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**Arthritis Care & Research**
Vol. 74, No. 2, February 2022, pp 268–273
DOI 10.1002/acr.24465


American College of Rheumatology
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**BRIEF REPORT**

# Determinants of the Physician Global Assessment of Disease Activity and Influence of Contextual Factors in Early Axial Spondyloarthritis

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**Objective.** To investigate determinants of the physician global assessment (PhGA) of disease activity and the influence of the contextual factors on this relationship in patients with early axial spondyloarthritis (SpA).

**Methods.** Five-year data of DESIR, a cohort of early axial SpA, were analyzed. Univariable generalized estimating equations (GEEs) were used to investigate contributory explanatory effects of various potential determinants of PhGA. Effect modification by contextual factors (age, sex, and educational level) was tested, and if significant, models were stratified. Autoregressive GEE models (i.e., models adjusted for PhGA at the previous time point) were used to confirm a longitudinal relationship.

**Results.** A total of 708 patients were included. Higher Bath Ankylosing Spondylitis Disease Activity Index individual questions, swollen joint count in 28 joints (SJC28), tender joint count in 53 joints, Maastricht Ankylosing Spondylitis Enthesitis Score, C-reactive protein (CRP) level, and Bath Ankylosing Spondylitis Metrology Index score were associated with a higher PhGA. Sex and age were effect modifiers of SJC28; the contributory effect of SJC28 was largest in the younger male stratum ($\beta = 1.07$ [95% confidence interval (95% CI) 0.71, 1.43]), and the smallest in the older female stratum ($\beta = 0.13$ [95% CI 0.04, 0.22]). Autoregressive GEE models revealed the same determinants as having a longitudinal association with PhGA and the same pattern of effect modification.

**Conclusion.** Patients' subjective symptoms, peripheral arthritis and enthesitis, higher CRP level, and impaired spinal mobility contribute to explaining PhGA in patients with early axial SpA, irrespective of sex and age. Intriguingly, physicians consider the presence of swollen joints as more important in males than in females.

## INTRODUCTION

Axial spondyloarthritis (SpA) is a rheumatic musculoskeletal disease primarily affecting the axial skeleton. Although axial SpA is mainly a disease of the spine, it may affect the peripheral joints and manifest itself in extramusculoskeletal manifestations. The goal of treatment in axial SpA is to improve the quality of life by abrogating inflammation that causes symptoms, structural damage, and physical disability. To achieve this goal, treatment needs to be adjusted through a shared decision based on a proper assessment of disease activity.

While the patient global assessment is considered an important item and is incorporated in the disease activity measurement in axial SpA, namely in the Ankylosing Spondylitis Disease Activity Score (1), far less attention is paid to the physician global assessment (PhGA). However, PhGA is still a major factor in the

The DESIR study is conducted as a Programme Hospitalier de Recherche Clinique with Assistance Publique Hopitaux de Paris as the sponsor and is supported by the French Society of Rheumatology. An unrestricted grant from Pfizer has been allocated for the first 10 years. The DESIR cohort is conducted under the control of Assistance Publique Hopitaux de Paris via the Clinical Research Unit Paris Center and under the umbrella of the French Society of Rheumatology and Institut National de la Santé et de la Recherche Medicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics by Jean-Pierre Daures, DIM, Nîmes, France. Dr. Hirano's work was supported by a scholarship from the Japan College of Rheumatology (Japan College of Rheumatology–European Alliance of Associations for Rheumatology Young Rheumatologist Training Program).

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication March 31, 2020; accepted in revised form September 22, 2020.

**SIGNIFICANCE & INNOVATIONS**

- Physician global assessment (PhGA) of disease activity is a major factor in the therapeutic decision-making process, but little is known about which disease manifestations actually contribute to PhGA in axial spondyloarthritis.
- The patient's subjective symptoms, the peripheral joints and enthesitis findings, C-reactive protein level, and spinal mobility determine PhGA.
- The presence of swollen joints is most associated with higher PhGA in young male patients and the least in older females.

therapeutic decision-making process (2,3). Holding responsibility for the outcomes and knowledge of the therapeutic options, the treating physician supposedly summarizes the patient's complaints and objective findings into his/her own assessment and takes the initiative in therapeutic decisions. This situation is especially true with the advent of new therapies, which are effective, yet expensive and with distinct safety profiles.

