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Original Article

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Factors Associated With the Absence of Cervical Spine Instability in Rheumatoid Arthritis: A >10-Year Prospective Multicenter Cohort Study

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Objective: To identify factors associated with the absence of cervical spine instability in patients with rheumatoid arthritis (RA).

Methods: Cervical spine instability was defined as the presence of at least one of the following: atlantoaxial subluxation, vertical subluxation of the axis, or subaxial subluxation. In 2001–2002, 634 enrolled outpatients with “classical” or “definite” RA underwent a radiographic cervical spine checkup. In 2012–2013, 233 (36.8%) prospectively underwent routine clinical follow-ups with a > 10-year radiographic evaluation. The prevalence and independent predictive factors for no instability were analyzed by multivariable logistic regression. Next, 85 of 292 outpatients (29.1%) without baseline cervical spine instability completed consecutive > 5-year and > 10-year radiographic examinations. The incidence and predictors for no new development of instability were assessed similarly.

Results: Among 233 patients, those without cervical spine instability decreased from 114 (48.9%) to 47 (20.2%) during > 10 years. Steinbrocker peripheral joint destruction stages I–II (odds ratio [OR], 3.797; $p = 0.001$), no corticosteroid administration (OR, 2.700; $p = 0.007$), and no previous joint surgery (OR, 2.480; $p = 0.020$) were predictors for no instability. Then, 33 of 85 (38.8%) consecutively followed patients without baseline cervical spine lesions did not develop instability throughout. Steinbrocker stages I–II (OR, 5.355; $p = 0.005$) and no corticosteroid therapy (OR, 3.868; $p = 0.010$) were predictors for no new onset of instability. C-reactive protein (CRP) level ≤ 1.0 mg/dL was marginal in both models ($n = 233$ [OR, 2.013; $p = 0.057$], $n = 85$ [OR, 2.453; $p = 0.075$]).

Conclusion: Steinbrocker stages I–II, no corticosteroids, no previous joint surgery, and possibly CRP ≤ 1.0 mg/dL are factors associated with > 10-year absence of cervical spine instability in RA.

Keywords: Rheumatoid arthritis, Cervical spine instability, Peripheral joint destruction, Corticosteroid, Previous joint surgery, C-reactive protein

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder with a prevalence of 0.5%–1.0% in adults.¹ RA causes chronic inflammation in the joint synovium and entheses, resulting in substan-

tial individual and socioeconomic burdens.² The cervical spine is commonly affected in patients with RA, the involvement of which can lead to 3 representative instabilities: atlantoaxial subluxation (AAS),^{3–7} vertical subluxation (VS) of the axis,^{8,9} and subaxial subluxation (SAS),¹⁰ potentially developing intractable

neck pain and neurological damage with loss of ambulation, respiratory dysfunction, or sudden death.¹¹ It is thus essential to understand the natural history and predictive risk factors for cervical spine involvement in RA. However, available evidence from prospective studies comprehensively evaluating prognostic factors remains limited.^{6,12-16}

In 2001–2002, we commenced a >10-year prospective multicenter cohort study at 21 institutions focusing on cervical spine instability in 634 outpatients with symptomatic RA fulfilling the “classical” or “definite” criteria.^{17,18} In 2006–2008, we began a >5-year radiographic examination to clarify the progression,¹⁹ incidence,²⁰ and predictors of instabilities severe enough to induce compression myelopathy.^{20,21} In 2012–2013, we launched a >10-year radiographic examination to identify more plausible predictive factors for impending neurological deficit:²² the atlanto-dental interval (ADI) ≥ 10 mm in severe AAS,²³ Ranawat value ≤ 10 mm in severe VS,^{11,24,25} and irreducible vertebral translation of ≥ 4 mm or ≥ 2 mm at multiple levels in severe SAS.^{10,26} However, these criteria are insufficient for the early detection of cervical spine lesions and symptoms before developing neurological damage. The information at earlier stages, i.e., much more tight controlled criteria, should be further helpful to prevent the involvement and development of cervical spine instabilities. During our >10-year follow-up, a certain number of patients, despite distinct RA characteristics, showed no instability throughout, who consistently fulfilled all of ADI ≤ 3 mm,^{3,4} Ranawat value ≥ 13 mm,⁸ and reducible vertebral translation < 2 mm.¹⁰ These patients do not correspond to the flipside of those with the severe category of instabilities. Therefore, understanding

this cohort would provide insights into RA treatment strategies. No reports have focused on favorable prognostic factors to date. In fact, C-reactive protein (CRP) level was set at ≥ 3.8 mg/dL for severe instability,²² a reported threshold for the deterioration of myelopathy,²⁷ whereas it was set at ≤ 1.0 mg/dL for no instability, the clinically important threshold for RA remission.²⁸ The objective of the present study was to identify factors associated with the absence and no new development of cervical spine instability in patients with RA.

MATERIALS AND METHODS

1. Ethics Statement

The current study was conducted at 21 research facilities in Hyogo, Japan. The study protocol was approved by the Institutional Review Board at each facility. Written informed consent was obtained from each patient at the study enrollment. This study was performed in accordance with the principles of the Declaration of Helsinki and the laws and regulations of Japan.

