

## Clinical science

# Prevalence and predictors of atlanto-axial subluxation in rheumatoid arthritis after 12-years' follow-up (ESPOIR Cohort)

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## Abstract

**Objectives:** Anterior atlanto-axial subluxation (AAS), defined as an anterior atlanto-dental interval  $\geq 3$  mm, can occur in RA and carries a risk of severe neurological impairments. Our objective was to determine the prevalence and predictors of radiographic aAAS after 12 years' follow-up of patients with early polyarthritis.

**Methods:** We studied patients enrolled in the early polyarthritis cohort ESPOIR (Study and Monitoring of Early Undifferentiated Arthritis) between 2002 and 2005 (at least two swollen joints for  $>6$  weeks and  $<6$  months, no other diagnosis than RA, and no previous exposure to glucocorticoids or DMARDs). All patients still in the cohort after 12 years had dynamic cervical-spine radiographs taken then read by two blinded observers. To evaluate how well combinations of tests performed at baseline and 10 years predicted aAAS after 12 years, univariate analysis and multiple logistic regression procedure were applied.

**Results:** Of 323 patients followed for 12 years, 15 (4.6%; 95% CI 2.8, 6.4) had aAAS. Among baseline variables, only IgA RFs were associated ( $P < 0.05$ ) with aAAS (sensitivity 60%, specificity 75%). Among data collected after 10 years, oral CS therapy during the 10-year interval, treatment by DMARDs, CRP (mg/dl) and positive tests for RFs were associated with aAAS after 12 years, but only CRP and RFs remained in a model of logistic regression (combination predicted aAAS with a sensitivity of 60% for a specificity of 90%).

**Conclusion:** In conclusion, the prevalence of aAAS after 12 years was 4.6% in the ESPOIR cohort, with no patients having severe aAAS. Although some factors were found to be statistically associated to AAS, the event is too rare to allow a clinical relevance.

**Keywords:** RA, cervical spine, radiography, atlanto-axial subluxation

### Rheumatology key messages

- Prevalence of anterior atlanto-axial subluxation in early RA followed up for 12 years is 4.6%.
- No patient had severe anterior atlanto-axial subluxation (anterior atlanto-dental interval  $\geq 9$  mm).
- Given that atlanto-axial subluxation is uncommon, routine screening of all patients would have a low yield.

## Introduction

Atlanto-axial subluxation (AAS) chiefly occurs in patients with RA, in whom chronic inflammation of the synovial membranes leads to bone erosions, ligament laxity and spinal instability with a risk of neurological damage [1, 2].

Anterior AAS (aAAS) is defined as an anterior atlanto-dental interval (aADI)  $\geq 3$  mm and severe aAAS as an aADI  $\geq 9$  mm and/or a posterior atlanto-dental interval  $<14$  mm.

Severe aAAS is associated with potentially severe neurological complications and requires surgical advice and radiological monitoring [3, 4]. Vertical atlanto-axial subluxation (vAAS) is defined by a Clark station grade 2 or 3 and/or a Sakaguchi-Kauppi grade 2–4 [5, 6].

Radiographic cervical-spine involvement has been reported in about 50% of patients with RA [5–10]. However, when radiography, CT and MRI were combined, up to 80%

of patients had some degree of cervical-spine involvement [1, 11–13]. The most common radiological abnormality was AAS, in 7.0% to 42.5% of patients [2, 5, 6, 10, 12, 14, 15].

There is general agreement that cervical-spine involvement with RA should be sought only in patients with suggestive symptoms [16]. The symptoms lack specificity, however. Thus, C1-C2 involvement may manifest as neck pain, headache, nausea [17] or, far more rarely, a progressive neurological deficit [18]. Moreover, cervical-spine instability is very often asymptomatic [8, 17, 19, 20]. In one study, pain intensity at the C1-C2 level decreased significantly as anterior vertebral slippage increased [9]. Cervical myelopathy, although rare [21], carries a poor prognosis with persistent disability despite surgery in many cases [17].

Therapeutic advances in recent decades have significantly improved the course of RA, thereby decreasing the complication rate. Thus, decreases in destructive lesions of the cervical spine have been reported [1, 12, 21–23]. A 2015 meta-analysis showed a reduction in the prevalence of aAAS from 36% (95% CI 30%, 42%) before the 1980s to 24% (95% CI 13%, 36%) in the 2000s ( $P=0.004$ ) [21].

