

Both the existence of SAS and the long fusion procedures were detected as risk factors for severe perioperative complications after cervical spine surgery for patients with RA. Cervical spine lesions with RA generally start at the atlantoaxial joint, and they progress from AAS to VS and then SAS

(31,32). Patients with SAS are expected to have progressive systemic joint damage (32,33), resulting in multiple comorbidities (34). In the present study, only SAS lesions were not associated with ASA-PS, and the patients with VS or SAS were significantly associated with higher ASA-PS than patients with AAS or without cervical spine lesions [OR: 2.276, 95% CI: 1.130-4.588,  $p=0.0214$ ]. In addition to the risks associated with systemic conditions before surgery, operative procedures for SAS were also related to perioperative complications. Treatment for symptomatic SAS usually requires a long fusion procedure, which fixes many vertebrae and places a much greater burden on the patient's body than laminoplasty or C1-2 fusion (3). In fact, long fusion was associated with significantly longer operation time [laminoplasty: 114 min, C1-2 fusion: 137 min, OC fusion: 168 min, long fusion: 214 min] and heavily bleeding volume [laminoplasty: 69 g C1-2 fusion: 52 g, OC fusion: 75 g, long fusion: 248 g] than the other procedures in the present study. Thus, the presence of preoperative comorbidities and an increase in surgical burden may be associated with perioperative complications in patients with SAS lesions who underwent long fusion. In addition, OC fusion was also detected as a risk factor for severe complications. OC fusion required longer surgery times than laminoplasty and C1-2 fusion, although there was no differences in the amount of bleeding, as shown in the previous discussion. This result suggested that OC fusion placed a moderate surgical burden on the patients but not as much as long fusion. Otherwise, poor general condition or highly invasive OC fusion procedures might influence the incidence of severe complications but not mild/moderate complications.

ASA-PS was generally associated with perioperative complications, such that as the class increased, the risk of complications increased (35). In adult spine surgery, ASA-PS class higher than class III was shown to be a significant risk factor for any complications compared to class II and lower (36,37). Although there was no significant difference, ASA-PS class III or higher also tended to increase the risk for perioperative complications compared to class II and lower [odds ratio: 2.265, 95% CI: 0.974-5.265,  $p=0.058$ ] in the present study. In addition, the mean value of ASA-PS was significantly higher in patients with perioperative complications than in patients with no complications. ASA-PS has been suggested to be one of the predictors of perioperative complications in patients with RA after all cervical spine surgeries. On the other hand, the CCI was not correlated with perioperative complications of cervical spine surgery in patients with RA, although previous reports have suggested that the CCI could be useful to predict perioperative complications in spine surgery(38,39). A previous report also showed a significant correlation between the CCI and ASA-PS (39), whereas there was no correlation in the present study. The CCI represents the simple sum of comorbidities weighted based on adjusted risk of mortality or resource use in the future. The ASA-PS are determined by anaesthesiologists considering not only types of comorbidity but also severity, which suggests that the ASA-PS could reflect the comorbidity status in more detail and more accurately than the CCI. The subtle differences between these two criteria concepts might make a difference in the strength of their relevance to complications depending on the underlying disease.

The use of high-dose prednisolone was also detected as a risk factor for severe perioperative complications. A few reports have investigated the correlation of prednisolone administration with perioperative complications in patients in studies that were not limited to RA (40–42). Prednisolone use

and its dose did not affect the incidence of perioperative complications in patients with Crohn's disease (42) or cause infections, including SSIs, in patients with RA who underwent cervical spine and prosthesis surgery (40,41). However, the use of prednisolone correlated with severe perioperative complications in the present study. Considering the background of the patients who were taking high-dose prednisolone for RA, these patients are expected to have high disease activity and a limited drug selection due to comorbidities. Administration of high-dose prednisolone might only identify a population prone to perioperative complications, and the increased risk for complications may not be an effect of the drug itself.

