Ten-Year Clinical Outcome of recent-onset Axial Spondyloarthritis: results from the DESIR inception Cohort

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Ten-Year Clinical Outcome of the Recent-Onset Axial Spondyloarthritis Patients of the DESIR inception Cohort: A Promising Shift in Long-Term Prognosis.

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See the COI filled by all the authors.

Contributorship :

MD proposed the idea of this research project . Both MD,CS ,SA,TL and AM were in charge of the statistical analysis plan. CS and SA were in charge of the statistical analysis. All the co-authors have reviewed the manuscript and in particular the interpretation of the results.

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Ethical approval:

The study was conducted according to the good clinical practice guidelines and was approved by the local ethical committee (EUDRACT#2007-A00608-45, Ethical committee file#2457, dated 17th September 2007).

Abstract

Objectives : This study aimed to evaluate the 10-year clinical outcome of patients with recent-onset axial spondyloarthritis (axSpA).

Methods : Study design : The DESIR cohort is an inception cohort of axSpA patients. Diagnosis and Management: The diagnosis and management of patients were based on the decision of the treating rheumatologist. Statistical Analysis: Both complete cases and imputed data analyses were conducted.

Results : Of the 708 enrolled patients, 45 were excluded due to a change in the baseline diagnosis, 3 patients died, and 300 were lost to follow-up over the 10y. In the completer population, one patient required bilateral total hip replacement, and 56 patients received a pension due to invalidity. The prevalence of main extra-musculoskeletal features increased from baseline to year 10: psoriasis from 18% to 30%, acute anterior uveitis from 10% to 18%, and inflammatory bowel disease from 5% to 10%. Page 3 of 20 Journal Pre-proof 3 The most frequent comorbidity was hypertension, with an increase from 5% to 15% from baseline to year 10. In the imputed data analysis the estimated proportions of patients with an acceptable status at year 10 were 70% [95% CI: 63; 77] for acceptable PASS, 43% [95% CI: 37; 49] for BASDAI < 3, and 48% [95% CI: 41; 56] for ASDAS < 2.1.

Conclusion: These findings suggest that despite a quite favorable 10-year outcome exists for severe outcomes, a large proportion of patients present with an important disease burden reflected by patient-reported outcomes. This information can be valuable for providing patients with information at the time of diagnosis.

Introduction

Historically, in the field of axial spondyloarthritis (axSpA) previous studies[1–3] have portrayed a rather severe and poor long-term prognosis, not only in terms of disease severity (e.g., approximately 15% estimated coxitis prevalence in Western European countries[4] and 50% in North Africa[4,5], or the 5-10% requirement for total hip replacement within 10 years of disease onset) [6], but also in terms of comorbidities such as cardiovascular morbidity and reduced life expectancy [7–9].This description can be distressing for patients who have recently received a diagnosis and are concerned about their long-term prognosis. .

Nevertheless, there have been in the past decades recent major therapeutical advances in the field[10], and a growing emphasis on early diagnosis[11–13] and proactive disease management[14,15]. Consequently, this shift has raised important questions about whether the long-term prognosis for individuals with this condition has indeed improved compared to historical cohorts in particular for patients with a recent diagnosis.

Given these preliminary considerations, we seized the opportunity provided by the DESIR cohort, which followed patients with recent-onset (symptom duration of less than 3 years) axSpA for 10 years, and the baseline factors associated with a low-disease activity status after 10 years.

Patients – Methods

- Patients

The DESIR cohort (NCT01648907) has been previously described[16]. Briefly, consecutive patients aged 18-50 with inflammatory back pain[17,18] and a duration of ≥3 months and <3 years were included in 25 centers in France if the treating rheumatologist considered the symptoms suggestive of axSpA (a score ≥5 on a scale from 0 to 10, where 0 indicated "not suggestive" and 10 indicated "very suggestive"). Between December 2007 and April 2010, 708 patients were included. A detailed description of the study protocol is available on the DESIR website (http:/www.lacohortedesir.fr).

The research proposal for this analysis was approved in January 2022 by the scientific committee of the DESIR cohort.