Cervical-spine involvement by RA has been described in studies with follow-ups of >5 years [10], 10 years [15] or 12 years [24]. A disease duration >10 years may be the strongest predictor of cervical-spine damage [17]. Other factors significantly associated with cervical involvement are onset before 45 years of age, neck pain, neurological symptoms, CRP elevation, structural joint damage at the hands and/or feet, Sharp score alteration, prolonged CS therapy, failure of DMARDs, cervical instability at study enrolment and presence of RFs [6, 15, 17, 18]. Whether screening for cervical-spine lesions in all patients with RA for at least 10 years or in a subset of these patients characterized by risk factors might decrease the occurrence of neurological impairments is unknown.

The objectives of this ancillary study of the ESPOIR (Study and Monitoring of Early Undifferentiated Arthritis) cohort of patients with early polyarthritis consistent with RA was to define the prevalence of aAAS after 12 years and to identify predictors of aAAS present at baseline.

## Methods

### ESPOIR cohort

The ESPOIR cohort is a French prospective multicentre cohort of patients with early arthritis consistent with RA (ClinicalTrials.gov NCT03666091) [25]. Adults aged 18–70 years with possible early RA were referred by rheumatologists and general practitioners to one of 14 regional centres in France, which included 813 patients between 2003 and 2005. The main inclusion criteria were at least two inflammatory joints for at least 6 weeks but no more than 6 months, a definite or probable clinical diagnosis of RA, and no previous DMARD or glucocorticoid therapy (except prednisone for <2 weeks in a dosage no more than 20 mg/day or as a single IA injection within 4 weeks before inclusion). The main exclusion criterion was a definite diagnosis of another inflammatory joint or CTD. Patients were treated and monitored by their rheumatologists according to the standard of care, without predefined therapeutic strategies. Study visits at the relevant regional centre occurred every 6 months during the first 2 years, then annually. At baseline and at each study visit,

clinical and laboratory variables recommended for the management of early arthritis were recorded. For each patient at baseline, blood samples were sent to a central laboratory for determination of the CRP level (normal <5 mg/l), IgM and IgA RFs, ACPAs (anti-CCP2), and HLA-DRB1\* alleles which have been described as being associated with radiological evolution of RA [25]. At each visit, each patient completed the HAQ Disability Index (HAQ DI). After 10 years, CRP level, RFs (yes/no) and anti-CCP2 tests were done at the relevant centre. Radiographs of the hands and feet taken at baseline then 10 years later were used for a centralized determination of the van der Heijde–modified total Sharp score (mTSS). The ESPOIR cohort study protocol was approved in July 2002 by the ethics committee of Montpellier, France (No. 020307). All patients gave their signed informed consent before inclusion. Only patients meeting 2010 ACR/EULAR criteria for RA [26] (at any time) were included in the current study.

### Cervical radiographs

Dynamic standard radiographs of the cervical spine in the fully flexed position were obtained 12 years after patient inclusion, digitized, and included in the ESPOIR database in ‘.bmp’ and ‘.jpeg’ formats. The odontoid sagittal diameter (O), aADI, Clark station and Sakaguchi–Kauppi grade were measured in pixels (Fig. 1).

The radiographs were read blindly by a junior radiologist (T.G.) and a junior rheumatologist (A.L.Q.). The intraclass correlation coefficients indicated excellent inter-observer and intraobserver agreement (>0.8) [27]. Each reader performed two measurements of each study variable. When the two readers disagreed about the presence of aAAS, they performed a second reading. If the disagreement persisted, the two readers and a more experienced reader worked together to achieve a consensus.

Each reader measured the distance from the anterior to the posterior border of the dens (O) and the distance from the posterior border of the anterior ring of C1 to the anterior margin of the odontoid (aADI). The Clark station of the atlas was determined by dividing the odontoid process into three equal parts in the sagittal plane; the anterior ring of the atlas being level with the middle and caudal third defined stations II and III, respectively. The Sakaguchi–Kauppi grade was determined based on the location of the superior facets of C2 relative to the line drawn along the inferior borders, mid-points, or superior borders of the arches of C1.

