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Disease activity and widespread pain are main contributors to patient-reported global health in axial spondyloarthritis: an analysis of 6064 patients

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Abstract

Global health (GH) and health-related quality of life are patient priorities in axial spondyloarthritis (axSpA). Our objective was to assess the relative importance of disease-related factors including disease activity, and patient-related factors including comorbidities, to explain GH in axSpA. Post hoc cross-sectional analyses of 4 sets (COMOSPA, PERSPA, COMEDSPA, and DESIR) of patients fulfilling ASAS criteria for axSpA. GH was assessed through the ASAS Health Index (ASAS-HI) or the EuroQoL-5D-3L (EQ-5D). Disease-related factors included disease activity (ASDAS, psoriasis, arthritis, enthesitis, and CRP), disease duration, diagnostic delay, bamboo spine, and treatment. Non-disease-related factors included sociodemographic characteristics, comorbidities and chronic widespread pain. Multivariable logistic and linear regressions and partial variances (R^2) were applied to identify independent determinants of GH. In 6064 patients (range 284–2756 across datasets), mean age ranged 38.9–45.8 years, 51–68% were male. GH was generally moderate: median ASAS-HI ranged 5.0–7.0. GH was explained by ASDAS (range of odds ratios, OR, 2.60–4.48) and chronic widespread pain (range of OR 2.19–8.39); other determinants included comorbidities and sociodemographic characteristics. Only 47–57% of the total variance in GH could be explained by the models; disease activity (partial variance, 16–26%) and chronic widespread pain (partial variance 12–15%) were the key contributing variables. A wide range of disease and non-disease-related variables usually collected in studies could only explain 47–57% of the variability in GH. Among these, disease activity and chronic widespread pain were most relevant and of similar magnitude of importance. These findings will be helpful for shared decision-making.

Keywords Axial spondyloarthritis · Patient reported outcome measures · Inflammation · Fibromyalgia

Introduction

Axial spondyloarthritis (axSpA) negatively impacts patients' functioning and global health (GH) [1]. GH is a priority for patients in chronic diseases, and the goal of axSpA management is to improve long-term GH through control of disease activity and improvement of physical function [2]. However, GH is multifactorial. Factors contributing to GH include both disease-related factors such as disease activity or disease duration, and non-disease-related factors such as comorbidities or sociodemographic factors [3–5].

Several studies and a systematic literature review have confirmed a link between disease activity and health-related quality of life (HRQoL) [6–8]. It is however difficult to define the exact proportion of GH explained by inflammation as the magnitude of the association varies according to the elements integrated into the concept 'inflammation' (e.g., patient-reported outcomes (PROs) such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); composite scores: the Axial Spondyloarthritis Disease Activity Score (ASDAS); CRP or Magnetic Resonance Imaging (MRI)), statistical methods used and the population analyzed. Other disease-related factors are also related to GH: extra-spinal manifestations e.g., peripheral arthritis,

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enthesitis or dactylitis, influence GH [9]; a worsened GH has been described in people experiencing longer diagnostic delay and shorter disease duration [7, 10]. AxSpA structural damage may alter GH; global kyphosis is significantly associated with functional status, spinal mobility and GH in axSpA patients [11]**.** Finally, axSpA is frequently associated to extra-musculoskeletal manifestations (EMMs), uveitis, inflammatory bowel disease (IBD) and/or psoriasis, which may also influence GH [12].

Non-disease-related factors also play a role in GH [13]. Comorbidities are frequent in axSpA, including cardiovascular events, cardio-metabolic diseases, malignancy, osteoporosis with vertebral fractures, and add to the burden of disease [14]. Anxiety, depression, psychological distress, and chronic widespread pain have a considerable impact on GH [15]. The co-occurrence of chronic widespread pain and axSpA is frequent, with a prevalence between 13 and 25% and there is an association between chronic widespread pain and GH, as well as mood disorders, and fatigue [16, 17]. Sociodemographic characteristics including sex and age, lower educational level, work issues, and lifestyle (smoking, exercise patterns) may also be associated with worse GH [18, 19].

Previous studies have tried to distinguish the role of these factors on HRQoL, yet without evaluating the relative contribution of each factor [4, 13, 20, 21]. It is important to gain a comprehensive understanding of factors contributing to GH, as it would help the clinician in the long-term management of patients, in improving specifically each of these factors. Indeed, the clinician could increase treatment (e.g., with biological Disease Modifying Antirheumatic Drugs, bDMARDs) if disease activity is uncontrolled, or manage comorbidities and/or EMMs, together with the dermatologist or gastroenterologist [14]. Moreover, knowing more about the impact of chronic widespread pain on GH in axSpA could encourage clinicians to manage better this comorbidity with specific treatments, in a multidimensional approach.

Thus, the objective of the present analysis was to assess factors associated with impaired GH in axSpA by defining the relative importance of disease-related and non-disease-related factors. To this end, we analyzed in 4 datasets the variance of GH explained by groups of variables. The hypothesis was that non-disease-related factors would be as important as disease-related factors.

Patients and methods

A post hoc cross-sectional analysis of 4 datasets (2 cross-sectional studies, one randomized trial and one ongoing cohort) was performed, without pooling the datasets, i.e., four separate analyses. The study followed the STROBE guidelines, ensuring transparent methodology and accurate data analysis (Supplementary Table 1).

Patients: This analysis used data from 4 sources, to cover the spectrum of axSpA [14, 22–24]. The COMOSPA cohort was a cross-sectional study of 3984 patients from 22 countries between 2013 and 2014, with the objective to assess comorbidities in spondyloarthritis [14]. PERSPA was a cross-sectional study of 4465 patients from 24 countries between 2018 and 2020, with the objective of assessing peripheral manifestations [24]. COMEDSPA was a multicenter, randomized controlled trial to assess comorbidities and patient education, in 502 patients, in 2015 (only data at baseline were used) (NCT02374749) [23]. The DESIR cohort is an ongoing prospective observational cohort, of 708 patients with recent axSpA in 25 centers in France, recruited in 2007–2009 (only data at 7 years were used, first year with Assessment of Spondyloarthritis international Society-Health Index (ASAS-HI) available) (NCT01648907) [22]. For all datasets, we selected patients fulfilling the ASAS classification criteria for axSpA with current back pain, and with complete data for ASAS-HI or EQ-5D, and we excluded duplicates (patients participating in several of these studies, Supplementary Box 1). Ethical approvals were obtained according to local regulations and all patients gave their informed consent in the 4 studies [14, 22–24].

