Predictors of flares in recent-onset psoriatic arthritis. Results of a multivariable model based on machine learning

Rubén Queiro

rubenque7@yahoo.es

Universidad de Oviedo

Daniel Seoane-Mato

Spanish Society of Rheumatology

Eva Galindez Agirregoikoa

Hospital Universitario Basurto

Juan D. Cañete

Hospital Clinic & IDIBAPS

Jordi Gratacós

Hospital Universitario Parc Taulí

Xavier Juanola

Hospital Universitari Bellvitge

Jordi Fiter

Hospital Universitario Son Espases

Ana González Marcos

Universidad Autónoma de Madrid

Ana Laiz

Hospital Universitari de la Santa Creu i Sant Pau

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Abstract

Background

Predicting the occurrence of a flare using tools and information that are readily available in daily clinical practice would provide added value in disease management. Scarcely any studies address this issue. The aim was to identify patient- and disease-related characteristics predicting flares in recent-onset PsA.

Methods

We performed a multicenter observational prospective study (2-year follow-up, regular annual visits). The study population comprised patients aged ≥ 18 years, fullfilling the CASPAR criteria and less than 2 years since the onset of symptoms. Flares were defined as inflammatory episodes affecting the axial skeleton and/or peripheral joints (joints, digits or entheses), diagnosed by a rheumatologist. The dataset contained data for the independent variables from the baseline visit and from follow-up visit number 1. These were matched with the outcome measures from follow-up visits 1 and 2, respectively. We trained a logistic regression model and random forest–type and XGBoost machine learning algorithms to analyze the association between the outcome measure and the variables selected in the bivariate analysis. A k-fold cross-validation with k = 5 was performed.

Results

At the first follow-up visit, 37.6% of the patients who attended the clinic had experienced flares since the baseline visit. Of those who attended the second visit, 27.4% had experienced flares since the first visit. The number of observations for the multivariate analysis was 295.The variables predicting flares between visits were PsAID, number of digits with onychopathy, age-adjusted Charlson comorbidity index and level of physical activity. The mean values of the measures of validity of the machine learning algorithms were all high, especially sensitivity (95.71%. 95% CI: 79.84–100.00).

Conclusions

These findings provide guidance not only on general measures (regular physical activity), but also on therapy (drugs addressing nail disease).

BACKGROUND

Psoriatic arthritis (PsA) is a chronic inflammatory disease that can affect approximately one-third of all patients with cutaneous psoriasis [1]. Recent data show that almost 0.6% of Spanish adults have PsA [2]. Patients with PsA are affected not only by a musculoskeletal disease that causes pain and undermines

their physical functioning, but also by a multidomain disease with manifestations that go beyond the joints and the skin. Consequently, the quality of life of affected patients is often seriously impaired [1].

In addition, the results recorded using instruments designed to estimate the inflammatory activity of PsA and those whose objective is to evaluate impact on quality of life, are quite frequently inconsistent, thus leading physicians and patients to view disease activity and severity differently [1, 3, 4]. This discrepancy complicates the definition of flares, since, for the patient, these are not necessarily synonymous with reactivation of inflammation, which is the most familiar concept for physicians [5, 6].

Interest in the concept of PsA flares is growing. At present, it is difficult to restrict this definition to merely physical or biological aspects of the disease [5, 6]. Randomized clinical trials offer a global vision of the disease and patient, since they include numerous metrics that evaluate inflammatory activity, physical functioning, quality of life, and structural damage. However, this vision is not feasible in daily clinical practice. Furthermore, reaching a definition of flare that is shared and accepted by both physicians and patients is still an unmet need in the field of PsA [5, 6].

While the definition of flare in PsA is an evolving field, physicians need a standardized tool to detect flares of inflammatory activity and take opportune therapeutic measures to return the patient to a situation of homeostasis. Even more interesting is to be able to predict the occurrence of a flare using tools and information that are readily available in daily clinical practice. This information would provide added value in disease management, yet, unfortunately, scarcely any studies provide it. The objective of the present study was to identify patient- and disease-related characteristics that make it possible to predict flares in recent-onset PsA.

METHODS

This work is part of the REAPSER study [7, 8, 9, 10]. The design of REAPSER has been described in detail elsewhere [7].

It is a multicenter observational prospective study (2-year follow-up, regular annual visits) promoted by the Spanish Society of Rheumatology. The study population comprised patients of both sexes aged ≥ 18 years who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) [11], with less than 2 years since the onset of symptoms attributable to the disease.

