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Age-stratified trends in the progression of spinal radiographic damage in patients with ankylosing spondylitis: a longitudinal study

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Abstract

Objective: The objective of this study was to investigate spinal radiographic progression in specific age ranges of ankylosing spondylitis (AS) patients.

Methods: Longitudinal data for 1125 AS patients at a single hospital from 2000 to 2018 were retrospectively reviewed. Radiographic intervals were obtained from patients with consecutive spinal radiographs. The radiographic progression rate was defined as the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) change per year within each interval. Using generalized estimating equations (GEEs), estimated marginal means were calculated for the mSASSS progression rate across age groups after adjusting for potential confounders.

Results: We obtained 4016 radiographic intervals and stratified them into five groups based on patient age at the interval start: <20 ($n = 122$); 20–29 ($n = 1124$); 30–39 ($n = 1690$); 40–49 ($n = 794$); and ⩾50 years ($n = 286$). The mean (SD) mSASSS progression rate for all the intervals was 0.8 (1.9). The GEE-estimated mean mSASSS progression rate increased with age, peaking in the 30–39 age group with a value of 1.15 [95% confidence interval (CI) 1.03, 1.27], and decreased slightly thereafter. In the presence of risk factors, rapid progression occurred at earlier ages: the GEE-estimated mean mSASSS progression rate in those with elevated C-reactive protein levels and preexisting syndesmophytes was 2.82 (95% CI 1.93, 3.71) in the 20–29 age group.

Conclusion: Spinal structural damage in AS seems to progress most rapidly when patients are age 30–39 years. An awareness of the trends in radiographic progression with advancing age could improve understanding of the natural course of AS.

Keywords: age, ankylosing spondylitis, mSASSS, radiographic progression

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Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease characterized by progressive structural damage in the axial skeleton that begins with the sacroiliac joint and spreads to the spine.[1,2] Assessment of radiographic changes using established scoring methods, primarily the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), has been a key outcome measure in studies addressing the course of structural disease progression.[3,4] A slow linear radiographic progression is assumed to occur at the group level, usually an increase of 2 mSASSS units every 2 years (rate: 1 unit per year); however, highly variable rates of progression have been noted between individuals, as is often seen in daily practice.[4] Thus, predicting future progression, particularly identifying factors that influence AS prognosis, has been a major interest of clinicians.[5]

Although age clearly has some prognostic significance among AS patients, similar to other demographic factors such as gender and smoking status, it has mainly been considered in terms of age at onset.[6] Studies have shown that AS onset at age 16 years or younger is linked with severe disease outcomes,[7] highlighting the differences in clinical features of juvenile- and adult-onset AS.

However, age-of-onset comparisons cannot easily predict how the disease will progress over time as those living with AS advance in age. Most AS patients develop the disease as young adults and live in a chronic disease condition for decades. Moreover, because disease progression can be unpredictable during working years, patients often report anxiety and fear about the uncertainty of their disease progress, which is a major cause of future health concerns.[8,9] In that respect, understanding how structural damage progresses at particular ages might be important to AS patients.[10]

In general, literature on the extent to which structural damage worsens as a function of age is sparse. Earlier studies have suggested a linear relationship between age and spinal radiographic progression.[11] On the other hand, a study of patients being treated with tumor necrosis factor (TNF) inhibitors found that radiographic progression was more likely to occur in patients older than 40 years than in those age 40 and younger.[12] Our aim in this study was to look for age-specific differences in spinal radiographic progression and estimate the rate of radiographic progression with advancing age in relation to factors known to affect radiographic progression.

Materials and methods

Study population and clinical assessment

Data for AS patients who fulfilled the modified New York criteria[13] and received treatment at a single hospital between January 2001 and December 2018 were retrospectively reviewed. Among the 1280 AS patients screened, consecutive 1125 patients who had at least two sets of cervical and lumbar spinal radiographs were included in this study. The institutional review board of our university hospital approved this study (HYUH 2021-10-004). The need for patient consent was waived because our study is retrospective. All patient details were de-identified. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[14]

The following demographic and clinical characteristics were obtained from patient medical records: age, sex, symptom duration, smoking status, history of eye involvement with uveitis, peripheral joint involvement with arthritis other than in axial joints, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and use of a TNF inhibitor. We also collected laboratory findings: human leukocyte antigen (HLA)-B27 positivity, serum erythrocyte sediment rate (ESR), and C-reactive protein (CRP) levels. Missing data on disease activity parameters (ESR, CRP, and BASDAI) for a given timepoint with a radiograph examination were imputed by performing linear interpolation from adjacent data (values measured within 3 months before and after).