Data collection: main outcome (GH)

To approach the concept of GH, two scores were assessed: the main outcome was the ASAS-Health Index (ASAS-HI), part of the core outcome set of axSpA, and if not available (i.e., in one study, COMOSPA), we used the EuroQoL-5D-3L (EQ-5D), a generic tool measuring utility. [25, 26]. The ASAS-HI is a specific patient-reported measure of GH and global functioning with 17 items (dichotomous response option: "I agree" and "I do not agree") which cover relevant domains of the ASAS/International Classification of Functioning, Disability and Health (ICF) core set for ankylosing spondylitis [27, 28]. Cut-offs have been validated to define good GH and normal functioning (≤ 5) or severe impairment (≥ 12) [25]. The EQ-5D is a generic composite measure with 5 items which evaluates utility on five dimensions of GH: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [26]. In this analysis, we used the 3-level version for EQ-5D. The score assigns a single index value on the health utility scale, where 1 is full health and 0 or negative values are a state equivalent to being dead or worse than death, based on preferences of the general population (here the index values were based on the Netherlands) [26].

Data collection: patients and disease characteristics

Data were classified into disease-related factors and patient-related factors.

Disease-related factors were assessed by: (a) disease activity measured by ASDAS, BASDAI, BASFI, patient global assessment (PaGA), physician global assessment (PhGA), axial pain (Supplementary Table 2) [2]. (b) objective inflammatory markers were collected, including last available CRP and sacroiliitis on MRI at any time. (c) diagnostic delay, symptom duration, disease duration, and presence of HLA B27 allele were also collected. (d) structural damage was assessed by bamboo spine (according to the local investigator) or sacroiliitis on X-ray at any time, and abnormal occiput-to-wall distance [29]. (e) extra-spinal manifestations included current arthritis, current enthesitis, and past or present dactylitis. (f) EMMs included current psoriasis, and uveitis or IBD at any time since disease onset [30]. (g) current non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and DMARD treatment intake were also collected.

Non-disease-related factors were assessed by (a) sociodemographic factors: sex, age, body mass index (BMI), marital status, educational level, smoking status, and current employment status. (b) comorbidities were assessed by the Rheumatic Disease Comorbidity Index (RDCI), a composite score that reflects the burden of comorbidities on functioning and mortality, specifically created for use in patients with rheumatic diseases—this instrument has been validated using a sample of patient data from self-reported questionnaires in different rheumatic disease, and has been used in axSpA [31, 32]. (c) anxiety or depression were approximated from different scores (Supplementary Table 2). (d) chronic widespread pain was also approached through the Fibromyalgia Rapid Screening Tool (FIRST) questionnaire when available, or through extreme values of PROs as a proxy (Supplementary Table 2) [33].

Statistical analysis

The analyses were performed separately in the 4 datasets to avoid complex data pooling, and to assess the robustness of the results in different populations.

For quantitative data, descriptive statistics with mean, standard deviation (SD), medians, and quartiles were applied. Distributions of EQ-5D and ASAS-HI were visually compared, and normality was assessed by Shapiro–Wilk test.

GH was analyzed in two ways: as a continuum (linear), or by dichotomizing the GH scores (logistic). The logistic model provides easy-to-interpret results to identify patients with impaired GH; the linear model provides more accurate results on variations of the overall GH score and was used for partial variance. To binarize GH, we defined a threshold for impaired GH: for ASAS-HI according to its distribution (visually and by quartiles), the threshold of 10 was chosen. Of note, the threshold of 12 has been published for severe impairment of GH; the threshold of 10 was used here for impairment of GH [25]; In one dataset (COMOSPA), where ASAS-HI was not available, we defined a threshold for EQ-5D. To this end, in PERSPA, where both outcomes were available, a ROC curve of EQ-5D corresponding to an ASAS-HI ≥ 10 was computed and the Youden index for EQ-5D was determined. This threshold of EQ-5D (derived from PERSPA) was used to define impaired GH in COMOSPA [34].

Bivariable and multivariable logistic and linear analyses of factors associated to GH were performed in each dataset, using non-parametric tests (Wilcoxon rank-sum test; Spearman test; Fisher's exact test). Supplementary Table 3 shows all other variables tested. Variables were included in the multivariable model according to clinical relevance, inter-variable correlation (variables were excluded if $r > 0.6$) and significant association with GH in bivariable analyses (Supplementary Table 4). The complete model included disease-related factors with (a) disease activity: ASDAS, CRP, current psoriasis, current arthritis, current enthesitis; (b) other disease-related factors: disease duration, diagnostic delay, structural damage (bamboo spine), and b/tsDMARD use; and non-disease-related factors with (a) sociodemographic data (sex, age, employment status and educational level), (b) comorbidities (RDCI, obesity and depression) and (c) the construct of chronic widespread pain. (FIRST questionnaire / extreme PRO, Supplementary Table 2).

According to the main objective, the principal analysis was the partial variance of GH explained by each group of variables (disease-related or non-disease-related), using the partial R-squared method (R^2) in each dataset. Because the total explained variance was less than 100%, and the sum of partial R^2 was higher than the total explained variance, we computed an adjusted (relative) variance, calculated by the formula: [Partial R^2] *[Total explained variance] / [Sum of partial R^2 of all groups of variables] (Supplementary Table 5).

Sensitivity analyses were performed with different variables in the model: without disease duration, without CRP, with any EMM (current psoriasis or uveitis or IBD) instead of current psoriasis, and without obesity. We also conducted sensitivity analyses consisting of (1) subgroup analyses for women, for patients receiving b/tsDMARDs in COMOSPA and PERSPA, (2) logistic regression in PERSPA using the validated threshold ≥ 12 for ASAS-HI to define severe impairment of GH [25].

p values less than 0.05 were considered statistically significant; we did not adjust for multiple analyses. There was

no imputation of missing data. All analyses were carried out using R.4.1 statistical software.

Results

Population

In all, the 4 datasets comprised 9501 patients (3984 patients in COMOSPA, 4465 patients in PERSPA, 501 patients at baseline in COMEDSPA, and 551 patients in DESIR at 7 years). Among them, 6205 fulfilled ASAS criteria for axSpA, of whom 6068 had complete data for EQ-5D or ASAS-HI. Four patients were excluded as potential duplicates; finally, 6064 patients were analyzed (Fig. 1).