The intention at the baseline visit was to reflect the patient's situation before disease progress was modified by the treatments prescribed in the rheumatology department. In this sense, participants could not have been receiving methotrexate, leflunomide, or apremilast for more than 3 weeks after initiation and could not be receiving biologic disease-modifying antirheumatic drugs (DMARDs). These intervals were fixed considering that the mean time from initiation of treatment until onset of the response to therapy is 4 weeks in the case of synthetic DMARDs and 1 week in the case of biologic DMARDs. In cases where the patient had been receiving synthetic DMARDs for more than 3 weeks, we obtained confirmation from the investigating rheumatologist that the patient had not yet responded to treatment at the baseline

visit; this information was sought in only 9 patients, and for all those involved, the time since initiation of synthetic DMARDs was under 2 months.

If patients with psoriasis receiving treatment with synthetic or biologic DMARDs developed PsA and were referred to the rheumatology department for diagnosis and management, then they could be included in the study, since this would not violate the criterion that the baseline visit reflected the situation of the patient before disease progress was modified by the treatment prescribed at the rheumatology clinic.

Patients were invited to participate consecutively at one of their scheduled visits to the rheumatologist. Recruitment began in November 2014 and ended in October 2016. A total of 25 centers from 11 of the 17 Spanish autonomous communities participated in the study.

2.1. Variables and measurement

Variables included in REAPSER have been previously described [7]. For this work, we considered:

a. Sociodemographic data: age; sex; educational level (none, primary, secondary, university).
b. Family history of PsA, other types of inflammatory arthritis, and psoriasis.
c. Personal history and comorbidities (at each visit; based on a review of medical records): age-adjusted Charlson comorbidity index [12], cardiovascular risk factors (arterial hypertension, hyperlipidemia, diabetes mellitus [differentiating between insulin and non–insulin-dependent]).
d. Anthropometric data: Body mass index (BMI).
e. Lifestyle: smoking. Alcohol consumption [13]. Level of physical activity (low, moderate, high) [14].
f. Clinical situation at diagnosis of PsA: year of presentation of symptoms of PsA; clinical form (1. axial, 2. peripheral. 3. mixed); articular pattern (1. oligoarticular, 2. polyarticular, 3. distal, 4. mutilans, 5. spondylitis); presence of dactylitis (yes/no).
g. Joint involvement and enthesitis: number of tender joints (NTJ68); number of swollen joints (NSJ66); extended version of the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [15]. Polyarthritis was defined as NSJ66 $\geq$ 5.
h. Pain and global assessment of disease during the previous week: Patient global pain on a scale ranging from 0 (no pain) to 10 (very intense); patient global assessment of disease, from 0 (feels very well) to 10 (feels very ill); physician global assessment of disease, from 0 (minimal activity) to 10 (maximum activity).
i. Cutaneous and nail involvement (evaluated by a dermatologist): cutaneous psoriasis (yes/no); year of onset of psoriasis; clinical type; specific locations; treatment of psoriasis at PsA diagnosis; Psoriasis Area and Severity Index (PASI) [16]; onychopathy (number of digits affected). For purposes of the analysis, severe psoriasis was defined as PASI > 10 [16].
j. Functional situation and quality of life: Health Assessment Questionnaire (HAQ) [17], Psoriatic Arthritis Impact of Disease (PsAID) [18].
k. Radiographic evaluation at baseline: Bath Ankylosing Spondylitis Radiology Index (BASRI) of sacroiliac region [19], hand involvement according to the modified Steinbrocker method for PsA [20].

l. Laboratory tests: C-reactive protein (CRP), uric acid, total cholesterol, LDL cholesterol, triglycerides. For purposes of the analysis, a series of cut-off points were established to define high values: >0.5 mg/dl for standard CRP; >0.3 mg/dl for high-sensitivity CRP; hyperuricemia if > 7 mg/dl in men and > 6 mg/dl in women; ≥200 mg/dl for total cholesterol; ≥100 mg/dl for LDL; ≥150 mg/dl for triglycerides.
m. Treatment of PsA with DMARDs, date of initiation, date of finalization: synthetic DMARDs (methotrexate, leflunomide, sulfasalazine, apremilast, cyclosporine), biologic DMARDs (adalimumab, etanercept, infliximab, golimumab, ustekinumab, certolizumab, secukinumab).
n. Flares of PsA between visits: this was the primary outcome measure, considering it as a dichotomous variable (yes/no). Flares affecting the axial skeleton (defined as any inflammatory episode that affects the axial skeleton [rib cage and/or spinal column-pelvis] and evaluated as such by a rheumatologist between the previous study visit and the current visit) and/or peripheral joints (defined as any inflammatory episode affecting the joints, digits, or entheses and diagnosed as such by a rheumatologist between the previous and the current visit) were considered.