Ethics

The study was conducted according to good clinical practice guidelines and was approved by the local ethical committee (EUDRACT#2007-A00608-45, Ethical committee file#2457, dated September 17th, 2007). All enrolled patients provided written informed consent to participate.

- Data Collected

At baseline, the following variables were collected: demographics (age, gender), socio-professional status, HLA B27 antigen, and symptom duration.

During all visits (semi-annually during the first 2 years and annually thereafter), the following variables were collected:

- Items to check if the patients fulfilled the ax-SpA criteria (Amor [19] and ASAS[20]).
- Disease activity and severity parameters, including BASDAI[21], ASDAS [22], CRP, and BASFI [23].
- Impact of the disease on the daily life of the patients, including ASAS HI[24] and SF-36 [25].
- Extra-spinal manifestations of the disease, including synovitis, dactylitis, and enthesitis.
- Extra-musculoskeletal manifestations of the disease, including psoriasis, uveitis, and inflammatory bowel disease (IBD).
- Main comorbidities, including severe gastrointestinal events, hypertension, major atherosclerotic cardiovascular events (MACE), diabetes, cancer, and infection (tuberculosis and other severe infections).
- Pharmacological treatment modalities, including NSAID intake according to the ASAS-NSAID scoring system [26], conventional synthetic and targeted DMARDs (cs/tsDMARDs).
- Requirement for surgical treatment modalities, including total hip replacement due to coxitis and spinal vertebrotomy

-Socio-professional status, including the number of days of sick leave and pension of invalidity, according to the procedures of the French health care system (category I: the patient can continue to work part-time, and the financial compensation is equal to 30% of the income of the previous 10 best years; category II: the patient is unable to work, and the financial compensation is equal to 50% of the income of the previous 10 best years; category III: same as category II, plus the necessity to get help from another person in daily life, and the financial compensation is the same as category II but increased by 40%).

- Statistical analysis

Studied populations :

This study includes two populations: "completers," referring to patients who had a full 10-year follow-up and "intention-to-follow" patients, including all patients that were originally included in the DESIR cohort (i.e. "completers" and patients who were lost-to-follow-up). For patients who were lost to follow-up,10-year outcomes were imputed by multiple imputation based on all the information available from the "completers" population and the patients who were excluded from the study for another diagnosis during follow-up (i.e., after year 2, as per protocol) (28).

Characteristics of the patients at year 10 are described. Quantitative variables are presented with their mean and standard deviation or median with interquartile range, and qualitative variables with their frequency and associated proportions.

Ten-year outcomes

Ten-year outcomes are presented in the two populations:

- Completers: all 10-year outcomes are described using the mean and standard deviation for quantitative variables, and frequency with proportions for qualitative variables.
- Intention-to-follow: to explore potential selection bias, a sensitivity analysis was conducted, including all patients thanks to previously imputed outcomes. In this analysis, patients with a documented change in the baseline diagnosis of AxSpA were excluded, as well as patients who died during the 10-year follow-up period. Estimations with their 95% confidence intervals are presented. This approach was not possible when there was too much missing data or too few events in completers for qualitative variables.

Baseline factors associated with long-term (10-year) low disease activity status

Finally, we evaluated the association between baseline potential predictive factors and low disease activity at year 10, defined as an ASDAS-CRP <2.1 [27] using a multivariate logistic regression analysis. Patients with a documented change in the baseline diagnosis were

excluded and the same variable selection principles were used than in the previous analyses. Odds-ratio with their 95% confidence interval are presented.

All statistical analyses were performed using SAS enterprise guide 7.1 software.

Results :

1. *Patients and study course*

The flowchart of the patients is summarized in Figure 1.