Description of the populations

Among the 6064 axSpA patients, 4009 were male (66.1%), with different sex ratios in each dataset: 51.1% men in DESIR compared to 63.0–67.7% in the 3 other datasets; mean age varied between 38.9 years in DESIR and 45.8 years in COMEDSPA (Table 1 and Supplementary Table 6).

Regarding disease-related factors, mean disease duration varied between 7.7 and 14.5 years; diagnostic delay was shorter in the inception cohort DESIR (1.2 year) than in COMOSPA and PERSPA (6.8 and 6.5 years, respectively, Supplementary Table 6). Overall, 2.2–17.7% patients had current arthritis. Regarding EMMs, 1588 (26.2%) patients ever suffered from uveitis or IBD or had current psoriasis. Disease activity was generally moderate, with however 42.0–66.1% patients in high disease activity according to ASDAS. Conventional, biological or targeted synthetic (cs/b/ts) DMARDs were currently taken by 3663 (60.4%) patients, with a higher proportion of csDMARDs in both international datasets (26.9% to 29.9% in PERPSA and COMOSPA versus 6.9% to 18.5% in the French datasets). Conversely, 2364 (39.0%) patients were currently receiving a TNF-inhibitor, with higher proportion in COMEDSPA (78.0% compared to 32.7–40.2% in the 3 other datasets).

Concerning non-disease-related factors, patients had higher levels of education in DESIR; obesity was present in 1106 (18.2%) patients, and more frequent in PERSPA and COMOSPA. The chronic widespread pain construct was screened positively in 14.2% to 24.2% patients, and the depression construct was present in 6.9% to 20.3% patients. Other comorbidities were not frequent (Table 1 and Supplementary Table 6).

Description of GH and choice of thresholds for impaired GH

GH had similar (and non-normal) distributions in each dataset. Median ASAS-HI ranged from 5.0 to 7.0 in DESIR and PERSPA respectively and the threshold value ≥ 10 was chosen to define impaired GH (Fig. 2). EQ-5D was available in 2 datasets (PERSPA and COMOSPA) (Fig. 2). The ROC

