Meta-analysis

Psoriatic arthritis screening: a systematic review and meta-analysis

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Abstract

Objective. To systematically review the accuracy and characteristics of different questionnaire-based PsA screening tools.

Methods. A systematic review of MEDLINE, Excerpta Medical Database, Cochrane Central Register of Controlled Trials and Web of Science was conducted to identify studies that evaluated the accuracy of self-administered PsA screening tools for patients with psoriasis. A bivariate meta-analysis was used to pool screening tool-specific accuracy estimates (sensitivity and specificity). Heterogeneity of the diagnostic odds ratio was evaluated through meta-regression. All full-text records were assessed for risk of bias with the QUADAS 2 tool.

Results. A total of 2280 references were identified and 130 records were assessed for full-text review, of which 42 were included for synthesis. Of these, 27 were included in quantitative syntheses. Of the records, 37% had an overall low risk of bias. Fourteen different screening tools and 104 separate accuracy estimates were identified. Pooled sensitivity and specificity estimates were calculated for the Psoriatic Arthritis Screening and Evaluation (cut-off = 44), Psoriatic Arthritis Screening and Evaluation (47), Toronto Psoriatic Arthritis Screening (8), Psoriasis Epidemiology Screening Tool (3) and Early Psoriatic Arthritis Screening Questionnaire (3). The Early Psoriatic Arthritis Screening Questionnaire reported the highest sensitivity and specificity (0.85 each). The I^2 for the diagnostic odds ratios varied between 76 and 90.1%. Meta-regressions were conducted, in which the age, risk of bias for patient selection and the screening tool accounted for some of the observed heterogeneity.

Conclusions. Questionnaire-based tools have moderate accuracy to identify PsA among psoriasis patients. The Early Psoriatic Arthritis Screening Questionnaire appears to have slightly better accuracy compared with the Toronto Psoriatic Arthritis Screening, Psoriasis Epidemiology Screening Tool and Psoriatic Arthritis Screening and Evaluation. An economic evaluation could model the uncertainty and estimate the cost-effectiveness of PsA screening programs that use different tools.

Key words: psoriatic arthritis, screening, ToPAS, PASE, PEST, EARP

Rheumatology key messages

- Several self-administered screening tools have been validated for PsA.
- The Early Psoriatic Arthritis Screening Questionnaire could be slightly more accurate for PsA screening among psoriasis patients.
- Health-economic modelling could account for parameter uncertainty and estimate the cost-effectiveness of PsA screening.

Introduction

PsA is an autoimmune and chronic musculoskeletal disorder that is associated with psoriasis of the skin [1]. Its presentation can vary from subtle manifestations to highly destructive forms. Joint pain, stiffness and swelling are the most common symptoms [2]. Similar to other arthritis-related diseases, early treatment is expected to control joint damage, which usually occurs within the first 2 years of disease [3]. Screening procedures are an important first step of early treatment.

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Patients with psoriasis are an easy-to-identify population at risk of PsA. The prevalence of PsA has been estimated to be between 6% and 42% for this population [4], and around 70% of PsA cases are preceded by psoriasis onset [5]. A systematic review and meta-analysis estimated an overall prevalence of undiagnosed PsA among psoriasis patients of 15.5% [6]. Consequently, dermatologists may be well placed to implement screening. However, making a diagnosis of PsA requires a detailed musculoskeletal examination, typically by a rheumatologist. Given this, several self-administered screening questionnaires to identify patients with PsA have been developed and validated for use prior to the more costly and intensive diagnostic procedures [7–10]. The Toronto Psoriatic Arthritis Screening (ToPAS) tool was validated in the general and psoriasis populations [7]. The Psoriasis Epidemiology Screening Tool (PEST), the Psoriatic Arthritis Screening and Evaluation (PASE) and the Early Psoriatic Arthritis Screening Questionnaire (EARP) follow a similar questionnaire structure and have all been validated for patients with psoriasis [8–10]. Screening tools for PsA have been tested in different settings, providing a vast array of accuracy estimates. Consensus regarding the best alternative is yet to be reached.

Although several studies have evaluated the screening accuracy for these tests, this information has not been systematically reviewed. The objective of this literature review is to synthesize the available evidence and obtain pooled sensitivity and specificity estimates for each tool. It also seeks to characterize the potential factors that might affect test accuracy.

Methods

Data sources and search strategies

A systematic review of electronic databases was conducted to identify studies that evaluated self-administered screening tools for PsA. We searched MEDLINE, Excerpta Medical Database, the Cochrane Central Register of Controlled Trials and Web of Science, between database inception and 8 January 2018. Search terms combined MeSH, Embase subject headings (Emtree) and keywords for PsA, screening and PsA screening tools. We also searched the reference lists of the included studies. No electronic search filters for date or language were used. For search strategies see supplementary data, electronic search strategies section, available at *Rheumatology* online. Ethics approval was not required to conduct this study.

Eligibility criteria

We included any study that presented accuracy estimates (sensitivity and specificity) for self-administered PsA screening tools or sufficient data to calculate the sensitivity and specificity. No restriction was applied to the study design or the type of screening tool (paper or electronic-based). Due to the lack of a specific PsA gold standard, any reference test was included. While our primary population of interest was patients with psoriasis, we also

included studies where not all patients had psoriasis for consideration in secondary analyses. Studies were excluded if at least one of the following criterion was met: population was not screened for PsA; the study was not focused on screening tools (i.e. diagnostic testing); accuracy data were not reported (or could not be estimated); the screening tool was not self-administered; or reported duplicate data. The search results were screened first by title/abstract, then the full text by two independent reviewers (N.I. and V.D.). Any article that either reviewer included at the title/abstract review stage was included for full-text review. Disagreements at the full-text stage were settled by discussion until a consensus was reached by the two reviewers.