Rheumatologists assessing the patients didn´t know the objectives of this work.

2.2. Sample size

As REAPSER study was planned as a registry intended to collect a large number of variables, without prespecified hypothesis, a sample size was not previously calculated for this work.

2.3. Statistical analysis

2.3.1. Imputation of missing data

- The duration of psoriasis was imputed with the median of the remaining patients from the same age range. The age ranges used were as follows: <41 years, 41–60 years, and > 60 years.
- Systemic treatment of psoriasis was imputed with 0 (that is, not receiving systemic treatment). The reason for this imputation was that when monitoring we observed that cases in which this data was not available were actually patients with no treatment or topical treatment. There were only two cases with missing information about systemic treatment of psoriasis that could not be compiled after monitoring.
- Radiological involvement of the hands at the baseline visit was not imputed, except for those patients with NTJ28 and NSJ28 of 0, in which case it was imputed with 0.
- For patients who stopped attending the visits owing to improvement of their condition, the missing values for the variables PsAID, HAQ and presence of flares affecting the axial skeleton and peripheral skeleton were imputed with 0.

2.3.2. Generation of the dataset

The analysis was performed to determine predictive ability, attempting to establish associations between the outcome measures and values at the previous visit for the remaining variables. To do so, the dataset used for bivariate and multivariate analysis contained data for the independent variables from the baseline visit and from follow-up visit number 1. These were matched with the outcome measures from follow-up visits 1 and 2, respectively. Atemporal variables such as sex and family history were matched with outcome measures from follow-up visits 1 and 2; therefore, their values are the same for each one. This was also true for variables that were only collected at the baseline visit, such as systemic treatment of psoriasis at PsA diagnosis and clinical form at diagnosis.

2.3.3. Bivariate analysis

We selected variables whose Spearman correlation was considered significant according to the threshold applied to the ρ correlation coefficient ($|p| > \frac{2}{\sqrt{N}}$, with N being the number of data items). We also applied methods based on artificial intelligence, specifically the XGBoost algorithm and the SHAP technique, in order to identify informative variables (See Additional file 1 for a detailed explanation of both approaches). Finally, of the variables identified in the previous steps, we selected those that were statistically significantly associated with the outcome measure ($p < 0.05$). To do so, we applied the Mann-Whitney test for continuous/discrete variables and the χ^2 test for categorical variables.

2.3.4. Multivariate analysis:

In order to generate models where the independent variables do not share information and have a significant contribution to the model when adjusting for the rest of the variables included, we selected statistically significant variables (ie, $p < 0.05$) in an iterative fashion using logistic regression models based on artificial intelligence. The steps were performed in the 75% of the sample (training dataset) (see Additional file 1 for a detailed explanation).

Next, based on the variables selected, random forest–type and XGBoost machine learning algorithms were trained to analyze the association between the outcome measure and the variables selected (see Additional file 1 for more detail). To train the machine learning models the sample is split in two subsets, one to train the model and the other to evaluate its functioning. The division is generated in such a way that the proportion for each class of the outcome measure is the same in both subsets.

When the subsamples generated are imbalanced, the oversampling technique is used to train the models. This is based on duplicating or triplicating those data whose value for the outcome variable is a minority value.

The parameters and thus the predictions of the trained algorithm might depend on the randomness that derives from the train/test split, which means that different splits of the data might result in different models. To reduce this effect, k-fold cross-validation was performed. Such method consists in splitting the original dataset into k subsets of the same size, and iteratively training the algorithm with k-1 of them while testing the model with the one left. After k iterations, the algorithm will have been trained and

evaluated with all the partitions. In this analysis, a k-fold cross-validation with k = 5 has been used for both the random forest and XGBoost. Hence, the models were trained with 80% of the data at each iteration, while their good functioning was evaluated with the remaining 20% of the data. The subsets used were the same for the random forest and XGBoost.

