What Characterizes the Severity of Psoriasis?

Results from an Epidemiological Study of over 3,300 Patients in the Iberian Region

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Key Words

Psoriasis epidemiology · Quality of life · Spain · Portugal

Abstract

Background: Understanding the epidemiology of moderate-to-severe psoriasis is essential for its management.

Objective: To assess the epidemiological characteristics of patients with moderate-to-severe psoriasis. **Methods:**

Cross-sectional, observational epidemiological study conducted in Spain and Portugal. Data were collected by 332 dermatologists for ≥ 10 consecutive presenting patients.

Results: Based on body surface area (BSA) and Psoriasis Area and Severity Index (PASI) criteria, moderate-to-severe psoriasis was confirmed in $\geq 79.3\%$ of patients ($n = 3,320$). Pre-existing comorbid conditions included psoriatic arthropathy (13%), dyslipidemia (14.1%) and hypertension (20.2%). The mean BSA involvement was 23% (95% confidence interval, CI: 22.2–23.3%), and the mean PASI score was 14.3 (95% CI: 13.9–14.6%). During the 2 years prior to assessment, 97.0% of

patients had received topical treatments, whereas 31.3% had not received systemic treatment or phototherapy. The median annual cost of treatment was 825 EUR. **Conclusion:** Moderate-to-severe psoriasis is accurately diagnosed, but inadequately treated in many patients in Spain and Portugal.

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Introduction

Psoriasis is a chronic, immune-mediated, recurrent disease of variable severity. It occurs more frequently in certain racial groups and geographical areas, possibly due to genetic and environmental factors [1]. Indeed, in country-specific studies, the estimated prevalence of psoriasis ranges from 0% in Australian Aborigines and Andean Indians to 11.8% in the inhabitants of Kazakhstan (an Arctic region of the Soviet Union) [1]. In Spain, it has been estimated that 1.2–1.4% of individuals have psoriasis [2]. If we assume that there is a similar prevalence in Portugal, it can be extrapolated that approximately 637,000–800,000 individuals are affected with psoriasis in these two Iberian countries.

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Although the clinical and epidemiological characteristics of the Spanish population with psoriasis have been studied [3, 4], there is little information about the subgroup of patients with moderate-to-severe psoriasis. From a disease management perspective, this is an important population because the disease has a considerable impact on the patient's quality of life (QoL), comparable to that of other chronic diseases such as asthma [5]. Moreover, the prognosis of these patients has improved dramatically since the introduction of effective systemic [6] and, more recently, biological therapies for the treatment of moderate-to-severe psoriasis [7, 8]. Despite the advantages of these therapies, there are additional healthcare costs [9] and different side effects compared with traditional interventions, such as topical treatments and phototherapy.

For the optimal management of moderate-to-severe psoriasis, it is essential to gain a better understanding of the sociodemographic characteristics of these patients and how these characteristics may be associated with disease course. A number of quantitative and qualitative measures of health-related QoL can be used to assess the effects of disease severity and treatment outcomes in these patients. Accordingly, the main aim of this study was to determine, using both objective and subjective clinical measures, the epidemiological characteristics of Spanish and Portuguese patients with moderate-to-severe psoriasis.

Methods

This was a large, cross-sectional, observational epidemiology study conducted at dermatology centers in Spain and Portugal. Data were collected between September 2004 and June 2005 by 332 dermatologists (292 in Spain and 40 in Portugal) working in private practice, public hospitals and primary healthcare clinics. All patients gave written, informed consent to participate in the study, and the study was assessed and approved by the Clinical Research Ethics Committee of the Hospital Germans Trias i Pujol in Badalona, Spain. Due to the nature of the analysis, it was not practical to randomize investigators or patients to the study. Instead, a proportional quota sample of dermatologists was identified on a population-proportional basis in each region (province) of Spain and Portugal. Only regions with dermatology centers and more than 100,000 inhabitants were considered. In these regions, dermatologists with a recognized interest in the treatment of psoriasis were then invited to participate in the study; of the 577 dermatologists invited to participate, 245 did not meet the criteria for participation in the study (for example, too few patients or the patients did not have psoriasis of at least moderate severity). To further minimize bias, each investigator completed an electronic case report form for the first 10 consecutive patients (minimum) with moderate-to-severe psoriasis, according to the investigator's judgement, who attended their practice.

Objectives

The primary objectives of this study were to analyze epidemiological data from patients with moderate-to-severe psoriasis, according to the dermatologists' judgement, who attended dermatology centers in Spain and Portugal, and to identify patients who may be suitable for systemic treatment. The secondary objectives were to assess QoL in these patients, identify factors associated with psoriasis pathology, characterize diagnostic and therapeutic procedures that are being used in routine clinical practice, and evaluate the indirect costs (healthcare utilization and social costs) of moderate-to-severe psoriasis. The direct monetary cost of psoriasis treatment was also assessed.