Data extraction and quality assessment

We extracted study characteristics including the author, year, country, sample size, setting, reference test, screening tool, test cut-off, PsA prevalence and psoriasis prevalence. The outcomes of interest were sensitivity and specificity, which were extracted or calculated from available data. Authors were contacted if further information was required. Quality assessment was conducted in duplicate (N.I. and V.D.) using the QUADAS-2 tool [11], where four domains were evaluated: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias (low, unclear or high) [11]. Studies with low risk of bias across all QUADAS-2 domains were deemed as high-quality evidence for further stratified analyses.

Populations of interest

For the base case, we pooled estimates of full-text studies with 100% psoriasis prevalence that used the same cut-offs for the same screening tools. A sensitivity analysis was conducted to assess the pooled estimates after including data from abstracts. A second sensitivity analysis pooled full-text studies with any psoriasis prevalence level. Finally, we stratified based on study quality to compare the high-quality evidence estimates vs the base case. Meta-analyses were conducted only for screening tools with at least four observations.

Data synthesis

Sensitivity and specificity estimates were estimated jointly to appropriately account for their paired nature [12]. Tool-specific estimates (sensitivity and specificity) were plotted on a receiving operating characteristic space (sensitivity vs $1 - \text{specificity}$). This 2D space represents the trade-off between sensitivity and specificity and allows the estimation of 95% confidence ellipses [13]. The meta-analysis was conducted with a bivariate random effects model [12]. Individual studies, weighted by study size, were plotted in a summary receiving operating characteristic space with a 95% confidence regions. Forest plots and tabulations were generated to summarize the studies included in the meta-analysis. The studies that did not provide sufficient input for a meta-analysis were synthesized narratively.

The DORs were pooled to evaluate between-study heterogeneity. These were estimated using the 2×2 contingency tables and were then transformed to the logarithm scale to estimate their standard errors. After conducting pooled analyses for the DORs per screening tool, the I^2 statistic was estimated to determine the degree of heterogeneity.

Meta-regression

A linear regression of the logarithm of the Diagnostic Odds Ratio (DOR) vs test cut-offs was run to determine whether the DORs varied across positivity thresholds [14]. We controlled for each screening tool using a categorical variable, where the EARP was set as the reference, i.e. $DOR = \beta_0 + \beta_1 * \text{tool} + \beta_2 * \text{cut-off}$. We then conducted a meta-regression to evaluate whether study characteristics were associated with the diagnostic accuracy of the screening tests. To increase the power to detect an association between study characteristics and diagnostic accuracy, we included all studies in a multivariate model and compared them with univariate meta-regressions. We meta-regressed the DOR on the following variables that were thought to introduce potential heterogeneity: the screening tool (ToPAS, PEST, PASE and EARP), mean age of study population, prevalence of psoriasis (100% psoriasis prevalence vs <100%), setting (dermatology vs other settings), reference standard [Classification Criteria for Psoriatic Arthritis (CASPAR) criteria vs any other criteria], patient selection risk of bias (low vs unclear or high risk of bias), and reference and index test blinding (low vs unclear or high risk of bias), i.e. $DOR = \beta + \beta_1 * \text{tool} + \beta_2 * \text{psoriasis prevalence} + \beta_3 * \text{age} + \beta_4 * \text{dermatology setting} + \beta_5 * \text{CASPAR} + \beta_6 *$. Analyses were done in Review Manager 5.3 and Stata 14, using `metandi` and `metareg` user-written commands.

Results

The systematic review of MEDLINE, Excerpta Medical Database, Cochrane Central Register of Controlled Trials and Web of Science identified 2280 records (supplementary Fig. S1, available at *Rheumatology* online). After title/abstract and full-text review, 42 were included for synthesis [7–10, 15–52]. A total of 27 articles (64.2%) were full text and 15 were conference or poster abstracts. No additional records were found after searching the reference lists of the included studies.

Study characteristics are summarized in Table 1 and supplementary Table S1, available at *Rheumatology* online. The dates of the included articles ranged from 2007 to 2018. The overall sample size was 10 923 and ranged between 49 and 1511 patients per study. Most studies (66.7%) enrolled patients with a mean age between 40 and 55 years. However, 10 (23.8%) studies reported a mean duration of psoriasis between 15–31 years and 23 (54.8%) failed to report it. Additionally, 31 studies (73.8%) were conducted in dermatology and/or rheumatology clinics, and 33 (78.5%) reported a psoriasis prevalence of 100%. The prevalence of PsA fluctuated between 8.9% and 79.9%, and 19 studies (45.2%) reported a prevalence between 20% and 35%. Regarding previous line of treatment, 15 (35.7%) studies reported the proportion of

patients under treatment with DMARDs or biologics. Finally, four (9.5%) studies explicitly excluded psoriasis patients with prior systemic therapy [10, 26, 43, 44].

Supplementary Table S1, available at *Rheumatology* online, summarizes the screening tools, diagnostic criteria and accuracy estimates. Overall, 104 separate sensitivity and specificity estimates were reported, and 21 (50%) studies evaluated a single screening tool at a single cut-off. A total of 14 different screening tools were identified in the review. The PASE was evaluated most frequently ($n=28$), followed by PEST ($n=19$), and ToPAS and EARP ($n=10$ each). The Psoriasis and Arthritis Screening Questionnaire (PASQ), ePASQ, ToPAS II, COMparisoN of ThrEe Screening Tools in Psoriatic Arthritis (CONTEST) and Center of Excellence for Psoriasis and Psoriatic Arthritis (CEPPA) were evaluated eight, seven, six, six and five times, respectively. There was not enough information to meta-analyse these screening tools for a specific cut-off value. Some tools were only registered once [Glasgow Ultrasound Enthesitis Scoring System (GUESS), German Psoriasis Arthritis Diagnostic (GEPARD), Fluorescence optical imaging (FOI), PASE-2 and The Siriraj Psoriatic Arthritis Screening Tool]. Questionnaire-based screening tools reported a completion time between 5 and 10 min [8, 10]. Diagnostic criteria varied across studies, as a third of the studies ($n=14$) used a rheumatologist evaluation along with the CASPAR criteria to establish a diagnosis [17–20, 24, 30, 33, 34, 37, 39, 47, 48, 51, 52], and four (9.5%) used the Moll Wright criteria alongside a clinical evaluation [8, 23, 38, 43]. Finally, a single study (2.4%) used ultrasound along with a clinical evaluation [35], and 21 (19%) used either clinical or rheumatologic assessment alone.