2. Patients

In 2001–2002, 634 outpatients who fulfilled the American Rheumatism Association 1958 criteria for “classical” or “definite” RA¹⁷ as well as the American College of Rheumatology 1987 revised criteria for RA¹⁸ were enrolled in our study.¹⁹ At baseline, 3 types of cervical spine instability were radiographically identified. In 2012–2013, 233 (36.8%) were prospectively followed as outpatients every 3 months and radiographically assessed again at >10 years.²² Among the entire cohort (Fig. 1),

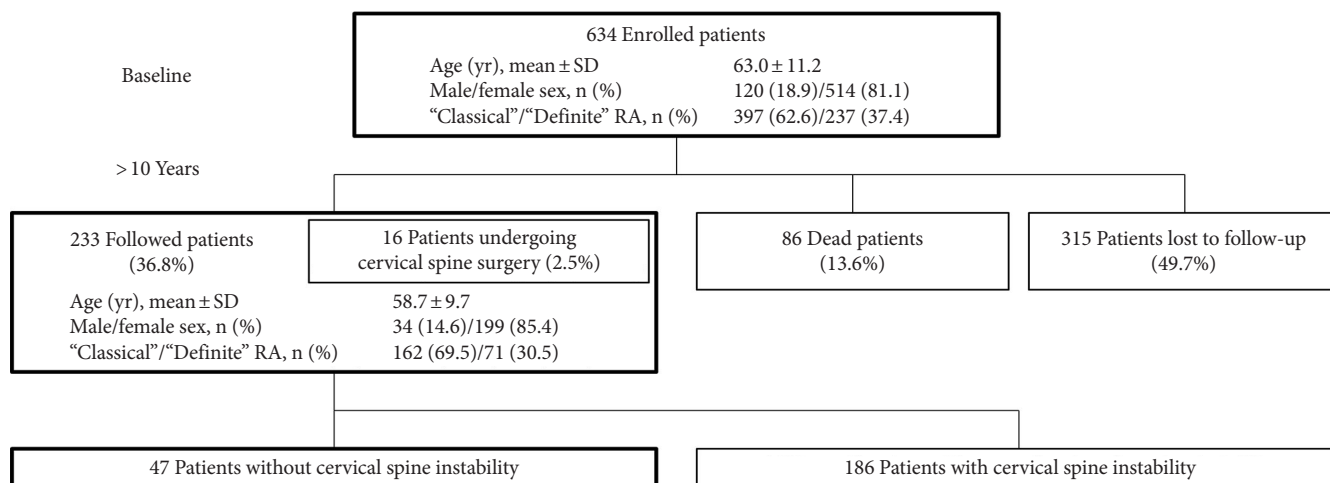


Fig. 1. Number of patients, fulfilling the American Rheumatism Association 1958 criteria for “classical” or “definite” RA, enrolled at baseline and prospectively followed as outpatients, patients undergoing cervical spine surgery, dead patients, or patients lost to follow-up at >10 years. RA, rheumatoid arthritis; SD, standard deviation.