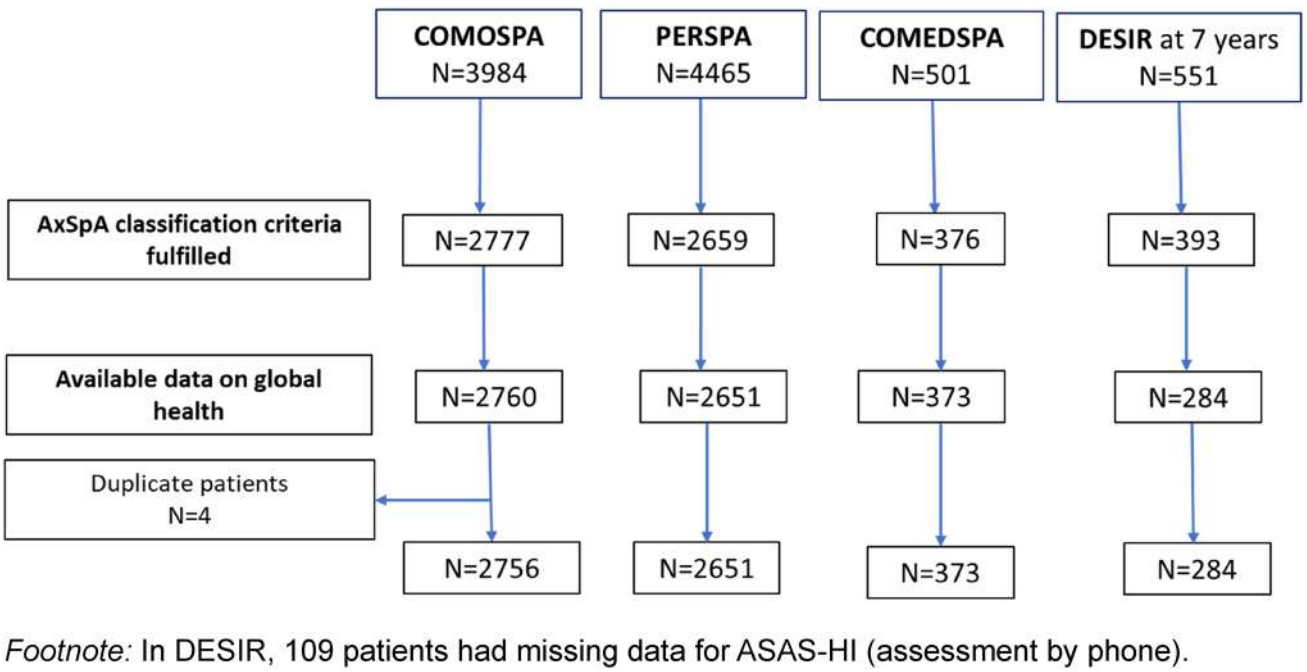


Fig. 1 Selection of 6064 axSpA patients from 4 datasets

Table 1 Description of the population in each dataset

	COMOSPA	PERSPA	COMEDSPA	DESIR
N patients	2756	2651	373	284
Socio-demographic characteristics				
Male sex, *N* (%)	1866 (67.7)	1763 (66.5)	235 (63.0)	145 (51.1)
Age, years, mean (SD), [median] {Q1, Q3}	41.6 (13.2), [40.3] {31.3, 50.4}	42.0 (12.8), [41.0] {32.3, 50.5}	45.8 (11.8), [45.0] {38.0, 53.0}	38.9 (7.4), [38.4] {32.8, 44.3}
Smoking, *N* (%)	681 (24.7)	586 (22.1)	125 (33.5)	91 (33.2)
Educational level (University vs Primary or Secondary), *N* (%)	1170 (42.5)	1100 (41.5)	179 (48.0)	191 (67.5)
Currently employed, *N* (%)	1654 (60.0)	1583 (59.8)	249 (66.9)	241 (85.2)
Diagnostic characteristics				
Disease duration (years), mean (SD), [median] {Q1, Q3}	8.5 (9.6), [5.1] {1.3, 12.2}	8.7 (9.2), [5.7] {2.0, 11.9}	14.5 (11.4), [11.0] {5.4, 22.5}	7.7 (1.9), [7.4] {7.1, 27.5}
Presence of HLA B27, *N* (%)	1835 (78.2)*	1581 (76.9)*	290 (81.9)	224 (78.9)
Presence of extra-spinal symptoms				
Current arthritis, *N* (%)	488 (17.7)	388 (14.7)	118 (32.8)[1]	6 (2.2)
Current enthesitis, *N* (%)	387 (14.0)	1007 (38.0)	178 (48.6)[2]	118 (44.0)
Disease activity				
ASDAS, mean (SD), [median] {Q1, Q3}	2.02 (1.08), [1.93] {1.15, 2.78}	2.70 (1.10), [2.62] {1.83, 3.43}	2.00 (0.81), [1.94] {1.39, 2.54}	2.00 (0.93), [1.86] {1.21, 2.68}
ASDAS ≥ 2.1, *N* (%)	1168 (44.8)	1735 (66.1)	164 (44.4)	111 (42.0)
BASDAI (0–100), mean (SD), [median] {Q1, Q3}	37.70 (24.05), [35.00] {18.00, 55.00}	41.17 (23.11), [38.00] {22.00, 59.50}	33.20 (18.05), [30.00] {19.00, 46.00}	31.12 (20.28), [28.50] {14, 45.25}
BASFI (0–100), mean (SD), [median] {Q1, Q3}	31.56 (27.06), [25.00] {8.00, 52.00}	33.31 (26.51), [28.00] {10.00, 53.00}	26.88 (21.69), [24.00] {9.00, 41.00}	20.93 (20.35), [14] {4.00, 33.00}
Axial pain (0–10), mean (SD),[median] {Q1, Q3}	4.51 (2.91), [4.00] {2.00, 7.00}	5.05 (2.71), [5.00] {3.00, 7.00}	3.93 (2.24), [3.00] {2.00, 6.00}	3.60 (2.62), [3.00] {1.00, 6.00}
Abnormal CRP (≥ 5 mg/L), *N* (%)[3]	625 (23.7)	1374 (52.1)	121 (32.5)	74 (28.0)
EMM				
Current psoriasis, *N* (%)	300 (10.9)	289 (10.9)	36 (10.1)	28 (10.4)
Any EMM (with current psoriasis), *N* (%)	516 (19.7)	840 (32.0)	146 (41.4)	86 (32.6)
Structural damage				
Radiological sacro-iliitis, *N* (%)	2145 (80.2)	2022 (77.8)	245 (70.4)	111 (42.4)
Comorbidities				
Obesity (BMI ≥ 30 kg/m^2), *N* (%)	502 (18.4)	508 (19.2)	60 (16.1)	36 (13.0)
RDCI (0–9), mean (SD), [median] {Q1, Q3}[4]	0.63 (0.98), [0.00] {0.00, 1.00}	NA	0.76 (0.98), [0.00] {0.00, 1.00}	0.51 (0.79), [0.00] {0.00, 1.00}
Presence of depression construct, *N* (%)[5]	360 (13.1)	184 (6.9)	39 (10.9)	57 (20.3)
Presence of widespread pain construct, *N* (%)[6]	391 (14.2)	480 (19.9)	90 (24.2)	43 (15.4)
Treatments				
NSAIDs, *N* (%)	1890 (68.6)	1933 (72.9)	153 (41.0)	135 (47.5)
csDMARDs, *N* (%)	825 (29.9)	712 (26.9)	69 (18.5)	19 (6.9)

Table 1 (continued)

	COMOSPA	PERSPA	COMEDSPA	DESIR
b/tsDMARDs, *N* (%)	904 (32.8)	1237 (46.7)	294 (78.8)	106 (39.3)
GH assessment				
ASAS-HI (0–17), mean (SD), [median] {Q1, Q3}	NA	7.1 (4.5), [7.0] {3.2, 10.2}	6.7 (3.7), [6.0] {4.0, 9.1}	5.4 (3.8), [5.0] {2.0, 8.0}
EQ-5D (0–1), mean (SD), [median] {Q1, Q3}	0.58 (0.34), [0.64] {0.28, 0.89}	0.63 (0.23), [0.65] {0.49, 0.79}	NA	NA

Data were "current" unless otherwise indicated

[1]Past or current arthritis (data on current arthritis were not available)

[2]Past or current heel enthesitis (data on current enthesitis were not available)

[3]Last available CRP

[4]Rheumatic Disease Comorbidity Index, calculated using the formula: 2 × lung disease + [2 × (heart attack, other CV or stroke) or 1 × hypertension] + fracture + depression + diabetes + cancer + (ulcer or stomach problem)

[5]Considered present if: SF36-MCS ≤ 38 in DESIR, using EQ5D question 5 PERSPA: "I am extremely anxious or depressed", or using the self-administered comorbidity questionnaire in COMEDSPA and COMOSPA

[6]Widespread pain was construct by either FIRST questionnaire (considered positive when FIRST ≥ 5/6) in DESIR, COMOSPA and PERSPA, or by a surrogate marker in COMEDSPA, defined by a score ≥ 8/10 on at least three of first five BASDAI items [33]

EMM extra-musculoskeletal manifestations, *NSAIDs* non-steroidal anti-inflammatory drugs

*Missing data were 10% or above in:

COMOSPA: HLA B27 (*N* = 410, 14.9%)

PERSPA: HLA B27 (*N* = 594, 22.4%)

curve of EQ-5D according to ASAS-HI category showed a satisfactory link between the 2 scores: area under the curve was 0.86. The threshold of 0.597 for EQ-5D maximized both sensitivity (0.82) and specificity (0.76) against the ASAS-HI cut-off of 10 (Supplementary Fig. 1). Thus, impaired GH was defined by ASAS-HI ≥ 10, or EQ-5D < 0.597 in COMOSPA. In all, 47.0%, 29.1%, 23.1%, and 16.5% patients had impaired GH in COMOSPA, PERSPA, COMEDSPA, and DESIR respectively, according to our binomial definition.

Factors associated to GH

In the bivariate analyses of each dataset separately (Table 2), variables associated to impaired GH were female sex, older age, lower educational level, unemployment, shorter disease duration, longer diagnostic delay, absence of B27 allele, higher disease activity, current EMMs, structural damage, b/tsDMARD intake, and comorbidities (including depression and chronic widespread pain). In multivariable analysis, impaired GH was explained in all databases by ASDAS (odds ratio, OR, ranging 2.60–4.48) and chronic widespread pain construct (OR ranging 2.19–8.39) (Table 3). Other factors associated to impaired GH were female sex, unemployment, current arthritis or enthesitis, lower CRP, b/ts DMARD intake, bamboo spine, longer diagnostic delay, shorter disease duration, depression construct, RDCI, and obesity.

