Running Head: PsA Sex-Specific Differences SLR

Sex-Specific Differences in Patients with Psoriatic Arthritis: A Systematic Review

Laura C. Coates (ORCID: 0000-0002-4756-663X); Irene van der Horst-Bruinsma (ORCID: 0000-0002-8086-9915); Ennio Lubrano (ORCID: 0000-0001-6189-5328); Steph Beaver (ORCID: NA); Emma Drane (ORCID: NA); Baran Ufuktepe (ORCID: 0000-0002-8909-4028); Alexis R.Ogdie (ORCID: 0000-0002-4639-0775)

Funding Statement

This study was sponsored by UCB Pharma. Support for third-party writing assistance for this article, provided by Costello Medical, was funded by UCB Pharma in accordance with Good Publication Practice (GPP3) guidelines. (http://www.ismpp.org/gpp3).

LCC: MBChB, MRCP, PhD. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, Oxfordshire, UK

IEvdHB: MD, PhD. Department of Rheumatology, ZH0D53, Amsterdam UMC/VU University Medical Centre, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands

EL: MD, MSc, PhD, Dipartimento di Medicina e Scienze, Della Salute "Vincenzo Tiberio", Università degli Studi del Molise, Via Giovanni Paolo II, C/da Tappino, 86100, Campobasso, Italy

SB: MSc, Costello Medical Consulting Ltd, Cambridge, Cambridgeshire, UK

ED: PhD, Costello Medical Consulting Ltd, Cambridge, Cambridgeshire, UK

Running Head: PsA Sex-Specific Differences SLR

BU: MD, PhD, UCB Pharma A.S (Turkey), Istanbul, Turkey

ARO: MD, MSCE, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Conflict of Interest

LCC: Grant/research support from AbbVie, Amgen, Celgene, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB Pharma; Consulting fees from: AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Domain, Gilead, Janssen, Lilly; Speaker's bureau for: AbbVie, Amgen, Biogen, Celgene, Gilead, GSK, Janssen, Lilly, Medac, Novartis, Pfizer and UCB Pharma.

IEvdHB: Grant/research support from AbbVie, MSD, Pfizer; Consultant for AbbVie, MSD, Novartis, UCB Pharma; Speaker's bureau: AbbVie, BMS, MSD and Pfizer.

EL: Consultant for AbbVie, Celgene, Novartis, Pfizer and UCB Pharma.

SB, ED: Employees of Costello Medical.

BU: Employee of UCB Pharma.

ARO: Grant/research support to researcher's institution from Pfizer Novartis to Penn, Amgen to Forward/NDB; Consultant for: AbbVie, Amgen, BMS, Celgene, Corrona, Eli Lilly, Janssen, Novartis and Pfizer.

Correspondence to:

Laura C Coates, University of Oxford, Oxford, UK

Running Head: PsA Sex-Specific Differences SLR

Tel: +44 (0)1865 737838

Email: laura.coates@ndorms.ox.ac.uk

Word count: 3,783 (excluding abstract)

Statement of Ethics and Consent

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

Key Indexing Terms

Psoriatic Arthritis; Gender; Patient Reported Outcome Measures.

Running Head: PsA Sex-Specific Differences SLR

Abstract (Word Count: 248/250)

Objective

A systematic review of published literature was conducted to collate evidence on sex-specific differences in clinical characteristics, disease activity and patient-reported outcomes (PROs) in psoriatic arthritis (PsA), including response to treatment.

Methods

Searches of MEDLINE, Embase and the Cochrane Database of Systematic Reviews were performed in November 2020 for observational studies of adults with PsA reporting outcomes by sex (published 2015–), with hand searches of systematic literature review and (network) meta-analysis bibliographies, plus searches of ClinicalTrials.gov and congress abstracts from the European League Against Rheumatism, American College of Rheumatology and American Academy of Dermatology (2019–2020). Eligible studies pre-specified a comparison by sex and reported clinical characteristics and/or disease activity (N>100). Data extracted included patient characteristics, study design, baseline clinical characteristics, and disease activity results (including PROs).

Results

Database searching yielded 3,283 unique records; 31 publications (27 unique studies) were included. The review found generally higher rates of peripheral disease in women, including higher tender joint counts (TJCs). There was some evidence of more axial disease in men, plus greater skin disease burden. There were consistently no differences in Dermatology Life Quality Index scores, though across other PROs women had worse scores, including pain and fatigue. Women had poorer responses to

treatment, indicated by outcome measures such as American College of Rheumatology responses and minimal disease activity.

Conclusion

This review indicates that important differences exist between the sexes in PsA. However, the limited evidence for this conclusion underlines the need for additional research in this area.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease affecting possibly as many as 30% of patients with psoriasis.[1,2] Affecting men and women at equal rates, PsA typically develops in patients aged 30 to 50 years old.[3,4] In addition to pain and swelling of peripheral, and often axial joints, other symptoms commonly experienced include psoriatic skin disease, nail disease, dactylitis and enthesitis.[4,5] Joint damage may be irreversible, resulting in severe functional impairment, and detriment to quality of life (QoL).[4,6]

Previous real-world investigations have suggested that sex-specific differences exist for axial spondyloarthritis (axSpA) and rheumatoid arthritis (RA), manifesting as differences in clinical presentation, response to treatment, and patient-reported outcomes (PROs).[7-9] The pathophysiology of PsA and disease impact has also been reported to differ by sex.[6] However, in contrast with RA

and axSpA, which have a higher prevalence in women and men respectively, PsA has equal sex prevalence.[3]

Investigating and identifying sex-specific differences in PsA is important to encourage greater awareness amongst clinicians when caring for patients, support more personalised care, and inform better clinical decision-making. To our knowledge, this is the first systematic review with the aim of collating real-world evidence on the sex-specific differences in clinical characteristics (such as joint and skin involvement), disease activity, response to treatment and PROs in adults with PsA.