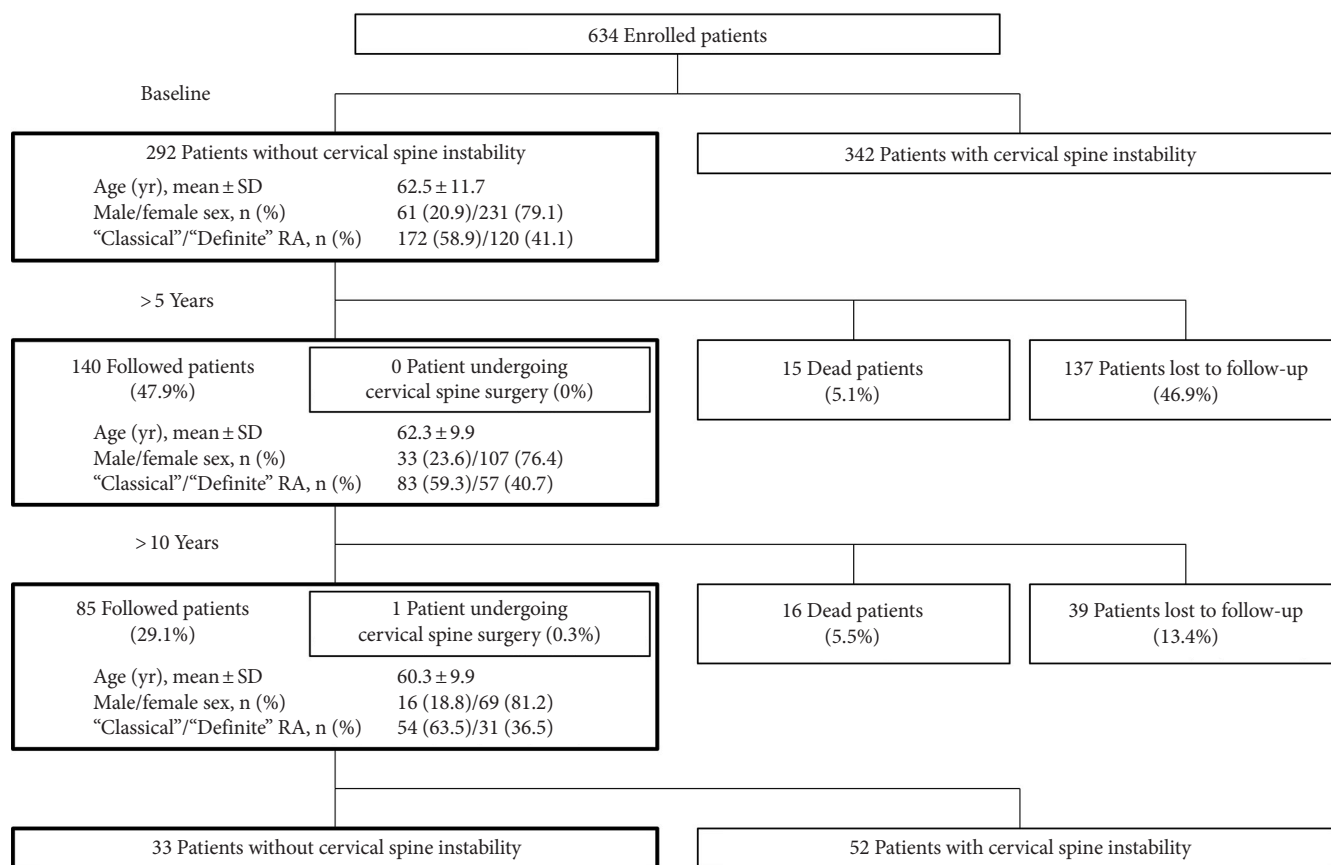


Fig. 2. Number of patients, fulfilling the American Rheumatism Association 1958 criteria for "classical" or "definite" RA but without cervical spine instability, enrolled at baseline and prospectively followed as outpatients, patients undergoing cervical spine surgery, dead patients, or patients lost to follow-up at > 5 years and > 10 years. RA, rheumatoid arthritis; SD, standard deviation.

16 (2.5%) underwent cervical spine surgery for myelopathy during the study period. The mean follow-up period was 11.0 ± 1.9 years. Letter and telephone surveys revealed that 86 (13.6%) had died; therefore, the final follow-up rate was 50.3%.

Of the 634 enrolled patients, 292 with no baseline cervical spine instability were further traced. In 2006–2008, 140 (47.9%) were radiographically assessed again at > 5 years.^{20,21} In 2012–2013, 85 (29.1%) were radiographically reassessed at > 10 years.²² Among this consecutive subcohort (Fig. 2), 1 patient (0.3%) underwent cervical spine surgery during the last > 5 years. The mean follow-up period was 6.1 ± 0.6 and 11.3 ± 0.5 years, respectively. In addition, 15 (5.1%) and 16 (5.5%) had died during the initial and last > 5 years, respectively; therefore, the follow-up rate at > 5 and > 10 years was 53.1% and 39.7%, respectively.

3. Radiographic Evaluation

Lateral cervical spine radiographs were obtained in full-flexion, neutral, and full-extension positions under a standardized

protocol (exposure time, 80 msec; distance, 150 cm; current, 250 mA; voltage, 72 kV) with the placement of a scale marker.^{19–22} Cervical spine instability was defined as the presence of at least one of the following: AAS with the anterior ADI of > 3 mm,^{3,4} VS with the Ranawat value of < 13 mm,⁸ or SAS with irreducible vertebral translation of ≥ 2 mm without osteophyte formation.¹⁰ Radiographs were analyzed twice at a 1-week interval by each of 4 rheumatologists blinded to this study. The average measurement values were used for the data analysis.

Bilateral hand radiographs were taken to classify the severity of peripheral joint destruction into 5 categories: Steinbrocker classification stages I–IV²⁹ and mutilating changes.^{30,31} Mutilating changes were separately identified in patients with ≥ 3 of 10 "mutilans fingers" in the bilateral hands,³⁰ as previously established.³¹ Radiographs were reviewed twice at a 1-week interval by 3 independent senior rheumatologists not involved in the clinical follow-up. Steinbrocker stages and mutilating changes were determined by majority decision. Steinbrocker nonadvanced peripheral joint destruction stages I–II at baseline was document-

ed as a possible variable for the absence and no new development of cervical spine instability in RA, based on prior evidence.¹⁹⁻²²

4. Clinical Evaluation

The patients' demographic and clinical characteristics were recorded at baseline. Given that an age of <55^{7,10} or ≥65 years,³² male sex,³³ and surgical treatment of RA in peripheral joints^{32,34,35} have been reported as risk factors of cervical spine instability, we considered an age of 55–64 years, female sex, and no previous joint surgery to be candidate variables for the absence of instability. Because the severity of RA clinically depends on the number of joints with erosion within the first 5–10 years,³⁶ we extracted data on patients with <5-year disease duration. In laboratory findings, we recorded the serum CRP level, as correlated with myelopathic deterioration,²⁷ when ≤1.0 mg/dL, the threshold for RA remission.²⁸ We also marked negative serum rheumatoid factor (RF) because positivity has been associated with subluxation.^{6,7}