Radiographic assessment

During the entire follow-up, we obtained 5141 spinal radiographs from 1125 patients, with a mean [standard deviation (SD)] number of 4.6 (1.2) spinal radiograph per patient in a mean (SD) follow-up duration of 8.4 (2.9) years per patient. Two radiologists, SL and KBJ, who were blinded to patients' clinical data except for radiograph chronology, independently scored lateral views of cervical and lumbar spinal radiographs according to the mSASSS.[15] The intra-observer and inter-observer reliability were both excellent, with intra-class correlation coefficient (ICC) values of 0.978 [95% confidence interval (CI) 0.976, 0.979] and 0.946 (95% CI 0.941, 0.950), respectively.[16] The inter-observer reliability for change in mSASSS over time was good, with an ICC of 0.760 (95% CI 0.731, 0.786). Baseline radiographic sacroiliitis was scored according to the modified New York criteria[13] by a trained rheumatologist (THL).

Because the interval between consecutive spinal radiographs varied across and within individuals, radiographic intervals derived from the radiographs of each patient were defined to account for progression during the period between consecutive radiographs. In total, 4016 radiographic intervals with a mean (SD) length of 2.4 (1.0) years were obtained. The degree of radiographic progression within each interval was determined using the mSASSS progression rate, which was defined as the difference in mSASSS at the beginning and end of each interval divided by the length of the respective interval (that is, mSASSS change per year).

Statistical analyses

Continuous variables are presented as mean (SD) and categorical variables as frequency with percentage. We used generalized estimating equations (GEEs) with an exchangeable correlation

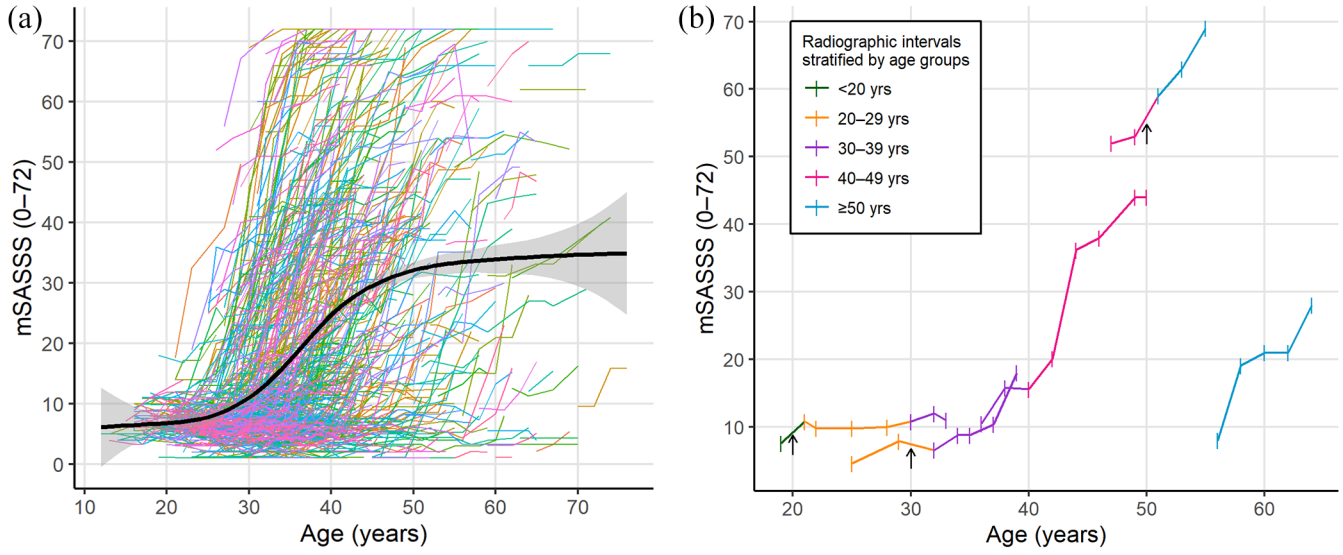

Figure 1. Progression in mSASSS plotted as a function of age at the individual patient level ($n = 1125$). (a) The black line shows the fitted values using a generalized additive model (adjusted $R^2 = 0.22$). The gray areas represent 95% confidence intervals. (b) The procedures for age-specific stratification of radiographic intervals derived from each patient (cases for five patients are shown as examples). Patients could contribute to several radiographic intervals. Radiographic intervals were assigned based on patient age at the beginning of each interval. If the age at the beginning and end of a given interval was different, the interval was assigned to the age group at the beginning (black arrows).
mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.