METHODS

Study design

MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR) were systematically searched for literature published January 1, 2015–November 13, 2020, for observational studies reporting outcomes separately by sex in adults with PsA. Interventional studies and studies with <100 included patients were not included. Full eligibility criteria can be found in **Supplementary Table S1.**

Search terms included combinations of free-text and Medical Subject Heading (MeSH) or Emtree terms for PsA, men and women, and study design terms using the Scottish Intercollegiate Guidelines Network (SIGN) filter.[10] Full database search terms can be found in **Supplementary Tables S2–S4**.

Additional keyword searches of annual proceedings for congresses of interest from 2019–2020 were performed; these were the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and American Academy of Dermatology (AAD) annual meetings (**Supplementary Table S5**).

In addition to the electronic databases and grey literature, the bibliographies of all relevant systematic reviews and (network) meta-analyses ([N]MAs) identified during the review were hand searched, to identify any additional, relevant studies for inclusion. ClinicalTrials.gov was also searched (**Supplementary Table S6**).

Record screening followed the most stringent process, as recommended by the Cochrane Collaboration. Each title and abstract were reviewed against the eligibility criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included here to ensure all potentially relevant studies were captured. The results of the two reviewers were compared, and any disagreements resolved by discussion, until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision. The same process was followed for full text publications included at the abstract stage. If the applicability of the inclusion criteria was unclear at the abstract stage, the publication was included so that the full text could be reviewed. This was to ensure only clearly relevant papers were included in the systematic literature review (SLR).

Data extraction

Data extraction was performed in line with guidelines from the York University Centre for Reviews and Dissemination (CRD).[11] Data were extracted by a single individual for each included study. When the initial extraction was complete, a second individual independently verified the extracted information, checking that no relevant information had been missed. Any discrepancies or missing information identified by the second individual was discussed by both until a consensus was reached on the information to present in the extraction grid. If necessary, a third individual arbitrated the final decision.

The data extracted included patient characteristics and characteristics of the included studies, such as study design, population size, interventions under investigation, outcomes stratified by sex, and inclusion and exclusion criteria.

Due to the wide heterogeneity of study designs included in the review, the quality of all included studies was assessed using an abbreviated version of the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields developed by Kmet et al.[12] Quality assessment was conducted by one individual, with decisions verified by a second independent reviewer. If necessary, a third individual arbitrated the final decision.

RESULTS

A total of 4,245 records were retrieved by the electronic database searches. After de-duplication, 3,283 unique records were suitable for review. After title/abstract review, 1,362 records were selected for full text review. Of these, 29 fulfilled the eligibility criteria for inclusion in the review. Following supplementary searches of congresses, ClinicalTrials.gov and systematic review bibliographies, 2 additional records fulfilling the eligibility criteria were identified. In total, 31 publications of 27 unique studies were included in the review (**Supplementary Figure S1**).

Of the included studies, 11 were prospective cohort or observational studies,[13-23] including one post hoc analysis of a prospective observational study.[15] Five included studies were retrospective observational studies,[24-28] plus nine cross-sectional studies.[29-37] One study was reported as a qualitative research study,[38] and lastly one study was reported as a population-based cohort study.[39] Population size varied greatly across the included studies, from 108 patients (Benavent 2019b) to 8,677 patients (Hagberg 2016b; **Supplementary Table S7**).

Quality assessment

Identified studies showed a general low-to-moderate risk of bias, with all conclusions sufficiently supported by the results. However, the studies tended not to report on methods for controlling bias, and in some studies the sources of information were not appropriate, or not accurately described (**Supplementary Table S8**).

Patient characteristics

Patient characteristics for the 27 included studies are presented in **Table 1**.

Nine studies reported fairly complete patient characteristics data, with seven reporting limited data and 11 reporting no patient characteristics, or only patient numbers by sex.

Where reported, there were usually more women than men (15/23 studies). The average age of men and women was similar within all of the included studies (statistically significant result in three studies, non-significant or p value not reported [NR] in 24 studies). Patients' mean age across the studies ranged from 41.9–58.3 years. In six studies, patients initiated a biologic disease-modifying anti-rheumatic drug (bDMARD) as part of their inclusion.[17,40-44] Seven further studies reported current or prior bDMARD exposure, by sex. One study reported significantly greater current/prior bDMARD exposure in women;[45] one reported significantly greater *current* bDMARD exposure in men, but no significant difference for overall exposure.[33] Three studies reported non-significant differences,[19,46,47] and one study did not give a p value.[48]

Where reported (12 studies), disease duration between the sexes was similar. The largest difference was observed in Nas et al. (2017), where the mean (SD) for men was 7.5 (6.8) years, and 10.2 (9.1) years for women (p value=0.023). Body mass index (BMI), which was reported in 10 studies, was

also similar between the sexes. All average BMI values, whether mean or median, were towards the overweight or obese categories (**Table 1**).

The included studies revealed that where recorded, greater proportions of women smoked tobacco than men (6/8 studies; **Table 1**). However, in the one study which reported pack-years (Grivas 2020), lifetime exposure to tobacco smoking was greater for men (**Table 1**).

Clinical and disease characteristics

Seventeen studies reported on clinical characteristics at baseline in patients with PsA (**Figure 1, Supplementary Table S9**).

Peripheral arthritis was generally observed to be more prevalent in women, and three of the four studies assessing this reported significantly more peripheral arthritis in women at baseline, compared with men. One study showed no significant difference by sex. This greater presence of peripheral arthritis in women, reported generally, was further supported by studies that specifically reported tender joint count (TJC). Eight studies (8/14) concluded that women had a significantly greater mean or median TJC than men, while one study reported a significantly greater mean TJC in men. Five studies did not report a significant difference by sex. Unlike the results for TJC, results were mixed with regard to swollen joint count (SJC), as three studies (3/14) reported a significantly higher mean or median SJC in women, whereas the remaining 11 studies did not report significant differences by sex.

When considering axial disease (**Supplementary Table S9**), three studies (3/8) reported significantly greater prevalence in men compared with women, and a further two studies reported that men had a numerically greater prevalence, although this was not statistically significant.

Three studies (3/4) demonstrated that women had significantly worse Maastricht Ankylosing Spondylitis Enthesitis (MASES) scores than men. When considering all ten studies that reported enthesitis, by simple count of men and women, and considering either the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) enthesitis domain or MASES scores, three reported numerically greater occurrence of enthesitis or worse scores for men. In Nas et al. (2017), although results were not statistically significant, women scored slightly worse in the MASES measure of enthesitis.