Patients

Patients of any age who had been diagnosed as having moderate-to-severe psoriasis within 1 year of the study were recruited. Currently, there is no consensus or widely accepted definition of what represents moderate-to-severe psoriasis [10]. Accordingly, a diagnosis of moderate-to-severe psoriasis was given based on the judgement of the enrolling dermatologists who assessed body surface area (BSA) involvement of the psoriasis, response to previous psoriasis treatment on the Psoriasis Area and Severity Index (PASI), and the QoL of each patient. To ensure the suitability of patients for inclusion in analyses, the collected data were reassessed, and patients with a BSA involvement of >10% or a PASI score of >10 were classified as having moderate-to-severe psoriasis. This definition is similar to the objective, 'operational' definition proposed by the European Medicines Agency: a BSA involvement of >10% or a PASI score of 10–20 [10]. Patients with a BSA involvement of <10% or a PASI score of <10 were also included in the analyses as they were originally diagnosed as having moderate-to-severe psoriasis according to the dermatologists' judgement (the *a priori* definition) and therefore provided an interesting comparator group. Furthermore, as BSA involvement and PASI score are not mutually inclusive, the severity of a patient's disease may be considered mild using one instrument but moderate-to-severe using the other.

To further establish a diagnosis of moderate-to-severe psoriasis, we assessed whether patients had also received systemic treatments or biological therapies for psoriasis within 24 months prior to the study visit, had concomitant psoriatic arthropathy (PsA) or had an Overall Lesion Severity (OLS) scale score ≥ 2 (at least moderate psoriasis). Those patients who refused to participate in the data gathering or who had difficulty understanding questions posed by the QoL questionnaire were excluded.

Assessments

Investigators completed a comprehensive electronic case report form for each consecutive patient participating in the study. Because this was a cross-sectional study without follow-up, a single form was completed for each patient using the patient's clinical records and/or personal recollection. The following information was collected: sociodemographics (age, sex, province of birth, employment status, level of education and citizenship), life habits (consumption of alcohol or tobacco, and participation in regular exercise), history of psoriasis (age at onset of psoriasis, clinical type of psoriasis at initial diagnosis, method of diagnosis and psoriasis treatments received within the previous 24 months), current disease status [presence of active lesions, clinical type of psoriasis, disease severity (based on BSA involvement, PASI score and

severity of pruritus on a visual analogue scale, VAS), psoriasis trigger or aggravation factors, and details of coexisting PsA], cost of psoriasis [direct monetary cost of treatment (annual median cost in euros) and indirect costs (number of working days lost, number of visits to the dermatologists, number of days in hospital and emergency visits)] and condition of well-being (QoL on the Psoriasis Disability Index, PDI). Health state utilities were assessed using the time trade-off and willingness to pay methods [11].

The BSA of psoriasis involvement was calculated according to the Wallace rule of 9, and the severity of psoriasis was estimated using PASI scores. The severity of erythema, induration and desquamation of lesions was assessed using the OLS scale score. An increasing OLS scale score provides a measure of increasing severity (ranging from 0 = no lesions to 4 = very severe lesions). The PDI, which was used to assess QoL, was completed by patients using a Tablet personal computer. The PDI is a 15-item test across 5 domains (daily activity, work or academic activities, personal relationships, free time and treatment) [12, 13]; total scores range from 0 to 40 (also expressed as a percentage of the maximum possible score), with the higher scores indicating greater impairment in QoL. Scores on the VAS range from 0 indicating 'no itching' to 10 indicating 'maximum bearable itching'. The time trade-off method was used to determine how many months of remaining life patients would be willing to offer to be permanently free from psoriasis lesions. The willingness to pay method was used to assess how much money patients would be willing to pay, as a percentage of their income, to be permanently free from psoriasis lesions.

Statistical Analysis

Data collected by the electronic case report form in each investigator's practice were fed into a central database, and their integrity was verified before statistical analyses were performed. Descriptive, univariate analyses of each of the quantitative and qualitative variables were performed. The mean age of patients at inclusion, the mean age at onset of psoriasis, the mean duration of disease and their 95% confidence intervals (CI) were calculated. Prior to study commencement, it was decided that a total sample size of 3,000 patients, with a diagnosis of moderate-to-severe psoriasis according to the dermatologists' judgement, would provide 80% power to detect between-group comparisons of 6% in severity of psoriasis (based on PASI scores of <10, 10–<20 and ≥20 and BSA involvement of <10%, 10–<20% and ≥20%), with a 5% significance level.

The differences in age of onset of psoriasis (stratified by patients who were ≤30 years of age and those who were >30 years of age) were assessed using the χ^2 test for each recorded category of family history of psoriasis (any family history, affecting immediate relatives, second-degree relatives or no family history).

Differences in age of onset of psoriasis and the sex of patients were assessed using a χ^2 test, and results were stratified by BSA involvement (<10%, 10–<20% and ≥20%) and PASI score (<10, 10–<20 and ≥20).

