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Pyoderma Gangrenosum Across the Rheumatologic Spectrum: A Systematic Review and Meta-Analysis

Jozélio Freire de Carvalho[1], Roberto Paulo Correia de Araujo[2]

[1,2]Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador, BA, Brasil

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Corresponding Author:
Prof. Dr. Jozélio Freire de Carvalho

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ABSTRACT

Background/Aim

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis frequently associated with systemic inflammatory diseases, particularly inflammatory bowel disease and rheumatic disorders. Although rheumatoid arthritis (RA) is widely recognized as the most common rheumatic comorbidity, the prevalence of RA among patients with PG has not been systematically quantified. The aim of this artic was to systematically evaluate rheumatic diseases associated with PG and to estimate the pooled prevalence of rheumatoid arthritis through a meta-analysis of observational studies.

Material and methods

A systematic review was conducted according to the PRISMA 2020 statement. PubMed/MEDLINE, Embase, Web of Science, SciELO, and LILACS were searched from database inception through June 2026. Observational studies reporting rheumatic diseases in patients with PG were included, whereas case reports, reviews, and studies without extractable data were excluded. A random-effects meta-analysis of proportions was performed to estimate the pooled prevalence of RA.

Results

Seven observational studies comprising 529 patients with PG were included in the qualitative synthesis. Four studies involving 492 patients provided sufficient data for quantitative analysis. Rheumatoid arthritis was the most consistently reported rheumatic disease, whereas other inflammatory disorders—including seronegative arthritis, psoriatic arthritis, systemic lupus erythematosus, Behçet disease, systemic sclerosis, ANCA-associated vasculitis, and Takayasu arteritis—were identified less frequently and were reported inconsistently across studies. The pooled prevalence of RA was 11.9% (95% confidence interval [CI], 9.3%–15.1%). No statistical heterogeneity was detected ($I^2 = 0\%$); however, this finding should be interpreted cautiously given the small number of studies included in the quantitative synthesis.

Conclusions

Rheumatoid arthritis is a frequent and consistent comorbidity in patients with PG, affecting approximately one in nine patients. Although additional rheumatic diseases have been described, current evidence remains insufficient for robust quantitative synthesis because of heterogeneous reporting. These findings support routine rheumatologic evaluation in patients with PG and reinforce the concept of PG as a systemic inflammatory disease with clinically relevant musculoskeletal involvement.

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Highlights

- Pyoderma gangrenosum is associated with both rheumatoid arthritis and non-RA arthritis.
- Pooled prevalence estimates show distinct patterns between RA and non-RA arthritis.
- Rheumatoid arthritis demonstrates consistent findings across studies (low heterogeneity).
- Non-RA arthritis shows broader variability, reflecting heterogeneity in clinical spectra.
- Findings support PG as a systemic inflammatory condition with musculoskeletal involvement.

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, noninfectious neutrophilic dermatosis characterized by rapidly progressive, painful ulcerations with undermined violaceous borders [1]. Although its pathogenesis remains incompletely understood, increasing evidence supports the involvement of dysregulated innate immunity, abnormal neutrophil activation and trafficking, and excessive inflammatory cytokine signaling, placing PG within the spectrum of immune-mediated inflammatory disorders [2]. Because no single pathognomonic test is available, diagnosis relies on compatible clinical findings, exclusion of mimicking conditions, and clinicopathological correlation. Although validated diagnostic frameworks have improved disease recognition, diagnostic delay and misclassification remain clinically important sources of morbidity [3,4].

A substantial proportion of patients with PG have an associated systemic disorder, most commonly inflammatory bowel disease, inflammatory arthritis, or hematologic disease [5,6]. Recognition of these comorbidities may influence diagnostic investigation, multidisciplinary management, therapeutic selection, and long-term follow-up. Accordingly, patients newly diagnosed with PG generally require a structured clinical assessment for underlying inflammatory, hematologic, and immune-mediated diseases.

Rheumatic diseases are repeatedly reported among patients with PG. Rheumatoid arthritis (RA) is among the most consistently described rheumatic comorbidities, whereas seronegative arthritis, psoriatic arthritis, spondyloarthritis, Behçet disease, systemic lupus erythematosus, systemic sclerosis, and vasculitis have also been documented [5–7]. The coexistence of PG and rheumatic disease is biologically plausible because these conditions share inflammatory mechanisms involving neutrophil activation, inflammasome signaling, cytokine dysregulation, and aberrant innate immune responses [2,8]. Nevertheless, the relative frequency of individual rheumatic diseases among patients with PG remains uncertain.