structure to account for the correlation of repeatedly measured within-subject data. Because we were interested in examining the trends in radiographic progression according to age, we first evaluated whether the progression rate over time is likely to vary across age groups, by testing the effect of the interaction between time and patient age on mSASSS progression. With mSASSS as the outcome and time (years) as the independent variable such that the obtained regression coefficient for time reflects the progression of mSASSS per year ($\beta = 0.839$, 95% CI 0.759, 0.919), a significant interaction was found between time and patient age (p value < 0.001), allowing clinical implications for age-stratified analyses regarding radiographic progression over time. Thereafter, we used generalized additive modeling with integrated smoothness estimation to visualize the relationship between patient age and mSASSS in our entire study population. Given the fitted trend spline, patient age at the time of each radiographic examination was categorized into five age groups for analysis: <20, 20–29, 30–39, 40–49, and ⩾50 years (Figure 1(a)). Radiographic intervals were then assigned to age groups based on patient age at the start of that interval (Figure 1(b)).

As a second step, we determined the clinical and demographic factors that affect the mSASSS progression rate, our dependent variable. For time-fixed confounders, we considered sex, HLA-B27 status, history of smoking, history of eye involvement or peripheral joint involvement, baseline sacroiliitis grade or presence of syndesmophytes, and use of TNF inhibitors. For time-varying confounders, we considered symptom duration, ESR, CRP, and BASDAI. Highly skewed continuous variables were transformed using a log or square-root function. CRP was chosen over ESR as a covariate given the potential influence of age on ESR values.[17] All variables with a potentially significant effect on the outcome (p value $\leqslant 0.1$) in the univariable analysis were entered into the multivariable analysis. Symptom duration and baseline sacroiliitis were excluded from multivariable analysis to avoid potential collinearity with age and presence of syndesmophytes, respectively. For continuous variables with a significant association with the outcome, stratification was conducted based on clinically relevant values. Because our main variable of interest was the effect of age on the radiographic outcome, and the longitudinal relationship between radiographic damage and

Table 1. Clinical characteristics of the study patients.

Variable	No. with data	Value
Age at baseline, years, mean (SD)	1125	31.5 (9.4)
Symptom duration at baseline, years, mean (SD)	910	8.8 (7.2)
Male sex, *n* (%)	1125	995 (88.4)
HLA-B27 positive, *n* (%)	1120	1081 (96.5)
Smoking (ever), *n* (%)	1071	655 (61.2)
Eye involvement (ever), *n* (%)	948	363 (38.3)
Peripheral joint involvement (ever), *n* (%)	938	401 (42.8)
CRP at baseline, mg/dl, mean (SD)	1025	2.3 (2.6)
Elevated CRP (⩾1.0 mg/dl), *n* (%)	1025	593 (55.4)
ESR at baseline, mm/h, mean (SD)	1033	33.2 (31.3)
BASDAI at baseline (0–10), mean (SD)	262	5.1 (2.7)
High disease activity (BASDAI ⩾ 4), *n* (%)	262	168 (64.1)
TNF inhibitor use (ever), *n* (%)	1125	593 (52.7)
mSASSS at baseline (0–72),[a] mean (SD)	1125	14.6 (16.3)
Syndesmophytes present at baseline, *n* (%)	1125	324 (28.8)
Sacroiliitis grade at baseline (0–4),[b] mean (SD)	1068	2.8 (0.9)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sediment rate; HLA, human leukocyte antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; SD, standard deviation; TNF, tumor necrosis factor.
[a]Complete spinal ankylosis (mSASSS of 72) was shown in 1.9% of patients (*n* = 21) at baseline.
[b]Calculated by averaging the grades of the right and left sacroiliac joints.

covariates was modeled based on interval-level data with mSASSS progression rate as the outcome to account for radiographic progression at the same interval length, time-varying variables measured at the start of each interval were used for estimating mSASSS progression rate within the respective interval.

Using the regression coefficients obtained from the GEE multivariable models, the mSASSS progression rate for each age group is presented as the estimated marginal mean with 95% CI. In addition, we performed separate analyses after stratifying the data into subgroups to estimate the course of radiographic progression in the presence and absence of factors predicting worse radiographic outcomes. Pairwise comparisons between groups in terms of the effect of age on the rate of radiographic progression were performed. A sensitivity analysis was performed after excluding data for radiographic intervals in which the patient ages at the beginning and end of a given interval belonged to different groups (Figure 1(b)). All analyses were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). A p value < 0.05 was deemed to indicate statistical significance.

Results

Characteristics of the study population

The clinical characteristics of our 1125 AS patients are summarized in Table 1. Most patients were male (88.4%) and positive for HLA-B27 (96.5%). The mean (SD) age and symptom duration at baseline were 31.5 (9.4) and 8.8 (7.2) years, respectively. At baseline, a range of radiographic damage status was observed among individuals, with a mean (SD) mSASSS of 14.6 (16.3). At baseline, 28.8% already had at least one syndesmophyte. About half the patients (52.7%) were exposed to TNF inhibitors during any part of the follow-up period.

