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REVIEW

The Impact of Comorbidity on Patient-Reported Outcomes in Psoriatic Arthritis: A Systematic Literature Review

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ABSTRACT

Introduction: A systematic literature review was conducted with the aim to analyse the impact of comorbidity on patient-reported outcomes (PROs) in patients with psoriatic arthritis (PsA).

Methods: A sensitive search strategy of the Medline, Embase and the Cochrane Library (up to March 2019) was applied to retrieve studies for inclusion in this systematic literature review. Abstracts of the ACR and EULAR scientific meetings were also searched. The selection criteria were: (1) patients with PsA (population) with a comorbidity (intervention) and (2) report of any impact of the comorbidity on PROs. Systematic literature reviews, randomized controlled trials and observational were included in this systematic literature review. Two of the authors selected the articles and collected the data.

Results: Eighteen articles were included in this systematic literature review, with most being cross-sectional studies that included more than 9000 patients with PsA. Some studies analysed the impact of an individual comorbidity, such as fibromyalgia (FM), and in others the analysis was according to the number of comorbidities. The most frequently analysed PROs were function, quality of life and fatigue. Analysis of the studies included in the review showed that patients with a higher number of comorbidities and/or more severe comorbidities reported worse impacts of their disease on function, patient's global assessment (PGA), pain, fatigue, work disability and quality of life. Specifically, FM had a negative impact on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), function, quality of sleep and quality of life; anxiety and depression had a negative impact on function and fatigue; metabolic syndrome had a negative impact on BASDAI, function, PGA and quality of life; obesity had a negative impact on function and pain; smoking

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(current and ex-smokers) had a negative impact on pain, function, fatigue, quality of life and overall health; alcohol intake had a negative impact on pain, function, fatigue, quality of life and overall health.
Conclusions: The prevalence and impact of medical comorbidity on PROs are very high in patients with PsA.

Keywords: Comorbidity; Patient-reported outcomes; Psoriatic arthritis; Systematic literature review

Key Summary Points

More than half of patients with psoriatic arthritis (PsA) have at least 1 comorbidity.

Comorbidity has several impacts at different levels in PsA, including patient-reported outcomes (PROs).

PsA patients with more number or severity of comorbidities reported a worse impact on: function, patient's global assessment (PGA), pain, fatigue, work disability and quality of life.

In PsA the prevalence and impact of comorbidity on PROs are very high.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease with an incidence and prevalence ranging from approximately 3–23 persons per 100,000 and 0.5–4 persons per 1000, respectively, in Western countries [1]. It has been reported that more than half of patients with PsA have at least one comorbidity [2, 3]. The most prevalent comorbidities associated with PsA are cardiovascular disease, metabolic syndrome, depression and anxiety, osteoporosis, ophthalmic, liver, kidney and inflammatory bowel disease [2, 4, 5].

The impact of comorbidity on PSA patients can be described at different levels [6–8]. The increased mortality risk observed in PsA patients is mainly explained by the high prevalence of these comorbidities, especially cardiovascular disease [6]. Similarly, the presence of comorbidities may also have an impact on the activity and/or the severity outcomes measures of PsA. For example, fibromyalgia (FM) or depression can considerably influence the score of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in PsA patients [9]. It has also been reported that the presence of comorbidities may influence the treatment response and decision-making process. Different studies have shown that both obesity and metabolic syndrome are associated with lower retention rates of and response rates to biological therapy [10–12], and a systematic literature review found that obesity and overweight reduce the odds to achieve minimal disease activity in patients with PsA receiving treatment with traditional or biologic drugs [13].

Comorbidity can also result in greater functional impairment and have an important negative impact on the quality of life [14]. These outcomes are included in the patient-reported outcomes (PROs), defined as health outcomes directly reported by the patients who experienced them, and they provide vital information to both patients and doctors for use in the decision-making process. However, little information is available on other PROs, such as patient global assessment (PGA), sleep quality or work-related variables.

In this context, the aim of the systematic literature review reported here was to analyse the impact of comorbidity on PROs in PsA patients. We are confident that these results will help healthcare professionals in their management of this patient population.

METHODS

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

A systematic review of the literature was conducted using a standardized, thorough and transparent approach, following the Cochrane dual-reviewer methodology [15] and PRISMA

statement [16]. As the first step, an investigation protocol was established in which a group of experts in PsA collaborated in defining the research question, the PICO framework and the data to be collected. This group of experts supervised all parts of the systematic review of the literature and resolved any disagreements and uncertainties.

Search Strategy

As search strategy, two expert librarians performed a comprehensive and sensitive electronic search strategy of databases, including the MEDLINE, Embase, and the Cochrane database, in March 2019. MeSH (Medical Subject Headings) terms and free text terms were used. Only articles on human studies and those written in English and Spanish were searched. The search method is described in detail in the Electronic Supplementary Material.

The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR) of 2017 and 2018 were also examined. All retrieved references were managed in Endnote (Clarivate Analytics, Philadelphia, PA, USA).

The last step in the search strategy was to conduct a hand search of the references of the included studies. Additional publications or other information provided by the experts related to the systematic review were also evaluated.