The contribution of the variables to the prediction of each iteration of the algorithms was calculated by the feature importance of each variable in the training data. To estimate the performance of the random forest and XGBoost algorithms we calculated the values of accuracy, sensitivity, specificity, positive predictive value and negative predictive value as the mean of the values obtained for each parameter in the five evaluations performed in the cross validation.

Data analysis was performed with Python (3.8.12 version), using open-source libraries: pandas 1.3.4, numpy 1.19.0, scikit-learn 1.0, scipy 1.5.2, statsmodels 0.13.0.

RESULTS

The sample eventually comprised 158 patients. Table 1 summarizes the baseline characteristics.

Thirty-three patients (20.9%) were lost to follow-up. For 10 of these patients, the investigating rheumatologist at their center could confirm that they had not attended the visit because their PsA had improved.

At the first follow-up visit, 37.6% of the patients who attended the clinic had experienced flares since the baseline visit. Of those who attended the second visit, 27.4% had experienced flares since the first visit.

3.1. Bivariate analysis

Table 2 shows the variables selected in the bivariate analysis.

3.2. Multivariate analysis

The number of observations for the multivariate analysis was 295.

Table 3 shows the results of the logistic regression analysis. The variables predicting flares between visits selected in this analysis were age-adjusted Charlson comorbidity index, PsAID score, number of digits with onychopathy, and level of physical activity. The direction of the association was positive (the higher the value of the variable, the more frequent is the presence of flares) for PsAID score and onychopathy, and negative for the Charlson index and physical activity.

When the random forest–type and XGBoost machine learning algorithms were trained with these 4 variables, PsAID was the most important variable in random forest models. Values of feature importances were more similar between variables in XGBoost models (Table 4).

Table 5 shows the mean of the values of accuracy, sensitivity, specificity, positive predictive value and negative predictive value in the different evaluations performed in the cross validation. Sensitivity (values over 85.0%) was higher than specificity (values around 75.0%).

DISCUSSION

In this multicenter prospective study carried out in patients with recent-onset PsA, assessed at baseline before the potential modification of its natural history because of the treatment prescribed by a rheumatologist, an artificial intelligence–based analysis revealed 4 variables that could predict flares of the disease between each study visit: PsAID score, number of digits with onychopathy, age-adjusted Charlson comorbidity index, and level of physical activity. Associations were positive for the first two and negative for the last two. The mean values of the measures of validity of the machine learning algorithms were all high, especially sensitivity.

A recent multicenter study performed in the United Kingdom found that the two factors weighted as most important by patients when defining a flare were pain and fatigue [6]. Curiously, both aspects carry the greatest weight in the global score in PsAID, the standard tool that is currently used to evaluate the impact of PsA on quality of life [21]. Together with the findings of the present study, these data provide considerable evidence in favor of PsAID being implemented in clinical practice, not only when addressing impact on the quality of life of affected patients, but also as a predictor of future flares and, therefore, when selecting the most appropriate treatment for the individual patient. Furthermore, though the PsAID values are not always well aligned with the results of activity scores or treatment targets, the data reported above lead us to believe that PsAID is probably capable of recording disease domains (eg, activity, functioning, quality of life) that go beyond the initial purpose for which it was designed [21].

Another interesting and practical finding of our study was discovering how nail disease in PsA was predictive of flares. This previously unreported finding has clear practical implications, in that not all currently available treatments for PsA address this domain with the same efficacy [22]. Nevertheless, the finding is in clear agreement with the results of another Spanish multicenter study, in which patients with distal interphalangeal joint involvement (most with associated nail disease) had significantly fewer possibilities of reaching a PsAID score indicating low impact of disease [23]. In a multicenter Turkish study, nail disease with involvement of the distal interphalangeal joint was identified as one of the main barriers for achieving minimal disease activity [24]. These data point to this disease domain as indicative of poor prognosis.