Table 2 provides information about time-varying variables related to disease assessment based on interval-level data. Age-stratified radiographic intervals were most prevalent in the 30–39 year group ($n = 1690$), followed by the 20–29 ($n = 1124$), 40–49 ($n = 794$), ⩾50 ($n = 286$), and <20 ($n = 122$) year groups. Although the status of radiographic damage showed an increasing trend with advancing age, as expected, the levels of inflammatory markers showed a decreasing trend with advancing age. Similarly, BASDAI decreased with age, except for those aged ⩾50 years, who saw an increase.

Factors affecting radiographic progression

The following independent variables were significantly associated with the mSASSS progression rate in univariable analysis: age, symptom duration, and log-transformed CRP at the interval start; being male; history of smoking, eye involvement, or peripheral joint involvement; the presence of syndesmophytes at baseline; and the grade of sacroiliitis at baseline. Multivariable analysis (Table 3) showed that age 20–29 ($\beta = 0.23$, 95% CI 0.09, 0.37), 30–39 ($\beta = 0.51$, 95% CI 0.34,

Table 2. Clinical characteristics based on radiographic interval overall and by age-stratified groups.

Variable	Radiographic intervals						
	Overall (*n* = 4016)		Stratified by age group, years				
	No. with data	Value	<20 (*n* = 122)	20–29 (*n* = 1124)	30–39 (*n* = 1690)	40–49 (*n* = 794)	⩾50 (*n* = 286)
Age at interval start, years	4016	34.7 (9.5)	17.6 (1.5)	25.4 (2.8)	34.3 (2.8)	43.6 (2.8)	55.9 (5.1)
Symptom duration at interval start, years	3457	12.7 (7.8)	3.9 (3.0)	7.9 (4.6)	13.3 (6.4)	16.6 (8.2)	19.9 (11.3)
CRP at interval start, mg/dl	3957	1.6 (1.9)	1.9 (2.4)	1.9 (2.2)	1.5 (1.8)	1.5 (1.9)	1.4 (1.6)
Elevated CRP (⩾1.0 mg/dl), *n* (%)	3957	1453 (36.7)	47 (38.5)	474 (42.2)	587 (34.7)	252 (31.7)	93 (32.5)
ESR at interval start, mm/h	3961	22.9 (25.1)	25.1 (28.8)	23.8 (26.3)	21.4 (23.4)	23.1 (25.2)	26.4 (28.1)
BASDAI at interval start (0–10)	2684	3.4 (2.2)	4.1 (2.7)	3.6 (2.3)	3.4 (2.2)	3.3 (2.1)	3.7 (2.0)
BASDAI ⩾ 4, *n* (%)	2684	946 (35.2)	21 (48.8)	243 (38.9)	412 (34.0)	186 (31.4)	84 (39.3)
mSASSS at interval start (0–72)	4016	17.6 (18.5)	7.0 (2.3)	8.3 (6.5)	17.2 (17.2)	27.9 (22.3)	32.9 (24.4)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sediment rate; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.
Values are mean (SD) unless otherwise indicated.

0.69), and 40–49 (β = 0.37, 95% CI 0.15, 0.60) at the interval start were independently associated with an increased rate of mSASSS progression compared with age <20 years, which was used as the reference. When age was assessed as a continuous variable, on the other hand, it showed no significant association with the rate of mSASSS progression (Supplementary Table 1). History of smoking (β = 0.30, 95% CI 0.15, 0.44) or eye involvement (β = 0.24, 95% CI 0.07, 0.40), log-transformed CRP at the interval start (β = 0.30, 95% CI 0.18, 0.41), and preexisting syndesmophytes (β = 0.87, 95% CI 0.65, 1.09) were confirmed to be independently associated with an increase in the mSASSS progression rate. Involvement of peripheral joints was associated with a reduced mSASSS progression rate (β = −0.23, 95% CI −0.37, −0.08). The use of TNF inhibitors had no significant effects on the mSASSS progression rate.

Age-stratified trends in the rate of radiographic progression

The mean (SD) mSASSS progression rate for all the intervals was 0.8 (1.9). The increase in mSASSS over time accelerated with age, peaking in the 30–39 and 40–49 year age groups and then decreasing slightly in the ⩾50 year age group (Table 4). The GEE-estimated mean mSASSS progression rate showed a similar pattern: the 30–39 year age group had the most prominent progression with a value of 1.15 (95% CI 1.03, 1.27), followed by the 40–49 year age group with 1.00 (95% CI 0.84, 1.17) (Table 4). The slowest rate of progression was estimated for those <20 years of age, who had mSASSS change of 0.64 per year (95% CI 0.48, 0.80). Pairwise comparisons of the estimated mean mSASSS progression rates among the stratified age groups are shown in Supplementary Figure 1. As a sensitivity analysis, we repeated our analyses using only data in which the patient ages at the beginning and end of a given interval were within the same age group and showed similar results, indicating that relatively slow or rapid progression can alternate with advancing age (Supplementary Table 2).