Infections were one of the considerable perioperative complications in patients with RA, since almost all patients took immunomodulatory reagents. In a US nationwide analysis, infection was the most common complication of spine surgery (18) and was the leading cause of readmission after cervical fusion surgery in patients with RA (43). Among DMARDs, biologics, JAK inhibitors and high doses of glucocorticoids have been associated with an increased risk of infections (44,45). However, conflicting results of biological DMARDs, mainly tumour necrosis factor antagonists, have been reported in many studies, including both increased and unchanged risks of superimposed infections after surgery (46). Regarding spinal surgery, the use of biologic DMARDs or prednisolone did not increase the risk of infection (41). The present study also revealed that postoperative infection, including SSI, was the most common complication but did not increase with any particular medication, such as biologics, JAK inhibitors or prednisolone, after cervical spine surgery. Among the identified risk factors for perioperative complications in this study, only OC fusion was significantly associated with infectious complications [vs. laminoplasty: OR: 4.72, 95% CI: 1.795-48.0,  $p=0.0079$ ].

Physical constitution could affect perioperative complications and anaesthesia management. In fact, obesity correlates with not only comorbidities in patients with RA (47) but also perioperative complications after many types of surgery (48–52). However, there have been only a few reports that shorter patients were at higher risk for perioperative complications, which were shown in coronal and carotid endarterectomy (53,54). Body size was suggested to have a direct impact on technical issues related to the surgery, such as limited access to the surgical field, since both BSA and height have been shown to correlate closely with the diameter of the common carotid artery (55). Surgery in a small, limited field might affect certain kinds of surgical techniques, resulting in an increase in perioperative complications. However, it was difficult to substantiate this possibility with cervical spine surgery because there were no significant inverse correlations between short height and operation time or bleeding volume in the present study.

A shorter duration of RA in the patients with perioperative complications than in the patients without complications was shown in the present study. However, the mean disease duration of RA at the time of cervical spine surgery was 20.2 years in the complication group and 17.6 years in the no-complication group. It is difficult to determine the clinical meaning of this 2.5 year difference over such a long disease duration. A possible reason might be related to the features of cervical spine lesions in patients with RA. Most studies have reported that cervical spine lesions are a feature of longstanding rather than early

disease, which are generally apparent ten years into the natural history of RA(56,57). On the other hand, cervical spine lesions have also been associated with the severity of peripheral radiographic joint damage (8,58), and the extent of progression at cervical spine lesions was well correlated with the number of erosive joints in the hand and foot (32,33). In addition, an increasing number of comorbidities were associated with poorer values for tender joint count and swollen joint count (34). These findings suggested that patients with uncontrollable inflammatory arthritis in the systemic joint progressed to cervical spine lesions early (i.e., with a short disease duration) and tended to have more comorbidities, which resulted in increased perioperative complications after cervical spine surgery.

There were two limitations in the present study. First, there could have been heterogeneity in the background conditions over time. The patients enrolled in the present study were enrolled over the last 20 years. During this 20-year period, the general condition of patients with RA and the pathophysiology of cervical spine lesions has changed, as pharmacological treatment for RA has changed dramatically after the emergence of biologics and JAK inhibitors. Considering that most patients used prednisolone and a few patients used biologics, the patient group in the present study seemed to be a distinct population with relatively progressed RA and some comorbidities. In addition, instruments for fixation have advanced or been modified year after year. These biases could have resulted in an underestimate or overestimate in the analysis. The second limitation was data deficiency. Physical examinations or questionnaires assessing disease activity or physiological function in the patients with RA could not be investigated. Anti-citrullinated protein antibodies, rheumatoid factor or matrix metalloproteinase-3 were not detected in some cases. In addition, many patients did not have radiographs available except for the cervical spine. These data deficiencies limited the ability to directly investigate correlations of perioperative complications with disease activity or progression of RA, biomarker contributions and the existence of systemic joint destruction.

