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SYSTEMATIC REVIEW

Underlying Systemic Diseases in Pyoderma Gangrenosum: A Systematic Review and Meta-Analysis

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Abstract

Background There is little consensus regarding the prevalence and distribution of underlying systemic diseases among patients with pyoderma gangrenosum.

Objective The objective of this study was to synthesize existing data on the prevalence of associated systemic diseases in patients with pyoderma gangrenosum.

Methods We performed a systematic review and meta-analysis of observational studies in MEDLINE, EMBASE, and Scopus (1823–2017). The quality of evidence was assessed using a modified Newcastle–Ottawa Scale. A meta-analysis was performed using random-effects models to estimate pooled prevalence rates with 95% confidence intervals.

Results Twenty-one eligible studies comprising 2611 patients with pyoderma gangrenosum were included in the quantitative synthesis. The overall random-effects pooled prevalence of associated systemic diseases was 56.8% (95% confidence interval 45.5–67.4). The leading underlying disease was inflammatory bowel disease (17.6%; 95% confidence interval 13.0–22.7), followed by arthritis (12.8%; 95% confidence interval 9.2–16.9), hematological malignancies (8.9%; 95% confidence interval 6.5–11.6), and solid malignancies (7.4%; 95% confidence interval 5.8–9.1). In 16.3% (95% confidence interval 7.7–27.1) of cases, the onset of pyoderma gangrenosum was attributed to the pathergy phenomenon.

Conclusions More than half of patients with pyoderma gangrenosum present with a relevant underlying disease. Inflammatory bowel disease and arthritis are the most frequently associated diseases. Relative to the reported literature, the pooled prevalence of arthritis and hematological malignancies is lower, while the pooled prevalence of solid malignancies is higher. Owing to the high level of heterogeneity among most of the comparisons, results should be interpreted with caution.

Key Points

The pooled prevalence of arthritis and hematological malignancies is lower than previously reported, while the pooled prevalence of solid malignancies is higher than believed.

The pooled prevalence of underlying solid malignancies was surprisingly high (7.4%).

The onset of pyoderma gangrenosum was attributed to the pathergy phenomenon in 16.3% of cases.

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1 Introduction

Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic dermatosis usually affecting the skin, with rare extracutaneous involvement. PG is classically characterized by a sudden onset of erythematous nodules or sterile pustules that rapidly develop into very painful ulcerations with violaceous undermined borders on the lower legs. Less frequently, PG can present as tender nodules or pustules on other sites of the body. The pathophysiological mechanisms underlying this chronic skin disorder are not fully established, but the predominance of other immune-mediated comorbidities, the over-expression of cytokines/chemokines and molecules amplifying the inflammatory network, and the typically good response to immunomodulatory drugs such as corticosteroids, antitumor necrosis factor-α modalities, and calcineurin inhibitors support an immune-mediated mechanism for PG, rather than an infectious one as was initially presumed [1–5].

PG may occur alone, in syndromic forms, or associated with systemic diseases [2, 6]. Current knowledge about associated comorbidities in PG is insufficient and based chiefly on small-scale case series and a few retrospective cohort studies. Based on this information, associations with systemic diseases were reported in up to 86% of patients, with inflammatory bowel disease (IBD), inflammatory arthritis, monoclonal gammopathy, and other hematological disorders being the most frequently associated diseases [1, 7]. The existence of one of these conditions was proposed as a minor criterion suggesting the diagnosis of PG [1, 8]. However, there is little consensus regarding the true prevalence and the distribution of these underlying diseases among patients with PG.

Given the gap in knowledge and the inconsistency of studies evaluating underlying diseases in patients with PG, there is a need to synthesize data across studies. A better characterization of underlying diseases is highly important because the type and the severity of these comorbidities are of prognostic significance for PG [9, 10]. A recalcitrant associated disease usually results in poorer prognosis and unfavorable outcomes, whereas a successful treatment of the associated disease may lead to improvement in PG [9]. A meta-analysis aimed at determining the prevalence of underlying conditions in PG has not been previously performed. The aim of the current study is to perform a systematic review and meta-analysis summarizing the prevalence of underlying systemic comorbidities among patients with PG.

2 Methods

2.1 Literature Search

The literature for this review was searched using MEDLINE (1946 to present), EMBASE (1947 to present), and Scopus (1823 to present) to identify eligible studies. Publications up to 10 September, 2017 were searched independently and cross-checked by two researchers (K.K. and A.D.C.). The search strategies were designed with assistance from a medical librarian and are detailed in the Table 1 of the Electronic Supplementary Material (ESM). Reference lists of included studies were further screened for additional eligible publications.