Mean pruritus score on the VAS, mean number of visits to a dermatologist in the previous year and mean number of days in hospital were stratified into categories according to BSA involvement (<10%, 10–<20% and ≥20%) and PASI score (<10, 10–<20 and ≥20), and differences between each category for each of these variables were assessed using an ANOVA (analysis of variance) test.

The mean number of months of life and percentage of income (95% CI) that patients were willing to sacrifice (time trade-off and willingness to pay analyses, respectively) were also stratified into categories according to BSA involvement (<10%, 10–<20% and ≥20%) and PASI score (<10, 10–<20 and ≥20) and differences were assessed using an ANOVA test.

Two multivariate analyses using a multiple linear regression model were performed: one treated PASI score as the independent variable and the other treated percentage BSA involvement as the independent variable. Correlation coefficients were calculated between these two independent variables and the following dependent variables, which were entered into the model in a single step: female sex, comorbidities, family history of psoriasis, topical, phototherapy, systemic or biological therapy in the previous 24 months, presence of arthropathy, direct monthly cost of treatment, number of visits to a dermatologist in the previous year, number of days in hospital in the previous year, number of emergency visits in the previous year, number of months of life and percentage of income that patients were willing to sacrifice, PDI score, BSA involvement or PASI score, OLS scale score ≥2 for head, trunk, arms or legs, severity of pruritus, number of days on sick leave in the previous year, and number of cigarettes smoked per day.

To assess the overall influence of variation in these independent variables on PASI score and BSA involvement, the coefficient of determination (R^2) was also calculated. The regression model was validated by analysis of residuals for the following assumptions: linearity of relationships, homoscedasticity of variables, independent observations (absence of autocorrection) leading to uncorrelated error terms and normality of data.

The mean direct monthly cost of treatment was calculated and stratified by PASI score (<10, 10–<20 and ≥20) and differences in cost between PASI categories were assessed using an ANOVA test. Estimates for the direct monthly cost of treatment were obtained from patient-reported costs.

There are some missing data. In this study, 12 patients were not evaluated for affected BSA and were thus excluded from analyses.

Results

Patient Demographics and Lifestyle

In total, electronic case report forms were completed for 3,320 patients considered by the investigators to have moderate-to-severe psoriasis: 87.6% (n = 2,908) from Spanish dermatology centers and 12.4% (n = 412) from Portuguese centers. The sociodemographic characteristics of patients are shown in table 1. Due to the method of data collection, the number of patients declining to participate was not reported.

The mean age of patients at study inclusion was 46.7 years (95% CI: 46.2–47.3 years) and a slightly higher proportion of patients were men than women (56.8 vs. 43.2%, respectively). Nearly half the patients were employed (46.2%) at the time of inclusion and two thirds of patients

Table 1. Patient demographics and lifestyle

	Number of patients
Sex	
Male	1,887 (56.8)
Female	1,433 (43.2)
Age of patients	
≤20 years	152 (4.6)
21–40 years	1,086 (32.7)
41–60 years	1,362 (41.0)
61–80 years	681 (20.5)
≥81 years	38 (1.1)
Employment status	
Unemployed	340 (10.2)
Housewife	584 (17.6)
Student	212 (6.4)
Self-employed	465 (14.0)
Employed	1,536 (46.3)
Retired	183 (5.5)
Level of education	
None	267 (8.0)
Primary school	1,556 (46.9)
Secondary school	502 (15.1)
College	491 (14.8)
4–5 years at college	504 (15.2)
Marital status	
Married/living with partner	2,203 (66.4)
Single	808 (24.3)
Separated/divorced	164 (4.9)
Widowed	145 (4.4)
Personal history	
High blood pressure	670 (20.2)
Type II diabetes mellitus	275 (8.3)
Heart disease	212 (6.4)
Liver disease	130 (3.9)
Dyslipidemia	467 (14.1)
Hyperuricemia	133 (4.0)
Tumors	139 (4.0)
Psychiatric diseases	243 (7.3)
Autoimmune diseases	125 (3.8)
Infectious diseases	83 (2.5)
Tobacco	1,098 (33.1)
Alcohol on weekends only	618 (18.6)
Alcohol >40 g (usually)	288 (8.7)
Habitual exercise	1,130 (34.0)

Figures in parentheses are percentages.

were married or lived with a partner (66.4%). In total, 92.0% of patients completed at least primary school education, with 46.9% having attended only primary school. One third of patients smoked tobacco (33.1%), and of these patients, the median daily tobacco consumption was 16 cigarettes. Two hundred and eighty-eight patients

(8.7%) admitted to drinking more than 40 g of alcohol per day. Thirty-four percent of patients reported that they exercised regularly (at least twice weekly). A total of 670 patients (20.2%) had hypertension and 14.1% of patients were dyslipidemic.