The available evidence is derived predominantly from retrospective cohorts and case series with limited sample sizes, heterogeneous populations, and inconsistent reporting of rheumatic comorbidities. Although several observational studies have reported RA and other inflammatory rheumatic diseases among patients with PG, their estimates vary and have not been systematically integrated into a reliable pooled prevalence.

Therefore, we conducted a systematic review to characterize the spectrum of rheumatic diseases reported in patients with PG. When sufficiently comparable numerator and denominator data were available, we additionally performed a meta-analysis of proportions to estimate the pooled prevalence of RA among patients with PG.

2. MATERIALS AND METHODS

2.1 Study design and reporting

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [12]. The review methods and eligibility criteria were established before study selection and data extraction; however, the study protocol was not prospectively registered. Because this study was based exclusively on previously published data, institutional review board approval and informed consent were not required.

2.2 Search strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Web of Science, SciELO, and LILACS from database inception through June 2026. The search strategy combined controlled vocabulary and free-text terms related to pyoderma gangrenosum and rheumatic diseases, including rheumatoid arthritis, inflammatory arthritis, psoriatic arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, vasculitis, Behçet disease, connective tissue diseases, autoimmune diseases, and autoinflammatory diseases. No language or publication date restrictions were applied. Reference lists of eligible studies and relevant review articles were manually screened to identify additional publications. Complete search strategies for all databases are provided in the Supplementary Material.

2.3 Eligibility criteria and study selection

Observational studies reporting rheumatic diseases among patients with pyoderma gangrenosum were eligible for inclusion. Eligible designs comprised prospective and retrospective cohort studies, cross-sectional studies, registry-based studies, and case series with

extractable aggregate data. Studies were required to report the total number of patients with PG and at least one associated rheumatic disease.

Case reports, narrative reviews, systematic reviews, meta-analyses, editorials, letters without original patient data, conference abstracts lacking sufficient information, experimental studies, and publications without extractable rheumatologic data were excluded. When multiple publications reported overlapping populations, the study with the largest or most complete dataset was retained.

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved by consensus. The study selection process is summarized in a PRISMA 2020 flow diagram [12].

2.4 Data extraction and quality assessment

Two reviewers independently extracted data using a standardized electronic form. Extracted variables included first author, publication year, country, study design, study period, number of patients with PG, demographic characteristics, associated rheumatic diseases, clinical subtype of PG, associated systemic diseases, treatment, follow-up, and clinical outcomes.

For studies reporting rheumatoid arthritis, the number of affected patients and the total PG population were specifically extracted for quantitative synthesis. Disagreements were resolved by review of the original publication and consensus.

Methodological quality was independently assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist appropriate for each study design [13]. Study-level quality assessments are provided in the Supplementary Material.

2.5 Outcomes

The primary outcome was the prevalence of rheumatoid arthritis among patients with pyoderma gangrenosum.

Secondary outcomes included the frequency and spectrum of other rheumatic diseases reported in the included studies, together with demographic characteristics, clinical manifestations, treatment, and clinical outcomes. Additional rheumatic diseases were synthesized qualitatively because the available data were insufficiently homogeneous for quantitative pooling.

2.6 Statistical analysis

Meta-analysis of proportions was performed when at least three independent studies reported comparable numerator and denominator data for rheumatoid arthritis. For each study, prevalence was calculated as the number of patients with rheumatoid arthritis divided by the total number of patients with pyoderma gangrenosum. Individual study estimates and pooled prevalence were reported with corresponding 95% confidence intervals (95% CI).

Random-effects models were used because clinical and methodological variability among studies was anticipated. Between-study heterogeneity was assessed using Cochran's Q statistic and quantified using the I^2 statistic and between-study variance (τ^2). Hartung–Knapp adjustment was applied to provide more conservative confidence intervals.

Leave-one-out sensitivity analyses were planned to evaluate the influence of individual studies on the pooled estimate. Publication bias and funnel plot asymmetry were not formally assessed because fewer than ten studies were available, making these methods unreliable.