Studies published online, in print, and in press from all years were considered. All search results with titles and abstracts written in English were eligible for inclusion. Studies were excluded based on the title, abstract, or both if there was no clear indication they were investigating comorbidities in patients with PG. If data were duplicated in more than one study, the most recent and complete study was included in the meta-analysis.

2.2 Data Extraction

The three researchers independently performed data extraction from these studies. Any disagreements regarding the suitability of individual studies were resolved by discussion. Each paper was critically reviewed and the following data extracted: study design and settings; country of origin; the period over which study was conducted; the midpoint of follow-up period; number of patients in the study; mean age of patients; percentage of female individuals; source of information; crude prevalence estimates of each comorbidity (number of cases divided by the sample size). Regarding the prevalence of overall associated comorbidities, the figure was explicitly provided by most authors. When this figure was missing, it was extracted by the addition of the prevalence rates of the well-established associated diseases: IBD, arthritis, and hematological and solid malignancies. Renal failure and endocrine and metabolic conditions were not considered as relevant associated diseases [10–12] because there is not enough evidence and biological plausibility to suggest that these conditions are implicated in the pathogenesis of PG. Prevalence figures and 95% confidence intervals (CIs) were extracted or calculated from the available data using Wilson's method [13].

2.3 Methodological Quality Assessment

The quality of the studies was peer reviewed by K.K. and A.D.C. using a modified version of the Newcastle–Ottawa Scale (NOS) for observational studies [14]. The original NOS was developed for case-control and cohort studies; however, some authors have adapted it for cross-sectional studies [15, 16], using the applicable items for this type of investigation. Because all eligible studies were cross-sectional, the scoring system summarized five aspects of each one of the included studies: case definition adequacy, representativeness of the cases, ascertainment of outcome data, and rate of sample loss. We have added a criterion concerning sample size, attributing one point for cohorts including more than 50 patients. The scale scores ranged from 0 (lowest grade) to 5 (highest grade). Studies with scores above the median (2) were classified as high-quality studies. Sensitivity analyses were performed for studies with modified NOS scores less than 3 or 3 and higher.

2.4 Statistical Analysis

Owing to the relative dearth of well-constructed studies regarding this topic, we decided a priori to include all studies in the meta-analysis regardless of study quality. The overall pooled estimate and 95% CI were obtained using either a fixed-effects (inverse variance methods) or random-effects (DerSimonian and Laird) meta-analysis model as appropriate depending on a test for heterogeneity. Significant heterogeneity of results was detected across studies as judged by a Cochrane Q statistic p value of < 0.05, an I^2 statistic $> 50\%$, or both. A two-sided p value of 0.05 was taken as significant. Begg rank correlation and funnel plot regression were used to assess for potential publication bias.

Potential influences on prevalence estimates were investigated using subgroup analyses and meta-regression. We assessed the influence on estimates of the following study-level variables identified a priori as potential sources of variation in the estimates of prevalence: (1) study settings (monocenter vs. multicenter vs. population based), (2) sample size ($\geq$ or $<$ the median number of patients [30]), and (3) study quality score ($>$ or $\leq$ the median score [2]). Statistical analyses were conducted by using the Comprehensive Meta-Analysis software, Version 3.3 (Biostat, Inc., Englewood, NJ, USA).

3 Results

The literature search yielded 547 manuscripts. Five additional articles were identified from other sources. One hundred and ninety-seven articles were duplicates, and 320 were not related to comorbidities in PG. Full-text review was performed on the remaining 35 articles. Overall, 21 studies fulfilled the eligibility criteria and were included in the quantitative synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is demonstrated in Fig. 1.

3.1 Study Characteristics

The 21 eligible studies comprised a total of 2611 patients with PG from 11 countries, encompassing participants of all ages, both male and female. Published years of studies ranged from 1985 to 2017, and the follow-up period covered the years 1970–2015. The mean age of patients with PG in the different study cohorts ranged between 48 years in Tunisia [17] and 71 years in Australia [18]. Apart from three studies from USA [19], Spain [20], and Tunisia [17], a female predominance was reported in all the remaining cohorts, with the female percentage ranging between 52% [21] and 79% [22]. One study was a prospective cohort study [21], whereas the remaining 20 were retrospective studies. Fourteen studies were monocentric, five studies were multicentric [12, 23–26], and two studies were population based [27, 28]. Quality assessment using the modified NOS revealed that the median score was 2, with seven studies scoring 3 or greater. The characteristics of the eligible studies are demonstrated in Table 1.

3.2 Overall Associated Systemic Diseases

The overall random-effects pooled prevalence of associated diseases among patients with PG was 56.8% (95% CI 45.5–67.4; $I^2 = 95.1\%$; $p < 0.001$) across the 21 studies. The prevalence of associated diseases ranged between 19.0% (95% CI 16.9–21.3) in Germany [28] and 86.2% (95% CI 68.5–94.7) in Australia [18] (Fig. 2).