Table 2 includes details of the meta-analysed tools. The PEST, PASE, EARP and ToPAS include 5, 15, 10 and 12 items or questions, respectively. They are mainly focused towards physical disability, and skin and joint symptoms. All of them include questions related to swollen joints and associated pain. The ToPAS and PEST include items related to affected nails and toes. They also include an item about previously diagnosed PsA. The PASE and the EARP refer to swollen fingers as ‘sausage-shaped’ for easier understanding. The PEST and EARP include an item related to swollen ankles. The ToPAS is the only tool that includes items directly related to psoriasis of the skin. The other tools were validated for patients with psoriasis, rendering the skin-related items redundant. The ToPAS and the PEST include images that help complete the questionnaires; a mannequin is available with the PEST for the patients to highlight which joints are affected. The ToPAS includes skin and nail images to assist patients in identifying potential symptoms.

The quality assessment is summarized in supplementary Table S2, available at *Rheumatology* online. Only full texts [27] were assessed at this stage. Overall, 10 (37%) studies were identified as high quality or low risk of bias across the four domains evaluated by the QUADAS-2 tool. We identified 10 (37%) studies that failed to state whether the index test was blinded to the reference test, and 10 that did not explain whether the reference test was

TABLE 1 Study characteristics by screening tools

Authors and year	Country	Sample Size	Mean age (s.d.)	Screening tools	PsA prevalence (%)	PsO prevalence (%)	Mean PsO duration (s.d.)	Mean PASI (s.d.)	Full text	Line of treatment
Garg <i>et al.</i> 2015 [27]	USA	517	46.3 (15.7)	CEPPA	22.63	100	17.9 (14.2)	NR	Yes	NR
Coates <i>et al.</i> 2016 [20]	UK	169	61 (48–68)	CONTEST	10.06	100	Median: 17 IQR: (14–39.5)	Median: 2.6 IQR: (1.1–5.4)	Yes	All: 1.1% DMARD
Haddad <i>et al.</i> 2017 [30]	Canada	208	NR	CONTEST	51.92	100	NR	NR	No	NR
Karremans <i>et al.</i> 2017 [33]	Netherlands	473	55.7 (13.9)	CONTEST	11.21	100	20.7 (16.2)	Median: 2.3 IQR: 3	Yes	NR
Busquets-Perez <i>et al.</i> 2015 [15]	UK	182	NR	EARP	24.18	NR	NR	NR	No	NR
Chiochanwisawakit <i>et al.</i> 2016 [18]	Thailand	159	46.5 (12.5)	EARP	78.62	100	Median: 11 IQR: 13.3	NR	Yes	NR
Gavin <i>et al.</i> 2016 [28]	Spain	377	48.1 (14.3)	EARP	NR	100	NR	NR	No	NR
Haddad <i>et al.</i> 2017 [30]	Canada	208	NR	EARP	51.92	100	NR	NR	No	NR
Karremans <i>et al.</i> 2016 [32]	Netherlands	473	NR	EARP	NR	100	NR	NR	No	All: 1.9% DMARDs
Liana <i>et al.</i> 2016 [37]	Philippines	49	44 (NR)	EARP	55.80	100	NR	NR	No	NR
Maejima <i>et al.</i> 2016 [39]	Japan	90	54.4 (15.1)	EARP	21.11	100	NR	3.8 (4)	Yes	PsA: 42% DMARD
Mishra <i>et al.</i> 2017 [42]	India	302	40.2 (14.2)	EARP	14.90	100	6.2 (NR)	NR	Yes	All: 4% any therapy
Tinazzi <i>et al.</i> 2012 [10]	Italy	228	49.3 (12.2)	EARP	37.28	100	NR	6.1 (2.95)	Yes	All: 0% DMARDs
Vidal <i>et al.</i> 2016 [49]	Spain	96	50.68 (14.13)	EARP	NR	100	18.75 (13.62)	4.09 (3.43)	Yes	All: 44% DMARD
Khraishi <i>et al.</i> 2011 [34]	Canada	54	NR	ePASQ	77.78	100	20.18 (13.5)	NR	Yes	NR
Koehm <i>et al.</i> 2016 [35]	Germany	150	NR	FOI	46.40	100	NR	NR	No	NR
Koehm <i>et al.</i> 2016 [35]	Germany	150	NR	GEPAED	46.40	100	NR	NR	No	NR
Cazenave <i>et al.</i> 2013 [16]	Argentina	51	42 (13)	GUESS	31.37	29	17 (13)	NR	No	NR
Coates <i>et al.</i> 2013 [19]	UK	195	47, CI: (45, 49)	PASE	24.10	100	Mean: 22.5 CI: (20.5, 24.5)	Mean: 6.5 CI: (5.52, 7.47)	Yes	All: 3% DMARD PsA: 11% DMARD
Dominguez <i>et al.</i> 2010 [22]	USA	1511	NR	PASE	22.96	100	NR	NR	No	NR
Dominguez <i>et al.</i> 2009 [23]	USA	190	NR	PASE	19.47	NR	NR	12.8 (NR)	Yes	All: 13% DMARD