Of the 708 enrolled patients, 45 were excluded from the cohort due to a change in the baseline diagnosis by their treating rheumatologist. These 45 patients represented 6.4% of the entire cohort and 12.4% of the completers. The diagnoses justifying the exclusion of the patients from the cohort were as follows: mechanical back pain (n = 30), fibromyalgia (n = 13), a non-axial spondyloarthritis (axSpA) undifferentiated inflammatory rheumatic disease (n = 1), and no information (n = 1). During the 10-year follow-up period, 3 patients died due to the following: suicide (n = 1), colorectal cancer (n = 1), sudden death (n = 1).
Of the remaining 660 patients, 300 were lost to follow-up during the 10-year period with the following estimations: 6%, 13%, 18%, 22%, 25%, 32%, 35%, 37%, 41%, 46% from the first to the tenth-year visits, respectively.

The baseline characteristics of the patients regarding these different populations are summarized in Table I. We also evaluated the fulfillment of axSpA classification criteria (e.g., AMOR and ASAS criteria) regarding the patients' status during the 10-year follow-up period. It should be noted that 21 (49%) and 16 (36%) out of the 45 patients with a documented change in diagnosis fulfilled the baseline Amor and ASAS criteria, respectively. The proportion of patients fulfilling these criteria in the completer population went from 85% to 100% for the Amor criteria and from 68% to 83% for the ASAS criteria from baseline to year 10, respectively.

2. *Ten-year outcomes*

- *Disease management during the 10 year follow-up period:*
    - Treatments: In the completers population, the percentage of patients with at least one session of supervised physiotherapy during the 6-month period preceding

the visit was 42% and 39% at baseline and after 10 years of follow-up, respectively. Regarding pharmacological treatment, in the completer population the percentage of patients with NSAID intake (ASAS NSAID score >0) during the week preceding the visit was 72% and 42% at baseline and after 10 years of follow-up, respectively. The percentage of patients with at least one intake of conventional synthetic disease-modifying antirheumatic drugs during the 10-year follow-up period was 18%/17% and 55% for sulfasalazine/methotrexate and bDMARDs (mainly TNF inhibitors), respectively.

- Work impact: during the 10-year follow-up period, 273 (75.8%) patients required at least one day of sick leave due to the disease, and the average number of days on sick leave was 193 ± 296. Additionally, 56 patients received a pension for invalidity due to the disease (19, 22, 3, and 13 patients received this pension in category I, II, III, and unknown category, respectively). Finally, among patients with a professional activity, 65 had to change their job due to the disease.

- *Extra-musculoskeletal manifestations and comorbidities*

The occurrence of the main extra-musculoskeletal manifestations and comorbidities in the completers is summarized in Figure 2. It is noteworthy that extra-musculoskeletal manifestations were frequent not only at baseline but also during the follow-up period. Hypertension was the most frequent incident comorbidity over time.

- *Disease activity/severity and its impact on the daily life of the patients*

Table II summarizes the observed (i.e. completers population) and imputed (i.e. in the intention-to-follow population) results in these different domains. These data suggest a favorable 10-year disease outcomes, particularly when looking at markers of severity, such as the requirement for total hip replacement (only 1 patient) or spinal vertebrotomy (not a single patient).

Moreover, the results in the completer population and in the intention-to-follow population are quite similar. This overall favorable outcome is also suggested by the high percentage (around 77%) of patients considering their status as acceptable at year 10. However, when considering either the quality of life and/or the impact of the disease on the daily life of the patients, as evaluated by the ASAS Health Index instrument, it seems that the percentage of patients in an acceptable condition was only around 40% to 50%. The same conclusion can be drawn regarding the percentage of patients in an acceptable condition when considering the composite indices evaluating axSpA disease activity (for example, around 48% to 55% of the patients with an ASDAS < 2.1).

3. *Predisposing factors of a low disease activity status at year 10*

The results of both the uni- and multivariate analyses are summarized in Table III. A few parameters have been identified in the multivariate analysis. However, for these parameters, the odds ratio could be considered relatively low (always below 2). The three parameters retained in the multivariate analysis reflect: 1) the management process of the patients (quick referral to a specialized center), 2) the patients' situation (better job situation), and 3) disease activity at baseline.

Discussion :

This study evaluates the 10-year outcome of patients enrolled in an inception cohort of recent-onset axSpA, allowing for a better understanding of the long-term prognosis of these patients.