Only a few studies have investigated PhGA as an outcome in patients with axial SpA (4–6). The main interest of these studies was the discordance with patient global assessment, and only 1 study has investigated the factors explaining PhGA (4). Cervical rotation, swollen joints, C-reactive protein (CRP) level, intermalleolar distance, and finger-to-floor were reported to explain PhGA. This analysis was based on cross-sectional data only and in patients with established ankylosing spondylitis, currently known as radiographic axial SpA. Nevertheless, little is known about which disease manifestations actually contribute to the PhGA over time and in particular in the early phase of the disease. Moreover, the patients' characteristics (such as age, sex, and educational level) are also hypothesized to have influence on the physician's interpretation of the disease manifestations. These patient characteristics are referred to as contextual factors and are important because they may have influence on outcomes as effect modifiers or confounders (7). The objectives of this study were to investigate the determinants of PhGA and the influence of contextual factors (age, sex, and educational level) on the contributory effects of the determinants of PhGA over time in patients with early axial SpA.

## PATIENTS AND METHODS

**Study design, study population, and outcome.** DESIR is a cohort of patients with early inflammatory back pain highly suggestive of axial SpA. The protocol has been described previously (8). Briefly, the inclusion criteria were patients ages 18–50 years, with inflammatory back pain of >3 months and <3 years duration and symptoms highly suggestive of axial SpA according to the rheumatologist. A total of 708 patients were included consecutively in 25 French centers between December 2007 and April 2010. Clinical data were collected every 6 months up to 2 years and annually up to 5 years. Magnetic resonance imaging (MRI) of the spine and sacroiliac (SI) joints was performed in all patients at baseline and in patients from 9 centers in Paris at 2 years and 5 years. Patients with PhGA scores collected at least once during the 5-year follow-up were subjects of the present analyses. The PhGA was collected on a 0–10 numerical rating scale by asking the physician's "overall assessment of the activity of the rheumatic disease during the last 48 hours," with inactive disease and active disease as anchors (a higher score means higher disease activity). The database used for this analysis was locked in June 2016. DESIR has been approved by the appropriate ethics committees and patients signed the informed consent upon participation.

**Potential explanatory variables of PhGA.** Potential explanatory variables were as follows: individual component questions of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; question 1 [Q1]: fatigue, Q2: back pain, Q3: peripheral joint pain, Q4: enthesitis, Q5: severity, and Q6: duration of morning stiffness; range 0–10 each), swollen joint counts in 28 joints (SJC28; range 0–28), tender joint counts in 53 joints (TJC53; range 0–159, with each joint graded as no tenderness = 0; tenderness = 1; tenderness and grimace = 2; tenderness, grimace, and withdrawal = 3), enthesitis measured with the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES; range 0–39) (9), CRP level in mg/liter, the presence of any extramusculoskeletal manifestations (EMM, i.e., cumulative presence of any of uveitis, psoriasis, or inflammatory bowel disease), the Bath Ankylosing Spondylitis Metrology Index linear definition (BASMI linear; range 0–10), Spondyloarthritis Research Consortium of Canada MRI indices for the spine (SPARCC-spine; range 0–414) (10) and for the SI joints (SPARCC-SI joints; range 0–72) (11). SPARCC-spine and SPARCC-SI joints were mean scores of 3 central readers from wave 3 (blinded for chronologic order and clinical information) (12).

**Contextual factors.** The patient's age, sex, and educational level were the contextual factors tested as potential effect modifiers or confounders of the relationship between the determinants of PhGA and PhGA measurements. If stratification for age, sex, or educational level was needed, the population was dichotomized by age at baseline (younger or older than the median age at baseline, 33.3 years), sex (male or female), or educational level at baseline (university level or not).