Selection Criteria

The studies retrieved using the above-mentioned strategies were included in our systematic review if they met a number of pre-specified criteria. First, the patients studied had to be PsA patients (according to international or medical criteria) and aged $\geq$ 18 years; no restrictions were applied regarding disease duration, activity, severity or treatments. Second, PsA subjects with a comorbidity were included (irrespective of the type or number). Third, studies reporting PROs, including pain, function, PGA, quality of life, work disability or sleep disturbance, were included (irrespective of the type of measures). Only systematic literature reviews, randomized controlled trials and observational studies were included; basic science and animal studies were excluded.

Screening of Studies and Data Collection

Two reviewers independently screened the titles and abstracts of the retrieved articles to assess whether the selection criteria were satisfied. This process was performed in 20-min sessions. In case of discrepancy/disagreement over the eligibility of an article, a third reviewer was asked to resolve the disagreement. The same two reviewers also collected the data from the included studies using ad hoc standard forms. All data collected from each article were checked by both reviewers independently and then independently reviewed. If during this process the reviewers found any discrepancy, then a consensus was reached by looking at the original article or by asking the third reviewer. Articles that did not fulfil all of the inclusion criteria or that had insufficient data were excluded. A modification of the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence, 2011 update [17], was used to grade the quality of the article. Evidence tables were then produced.

Data Analysis and Presentation

The main features of the studies included in the present systematic literature review are described in the evidence tables (see Results section). Depending on the variable, the results are expressed as a number and a percentage, mean and standard deviation or mean and interquartile range (p25–p75), and as odds ratio (OR), relative risk or hazard ratio, with 95% confidence intervals (CIs).

Meta-analysis was only planned when sufficient homogeneity was present among the included studies.

RESULTS

The search strategies retrieved 1155 articles, of which 82 were reviewed in detail in addition to

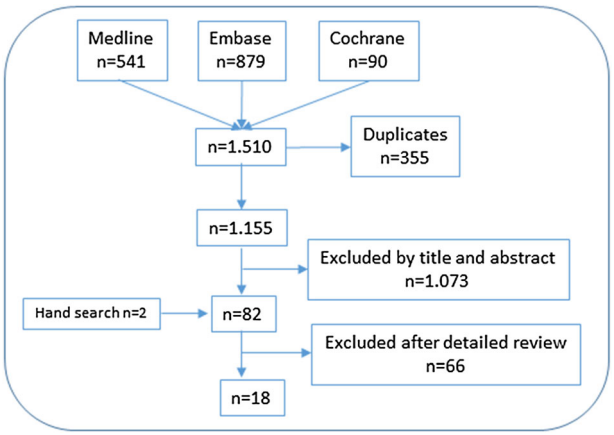

Fig. 1 Flowchart of study inclusion strategy

two additional studies identified from the hand search (Fig. 1). Ultimately, 66 of the 84 studies were excluded from inclusion in the systematic literature review (Table 1) [12, 18–82], and 18 articles were included [9, 14, 83–98], one of which had been identified from the hand search (see Tables 2 and 3 for more detail).

Most of the studies included in the systematic literature review were cross-sectional [9, 84, 85, 87–90, 92–97], although prospective observational studies were also found [14, 83, 86, 91, 98], and most were of moderate quality (predominantly Oxford CEBM levels of evidence 2b or 4). The total number of PsA patients included in each study ranged from 3571 [91] to 40 [97]. The majority of patients were middle-aged women, and almost all diagnoses were based onthe Classification Criteria for Psoriatic Arthritis (CASPAR) criteria. There was a great variability in the number and types of comorbidities. Some studies analysed the impact of an individual comorbidity, such as obesity [86, 98], FM [9, 94, 96] or anxiety and depression [85, 87], but others analysed the impact of the number of comorbidities [14, 88, 95], using indexes such as the Charlson Comorbidity Index (CCI).

The most frequently analysed PROs were function [83, 84, 86, 89, 92, 94], quality of life [9, 14, 84, 91–93] and fatigue [83, 85, 87, 93], but some studies evaluated the impact of comorbidity on pain [83, 84, 91, 98], work disability [88] or sleep quality [93, 96, 97]. Most of PROs were evaluated with validated questionnaires, such as the Health Assessment Questionnaire (HAQ) or the Bath Ankylosing Spondylitis Functional Index (BASFI) for the assessment of function or the 36 Item Short Form Health Survey (SF-36), the EuroQol 5 dimensions (EQ-5D) or Ankylosing Spondylitis Quality of Life Index (ASQoL) for quality of life. However, some studies on other PROs, such as pain or PGA, were analysed with a visual analogue scale or numerical scale.

The impact of comorbidity on PROs of PsA patients was examined using the CCI in two large, high-quality prospective cohorts [83, 86]. In the first study (using DANBIO, a nationwide registry of biological therapies in Denmark), the authors noted that a higher score on the CCI was associated with worse function, pain, fatigue and PGA (univariate analyses) [83]. The second study, i.e. the CARMA study, was designed to evaluate cardiovascular risk in patients with chronic inflammatory rheumatic diseases [86]. In this study multivariate analyses were performed, and a higher CCI was also found to be associated with worse function, as assessed with HAQ (coefficient β 0.09, $p = 0.040$).