As digitized radiographs in ‘.bmp’ and ‘.jpeg’ formats did not allow usual measurements, we used proportions as previously described [27] to obtain the aADI from aADI/O, with aADI/O  $\geq 0.23$  indicating aADI  $\geq 3$  mm and aADI/O  $> 0.74$  indicating aADI  $\geq 9$  mm (Fig. 1). We defined vAAS as Clark station II or III and/or Sakaguchi–Kauppi grade 2–4.

### Statistical analysis

Categorical data were described as  $n$  (%) and continuous data as mean (s.d.). Comparisons were with the  $\chi^2$  test or Fisher’s exact test for binary variables and the Mann–Whitney  $U$  test for continuous variables.

We studied the prevalence of aAAS after 12 years of follow-up then compared patients with and without aAAS. Univariate analyses were carried out to look for associations linking aAAS to the baseline variables listed in Table 1. We built the same method to assess the ability of data collected after 10 years (listed in Table 2) to predict aAAS after 12 years.

**(a) Lateral flexion plain radiograph showing the method used for AADI and O measurements****(b) Clark station**

The station of the first cervical vertebra is determined by dividing the odontoid process into three equal parts in the sagittal plane. If the anterior ring of the atlas is level with the middle third (station II) or caudal third (station III) of the odontoid process, basilar invagination is diagnosed

**Figure 1.** Standard lateral radiograph of the cervical spine in full flexion used to measure schematic representation of (a) the anterior atlanto-dental interval (aADI) and odontoid sagittal diameter (O) measurements and (b) of Clark station determination

The statistical analyses were performed using SPSS software version 25.0 (IBM, Armonk, NY, USA) and the R programme for logistic regression. *P*-values <0.05 were considered significant, and all tests were two-sided.

To evaluate how well combinations of tests predicted aAAS after 12 years, two different procedures were developed. First, all tests with *P*-values <0.2 in the univariate analysis were combined by pairs; then the pair with the best diagnostic value was combined with a third selected laboratory test to determine the best combination of three tests and receiver operating characteristic curves were plotted. Second, a multiple logistic regression procedure was applied to tests with *P*-values <0.20 in the univariate analysis.

Finally, and as aAAS is not normally distributed, we evaluated the correlation between the DAS28 and aAAS (in millimeters) using Spearman coefficient correlation.

## Results

### Patients and prevalence of aAAS and vAAS

Fig. 2 is the patient flow chart. Table 1 reports the main characteristics of the 323 patients. All patients had a diagnosis of RA, which was established at a mean age of 47.9 (s.d. 11.2) years.

For eight patients, the two readers agreed that aAAS was present. The two readers disagreed about 18 other patients at the first reading but agreed for 16 patients at the second reading; 5 of these 16 patients were diagnosed with aAAS. For the two patients with persistent disagreement, the consensus reading established the presence of aAAS. Thus, aAAS was found

in 15 (4.6%; 95% CI 2.8, 6.4) patients. No patient had severe aAAS.

Both readers agreed that 5 (1.5%) patients had vAAS defined as Sakaguchi-Kauppi grade 2 and that no patients had Clark station II or III.

### Baseline factors associated with aAAS at 12 years

Among baseline variables, mean IgA RFs were associated with aAAS (*P*=0.03) but their binary evaluation (yes or no) was not significantly associated with aAAS (*P*=0.06), predicting it with a sensitivity of 60% for a specificity of 75% (Table 1). None of these binary items remained in the model of logistic regression.

### 10 years factors associated with aAAS at 12 years

At 10 years, two received a biologic and/or targeted DMARD (one etanercept and one rituximab) among the 15 patients with aAAS vs 51/308 in the group without aAAS (*P*=1.00) but more patients received steroids in the group with aAAS (8/15) than in the group without aAAS (83/303) (*P*=0.03). Among data collected after 10 years, oral CS therapy during the 10-year interval, CRP (mg/l), and positive tests for RFs were associated with aAAS after 12 years (Table 2). Zero patients in the group with AAS and 20 in the group with AAS developed anti CCP, and only 4 in the group in the group with AAS and 19 in the group with AAS developed RF (*P*=NS).