In contrast, results for skin disease (plaque psoriasis), measured by the body surface area (BSA) score or Psoriasis Area and Severity Index (PASI), indicated a tendency to worse skin disease in men than women. Five studies (5/12) reported significantly worse scores for men, and this was five of the seven studies that specifically reported PASI scores. In the remaining two, scores for men were numerically higher but without a statistically significant difference.

No significant differences were observed in current dactylitis by sex (0/6). However, considering the presence of nail disease, the three studies reporting

on this showed numerically greater occurrence in men. In one study this was statistically significant (**Supplementary Table S9**).

Comorbidities reported at baseline included measures such as the Charlson Comorbidity Score, Fibromyalgia Rapid Screening Tool (FIRST) score and counts of patients with specific comorbidities e.g. cardiovascular disease, diabetes, and depression (**Supplementary Table S10**). Many of the outcomes were only reported in one study. Four studies reported total number of comorbidities by sex, and in three of four studies with relevant results, there were greater numbers of comorbid or concomitant diseases in women than men. However, when looking at diabetes mellitus specifically, and while there were no statistically significant differences in prevalence between the sexes, there were numerically greater proportions of men with the condition (4/6 results). Liver disease was reported in two studies,[17,49] with one statistically significant result towards greater prevalence in men. Where reported, fibromyalgia was significantly worse in women than men, measured by the FIRST score (2/2) (**Supplementary Table S10**).

Clinical characteristics reported after treatment were also collated (**Supplementary Table S11**); these included TJC and SJC, painful joint count, enthesitis, dactylitis, nail disease and C-reactive protein (CRP). Limited evidence was identified, and no consistent differences were observed by sex. Only one study reported statistically significant outcomes: Colombo et al. (2016) demonstrated that women had significantly higher painful joint counts

at Month 6, and significantly higher swollen joint counts at Month 12 following treatment with immunosuppressive therapies. In Zavada et al. (2020), men showed a greater reduction from baseline in CRP levels (mg/L) at Month 12, however this result was not adjusted for differences at baseline**.**

Disease activity thresholds and scores with treatment

Four studies reported changes in achievement of specific disease activity thresholds over time on treatment, by sex (**Supplementary Table S12**).

17 August 2022

The majority (3/4) of studies reported responses with TNF inhibitors; one study looked at unspecified biologic therapy. The outcomes reported included ACR20, ACR50, ACR70, low disease activity, delta Disease Activity Score 28 (dDAS28) improvement of ≥1.2, Disease Activity in Psoriatic Arthritis (DAPSA) remission, Good EULAR Response, minimal disease activity (MDA), minimal joint activity, and Psoriatic Arthritis Response Criteria (PsARC) response. Most outcomes were only reported by one study, however Good EULAR response featured in two studies, and minimal disease activity in three studies.

As well as these thresholds of response, some studies reported absolute disease activity scores after time on treatment. This included Ankylosing Spondylitis Disease Activity Score (ASDAS), BASDAI, Disease Activity Score 28 (DAS28), patient's global assessment of disease activity (PtGA) and physician's global assessment of disease activity (PhGA). Only one study reported on each of these absolute disease activity scores (**Supplementary Table S12**).

Aside from disease activity thresholds at single timepoints, four of these studies reported changes in disease activity on treatment over multiple timepoints (**Supplementary Table S12**). Evidence of higher response rates in men remained consistent over time and across all reported outcomes. Of the studies that reported Good EULAR response, higher response rates among men (with tumor necrosis factor inhibitor [TNFi] treatment) were seen

at both Month 3 and Month 6. The identified evidence also found that men had higher rates of MDA, and ACR20/50/70, than women, following treatment with TNFis. Similar to Good EULAR response, these results remained consistent between Month 3 and Month 6. In one study reporting minimal disease activity at Month 12, there was similarly a greater response rate in men than women.

In terms of absolute disease activity scores, overall women had higher disease activity than men across most outcomes at the time points studied (**Supplementary Table S12**).

Patient-reported outcomes

Seventeen studies reported PROs separately by sex at baseline, including a wide range of outcomes and PRO instruments that measure symptom burden, functional status, and health-related quality of life (HRQoL) (**Figure 2, Supplementary Table S13**). The overall picture across studies and across all PRO measures was that scores in women were significantly worse than in men, with few exceptions.

For 8/13 study outcomes that included self-reported pain at baseline, women had significantly worse pain than men. Across the nine studies that recorded it, women also reported significantly higher levels of fatigue compared with men. Women also scored significantly worse on the Health Assessment

17 August 2022

Questionnaire (HAQ) – the gold standard tool for measuring functional status in rheumatoid arthritis, which has been validated for use in PsA.[50] Higher scores on the HAQ indicate increased difficulty with activities of daily living. All 12 studies that reported HAQ, HAQ-Disability Index (HAQ-DI), or HAQ for Spondyloarthropathies (HAQ-S) results demonstrated significantly worse scores for women. Though one study found a non-significant difference (Nas 2017; when results were adjusted for various baseline characteristics), women still had numerically worse scores.

While other outcomes such as EuroQol-5 Dimensions (EQ-5D), Psoriatic Arthritis Impact of Disease 12-Item (PsAID-12), sleep disturbances, depression, Modified Health Assessment Questionnaire (MHAQ), 15-dimensional instrument (15D), Global Health VAS, and several Short Form-36 (SF-36) domains (e.g. role limitation and social functioning) were less frequently reported, it was predominantly women that had worse scores. The Dermatology Life Quality Index ([DLQI], a validated measure assessing dermatology-specific HRQoL) was the only measure where there were consistently no differences in scores between women and men (**Figure 2, Supplementary Table S13**).

PROs (pain, fatigue, HAQ scores and EQ-5D scores) reported by sex after treatment were also collated. Limited evidence was identified, and no consistent differences were observed by sex (**Supplementary Table S11**).