## Conclusion

In conclusion, low height, high ASA-PS, high-dose prednisolone use and the progression of cervical spine lesions in early disease stages could be risk factors for perioperative complications. Since medical treatment of RA has been improved with the T2T strategy using DMARDs and biologics, the likelihood of prescribing prednisolone and the prevalence of comorbidities is expected to decrease. Furthermore, effective medications have been shown to decrease the incidence of initial cervical spine involvement, although the progression of cervical lesions once they occur cannot be prevented (16,58,59). Moreover, surgical stabilization has been shown to delay and sometimes prevent cervical lesions, such as the extension of AAS to VS or SAS, and improved status in certain patients who have symptomatic cervical spine lesions (14,60,61). These results suggested that surgical intervention should be considered when patients have symptomatic AAS to prevent the progression of cervical spine lesions, and this approach could also prevent further perioperative complications that might occur in later surgery for more advanced cervical spine lesions.

## Abbreviations

RA: rheumatoid arthritis, ASA-PS: American Society of Anesthesiologists Physical Status, CCI: Charlson comorbidity index, CTCAE: Common Terminology Criteria for Adverse Event, AAS: atlantoaxial subluxation, ADI: atlantodental interval, VS: vertical subluxation, SAS: subaxial subluxation, C1-2 fusion: atlantoaxial fusion, OC fusion: occipito-cervical fusion, SSI: surgical site infection

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Institutional Review Board of National Hospital Organization Kyushu Medical Center. All the individual data were anonymized before analysis, and informed consent was waived.

### *Consent for publication*

All of the subjects provided written informed consent for publication.

### *Availability of data and materials*

The datasets used and/or analysed during the current study are included in this publication article or otherwise available from the corresponding author on reasonable request.

### *Competing interests*

The authors declare that they have no competing interests.

### *Funding*

No funding or sponsorship was received for this study or publication of this article.

### *Authors' contributions*

JF conceived of the study. KS and OY designed and coordinated the study. KS, OY, KK, SK, KF, HB, MO and HM contributed to the data acquisition and analysis. KT and NK are spine surgeons who performed all cervical spine surgeries in the present study. KS drafted the manuscript. All authors read, revised and approved the final manuscript.

### *Acknowledgements*

We thank Shoji Tokunaga for his valuable contribution as an advisor for the statistical analysis.

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## Tables

Table 1. Baseline characteristics at the time of surgery

Items	Data
Patients (male/female), <i>n</i>	139 (35/104)
Age, years	66.5±1.0
Height, m	1.52±0.09
Weight, kg	51.1±11.6
BMI, kg/m <sup>2</sup>	21.9±3.9
BSA, m <sup>2</sup>	1.42±0.18
Serum albumin, g/dl	3.7±0.5
Charlson comorbidity index	1.60±0.8
ASA-PS	2.3±0.5
Disease duration, years	19.7±14.0
CRP, mg/dl	1.11±1.33
Medication	
Biologics/JAK inhibitor, <i>n</i> (%)	18 (13)
Methotrexate, <i>n</i> (%)	57 (41)
Prednisolone, <i>n</i> (%)	118 (84.9)
Cervical spine lesion	
Spondylosis, <i>n</i> (%)	26(18.7)
AAS, <i>n</i> (%)	92 (66.2)
VS, <i>n</i> (%)	60 (43.5)
SAS, <i>n</i> (%)	41 (30.0)
Mean ± standard deviation (SD).	
BMI: body mass index; CRP: C-reactive protein; ASA-PS: American Society of Anesthesiologists Physical Status; AAS: atlantoaxial subluxation; VS: vertical subluxation; SAS: subaxial subluxation.	

Table 2. Perioperative complications of cervical spine surgery in patients with RA

	Total (n=139)	Laminoplasty (n=63)	C1/2 fusion (n=33)	OC fusion (n=30)	Long fusion (n=13)
Severe, <i>n</i> (%)	10 (7.19)	1 (0.72)	1 (0.72)	3 (2.16)	5 (6.95)
Airway constriction	2			1	1
Acute deterioration of interstitial pneumonia	1	1			
Acute myocardial infarction	1				1
Postoperative hyponatremia	1				1
Pneumonia	3		1	2	
Prolonged severe delirium	1				1
Upper gastrointestinal bleeding	1				1
Mild/Moderate, <i>n</i> (%)	20 (14.4)	8 (5.76)	2 (1.49)	8 (5.76)	2 (1.49)
Anaphylactic shock	1		1		
C5 palsy	2	2			
Delayed wound healing	3	2			1
Delirium	1	1			
Dural injury	3	1		2	
Herpes zoster	1			1	
SSI	6	1	1	3	1
UTI	1	1			
Skin infection	2			2	

C1/2 fusion: atlantoaxial fusion; OC fusion: occipito-cervical fusion; SSI: surgical site infection; UTI: urinary tract infection.