Disease Characteristics

The mean age at onset of psoriasis was 28 years (95% CI: 27.4–28.5 years; 26.5 years in women and 28.9 years in men), and the mean duration of psoriasis was 18 years (95% CI: 17.4–18.5). The most common type of psoriasis at initial diagnosis was vulgaris (76.0% of patients), followed by guttate (12.1%), palmoplantar (4.4%), erythrodermic (1.8%), pustular (1.3%) and other types (4.3%). At the time of the study assessment, the proportions of patients with each of these types of psoriasis were similar: vulgaris (79.8%), guttate (6.7%), palmoplantar (4.0%), erythrodermic (4.3%), pustular (1.8%) and other types (3.3%). The majority of patients were diagnosed as having psoriasis by a dermatologist (75.8%), and 22.1% of patients were diagnosed in the primary care setting. The remaining patients were diagnosed by a pediatrician (1.6%) or a rheumatologist (0.5%). In 15% of cases, the diagnosis included a skin biopsy.

At the study visit, the mean affected BSA was 23% (95% CI: 22.2–23.3%), and the majority (77.2%) of patients presented with a BSA affected of >10%. Correspondingly, the mean PASI score in these patients was 14.3 (95% CI: 13.9–14.6%), and 65.1% of patients presented with a PASI score of >10. The proportions of patients who had an OLS scale score ≥2 were 96.1% for the arms, 95.1% for the legs, 83.8% for the trunk and 64.1% for the head.

The majority (79.3%) of patients included in the analyses were confirmed as having ‘moderate-to-severe’ psoriasis at the time of the study visit when our core definition (BSA involvement of >10% or a PASI score of >10) was used to define moderate-to-severe psoriasis. If patients with concomitant PsA are also included, the proportion of patients considered to have moderate-to-severe psoriasis increased to 82.9%. This proportion increased further (89.5%) if the patients who had received systemic or biological therapy in the 24 months prior to the study visit are included. Lastly, if the patients who had an OLS scale score of ≥2 are considered in isolation, the proportion of patients judged to have moderate-to-severe psoriasis was 99.3%.

When the study data were stratified by BSA involvement (<10%, 10–<20% and ≥20%) or PASI score (<10, 10–<20 and ≥20), we found that disease severity was

greater in men than women across all categories for BSA involvement and PASI score ($p < 0.001$ for both comparisons; fig. 1). Severity of disease was found to be significantly greater in patients with an earlier onset of psoriasis (≤ 30 years of age) than those with a later onset (> 30 years of age) across all categories for BSA involvement and PASI score ($p < 0.001$ for both comparisons). As expected, there were also significant differences in OLS scale score (erythema + induration + desquamation) for head, trunk, arm and leg involvement between the different categories of BSA involvement and PASI score ($p < 0.001$ for all comparisons); scores on the OLS scale increased with increasing BSA involvement or increasing PASI score.

At the time of the study visit, 80% of patients presented with an active psoriasis recurrence. The mean number of acute psoriasis recurrences experienced by patients in the 24 months prior to the study visit was 3 (95% CI: 3.0–3.2) and the mode number of psoriasis recurrences was 2, i.e. 1 per year. A recurrence or worsening of psoriasis was reported to be related to a triggering factor in 78% of patients; 85 and 50% of patients indicated stress and changes in weather, respectively, as triggering factors.

A total of 1,648 patients (49.6%) reported that other members of the family had psoriasis. Of these, 36.4% ($n = 1,208$) were first-degree relatives and 13.3% ($n = 440$) second-degree relatives. Analyses revealed that in the patient group who had a family history of psoriasis, a significantly higher proportion of patients had developed psoriasis before the age of 30 than at 30 years or older ($p < 0.001$ for all comparisons; fig. 2). The frequency of a family history of psoriasis was inversely related to the age at onset of psoriasis: as the age at onset increased, there was a decreasing tendency to have a family history of psoriasis ($p < 0.001$). Patients who did not have a family history of psoriasis were significantly more likely to develop psoriasis at 30 years of age or older than before the age of 30 years ($p < 0.001$).

Psoriasis-Associated Comorbid Conditions

PsA and Pruritus

Psoriatic arthropathy was confirmed in 12.8% of patients and suspected (but unconfirmed) in 7.6% patients. The mean age at onset of PsA was 45 years (95% CI: 43.6–45.8). Only 5% of patients developed arthropathy prior to psoriatic skin lesions, with an average time from diagnosis of psoriasis to development of psoriatic arthropathy of 17 years.

The mean score for pruritus on the VAS was 4.72 (95% CI: 4.6–4.8). When mean VAS scores for pruritus were stratified by psoriasis BSA involvement ($< 10\%$, 10 – $< 20\%$

and $\geq 20\%$), a significant difference between the categories of BSA involvement was found ($p < 0.001$): the VAS score increased (indicating increased 'itchiness') with increasing BSA involvement. A similar significant difference was seen when mean VAS scores were stratified by PASI score (< 10 , 10 – < 20 and ≥ 20), indicating that 'itchiness' increased with increasing disease severity.

Other Comorbid Conditions

Preexisting conditions, including hypertension (20.2%) and dyslipidemia (14.1%), were reported by 43% of patients. A total of 24.3% patients had at least one comorbid condition in addition to psoriasis, and 17.2% of patients reported more than one associated comorbidity. Furthermore, 38.5% of patients were receiving treatment for conditions other than psoriasis, with antihypertensive therapies being the most frequently used.