Our results from this inception cohort in terms of long-term outcomes are quite reassuring, as a favorable outcome was observed in stringent parameters such as the need for surgery (only one patient requiring total hip replacement in our cohort, compared to 5 to 10% in conventional retrospective cohorts [6]).

The interpretation of the results in terms of Patient-Reported Outcomes is more debatable. The data appear favorable when considering the overall evaluation by the patients, as around 77% of them rated their condition as acceptable at year 10. However, when examining other parameters, such as those evaluating disease activity levels (e.g., BASDAI, ASDAS) and/or the impact of the disease on daily life (e.g., ASAS-HI, SF 36), data suggest that a significant percentage of patients (around 50%) do not meet the recommended criteria to be considered as having an acceptable condition (e.g., ASDAS <2.1, for example [28]).

Furthermore, the analysis evaluating the baseline predisposing factors of an acceptable disease activity status (defined here as an ASDAS value <2.1[27]) identified different parameters: a) a baseline BASDAI <40/100; however, this parameter may be considered irrelevant due to circular reasoning, as some items of the ASDAS composite index are included in the BASDAI; b) the short delay from the onset of symptoms is more challenging to interpret but potentially supports early referral to a specialist [13]; c) Anterior chest-wall pain is considered as "axial enthesitis," frequently associated with a polyenthesitis condition [29], which contributes to a disabling disease [30]. Therefore, it is not surprising that the absence of these parameters at baseline is associated with an acceptable condition at year 10; d) socio-professional parameters (e.g., job, situation, and education level) highlight the issue of inequity observed in axSpA [31,32]

In summary, these data suggest a favorable 10-year outcome in terms of stringent measures, such as the need for surgery, much different from historic reports. Nevertheless, these contrast with a less favorable outcome in terms of disease activity parameters, with identified predictive factors. These data should improve and facilitate the information

provided to patients at the time of diagnosis. Further studies are required to evaluate this long-term outcome in different countries, different healthcare systems, and potentially over longer durations.

FIGURES:

Figure 1: Flow-chart of the axSpA patients during their 10-year follow-up

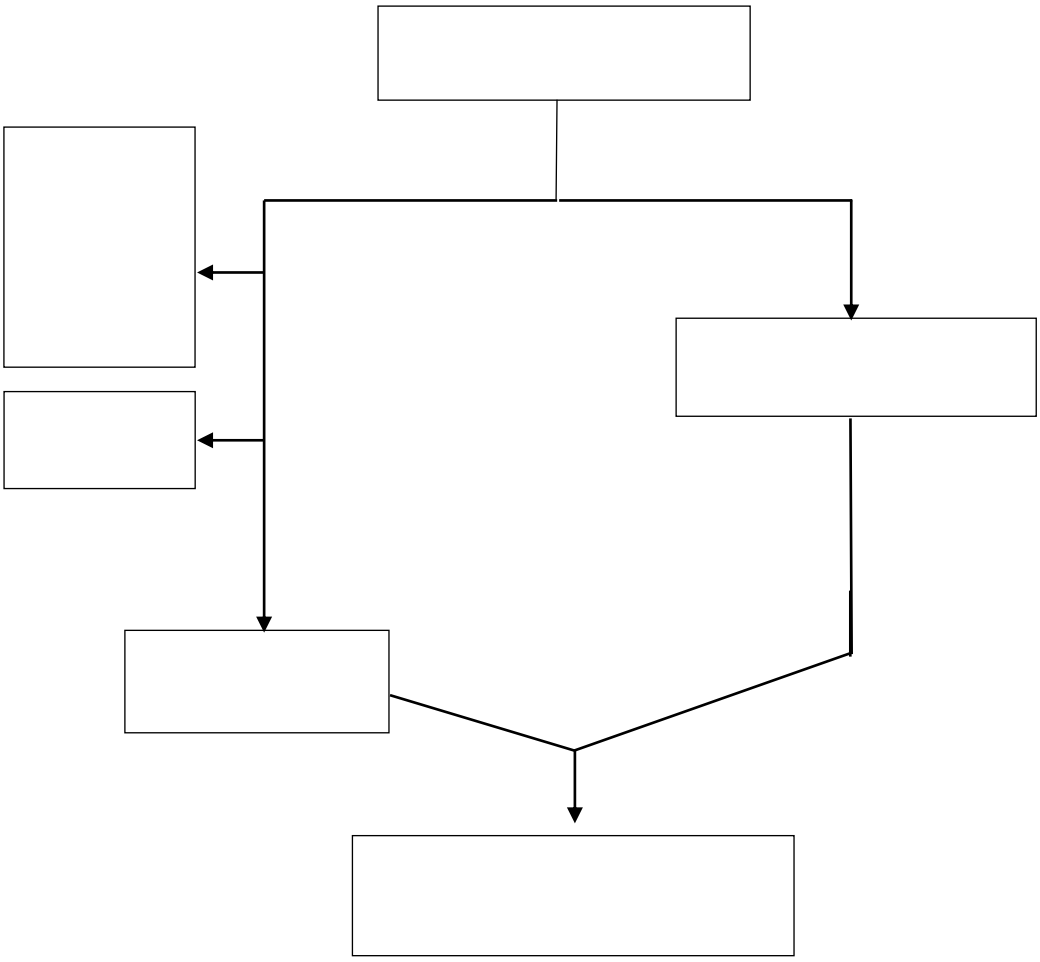
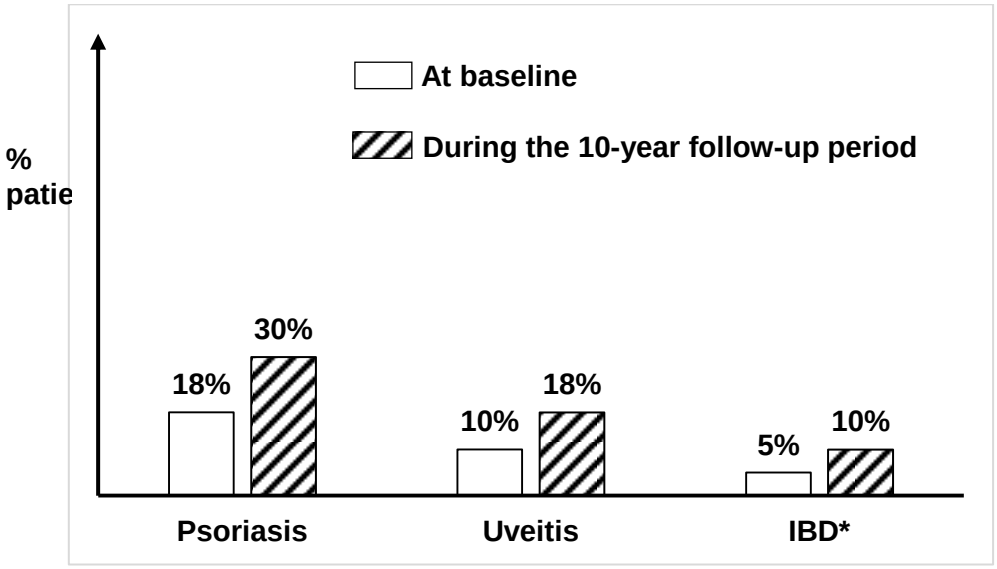