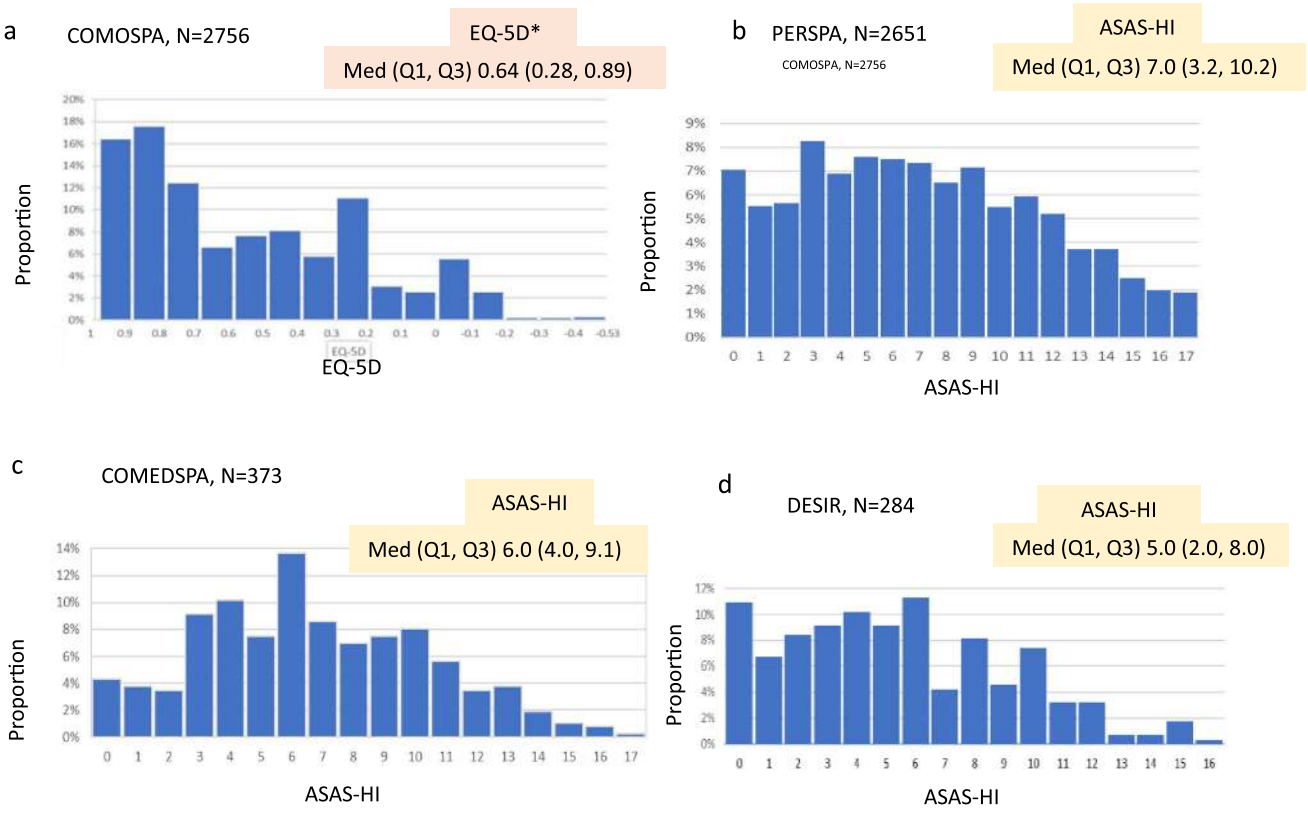
The models only explained around half of the variance of GH (global R^2 ranging from 47 to 57%), indicating that only half of GH was linked to the variables analyzed: the other half was probably explained by unmeasured or intangible variables (or interactions). The analysis of the proportion of the variance of GH attributable to groups of variables (main analysis) showed that disease activity (partial R^2 16% to 26%) and chronic widespread pain construct (partial R^2 12–15%) were the key variables explaining GH. Each group of variables explained a similar proportion of GH in the different datasets (Fig. 3, Supplementary Table 5).

Sensitivity analyses

The multivariable models in each dataset remained generally stable when substituting a variable with another, or when deleting CRP (Supplementary Table 7).

In a subgroup analysis of women, the same variables were associated to GH, except for current enthesitis; the relative variance of GH explained by each group of variables was globally similar to the principal analysis: disease activity and widespread pain were the key variables, explaining 22–25% and 12–16% of the variance respectively (Supplementary Table 8 and Supplementary Fig. 2).

In 1225 patients taking a b/tsDMARD in PERSPA and 904 in COMOSPA, the results were also stable (Supplementary Table 8 and Supplementary Fig. 2).



Footnote:
(a) COMOSPA (EQ-5D), (b) PERSPA (ASAS-HI), (c) COMEDSPA (ASAS-HI), (d) DESIR (ASAS-HI)
* The axis for EQ-5D is reversed to present best results on the left, to facilitate usual comparisons.
Med: Median; Q1, Q3: 1^{rst} and 3rd quartiles

Fig. 2 Distribution of GH in axSpA patients in each dataset

When defining severe impairment of GH by the validated cut-off of ASAS-HI ≥ 12, the same variables were independently associated to GH as when we used a cut-off of ≥ 10 (Supplementary Table 9).

Discussion

In these four heterogeneous populations of axSpA patients, collected world-wide, the level of reported GH was generally moderate. Multivariable models with disease- and non-disease-related variables commonly collected in axSpA cohort studies, could only account for 47–57% of the variability in GH. However, two factors were consistently associated with impaired GH and explained globally similar fractions of GH: disease activity and chronic widespread pain. Thus, interventions aimed at preserving GH should prioritize these aspects.