Statistical analyses were performed using JASP version 0.19.6 (JASP Team, Amsterdam, The Netherlands). All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

3. RESULTS

3.1 Study selection and characteristics of the included studies

The study selection process is summarized in Figure 1. Following title, abstract, and full-text screening according to the predefined eligibility criteria, seven observational studies were included in the qualitative synthesis. These comprised one population-based cohort, two retrospective cohort studies, and four retrospective case series conducted in North America, Europe, Asia, and North Africa. Study characteristics are summarized in Table 1.

Sample sizes ranged from 10 to 313 patients with pyoderma gangrenosum (PG), totaling 529 patients across all included studies. Most investigations were conducted in tertiary referral centers, whereas the study by Langan et al. was population-based using the United Kingdom General Practice Research Database. Although all studies reported demographic and clinical characteristics, the extent of information regarding associated systemic diseases, treatment, and outcomes varied substantially among cohorts [8,9,14–20].

3.2 Rheumatic diseases associated with pyoderma gangrenosum

Inflammatory bowel disease was the most frequently reported systemic comorbidity across the included studies, followed by inflammatory arthritis and hematological disorders. Rheumatoid arthritis (RA) was the most consistently reported rheumatic disease, with reported prevalence ranging from 9.1% to 15.6% among studies providing disease-specific data [15,17,18].

Additional inflammatory arthritides included seronegative arthritis and psoriatic arthritis, particularly in the cohorts reported by Binus et al. and Ramos-Rincón et al. Less frequently reported rheumatic diseases included Behçet disease, systemic lupus

erythematosus, systemic sclerosis, ANCA-associated vasculitis, and Takayasu arteritis, which were identified mainly in the Moroccan case series [15,18,19].

Not all studies reported individual rheumatic diagnoses. In particular, the Turkish series by Adışen et al. documented the presence of associated systemic diseases but did not specify the distribution of individual rheumatic disorders [16].

The distribution of rheumatic diseases across the included studies is summarized in Table 2.

3.3 Clinical characteristics

Women predominated in most cohorts, representing 50% to 76% of patients. Mean or median age at diagnosis ranged from 40 to 59 years. Ulcerative PG was the predominant clinical subtype whenever subtype classification was reported. Lesions most frequently affected the lower extremities, with involvement ranging from 63.6% to 92.5% of patients. Pain was consistently described as a major clinical symptom, whereas pathergy was reported only in studies in which this feature was specifically evaluated [14–21].

3.4 Treatment and clinical outcomes

Treatment approaches varied across the included observational studies and were primarily reported descriptively rather than evaluated comparatively. Systemic corticosteroids were frequently used, either alone or in combination with conventional immunosuppressive agents such as cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and dapsone. Biologic therapies, particularly tumor necrosis factor (TNF) inhibitors, were also reported in some cohorts, generally in patients with severe or refractory disease. Because the included studies were not designed to compare treatment efficacy, these treatment data should be interpreted as descriptive patterns of clinical management rather than evidence of comparative therapeutic effectiveness [14–21].

Clinical outcomes varied across studies. Most cohorts reported complete or partial ulcer healing following systemic therapy, although relapses remained frequent during follow-up. Mortality ranged from 0% to 16%, with deaths occurring predominantly among older patients or those with significant systemic comorbidities [8,9,14–20].

3.5 Quantitative synthesis

Four studies comprising 492 patients with pyoderma gangrenosum provided sufficient numerical data for quantitative synthesis of rheumatoid arthritis prevalence. Across these studies, 58 patients had rheumatoid arthritis. The pooled prevalence estimated using a random-effects model was 11.9% (95% confidence interval [CI], 9.3%–15.1%). No statistical heterogeneity was detected ($I^2 = 0\%$; $\tau^2 = 0$; Cochran's $Q = 1.31$, $p > 0.05$). However, given the small number of studies included in the quantitative synthesis, the precision of the heterogeneity assessment is limited (Figure 2). Because fewer than ten studies were available for quantitative synthesis, formal assessment of publication bias using funnel plot asymmetry or Egger's regression test was not performed.

Figure 2 presents the forest plot of the random-effects meta-analysis, showing the individual study estimates and the pooled prevalence of rheumatoid arthritis among patients with pyoderma gangrenosum.