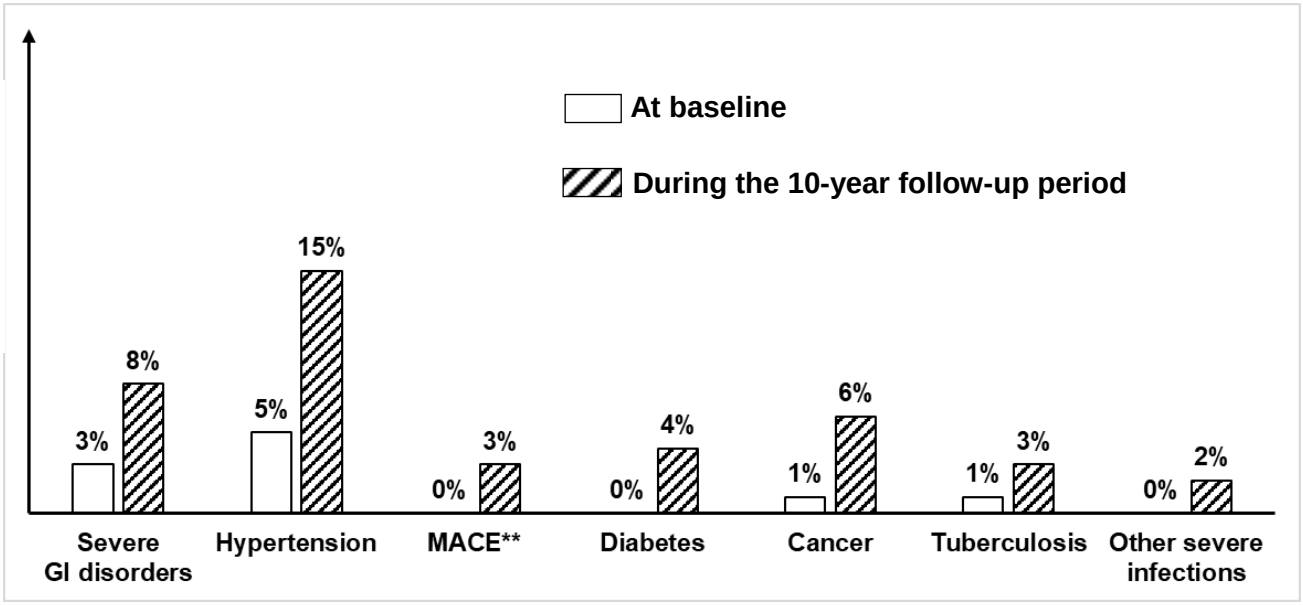
Figure 2: Main axSpA extra-musculoskeletal manifestations and comorbidities observed during the 10 year follow-up period

2. A. Main extra-musculoskeletal manifestations



***IBD : Inflammatory Bowel Disease**

2.B. Main comorbidities



*GI : Gastro-Intestinal

**MACE : Major Adverse Cardiovascular Events

TABLES:

Table I: Baseline characteristics of the patients with regard to their status during the 10 year follow-up period

Baseline characteristics	**Baseline population** **n = 708**	**Completers** **n = 360**	**Lost of follow-up** **n = 300**
Age (years) †	34 ±9	34 ± 9	32± 8
Female	381 (54%)	192 (53%)	163 (54%)
Ethnicity : white caucasien	641 (91%)	328 (91%)	266 (89%)
Educational level : university	418 (59%)	231 (64%)	159 (54%)
Time from first symptoms to baseline (years)	1.5 ± 0.9	1.5 ± 0.9	1.6 ± 0.9
HLA B27 : positive	410 (58%)	231 (64%)	160 (54%)
Extraspinal manifestations (past or present) - Enthesitis -Synovitis -Dactylitis	 348 (49%) 151 (21%) 92 (13%)	 177 (49%) 85 (24%) 50 (14 %)	 147 (49%) 62 (21%) 39 (13%)
Extra-musculoskeletal manifestations (past or present) - Psoriasis - Uveitis - IBD*	 119 (17%) 60 (8%) 28 (4%)	 67 (19%) 35 (10%) 17 (5 %)	 48 (16%) 23 (8%) 11 (4%)

Disease activity			
- BASDAI (0-100)	45 ±20	43 ± 21	46 ± 20
- ASDAS	2.7 ± 0.9	2.6 ± 1.0	2.7 ± 1.0
- CRP (mg/l)	7.9 ± 13.5	8.6 ± 14.0	7.7 ± 13.0
- MRI-SIJ Inflammation**	231 (34%)	143 (41%)	86 (30%)
- X-Rays SIJ Structural damage***	187 (27%)	112 (32%)	72 (25%)
Quality of life/impact			
- BASFI	30.5 ± 22.8	29.4 ± 23.1	31.4 ± 22.6
- SF 36 Physical score	39.2 ± 9.5	39.9 ± 9.6	38.7 ± 9.2
- SF 36 Mental score	40.2 ± 11.3	41.4 ± 11.1	38.9 ± 11.2
- PASS****	290 (41%)	156 (44%)	117 (39%)