Table 3. Associations between medications and perioperative infectious complications of cervical spine surgery in patients with RA (n=12)

	Total (139)	Infection (12)	<i>p</i> Value	SSI (6)	<i>p</i> Value
Biologics/JAK inhibitor, <i>n</i> (%)	18	2 (11.1)	.688	1 (5.56)	.789
w/o Biologics/JAK inhibitor, <i>n</i> (%)	121	10 (8.26)		5 (4.41)	
Methotrexate, <i>n</i> (%)	57	4 (7.02)	.572	2 (3.51)	.693
w/o Methotrexate, <i>n</i> (%)	82	8 (9.76)		4 (4.89)	
Prednisolone, <i>n</i> (%)	118	10 (8.47)	.875	6 (5.1)	.156
w/o Prednisolone, <i>n</i> (%)	21	2 (9.52)		0 (0)	

w/o: without; SSI: surgical site infection.

Table 4. Univariate logistic regression analysis of risk factors for all complications at the time of surgery

	No complication	Complication	Univariable	
	(111)	(28)	OR (95% CI)	<i>p</i> Value
Age, <i>years</i>	66.1 ± 9.60	68.0 ± 11.4	1.019 (0.977-1.063)	.379
Sex, male/female, <i>n</i>	30/81	5/23	1.704 (0.594-4.888)	.322
Height, <i>m</i>	1.532 ± 0.089	1.479 ± 0.091	0.928 (0.880-0.980)	.007
Weight, <i>kg</i>	51.6 ± 11.1	49.2 ± 13.2	0.982 (0.946-1.019)	.327
BMI, <i>kg/m<sup>2</sup></i>	21.8 ± 3.7	22.3 ± 4.7	1.029 (0.925-1.144)	.602
BSA, <i>m<sup>2</sup></i>	1.43 ± 0.18	1.37 ± 0.21	0.128 (0.011-1.428)	.095
Serum albumin, <i>g/dl</i>	3.72 ± 0.48	3.60 ± 0.46	0.594 (0.247-1.428)	.243
Charlson comorbidity index	1.73 ± 1.02	1.68 ± 0.86	0.947 (0.614-1.460)	.806
ASA-PS	2.29 ± 0.49	2.50 ± 0.51	2.296 (1.007-5.235)	.048
Disease duration, <i>years</i>	20.2 ± 14.5	17.6 ± 12.1	0.986 (0.955-1.017)	.363
CRP, <i>mg/dl</i>	1.07 ± 1.20	1.12 ± 1.37	0.972 (0.707-1.337)	.862
Medication				
Biologics/JAK inhibitor, <i>n</i> (%)	13 (11.7)	5 (17.9)	1.639 (0.531-5.058)	.390
Methotrexate, <i>n</i> (%)	46 (41.4)	11 (39.3)	0.914 (0.392-2.133)	.836
Methotrexate, <i>mg</i>	2.67 ± 0.35	2.29 ± 0.59	0.969 (0.858-1.095)	.612
Prednisolone, <i>n</i> (%)	92 (82.9)	26 (92.9)	2.685 (0.587-12.28)	.203
Prednisolone, <i>mg</i>	4.79 ± 0.33	5.73 ± 0.52	1.083 (0.961-1.221)	.193
Cervical spine lesion				
AAS, <i>n</i> (%)	73 (65.8)	19 (67.9)	1.099 (0.454-2.662)	.834
VS, <i>n</i> (%)	42 (38.2)	18 (64.3)	2.914 (1.229-6.911)	.015
SAS, <i>n</i> (%)	28 (25.7)	13 (46.4)	2.507 (1.063-5.913)	.036
Operation time	134.3 ± 43.3	167.1 ± 62.4	1.013 (1.004-1.021)	.003
Bleeding volume	72.5 ± 79.2	124.0 ± 177.5	1.004 (1.000-1.007)	.040
Procedure				
Laminoplasty, <i>n</i> (%)	55 (49.6)	8 (28.6)	Ref	Ref
C1/2 fusion, <i>n</i> (%)	30 (27.0)	3 (10.7)	0.688 (0.170-2.787)	.600
OC fusion, <i>n</i> (%)	20 (18.0)	10 (35.7)	3.438 (1.189-9.934)	.023