17 August 2022

DISCUSSION

The results of this systematic review support the existence of sex-specific differences in PsA. Further research in the form of large-scale observational studies, qualitative patient interviews, and analyses of particular outcomes adjusted for comorbidities or clinical characteristics would be valuable to confirm and further elaborate on these findings, as well as investigation of the mechanisms for these differences. Nonetheless, this systematic review of published literature about real-world populations may be the first of its kind to capture this breadth of psoriatic arthritis disease aspects compared by sex.

Several studies identified in this review found sex-specific differences in clinical characteristics, with a significantly greater presence of peripheral arthritis in women. This result aligns with previous investigations that suggest peripheral disease is more prevalent in women.[3] However, the evidence for this from our included studies was principally from higher TJCs rather than SJCs, and peripheral arthritis stemming from joint inflammation would be expected to encompass both. Therefore the question remains of whether these observations in women are more linked to differences in inflammation or pain perception. Differences are unlikely to be related to treatment durations, which were shown to be similar between the sexes.

In line with the majority of other available literature, this review found some evidence to support findings that axial disease (recorded in our findings if it

was described as present or indicated with Bath Ankylosing Spondylitis Metrology Index [BASMI] scores), typically associated with greater detriment to QoL, is more prevalent in men.[3,4] However, alternative evidence suggests that there is no difference in axial disease prevalence between men and women with PsA. Most notably, analysis of the US Corrona PsA/Spondyloarthritis Registry found no significant differences in the proportions of men and women with axial involvement.[51]

Differences in the prevalence of axial PsA disease by sex may be analogous to what is seen for axSpA. For example, there is a significant male predominance in ankylosing spondylitis (AS), whose diagnostic criteria (modified New York criteria) include radiographic changes in the sacroiliac joints. By contrast, there are approximately equal numbers of men and women with *non-radiographic* axSpA.[52] It is possible that these differences by sex also exist in PsA, depending on the presence of axial radiographic changes. However, it was not possible to discern from the included studies whether patients with axial disease had radiographic changes. Additionally, sex differences in axial PsA disease are not known to relate to disease severity or prognosis.

Many studies identified in this review found no difference between sexes in the presence or severity of particular clinical characteristics, but these results should be considered in the context of evidence suggesting that the

instruments used in this field are not sensitive to sex-specific differences.[53] For example, men and women in this review had similar SJCs, but the same number of swollen joints may be associated with more pain and functional deterioration for members of one sex, which would not be captured.[53] We considered study sample sizes, regarding outcomes where the picture was more mixed between significant and non-significant or opposing results. For presence of peripheral arthritis at baseline, as well as the TJC, worse outcomes in women are a consistent result across a range of study sample sizes. In the skin domain the significant results came from smaller studies, but it is notable that where there was a significant result it tended to be in men.

In this review, women tended to record worse PRO scores compared with men. This was particularly clear in the case of pain, fatigue and HAQ scores, suggesting greater disease impact in women. One reason for these observations might be differences in patterns of unpaid work. If women are more likely to take on caring responsibilities and household work, this may make it particularly difficult, for example, to avoid using a specific joint. A further reason might be biological differences between men and women affecting the experience of disease, including the effect of sex hormones on pain perception[54] (though it is unclear what the effect of menopause might be). Furthermore, sex differences in levels of central sensitisation to pain

might impact on patient-reported pain.[3,55] Research is ongoing in this area and studies of mice have demonstrated the potential protective role of testosterone against arthritis and chronic pain.[56,57]

Interestingly, while higher PASI and BSA scores were observed for men, no differences in DLQI scores were observed between men and women. In an observational study in patients with psoriasis, men had higher PASI scores, however women gave worse ratings than men with the DLQI.[58] This discrepancy in PASI and DLQI score might be because women are more likely to adhere to emollient application, and thus could be systematically underscored with the physician-administered PASI. Furthermore, due to possibly greater stigmatization of women with skin conditions, they may report worse scores on PRO measures.[59]

Psychological distress has been demonstrated to lead to heightened symptom burden and decreased treatment adherence.[8] Thus, measuring patients' perceptions of their health with PROs is key to providing more patient-centred and personalised care. PsA-specific PRO instruments such as the PsA-specific Quality of Life (PsAQoL) instrument and PsAID-12, studied separately for each sex, would have a greater ability to detect changes in patients' health, and assess the aspects of QoL that are most important to men and women. PsA-specific measures may represent a better way to illustrate sex-specific

17 August 2022

differences in the experience of the disease, however, they were only employed in six included studies.[18,19,36,45,46,60]

Furthermore, it is important to consider that while PROs can capture levels of self-reported physical function, the source of pain or reason for the functional impairment cannot be known in detail. In order to better capture the impact of disease on patients and pursue the most relevant improvements in clinical outcomes, qualitative patient interviews might be a useful way to explore sex-specific differences in PsA. They could also be used to understand how differences in clinical characteristics such as peripheral or axial disease might translate into functional differences between the sexes. Patient interviews could also help elucidate whether there are patterns in which aspects of PsA matter most to men and women.

Although few studies reported treatment response, a general trend observed was that men had better treatment responses than women. This effect has been observed across various rheumatic diseases.[3,61] While it is possible that intrinsic physiological differences impact on the way men and women respond to treatment, differences in coping mechanisms between the sexes have also been shown to influence response to treatments.[62] Thus, the difference in response rates are interesting to consider alongside the PRO results in this SLR, which suggest that the impact of PsA on men is smaller than it is on women.

17 August 2022

Clinical manifestations and pathophysiology of other rheumatological diseases have been shown to differ by sex.[7] Causes for these differences may relate to the effect of sex hormones, different gene expression, occupational exposures or differences in pain perception.[3] Although exact mechanisms are currently unclear, it is likely that a complex interplay of biological and social factors are responsible for the sex-specific differences observed in PsA and the wider group of rheumatological diseases. This review highlights that further investigation of the sex-specific differences in PsA is warranted, including the potential mechanisms producing these differences. It is likely that both biological (sex) and sociological (gender) factors contribute to these differences. The differences highlighted are marked and should be considered when designing future research studies, particularly head-to-head comparisons of different treatments. This is also an issue that should be considered by clinicians caring for people with PsA as it may support more tailored management strategies for all patients with PsA in clinical practice. Such strategies might ultimately include a lower threshold to provide women with adequate pain medication, or greater readiness to offer support with the management of skin disease in men.