4. DISCUSSION

This systematic review and meta-analysis found that rheumatoid arthritis (RA) is a relevant rheumatic comorbidity among patients with pyoderma gangrenosum (PG). Across four observational studies included in the quantitative synthesis, the pooled prevalence of RA was 11.9% (95% CI 9.3–15.1%). No statistical heterogeneity was detected ($I^2 = 0\%$); however, this finding should be interpreted cautiously because only four studies were available for quantitative synthesis, limiting the ability to reliably estimate between-study heterogeneity. Therefore, the absence of detected statistical heterogeneity should not be interpreted as evidence of true homogeneity across populations, study designs, or clinical settings. Overall, these findings support an association between PG and RA and are consistent with previous reports describing inflammatory arthritis among the systemic comorbidities observed in patients with PG [8,9,15,17,18].

The biological plausibility of this association is well supported by current knowledge of PG pathogenesis. PG is increasingly recognized as a neutrophilic dermatosis characterized by dysregulated innate immunity, excessive neutrophil activation, inflammasome signaling, and overexpression of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, IL-17, and IL-23 [4,5,11]. These inflammatory pathways substantially overlap with those implicated in RA, particularly the central role of TNF and IL-1 signaling in sustaining chronic synovial inflammation [23,24]. Moreover, neutrophil extracellular traps (NETs) have emerged as an important mechanistic link between PG and systemic autoimmune diseases, providing additional biological support for the coexistence of PG and RA [22]. Rather than representing isolated disorders, both conditions appear to share a common inflammatory network involving innate immune activation and neutrophil-mediated tissue injury.

From a clinical perspective, our findings reinforce the importance of systematically investigating inflammatory arthritis in patients presenting with PG. Approximately one in every nine patients included in the quantitative synthesis had concomitant RA, a prevalence considerably higher than that expected in the general population. This observation has direct implications for clinical practice because musculoskeletal complaints should not automatically be attributed to pain secondary to skin ulceration. Instead, careful rheumatologic evaluation may permit earlier diagnosis of inflammatory arthritis and facilitate appropriate multidisciplinary management. Treatment considerations may also favor multidisciplinary management because some immunomodulatory therapies

used for PG overlap with those used for inflammatory arthritis. However, the strength of evidence differs substantially among therapeutic agents and should not be inferred from the observational studies included in the present review. Systemic corticosteroids and cyclosporine are commonly used systemic treatment options for PG. Among biologic therapies, infliximab has been evaluated in a randomized, double-blind, placebo-controlled trial, whereas adalimumab has been investigated in prospective single-arm studies and real-world observational settings. Evidence for other immunosuppressive and biologic therapies is derived predominantly from observational studies, case series, and treatment reviews. Accordingly, treatment patterns reported in the studies included in this review should be interpreted descriptively and not as evidence of comparative therapeutic efficacy [25–29].

Although RA was the only rheumatic disease suitable for quantitative synthesis, the qualitative review confirmed that PG occurs in association with a broader spectrum of inflammatory rheumatic diseases. Seronegative arthritis, psoriatic arthritis, systemic lupus erythematosus, Behçet disease, systemic sclerosis, ANCA-associated vasculitis, and Takayasu arteritis were identified across several cohorts, although inconsistent definitions and heterogeneous reporting precluded pooled analyses [15–20]. Rather than suggesting the absence of association, these findings highlight an important limitation of the current literature. Future observational studies should adopt standardized definitions and consistently report disease-specific comorbidities to allow reliable quantitative synthesis of rheumatic diseases beyond RA.

The present study has several strengths. To our knowledge, this is the first systematic review and meta-analysis specifically quantifying the prevalence of RA among patients with PG. A comprehensive search strategy was applied across multiple databases, study selection followed PRISMA recommendations, and only studies with extractable numerator and denominator data were included in the quantitative synthesis. Although no statistical heterogeneity was detected, the small number of studies limits the precision of heterogeneity estimates and warrants cautious interpretation of this finding.

Nevertheless, several limitations should be acknowledged. First, all included studies were observational and predominantly retrospective, making them susceptible to selection bias, referral bias, and incomplete reporting. Second, only four studies contained sufficient numerical data for quantitative synthesis, preventing formal assessment of publication bias. Third, considerable variability existed in the reporting of associated rheumatic diseases other than RA, limiting comparisons across studies. Finally, changes in diagnostic criteria and therapeutic approaches over the study period may have contributed to clinical heterogeneity despite the absence of statistical heterogeneity in the pooled analysis.