Long fusion, <i>n</i> (%)	6 (5.4)	7 (25.0)	8.021 (2.145-29.99)	002
Mean ± standard deviation (SD); OR: odds ratio; CI: confidence interval; Ref: reference;				
BMI: body mass index; CRP: C-reactive protein; ASA-PS: American Society of Anesthesiologists Physical Status; AAS: atlantoaxial subluxation; VS: vertical subluxation; SAS: subaxial subluxation; C1/2 fusion: atlantoaxial fusion; OC fusion: occipito-cervical fusion.				

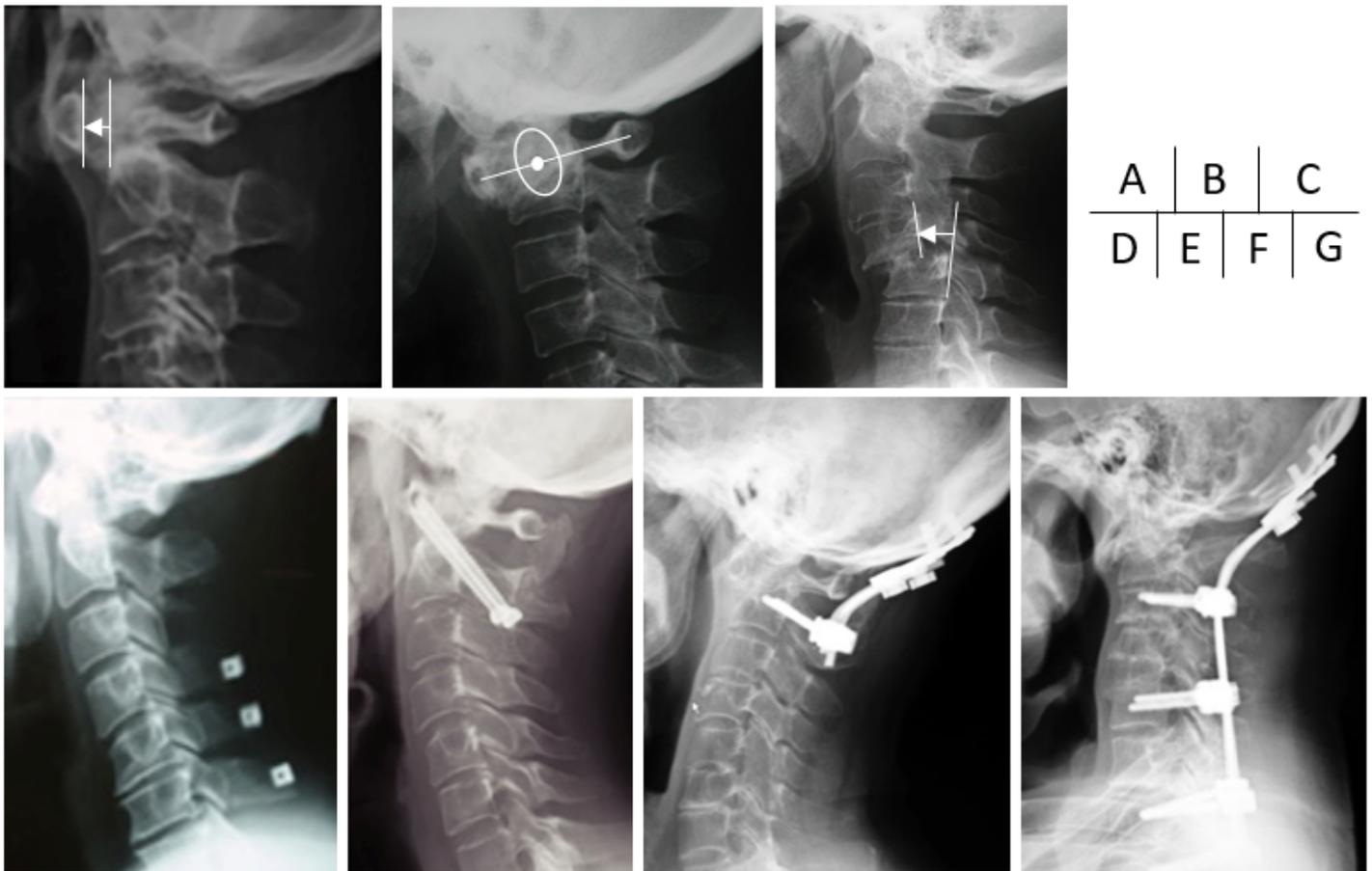
Table 5. Multivariate logistic regression analysis of risk factors for all complications at the time of surgery