(continued)

TABLE 1 Continued

Authors and year	Country	Sample Size	Mean age (s.d.)	Screening tools	PsA prevalence (%)	PsO prevalence (%)	Mean PsO duration (s.d.)	Mean PASI (s.d.)	Full text	Line of treatment
Ferreira et al. 2013 [26]	Argentina	111	56.9 (13.6)	PASE	22.52	63	16.97 (14.43)	3.57 (4.44)	Yes	PsA: 0% DMARD
Haddad et al. 2017 [30]	Canada	208	NR	PASE	51.92	100	NR	NR	No	NR
Haro et al. 2013 [31]	Ireland	100	50.9 (12.9)	PASE	29.00	100	27.14 (14.2)	1.85 (1.85)	Yes	All: 20% DMARD PsA: 36% DMARD
Husni et al. 2007 [8]	USA	69	51 (NR)	PASE	24.64	100	NR	NR	Yes	NR
Karremans et al. 2016 [32]	Netherlands	473	NR	PASE	NR	100	NR	NR	No	All: 1.9% DMARDs
Koehn et al. 2016 [35]	Germany	150	NR	PASE	46.40	100	NR	NR	No	NR
Lopez-Esteban et al. 2015 [38]	Spain	375	47.4 (13.3)	PASE	22.93	100	18.4 (13.1)	6.5 (6.7)	Yes	NR
Mease et al. 2014 [41]	Belgium, Canada, Denmark, France, Germany, Hungary, and USA	315	49.4 (13.9)	PASE	30.16	100	19.9 (13.8)	6.1 (6.1)	No	NR
Mishra et al. 2017 [42]	India	302	40.2 (14.2)	PASE	14.90	100	6.2 (NR)	NR	Yes	All: 4% any therapy
Oyur et al. 2014 [43]	Turkey	113	Range: 18–85	PASE	11.50	100	NR	5.3 (5.03)	Yes	All: 0% DMARDs
Piaserico et al. 2016 [44]	Italy	298	NR	PASE	18.79	100	NR	NR	Yes	All: 0% DMARDs
Ranza et al. 2013 [45]	Brazil	465	48.8 (15.7)	PASE	33.98	100	15.5 (11.8)	NR	No	NR
Tinazzi et al. 2012 [10]	Italy	228	49.3 (12.2)	PASE	37.28	100	NR	6.1 (2.95)	Yes	All: 0% DMARDs
Urbancsek et al. 2016 [48]	Slovakia	831	40–59	PASE	21.30	100	NR	NR	Yes	All: 26.4% systemic therapy
Vidal et al. 2016 [49]	Spain	96	50.68 (14.13)	PASE	NR	100	18.75 (13.62)	4.09 (3.43)	Yes	All: 44% DMARD
Walsh et al. 2013 [50]	USA	183	52.1 (14.2)	PASE	73.22	100	20.5 (15.8)	NR	Yes	PsA: 31% MTX No PsA: 15% MTX
Walsh et al. 2013 [50]	USA	183	52.1 (14.2)	PASE	73.22	100	20.5 (15.8)	NR	Yes	PsA: 31% MTX No PsA: 15% MTX
You et al. 2015 [51]	Korea	148	43.2 (NA)	PASE	12.16	100	NR	11.1 (NR)	Yes	All: 0% DMARDs

(continued)

TABLE 1 Continued

Authors and year	Country	Sample Size	Mean age (s.d.)	Screening tools	PsA prevalence (%)	PsO prevalence (%)	Mean PsO duration (s.d.)	Mean PASI (s.d.)	Full text	Line of treatment
Zisman <i>et al.</i> 2012 [52]	Israel	114	NR	PASE	33.33	100	NR	NR	No	NR
Thompson <i>et al.</i> 2016 [46]	USA	190	55 (median)	PASE 2	NR	NR	NR	NR	No	NR
Khraishi <i>et al.</i> 2011 [34]	Canada	54	NR	PASQ	77.78	100	20.18 (13.5)	NR	Yes	NR
Mease <i>et al.</i> 2014 [41]	Belgium, Canada, Denmark, France, Germany, Hungary and USA	317	49.9 (13.7)	PASQ	29.02	100	19.9 (13.8)	6.1 (6.1)	No	NR
Chamurlieva <i>et al.</i> 2016 [17]	Russia	103	44 (13.69)	PEST	59.20	100	NR	15.39 (12.59)	No	NR
Chiochanwisawakit <i>et al.</i> 2016 [18]	Thailand	159	46.5 (12.5)	PEST	78.62	100	Median: 11 IQR: 13.3	NR	Yes	NR
Coates <i>et al.</i> 2013 [19]	UK	195	47, CI: (45, 49)	PEST	24.10	100	Mean: 22.5 CI: (20.5, 24.5)	Mean: 6.5 CI: (5.52, 7.47)	Yes	All: 3% DMARD PsA: 11% DMARD
Coates <i>et al.</i> 2016 [20]	UK	169	61 (48–68)	PEST	10.06	100	Median: 17 IQR: (14–39.5)	Median: 2.6 IQR: (1.1–5.4)	Yes	All: 1.1% DMARD
Colaco <i>et al.</i> 2017 [21]	Canada	77	NR	PEST	10.39	100	NR	NR	No	NR
Ha <i>et al.</i> 2016 [29]	Korea	191	45.1	PEST	8.90	100	NR	NR	No	NR
Haddad <i>et al.</i> 2017 [30]	Canada	208	NR	PEST	51.92	100	NR	NR	No	NR
Haroony <i>et al.</i> 2013 [31]	Ireland	100	50.9 (12.9)	PEST	29.00	100	27.14 (14.2)	1.85 (1.85)	Yes	All: 20% DMARD PsA: 36% DMARD
Ibrahim <i>et al.</i> 2009 [9]	UK	89	54.9 (9.2) (only for PsA)	PEST	37.08	NR	31.8 (17.9) (only for PsA)	2.1 (2.0) (only for PsA)	Yes	NR
Karremans <i>et al.</i> 2016 [32]	Netherlands	473	NR	PEST	NR	100	NR	NR	No	All: 1.9% DMARDs
Koehn <i>et al.</i> 2016 [35]	Germany	150	NR	PEST	46.40	100	NR	NR	No	NR
Leijten <i>et al.</i> 2017 [36]	Netherlands	86	48.8 (15.9)	PEST	20.93	100	17.5 (13.2)	Median: 4.1 Range: (0–19)	Yes	NR
Mease <i>et al.</i> 2014 [41]	Belgium, Canada, Denmark, France, Germany,	314	50.6 (13.9)	PEST	30.89	100	19.9 (13.8)	6.1 (6.1)	No	NR