Three other studies used a list of comorbidities to evaluate the impact of the number of reported comorbidities on PROs in PsA patients [14, 88, 95]. One of these studies, a prospective observational study with more than 600 patients with PsA, found that the presence of at least three comorbidities significantly worsened a patient's quality of life, as assessed with the SF-

Table 1 Studies excluded from systematic literature review and reasons for exclusion

Study number (arbitrary)	Study (first author/ year)	Reason for exclusion
1	Abou-Raya/2014 [18]	No data regarding the impact of comorbidity on PROs
2	Aguiar/2013 [20]	No data regarding the impact of comorbidity on PROs
3	Aguiar/2013 [19]	No data regarding the impact of comorbidity on PROs
4	Akhtari/2018 [21]	No data regarding the impact of comorbidity on PROs
5	Aljohani/2017 [22]	No data regarding the impact of comorbidity on PROs
6	Arancibia/2014 [24]	No data regarding the impact of comorbidity on PROs
7	Arancibia/2015 [23]	No data regarding the impact of comorbidity on PROs
8	Bandinelli/2009 [25]	No numerical data provided
9	Batkaeva/2018 [26]	No data regarding the impact of comorbidity on PROs
10	Bessette/2018 [27]	Comorbidities were eventually not analysed
11	Bird/2017 [28]	Comorbidities were eventually not analysed
12	Birra/2018 [29]	Obesity was not analysed regarding to any PROs
13	Cano-Garcia/2016 [31]	No numerical/statistical data provided
14	Cano-Garcia/2017 [30]	No numerical/statistical data provided
15	Cano-Garcia/2018 [32]	No numerical/statistical data provided
16	Carneiro/2010 [33]	Congress abstract. The authors subsequently published an article which is included in this systematic literature review
17	Castañeda/2015 [34]	No data regarding the impact of comorbidity on PROs
18	Cauli/2011 [35]	No data regarding the impact of comorbidity on PROs
19	Cetin/2015 [36]	No numerical data provided
20	Chimenti/2017 [38]	No data regarding the impact of comorbidity on PROs
21	Chimenti/2019 [37]	No sub-analysis for PsA patients
22	Da Cruz Ribeiro/2018 [39]	No numerical data provided
23	Dan/2011 [40]	No sub-analysis for PsA patients
24	De Gaspari/2015 [41]	No data regarding the impact of comorbidity on PROs
25	Duffin/2009 [42]	No data regarding the impact of comorbidity on PROs
26	Duruöz/2013 [44]	No data regarding the impact of comorbidity on PROs
27	Duruoz/2018 [43]	No data regarding the impact of comorbidity on PROs
28	Eder/2015 [45]	No data regarding the impact of comorbidity on PROs

Table 1 continued

Study number (arbitrary)	Study (first author/ year)	Reason for exclusion
29	Farkas/2017_1 [46]	No data regarding the impact of comorbidity on PROs
30	Farkas/2017_2 [47]	No data regarding the impact of comorbidity on PROs
31	Fonti/2018 [48]	No sub-analysis for PsA patients
32	Frede/2018 [49]	No data regarding the impact of comorbidity on PROs
33	Gezer/2014 [50]	No numerical data provided
34	Gossec/2011 [51]	No data regarding the impact of comorbidity on PROs
35	Gottlieb/2019 [52]	PsA diagnosis notvalidated
36	Grubišić/2013 [53]	No data regarding the impact of comorbidity on PROs
37	Gulati/2018 [54]	No numerical/statistical data provided
38	Haglund/2013 [55]	No sub-analysis for PsA patients
39	Haroon/2013 [56]	No numerical data provided
40	Huscher/2016 [57]	No data regarding the impact of comorbidity on PROs
41	Husted/2010 [58]	No numerical/statistical data provided
42	Husted/2012 [59]	No data regarding the impact of comorbidity on PROs
43	Hyphantis/2013 [60]	No numerical/statistical data provided
44	Khraishi/2014 [61]	No data regarding the impact of comorbidity on PROs
45	Kotsis/2012 [62]	No data regarding the impact of comorbidity on PROs
46	Kurizky/2012 [63]	No data regarding the impact of comorbidity on PROs
47	Kuru/2014 [64]	No data regarding the impact of comorbidity on PROs
48	Madeira/2017 [65]	No sub-analysis for PsA patients
49	McDonough/2012 [66]	No data regarding the impact of comorbidity on PROs
50	Meesters/2018 [67]	No data regarding the impact of comorbidity on PROs
51	Michelsen/2017 [68]	No numerical/statistical data provided
52	Miller/2013 [12]	No numerical/statistical data provided
53	Nemes/2013 [69]	No data regarding the impact of comorbidity on PROs
54	Ogdie/2014 [70]	Study design
55	Pistone/2013 [71]	No data regarding the impact of comorbidity on PROs
56	Rhee/2011 [74]	No numerical/statistical data provided
57	Rhee/2012 [72]	Provides the same data as Rhee/2011 [56]