We found that the comorbid conditions recorded using the age-adjusted Charlson index behaved as predictors with a negative association. A priori, this finding may seem somewhat contradictory, since patients with PsA aged > 65 years (and probably with greater comorbidity) have been associated with more severe forms of PsA [25, 26]. Nevertheless, other studies have shown that outcomes are better in patients with established PsA receiving systemic treatment, both in terms of activity and in terms of impact, than in individuals with PsA aged under 40 years [27]. Moreover, when the capacity of response to

biologics is analyzed in patients with comorbid conditions, the magnitude of the positive changes achieved with these agents is similar to that obtained by patients with no comorbid conditions [27, 28]. In summary, the association between comorbid conditions and disease in patients with PsA continues to be confusing; the direction of the association is not altogether clear owing to the cross-sectional design of the most studies. We might speculate that patients with comorbid conditions have more checkups, attend visits more frequently, and adhere to recommended measures and treatments more meticulously (eg, measures aimed at controlling weight in patients with cardiovascular risk that may in turn lead to better control of skin and joint disease). A recent study found a low impact of disease in terms of PsAID score in patients with PsA who had a history of coronary events [27].

Physical activity was the other predictor of flares with a negative association. The potential biological reasons associating physical exercise with reduced inflammation are beyond the scope of this study. However, the connection between regular physical exercise and reduced inflammatory burden seems to be well documented in the literature [29, 30]. Evidence from epidemiology studies shows an inverse relationship between physical activity and markers of systemic inflammation such as CRP and IL-6 levels. Furthermore, regular physical activity may be associated with transitory release of certain cytokines with anti-inflammatory effects in tissues other than muscle tissue [29, 30].

The main limitation of this study is its sample size and the fact that some data are missing for some variables. This affected the power of the statistical analysis and, therefore, the ability of the study to detect variables associated with the outcome measure. We tried to compensate for this by using models based on artificial intelligence and machine learning. Random forests are “joint” algorithms in which decision trees are trained with different subsets of variables and data. Decision trees are more flexible than many statistical models, since they make it possible to identify many types of association between explanatory variables and the outcome measure. Furthermore, the fact that random forests add variability prevents the model from being overadjusted to the data and can be re-run with new data, thus increasing the robustness of the predictions. On the other hand, XGBoost algorithms use ensembles of decision trees in a sequential manner. In each tree, the observations that were wrongly-classified in the previous one are given a larger weight, thus creating models with very little bias which usually result in very accurate predictions. The counterpart of this phenomenon is a higher risk of the model being overfit to the training dataset. Our analysis showed that the random forest models tended to perform better than XGBoost in terms of all the metrics, which is probably due to the reduced number of observations in the dataset causing the training and test subsets to be quite disparate. Therefore, we could conclude that for such small datasets, an algorithm that overfits less to the training subset such as random forest is more appropriate.

Although the concept of PsA flare is currently being debated, we have chosen for its definition the presence of axial and/or peripheral inflammatory activity diagnosed by a rheumatologist, being aware that it is an ad hoc definition without endorsement in the current literature. In any case, we must not forget that the opinion of expert clinicians in PsA was the gold standard on which the construct validity of

the CASPAR criteria for the disease was based. Therefore, the definition of flare provided in this study may be familiar to many practicing rheumatologists.

The main strength of this study is its ability to record the course of PsA from an early phase before the natural disease evolution is modified by treatment prescribed by the rheumatologist.

CONCLUSIONS

Our artificial intelligence–based analysis revealed that higher PsAID score, nail disease, reduced physical activity and a low age-adjusted Charlson comorbidity index could predict flares with high sensitivity. The implications of these findings for clinical practice are clear, since they provide guidance not only on general measures for patients (regular physical activity), but also on therapy itself (drugs adressing nail disease). The PsAID score was the first variable in the predictive hierarchy generated by most of the models, thus supporting its importance in the management and follow-up of affected patients.

Declarations

Ethics approval and consent to participate: All patients gave their informed consent to participate. The study centers assigned each participant an identification code in order to ensure data confidentiality in line with current legislation. The study complies with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committees of the Principality of Asturias (study number 14/2014).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and analysed during the current study are available from proyectos@ser.es on reasonable request.

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Authors´ contributions: RQ participated in the design of the work, the acquisition and interpretation of data, and was a major contributor in writing the manuscript. DS participated in the design of the work, the analysis and interpretation of data, and was a major contributor in writing the manuscript. EGA and AL made substantial contributions to the acquisition of data. JC, JG, XJ and JF participated in the design of the work. AGM participated in the analysis of data. All authors revised the manuscript critically, and read and approved the final version.