(continued)

TABLE 1 Continued

Authors and year	Country	Sample Size	Mean age (s.d.)	Screening tools	PsA prevalence (%)	PsO prevalence (%)	Mean PsO duration (s.d.)	Mean PASI (s.d.)	Full text	Line of treatment
	Hungary and USA									
Mishra et al. 2017 [42]	India	302	40.2 (14.2)	PEST	14.90	100	6.2 (NR)	NR	Yes	All: 4% any therapy
Walsh et al. 2013 [50]	USA	183	52.1 (14.2)	PEST	73.22	100	20.5 (15.8)	NR	Yes	PsA: 31% MTX No PsA: 15% MTX
Chiochanwisawakit et al. 2016 [18]	Thailand	159	46.5 (12.5)	SIPAT	78.62	100	Median: 11 IQR: 13.3	NR	Yes	NR
Coates et al. 2013 [19]	UK	195	47, CI: (45, 49)	ToPAS	24.10	100	Mean: 22.5 CI: (20.5, 24.5)	Mean: 6.5 CI: (5.52, 7.47)	Yes	All: 3% DMARD PsA: 11% DMARD
Fernández-Ávila et al. 2017 [25]	Colombia	108	51.19 (18.9)	ToPAS	33.30	100	31.46 (17.3)	NR	Yes	NR
Gladman et al. 2009 [7]	Canada	688	47.7 (14.4)	ToPAS	24.56	18	NR	NR	Yes	NR
Haroony et al. 2013 [31]	Ireland	100	50.9 (12.9)	ToPAS	29.00	100	27.14 (14.2)	1.85 (1.85)	Yes	All: 20% DMARD PsA: 36% DMARD
Marshall et al. 2010 [40]	UK	87	Median: 50.3 IQR: 19.9	ToPAS	58.62	100	NR	NR	No	NR
Urbancsek et al. 2016 [48]	Slovakia	831	40-59	ToPAS	21.30	100	NR	NR	Yes	All: 26.4% systemic therapy
Walsh et al. 2013 [50]	USA	169	52.1 (14.2)	ToPAS	79.29	100	20.5 (15.8)	NR	Yes	PsA: 31% MTX No PsA: 15% MTX
Zisman et al. 2012 [52]	Israel	114	NR	ToPAS	33.33	100	NR	NR	No	NR
Colaco et al. 2017 [21]	Canada	77	NR	ToPAS II	10.39	100	NR	NR	No	NR
Duruöz et al. 2018 [24]	Turkey	150	41.07 (12.59)	ToPAS II	28.67	31	NR	NR	Yes	NR
Haddad et al. 2017 [30]	Canada	208	NR	ToPAS II	51.92	100	NR	NR	No	NR
Mishra et al. 2017 [42]	India	302	40.2 (14.2)	ToPAS II	14.90	100	6.2 (NR)	NR	Yes	All: 4% any therapy
Tom et al. 2015 [47]	Canada	556	49.9 (14.1)	ToPAS II	23.56	60	19.1 (14.6)	4.7 (5.6)	Yes	NR

PASI: Psoriasis Area and Severity Index; PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; SIPAT: The Siriraj Psoriatic Arthritis Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire; NR: not reported; IQR: interquartile range; PsO: psoriasis.

TABLE 2 Details of meta-analysed PsA screening tools

Tool	PEST	PASE	EARP	ToPAS
Validation study	Ibrahim <i>et al.</i> (2009) [9]	Husni <i>et al.</i> (2007) [8]	Tinazzi <i>et al.</i> (2012) [10]	Gladman <i>et al.</i> (2009) [7]
Total score	5	75	10	12
Cut-off	3	47	3	8
Additional resources	Mannequin (affected joints)	NA	NR	Skin and nail images
Setting	Community setting and hospital clinic	Dermatology and rheumatology clinics	Dermatology clinics	Dermatology, Rheumatology, PsA, and family medicine clinics
Time to complete	NR	5–6 min	Less than 5 min	NR
Items	Have you ever had a swollen joint (or joints)?	I feel tired for most of the day	Do your joints hurt?	Have you ever had a skin rash consisting of red AND silvery-white scaly areas particularly on the elbows, knees or scalp as shown in Fig. 1
	Has a doctor ever told you that you have arthritis?	My joints hurt My back hurts My joints become swollen My joints feel 'hot'	Have you taken an anti-inflammatory more than twice a week for joint pain in the last 3 months? Do you wake up at night because of low back pain? Do your wrists and fingers hurt?	Have you ever noticed any of these changes in your fingernails: pits in the nails as shown in Fig. 2; lifting of the nail from the nail bed as shown in Fig. 3
	Do your fingernails or toenails have holes or pits?	Occasionally, an entire finger or toe becomes swollen, making it look like a 'sausage'	Do your wrists and fingers swell?	Have you ever seen a doctor about a skin rash?
	Have you had pain in your heel?	I have noticed that the pain in my joints moves from one joint to another, e.g. my wrist will hurt for a few days then my knee will hurt and so on I feel that my joint problems have affected my ability to work My joint problems have affected my ability to care for myself, e.g. getting dressed or brushing my teeth I have trouble wearing rings on my fingers or my watch I have trouble getting into or out of a car I am unable to be as active as I used to be	Does one finger hurt and swell for more than 3 days Does your Achilles tendon swell?	Have you ever had joint pain, joint stiffness or swollen red joints that was not the result of injury? Have you ever had a 'sausage shaped' swollen finger or toe that was not the result of an injury? Have you ever had neck pain lasting at least 3 months that was not injury related? Have you ever had back pain lasting at least 3 months that was not injury related? Have you ever had a skin rash on any part of your body at the same time as joint pain, joint-stiffness or swollen red joints?
	Have you had a finger or toe that was completely swollen and painful for no apparent reason?	I feel stiff for more than 2 h after waking up in the morning The morning is the worst time of day for me It takes me a few minutes to get moving to the best of my ability, any time of the day	Do your feet or ankles hurt? Do your elbow or hips hurt?	Have you ever seen a doctor about any joint pain? Have you ever been diagnosed with any form of arthritis other than PsA? Has a doctor ever diagnosed you with PsA?