Only CRP and RFs remained in the model of logistic regression and their combination predicted aAAS with a sensitivity of 60% for a specificity of 88% (Fig. 3) but predictive value

**Table 1.** Baseline and 10 years features of patients with and without AAS after 12 years

	aAAS, <i>n</i> = 15	No aAAS, <i>n</i> = 308	<i>P</i> -value
At baseline			
Females, <i>n</i> (%)	11 (73.3)	239 (77.6)	0.70
Age (years), mean (s.d.)	43.6 (11.2)	48.1 (11.2)	0.12*
Height (cm), mean (s.d.)	166 (6.2)	164.9 (8.3)	0.43
Smokers (current or past), <i>n</i> (%)	9 (60.0)	144 (46.8)	0.43
Alcohol abuse, <i>n</i> (%)	2 (13.3%)	51 (16.6%)	0.99
Tender joint count (/28), mean (s.d.)	9.5 (7.2)	8.7 (7.0)	0.59
Swollen joint count (/28), mean (s.d.)	7.1 (6.3)	7.7 (5.2)	0.37
CRP mg/dl, mean (s.d.)	2.6 (3.9)	2.0 (2.9)	0.82
DAS28, mean (s.d.)	5.2 (1.2)	5.1 (1.3)	0.68
HAQ DI, mean (s.d.)	1.0 (0.6)	1.0 (0.7)	0.74
IgM RF, <i>n</i> (%)	10 (66.7)	167 (54.2)	0.34
IgA RF, <i>n</i> (%)	9 (73.3)	161 (52.3)	0.06*
Anti-CCP antibodies, <i>n</i> (%)	9 (73.3)	83 (26.9)	0.12*
HLA-DRB1 shared epitope, <i>n</i> (%)	10 (76.9)	171 (57.8)	0.25
van der Heijde–modified total Sharp score mean (s.d.)	3.7 (4.2)	2.2 (5.2)	0.28
At 10 years			
Tender joint count (/28), mean (s.d.)	2.9 (7.4)	2.1 (4.3)	0.90
Swollen joint count (/28), mean (s.d.)	1.2 (1.9)	0.9 (2.2)	0.39
CRP mg/dl, mean (s.d.)	1.4 (1.7)	0.63 (1.9)	0.001**
DAS 28, mean (s.d.)	2.8 (1.5)	2.5 (1.3)	0.23
HAQ, mean (s.d.)	0.74 (0.61)	0.51 (0.59)	0.07*
RF, <i>n/N</i> (%)	13/15 (86.7)	152/299 (50.8)	0.007**
Anti-CCP antibodies, <i>n</i> (%)	9/15 (60)	141/308 (45.8)	0.54
Seropositivity (RF or anti-CCP antibodies), <i>n</i> (%)	13/15 (86.7)	161/286 (56.3)	0.02**
van der Heijde–modified total Sharp score, mean (s.d.) [28, 29]	19.2 (25.9)	12.9 (19.1)	0.76
Radiographic abnormalities, <i>n/N</i> (%)	9/15 (60)	116/300 (38.7)	0.11*
Oral CS, <i>n/N</i> (%)	8/15 (53.3)	83/303 (27.4)	0.03**
DMARDs, <i>n/N</i> (%)	14/15 (93.3)	227/303 (74.9)	0.13*

\* *P*-value <0.2 but >0.05 statistically insignificant but included in the evaluation to determine the best tests.

\*\* *P* < 0.05 statistically significant in the univariate analysis. aAAS: anterior atlanto-axial subluxation; VAS: visual analogue scale.

**Table 2.** Logistic regression using features at 10 years associated with AAS after 12 years in the cohort

	OR (95% CI)	<i>P</i>
RFs (positive vs negative)	5.4 (1.2, 24.7)	0.03
CRP (elevated vs normal)	5.5 (1.7, 18.1)	0.005

AAS: anterior atlanto-axial subluxation.

was not good enough to replace radiographs (positive predictive value 69% and negative predictive value 80%).

### Correlation between the DAS28 and aAAS at baseline and 10 years

We did not find any correlation between DAS28 and AAS at inclusion ( $r=0.05$ ,  $P=0.88$ ) or at 10 years ( $r=-0.23$ ;  $P=0.66$ ).