In the current analyses, only 47–57% of GH was explained. Other studies explored HRQoL with similar results [3, 35]. This means that certain potentially relevant determinants have simply not been measured. Examples are numerous and include: sociodemographic factors (e.g., ethnicity, socio-professional category, type of work and work productivity); lifestyle habits, personal factors, e.g., alcohol intake and exercise habits, personal relationships, self-image and personality traits [4, 36]. Alternatively, existing interactions between measured variables, that were not further analyzed here, could have optimized explained variance in GH. It is also possible that ASAS-HI is not an appropriate surrogate for the broader concept of GH, or is not an appropriate surrogate in all settings since here we used international data. However, ASAS-HI has been validated in many countries [37]. Similarly, thresholds to binarize GH may not be appropriate for all patients and all cultures. The difficulty to explain variation in GH

Table 2 Factors associated to GH in axSpA, bivariable logistic and linear analysis

Database	COMOSPA		PERSPA		COMEDSPA		DESIR	
Type of model	Log	Lin	Log	Lin	Log	Lin	Log	Lin
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
N patients	2756		2651		373		284	
Male sex	0.58 [0.49; 0.68]	< 0.001	0.57 [0.48; 0.67]	< 0.001	0.41 [0.25; 0.67]	< 0.001	0.30 [0.15; 0.59]	< 0.001
Age (per year)	1.02 [1.01; 1.02]	< 0.001	1.01 [1.00; 1.02]	< 0.001	1.00 [0.98; 1.02]	0.525	1.06 [1.02; 1.11]	0.009
Educational level	0.67 [0.57; 0.78]	< 0.001	0.54 [0.45; 0.64]	< 0.001	0.53 [0.32; 0.87]	< 0.001	0.41 [0.22; 0.78]	0.021
Current employment	0.36 [0.31; 0.42]	< 0.001	0.41 [0.34; 0.48]	< 0.001	0.28 [0.17; 0.46]	< 0.001	0.32 [0.15; 0.68]	0.004
Disease duration (per year)	1.01 [1.00; 1.02]	0.713	1.00 [0.99; 1.01]	0.446	0.98 [0.96; 1.01]	0.031	1.06 [0.91; 1.21]	0.272
Diagnostic delay (per year)	1.02 [1.01; 1.03]	< 0.001	1.02 [1.01; 1.03]	< 0.001	NA	NA	1.06 [0.75; 1.47]	0.227
Current arthritis	4.93 [3.94; 6.21]	< 0.001	2.80 [2.25; 3.49]	< 0.001	1.28 [0.76; 2.13]	0.682	1.00 [0.05; 6.40]	0.746
Current enthesitis	3.29 [2.61; 4.18]	< 0.001	2.46 [2.08; 2.93]	< 0.001	1.29 [0.79; 2.11]	0.084	3.92 [1.99; 8.13]	< 0.001
ASDAS (per unit)	3.69 [3.32; 4.12]	< 0.001	2.87 [2.60; 3.17]	< 0.001	3.10 [2.21; 4.47]	< 0.001	2.94 [1.99; 4.53]	< 0.001
CRP (per 10 mg/L increase)	1.17 [1.09; 1.27]	< 0.001	1.06 [1.03; 1.09]	< 0.001	1.11 [0.79; 1.52]	0.858	1.00 [0.67; 1.32]	0.075
Current psoriasis	1.83 [1.43; 2.34]	< 0.001	1.61 [1.25; 2.07]	< 0.001	1.80 [0.83; 3.72]	0.123	2.14 [0.83; 5.06]	0.088
Any EMM (with current psoriasis)	1.40 [1.16; 1.70]	< 0.001	1.10 [0.91; 1.31]	0.086	1.18 [0.71; 1.94]	0.981	1.32 [0.67; 2.55]	0.667
Abnormal occiput-to-wall distance	NA	NA	1.50 [1.26; 1.80]	< 0.001	1.14 [0.51; 2.43]	0.819	0.82 [0.30; 1.98]	0.908
Bamboo spine	1.35 [1.03; 1.76]	0.003	1.31 [1.04; 1.63]	< 0.001	0.88 [0.41; 1.74]	0.630	1.38 [0.07; 9.58]	0.316
Obesity (BMI≥ 30kg/m^2)	2.25 [1.84; 2.75]	< 0.001	1.38 [1.12; 1.69]	< 0.001	2.74 [1.51; 4.92]	0.020	2.58 [1.13; 5.61]	0.003
RDCI (per point)	1.88 [1.71; 2.07]	< 0.001	NA	NA	1.35 [1.06; 1.72]	0.002	3.03 [2.04; 4.67]	< 0.001
Depression construct	5.03 [3.88; 6.59]	< 0.001	10.53 [7.42; 15.32]	< 0.001	3.14 [1.56; 6.25]	< 0.001	12.61 [6.24; 26.35]	< 0.001
Widespread pain construct	18.44 [12.82; 27.56]	< 0.001	8.43 [6.76; 10.55]	< 0.001	6.32 [3.73; 10.84]	< 0.001	15.73 [7.48; 34.29]	< 0.001
csDMARDs intake	1.49 [1.26; 1.75]	< 0.001	1.58 [1.31; 1.89]	< 0.001	1.61 [0.89; 2.85]	0.416	1.49 [0.41; 4.36]	0.657
b/ts DMARDs intake	1.16 [0.99; 1.36]	0.129	0.79 [0.66; 0.93]	< 0.001	4.55 [2.05; 12.08]	< 0.001	2.04 [1.05; 3.99]	0.039

Green boxes corresponds to p value < 0.05. Log: logistic regression, lin: linear regression. OR: Odds ratio. NA: not available

p values were derived from Wilcoxon/Fisher test in logistic regression and Spearman/Wilcoxon test in linear regression

confirms the multifactorial nature of the complicated concept of GH and HRQoL [38].

Among the factors that contributed to explaining GH, disease activity participated for 16% to 26% of the variance of GH. ASDAS was thus strongly linked to impaired GH, as has been reported previously [4, 13]. ASDAS is a 'mixed' measure, containing objective inflammation (ESR, CRP) as well as patients' perceptions of relevant elements of disease activity, such as pain and stiffness (PROs). Especially these latter come close to GH, being a measure based on the patient's perception itself [38, 39]. Although disease activity plays a significant role in GH, it only explained a fraction of GH in all the datasets. This finding contradicts prescribers' and patients' expectations (based on drug trials with patients selected on high levels of disease activity) of substantial improvement in patients' well-being through pharmacological interventions [40].

MRI inflammation did not show a significant association, as previously already suggested [7, 41]. This could be explained by limited power for MRI due to missing data, or by a real absence of association.