Strengths of this review include adherence to best practice systematic review methods, and the focus on observational studies from a range of geographies. These studies characterise disease in real-world clinical practice,

so are expected to be broadly generalisable to the PsA population versus randomised controlled studies. However, the focus on observational studies means that there is variation, both in patient characteristics and the measurement of outcomes, which sometimes used a variety of instruments. This impeded adequate aggregation of some results, and given that many outcomes were reported from single studies, pooling of results was often not possible. Studies with populations <100 were omitted, as they were less likely to detect differences between the sexes. However, it is still possible that these studies had potentially relevant findings. While included studies had populations ≥100, certain outcomes within studies had results for <100 patients.

In conclusion, evidence from this systematic review suggests that some clinical characteristics in PsA differ between the sexes, particularly the presence of peripheral arthritis, and specifically TJC—shown to be greater in women—as well as skin disease burden, shown to be greater in men. Women report worse scores across a range of PROs, while there is evidence that men respond better to treatments. While this review did not find consistent evidence of the differences across all included studies, or for all clinical characteristics, clinician awareness of the potential differences in clinical characteristics and patients' perceptions of their disease may help to improve patient outcomes.

ACKNOWLEDGEMENT

The authors acknowledge Susana Lobo Berastegui, MSc, MBA, UCB Pharma, Madrid, Spain for publication coordination. The authors also acknowledge Harry Freeman, BSc, Emma Worthington, MPH and Ashley Jaggi, PhD, from Costello Medical, for support with the SLR and Ashley Jaggi, PhD, and Lucy Berry, MBBS, from Costello Medical, for medical writing and editorial assistance based on the authors' input and direction.

AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: LCC, IEvdHB, EL, SB, ED, BU, ARO; substantial contributions to analysis and interpretation of the data: LCC, IEvdHB, EL, SB, ED, BU, ARO; drafting the article or revising it critically for important intellectual content: LCC, IEvdHB, EL, SB, ED, BU, ARO; final approval of the version of the article to be published: LCC, IEvdHB, EL, SB, ED, BU, ARO.

REFERENCES

1. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. Ann Rheum Dis 2013;72:736-40.
2. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014;73:48-55.
3. Eder L, Chandran V, Gladman D. Gender-related differences in patients with psoriatic arthritis. Int J Clin Rheumtol 2012;7:641-9.

4. Gottlieb AB, Merola JF. Axial psoriatic arthritis: An update for dermatologists. J Am Acad Dermatol 2021;84:92-101.
5. Haroon M, FitzGerald O. Psoriatic arthritis: complexities, comorbidities and implications for the clinic. Expert Rev Clin Immunol 2016;12:405-16.
6. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis Suppl 2005;64 (Suppl 2):ii14-ii17.
7. Maynard C, Mikuls TR, Cannon GW, et al. Sex Differences in the Achievement of Remission and Low Disease Activity in Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2020;72:326-33.
8. Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). Clin Rheumatol 2021;40:2753-61.
9. Lubrano E, Perrotta FM, Manara M, et al. The Sex Influence on Response to Tumor Necrosis Factor-α Inhibitors and Remission in Axial Spondyloarthritis. J Rheumatol 2018;45:195-201.
10. Scottish Intercollegiate Guidelines Network (SIGN) filter for observational studies. N.D. Available at: https://www.sign.ac.uk/what-we-do/methodology/search-filters/. [Accessed on: 5th May 2021].
11. University of York, Centre for Reviews and Dissemination (CRD). 2009. Systematic Reviews: CRD's guidance for undertaking reviews in health care. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. [Accessed on: 4th May 2021].
12. Kmet LM, Cook LS, Lee RC. Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields. Education & Research Archive: University of Alberta, 2004. (https://era.library.ualberta.ca/items/48b9b989-c221-4df6-9e35-af782082280e/view/a1cffdde-243e-41c3-be98-885f6d4dcb29/standard_quality_assessment_criteria_for_evaluating_primary_research_papers_from_a_variety_of_fields.pdf).
13. Benavent D, Plasencia C, Navarro-Compán V, et al. Differences and similarities according to gender in patients with psoriatic arthritis initiating biological therapy. Ann Rheum Dis 2019;78:901.
14. Benavent D, Plasencia C, Navarro-Compán V, et al. Gender influence on treatment effectiveness in Psoriatic Arthritis. Ann Rheum Dis 2019;78:1832.
15. Colombo D, Chimenti S, Grossi PA, et al. Prevalence of acute and chronic viral seropositivity and characteristics of disease in patients with psoriatic arthritis treated with cyclosporine: a post hoc analysis from a sex point of view on the observational study of infectious events in psoriasis complicated by active psoriatic arthritis. Clin Cosmet Investig Dermatol 2016;9:1-7.