To treat RA, patients received single or multiple disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) and tacrolimus. Oral corticosteroids were permitted to relieve symptoms. In more aggressive cases, biological agents or a Janus kinase inhibitor tofacitinib were applied (Table 1). Patients were categorized based on drug administration at baseline and throughout ≥3 years during the initial >5 years. Patients who had therapy with tacrolimus, biological agents, or tofacitinib for ≥3 years were similarly identified, because these drugs had not been approved for RA at baseline. Consequently, 35 of 233 patients (15.0%) and 16 of 85 patients (18.8%) were positive for ≥3-year biological agent therapy, in which etanercept was the most commonly used (19 of 233 patients [8.2%] and 7 of 85 patients [8.2%]) while infliximab was the second most frequently used (14 of 233 patients [6.0%] and 7 of 85 patients [8.2%]). There were no patients undergoing ≥3-year treatment with tacrolimus or tofacitinib.

5. Statistical Analysis

As descriptive statistics, continuous variables are presented as mean ± standard deviation and categorical variables are presented as frequency (percentage). Data analysis was performed using IBM SPSS Statistics ver. 28.0 (IBM Co., Armonk, NY, USA). Statistical significance was determined using p-values of <0.05 and <0.01.

Among the entire cohort of 233 patients, the prevalence of no cervical spine instability was compared between the beginning and end of >10-year observation period using the chi-square

Table 1. List of the medications used to treat rheumatoid arthritis during the study period of 2001–2013

Variable	Dosage	Year approved in Japan
Corticosteroids		
Prednisolone	≤ 10 mg/day	1956
DMARDs		
MTX	≤ 8 mg/wk	1999
	≤ 16 mg/wk	2011
Salazosulfapyridine	≤ 1,000 mg/day	1995
D-penicillamine	≤ 100 mg/day	1978
Intramuscular gold	≤ 25 mg every 2 wk	1970
Tacrolimus	1.5–3 mg/day	2005
Biological agents		
Infliximab	3 mg/kg every 8 wk	2003
Etanercept	10–25 mg twice a wk	2005
Adalimumab	40 mg every 2 wk	2008
Tocilizumab	8 mg/kg every 4 wk	2008
Abatacept	125 mg/wk	2010
Golimumab	50–100 mg every 4 wk	2011
Certolizumab	200 mg every 2 wk	2013
Janus kinase inhibitor		
Tofacitinib	5–10 mg/day	2013

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

test. Among the subcohort of 85 consecutively followed patients without baseline cervical spine instability, the incidence of no *de novo* development of instability was compared at >5-year and >10-year examinations using the chi-square test or Fisher exact test when $n \leq 5$ in a cell. Next, the chi-square test or Fisher exact test for categorical variables and Student t-test for continuous variables were used to assess baseline and >10-year differences between patients with and without cervical spine instability at >10-year follow-up. In addition, the intraclass correlation coefficient (ICC) and Cohen kappa coefficient (κ) were calculated to assess the intraobserver and interobserver reliability for parametric and nonparametric radiographic parameters, respectively.

Univariable and multivariable logistic regression models were developed to identify independent predictive factors for the absence of cervical spine instability among the entire cohort ($n = 233$). All baseline and >10-year variables with $p < 0.200$ in univariable analysis between patients with and without cervical spine instability at >10-year follow-up were eligible for inclusion as potential predictors in multivariable logistic regression

analysis. Next, to identify independent predictors for no new onset of cervical spine instability among the subcohort without baseline instability ($n = 85$), all baseline and > 10 -year variables with $p < 0.200$ in univariable analysis were also eligible for inclusion in multivariable logistic regression analysis. In both multivariable models, the Hosmer-Lemeshow test for goodness-of-fit and the concordance (C)-statistic for discriminatory ability were used to ensure the accuracy of the estimated probabilities.

RESULTS

In radiographic measurements, the intraobserver reliability by the ICC for parametric ADI, Ranawat value, and subaxial vertebral translation was 0.91–0.95, 0.81–0.85, and 0.80–0.84, respectively, while the interobserver reliability by the ICC was 0.96, 0.91, and 0.91, respectively. The intraobserver and interobserver reliability by κ for nonparametric Steinbrocker stages and mutilating changes was 0.75–0.81 and 0.87, respectively. All ICC and κ values indicated acceptable reproducibility.

1. Greater Than 10-Year Prevalence and Predictors for the Absence of Cervical Spine Instability

Among the entire cohort of 233 patients, 114 (48.9%) at baseline and 47 (20.2%) at endpoint had the absence of cervical spine instability, showing a significant decrease ($p < 0.001$). Therefore, 186 with and 47 without cervical spine instability at > 10 -year follow-up were compared.