† values given are mean ±standard deviation for continuous variables and numbers (percentage) for binary variables,
*IBD = Inflammatory Bowel Disease, **MRI-SIJ-inflammation = Presence of inflammation at the sacroiliac level on MRI based on the opinion of the local reader (either radiologist or rheumatologist), ***X-Rays-SIJ structural damage = Presence of structural damage suggestive of axSpA on pelvic X-Rays based on the local reader (either radiologist or rheumatology, ****PASS = Patient Acceptable Symptom State

Table II: Disease activity, severity and disease impact on the daily life of the patients after a 10-year follow-up period

Characteristics	Populations		
	Baseline **Whole population** **N=660**	**Year 10** **Observed data** **n = 360**	**Year 10** **Imputed data** **N = 660**
Disease activity			
- BASDAI	44.4 ± 20.2	33.7 ± 22.2	37.0 [32.0 ; 42.1]
- BASDAI ≤ 30.	183 (28%)	171 (49%)	43 [37 ; 49]%
- Acceptable PASS .	273 (42%)	258 (77%)	70 [63 ; 77]%
- ASDAS	2.65 ± 0.96	2.03 ± 1.03	2.39 [1.80 ; 2.98]
- ASDAS < 2.1	190 (30%)	161 (55%)	48 [41 ; 56]%
- ASDAS < 1.3	49 (8%)	88 (30%)	25 [19 ; 32]%
- CRP < 6 mg/l.	440 (69%)	237 (77%)	77 [NA]%
Disease severity			
- X-Rays-SIJ structural damage.	184 (28%)	92 (32%)	34 [30 ; 39]%
- Total hip remplacement	0	1 (< 1%)	NA*
Impact of the disease			
- ASAS HI ≤ 5.	NA*	165 (48%)	41 [35 ; 47]%
- ASAS HI	NA*	5.9 ± 4.2	6.7 [5.8 ; 7.6]
- BASFI	30.3 ± 22.9	23.4 ± 21.6	27.4 [22.9 ; 31.9]
- SF36 physical score	39.4 ± 9.5	42.9 ± 10.4	41.5 [39.5 ; 43.6]
- SF36 mental score	40.0 ± 11.2	45.0 ± 10.5	43.1 [40.3 ; 45.8]

*NA= Not Available

Table II: Baseline predisposing factors of a low disease activity status (ASDAS <2.1) at year 10

Baseline characteristics	Low disease activity status at year 10		Statistical analysis	
	Yes	**No**	**Univariate**	**Multivariate**
	48.1 [42.9 - 51.7]	**51.9 [48.3 - 57.1]**	**(Odds ratio [95% CI]**	**(Odds ratio [95% CI]**
Male (%)	48.7 [47.6 - 51.3]	58.8 [56.1 - 60.2]	1.45 [0.99 ; 2.11]	-
Delay from first syptoms to baseline < 1.5 years (%)	57 [53.6 - 58.6]	48 [45.9 - 50.9]	1.39 [0.91 ; 2.13]	1.46 [0.93 ; 2.29]
Job situation (white collar) (%)	56.7 [54.8 - 61.1]	38.6 [36.6 - 41]	2.11 [1.39 ; 3.21]	1.87 [1.20 ; 2.90]
Education level (≥university) (%)	65.4 [64.8 - 71.7]	53.3 [49.9 - 54]	1.79 [1.11 ; 2.90]	-
Absence of anterior chest wall pain (%)	57.5 [55.5 - 58.7]	50.5 [49.1 - 52.6]	1.31 [0.91 ; 1.90]	-
BASDAI score < 40 (%)	49.8 [47.1 - 53.7]	31.7 [30.2 - 33.7]	2.13 [1.4 ; 3.23]	1.91 [1.23 ; 2.94]

° Data provided are the observed median, along with the minimal and maximal percentage values from the imputed datasets

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