NR: not reported; PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire.

blinded to the index test. These were rated as having unclear risk of bias. No studies were ranked with high risk of bias for these domains as no study clearly failed to blind the test results. Furthermore, eight (29.6%) studies had an unknown risk of bias due to the sampling procedure (not clear whether random or consecutive patients were enrolled). A third of the full-text studies ($n=9$) included patients that were already diagnosed with PsA in a case-control study design. They were identified as having a high risk of bias and applicability concerns for the study design and patient selection category.

Head-to-head studies

A total of 17 studies evaluated and compared two or more PsA screening tools. Tinazzi *et al.* [10] found that the EARP was slightly better than the PASE at identifying PsA; Mishra *et al.* [42] compared the sensitivity and specificity of the EARP, ToPAS II, PEST and PASE. The EARP was the most sensitive and the ToPAS II the most specific. Most studies found that the questionnaire-based screening tools were very similar in terms of accuracy [31, 32, 41, 48, 50, 52]. Chiowchanwisawakit *et al.* [18] compared the The Siriraj Psoriatic Arthritis Screening Tool with the PEST and EARP. They found that the The Siriraj Psoriatic Arthritis Screening Tool was more sensitive and required less time to complete. Khraishi *et al.* [34] compared the electronic version of the PASQ (ePASQ) with its paper version, finding similar accuracy estimates. Walsh *et al.* [50] found considerably lower specificity estimates for the ToPAS, PEST and PASE, compared with the initial validation studies, due to the inability to differentiate PsA from other musculoskeletal diseases.

Meta-analyses

We included 31 different test accuracy estimates of full-text studies with 100% psoriasis prevalence for meta-analysis. There was enough information to pool accuracy estimates for the PASE (seven and six studies with cut-offs = 44 and 47, respectively), ToPAS (five studies with cut-off = 8), PEST (eight studies with cut-off = 3) and EARP (five studies with cut-off = 3). The forest plots of these studies with their 2×2 contingency tables can be found in Fig. 1. The meta-analyses (base case and sensitivity analyses) are summarized in Table 3. The EARP had the highest pooled sensitivity and specificity estimates, at 0.85 each for the base case. Sensitivity estimates for the ToPAS, PASE and PEST fluctuated between 0.65 and 0.74. Specificity estimates ranged between 0.68 and 0.83. Fig. 2 summarizes the pooled estimates with their respective 95% confidence ellipses. Fig. 3 shows the individual meta-analyses with their pooled estimates and 95% confidence ellipses.

Sensitivity and specificity estimates were robust to the inclusion of data from abstracts (first sensitivity analysis) and studies with different psoriasis prevalences (second sensitivity analysis); estimates varied by at most four percentage points across all tools for both stratified analyses compared with the base case (Table 3). Stratified meta-analyses were conducted based on study quality or risk of

bias. Study quality had a minimal impact on most estimates of sensitivity or specificity (Table 3). The greatest difference was for the specificity with EARP, which dropped from 0.85 (95% CI: 0.61–0.95) when all five studies were included, to 0.78 (95% CI: 0.53–0.91) for the four studies rated as high quality.

Meta-regression and positivity threshold

We found substantial heterogeneity across studies after meta-analysing the diagnostic odds ratios. The I^2 estimates ranged from 76 to 90.1%. The regression and meta-regression results are available in supplementary Table S3, available at *Rheumatology* online. Based on the linear regression, the DOR was not associated with the cut-off used by each tool ($P=0.657$). On the other hand, the multivariate meta-regression estimated statistically significant coefficients for mean age ($P=0.004$), patient-selection risk of bias ($P=0.02$) and the three screening tools relative to EARP (ToPAS $P=0.01$, PEST $P=0.026$, PASE $P=0.002$). The screening tools are expected to be less accurate as the mean age of the study population increases. The estimated DOR is reduced by 11% for each additional year. Furthermore, studies with low risk of bias in the patient selection domain of the QUADAS-2 are associated with lower test accuracy (85% smaller DOR) compared with studies with high or unclear risk of bias. Regarding screening tools, the DORs of the PEST, ToPAS and PASE are expected to be 70.3, 80.7 and 81.7% smaller compared with the EARP, respectively. Finally, the conclusions for the univariate and multivariate regressions were maintained. The setting, diagnostic criteria, test blinding risk of bias and psoriasis prevalence were not statistically significant in the individual meta-regressions or in the multivariate meta-regression.