In the comparison of baseline and > 10 -year demographic, clinical, and disease characteristics between patients with and without cervical spine instability, those without instability tended to have a shorter duration of RA ($p = 0.002$) (especially < 5 years [$p = 0.004$]), lower level of CRP ($p = 0.062$) (especially ≤ 1.0 mg/dL [$p = 0.005$]), higher frequency of no previous joint surgery ($p < 0.001$), no corticosteroid administration ($p < 0.001$), no MTX administration ($p = 0.115$), and Steinbrocker stages I–II ($p < 0.001$), and lower frequency of no conventional DMARD administration other than MTX ($p = 0.171$). Thus, these variables were considered possible baseline predictive factors for the absence of cervical spine instability. In patients without instability, no administration of biological agents was also common, with marginal significance ($p = 0.070$), suggesting its potential as a > 10 -year predictor for the absence of instability (Table 2).

In logistic regression analysis, univariable models showed that the following variables had $p < 0.200$: RA duration < 5 years ($p = 0.005$), CRP level ≤ 1.0 mg/dL ($p = 0.006$), no previous joint surgery ($p = 0.001$), no corticosteroid therapy ($p < 0.001$), no

Table 2. Baseline and > 10 -year demographic, clinical, and disease characteristics of 233 patients with and without cervical spine instability at > 10 -year follow-up

Variable	Patients with cervical spine instability (n = 186)	Patients without cervical spine instability (n = 47)	p-value
Age (yr)	58.4 $\pm$ 9.4	59.6 $\pm$ 10.6	0.455
< 55	62 (33.3)	15 (31.9)	0.833
55–64	69 (37.1)	16 (34.0)	
≥ 65	55 (29.6)	16 (34.0)	
Female sex	161 (86.6)	38 (80.9)	0.322
RA duration (yr)	14.6 $\pm$ 10.6	8.7 $\pm$ 10.2	0.002*
< 5	32 (17.2)	17 (36.2)	0.004*
CRP (mg/dL)	2.4 $\pm$ 2.8	1.5 $\pm$ 2.6	0.062
≤ 1.0	76 (40.9)	30 (63.8)	0.005*
RF negative	39 (20.9)	13 (27.7)	0.325
No previous joint surgery	85 (45.7)	35 (74.5)	< 0.001 *
Medications			
No corticosteroids	55 (29.6)	28 (59.6)	< 0.001 *
No MTX	103 (55.4)	32 (68.1)	0.115
No other DMARDs	92 (49.5)	18 (38.3)	0.171
No biological agents	154 (82.8)	44 (93.6)	0.070†
Steinbrocker stages and mutilating changes			< 0.001 *
Stages I–II	24 (12.9)	20 (42.6)	
Stages III–IV	141 (75.8)	26 (55.3)	
Mutilating changes	21 (11.3)	1 (2.2)	

Values are presented as mean $\pm$ standard deviation or number (%).

RA, rheumatoid arthritis; CRP, C-reactive protein; RF, rheumatoid factor; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

Calculated by the chi-square test (Fisher exact test† when $n \leq 5$ in a cell) and Student t-test.

* $p < 0.05$, statistically significant differences.

MTX therapy ($p = 0.117$), no other DMARD therapy ($p = 0.073$), and Steinbrocker stages I–II ($p < 0.001$) at baseline and no biological agent therapy ($p = 0.076$) at > 10 -year follow-up (Table 3). We therefore designed a multivariable logistic regression model including these variables, showing good predictive ability. This multivariable model identified the following as significant predictive factors for the absence of cervical spine instability: Steinbrocker stages I–II (odds ratio [OR], 3.109; 95% confidence interval [CI], 1.325–7.298; $p = 0.009$), no corticosteroids (OR, 2.711; 95% CI, 1.314–5.592; $p = 0.007$), no previous joint surgery (OR, 2.192; 95% CI, 1.004–4.787; $p = 0.049$), and CRP ≤ 1.0 mg/dL (OR, 2.156; 95% CI, 1.021–4.553; $p = 0.044$) (Table 3). To reduce the risk of overfitting variables,³⁷ we further designed a multi-

Table 3. Univariable, multivariable, and stepwise multivariable logistic regression models to identify predictors for the absence of cervical spine instability at > 10-year follow-up in 233 patients

Variable	Univariable analysis			Multivariable analysis [†]			Stepwise multivariable analysis [‡]		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age, 55–64 yr	0.875	0.447–1.715	0.698	-	-	-	-	-	-
Female sex	0.656	0.283–1.519	0.325	-	-	-	-	-	-
RA duration < 5 yr	2.727	1.346–5.527	0.005**	1.617	0.667–3.920	0.288	-	-	-
CRP ≤ 1.0 mg/dL	2.554	1.316–4.956	0.006**	2.156	1.021–4.553	0.044*	2.013	0.979–4.139	0.057
RF negative	1.495	0.719–3.109	0.280	-	-	-	-	-	-
No previous joint surgery	3.466	1.693–7.094	0.001**	2.192	1.004–4.787	0.049*	2.480	1.153–5.334	0.020*
Medications									
No corticosteroids	3.510	1.810–6.806	<0.001**	2.711	1.314–5.592	0.007**	2.700	1.319–5.525	0.007*
No MTX	1.719	0.873–3.387	0.117	0.934	0.365–2.393	0.887	-	-	-
No other DMARDs	0.634	0.330–1.220	0.073	0.656	0.264–1.631	0.364	-	-	-
No biological agents	3.048	0.891–10.426	0.076	2.895	0.730–11.487	0.131	-	-	-
Steinbrocker stages and mutilating changes									
Stages I–II	5.000	2.434–10.270	<0.001**	3.109	1.325–7.298	0.009**	3.797	1.743–8.270	0.001**

OR, odds ratio; CI, confidence interval; RA, rheumatoid arthritis; CRP, C-reactive protein; RF, rheumatoid factor; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug.