**Statistical analysis.** To investigate the relationship between the independent variables and PhGA, we used generalized estimating equations (GEEs) (13). This method enabled us to make use of all available data and estimate a population-averaged parameter, correcting for within-patient correlation of outcomes at multiple time points. A linear GEE model was used

**Table 1.** Factors associated with the physician global assessment over time in sex- and age-stratified groups in univariable analysis*

| | Female (younger) (n = 181) | Female (older) (n = 200) | Male (younger) (n = 173) | Male (older) (n = 154) |
|---|---|---|---|---|
| BASDAI Q1 (fatigue, 0–10) | 0.39 (0.34, 0.44) | 0.39 (0.34, 0.44) | 0.46 (0.41, 0.51) | 0.41 (0.35, 0.46) |
| BASDAI Q2 (back pain, 0–10) | 0.53 (0.49, 0.57) | 0.49 (0.45, 0.54) | 0.58 (0.54, 0.63) | 0.48 (0.43, 0.53) |
| BASDAI Q3 (peripheral joint pain, 0–10) | 0.36 (0.31, 0.41) | 0.31 (0.27, 0.36) | 0.43 (0.37, 0.48) | 0.32 (0.27, 0.37) |
| BASDAI Q4 (enthesitis, 0–10) | 0.42 (0.37, 0.46) | 0.37 (0.33, 0.41) | 0.52 (0.47, 0.56) | 0.36 (0.31, 0.41) |
| BASDAI Q5 (severity of morning stiffness, 0–10) | 0.45 (0.40, 0.49) | 0.42 (0.37, 0.46) | 0.58 (0.54, 0.63) | 0.44 (0.40, 0.49) |
| BASDAI Q6 (duration of morning stiffness, 0–10) | 0.35 (0.30, 0.39) | 0.30 (0.25, 0.35) | 0.50 (0.45, 0.56) | 0.36 (0.31, 0.41) |
| BASMI linear (0–10) | 0.67 (0.48, 0.86) | 0.61 (0.45, 0.78) | 0.95 (0.75, 1.15) | 0.49 (0.30, 0.68) |
| SJC28 (0–28) | 0.52 (0.31, 0.73) | 0.13 (0.04, 0.22) | 1.07 (0.71, 1.43) | 0.58 (0.40, 0.76) |
| TJC53 (0–159)† | 0.13 (0.11, 0.16) | 0.05 (0.04, 0.06) | 0.15 (0.13, 0.18) | 0.13 (0.11, 0.16) |
| MASES (0–39) | 0.15 (0.12, 0.17) | 0.10 (0.08, 0.12) | 0.30 (0.25, 0.35) | 0.18 (0.14, 0.23) |
| CRP, mg/liter | 0.03 (0.01, 0.05) | 0.02 (0.01, 0.04) | 0.04 (0.03, 0.05) | 0.06 (0.04, 0.07) |
| Any EMM (presence vs. absence) | –0.20 (–0.58, 0.19) | –0.13 (–0.49, 0.23) | –0.28 (–0.69, 0.14) | –0.26 (–0.68, 0.17) |
| SPARCC-spine (0–414)‡ | 0.05 (–0.11, 0.20) (n = 56) | 0.06 (–0.11, 0.22) (n = 59) | 0.05 (–0.04, 0.14) (n = 57) | 0.02 (–0.03, 0.06) (n = 46) |
| SPARCC-SI joints (0–72)‡ | 0.01 (–0.08, 0.10) (n = 56) | –0.02 (–0.13, 0.09) (n = 60) | 0.01 (–0.04, 0.06) (n = 57) | 0.05 (–0.01, 0.11) (n = 46) |