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Non-author members of REAPSER Study Group: Jesús Rodriguez-Moreno, Jaime Notario Rosa (Hospital Universitari de Bellvitge, Barcelona, Spain); Andrés Lorenzo Martín, Anahy Brandy García, Pablo Coto Segura (Hospital Universitario Central de Asturias, Oviedo, Spain); Hye-Sang Park, Anna López Ferrer (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Silvia Pérez Barrio (Hospital Universitario Basurto, Bilbao, Spain); Carlos Montilla, Andrés J Plata Izquierdo (Hospital Clínico Universitario de Salamanca, Salamanca, Spain); Juan J. Bethencourt Baute, Sagrario Bustabad, Francisco J Guimerá Martín-Neda (Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain); Jose A. Pinto-Tasende, Eduardo Fonseca Capdevilla (Complexo Hospitalario Universitario A Coruña, A Coruña, Spain); Beatriz Joven Ibáñez, Raquel Rivera Díaz (Hospital Universitario 12 Octubre, Madrid, Spain); Julio Ramírez, Andrea Cuervo, Mercè Alsina Gibert (Hospital Clinic i Provincial, Barcelona, Spain); Pilar Trenor Larraz, Isabel de la Morena Barrio, Laura Puchades Lanza, Diego Bedoya Sanchís (Hospital Clínico Universitario de Valencia, Valencia, Spain); Elide Toniolo, Catalina Meliá Mesquida, Claudia Murillo (Hospital Son Llàtzer, Palma de Mallorca, Spain); Manuel J Moreno Ramos, María D Beteta, Paloma Sánchez-Pedreño Guillén (Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain); Leticia Lojo Oliveira, Teresa Navío Marco, Laura Cebrián, Pablo de la Cueva Dobao (Hospital Universitario Infanta Leonor, Madrid, Spain); Martina Steiner, Santiago Muñoz-Fernández, Ricardo Valverde Garrido (Hospital Universitario Infanta Sofía, Madrid, Spain); Manuel León, Esteban Rubio, Alejandro Muñoz Jiménez, Lourdes Rodríguez Fernández-Freire (Hospital Universitario Virgen del Rocío, Sevilla, Spain); Julio Medina Luezas, María D Sánchez-González, Carolina Sanz Muñoz (Hospital Clínico Universitario de Valladolid, Valladolid, Spain); José M Senabre, José C Rosas, Gregorio Santos Soler, Francisco J Mataix Díaz (Hospital Marina Baixa, Villajoyosa, Spain); Juan C Nieto-González, Carlos González, Juan G Ovalles Bonilla, Ofelia Baniandrés Rodríguez (Hospital Universitario Gregorio Marañón, Madrid, Spain); Fco Javier Nóvoa Medina, Dunia Luján (Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain); María D Ruiz Montesino, Ana M Carrizosa Esquivel (Hospital Universitario Virgen Macarena, Sevilla, Spain); Cristina Fernández-Carballido, María P Martínez-Vidal, Laura García Fernández (Hospital General Universitario de Elda, Elda, Spain); Vega Jovani, Rocío Caño Alameda, Silvia Gómez Sabater, Isabel Belinchón Romero (Hospital General Universitario de Alicante, Alicante, Spain); Ana Urruticoechea-Arana, Marta Serra Torres (Hospital Can Misses, Ibiza, Spain); Raquel Almodóvar, José L López Estebaranz (Hospital Universitario Fundación Alcorcón, Alcorcón, Spain); María D López Montilla, Antonio Vélez García-Nieto (Hospital Universitario Reina Sofía, Córdoba, Spain) collected data.

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Tables

Table 1. Baseline characteristics of the sample

Variable	
Age	49.35 (13.53)
Sex	
Male	90 (57)
Female	68 (43)
Educational level	
None	3 (1.9)
Primary	58 (36.7)
Secondary	66 (41.8)
University	31 (19.6)
BMI	27.63 (5.27)
Smoking	
Never smoked	61 (38.6)
Exsmoker	44 (27.8)
Occasional smoker	6 (3.8)
Daily smoker	47 (29.7)
Level of physical activity	
Low	35 (24.1)
Moderate	66 (45.5)
High	44 (30.3)
Weekly alcohol consumption	0 [0-4]
Family history of psoriasis	62 (39.2)
Family history of psoriatic arthritis and other types of inflammatory arthritis	21 (13.3)
Age-adjusted Charlson comorbidity index	1 [0-2]
Arterial hypertension	39 (24.7)
Hyperlipidemia	53 (33.5)
Diabetes mellitus	
Non–insulin-dependent	13 (8.2)
Insulin-dependent	3 (1.9)
Psoriasis	149 (94.3)