* $p < 0.05$ and ** $p < 0.01$, statistically significant differences. [†]The Hosmer-Lemeshow goodness-of-fit chi-square test $p = 0.672$ (8° of freedom) and the concordance statistic for the model = 0.799. [‡]The Hosmer-Lemeshow goodness-of-fit chi-square test $p = 0.744$ (7° of freedom) and the concordance statistic for the model = 0.783.

variable model based on backward stepwise variable selection. This model also showed acceptable predictive ability, revealing the following statistically significant predictors for the absence of instability: Steinbrocker stages I–II (OR, 3.797; 95% CI, 1.743–8.270; $p = 0.001$), no corticosteroids (OR, 2.700; 95% CI, 1.319–5.525; $p = 0.007$), and no previous joint surgery (OR, 2.480; 95% CI, 1.153–5.334; $p = 0.020$). Additionally, CRP ≤ 1.0 mg/dL was a likely predictor, approaching statistical significance (OR, 2.013; 95% CI, 0.979–4.139; $p = 0.057$) (Table 3).

2. Greater Than 10-Year Incidence and Predictors for No New Development of Cervical Spine Instability

Among the consecutive subcohort of 85 patients without baseline cervical spine instability, 46 (54.1%) had not developed instability at > 5-year follow-up ($p < 0.001$). The number of patients without instability decreased to 33 (38.8%) at > 10-year follow-up ($p = 0.046$). *De novo* development of instability was observed with time but primarily within the first > 5 years, which may have resulted from drastic changes in RA treatment during 2001–2013.³⁸ Therefore, 52 with and 33 without newly developed cervical spine instability throughout > 10 years were compared.

In the comparison of baseline and > 10-year demographic, clinical, and disease characteristics between patients with and

without newly developed cervical spine instability, those who did not develop instability throughout to have a shorter RA duration ($p = 0.079$) (especially < 5 years [$p = 0.088$]), lower CRP level ($p = 0.123$) (especially ≤ 1.0 mg/dL [$p = 0.037$]), higher frequency of RF negativity ($p = 0.059$), no previous joint surgery ($p = 0.016$), no corticosteroid administration ($p = 0.011$), and Steinbrocker stages I–II ($p = 0.019$) at baseline as well as no biological agent administration ($p = 0.090$) at > 10-year follow-up. Therefore, these variables were assumed to be predictive factors of new onset of instability (Table 4).

In logistic regression analysis, univariable models showed that the following factors had $p < 0.200$: < 5-year RA duration ($p = 0.072$), CRP ≤ 1.0 mg/dL ($p = 0.039$), RF negativity ($p = 0.064$), no previous joint surgery ($p = 0.018$), no corticosteroid therapy ($p = 0.013$), and Steinbrocker stages I–II ($p = 0.008$) at baseline and no biological agent therapy ($p = 0.079$) at > 10-year follow-up (Table 5). A multivariable logistic regression model including these variables, with adequate predictive ability, found the following as significant predictors of no new onset of instability: Steinbrocker stages I–II (OR, 4.278; 95% CI, 1.095–16.719; $p = 0.037$) and no corticosteroids (OR, 3.542; 95% CI, 1.216–10.319; $p = 0.020$) (Table 5). Finally, a backward stepwise multivariable logistic regression model, also with sufficient predictive ability,

Table 4. Baseline and >10-year demographic, clinical, and disease characteristics of 85 consecutively followed patients with and without cervical spine instability at >10-year follow-up

Variable	Patients with cervical spine instability (n = 52)	Patients without cervical spine instability (n = 33)	p-value
Age (yr)	61.5 ± 9.1	58.5 ± 10.9	0.180
< 55	12 (23.5)	11 (33.3)	0.552
55–64	20 (38.5)	12 (36.7)	
≥ 65	20 (38.5)	10 (30.3)	
Female sex	42 (80.8)	27 (81.8)	0.904
RA duration (yr)	14.0 ± 9.9	10.1 ± 10.8	0.079
< 5	11 (21.2)	13 (39.4)	0.088
CRP (mg/dL)	1.8 ± 1.7	1.2 ± 1.6	0.123
≤ 1.0	21 (40.4)	21 (63.6)	0.037*
RF negative	7 (13.5)	10 (30.3)	0.059
No previous joint surgery	24 (46.2)	24 (72.7)	0.016*
Medications			
No corticosteroids	20 (38.5)	22 (66.7)	0.011*
No MTX	23 (44.2)	18 (54.5)	0.354
No other DMARDs	31 (59.6)	16 (48.5)	0.314
No biological agents	39 (75.0)	30 (90.9)	0.090†
Steinbrocker stages and mutilating changes			0.019*
Stages I–II	7 (13.5)	13 (39.4)	
Stages III–IV	44 (84.6)	20 (60.6)	
Mutilating changes	1 (1.9)	0 (0)	

Values are presented as mean ± standard deviation or number (%).