16. García R, Fernandez-Prada M, Conesa A, et al. Are there any differences in the effectivity and saftey of Certolizumab Pegol in patients with Psoriatic Arthritis according to their gender? Ann Rheum Dis 2019;78:1840.
17. Højgaard P, Ballegaard C, Cordtz R, et al. Gender differences in biologic treatment outcomes-a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. Rheumatology (Oxford) 2018;57:1651-60.
18. Nurmohamed MT, Van der Horst-Bruinsma I, Van Kuijk AW, et al. Effect of sex on disease characteristics and disease impact in patients with Psoriatic Arthritis (PsA): Insights from the real-world, observational multinational PsABio cohort. Ann Rheum Dis 2020;79:1171.
19. Nas K, Capkin E, Dagli AZ, et al. Gender specific differences in patients with psoriatic arthritis. Mod Rheumatol 2017;27:345-9.
20. Nas K, Kiliç E, Tekeoğlu İ, et al. The effect of gender on disease activity and clinical characteristics in patients with axial psoriatic arthritis. Mod Rheumatol 2020;31:1-6.
21. Passia E, Vis M, Coates LC, et al. Sex specific Differences in Psoriatic Arthritis. Ann Rheum Dis 2020;79:38.
22. Vieira-Sousa E, Eusébio M, Ávila-Ribeiro P, et al. Gender differences in psoriatic arthritis – Impact on tumour necrosis factor inhibitors persistance and response. Ann Rheum Dis 2019;78:1264.
23. Zavada J, Nekvindova L, Pavelka K, Horak P, Vencovský J. Gender difference in disease severity and treatment outcomes among patients with Rheumatoid Arthritis (RA), Axial Spondyloarthritis and Psoriatic Arthritis (PsA) starting treatment with targeted therapy in the Czech Republic. Ann Rheum Dis 2020;79:1907.
24. Hagberg KW, Li L, Peng M, Shah K, Paris M, Jick S. Incidence rates of suicidal behaviors and treated depression in patients with and without psoriatic arthritis using the Clinical Practice Research Datalink. Mod Rheumatol 2016;26:774-9.
25. Hagberg KW, Li L, Peng M, Paris M, Shah K, Jick SS. Rates of Cancers and Opportunistic Infections in Patients With Psoriatic Arthritis Compared With Patients Without Psoriatic Arthritis. J Clin Rheumatol 2016;22:241-7.
26. Ng CR, Loh YL. Gender differences in the prevalence of metabolic comorbidities among psoriatic arthritis patients-a single centre experience in Malaysia. Int J Rheum Dis Suppl 2018;21 Suppl 1:63.
27. Kalyoncu U, Bayindir Ö, Ferhat Öksüz M, et al. The Psoriatic Arthritis Registry of Turkey: results of a multicentre registry on 1081 patients. Rheumatology (Oxford) 2017;56:279-86.
28. Duruoz MT, Gezer HH, Nas K, et al. Gender-based Analysis of Disease Activity and Its Relationship with Anxiety, Depression, Fatigue, and Fibromyalgia in Psoriatic [abstract]. Arthritis Rheumatol Suppl 2019;71 Suppl 10.

29. Braaten TJ, Zhang C, Presson AP, Breviu B, Clegg D, Walsh JA. Gender Differences in Psoriatic Arthritis With Fatigue, Pain, Function, and Work Disability. J Psoriasis Psoriatic Arthritis 2019;4:192-7.
30. Gossec L, Walsh JA, Michaud K, et al. Differenes in clinical characteristics, Quality of Life, Disability, and work productivity in psoriatic arthritis by gender: findings from a cross-sectional survey in the US and Europe. Ann Rheum Dis 2019;78:1272.
31. Grivas A, Kapniari I, Tzannis K, et al. Gender differences in Psoriatic Arthritis disease characteristics: evidence for worse disease in women. Ann Rheum Dis 2020;1692-3.
32. Haque N, Lories RJ, de Vlam K. Comorbidities Associated with Psoriatic Arthritis Compared with Non-psoriatic Spondyloarthritis: A Cross-sectional Study. J Rheumatol 2016;43:376-82.
33. Haugeberg G, Michelsen B, Kavanaugh A. Impact of skin, musculoskeletal and psychosocial aspects on quality of life in psoriatic arthritis patients: A cross-sectional study of outpatient clinic patients in the biologic treatment era. RMD Open 2020;6:e001223.
34. Haugeberg G, Hoff M, Kavanaugh A, Michelsen B. Psoriatic arthritis: exploring the occurrence of sleep disturbances, fatigue, and depression and their correlates. Arthritis Res Ther 2020;22:198.
35. Kenar G, Yarkan H, Zengin B, Can G, Birlik M, Önen F. Gender does not make a difference in "composite psoriatic disease activity index (CPDAI)" in patients with psoriatic arthritis. Rheumatol Int 2018;38:2069-76.
36. Gorlier C, Gossec L, Puyraimond-Zemmour D, et al. Interpretation of Symptoms Should Take into Account Gender in Psoriatic Arthritis: An Analysis of 451 Patients [abstract]. Arthritis Rheumatol Suppl 2018;70: Suppl 10.
37. Lindström U, Bremander A, Haglund E, Bergman S, Petersson IF, Jacobsson LT. Back pain and health status in patients with clinically diagnosed ankylosing spondylitis, psoriatic arthritis and other spondyloarthritis: a cross-sectional population-based study. BMC Musculoskelet Disord 2016;17:106.
38. Landgren AJ, Bilberg A, Eliasson B, et al. Cardiovascular risk factors are highly overrepresented in Swedish patients with psoriatic arthritis compared with the general population. Scand J Rheumatol 2020;49:195-9.
39. Kristensen LE, Jørgensen TS, Coates LC, et al. THU0284 Haq in psoriatic arthritis is driven by gender, inflammation and ageing: observational data from cohort studies in uk, denmark, iceland and sweden. Ann Rheum Dis 2018;77:360.
40. Nurmohamed MT, Van der Horst-Bruinsma I, Van Kuijk AW, et al. Effect of sex on disease characteristics and disease impact in patients in with Psoriatic Arthritis (PsA): Insights from the real-world, observational multinational PsABio cohort [abstract]. Ann Rheum Dis Suppl 2020;79 Suppl 1:1171-2.