	Model #1		Model #2	
	OR (95% CI)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value
Height	0.915 (0.860-0.974)	.005	0.931 (0.872-0.995)	.034
ASA-PS	2.622 (1.023-6.717)	.045	2.141 (0.817-5.611)	.123
Median duration of RA	0.953 (0.918-0.990)	.012	0.950 (0.911-0.991)	.017
Cervical spine lesion				
SAS	2.555 (0.993-6.571)	.052		
Procedure				
Laminoplasty			Ref	
C1/2 fusion			0.956 (0.221-4.132)	.952
OC fusion			2.467 (0.777-7.826)	.125
Long fusion			7.289 (1.694-31.36)	.008
OR: odds ratio; CI: confidence interval; Ref: reference; ASA-PS: American Society of Anesthesiologists Physical Status; AAS: atlantoaxial subluxation; VS: vertical subluxation; SAS: subaxial subluxation; C1/2 fusion: atlantoaxial fusion; OC fusion: occipito-cervical fusion.				

Table 6. Multivariate logistic regression analysis of risk factors for severe complications at the time of surgery

	1 <sup>st</sup> Multivariable		2 <sup>nd</sup> Multivariable	
	OR (95% CI)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value
Height	<0.001 (<0.001-1.310)	.057		
PSL	1.247 (1.024-1.519)	.028	2.141 (0.817-5.611)	.072
Median duration of RA			0.950 (0.911-0.991)	.126
Cervical spine lesion				
SAS	6.413 (1.381-29.79)	.018		
Procedure				
Laminoplasty			Ref	
C1/2 fusion			2.919 (0.146-58.29)	.483
OC fusion			17.93 (1.242-258.8)	.034
Long fusion			108.1 (6.876-1699)	<.001
OR: odds ratio; CI: confidence interval; Ref: reference; PSL: prednisolone; SAS: subaxial subluxation; C1/2 fusion: atlantoaxial fusion; OC fusion: occipito-cervical fusion.				

## Figures



**Figure 1**

Cervical lesions associated with RA and surgical procedures for individual cervical lesions. A: Atlantoaxial subluxation (AAS) was defined as an expansion of the atlantodental interval over 3 mm (between the white lines) at the flexed position on X-ray lateral view. B: Vertical subluxation (VS) was defined as a shortening of the Ranawat C1-C2 index to less than 15 mm for men and 13 mm for women. The measurement of the Ranawat index was made from the centre of the pedicles of the axis (white circle and dot) to a line connecting the midpoint of the anterior and posterior arches of the atlas (white line). C: Subaxial subluxation (SAS) was diagnosed as migration of the superior vertebra compared to the inferior vertebra over 3 mm. Migration distance was measured between posterior walls of adjacent vertebrae (between the lines). D-G: Four types of surgical procedures were performed for cervical spine lesions in patients with RA. Laminoplasty was performed for myelopathy in the stable cervical spine (D). Fixative procedures were chosen depending on how unstable the cervical spine was: atlantoaxial fusion for unstable AAS (E), occipital-cervical fusion for VS with or without AAS (F), and occipital/thoracic fusion for SAS that included AAS and/or VS (G).