Table 1 continued

Study number (arbitrary)	Study (first author/year)	Reason for exclusion
58	Rhee/2012_2 [73]	No data regarding the impact of comorbidity on PROs
59	Rosen/2012 [75]	No data regarding the impact of comorbidity on PROs
60	Salaff/2009 [76]	No data regarding the impact of comorbidity on PROs
61	Sinnathurai/2018 [77]	No data regarding the impact of comorbidity on PROs
62	Sinnathurai/2018 [78]	No numerical data provided
63	Szentpetery/2016 [79]	No data regarding the impact of comorbidity on PROs
64	Tillet/2013 [80]	No data regarding the impact of comorbidity on PROs
65	Urruticoechea Arana/2015 [81]	No numerical/statistical data provided
66	Vacca/2014 [82]	No numerical/statistical data provided

PsA Psoriatic arthritis, *PROs* Patient-reported outcomes

36 (multivariate analyses), in both the physical and mental dimensions (β coefficients of − 4.91 [$p < 0.001$] and − 2.84 [$p = 0.005$], respectively) [14]. A second study, a small prospective study, used the Functional Comorbidity Index (FCI) to corroborate that an increase in the number of comorbidities was significantly associated with moderate–severe work disability (OR 2.31, 95% CI 1.19–4.50). The third study was a cross-sectional study that included 189 PsA patients [95]. The authors compared PsA patients with ≥ 5 comorbidities to those with none and found that more comorbidities was associated with a worse BASFI score (β coefficient 2.33, $p = 0.040$).

The remaining studies included in the systematic literature review analysed the impact of individual comorbidities on patient PROs. In three such studies, the authors focussed on the impact of FM on patient PROs [9, 94, 96]. In the small prospective study of Brikman et al. [9], the presence of FM (vs. its absence) was associated with worse median HAQ scores (1.75 vs. 0.25, $p < 0.001$) and worse median BASDAI (7.18 vs. 2.87, $p < 0.001$). We also included a cross-sectional study that in addition to evaluating the presence of FM also evaluated the impact of the extent and severity of the disease using the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS) [94]. Similar to the results reported by Brikman et al. [9], patients with FM had significantly worse scores on the HAQ (unadjusted data). In addition, the WPI was strongly correlated with the BASDAI ($r = 0.804$, $p < 0.001$), although the correlation with the HAQ was weak ($r = 0.478$, $p < 0.001$). The SSS score also showed a weak correlation with the HAQ ($r = 0.3$, $p < 0.001$). Another small cross-sectional study that included 50 FM patients used the Fibromyalgia Impact Questionnaire (FIQ) to assess the impact of FM on patient PROs [96]. The authors of this study reported a moderate correlation between the FIQ and the Pittsburgh Sleep Quality Index (PSQI) ($r = 0.56$, $p < 0.001$) and a moderate–strong correlation with quality of life (as measured on the Psoriatic Arthritis Quality of Life questionnaire [PsA-QoL]) ($r = 0.69$, $p < 0.001$).

Anxiety and depression were examined in two small cross-sectional studies using the Hospital Anxiety and Depression Scale (HADS) questionnaire [85, 87]. Both studies found

Table 2 Evidence table constructed, showing main characteristics of studies included in the systematic literature review

Study number of included study (arbitrary)	Study (first author/year) and type of study	Population	Comorbidity	PROs	Quality[a]
1	Ballegaard/2018 [83], observational prospective cohort (DANBIO registry)	*n* = 1750 PsA patients; 55% women; mean age 48 years; PsA duration 1–11 years; CCI 0 (61%), 1 (28%), ≥ 2 (11%)	CCI	Function (HAQ) PGA (VAS 0–100) Pain (VAS 0–100) Fatigue (VAS 0–100)	2b
2	Bremander/2014 [84], cross-sectional study	*n* = 1.73 PsA patients; 58% women; mean age 57 years; duration PsA 12 years; 38% never smoking, 62% yes (18% current, 44% ex-smokers)	Smoking (self declared)	Quality of life (EQ-5D) Function (HAQ) Global health (numeric scale 0–10) Fatigue (numeric scale 0–10) Pain (numeric scale 0–10)	4
3	Brikman/2016 [9], cross-sectional study	*n* = 73 PsA patients (CASPAR criteria; 57% women; mean age 52 years; PsA duration 10 years; 17.8% FM	FM (ACR 2010 and 1990 criteria)	Function (HAQ) Quality of life (DLQI)	3a
4	Carneiro/2017 [85], cross-sectional study	*n* = 101 PsA patients (CASPAR criteria); 44% women; mean age 51 years; mean HADS 7.39	Anxiety and depression (HADS)	Fatigue (FACIT-F)	4
5	Fernández-Carballido/2018 [86], observational prospective cohort	*n* = 721 PsA patients; mean CCI 1.30	CCI Obesity (BMI)	Function (HAQ)	2a