Radiographic progression according to risk factors

The mean age-stratified mSASSS progression rate in the presence of factors predictive of worse radiographic outcomes is shown in Figure 2 as a visualization of individual observations and the shape of data distributions. In the presence of risk

Table 3. Longitudinal associations between covariates and mSASSS progression rate.[a]

Covariates	Univariable analysis		Multivariable analysis[b]	
	Beta estimate[c] (95% CI)	*p* value	Beta estimate[c] (95% CI)	*p* value
Age at interval start				
<20 years	Reference		Reference	
20–29 years	0.32 (0.20, 0.45)	<0.001	0.23 (0.09, 0.37)	0.001
30–39 years	0.75 (0.61, 0.89)	<0.001	0.51 (0.34, 0.69)	<0.001
40–49 years	0.80 (0.62, 0.99)	<0.001	0.37 (0.15, 0.60)	0.001
⩾50 years	0.65 (0.42, 0.88)	<0.001	0.16 (−0.17, 0.48)	0.344
Symptom duration at interval start[d]	0.01 (0.00, 0.02)	<0.001	–	–
Male sex	0.48 (0.33, 0.62)	<0.001	0.09 (−0.08, 0.26)	0.312
HLA-B27 positivity	0.15 (−0.19, 0.48)	0.397	–	–
Smoking (ever)	0.50 (0.37, 0.63)	<0.001	0.25 (0.11, 0.39)	<0.001
Eye involvement (ever)	0.28 (0.12, 0.44)	<0.001	0.21 (0.05, 0.38)	0.009
Peripheral joint involvement (ever)	−0.33 (−0.48, −0.18)	<0.001	−0.22 (−0.37, −0.08)	0.002
TNF inhibitor use (ever)	0.10 (−0.04, 0.24)	0.144	–	–
CRP at interval start (log)	0.28 (0.17, 0.39)	<0.001	0.32 (0.20, 0.43)	<0.001
Elevated CRP (⩾1.0 mg/dl)	0.53 (0.40, 0.67)	<0.001	–	–
BASDAI (square-root) at interval start	−0.01 (−0.11, 0.10)	0.933	–	–
High disease activity (BASDAI ⩾ 4)	0.03 (−0.12, 0.18)	0.690	–	–
Preexisting syndesmophytes	1.06 (0.89, 1.22)	<0.001	0.85 (0.64, 1.07)	<0.001
Sacroiliitis grade at baseline[d]	0.41 (0.34, 0.47)	<0.001	–	–

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; HLA, human leukocyte antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; TNF, tumor necrosis factor.
[a]The difference between mSASSS values at the start and end of each interval divided by the length of the interval.
[b]Variables that were potentially significant in the univariable analysis ($p \leqslant 0.1$) were entered into the multivariable analysis.
[c]Unstandardized regression coefficient.
[d]Excluded from the multivariable analysis due to high correlation with age (symptom duration) or syndesmophytes (sacroiliitis grade).

factors, a greater increase in mSASSS progression was observed across almost all age groups. The individual mSASSS progression rate of those with elevated CRP level at the interval start or syndesmophytes at baseline showed a broader range of data distribution in the 20–29 and 30–39 year age groups than in the other groups, which indicates more cases with rapid progression in those age groups.

The GEE-estimated mean mSASSS progression rate according to risk factors also revealed that structural progression is likely to accelerate among earlier age groups if CRP level is elevated

Table 4. GEE-estimated mSASSS progression rate[a] across age groups.