Treatment History

In the 24 months prior to the study visit, almost all patients (97.0%) had received topical treatments (as both mono- and combination therapies), and almost one half (48.6%) had received systemic treatments (table 2). Roughly one third of patients (31.3%) did not receive either systemic treatment or phototherapy, and a similar proportion of patients (27.7%) received monotherapy (topical treatments in 26.8% of patients and systemic or phototherapy in 0.8% of patients). Among the patients who received concomitant medications for their psoriasis, the most frequently used combinations were topical + systemic treatment (48.0% of patients), and systemic treatment + phototherapy (23.0%).

Fifteen percent of patients reported that they had experienced a side effect due to treatment in the 24 months prior to the study visit. Patients who were receiving systemic treatments reported the greatest number of side effects: 22.0% of patients receiving cyclosporine, 18.9% receiving methotrexate and 13.3% receiving retinoids. For topical treatments, side effects were reported most frequently in patients receiving topical retinoids (6.1% of patients), followed by topical corticosteroids (2.0%) and vitamin D derivatives (1.7%). A similar proportion of patients receiving phototherapy reported side effects as those given topical treatments: 7.8% of patients for psoralen and ultraviolet A light, 2.6% of ultraviolet B light and 0.7% for heliotherapy. Twenty percent of patients had discontinued a psoriasis treatment in the 24 months prior to the study visit. The treatment discontinuation rate was highest in patients receiving systemic therapies (24%) followed by phototherapies (23%).

Burden of Disease

Indirect Costs – Healthcare Utilization and Social Costs

Thirteen percent of patients had taken at least 1 day of psoriasis-related sick leave in the 12 months prior to the study visit. The mean amount of time lost to psoriasis was nearly 2 months (59 days; 95% CI: 50.1–68.6) over a period of up to 1 year (assessed in 24 patients). Patients with severe psoriasis took proportionately more days of sick leave (111 days; 16.0%) than those with moderate psoriasis (175 days; 11.9%). Statistical analyses were not performed for this comparison. The majority of patients (70%) had visited a dermatologist about their psoriasis during the year prior to the study visit; 30.2% of these patients made 1–2 visits/year, 30.2% made 3–4 visits/year, and 39.7% made more than 4 visits/year. Significant differences in the number of visits to a dermatologist (but not number of days of hospitalization) were found when

the results were stratified by PASI score (<10, 10–<20 and ≥ 20) or BSA involvement (<10%, 10–<20% and $\geq 20\%$), with the number of visits increasing with increasing PASI score or BSA involvement ($p < 0.001$ for both comparisons; fig. 3a, b). Twenty percent of patients used private healthcare and the remaining patients used public healthcare services. In total, 12.5% of patients had required an emergency visit during the 12 months prior to the study visit, with a mean number of 1.7 visits (95% CI: 1.5–1.8). A total of 217 patients (6.5%) required hospitalization during this time period and the mean time spent in hospital for these patients was 13 days.

Direct Cost of Treatment

The majority of patients (89.4%) reported that the monthly cost of psoriasis treatment was an important financial consideration. The mean cost paid by patients for treatment was 68 EUR/month. In some patients, the

Fig. 1. Comparison of disease severity by age and sex and stratified by BSA involvement (a) and PASI score (b); p values were calculated using χ^2 tests.

monthly cost was as high as 1,000 EUR. Significant differences in the cost of treatment were found when cost was stratified by PASI score, with the cost increasing with increasing PASI score ($p < 0.001$). Patients with PASI scores less than 9.9 had a mean monthly expense of 58.8 EUR, compared with 66.2 EUR in patients with PASI scores of 10–19.9, and 87.4 EUR for patients with PASI scores of ≥ 20 . We also noted that there were differences in cost for psoriasis that involved the face and scalp compared with other areas of involvement.

Quality of Life: Health State Utilities

Using the time trade-off method, 37% of patients indicated that they were willing to sacrifice at least 1 month of their remaining life to be free from psoriasis lesions. The mean amount of remaining life that patients were willing to sacrifice was 25 months (95% CI: 23.4–26.8). Using the willingness to pay method, 66% of patients in-

dicated that they were willing to pay to be free from psoriasis lesions. The mean proportion of monthly income that these patients were willing to pay was 29% (95% CI: 28.1–30.1). Significant differences in the amount of remaining life or proportion of income that patients were willing to sacrifice to be free of psoriasis lesions were found when the results were stratified by PASI score (<10 , $10-<20$ and ≥ 20) or BSA involvement ($<10\%$, $10-<20\%$ and $\geq 20\%$), with the amount of time or income increasing with increasing PASI score or BSA involvement ($p < 0.001$ for both comparisons; fig. 3c, d).

The mean total PDI score was 8.8 (out of a maximum of 40 points, representing a percentage score of 19.9%); a higher score indicates a worse impact on QoL. Detailed results by PDI domain (daily activity, work or academic activities, personal relationships, free time and treatment) have been published elsewhere [14].