Table 2 continued

Study number of included study (arbitrary)	Study (first author/year) and type of study	Population	Comorbidity	PROs	Quality[a]
6	Gubar_2018 [87], cross-sectional study	*n* = 78 early PsA patients (CASPAR criteria); 50% women; mean age 36 years; mean anxiety score 5.7; mean depression score 3.8	Anxiety and depression (HADS)	Fatigue (FACIT-F) Function (HAQ)	4
7	Husted/2013 [14], cross-sectional study	*n* = 631 PsA patients(CASPAR criteria); 41% women; mean age 50 years; PsA duration 13 years; mean number of comorbidities 2.5	Presence of 15 comorbidities	Quality of life (SF-36)	3a
8	Kennedy/2014 [88], cross-sectional study	*n* = 146 PsA patients (CASPAR criteria); 39% women; mean age 50 years; PsA duration 14 years; mean FCI 1.08	FCI comorbidity index	Work disability (WLQ)	4
9	Oten/2017 [89], cross-sectional study	*n* = 58 PsA patients (CASPAR criteria); 57% women; mean age 42 years; PsA duration 16 years; 31% osteoporosis	Osteoporosis (DEXA)	BASDAI Function (HAQ)	4
10	Pehlevan/2014 [90], cross-sectional study	*n* = 55 PsA patients (CASPAR criteria); 62% women; mean age 46 years; 24% metabolic syndrome	Metabolic syndrome (NCEP-ACT III criteria)	BASDAI Function (HAQ, RAPID-3)	4
11	Piche/2015 [91], observational prospective cohort	*n* = 3.571 PsA patients; 36% women; mean age 50 years; PsA duration 14 years	Smoking (past, current, duration) Alcohol intake (past, current, duration)	Function (HAQ, FSS, BASFI) Pain (HAQ) Fatigue (FACIT) Quality of life (EQ 5D, DLQI, ASQoL, SF-36)	2b

Table 2 continued

Study number of included study (arbitrary)	Study (first author/year) and type of study	Population	Comorbidity	PROs	Quality[a]
12	Sanci/2018 [92], cross-sectional study	*n* = 104 PsA patients (CASPAR criteria); 63.5% women; mean age 50 years; PsA duration 8 years; 45.2% metabolic syndrome	Metabolic syndrome (NCEP-ACT III criteria)	BASDAI Function (BASFI, HAQ) PGA (VAS 0–100) Quality of life (DLQI, ASQoL)	4
13	Sandikci/2018 [93], cross-sectional study	*n* = 50 PsA patients (CASPAR criteria); 33% women; mean age 45 years; 64% restless legs syndrome	Restless legs syndrome (RLS Study Group recommendations)	Fatigue (FSS) Quality of life (SF-36) Sleep quality (PSQI)	4
14	Sharma/2017 [94], cross-sectional study	*n* = 102 PsA patients; 50% women; mean age 43 years	FM (WPI, SSS)	BASDAI Function (PROMIS-HAQ)	4
15	Tanner/2014 [95], cross-sectional study	*n* = 189 PsA patients; 52% women; mean age 50 years; 75% comorbidity	Number of comorbidities	BASFI	4
16	Ulutatar/2018 [96], cross-sectional study	*n* = 50 PsA patients (CASPAR criteria); 64% women; mean age 49 years; PsA duratation 90 months; 64% FM	FM (FIQ)	Quality of life (PSQI) Quality of life (PsASQoL)	4
17	Unal/2018 [97], cross-sectional study	*n* = 40 PsA, patients; 68% women; mean age 50 years; PsA duration 99 months; 30% neuropathic pain	Neuropathic pain (painDETECT questionnaire)	Quality of life (PSQI) Quality of life (PsASQoL)	4

Table 2 continued

Study number of included study (arbitrary)	Study (first author/year) and type of study	Population	Comorbidity	PROs	Quality[a]
18	Zaffarana/2016 [98], observational prospective cohort (RPSAODIA registry)	*n* = 110 PsA patients (CASPAR criteria); 64% women; mean age 49 years; PsA duratation 90 months; 37.3% obesity	Obesity (BMI)	BASFI Pain (VAS 0–10)	3a

ACR American College of Rheumatology, *ASQoL* Ankylosing Spondylitis Quality of Life Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BMI* body mass index, *CASPAR* Classification Criteria for Psoriatic Arthritis, *CCI* Charlson Comorbidity Index, *DEXA* dual-energy X-ray absorptiometry, *DLQI* Dermatology Quality of Life Index, *EQ-5D* EuroQol 5 dimensions, *FACIT* Functional Assessment of Chronic Illness Therapy scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue scale, *FCI* Functional Comorbility Index, *FIQ* Fibromyalgia Impact Questionnaire, *FM* fibromyalgia, *FSS* Fatigue Severity Scale, *HADS* Hospital Anxiety and Depression Scale, *HAQ* Health Assessment Questionnaire, *NCEP* National Commission for Employment Policy, *PGA* patient global assessment, *PROMIS* Patient-Reported Outcomes Measurement Information System, *PsASQol* Psoriatic Arthritis Quality of Life questionnaire, *PSQI* Pittsburgh Sleep Quality Index, *SF-36* 36 Item Short Form Health Survey, *SSS* Symptom Severity Scale, VAS visual analogic scale, WPI Widespread Pain Index, *WLQ* Work Limitations Questionnaire

[a] Quality assessed with the 2011 Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence [17]

weak–moderate correlations with function and fatigue.