Discussion

In this systematic review and meta-analysis, we synthesized the evidence on PsA screening and generated pooled estimates for screening tools that reported sensitivity and specificity outcomes. The pooled sensitivity and specificity for the most commonly reported questionnaire-based screening tools (ToPAS, PEST, PASE and EARP) ranged between 0.65 and 0.85, and 0.68 and 0.85, respectively. The EARP was the most accurate screening tool with the highest sensitivity and specificity (0.85 each), including when only high-quality studies were included. However, further evidence and direct comparisons are required to account for the uncertainty and to determine whether the EARP's accuracy is comparably higher than that of the other questionnaire screening tools. Results were robust to the inclusion of data from abstracts and studies with different psoriasis prevalence levels. Considerable between-study heterogeneity was found for all screening tools. A multivariable meta-regression found that the mean age, psoriasis prevalence, risk of bias of patient selection and the screening tools explained some of the heterogeneity. Furthermore, a few head-to-head studies suggested that the self-administered PsA screening tools were similar to each other in terms of

Fig. 1 Forest plot of the sensitivity and specificity estimates of the studies included for meta-analysis according to screening tool

PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire.

TABLE 3 Summary estimates

Test (cut-off)	Studies	Sensitivity (95% CI)	Specificity (95% CI)	I ² (%)
PASE [44]				
Base case (full text and PsO = 100%)	7	0.67 (0.49, 0.81)	0.77 (0.58, 0.89)	88.5
Including abstracts (PsO = 100%)	8	0.68 (0.52, 0.80)	0.73 (0.63, 0.90)	88.1
Any psoriasis prevalence (Full-text)	8	0.68 (0.52, 0.81)	0.77 (0.61, 0.88)	87.2
High quality (full text and PsO = 100%)	5	0.66 (0.41, 0.84)	0.82 (0.63, 0.93)	91.4
PASE [47]				
Base case	6	0.67 (0.59, 0.73)	0.72 (0.60, 0.74)	90.1
Including abstracts (PsO = 100%)	7	0.65 (0.59, 0.71)	0.76 (0.57, 0.88)	89.8
Any psoriasis prevalence (full text)	7	0.71 (0.52, 0.79)	0.67 (0.46, 0.82)	88.1
High quality (full text)	4	0.66 (0.57, 0.74)	0.76 (0.48, 0.91)	92.9
ToPAS [8] ^a				
Base case	5	0.70 (0.61, 0.78)	0.75 (0.49, 0.90)	88.5
Including abstracts (PsO = 100%)	7	0.70 (0.60, 0.78)	0.79 (0.60, 0.90)	84.6
Any psoriasis prevalence (full text)	6	0.74 (0.63, 0.82)	0.79 (0.58, 0.92)	94.8
PEST [3]				
Base case	8	0.66 (0.52, 0.77)	0.80 (0.58, 0.92)	76
Including abstracts (PsO = 100%)	11	0.67 (0.57, 0.76)	0.83 (0.68, 0.92)	81.2
Any psoriasis prevalence (full text)	9	0.68 (0.55, 0.78)	0.79 (0.61, 0.91)	78.3
High quality (full text)	6	0.66 (0.50, 0.78)	0.83 (0.62, 0.94)	82.6
EARP [3]				
Base case	5	0.85 (0.81, 0.89)	0.85 (0.61, 0.95)	89.7
Including abstracts (PsO = 100%)	6	0.84 (0.80, 0.87)	0.87 (0.68, 0.95)	87.6
Any psoriasis prevalence ^b (full text)	5	0.85 (0.81, 0.89)	0.85 (0.61, 0.95)	89.7
High quality (full text)	4	0.85 (0.80, 0.88)	0.78 (0.53, 0.92)	89.4

Base case: full-text studies with 100% psoriasis prevalence. ^aMeta-analyses with three or fewer studies was not conducted (high-quality ToPAS). ^bAll EARP studies had 100% psoriasis prevalence. PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire.

accuracy. Further studies could evaluate the effect of different predictors, such as disease severity, on test accuracy. This review suggests that the EARP has a slightly better accuracy than the PEST, PASE and ToPAS to screen for PsA in psoriasis patients.

Entities such as the UK National Health Service have recommended the early identification of PsA with screening questionnaires and further diagnostic testing to slow disease progression [53]. Ever since, several efforts have been directed towards creating screening tools that would allow PsA patients with psoriasis to be identified in secondary care settings (specifically dermatology and/or rheumatology) [7–10]. This review creates a novel synthesis of the available information and evaluates the evidence of both new interventions and further validations of already popular screening tools. It provides evidence that the meta-analysed questionnaire screening tools are not only similar to each other in terms of structure, time to complete (between 5–10 min) [8, 10] and validation setting, but also in terms of accuracy. Other questionnaire tools such as the CEPPA, CONTEST and GEPARD have tried to put together different parts of other questionnaires to create a new and improved version [20, 27, 35]. However, separate studies do not appear to present compelling evidence of superior screening accuracy. On the other hand, biomarker testing for PsA screening is becoming an increasingly popular field of study [54, 55]. These

studies were not included in this review as they are not self-administered screening tests. The comparison and feasibility of biomarker vs questionnaire screening for PsA or the combining of the two is yet to be evaluated.

It has been previously concluded that PsA screening tests usually have low specificity because of the heterogeneous nature of the disease [20]. Similar musculoskeletal disorders, such as OA, might be identified as false-positive cases [50]. The reason why specificity fluctuates considerably across screening tools and studies in this review could be explained by different prevalence levels of similar musculoskeletal disease within the study populations. These questionnaires prioritize the identification of undiagnosed PsA before trying to differentiate it from similar conditions. Generally, because screening tests seek to rule out disease, they are expected to be highly sensitive [56]. If the follow-up tests are not too invasive and/or expensive, false positives are often preferred to false negatives. The costs and benefits of sensitivity vs specificity could be compared using cost-effectiveness modelling.