RA, rheumatoid arthritis; CRP, C-reactive protein; RF, rheumatoid factor; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

Calculated by the chi-square test (Fisher exact test† when n ≤ 5 in a cell) and Student t-test.

*p < 0.05, statistically significant differences.

disclosed Steinbrocker stages I–II (OR, 5.355; 95% CI, 1.652–17.352; p = 0.005) and no corticosteroids (OR, 3.868; 95% CI, 1.387–10.789; p = 0.010) as key predictive factors for no *de novo* development of cervical spine instability, although CRP level ≤ 1.0 mg/dL did not reach statistical significance (OR, 2.453; 95% CI, 0.915–6.576; p = 0.075) (Table 5).

DISCUSSION

The prevalence and incidence of cervical spine involvement depends on the diagnostic criteria, disease severity, and paradigm shifts in RA treatment. In this >10-year prospective mul-

ticenter follow-up, we enrolled only patients with clinically relevant “classical” or “definite” RA^{17,18} and applied known radiographic definitions of cervical spine instability.^{3,4,8,10} Then, more common approach is to clarify predictors of disease progression, whereas several studies have investigated factors for low RA progression, by multivariate analysis.³⁹ We arranged variables based on low disease activity and remission of RA,²⁸ potentially providing clinically useful information to prevent cervical spine instability. Consequently, Steinbrocker stages I–II, no corticosteroid administration, no previous joint surgery, and possibly CRP level of ≤ 1.0 mg/dL were identified as predictive factors for the absence of cervical spine instability among the entire cohort (n = 233). Moreover, Steinbrocker stages I–II and no corticosteroid therapy were determined to be predictors for no new development of instability among the consecutive subcohort without baseline instability (n = 85). Given the consistency between the 2 different study cohort settings, Steinbrocker nonadvanced stages I–II and no concomitant corticosteroids are relatively robust indicators for a favorable prognosis of the cervical spine in patients with RA. These results might not be surprising, which however involve valuable assessments during >10 years and highlight the importance of low disease activity and early clinical remission in patients with RA.

Steinbrocker nonadvanced peripheral joint destruction stages I–II was the most relevant predictive factor for the absence of cervical spine instability in both cohorts. A 2010–2011 cross-sectional study refocused a significant association of advanced Steinbrocker stages with cervical spine involvement.⁴⁰ Another cross-sectional study of patients with RA onset in 2000–2009 and biological agent therapy also identified advanced Steinbrocker stages as a predictor of cervical spine lesions.⁴¹ One multivariate analysis showed ≥ 10% peripheral joint damage at 5 years as a predictive risk factor for the development of AAS at 8–13 years with OR = 15.9.³² Prior studies have demonstrated mutilating changes as a robust risk factor for aggressive cervical spine involvement.^{19–22,27,31,35,40–43} Maintaining Steinbrocker stages I–II in peripheral joints is a key indicator of low RA activity in the cervical spine.

No corticosteroid administration was another relevant predictor in both cohorts. High-dose and long-term intake of corticosteroids can lead to aggravation of cervical spine subluxations in RA.^{5,6,10,42} While intensive corticosteroid treatment is often concomitant with high disease activity, no need for corticosteroid administration is associated with low disease activity. However, a prior study showed an increased incidence of SAS even in non-RA, related to the duration of corticosteroid therapy.⁴⁴

Table 5. Univariable, multivariable, and stepwise multivariable logistic regression models to identify predictors for no new development of cervical spine instability at > 10-year follow-up in 85 consecutively followed patients

Variable	Univariable analysis			Multivariable analysis [†]			Stepwise multivariable analysis [‡]		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age, 55–64 yr	1.008	0.407–2.494	0.987						
Female sex	0.933	0.304–2.865	0.904						
RA duration < 5 yr	2.423	0.923–6.357	0.072	1.346	0.393–4.604	0.636			
CRP ≤ 1.0 mg/dL	2.583	1.050–6.354	0.039*	2.026	0.707–5.802	0.189	2.453	0.915–6.576	0.075
RF negative	2.795	0.941–8.303	0.064	2.064	0.561–7.592	0.275			
No previous joint surgery	3.111	1.215–7.967	0.018*	2.078	0.708–6.097	0.183			
Medications									
No corticosteroids	3.200	1.283–7.984	0.013*	3.542	1.216–10.319	0.020*	3.868	1.387–10.789	0.010*
No MTX	1.513	0.630–3.637	0.355						
No other DMARDs	0.638	0.265–1.536	0.316						
No biological agents	3.333	0.871–12.763	0.079	3.284	0.697–15.481	0.133			
Steinbrocker stages and mutilating changes									
Stages I–II	4.179	1.449–12.050	0.008**	4.278	1.095–16.719	0.037*	5.355	1.652–17.352	0.005**

OR, odds ratio; CI, confidence interval; RA, rheumatoid arthritis; CRP, C-reactive protein; RF, rheumatoid factor; MTX, methotrexate; DMARD, disease-modifying antirheumatic drug.