The impact of the metabolic syndrome on PROs of PsA patients, according to the National Commission for Employment Policy (NCEP)-ACT III guidelines, was evaluated in two cross-sectional studies, which recruited more than 150 patients with PsA [90, 92]. In one of these studies [90], no statistically significant association was found between the metabolic syndrome and the BASDAI, HAQ and Routine Assessment of Patient Index Data 3 (RAPID3) index, although it should be noted that the small size of the study sample (50 patients) may have influenced this result [90]. In the second study, the authors observed a negative impact of metabolic syndrome (compared with patients without it; higher values indicating more active disease/worse function/great disability) on the BASDAI (22 vs. 11, $p = 0.042$), BASFI (18 vs. 5, $p = 0.009$), HAQ (0.375 vs. 0.125, $p = 0.011$), PGA (31 vs. 20, $p = 0.030$), and ASQoL (7 vs. 3, $p = 0.017$) [92].

The impact of obesity on patients with PsA was analysed in two prospective cohorts included in this systematic literature review. One was the CARMA study (described earlier in this review; [86]) and the other was the PsA registry of Argentina (RAPSODIA registry [98]). The multivariate analyses of the CARMA cohort revealed that obesity was significantly associated with worse patient function (HAQ; β coefficient 0.09, $p = 0.005$) [86], while the bivariate analyses of the RAPSODIA registry also found a significant negative association with function (BASFI) and pain [98].

The effect of smoking on PsA patient PROs was examined in two studies [84, 91]. One of these studies was a cross-sectional study that included more than 1000 patients with PsA [84]. The multivariate analyses comparing smokers and ex-smokers with patients who have never smoked demonstrated that smoking was

Table 3 Main results of the studies included in the systematic literature review

Number of study (arbitrary)	Study (first author/year)	Results
1	Ballegaard/2018 [83]	CCI 0 vs. 1 vs. $\geq$ 2
		HAQ 0.88 vs. 1.1 vs. 1.4 ($p < 0.001$)
		PGA 68 vs. 69 vs. 75 ($p = 0.021$)
		Pain 60 vs. 62 vs. 69 ($p = 0.008$)
		Fatigue 65 vs. 67 vs. 78 ($p = 0.002$)
2	Bremander/2014 [84]	Current smokers/ex-smokers vs. never smoking (multivariate analyses)
		EQ-5D β coefficient $-$ 0.04 ($p = 0.009$)
		HAQ β coefficient 0.043 ($p = 0.210$)
		Global Health β coefficient 0.36 ($p = 0.010$)
		Pain β coefficient 0.38 ($p = 0.010$)
		Fatigue β coefficient 0.34 ($p = 0.040$)
		Pain locations β coefficient 0.54 ($p = 0.04$)
		Current smokers vs. ex-smokers worse EQ-5D ($p = 0.02$) and number of pain locations ($p = 0.04$)
3	Brikman/2016 [9]	FM vs. no FM
		HAQ median (IQR) 1.75 (1.07–237) vs. 0.25 (0–1). $p < 0.00$
		BASDAI (mean $\pm$ SD) 7.18 $\pm$ 1.73 vs. 2.87 $\pm$ 2.35 ($p < 0.001$)
4	Carneiro/2017 [85]	Correlation HADS and FACIT-F
		HADS (anxiety) $r = -0.306$ ($p = 0.002$)
		HADS (depression) $r = -0.339$ ($p < 0.001$)
5	Fernández-Carballido/2018 [86]	Obesity (multivariate analyses)
		HAQ β coefficient 0.09 ($p = 0.005$)
		Higher CCI (multivariate analyses)
		HAQ β coefficient 0.09 ($p = 0.040$)
6	Gubar/2018 [87]	Correlation HADS and HAQ
		HADS (anxiety) $r = 0.26$
		HADS (depression) $r = 0.33$
		Correlation HADS and FACIT-F
		HADS (anxiety) $r = -0.49$
		HADS (depression) $r = -0.48$

Table 3 continued

Number of study (arbitrary)	Study (first author/ year)	Results
7	Husted/2013 [14]	Presence 3 comorbidities (multivariate analyses)
		SF-36 (physical component) β coefficient − 4.91 ($p < 0.001$)
		SF-36 (mental component) β coefficient − 2.84 ($p = 0.005$)
8	Kennedy/2014 [88]	Correlation FCI and WLQ $r = 0.30$ ($p < 0.001$)
		Moderate-severr vs. mild-none work disability (multivariate analyses)
		FCI (1 unit increment) OR = 2.31 (95% CI 1.19–4.50)
9	Öten/2017 [89]	Osteoporosis vs. no osteoporosis
		BASDAI (mean ± SD) 5.08 ± 2.53 vs. 4.08 ± 2.34 (p = ns)
		HAQ (mean ± SD) 0.64 ± 0.63 vs. 0.44 ± 0.44 (p = ns)
10	Pehlevan/2014 [90]	Metabolic syndrome vs. no metabolic syndrome
		BASDAI (mean ± SD) 3.9 ± 2.1 vs. 3.8 ± 2.4 (p = ns)
		HAQ (mean ± SD) 2.2 ± 2 vs. 1.6 ± 1.5 (p = ns)
		RAPID 3 (mean ± SD) 5.8 ± 1.2 vs. 6.8 ± 1.1 (p = ns)
11	Piche/2015 [91]	Correlation smoking (past, current, duration)
		HAQ, FSS, BASFI, pain, FACIT, BASDAI, ASQoL, SF-36 (physical and mental component) $r^2 < 0.2$ ($p < 0.050$)
		DLQI (p = ns)
		Correlation current alcohol intake
		HAQ, FSS, BASFI, pain, FACIT, BASDAI, ASQoL, EQ 5D, DLQI, SF-36 (physical and mental component) $r^2 < 0.2$ ($p < 0.050$)
		Alcohol intake at PsA diagnosis
		SF-36 (physical component) $r^2 < 0.1$ ($p < 0.050$)
12	Sanci/2018 [92]	Metabolic syndrome vs. no metabolic syndrome
		BASDAI median 22 vs. 11 ($p = 0.042$)
		BASFI median 18 vs. 5 ($p = 0.009$)
		HAQ median 0.375 vs. 0.125 ($p = 0.011$)
		PGA median 31 vs. 20 ($p = 0.030$)
		DLQI median 0 vs. 1 (p = ns)
		ASQoL median 7 vs. 3 ($p = 0.017$)