		Radiographic intervals ($n = 4016$)				
		<20 years ($n = 122$)	20–29 years ($n = 1124$)	30–39 years ($n = 1690$)	40–49 years ($n = 794$)	⩾50 years ($n = 286$)
mSASSS progression rate (unadjusted)[b]		0.1 (0.5)	0.5 (1.5)	1.0 (2.0)	1.1 (2.0)	0.8 (1.8)
mSASSS progression rate[c]		0.64 (0.48, 0.80)	0.87 (0.71, 1.03)	1.15 (1.03, 1.27)	1.00 (0.84, 1.17)	0.78 (0.52, 1.04)
Smoking	yes	0.66 (0.38, 0.93)	0.98 (0.73, 1.23)	1.33 (1.17, 1.49)	1.18 (0.96, 1.40)	0.69 (0.37, 1.01)
	no	0.51 (0.33, 0.69)	0.75 (0.57, 0.92)	0.90 (0.72, 1.08)	0.78 (0.57, 0.99)	1.03 (0.62, 1.44)
Elevated CRP (⩾1.0 mg/dl)	yes	0.89 (0.60, 1.18)	1.26 (1.00, 1.52)	1.64 (1.41, 1.87)	1.16 (0.89, 1.43)	0.82 (0.23, 1.41)
	no	0.46 (0.30, 0.62)	0.57 (0.40, 0.75)	0.84 (0.70, 0.97)	0.90 (0.71, 1.10)	0.65 (0.36, 0.94)
Preexisting syndesmophytes	yes	–[d]	2.40 (1.54, 3.27)	1.72 (1.49, 1.96)	1.27 (0.99, 1.55)	0.76 (0.46, 1.06)
	no	0.21 (0.09, 0.33)	0.34 (0.25, 0.42)	0.67 (0.54, 0.81)	0.73 (0.55, 0.91)	1.03 (0.63, 1.42)
Elevated CRP with syndesmophyte at baseline		–[d]	2.82 (1.93, 3.71)	2.31 (1.89, 2.72)	1.50 (1.06, 1.94)	1.04 (0.45, 1.62)

CRP, C-reactive protein; GEE, generalized estimating equation; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.
[a]The difference between mSASSS values at the start and end of each interval divided by the length of the interval.
[b]Values are mean (SD) calculated from observed data.
[c]Values are estimated marginal means (95% CI) obtained by fitting the multivariable model that was adjusted for smoking, eye involvement, peripheral joint involvement, CRP at interval start (log), and syndesmophyte presence at baseline.
[d]No syndesmophytes were observed on spinal radiographs in this age group.

or syndesmophytes are present at baseline (Table 4, Supplementary Figure 2): the estimated mean mSASSS progression rate in those with elevated CRP level was 1.26 (95% CI 1.00, 1.52) in the 20–29 year age group and 1.64 (95% CI 1.41, 1.87) in the 30–39 year age group. The steepest progression was an mSASSS change of 2.82 per year (95% CI 1.93, 3.71) among patients in the 20–29 age group with signs of high inflammation and preexisting structural damage.

Discussion

In this study, we investigated the course of radiographic progression over time using age groups stratified in 10-year increments and changes in mSASSS within radiographic intervals. The estimated yearly progression rate, which was defined as change in mSASSS between the start and end of each interval divided by the length of the interval, exhibited a trend toward an alternating increase across age groups, with progression gradually accelerating with age, peaking in the 30–39 year age group, and then gradually decreasing. It was also evident that rapid progression could occur among younger patients if risk factors, particularly elevated CRP level or preexisting syndesmophytes, were present.

In several AS cohort studies of radiographic progression, status scores for spinal damage over time have been presented as a function of follow-up duration or symptom duration.[3,4,11] Here, on the other hand, we used patient age as the marker of time and stratified age groups to capture radiographic changes over time. We found that different ages could be associated with somewhat rapid or slow progression. In contrast, age-stratified trends in inflammatory markers revealed that burden of inflammation is highest among young patients (aged <20 and 20–29 years), which can be deemed the early stage of the disease. Given that it can take a certain amount of time for inflammation in the axial joints to progress to structural changes such as new bone formation,[18] the discrepancy between the age group in which