Future multicenter prospective studies should adopt standardized diagnostic criteria for both PG and associated rheumatic diseases and systematically report individual rheumatic diagnoses using uniform definitions. Such an approach would facilitate future meta-analyses of specific inflammatory arthritides and improve understanding of shared immunopathogenic mechanisms. In parallel, advances in translational research focusing on neutrophil biology, inflammasome activation, and cytokine signaling may identify novel therapeutic targets applicable to both PG and inflammatory arthritis [5,11,22–25].

5. CONCLUSION

This study demonstrates that pyoderma gangrenosum is associated with both rheumatoid arthritis and non-RA arthritis, reinforcing its classification as a systemic inflammatory condition with significant musculoskeletal involvement.

Importantly, these findings indicate that the relationship between PG and arthritis is not confined to rheumatoid arthritis alone, but extends to a broader spectrum of inflammatory arthritides. Both RA and non-RA arthritis contribute meaningfully to the overall rheumatologic profile of PG, supporting the concept of a shared inflammatory continuum rather than a single disease-specific association.

This integrated perspective has important clinical implications, emphasizing the need for comprehensive rheumatologic evaluation in patients with PG and supporting a multidisciplinary approach that considers the full spectrum of arthritis rather than focusing exclusively on RA.

Further research is required to refine the classification of these associations and to better understand their implications for disease mechanisms, prognosis, and targeted therapeutic strategies.

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TABLE 1. Summary of included studies on pyoderma gangrenosum and rheumatic diseases.

Study (Author, Year [Ref])	Country	Study design	PG patients (n)	Female (%)	Mean/Median age (years)	Main rheumatic diseases reported	RA, n (%)	Main clinical findings	Main treatments
Langan et al., 2012 **[8]**	United Kingdom	Population-based retrospective cohort	313	59	59	RA, IBD, hematologic disorders	39 (12.5)	Population-based cohort; systemic comorbidities	Not reported
Al Ghazal et al., 2013 **[9]**	Germany	Multicenter retrospective cohort	259	61	53	IBD, inflammatory arthritis, hematologic disorders	NR	Large multicenter cohort	Corticosteroids, immunosuppressants
Ye & Ye, 2014 **[14]**	China	Retrospective case series	23	65	53	RA, SLE	3 (13.0)	Predominantly ulcerative PG affecting lower limbs	Corticosteroids, immunosuppressants
Binus et al., 2011 **[15]**	United States	Retrospective cohort	103	76	52	RA, seronegative arthritis, IBD, Behçet disease	**10 (9.7)**	Classic ulcerative PG; lower limb predominance	Corticosteroids, cyclosporine, biologics
Adışen et al., 2016 **[16]**	Turkey	Retrospective case series	27	63	49	Associated systemic diseases reported, but individual rheumatic diagnoses not specified	NR	Ulcerative PG; lower limb predominance	Corticosteroids, cyclosporine, immunosuppressants
Bardazzi et al., 2024 **[17]**	Italy	Retrospective case series	44	NR	NR	RA, PsA, IBD	4 (9.1)	Ulcerative PG was the predominant subtype	Corticosteroids, immunosuppressants, biologics
Ramos-Rincón et al., 2025 **[18]**	Spain	Retrospective case series	32	75	41	RA, seronegative arthritis, PsA, Behçet disease	5 (15.6)	Lower limb predominance	Corticosteroids, conventional immunosuppressants, biologics
El Kassimi et al., 2026 **[19]**	Morocco	Retrospective case series	10	50	40	Behçet disease, Takayasu arteritis, SLE, systemic	0	Predominantly ulcerative PG	Corticosteroids, immunosuppressants

Study (Author, Year [Ref])	Country	Study design	PG patients (n)	Female (%)	Mean/Median age (years)	Main rheumatic diseases reported	RA, n (%)	Main clinical findings	Main treatments
						sclerosis, ANCA-associated vasculitis			

Abbreviations: IBD, inflammatory bowel disease; NR, not reported; PG, pyoderma gangrenosum; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

TABLE 2. Clinical patterns, pathophysiological features, and therapeutic responses of pyoderma gangrenosum according to associated rheumatic diseases.