Table 3 continued

Number of study (arbitrary)	Study (first author/ year)	Results
13	Sandikci/2018 [93]	Correlation restless legs syndrome
		FSS r 0.324 (p = 0.001)
		PSQI r 0.305 (p = 0.001)
		SF-36 (physical component) r = − 0.418 (p = 0.001)
		SF-36 (mental component) r = − 0.212 (p = 0.010)
		Restless legs syndrome vs. no syndrome (multivariate analyses)
		FSS β coefficient 0.243 (p = 0.003)
		PSQI β coefficient 0.269 (p = 0.002)
		SF-36 (physical component) β coefficient 0.242 (p = 0.004)
14	Sharma/2017 [94]	FM vs. no FM
		PROMIS HAQ (mean ± SD) 49.26 ± 18.95 vs. 28.88 ± 13.42 ($p < 0.001$)
		HAQ-Pain (mean ± SD) 64.74 ± 11.72 vs. 43.37 ± 13.36 ($p < 0.001$)
		HAQ-Health (mean ± SD) 52.11 ± 14.74 vs. 24.10 ± 14.52 ($p < 0.001$)
		Correlation WPI
		BASDAI r = 0.804 ($p < 0.001$)
		PROMIS HAQ r = 0.478 ($p < 0.001$)
		Correlation SSS
		PROMIS HAQ r = 0.3 ($p < 0.001$)
15	Tanner/2014 [95]	BASFI according to the number of comorbidities
		≥ 5 comorbidities vs. 0 β coefficient 2.33 (p = 0.040)
		≥ 5 comorbidities vs. 1 β coefficient 2.51 (p = ns)
		≥ 5 comorbidities vs. 2 β coefficient 2.18 (p = 0.030)
		≥ 5 comorbidities vs. 3 β coefficient 3.84 (p = ns)
		≥ 5 comorbidities vs. 4 β coefficient 4.20 (p = ns)
16	Ulutatar/2018 [96]	Correlation FIQ
		PSQI r = 0.56 ($p < 0.001$)
		PsAQoL r = 0.69 ($p < 0.001$)
17	Unal/2018 [97]	Correlation painDETECT
		PSQI r = 0.40 (p = 0.010)
		PsAQoL r = 0.66 (p = 0.001)

Table 3 continued

Number of study (arbitrary)	Study (first author/ year)	Results
18	Zaffarana/2016 [98]	Obesity vs. normal weight
		BASFI (mean ± SD) 54.4 ± 2.8 vs. 2.7 ± 2.5 (p = 0.030)
		Pain (mean ± SD) 6.7 ± 7.6 vs. 4.6 ± 2.4 (p = 0.050)

CI Confidence interval, *ns* non-significant, *OR* odds ratio, *RAPID* Routine Assessment of Patient Index Data 3 index

significantly associated with the EQ-5D (β coefficient − 0.04, p = 0.009), the HAQ (β coefficient 0.043, p = 0.210), overall health (β coefficient 0.36, p = 0.010), pain (β coefficient 0.38, p = 0.010), fatigue (β coefficient 0.34, p = 0.040) and pain location (β coefficient 0.54, p = 0.04) [84]. The second study was a prospective cohort of 3571 PsA patients [91]. The results showed a weak correlation between smoking (past and current) and HAQ, Fatigue Severity Scale (FSS), BASFI, pain, Functional Assessment of Chronic Illness Therapy (FACIT), BASDAI, ASQoL and SF-36 (physical and mental component) ($r^2 < 0.2$, $p < 0.050$) [77]. This study also evaluated current alcohol consumption and found that it was also weakly correlated with HAQ, FSS, BASFI, pain, FACIT, BASDAI, ASQoL, EQ-5D, Dermatology Quality of Life Index (DLQI), and SF-36 (physical and mental component) ($r^2 < 0.2$, $p < 0.050$) [91].