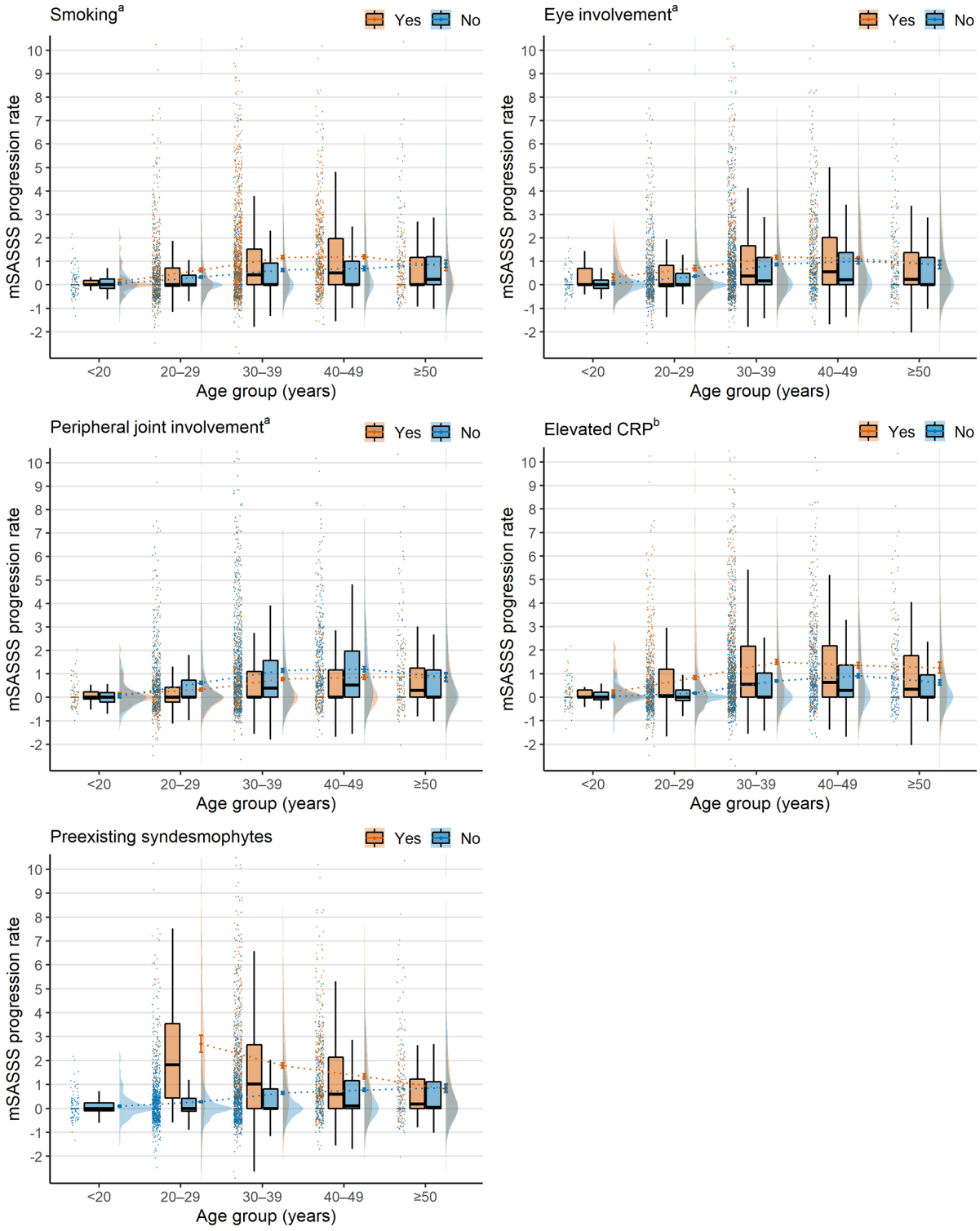

Figure 2. Age-stratified trends in the rate of mSASSS progression according to the presence or absence of risk factors. The mean mSASSS progression rate for each age group is presented in dotted lines with overlaid boxplots. The actual individual observations, indicated as datapoints, and the density probability plot are displayed to provide maximal statistical information and show the wide range of values. Observations with mSASSS progression rate >10 units or <−2.5 units are not shown ($n = 17$).
CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.
[a]Refers to patients who experienced this factor at any time in the follow-up period.
[b]The cutoff value was 1.0 mg/dl.

the degree of inflammation is greatest and that in which worsening radiographic damage reaches a peak is unsurprising. In addition, treatment adherence can vary by patient age, which could also contribute to radiographic outcomes.[19] Studies have shown that middle-aged AS patients had lower adherence to medications and a reduced rate of drug persistence than did older patients.[20,21] Those patterns of nonadherence behavior, therefore, could be another explanation for our finding that radiographic progression is greater in the 30–39 age group than in older patients. Furthermore, considering the differences in common occupation-related physical activities between the age groups, mechanical stress on the spine, which is linked with worsening disease progression, could be an important contributor to progression in specific age groups, although it is difficult to quantify excess mechanical load.[22,23]

Despite the statistical significance of our age-specific findings in mSASSS changes, their clinical relevance may be controversial because the average differences in rates of progression between age groups are relatively small; however, the radiographic outcomes of those with particular risk factors could have larger clinical implications. As depicted in Figure 2, in the presence of risk factors for progression, a broad distribution of individual progression rates was seen across the age groups, indicating that rapid progression can occur at any age in patients with particular characteristics. Of note, the GEE-estimated mean mSASSS progression rate in the 20–29 year age group in the presence of both preexisting syndesmophytes and elevated CRP level was more than three times greater than the estimated mean value for that age group as a whole (Table 4). Because such rapid structural change might be pointedly relevant to young patients with concerns about their ability to work, choice of profession, and family planning,[10,24,25] patient-tailored disease monitoring based on risk factors should be emphasized for young AS patients. Setting optimized treatment goals with consideration of the trends in disease progression at a given age can facilitate the development of individually coordinated treatment plans.[9,26]