Rheumatic disease	Evidence from included studies	Main PG pattern	Typical temporal relationship	Treatments reported in the literature	References
Rheumatoid arthritis	Most consistent association; pooled prevalence 11.9%	Classic ulcerative PG, predominantly lower limbs	Usually concomitant	Corticosteroids, methotrexate, cyclosporine, TNF inhibitors	**[8,14,15,17,18]**
Seronegative arthritis	Reported in two cohorts	Ulcerative PG	Concomitant	Conventional immunosuppressants; biologics	**[15,18]**
Psoriatic arthritis	Reported in two cohorts	Ulcerative PG	Concomitant	Anti-TNF agents and other biologics	**[17,18]**
Systemic lupus erythematosus	Sporadically reported	Ulcerative PG	Variable	Individualized immunosuppressive therapy	**[14,19]**
Behçet disease	Rare	Ulcerative PG	Concomitant	Immunosuppressive therapy	**[15,18,19]**
Systemic sclerosis	Rare	Ulcerative PG	Variable	Disease-specific immunosuppression	**[19]**
ANCA-associated vasculitis	Rare	Ulcerative or necrotic lesions	Variable	Treatment directed at the underlying vasculitis	**[19]**
Takayasu arteritis	Very rare	Ulcerative PG	Variable	Disease-specific immunosuppressive therapy	**[19]**

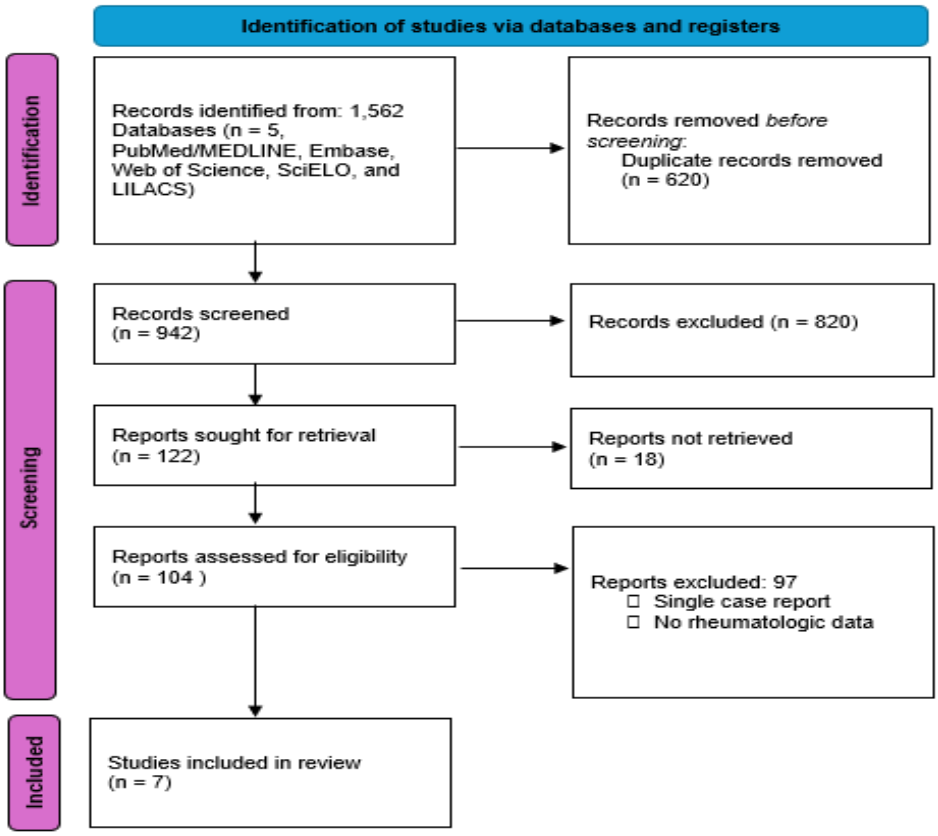
Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; PG, pyoderma gangrenosum; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Note: Treatment information is presented descriptively and should not be interpreted as evidence of comparative efficacy or as treatment recommendations. The level of therapeutic evidence varies considerably across agents and associated rheumatic diseases.

Figure 1. Flowchart of the included studies.