This systematic literature review identified a small cross-sectional study that examined the impact of osteoporosis (detected using dual-energy X-ray absorptiometry [DEXA]) on 58 patients with PsA [89]. A comparison of PsA patients with and without this comorbidity did not detect any statistically significant differences in the BASDAI (5.08 ± 2.53 vs. 4.08 ± 2.34, $p > 0.050$) and HAQ scores (0.64 ± 0.63 vs. 0.44 ± 0.44, $p > 0.050$). However, the small size of the study sample may have influenced these results.

A study was also selected for inclusion in our systematic literature review which enrolled 50 PsA patients with restless legs syndrome [93]. In the multivariate analyses and in the comparison with patients who did not have the syndrome, an association was found with the FSS (β coefficient 0.243, p = 0.003), PSQI (β coefficient 0.299, p = 0.002) and the SF-36 (physical component) (β coefficient 0.242, p = 0.004).

Finally, a cross-sectional study with PsA patients diagnosed with neuropathic pain was also included in this review. These patients were evaluated using the painDETECT questionnaire [97]. The authors reported that neuropathic pain was moderately correlated with the PSQI (r = 0.40, p = 0.010) and with the PsAQoL (r = 0.66, $p < 0.001$).

DISCUSSION

Our evaluation of the studies compiled in our systematic literature review confirms that comorbidity has a great impact on PROs in PsA patients.

It should be highlighted that, compared with the number of prevalence studies published on comorbidity and PsA or of those analysing the impact on disease activity or treatment, the number of studies that examine the impact of comorbidity on patient PROs is significantly lower. It is also important to note that much of the current evidence comes from abstracts of scientific meetings that are not subsequently published in the main bibliographic databases. Moreover, the impact of comorbidity on PROs is usually a sub-analysis and not the main objective of the study. Taking also into account the increasing size of the aging population and improvements in the recognition of comorbidity and its treatments, it is clear that more research is needed to properly estimate the real impact of comorbidity on PsA.

We included 18 articles in our systematic literature review, but many of these described small observational studies of moderate quality, some of which were reported in scientific meetings [89, 94]. However, the results of these studies are in line with those depicted in the cohort studies [83, 86], reinforcing the validity of their findings.

Our evaluation of the selected studies revealed a great variability in the number and type of comorbidities studied, as well as in their definitions and measures. In some studies the impact of an individual comorbidity was examined, such as obesity [86, 98], FM [9, 96] or anxiety and depression [85, 87], while in other studies the impact of the number of comorbidities was examined [14, 95], using indexes such as the CCI or FCI. With respect to the PROs, we included a very long list in our review, including function [83, 86, 92], quality of life [14, 84, 93], fatigue [83, 85], pain [83, 91, 98], work disability [88] and/or or sleep quality [93, 6, 97].

We also considered in our evaluation the impact of comorbidity on PROs as observed both in early (though preliminary data) and established PsA. At the time of disease diagnosis, comorbidity might not only be present but also have a relevant impact on PROs, possibly having important consequences in the clinical setting in terms of identifying the comorbidities and treating them as soon as possible.

As expected, we found that the impact of comordidity was greater with an increasing number of comorbidities, as well as with the severity of the comorbidity [83, 86]. Our analysis showed that even just one comorbidity had an impact on the PROs, but we were unable to determine which comorbidity had the greatest impact. We found good-quality evidence showing that obesity might have a negative effect on relevant PROs like function and pain. The same level of evidence examined the effect of smoking (smokers and ex-smokers) on different PROs, including pain, function, fatigue, quality of life and overall health. The multivariate analyses described a significant impact of comorbidity on all of these aspects. Data from low-quality studies suggested that metabolic syndrome might also have a negative impact on BASDAI, function, PGA and quality of life.

Some studies used correlations to assess the impact of comorbidity on PROs in PsA patients. The results from these studies were variable. For example, anxiety and depression wer found to have weak–moderate correlations with function and fatigue. The correlations between FM and BASDAI, function, quality of sleep and quality of life were weak, moderate or strong depending on the PROs. Also, although the impact of alcohol intake on PROs in PsA patients was statistically significant, its correlations with pain, function, fatigue, quality of life and overall health were weak.

Finally, the impact of other comorbidities, such as osteoporosis, restless legs syndrome and neuropathic pain, was also described in the studies included in our systematic literature review, but more data are required to establish their impact on PROs in PsA patients.

There are a number of limitations to the present systematic literature review, of which the most important is the inter-study variability regarding the definition of comorbidities and PROs and the associated criteria and measures; this variability limits the comparability of results among studies. A second limitation is the lack of studies specifically designed to assess the impact of comorbidity on the PROs in PsA patients; such analyses are mostly secondary analyses in the studies included in our systematic literature review.

CONCLUSIONS

In summary, there is sufficient evidence demonstrating the high prevalence of comorbidity [2, 4, 5] in patients with PsA and its impact on outcome measures, treatment response and clinical decision-making [6, 9–13]. A number of studies have also highlighted that comorbidity clearly impairs function and quality of life in PsA patients. Our systematic literature review demonstrates the impact of comorbidity on a wide variety of PROs, such as work disability or sleep quality. We conclude that recognizing and addressing comorbidities

is critical to providing safe and effective treatment to patients with PsA.

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