The construct of chronic widespread pain explained 12% to 15% of GH. Thus, as we had hypothesized, non-disease-related factors played a significant role in impaired GH; in

Table 3 Factors associated to GH in axSpA, multivariable logistic and linear models

Database	COMOSPA		PERSPA		COMEDSPA		DESIR	
N patients	2756		2651		373		284	
Type of model	Log	Lin	Log	Lin	Log	Lin	Log	Lin
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
ASDAS (per unit)	4.48 [3.80; 5.32]	< 0.001	2.60 [2.25; 3.01]	< 0.001	3.42 [1.96; 6.30]	< 0.001	3.90 [1.51; 11.39]	< 0.001
Presence of widespread pain construct	2.19 [1.39; 3.56]	< 0.001	4.39 [3.35; 5.76]	< 0.001	4.11 [1.96; 8.78]	< 0.001	8.39 [2.07; 38.08]	0.001
Current unemployment	1.67 [1.33; 2.11]	< 0.001	1.70 [1.34; 2.16]	< 0.001	4.69 [2.21; 10.34]	< 0.001	3.83 [0.74; 21.60]	0.234
Presence of depression construct	1.93 [1.28; 2.92]	< 0.001	6.04 [3.83; 9.77]	< 0.001	1.27 [0.43; 3.70]	0.021	1.76 [0.30; 9.75]	< 0.001
b/tsDMARDs intake	1.56 [1.22; 1.99]	< 0.001	1.07 [0.84; 1.35]	0.679	4.37 [1.59; 14.43]	0.001	1.80 [0.51; 6.47]	0.324
Current enthesitis	1.44 [1.03; 2.00]	0.014	1.34 [1.06; 1.70]	0.004	1.22 [0.60; 2.50]	0.650	0.52 [0.11; 2.20]	0.073
Current arthritis	2.25 [1.65; 3.07]	< 0.001	1.13 [0.82; 1.55]	0.840	0.66 [0.30; 1.44]	0.193	2.09 [0.07; 26.87]	0.841
RDCI (per point)	1.43 [1.22; 1.67]	< 0.001	NA	NA	1.02 [0.70; 1.47]	0.799	2.23 [0.79; 7.31]	0.767
Obesity (BMI ≥ 30kg/m^2)	1.29 [0.96; 1.74]	0.024	0.78 [0.58; 1.04]	0.179	2.61 [1.13; 6.01]	0.185	3.47 [0.77; 16.12]	0.162
Age (per year)	1.01 [1.00; 1.03]	0.150	1.01 [0.99; 1.02]	0.126	0.98 [0.94; 1.01]	0.410	1.07 [0.97; 1.18]	0.126
CRP (per 10 mg/L increase)	0.54 [0.48; 0.61]	< 0.001	0.92 [0.88; 0.96]	< 0.001	0.75 [0.39; 1.34]	0.222	0.05 [0.00; 0.57]	0.174
Bamboo spine	1.26 [0.86; 1.86]	0.003	1.04 [0.75; 1.44]	0.087	1.24 [0.40; 3.61]	0.657	NA	NA
Current psoriasis	1.16 [0.81; 1.67]	0.594	1.28 [0.88; 1.84]	0.117	1.50 [0.46; 4.62]	0.341	3.38 [0.52; 20.33]	0.554
Educational level	0.99 [0.79; 1.25]	0.891	0.92 [0.72; 1.17]	0.158	0.97 [0.47; 2.00]	0.225	0.64 [0.16; 2.63]	0.312
Diagnostic delay (per year)	0.99 [0.98; 1.01]	0.737	1.01 [0.99; 1.03]	0.399	NA	NA	0.99 [0.44; 2.13]	0.043
Disease duration (per year)	0.98 [0.97; 1.00]	0.032	1 .00 [0.99; 1.02]	0.369	0.97 [0.93; 1.01]	0.104	1.50 [0.69; 3.27]	0.386
Male sex	0.91 [0.71; 1.16]	0.512	0.89 [0.69; 1.15]	< 0.001	0.65 [0.31; 1.37]	0.001	0.49 [0.11; 2.03]	< 0.001

The model included each variable presented in the table, except from RDCI in PERSPA (not collected), diagnostic delay in COMEDSPA (not collected) and bamboo spine in DESIR (only 5/284 patients)

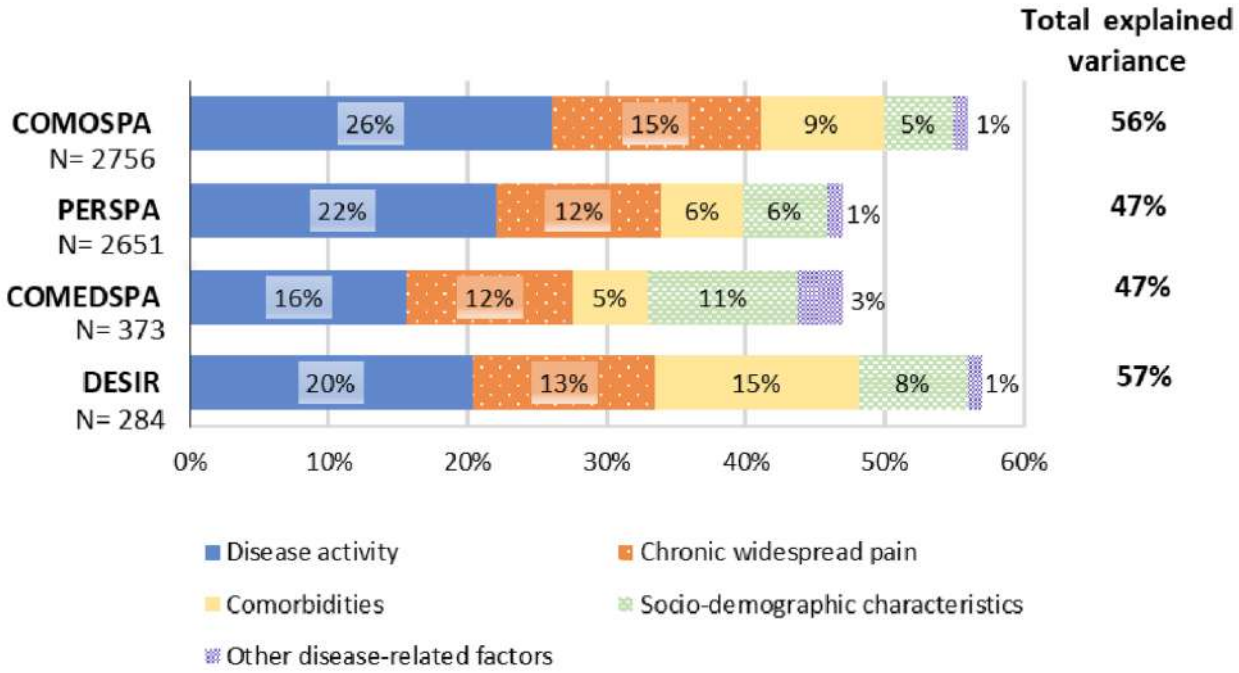
Green boxes correspond to p value < 0.05. Log: logistic regression, lin: linear regression