## Discussion

Among patients with early RA, 4.6% had aAAS after 12 years. None had severe aAAS.

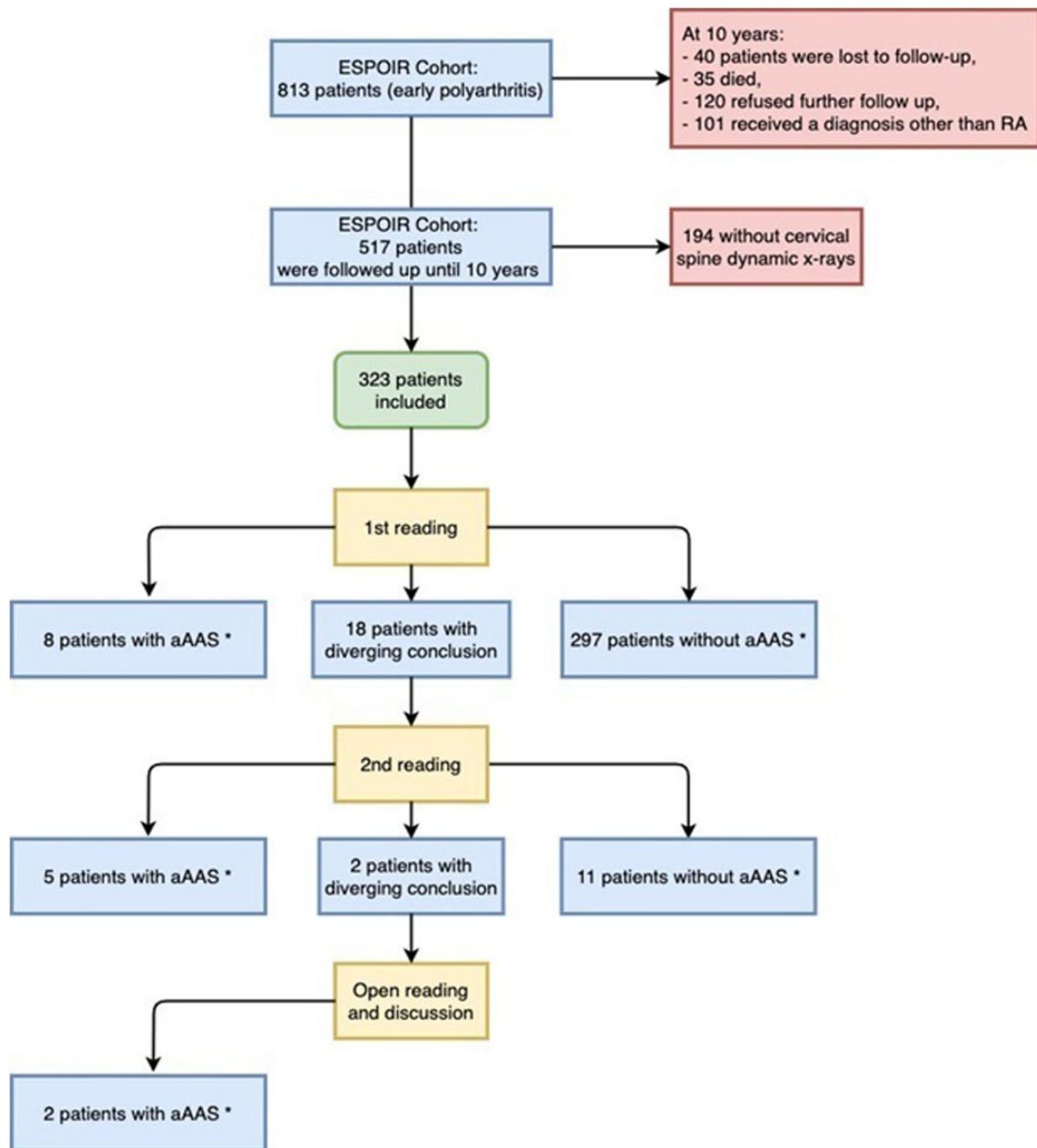
This prevalence is lower than in earlier studies: aAAS was found in 36% of patients before the 1980s and 24% in the 2000s [21]. Inclusion in the ESPOIR cohort began in 2003, at a time when biological therapies were already available, allowing better disease control compared with earlier years.