3.3 Inflammatory Bowel Disease

The pooled prevalence of IBD was 17.6% (95% CI 13.0–22.7; $I^2 = 86.1\%$; $p < 0.001$) across all studies (Fig. 1 of the ESM). This combined estimate represents the leading underlying comorbidity in patients with PG. IBD was the most common associated disease in 13 out of the 21 eligible studies, and its prevalence ranged between 4.8% (95% CI 0.7–27.1) in Italy [21] and 42.3% (95% CI 25.2–61.5) in Spain [29] (Table 1).

Ulcerative colitis was the more frequent subtype with a pooled prevalence of 11.5% (95% CI 7.2–16.6; $I^2 = 83.7\%$; $p < 0.001$), and embodied the most common comorbidity in four studies [17, 20, 24, 29]. Crohn's disease was less common in most cohorts, showing a pooled prevalence of 6.0% (95% CI 3.9–8.5; $I^2 = 66.5\%$;

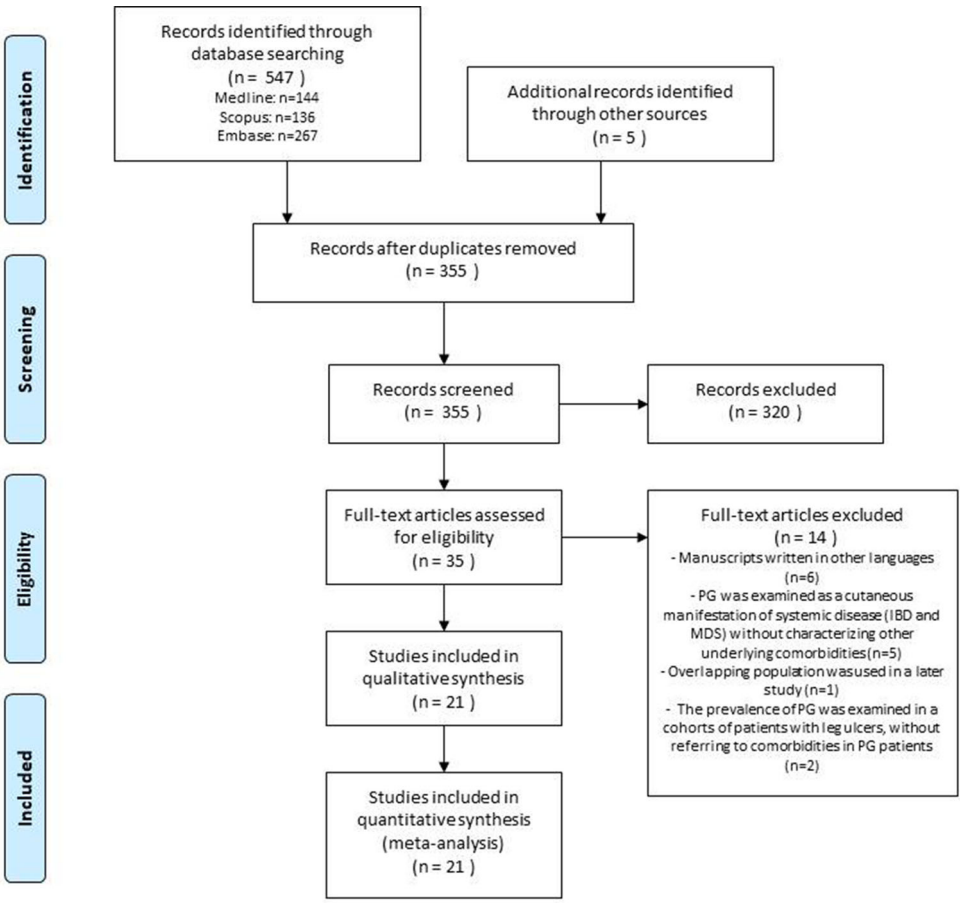

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search and study selection for the meta-analysis. *IBD* inflammatory bowel disease, *MDS* myelodysplastic syndrome, *PG* pyoderma gangrenosum

$p < 0.001$). Ulcerative colitis was more prevalent than Crohn's disease in 70.6% of the cohorts that differentiated between the different subtypes of IBD ($n = 17$), whereas the distribution of the two subtypes was equal in 17.6% of these cohorts [10, 30, 31]. In the remaining two studies (11.8%) [18, 28], Crohn's disease was more prevalent (Table 1).