Factors Affecting Severity of Psoriasis

The coefficient of determination indicated that 78% ($R^2 = 0.78$) of the total variation in PASI score was accounted for by variation in the independent variables (table 3). Similarly, variation in the independent variables accounted for 75% of the total variation in BSA involvement. Significant correlations were found between PASI score and number of cigarettes smoked ($p < 0.001$), OLS scale score ≥ 2 for the head, trunk, arm and leg regions ($p < 0.001$), BSA involvement ($p < 0.001$), pruritus ($p < 0.05$), number of days of sick leave in the previous year ($p < 0.05$), cost of treatment ($p < 0.001$) and PDI score ($p < 0.001$). Significant correlations were also found between BSA involvement and a number of independent variables (table 3).

Discussion

To the authors' knowledge, this is the largest study of the epidemiology of moderate-to-severe psoriasis. It is the first to also assess the burden of moderate-to-severe psoriasis on the healthcare system and the wider economy in Spain and Portugal, the types of treatment that patients receive in routine clinical practice and the cost of that treatment to the patients. Other outcome measures highlight the negative impact that psoriasis can have on patient QoL and the amount of income or remaining life that patients are willing to sacrifice to be disease-free.

Our study demonstrates that in the majority of cases (79–99%) the subjective diagnosis of moderate-to-severe psoriasis made by dermatologists in routine clinical practice is appropriate, as confirmed by objective criteria proposed in the literature [10]. This was important to

Fig. 2. Comparisons of age of onset of psoriasis with respect to family history of psoriasis.

establish because morbidity, treatment options and healthcare cost are related to the severity of the disease [15–17]. However, it was noticeable that approximately one quarter of the patients in this study were receiving topical treatment only for their moderate-to-severe psoriasis, and roughly one third of patients had received neither systemic treatment nor phototherapy. Given that the mean BSA involvement of psoriasis was 23%, it seems likely that a more aggressive treatment would have been appropriate in many of these patients [18]. Indeed, the results of our multivariate analysis showed that there were statistically significant positive correlations between systemic therapy or phototherapy received in the 2 years prior to the study visit and BSA involvement. Correlations were not significant for topical therapy or biological therapy. It is possible, however, that the patients who did not receive systemic treatment or phototherapy had concerns about the potential side effects of systemic treatments or phototherapy. These concerns and dermatologists' treatment preferences (including rotational treatment strate-

Table 2. Treatment received by patients in the 24 months prior to the study visit

Treatment	Number of patients
Topical	3,221 (97.0)
Phototherapy	1,427 (43.0)
PUVA	575 (17.3)
Heliotherapy	557 (16.7)
UVB	344 (10.4)
UVA	173 (5.2)
Systemic	1,615 (48.6)
Retinoids	849 (25.5)
Cyclosporine	599 (18.0)
Methotrexate	513 (15.4)
Biological	105 (3.2)
Monotherapy	922 (27.7)
Combination therapy	
Topical + systemic	1,593 (48.0)
Systemic + phototherapy	762 (23.0)

PUVA = Psoralen and ultraviolet A light; UVB = ultraviolet B light; UVA = ultraviolet A light. Figures in parentheses are percentages.

Table 3. Outcomes of the multivariate analysis on predictable variables of clinical measurements of severity of psoriasis

Independent variables	Dependent variables	
	PASI (R ² = 0.78)	BSA (R ² = 0.75)
Female sex	–0.287	–0.69*
Personal history	–0.200	0.865**
Family history	–0.006	–0.130
Topical therapy in the previous 24 months	–0.293	–0.215
Phototherapy in the previous 24 months	–0.028	0.621*
Systemic therapy in the previous 24 months	–0.218	1.153**
Biological therapy in the previous 24 months	0.248	0.708
Presence of arthropathy	–0.058	0.193
Cost of treatment to the patient	0.001**	0.000
Visits to a dermatologist in the previous year	–0.006	0.065*
Number of days of hospitalization in the previous year	0.017	0.101**
Number of emergency visits in the previous year	–0.050	0.493*
Months of remaining life that patients will sacrifice to be free from psoriasis lesions	0.001	0.005
Percentage of income that patients will sacrifice to be free from psoriasis lesions	0.005	–0.003
PDI	0.042**	0.035
BSA involvement or PASI score	0.409**	1.636**
OLS scale score ≥2 for the head	1.254**	–0.899**
OLS scale score ≥2 for the trunk	1.387**	1.078*
OLS scale score ≥2 for the arms	2.387**	–3.683**
OLS scale score ≥2 for the legs	2.862**	–2.644**
Pruritus	0.065*	0.047
Number of days of sick leave in the previous year	0.005*	–0.007
Number of cigarettes	0.045**	0.087**

* p < 0.05; ** p < 0.001.

Fig. 3. Comparisons of the mean annual number of visits to a dermatologist and number of days of hospitalization (**a, b**), and mean scores on the time trade-off and willingness to pay health state utility measures (**c, d**), when stratified by psoriasis BSA involvement or PASI.