* Values are the coefficient (95% confidence interval). Univariable generalized estimating equation models with stratification for sex and age were used to investigate contributory explanatory effects of each factor on physician global assessment (PhGA). Age and sex were shown to be effect modifiers of the relationship between swollen joint count in 28 joints (SJC28) and PhGA and therefore analyses were conducted in Strata. BASDAI questions (Q) 1–6 = individual component questions of the Bath Ankylosing Spondylitis Disease Activity Index; BASMI linear = linear definition of Bath Ankylosing Spondylitis Mobility Index; CRP = C-reactive protein; EMM = extramusculoskeletal manifestation; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC-spine/SPARCC-SI joints = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging indices for the spine/sacroiliac joints; TJC53 = tender joint count in 53 joints.
† Total score of the 53 joints with each joint graded 0–3 (0 = no tenderness, 1 = tenderness, 2 = tenderness + grimace, 3 = tenderness + grimace + withdrawal).
‡ Coefficients of SPARCC-spine/SPARCC-SI joints were estimated in a subgroup of patients with magnetic resonance imaging performed at least once at either 2 years or 5 years.

because the outcome was continuous. An exchangeable correlation matrix was selected because it showed the best fit.

First, we tested interactions between the contextual factors and the potential explanatory variables of PhGA. If the interaction term was significant with a predefined criterion of a *P* value less than 0.15 (14), analyses were further stratified. Effect modification was judged based on a clinically relevant difference in the regression coefficients across the strata. Univariable analysis was chosen to better assess the contributory explanatory effect of each of the determinants in each of the strata. This method was preferred to multivariable analysis, in which only the independent effect of a specific determinant, i.e., independent of confounders, would be considered. We were rather interested in the overall effect that a given determinant had on PhGA across different strata, also to allow proper comparisons across strata.

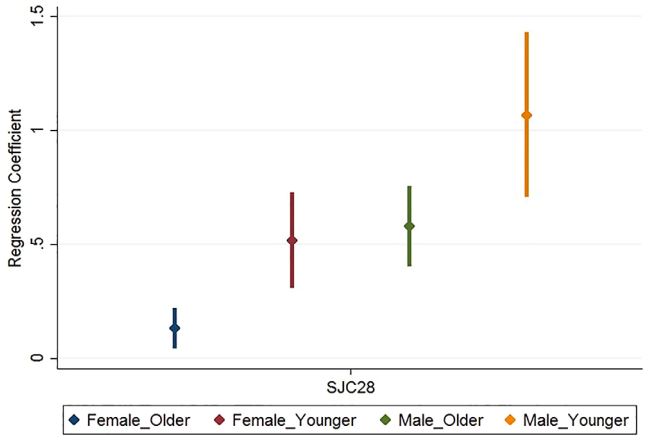


**Figure 1.** Impact of swollen joint count on the physician global assessment of disease activity across sex and age groups. Regression coefficients of the relationship of interest are plotted in an ascending order, reflecting an increasing impact of the swollen joint count on 28 joints (SJC28) on the physician global assessment of disease activity from older females to younger males (stratification according to median age at baseline, 33.3 years).

As relationships found in GEE models can be attributable both to cross-sectional and longitudinal effects, an autoregressive GEE model (i.e., a model adjusted for the outcome [PhGA] at the previous time point) was used to investigate whether the determinants had a true longitudinal association with PhGA. We used only data from yearly assessments (baseline, 12, 24, 36, 48, and 60 months), so that the intervals between the time points were similar. Contextual factors that proved not to be effect-modifiers were tested as confounders. If the addition of the contextual factor to a univariable GEE model made a relevant difference in the regression coefficient, it was deemed a confounder.

As MRI was repeated only in the patients from the centers in Paris, univariable GEE analyses with the MRI scores as potential explanatory variables could only be conducted in a subgroup of patients. A sensitivity analysis, similar to the main analysis, was conducted in patients fulfilling the Assessment