OR: Odds ratio

RDCI (Rheumatic Disease Comorbidity Index), calculated using the formula: 2 × lung disease + [2 × (heart attack, other CV or stroke) or 1 × hypertension] + fracture + depression + diabetes + cancer + (ulcer or stomach problem)

fact, widespread pain was of only slightly lower importance compared to disease activity. These results add information compared to previous studies, since here we were able to attribute a fraction of GH to widespread pain [13, 42]. While the management of axSpA aims to reduce disease activity, our results indicate that closer attention should be paid to widespread pain. This may include screening for widespread pain and considering individualized interventions. Screening can be easily performed in the clinic using the FIRST questionnaire; management is more challenging [43]. Here chronic widespread pain was assessed as a construct which may overlap with fibromyalgia or with nociplastic pain [43]. It seems to us that a holistic management cannot be performed without proper and specific measures taken to address chronic widespread pain and nociplastic pain [44].

Some other elements were linked to GH. As expected, enthesitis and peripheral arthritis were associated to lower GH. Obesity, older age, and comorbidities were also confirmed as altering GH [13, 20]. Current use of b/tsDMARDs was associated with impaired GH, which has been previously described, probably due to confounding by indication [3, 45]. Women reported impaired GH, which has been extensively reported in the literature [10, 46]; nevertheless, the relative impact of disease-related and non-disease-related factors on GH was similar in both men and women. These elements should push clinicians to



Footnote: % are percentage of relative partial variance explained by each group of variables, relative to the total variance explained by the model.
Group of variables:

- Disease activity includes ASDAS, CRP, current psoriasis, current arthritis and current enthesitis.
- Chronic widespread pain includes only chronic widespread pain construct
- Comorbidities include Rheumatic Disease Comorbidities Index (RDCI), obesity and depression.
- Sociodemographic characteristics include sex, age, employment status and educational level.
- Other disease related factors include disease duration, diagnostic delay, bamboo spine and b/tsDMARD intake.

RDCI was not available in PERSPA, diagnostic delay was not available in COMEDSPA

Fig. 3 Relative contribution of group of variables to GH in 4 datasets in patients with axSpA

treat extra-axial manifestations and to encourage patients to lose weight.

This study has strengths and weaknesses. We selected patients with a diagnosis of axSpA, fulfilling ASAS classification criteria for axSpA. The 4 datasets analyzed here included patients with varying profiles in terms of sex ratio, diagnostic delay, disease duration, peripheral arthritis, comorbidities and b/tsDMARDs intake. This heterogeneity between population profiles may partly account for varying rates of patients with impaired GH (ranging 16–47%). This comprehensive panel of patients encompasses the broader spectrum of the disease, enhancing generalizability. Furthermore, our findings in terms of factors associated to GH were remarkably consistent across studies, confirming the robustness of our results. The primary outcome of this study was GH, assessed by ASAS-HI or EQ-5D (in one dataset, COMOSPA). Because these scores assess different aspects of GH, we did not pool the results. EQ-5D does not directly capture the patient's perception of GH but reflects a perception of GH according to a health state profile. Both scores do not fully overlap, but statistically showed similar distributions and good correlation [34]. The chosen cutoff of 10 for impaired GH with ASAS-HI was patient-derived, based on the distribution in the present population. This cut-off only influenced the results of the logistic regression. Furthermore, sensitivity analyses using the threshold of 12 showed similar results [25]. Finally, chronic widespread pain and depression were assessed differently across the datasets, which may

have led to an incorrect estimation of their prevalence and of their effect on GH; nevertheless, the associations were consistently strong.

In conclusion, this study provides robust evidence and consistent associations between GH and both disease-related and patient-related factors in axSpA. Our findings allow us to assign a relative importance to groups of variables in explaining GH in axSpA. Disease activity and chronic widespread pain were the most significant factors influencing GH, and should be prioritized. In addition, since disease activity explained only a proportion of GH, both patients and rheumatologists should be aware that DMARDs are only part of the solution for impaired perception of GH. These results may guide clinicians in improving the management of patients with axSpA and facilitate effective patient–physician communication and shared decision-making. Further studies assessing the efficacy of a holistic approach to improve GH are needed.

Author contributors

LG, JD, BF designed the data analysis. JD performed the literature search and the statistical analyses, developed the figures and tables. LG supervised the work. All authors contributed to data analysis, interpretation, writing and reviewed the manuscript and approved the final version. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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Data availability Data that underlie the results presented here were shared from the 4 databases' principal investigators. This data will be shared upon reasonable request while preserving patient anonymity. Researchers willing to use data collected during the study should contact the first author of the main manuscript of each study.

Declarations

Conflict of interests JD, CLM, BF, MD, CGV declare that they have no competing interests relevant to this study. Benjamin Granger has received consultancy fees from MSD, and Boston scientific. Robert Landewé: Speaker fees/honoraria or research support from AbbVie, Eli-Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer and UCB. Anna Molto: Speaker honoraria/participated in advisory boards for AbbVie, Biogen, Janssen, Lilly, Gilead, Galapagos, Pfizer and UCB; Research grants from Pfizer and UCB. Uta Kiltz: Dr. Kiltz has received grant and research support and consultancy fees from AbbVie, Amgen, Biocad, Biogen, BMS, Chugai, Eli Lilly, Fresenius, Gilead, Grünenthal, GSK, Hexal, Janssen, MSD, Novartis, onkowissen.de, Pfizer, Roche, UCB and Viatris. Laure Gossec: research grants: AbbVie, Biogen, Lilly, Novartis, UCB; consulting fees: AbbVie, Amgen, BMS, Celltrion, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, UCB.

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