*During the 12 months prior to the study visit.

[†]Months of remaining life patients would be willing to offer to be permanently free from psoriasis lesions, determined using the Time Trade-off method.

[‡]Amount of money patients would be willing to pay, as a percentage of their income, to be permanently free from psoriasis lesions, determined using the Willingness to Pay method.

gies) may account for the large variability in the treatments that patients were receiving [19, 20]. The virtual absence of biological therapies in our study (3.1% of patients) may be a reflection of the low awareness of these relatively new treatment options. However, it is worth noting that topical, systemic, phototherapy and biological therapies each play a role in the management of psoriasis, depending on the circumstances of each patient [18].

The mean age at onset of psoriasis in our study (28 years) was within the range reported previously in the literature (23–37 years) [21, 22] and similar to that reported by another epidemiology study conducted in Spain (29 years) [3]. Also in common with other epidemiology studies, a higher proportion of men had psoriasis and developed the condition later in life than women [3, 21, 23–25]. We also found significant differences in the severity of psoriasis between men and women, by age of onset (≤ 30 years or >30 years) and by family history of psoriasis. The severity of psoriasis, both in terms of BSA involvement and PASI score, was significantly greater in men than women. Psoriasis was also severer in patients aged 30 years or less than in patients who were older than 30 years. Again, these findings are confirmed by the results of other studies [3].

Genetic inheritance has been implicated as a risk factor for psoriasis in numerous studies [26–29]. The epidemiological evidence from our study supports a genetic element in the etiology of the disease – half the patients reported psoriasis in other members of their family, the majority (73.3%) of which were first-degree relatives. Another interesting finding was that patients who had a family history of psoriasis were significantly more likely to develop psoriasis early (before the age of 30 years) than later (>30 years), whereas patients with no family history of psoriasis were significantly more likely to develop psoriasis after the age of 30 years. In other studies that assessed the familial aggregation of psoriasis, the proportion of patients with a positive family history varied between 20 and 37% [3, 22, 30, 31]. It is probable that the higher prevalence of a family history of psoriasis in our study (49.6%) can be accounted for by the fact that patients with mild psoriasis were excluded, rather than geographical differences; another Spanish psoriasis study reported a family history of psoriasis in 28% of patients [3]. This and other studies also found that the frequency of a family history of psoriasis was inversely related to the age at onset of psoriasis [3, 24, 32–34]. The prognosis for patients with an early onset of psoriasis, generally those with a family history, is poor. These patients have an irregular disease course, which shows a strong tendency to

become generalized and severe [3, 35]. These findings, as well as the strong association of early-onset psoriasis with HLA-Cw6 [35–37], has led some investigators to postulate that there are in fact two separate types of psoriasis [32]. The results of our study would certainly lend indirect support to this idea. OLS scale score, PASI score and BSA involvement were all significantly different between the two age groups that were assessed (patients ≤ 30 years and those >30 years), with greater disease severity and more generalized psoriasis in patients with an earlier onset of disease.

A great deal of attention has been focussed on the influence of tobacco and alcohol on psoriasis. Numerous studies indicate that the risk of psoriasis is increased with alcohol or tobacco consumption [31, 38–45]. However, the magnitude of risk is difficult to define due to differences in study design and population, and conflicting results. Our study design does not allow us to establish causal relationships, but the multivariate analysis demonstrated a statistically significant positive correlation between the daily number of cigarettes smoked and both PASI score and BSA involvement. Interestingly, our study identified stress and changes in the weather as key triggering factors of recurrence or worsening of psoriasis. Other studies have also found a relationship between stress and exacerbation of psoriasis [33, 46, 47], as well as severity of psoriasis [48], but we are unaware of other investigators reporting changes in weather as a key trigger.

Itching is a common complaint among patients with psoriasis that affects QoL and activities of daily living [49]. However, this aspect of the disease has received little attention. Indeed, although attenuation of pruritus is often assessed in clinical trials of interventions for psoriasis, leading textbooks only give this symptom of psoriasis a brief mention [50, 51]. Studies indicate that pruritus occurs in the majority of patients with psoriasis (64–84%) [49, 52, 53]. A study by Yosipovitch et al. [49] quantitatively evaluated the severity of pruritus on the VAS in patients with extensive psoriasis ($>30\%$ BSA involvement) and found that mean scores ranged between 0.4 and 7.2, depending on the patients' recollection of the pruritus when it was at its 'best' and 'worst', respectively. At the time of the assessment, the mean VAS score was 1.3 (standard deviation: 2.0). In our study, patients reported that they had severer pruritus at the time of assessment, as indicated by the mean VAS score (4.72; 95% CI: 4.6–4.8). This higher score cannot be accounted for by differences in severity of disease between the two studies, but both studies highlight the relevance of this symptom

of psoriasis. Furthermore, our study shows that the severity of pruritus increases with both increasing BSA involvement and increasing disease severity on the PASI, and that it has a statistically significant positive correlation with PASI score.