**Table 2.** Factors longitudinally associated with the change of physician global assessment from previous time points in sex- and age-stratified groups in univariable analysis*

| | Female (younger) (n = 181) | Female (older) (n = 200) | Male (younger) (n = 173) | Male (older) (n = 154) |
|---|---|---|---|---|
| BASDAI Q1 (fatigue, 0–10) | 0.39 (0.33, 0.45) | 0.37 (0.31, 0.43) | 0.37 (0.31, 0.44) | 0.34 (0.27, 0.41) |
| BASDAI Q2 (back pain, 0–10) | 0.53 (0.47, 0.58) | 0.48 (0.42, 0.54) | 0.55 (0.49, 0.60) | 0.41 (0.35, 0.47) |
| BASDAI Q3 (peripheral joint pain, 0–10) | 0.41 (0.35, 0.48) | 0.33 (0.27, 0.38) | 0.41 (0.34, 0.48) | 0.27 (0.20, 0.33) |
| BASDAI Q4 (enthesitis, 0–10) | 0.42 (0.37, 0.48) | 0.37 (0.31, 0.42) | 0.47 (0.41, 0.54) | 0.34 (0.27, 0.40) |
| BASDAI Q5 (severity of morning stiffness, 0–10) | 0.45 (0.39, 0.51) | 0.38 (0.32, 0.44) | 0.55 (0.49, 0.61) | 0.38 (0.32, 0.44) |
| BASDAI Q6 (duration of morning stiffness, 0–10) | 0.34 (0.28, 0.40) | 0.29 (0.23, 0.35) | 0.45 (0.37, 0.52) | 0.29 (0.22, 0.35) |
| BASMI linear (0–10) | 0.65 (0.42, 0.88) | 0.54 (0.35, 0.72) | 0.62 (0.40, 0.85) | 0.34 (0.11, 0.56) |
| SJC28 (0–28) | 0.73 (0.36, 1.10) | 0.10 (–0.00, 0.21) | 1.33 (0.73, 1.93) | 0.61 (0.30, 0.92) |
| TJC53 (0–159)† | 0.15 (0.11, 0.18) | 0.05 (0.03, 0.06) | 0.14 (0.11, 0.17) | 0.13 (0.09, 0.17) |
| MASES (0–39) | 0.13 (0.10, 0.16) | 0.10 (0.07, 0.12) | 0.25 (0.20, 0.31) | 0.18 (0.13, 0.23) |
| CRP, mg/liter | 0.02 (0.00, 0.04) | 0.03 (0.01, 0.05) | 0.02 (0.00, 0.03) | 0.04 (0.02, 0.07) |
| Any EMM (presence vs. absence) | 0.04 (–0.35, 0.44) | 0.32 (–0.03, 0.68) | –0.26 (–0.63, 0.11) | –0.23 (–0.71, 0.24) |
| SPARCC-spine (0–414)‡ | –0.11 (–0.28, 0.06) (n = 50) | 0.03 (–0.13, 0.19) (n = 58) | 0.08 (–0.02, 0.17) (n = 52) | –0.07 (–0.14, 0.00) (n = 46) |
| SPARCC-SI joints (0–72)‡ | –0.01 (–0.13, 0.10) (n = 50) | 0.12 (–0.01, 0.26) (n = 58) | 0.02 (–0.05, 0.08) (n = 52) | 0.01 (–0.08, 0.10) (n = 46) |

* Values are the coefficient (95% confidence interval). Univariable autoregressive generalized estimating equation models (i.e., models adjusted for physician global assessment [PhGA] at the previous time point using data at 0, 12, 24, 36, 48, and 60 months) with stratification for sex and age were used to investigate longitudinal contributory effects of each factor on PhGA. Age and sex were shown to be effect modifiers of the relationship between swollen joint count in 28 joints (SJC28) and PhGA and therefore analyses were conducted in Strata. BASDAI questions (Q) 1–6 = individual component questions of the Bath Ankylosing Spondylitis Disease Activity Index; BASMI linear = linear definition of Bath Ankylosing Spondylitis Mobility Index; CRP = C-reactive protein; EMM = extramusculoskeletal manifestation; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; SPARCC-spine/SPARCC-SI joints = Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging indices for the spine/sacroiliac joints; TJC53 = tender joint count in 53 joints.
† Total score of the 53 joints with each joint graded 0–3 (0 = no tenderness, 1 = tenderness, 2 = tenderness + grimace, 3 = tenderness + grimace + withdrawal).
‡ Coefficients of SPARCC-spine/SPARCC-SI joints were estimated in a subgroup of patients with magnetic resonance imaging performed at least once at either 2 years or 5 years.

of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA. *P* values less than 0.05 were considered significant unless specified otherwise. All statistical analyses were conducted using Stata software, version 14.