41. Vieira-Sousa E, Eusébio M, Ávila-Ribeiro P, et al. Gender differences in psoriatic arthritis – Impact on tumour necrosis factor inhibitors persistance and response [abstract]. Ann Rheum Dis Suppl 2019;78: Suppl 2:1264-5.
42. Benavent D, Plasencia C, Navarro-Compán V, et al. Differences and similarities according to gender in patients with psoriatic arthritis initiating biological therapy [abstract]. Ann Rheum Dis Suppl 2019;78 Suppl 2:901.
43. Benavent D, Plasencia C, Navarro-Compán V, et al. Gender influence on treatment effectiveness in Psoriatic Arthritis [abstract]. Ann Rheum Dis Suppl 2019;78 Suppl 2:1832-3.
44. Zavada J, Nekvindova L, Pavelka K, Horak P, Vencovský J. Gender difference in disease severity and treatment outcomes among patients with Rheumatoid Arthritis (RA), Axial Spondyloarthritis and Psoriatic Arthritis (PsA) starting treatment with targeted therapy in the Czech Republic [abstract]. Ann Rheum Dis Suppl 2020;79 Suppl 1:1907-8.
45. Braaten TJ, Zhang C, Presson AP, Breviu B, Clegg D, Walsh JA. Gender Differences in Psoriatic Arthritis With Fatigue, Pain, Function, and Work Disability. J Psoriasis Psoriatic Arthritis 2019;4:192-7.
46. Gossec L, Walsh J, Michaud K, et al. Differences in clinical characteristics, Quality of Life, Disability, and work productivity in psoriatic arthritis by gender: findings from a cross-sectional survey in the US and Europe. Ann Rheum Dis Suppl 2019;78 Suppl 2:1272.
47. Haugeberg G, Hoff M, Kavanaugh A, Michelsen B. Psoriatic arthritis: exploring the occurrence of sleep disturbances, fatigue, and depression and their correlates. Arthritis Res Ther 2020;22:198.
48. García R, Fernández-Prada M, Conesa A, et al. Are there any differences in the effectivity and saftey of Certolizumab Pegol in patients with Psoriatic Arthritis according to their gender? [abstract]. Ann Rheum Dis Suppl 2019;78 Suppl 2:1840.
49. Grivas A, Kapniari I, Tzannis K, et al. Gender differences in Psoriatic Arthritis disease characteristics: evidence for worse disease in women [abstract]. Ann Rheum Dis Suppl 2020:79 Suppl 1:1692-3.
50. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken) 2011;63:S4-S13.
51. Mease PJ, Palmer JB, Liu M, et al. Influence of Axial Involvement on Clinical Characteristics of Psoriatic Arthritis: Analysis from the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. J Rheumatol 2018;45:1389-96.
52. Kenar G, Can G, Cetin P, et al. Gender Differences in Axial Spondyloarthritis [abstract]. Ann Rheum Dis Suppl 2015;74 Suppl 2:1154.

17 August 2022

53. van Vollenhoven RF. Sex differences in rheumatoid arthritis: more than meets the eye. BMC Medicine 2009;7:12.
54. Tannenbaum C, Day D. Age and sex in drug development and testing for adults. Pharmacol Res 2017;121:83-93.
55. Aloisi AM. Why We Still Need To Speak About Sex Differences and Sex Hormones in Pain. Pain Ther 2017;6:111-4.
56. Keith RC, Sokolove J, Edelman BL, et al. Testosterone is protective in the sexually dimorphic development of arthritis and lung disease in SKG mice. Arthritis Rheum 2013;65:1487-93.
57. Lesnak JB, Inoue S, Lima L, Rasmussen L, Sluka KA. Testosterone protects against the development of widespread muscle pain in mice. Pain 2020;161:2898-908.
58. Lesuis N, Befrits R, Nyberg F, van Vollenhoven RF. Gender and the treatment of immune-mediated chronic inflammatory diseases: rheumatoid arthritis, inflammatory bowel disease and psoriasis: an observational study. BMC Med 2012;10:82.
59. Schmid-Ott G, Künsebeck HW, Jäger B, et al. Significance of the stigmatization experience of psoriasis patients: a 1-year follow-up of the illness and its psychosocial consequences in men and women. Acta Derm Venereol 2005;85:27-32.
60. Nas K, Kiliç E, Tekeoğlu İ, et al. The effect of gender on disease activity and clinical characteristics in patients with axial psoriatic arthritis. Mod Rheumatol 2020;31:869-74.
61. Jawaheer D, Olsen J, Hetland ML. Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis - results from the DANBIO registry. J Rheumatol 2012;39:46-53.
62. Intriago M, Maldonado G, Cárdenas J, Ríos C. Clinical Characteristics in Patients with Rheumatoid Arthritis: Differences between Genders. Sci World J 2019;2019:8103812.

17 August 2022

FIGURE LEGENDS

Figure 1. Summary of clinical characteristics

[a]Study reported p values for more than one comparison and the result was different between comparisons. SJC: swollen joint count; TJC: tender joint count.

Figure 2. Summary of Patient-Reported Outcomes

[a]Study reported p values for the comparison of results with (left hand side of the circle) and without (right hand side of the circle) adjustment for age, BMI, smoking and disease progression. ASQoL: Ankylosing Spondylitis Quality of Life; BASFI: Bath Ankylosing Spondylitis Functional Index; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQoL-5 Dimensions; HAQ: Health Assessment Questionnaire; HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies; MHAQ: Modified Health Assessment Questionnaire; PsAQoL: Psoriatic Arthritis Quality of Life: SF-36 PCS: Short Form-36 physical component summary; SF-36 MSC: Short Form-36 mental component summary; VAS: visual analogue scale.

TABLE LEGENDS

Table 1. Patient characteristics

BMI: body mass index; NR: not reported; SD: standard deviation.