Of our patients, 33.4% of patients received a biological DMARD within the first 10 years, including 23.5% within the first 5 years.

Radiographs should be obtained routinely in patients with neurological manifestations [30, 31]. Cervical spine imaging is also necessary before anaesthesia, as neck manipulation during anaesthesia may cause neurological injury if the spine is unstable [32, 33]. Outside these two situations, screening radiographs might be useful in patients at high risk for AAS. Thus, predictors of AAS would help to identify patients for screening.

At inclusion, only mean IgA RF predicted aAAS in our population. No binary items predicted aAAS. Anti-CCP gave close results, but the difference was not statistically significant. These factors are of adverse prognostic significance and indicate a higher risk of unresponsiveness to TNF antagonists [34]. The predictive value as assessed in our patients was nevertheless too limited to serve in everyday practice.

At 10 years, CRP elevation was the best test to predict aAAS 12 years later, although RFs positive tests, and previous treatment by oral CS were associated with aAAS after 12 years. Earlier studies also found an association between RFs and cervical-spine involvement by RA [15, 17]. A gradual decline in RF levels has been reported to accompany the decrease in clinical activity in patients given DMARDs [35] or biologic agents [36–39]. However, RF assays have not been found helpful for monitoring disease activity [40] or the treatment response [41]. Structural damage to the hands and/or



**Figure 2.** Flow chart of the study patients

feet and mTSS changes were associated with cervical-spine involvement by RA in several studies [6, 15, 17, 18]. Nevertheless, these factors did not predict aAAS in our cohort. Another risk factor was failure of DMARD therapy, sometimes with persistent CRP elevation [18].

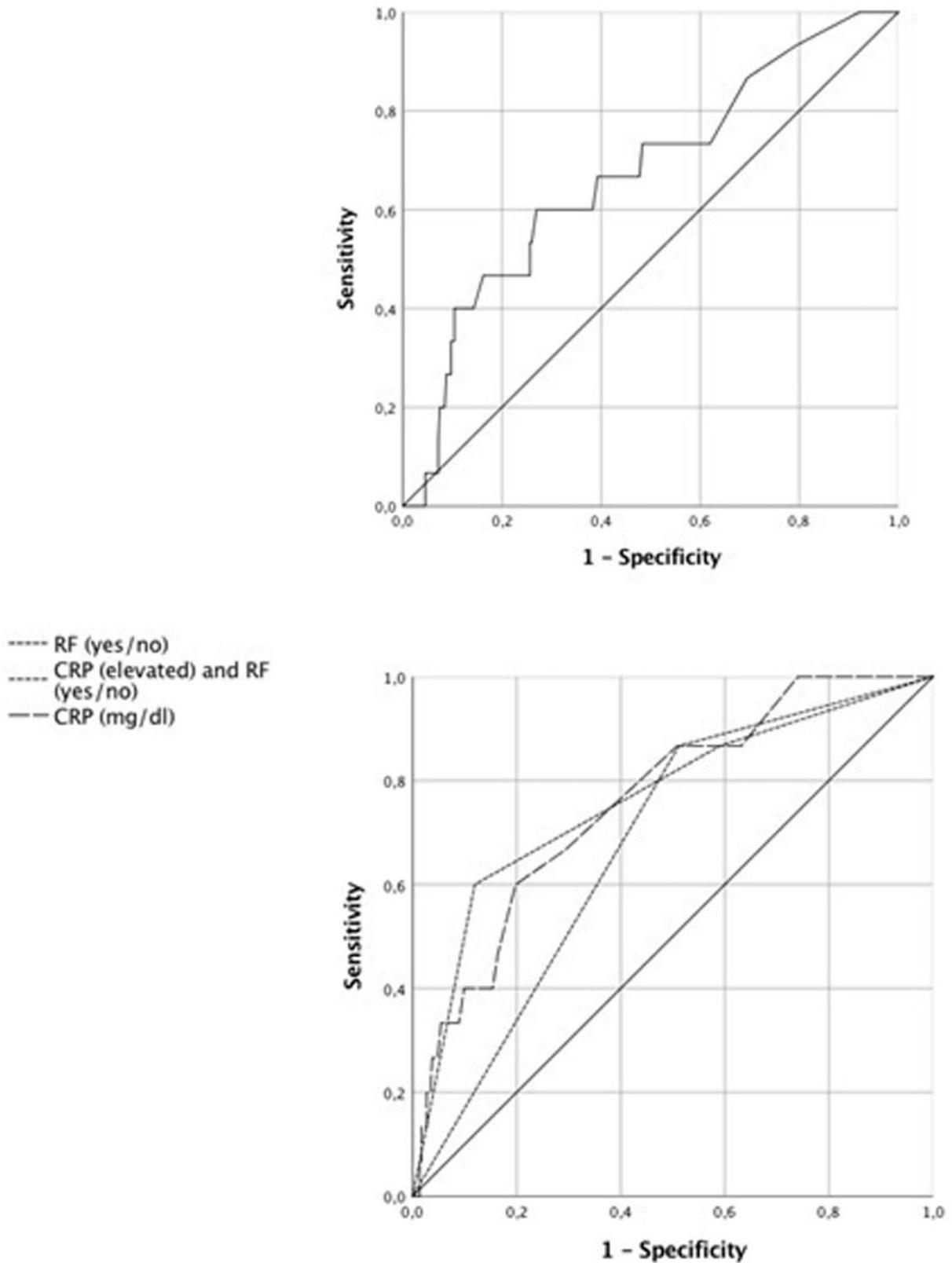
The evaluation of the risk of aAAS at inclusion was useful to justify a systematic evaluation of aAAS during the follow-up, and the evaluation of at 10 years of the risk of aAAS at 12 years to justify an evaluation 2 years later. Another study could evaluate the area under the curve of inflammation and treatment course to estimate their impact on the risk, but the number of patients seems too small for relevant data.