## RESULTS

A total of 708 patients were the subjects of the analyses. The subgroup of patients with repeated MRI consisted of 220 patients. Baseline characteristics of the total study population and the subgroup are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24465/abstract. No important differences were found between the groups.

Higher scores of the BASDAI individual questions on fatigue (Q1), back pain (Q2), peripheral joint pain (Q3), enthesitis (Q4), severity and duration of morning stiffness (Q5 and Q6), SJC28, TJC53, MASES, CRP level, and BASMI linear were all associated with a higher PhGA (Table 1). Neither the presence of EMM nor inflammation captured on MRI had a contributory effect on PhGA. Sex and age were found to be effect modifiers of the relationship between SJC28 and PhGA; the contributory effect of SJC28 was largest in the younger male stratum, moderate in the younger female and the older male strata, and the smallest in the older female stratum (Table 1 and Figure 1). Sensitivity analyses in patients fulfilling the ASAS classification criteria retrieved similar results except for the lack of effect modification by age in female patients. The baseline characteristics of the age- and sex-stratified groups are shown in Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24465/abstract. Patients in the younger male stratum showed numerically more positivity for HLA–B27, higher modified New York grading, higher SPARCC-spine, and higher CRP level than the other strata. SPARCC-spine score was higher in male patients than in female patients.

Autoregressive GEE models yielded the same determinants as being longitudinally associated. A similar pattern of effect modification on SJC28 by sex and age (Table 2) was found. In other words, the determinants of PhGA (absolute value) are also associated with a change in PhGA over time.

## DISCUSSION

In this study we have shown that patients' subjective symptoms, peripheral arthritis and enthesitis, higher CRP level, and impaired spinal mobility contribute to explaining PhGA in patients with early axial SpA, irrespective of sex and age. Interestingly, age and sex modify the impact of swollen joints on PhGA;

rheumatologists consider the presence of swollen joints as more important for the overall assessment of disease activity in male patients than in female patients, and more important in younger patients than in older patients.

Sex differences have been reported in outcomes of patients with axial SpA: male sex is associated with more progression of spinal structural damage in radiographic axial SpA (15). At the same time, a higher prevalence of fibromyalgia has been reported in female patients than in male patients with axial SpA (16), and a higher level of fatigue was observed in female patients in DESIR (17). In our particular cohort, male patients had higher CRP levels and more structural damage in the SI joints at baseline than the female patients. As a result, physicians may have related these characteristics to a higher risk of further progression. However, this explanation does not account for the fact that the different impact on PhGA across sex and age groups was only present for swollen joints. As we chose to use univariable analyses to properly compare the effect of each determinant across the different strata, rather than to investigate the independent effects, a higher SJC was possibly associated with other determinants in male patients compared to female patients and thus have a higher effect on PhGA; however, adjusted analyses, e.g., for CRP level, did not show this (results not shown). Or perhaps swollen joints are a finding that is likely to be attributed to other causes than disease activity in older and female patients. This different impact of the SJC across sex and age has not been previously reported. Physicians should become aware of this different impact, as it may represent a source of inequity for patients, especially if it influences therapeutic choices.

With regard to the determinants of PhGA, the individual BASDAI questions could be expected to contribute to PhGA, because these questions are, by definition, relevant items chosen for the assessment of disease activity. Likewise, the physicians reasonably took the findings of peripheral joints and entheses as a representation of the peripheral involvement and CRP level as a marker of inflammation. Spinal mobility was also a determinant of PhGA over time. Physicians probably relied on spinal mobility due to the lack of clinical objective findings reflecting spinal inflammation well. Also, this may be based on the knowledge that spinal mobility impairment is caused by inflammation as well as irreversible structural damage (18). However, by taking spinal mobility into account, physicians may be falsely reflecting structural damage on disease activity. Nevertheless, given the fact that DESIR is a cohort of early axial SpA with low levels of structural damage, this impact will be low in these patients (19).