PsA is a chronic inflammatory arthropathy of the peripheral joints and axial skeleton, which is estimated to occur in 1–3% of the general population but in 7–42% of patients with psoriasis [54]. However, estimates of prevalence are complicated, partly due to the lack of consensus on how best to define PsA, and partly due to misdiagnosis [55]. The proportion of patients in our study who had confirmed PsA was low at only 12.8%. An additional 7.6% had unconfirmed PsA, giving an upper prevalence estimate of 20.4% of patients within the recent study. Both values lie within the range of published estimates. The clinical evidence suggests that inflammation of the skin and the joint in PsA are independent [56]. The timing of PsA in patients with psoriasis varies, with 60% of patients developing PsA after psoriasis has become established, simultaneous development in 20% of patients, and development of PsA before psoriasis in 20% of patients [57]. In the present study, 95% of patients with coexisting PsA developed arthropathy after psoriatic skin lesions. The implication of this finding is that dermatologists need to play an active role in recognizing the signs and symptoms of PsA to facilitate prompt referral to a rheumatologist.

The key QoL measure used in our study, the PDI, has been used effectively in psoriasis for over 20 years [12], is sensitive to changes in the extent of lesions [58], and changes in PDI score are significantly correlated with changes in willingness to pay and time trade-off [59, 60], the other two QoL measures employed in our study.

In agreement with PDI scores, the number of months of life and the proportion of income that patients were willing to sacrifice to be disease-free increased with increasing disease severity on the PASI. Other studies have produced similar findings, although there is a scarcity of information on these health state utility measures in psoriasis. A study by Schiffner et al. [59] demonstrated a significant drop in the number of hours per day that patients are willing to sacrifice between patients who had received synchronous balneophototherapy (mean PASI score: 5.6) and those who were yet to receive this treatment (mean PASI score: 14.9). Patients were willing to sacrifice 2.7 h/day before treatment compared with 2.3 h after treatment ($p < 0.001$). Patients were willing to pay between 12 and 22% of their monthly income to be free from psoriasis. A Swedish study conducted in 1997 found that patients with psoriasis (any severity) were willing to pay approxi-

mately 140–220 EUR for a psoriasis cure [5], which represented roughly 9–14% of their average personal income. The higher proportion of income that patients in our study were willing to pay (29%) is possibly a reflection of greater disease severity.

Patients' subjective assessment of their willingness to pay to be disease-free was mirrored by their actual willingness to pay for treatment – the median annual cost of treatment to patients was 825 EUR. We believe that one of the primary contributions of this study is to establish a relationship between severity of psoriasis and the amount of money patients pay for treatment. There were significant differences in the monthly amounts paid for treatment by patients with different PASI scores, with the amount being lowest in patients with PASI scores lower than 9.9 (59 EUR) and highest in those with PASI scores over 20 (87 EUR). In an Italian study conducted in 1994 [47], the mean cost of annual treatment, which was paid for, or reimbursed by, the National Health Service, was similar (905 EUR) to that in our study. The majority (80%) of this cost was accounted for by hospitalization. In the USA, the annual cost of treatment appears to be less than half that in Spain, Portugal or Italy (roughly 350 EUR) [61, 62]. However, only 3% of patients in this American study had severe psoriasis. As would be expected, nearly 90% of patients in our study reported that the cost of treating their psoriasis was an important financial consideration. The indirect cost of psoriasis was also quite considerable, with 13% of patients having at least 1 day off work per year due to psoriasis. In the small sample of patients ($n = 24$), in which we assessed the number of sick days taken annually, the mean amount of working time lost was nearly 2 months. The burden of psoriasis on the healthcare system was also high. One eighth of patients required an emergency visit (6.5% requiring hospitalization), and the majority of patients (70%) visited a dermatologist at least once.

It should be noted that as the number and characteristics of patients who declined to participate were not reported, it was not possible to accurately assess any influence that their inclusion would have had on the study findings. However, the large number of patients who were recruited, through over 300 dermatologists in study centers across Spain and Portugal, is likely to have minimized this potential limitation. Furthermore, the similarity of the demographics and disease characteristics of this patient population to those of other studies indicates that this population is largely representative of the general psoriasis population.

The results of this large study demonstrate that psoriasis not only places a considerable direct financial pressure on the individual, but it also places a considerable burden on a country's healthcare system. We did not, however, intend to produce a detailed pharmacoeconomic analysis of the treatment of psoriasis. Instead, our study will hopefully highlight some useful avenues for future research and underline some important considerations for practicing dermatologists. In particular, our results indicate that moderate-to-severe psoriasis is accurately diagnosed, but inadequately treated in many patients, who might benefit from more aggressive, systemic therapies. The results are also consistent with those of numerous other studies. Most notably, we can confirm that the risk of psoriasis is increased if patients have a family history, and psoriasis can be broadly categorized into early- and late-onset types based on the characteristics of the disease.

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Appendix

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