One limitation of our study is that some of the initially included patients left the cohort within the first 10 years. The baseline characteristics did not differ significantly between

these patients and those remaining in the cohort [42]. Another limitation is that patients in the ESPOIR cohort may be treated more aggressively than the general population of patients with RA (33.4% received a biological DMARD within the first 10 years) but this cohort started 20 years ago and the treatment of RA is now more standardized. AAS was sought using only standard radiographs, and more sensitive imaging techniques might have produced a higher prevalence. Cervical radiographs were not performed at inclusion and we cannot exclude fortuitous aAAS pre-existing to RA, although the risk is very low as the prevalence in the normal population is very low. Finally, we did not confirm our cases by imaging follow up including MRI.

In conclusion, the prevalence of aAAS after 12 years was 4.6% in the ESPOIR cohort, with no patients having severe

IgA Rheumatoid factors (continuous value)



**Figure 3.** Receiver operating characteristic curve at baseline and at 10 years. The curves show the relationships between sensitivity and 1-specificity of each test at baseline (IgA RF assays) (upper) and at 10 years (for CRP, RF assays and their combination) (lower) in discriminating between patients with and without aAAS at 12 years. We included in the model tests with *P*-values <0.20 in the univariate analysis which remained in a model of logistic regression. aAAS: anterior atlanto-axial subluxation

aAAS. Although some factors were found statistically associated to AAS at 10 years, given that aAAS is uncommon, routine screening of all patients would have a low yield. Indeed, the best combination of tests gave a predictive value (positive predictive value 69% and negative predictive value 80%) that was not good enough to replace radiographs.

### Data availability

The study data are available upon reasonable request to the principal ESPOIR cohort investigator Alain Saraux (Brest).

### Contribution statement

Substantial contributions to study conception and design: A.L.Q., T.G., G.C.A., F.G. and A.S.; substantial contributions to analysis and interpretation of the data: A.L.Q., T.G., G.C.A., A.R.-W., R.M.F., F.G. and A.S.; drafting the article or revising it critically for important intellectual content: A.L.Q., T.G., G.C.A., A.R.-W., R.M.F., F.G. and A.S.; final approval of the version of the article to be published: A.L.Q., T.G., G.C.A., A.R.-W., R.M.F., F.G. and A.S.

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**Disclosure statement:** The authors have declared no conflicts of interests.

**Patient and public involvement:** Patients and members of the public were involved in the design, conduct and reporting of the research via a detailed description of the protocol available at <http://www.lacohorteespoir.fr>.

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