Flow diagram illustrating the process of study identification, screening, eligibility assessment, and inclusion in this systematic review and meta-analysis, in accordance with PRISMA 2020 guidelines. A total of 1,562 records were identified through database searching. After removal of duplicates (n = 620), 942 records underwent title and abstract screening, of which 820 were excluded. A total of 122 reports were sought for retrieval, of which 18 were not retrieved. Consequently, 104 reports were assessed for eligibility, and 97 were excluded because they were single case reports or lacked relevant rheumatologic data. Ultimately, seven studies were included in the qualitative synthesis, of which four provided sufficient data for inclusion in the quantitative meta-analysis.

Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



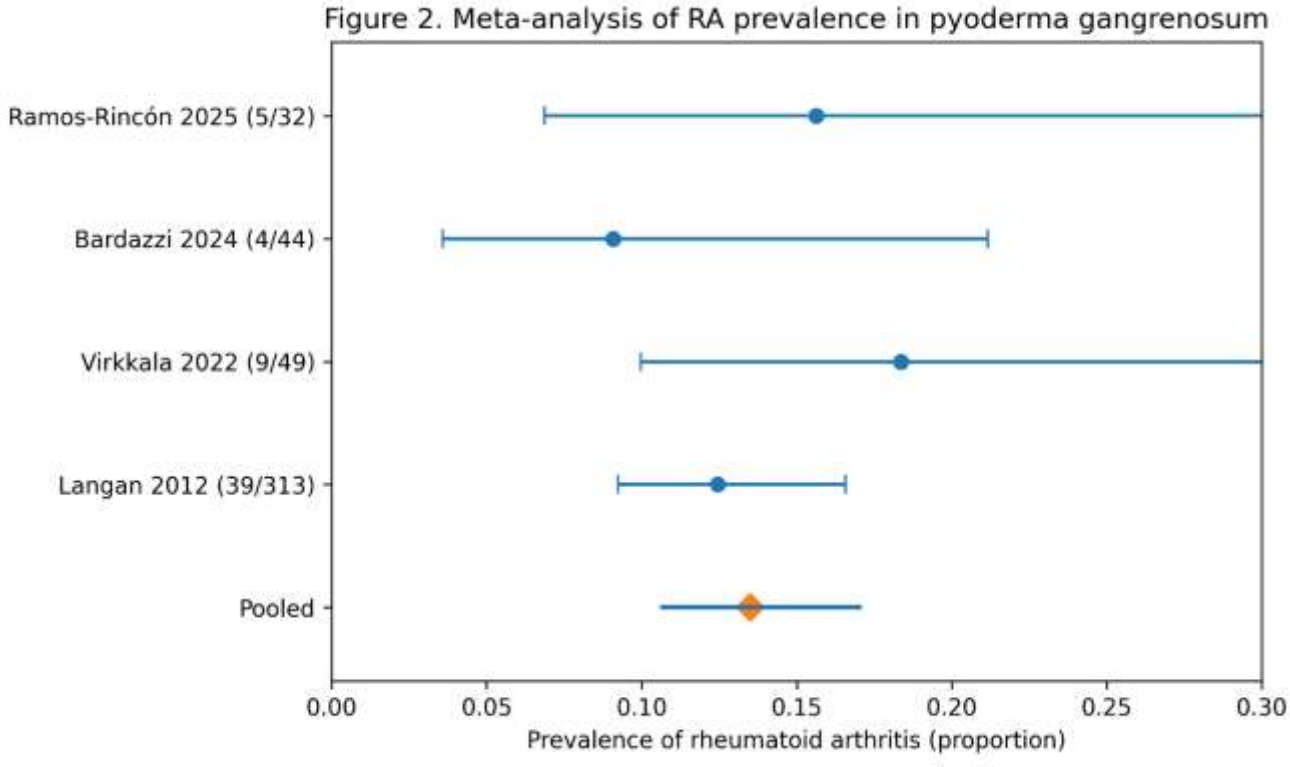


Figure 2. Random-effects meta-analysis of rheumatoid arthritis prevalence among patients with pyoderma gangrenosum. Forest plot showing the prevalence of rheumatoid arthritis in the four included observational studies. The pooled prevalence was 11.9% (95% CI 9.3–15.1%), with no evidence of between-study heterogeneity (I^2 = 0%).