We confirmed the importance of several established predictors of spinal radiographic progression. In line with previous reports, CRP at the interval start was significantly associated with an increase in the rate of mSASSS progression, supporting the idea that inflammation leads to subsequent osteoproliferation.[27] Although BASDAI at the interval start displayed a pattern of change similar to that of inflammatory markers across age groups, it was not predictive of radiographic progression. As is well known, the presence of syndesmophytes at baseline was a strong predictor of future radiographic progression.[28] Eye involvement and peripheral joint involvement were significantly associated with rate of mSASSS progression, as identified in previous studies.[29] However, we judged the presence or absence of uveitis and peripheral arthritis in terms of their occurrence during any part of the follow-up period, not whether they occurred within a given age group. Further studies that focus on evaluating the effects of uveitis or peripheral joint disease at each visit are needed, with extended follow-up, to clarify the effects of those clinical characteristics on spinal radiographic changes over time.

Although growing evidence has reported that long-term TNF inhibitor therapy might have beneficial effects on spinal progression in AS,[30] we found no significant association between TNF inhibitor use and the rate of mSASSS progression in this study. That result is most likely attributable to our use of binary measures; we defined TNF inhibitor use as exposure to a TNF inhibitor during any part of the follow-up period. In other words, we did not consider the period of drug administration within each radiographic interval. A dedicated study design that handles potential confounding by indication is required to address the causal effects of medication.[16,31] In this study, we set out to trace the course of radiographic progression in stratified age groups, so we acknowledge that the underrated effect of TNF inhibitors in our results is probably due to our rather simple binary measure for TNF inhibitor use. Data for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) were not used because a considerable number of our patients received on-demand NSAID treatment; therefore, obtaining complete information about the dose and frequency of NSAID intake was infeasible. Thus, the potential effects of NSAID use on radiographic progression were not considered, which might also have influenced our results.[32] The use of conventional synthetic disease-modifying antirheumatic drugs was not included among our covariates because the results of our preceding studies showed no significant association between those drugs and radiographic progression.[33]

This study has several other limitations that should be noted. Our study population was predominantly distributed in the 20–49 year age

group, with relatively few data points for patients aged <20 and ⩾50 years, which could introduce bias. Despite obtaining similar results in our sensitivity analysis, our age-stratification method might have limited our ability to evaluate the degree of mSASSS changes at the transition points among adjacent age groups when the beginning and end of an interval spanned two groups. In addition, there is a probable lack of generalizability of our results because this was a single-institution study. Further studies are required to ensure the validity of our results. Another limitation is that the covariates did not include occupational or circumstantial status or obesity, which could be linked to structural disease progression.[34,35] We did not consider the dose-dependent effect of smoking on radiographic outcomes.[36] We could not fully exclude information bias. Although the composite Ankylosing Spondylitis Disease Activity Score based on CRP, namely ASDAS-CRP,[37] calculated using CRP with three BASDAI questions and Patient Global Assessment of disease activity (PGA), is a preferred tool for assessing disease activity, we employed the BASDAI score. Because a considerable number of patients lacked data for PGA, which is required for calculation of the ASDAS, and BASDAI total scores were collected without individual BASDAI questions in some patients, there were fewer missing values for BASDAI than ASDAS-CRP. However, the imputed CRP and BASDAI values, which used the method of linear interpolation, might also have influenced the outcome. The limitations about unmeasured lifestyle factors and missing data are inherent to the retrospective nature of this study, which was limited to information available in patient medical records. However, given that a prospective observation for several decades from the time of diagnosis to address age-related progression in AS patients is quite time-consuming and infeasible, our longitudinal analyses of a large population across the clinical spectrum of this disease is a reasonable alternative to estimate the long-term course of disease progression according to age. Reading radiographs with known chronology might be seen as an additional limitation. However, this approach has been shown to be more sensitive for detecting changes than reading with paired time order,[38] and readers were blinded to clinical details.

In summary, we estimated the degree of structural damage progression with advancing age by establishing decadal age groups in a real-life clinical setting. Our observations, taking into account progression trends by age group and factors predictive of radiographic outcome, add value in understanding the natural course of structural damage progression with advancing age in patients with AS.

Author contribution(s)

Tae-Han Lee: Conceptualization; Data curation; Formal analysis; Writing – original draft.

Bon San Koo: Data curation; Investigation; Writing – review & editing.

Bora Nam: Investigation; Writing – review & editing.

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Availability of data and materials

The data underlying this article are available upon reasonable request to the corresponding author.

Supplemental material

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