The previous study that reported determinants of PhGA in radiographic axial SpA identified, through factor analysis, 4 latent factors of PhGA, which were labeled as "patient assessment," "mobility and function," "physician assessment," and "lab." Based on the individual items, these factors can be interpreted as "the patient's subjective symptoms," "spinal mobility and physical function," "peripheral arthritis," and "acute phase reactants" (4). Our results are similar except that we chose not to include physical function in the analyses as a potential explanatory variable, because it is usually considered a remote and indirect consequence of disease activity. Another previous study investigating PhGA as an outcome was from DESIR (5). This analysis focused on the discordance between patient global assessment and PhGA over time and the factors of the discordance and did not investigate the determinants of PhGA.

Our study has some limitations. First, whether the physician assessed PhGA while aware of the MRI findings for each patient is not clear. At least the physicians could not be aware of the MRI scores by the central readers at the time of assessment, as the scoring sessions only took place later. Therefore, a possible interpretation for the lack of impact of the MRI scores on PhGA is that the physicians did not have access to the MRI findings when making their judgment on the disease activity, because MRIs were usually made after the visit to the rheumatologist. Nevertheless, physicians possibly rate the findings of MRI as less important for their impression of the patient's disease than we may have thought. Likewise, in some centers, CRP levels were not available at the time of assessment. This absence may have led to a possible underestimation of the impact of CRP level. As a second limitation, we used a summary variable of the cumulative presence for EMM. This variable did not necessarily represent the presence of EMM at the time of assessment and using this summary variable may be the reason why the presence of EMM was not contributing to PhGA.

In conclusion, patients' subjective symptoms, peripheral arthritis and enthesitis, higher CRP level, and impaired spinal mobility contribute to explain PhGA in patients with early axial SpA irrespective of sex and age. However, physicians consider the presence of swollen joints as more important in males than in females.

## ACKNOWLEDGMENTS

The authors thank the different regional participating centers in DESIR: Pr. Maxime Dougados (Paris–Cochin B), Pr. Andre Kahan (Paris–Cochin A), Pr. Philippe Dieudé (Paris–Bichat), Pr. Bruno Fautrel (Paris–La Pitié-Salpêtrière), Pr. Francis Berenbaum (Paris–Saint-Antoine), Pr. Pascal Claudepierre (Créteil), Pr. Maxime Breban (Boulogne-Billancourt), Dr. Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr. Philippe Goupille (Tours), Pr. Jean Francis Maillefert (Dijon), Dr. Emmanuelle Dernis (Le Mans), Pr. Daniel Wendling (Besançon), Pr. Bernard Combe (Montpellier), Pr. Liana Euller-Ziegler (Nice), Pr. Pascal Richette (Paris Lariboisière), Pr. Pierre Lafforgue (Marseille), Dr. Patrick Boumier (Amiens), Pr. Martin Soubrier (Clermont-Ferrand), Dr. Nadia Mehsen (Bordeaux), Pr. Damien Loeuille (Nancy), Pr. René-Marc Flipo (Lille), Pr. Alain Saraux (Brest), Pr. Xavier Mariette (Le Kremlin-Bicêtre), Pr. Alain Cantagrel (Toulouse), Pr. Olivier Vittecoq (Rouen). The authors also thank the research nurses, the staff members of the Clinical Research Unit of Paris Center, the staff members of the Biological Resource Center of Bichat Hospital, the staff members of the Department of Statistics of Nîmes and all the investigators and in particular Jerome Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnes Timsit, and Eric Toussirot for active patient recruitment and monitoring.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ramiro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Hirano, van Gaalen, van der Heijde, Ramiro.

**Analysis and interpretation of data.** Hirano, Landewé, van Gaalen, van der Heijde, Gaujoux-Viala, Ramiro.

## ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

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