This review faced some limitations. The meta-analysis estimated high heterogeneity for each screening tool. The predictor variables evaluated through meta-regression accounted for some between-study variation, but some predictors were not statistically significant. This could be due to the low statistical power of the meta-regression.

Fig. 2 Summary receiver operating characteristics plot: tool-specific pooled sensitivity and specificity estimates

PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire.

Furthermore, there are additional factors that might explain this heterogeneity. Mease *et al.* [41] concluded that interpreting the findings of several PsA screening studies was problematic due to differences in study population characteristics, such as psoriasis severity [Psoriasis Area and Severity Index (PASI) score], treatment, and duration of PsA. Eder *et al.* [57] also concluded that severe cases of psoriasis (PASI score >20) have been associated with an increased risk of PsA. Although we extracted PASI, only 18 studies reported it. The reported ranges and measures of spread suggest that only the study conducted by Chamurlieva *et al.* [17] might have included a significant proportion of severe PASI cases (mean = 15.36). If the studies had reported PASI consistently, we could have evaluated this as an additional predictor. Additionally, PsA severity is expected to have a considerable effect on test accuracy. Severe PsA cases are expected to be easier to identify [58]. That is why including already diagnosed PsA cases will most likely bias the accuracy estimates. These patients are expected

to have more severe disease and be easier to identify. Additionally, evaluating the difference between primary vs secondary dermatology clinics could potentially explain some of the heterogeneity. However, this sub-analysis could not be conducted due to a lack of studies. Consistency across studies needs to be maintained if further analyses are to compare PsA screening tools. Finally, improved reporting standards or additional and larger head-to-head studies could reduce the heterogeneity of these pooled estimates.

It is not entirely clear whether the EARP is the most accurate tool due to its increased capacity to identify early disease, the low cut-off or the lack of a larger head-to-head study that compares the four tools among the same cohort. Regarding its structure, the EARP has a few characteristics and items that might explain its higher accuracy. Unlike the other tools, the EARP asks specifically about pain and swelling of joints that are often affected by PsA, such as the Achilles tendon, wrists, hips, feet, fingers and ankles. While the PEST, PASE and

Fig. 3 Tool-specific bivariate meta-analyses for full-text studies with psoriasis patients only

HSROC: hierarchical summary receiver operating characteristic; PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; ToPAS: Toronto Psoriatic Arthritis Screening Tool; EARP: Early Psoriatic Arthritis Screening Questionnaire.

ToPAS ask more generally about finger or joint pain (i.e. Have you ever had a swollen joint?—PEST; My joints hurt—PASE; Have you ever had a sausage-shaped swollen finger...—ToPAS), the EARP has specific questions for regularly affected joints by PsA (i.e. Do your fingers and wrists hurt? Do your elbow or hips hurt?). On the other hand, the low 3/10 cut-off might also explain why the EARP is more sensitive. However, a low cut-off usually translates to reduced specificity. Finally, obtaining head-to-head evidence could allow for direct comparisons and organizing tools into a relative ranking to inform decision makers. Considering that this evidence is difficult and costly to obtain, diagnostic network meta-analyses are useful to evaluate indirect comparisons with the limited available evidence [59].

The results of this first literature review of PsA screening provide a foundation for further research. After summarizing the available information and obtaining pooled clinical

efficacy estimates, it is necessary to further evaluate the factors that might explain the heterogeneity. However, PsA screening is but the first step in the treatment pathway meant to slow down disease progression and improve health outcomes. To understand the effect of investing in a systematic PsA screening program, a healthcare system must take into account the entire diagnostic and treatment pathway. The information on PsA screening is only valuable if it has the potential to modify clinical practice and improve health outcomes. Therefore, although this review concludes that these tools have a moderate capability to identify PsA, it is imperative to determine whether implementing screening procedures (and diagnostic and treatment follow-ups) are cost-effective. A cost-effectiveness analysis has the capability to evaluate the value of PsA screening, taking into account the uncertainty around test accuracy and different parameters that might have an impact on

screening accuracy such as PsA severity and disease progression. An economic evaluation would be able to use these pooled estimates and raw data from the identified individual studies and quantify the trade-off between sensitivity and specificity, and determine the threshold at which a screening tool would be cost-effective for implementation.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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Clinical vignette

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An important cause of chest pain in granulomatosis with polyangiitis

A 70-year-old female ex-smoker with weight loss was referred with dyspnoea after walking 100 metres. She had a normal CT head after reporting a 2–3 week history of headaches and blocked nose. A right-sided suspicious opacity on her chest X-ray prompted a CT-PET scan. This revealed multiple bilateral nodules with a biopsy establishing focal areas of necrosis (Fig. 1A). C-ANCA was positive, with a PR3 level of 77.1 IU/ml (range 0–3.1), confirming the diagnosis of granulomatosis with polyangiitis. She was started on oral prednisolone 1 mg/kg and intravenous CYC. While receiving CYC she was admitted acutely with pleuritic central chest pain, relieved sitting forward. ECG was normal, and an echocardiogram demonstrated a small pericardial effusion. Her troponin was elevated, at 36 ng/l (range 0–11.6). She was discharged with a tentative diagnosis of pericarditis. A follow-up CT thorax demonstrated multiple bilateral pulmonary nodules, with significant improvement in her pulmonary infiltrates (Fig. 1B).

Our case highlights pulmonary embolism risk is elevated in granulomatosis with polyangiitis and the need to consider the diagnosis during active stages of the disease. The incidence of thromboembolism during active disease is 7.0/100 person-years, compared with 0.3/100 person-years in a healthy population [1, 2].

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Fig. 1 (A) CT-PET image showing multiple FDG-avid pulmonary nodules. (B) CT thorax image showing the so-called Polomint sign, indicating partial occlusion with multiple pulmonary emboli