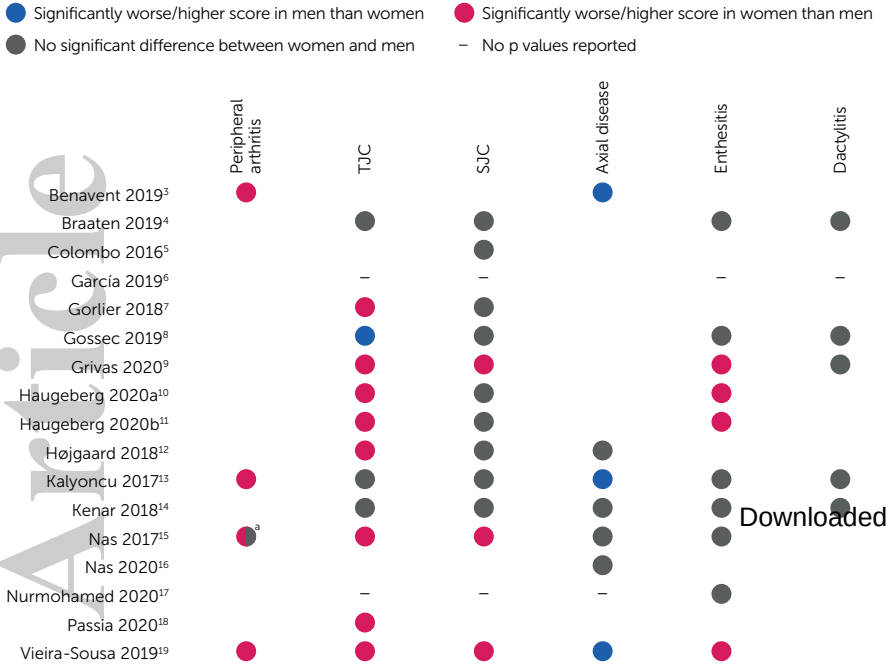

Table 1. Patient characteristics

Study name	Patients (N)	Sex Male (N, %)	Age (years) Male/Female		Disease duration (years) Male/Female		BMI (kg/m²) Male/Female		Smoking status Male/Female	
			Outcome	p value	Outcome	p value	Outcome	p value	Outcome	p value
Benavent 2019a	109	55 (51)	Mean (SD): 55.8 (12.2)/58.3 (16.7)	0.2	Mean (SD): 17.3 (7.3)/18.1 (10.9)	0.6	Mean (SD): 27.7 (3.8)/26.7 (5.9)	0.3	NR/NR	NR
Benavent 2019b	108	55 (50.9)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Braaten 2019	253	115 (45.4)	Mean (SD): 47.0 (12.3)/51.4 (14.1)	0.01	Mean (SD): 5.6 (8.8)/5.2 (10.2)	0.44	NR/NR	NR	NR/NR	NR
Colombo 2016	225	121 (53.8)	Mean (SD): 48.9 (12.8)/50.8 (12.5)	0.2499	NR/NR	NR	NR/NR	NR	NR/NR	NR
Duruoz 2019	1134	408 (36)	Mean (SD): 46.0 (12.2)/47.4 (12.1)	NR	Median (range): 5 (0–42)/4 (0–44)	NR	Mean (SD): 27.7 (3.7)/29.3 (5.5)	NR	NR/NR	NR
Garcia 2019	347	151 (43.5)	Mean (Min–Max): 50.5 [22–78]/48.5 [22.3–81.1]	NR	Mean (IQR): 6.9 [1.2–10.0]/6.5 [1.8–8.7]	NR	NR/NR	NR	NR/NR	NR
Gossec 2019	2270	1223 (53.9)	Mean (SD): 48.8 (12.8)/48.3 (13.7)	0.42	Mean (SD): 4.95 (5.79)/4.87 (6.15)	0.42	NR/NR	NR	NR/NR	NR
Grivas 2020	135	52 (38.5)	Median (IQR): 56.6 (50–65.7)/55.1 (46.8–63)	0.419	Mean: 2.8/2.4	0.605	Mean (range): 30.1 (26.8–33.3)/27.9 (24.9–35)	0.181	Pack years (range): 27.5 (0–46)/ 15 (5–30)	0.002

Hagberg 2016a	8493	4248 (50.0)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Hagberg 2016b	8677	4325 (49.8)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Haque 2016	262	158 (60.3)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Haugeberg 2020a	137	68 (49.6)	Mean (SD): 51.8 (10.4)/52.8 (10.4)	0.56	Mean (SD): 8.6 (7.3)/9.0 (6.3)	0.70	Mean (SD) 28.5 (3.9)/28.2 (4.8)	0.67	n (%): 9 (13.2)/15 (21.7)	0.19
Haugeberg 2020b	131	66 (50.4)	Mean (SD): 51.4 (10.2)/52.5 (10.2)	0.55	Mean (SD): 8.4 (7.0)/8.8 (6.1)	0.73	Mean (SD): 28.6 (3.9)/27.9 (4.9)	0.36	n (%): 9 (13.6)/12 (18.5)	0.45
Hojgaard 2018	1750	815 (46.6)	Mean (SD): 46.9 (11.4)/48.8 (12.6)	<0.01	Mean (range):4 (1–10)/3 (1–8)	<0.01	Mean (SD): 28.1 (5.1)/27.5 (6.1)	0.18	n (%): 155 (26)/233 (32) (N=591/733)	0.03
Kenar 2018	117	39 (33.3)	Median (range): 46 [25–73]/49 [24–70]	0.28	Median (range): 6 (1–44)/6 (1–44)	0.80	Mean (min–max): 26.8 (21.0–33.9)/27.8 (18.9–41.0)	0.52	%: 20.5/25.6	0.15
Kristensen 2018	1473	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Landgren 2020	692	332 (48.0)	Mean (SD): 54.8 (10.8)/56.4 (11.9)	0.066	NR/NR	NR	Mean (SD): 27.5 (4.1)/28.0 (6.1)	0.194	N (%): 25 (7.5)/49 (13.6)	0.008
Lindstrom 2016	1310	552 (42.1)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Nas 2017	187	72 (38.5)	Mean (SD): 43.8 (13.6)/41.9 (11.6)	0.309	Mean (SD): 7.5 (6.8)/10.2 (9.1)	0.023	Mean (SD): 25.9 (3.8)/28.5 (7.0)	0.001	N (%):34 (47.2)/26 (22.8)	0.001

Nas 2020	373	150 (40.2)	Mean (SD): 45.9 (12.2)/47.4 (12.0)	0.25	Mean (range): 5 (0–42)/4 (0–41)	0.206	Mean (SD): 28.1 (4.1)/30.0 (5.7)	<0.001	NR/NR	NR
Ng 2018	163	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Nurmohamed 2020	929	417 (44.5)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Passia 2020	567	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Kalyoncu 2017	1081	379 (35.1)	Mean (SD): 44.4 (12.5)/48.3 (12.8)	<0.001	NR/NR	NR	NR/NR	NR	NR/NR	NR
Gorlier 2018	451	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Vieira-Sousa 2019	750	373 (49.7)	NR/NR	NR	NR/NR	NR	NR/NR	NR	NR/NR	NR
Zavada 2020	493	262 (53.1)	NR/NR	NR	NR/NR	NR	NR/NR	NR	N (%): 100 (43.3)/132 (63.2)	0.168