* $p < 0.05$ and ** $p < 0.01$, statistically significant differences. [†]The Hosmer-Lemeshow goodness-of-fit chi-square test $p = 0.307$ (8° of freedom) and the concordance statistic for the model = 0.792. [‡]The Hosmer-Lemeshow goodness-of-fit chi-square test $p = 0.404$ (5° of freedom) and the concordance statistic for the model = 0.768.

This could be attributed to corticosteroid-induced osteoporosis;⁴⁵ e.g., the development of VS induced by facet joint collapse at C1–2.⁴³ By contrast, another study showed that 10-mg/day prednisolone within 2 years increased the benefits of DMARDs and had joint-sparing properties in early RA.⁴⁶ In a 4-year prospective cohort study, a lower dosage of corticosteroids (< 5-mg/day prednisolone) was a risk factor of large joint destruction in the lower extremities compared with a higher dosage.⁴⁷ Therefore, maintaining low RA activity without the need for concomitant corticosteroids, rather than avoiding adverse corticosteroid effects (except for their prolonged use), is important to prevent cervical spine instability.

No previous joint surgery was a predictive factor among the entire cohort. Radiographic evidence of cervical spine instability was observed in 40.8%–61.1% of patients with RA who underwent total hip or knee arthroplasty.^{34,48} The absence of operated peripheral joints suggests low RA activity without any requirements of surgical intervention, potentially leading to less cervical spine erosion.

Additionally, CRP level of ≤ 1.0 mg/dL was a marginal predictor in both cohorts. According to the Boolean-based definition of RA remission, patients must satisfy the criterion of CRP ≤ 1.0 mg/dL.²⁸ In a meta-analysis, CRP level was found to be a

risk factor for cervical spine involvement in RA.³³ In the present study, however, CRP ≤ 1.0 mg/dL did not reach statistical significance. Consequently, CRP ≤ 1.0 mg/dL might be insufficient to prevent cervical spine instability. This is consistent with the association between the progression of radiographic damage and residual joint swelling even with CRP ≤ 1.0 mg/dL.⁴⁹ More rigorous goal setting in RA management is necessary to achieve no > 10-year involvement or development of cervical spine instability.

Taken together, our findings indicate that sustained low RA activity without concomitant demands of corticosteroid therapy, thus underdeveloping radiographic peripheral joint damage, is essential for no cervical spine instability during > 10 years. This is in agreement with the current treat-to-target and early intervention strategy before joint destruction; e.g., biological DMARD therapy.⁵⁰ In this 2001–2013 study, biological agent administration, approved since 2003 in Japan, failed to prevent cervical spine instability. However, biological agents might not have fully exerted their treatment effects on our cohort of patients, who had long histories of RA predating the administration. In this first decade of biological agent application, the frequency (15.0%–18.8%) was not as high as the more recent situation (29.5% in Japan, 2018).⁵¹ Nevertheless, this highlights the

importance of early diagnosis and intervention. In literature, the incidence of cervical spine lesions was still high at 31.8%–41.8% in the early biological agent era.^{40,41} However, biological agent therapy prevented new onset of cervical spine lesions but failed to control the progression of pre-existing lesions.^{52–54} A more recent cross-sectional study revealed a decrease in the prevalence of AAS by 50%, VS by 75%, and SAS by 5% from 1999 to 2015.⁵⁵ Collectively, the current study provides the important basis as a reference of synthetic DMARD treatment to prevent cervical spine instability in RA.

This study has several limitations. The number of patients, particularly in the subcohort analysis, was small. As shown in our >5-year observation,²¹ patients of advanced age with established RA were more likely to be lost to follow-up in this >10-year observation. In fact, the difficulty in visiting outpatient clinics due to polyarthralgia, worsening general condition, and/or death was a major cause of the low follow-up rate. Among the subcohort, mortality increased with time while we observed additional dropout of patients without baseline cervical spine instability, neck pain, or neuropathy. Another limitation is that data were missing on magnetic resonance imaging, physical and neurological function,⁵⁶ and clinical symptoms related to the remission, e.g., disease activity score-28,²⁸ because the study began in 2001. Clinical data should be retrieved longitudinally at multiple time points. The retrospective data acquisition was also difficult because of the national law to protect personal information, the 5-year storage period of medical records in Japan, and the nature of the prospective study design. Further investigation taking these factors into account is warranted to clarify management goals of the cervical spine in RA.

CONCLUSION

Steinbrocker nonadvanced peripheral joint destruction stages I–II, no need for corticosteroid administration, no need for peripheral joint surgery, and possibly CRP level of ≤ 1.0 mg/dL are factors associated with the absence of cervical spine instability at >10 years. Furthermore, Steinbrocker stages I–II, no concomitant corticosteroids, and marginally CRP ≤ 1.0 mg/dL are factors associated with no new development of instability at >10 years. These predictors highlight the importance of a treat-to-target strategy aiming at low disease activity and remission of RA. The present study provides clinically useful information on the timing for rheumatologists to consult cervical spine practitioners during the routine follow-up of patients with RA.

NOTES

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