Duration of psoriasis until onset of PsA (years)	10 [2-20]
Clinical form of psoriasis	
Vulgaris	126 (80.3)
Guttate	5 (3.2)
Localized pustular	10 (6.4)
Inverse	7 (4.5)
Psoriasis specific sites	
Scalp	88 (59.5)
Nails	91 (61.5)
Palms and soles	13 (8.8)
Gluteal cleft and/or perianal region	34 (23.0)
Mucous membranes	1 (0.7)
PASI	1.2 [0.3-3.1]
Systemic treatment of psoriasis	21 (14.3)
Clinical form of PsA	
Axial	12 (7.6%)
Peripheral	126 (79.7%)
Mixed	20 (12.7%)
Main joint pattern in PsA	
Oligoarticular	87 (55.1%)
Polyarticular	47 (29.7%)
Distal	9 (5.7%)
Spondylitis	15 (9.5%)
Dactylitis at diagnosis	71 (44.9%)
Enthesitis at diagnosis	43 (27.2%)
Uveitis at diagnosis	1 (0.6%)
Pain in the previous week	5 [3-7]
Patient global assessment of disease	5 [3-7]
PsAID	3.75 [1.65-5.90]

Sacroiliac involvement (BASRI)	0 [0-1]
Hand involvement (modified Steinbrocker)	0 [0-2]

Categorical variables are expressed as n (%). Numerical variables are expressed as mean (SD) if normally distributed and as median [IQR] if not.

Table 2. Variables associated with flares between visits: Bivariate analysis.

Variable	P value
Age	0.001
Physical activity	0.02
Weekly alcohol consumption	0.01
Age-adjusted Charlson comorbidity index	0.001
No. of digits with onychopathy	0.01
No. of tender joints	0.01
Global pain	0.01
Physician global assessment of disease	0.001
Patient global assessment of disease	0.001
PsAID score	<0.001
HAQ score	<0.001

Table 3. Variables associated with flares between visits selected in the logistic regression analysis.

Variable	Regression coefficient	95% CI	p value (Wald test)
Age-adjusted Charlson comorbidity Index	-4.655	[-7.021, -2.289]	<0.001
PsAID score	2.212	[1.171, 3.254]	<0.001
No. of digits with onychopathy	1.420	[0.331, 2.511]	0.011
Level of physical activity	-1.221	[-1.87, -0.572]	<0.001

*Positive values indicate that the higher the value of the variable, the more frequent is the presence of flares

Table 4. Feature importances of the variables in the different models trained in the cross validation.

Variable	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5
Random Forest					
PsAID score	0.556	0.530	0.559	0.543	0.559
No. of digits with onychopathy	0.235	0.234	0.223	0.216	0.256
Age-adjusted Charlson comorbidity Index	0.133	0.157	0.139	0.153	0.123
Level of physical activity	0.077	0.079	0.079	0.088	0.063
XGBoost					
PsAID score	0.242	0.264	0.266	0.248	0.273
No. of digits with onychopathy	0.300	0.262	0.252	0.278	0.318
Age-adjusted Charlson comorbidity Index	0.207	0.240	0.279	0.238	0.220
Level of physical activity	0.250	0.233	0.202	0.236	0.189

*Values from 0 to 1. The higher the value, the greater the importance of the variable in the model. Values are normalized, i.e. in each iteration the sum of the values equals 1.

Table 5. Measures of validity in the different evaluations performed in the cross validation.

Metric	Accuracy	Sensitivity	Specificity	NPV	PPV
Random Forest					
Mean	85.42	95.71	75.89	95.24	78.85
SD	5.93	5.71	8.18	6.02	6.27
95% CI	68.42, 100.00	79.84, 100.00	53.18, 98.60	78.51, 100.00	61.45, 96.26
XGBoost					
Mean	80.33	85.79	75.16	86.01	76.10
SD	5.83	9.87	4.38	8.94	4.44
95% CI	64.15, 96.53	58.37, 100.00	63.01, 87.32	61.20, 100.00	63.76, 95.20

SD: standard deviation

*Mean of the values obtained in the 5 evaluations performed in the cross validation in Random Forest analysis.

&Mean of the values obtained in the 5 evaluations performed in the cross validation in XGBoost analysis.

Supplementary Files

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