3.4 Arthritis

The second leading associated disease was inflammatory arthritis, with a combined prevalence of 12.8% (95% CI 9.2–16.9; $I^2 = 82.9\%$; $p < 0.001$). The prevalence ranged between 0% [21] and 32.6% (95% CI 23.5–43.1) [19], and the disease was reported as the predominant associated disease in three studies, including two Australian cohorts [12, 18, 32] (Table 1; Fig. 2 of the ESM). Rheumatoid arthritis was the most common associated arthritis, with a pooled prevalence of 8.7% (95% CI 7.2–10.3; $I^2 = 67.7\%$; $p < 0.001$).

3.5 Hematological Malignancies

Hematological malignancies represented the third leading comorbid condition among patients with PG with a pooled prevalence of 8.9% (95% CI 6.5–11.6; $I^2 = 69.7\%$; $p < 0.001$). These conditions were the leading comorbidity in PG in three studies [11, 21, 22], and its prevalence ranged between 0% [20] and 25% (95% CI 11.7–45.6; Fig. 3 of the ESM) [22]. Monoclonal gammopathy was the most common specific hematological malignancy, and its pooled prevalence was 4.8% (95% CI 2.5–7.8; $I^2 = 75.9\%$; $p < 0.001$).

3.6 Solid Malignancies

Solid malignancies showed a pooled prevalence of 7.4% (95% CI 5.8–9.1; $I^2 = 79.5\%$; $p < 0.001$) among patients with PG at their presentation. Reported prevalence of these conditions ranged between 0% [10, 17, 20, 25, 33] and 20.7% (95% CI 8.2–37.0) [18], with three studies [23, 27, 28] lacking the precise prevalence (Fig. 4 of the ESM). No predilection for a specific solid tumor was observed across eligible studies.

Table 1 Characteristics of the eligible studies

Study, year	Settings	Location	Period	No. of patients	Average (range) age, y	Female patients, %	Relevant comorbidity, %	UC, %	CD, %	Hematological (gammopathy), %	Solid malignancy, %	Arthritis (RA), %	Pathergy, %	NOS
Powell et al., 1985 [19]	Retrospective, monocentric	USA	1970–83	86	NR (7–71)	50.0	77.9	19.8	16.3	12.8 (10)	5.8	32.6 (NR)	26.7	3
von den Driesch, 1997 [30]	Retrospective, monocentric	Germany	1985–96	44	50.3 (11–80)	68.2	77.3	6.8	6.8	9.1 (0)	11.4	NR (11.4)	38.6	2
Bennett et al., 2000 [23]	Retrospective, 2 centers	USA	1986–8	86	48.4 (2–83)	55.8	50.0	11.6	9.3	9.3 (5)	NR[a]	18.6 (11.6)	0	4
Milka et al., 2002 [17]	Retrospective, monocentric	Tunisia	1981–2000	21	41.8 (2–84)	47.6	52.4	19.0	4.8	14.3 (0)	0	4.8 (4.8)	0	3
Vidal et al., 2004 [29]	Retrospective, monocentric	Spain	1986–2000	26	45 (17–72)	69.2	84.6	26.9	15.4	23.1 (23)	11.5	23.1 (0)	7.7	2
Hasselmann et al., 2007 [10]	Retrospective, monocentric	Germany	1995–2005	18	53.1 (23–78)	77.8	38.9[b]	5.6	5.6	11.1 (11.1)	0	11.1 (5.6)	0	2
Binus et al., 2011 [25]	Retrospective, 2 centers	USA	2000–7	103	51.6 (22–88)	75.7	78.6	17.5	16.5	10.7 (9.7[c])	0	29.1 (9.7)	31.1	4
Marzano et al., 2011 [21]	Prospective, monocentric	Italy	2006–9	21	45 (13–80)	52.4	42.9	4.8	0	9.5 (4.8)	4.8	0 (0)	0	2
Suárez-Pérez et al., 2011 [20]	Retrospective, monocentric	Spain	2000–9	15	49.2 (25–75)	46.7	60.0	26.7	6.7	0 (0)	0	6.7 (0)	20.0	2
Langan et al., 2012 [27]	Retrospective, population based	UK	1992–2008	313	59[d]	59	32.9	20.2		3.8 (NR)	NR	NR (11.8)	NR	2
Al Ghazal et al., 2012 [11]	Retrospective, monocentric	Germany	2002–10	49	59.7 (22–95)	59.2	36.7[e]	4.1	2.0	10.2 (4)	12.2	8.2 (6)	32.6	2
Al Ghazal et al., 2013 [12]	Retrospective, 20 centers	Germany	2010–11	259	57.3 (21–94)	54.8	41.3[f]	6.6	2.7	3.9 (1.2)	12.4	15.8 (9.3)	42.9	4
Saracino et al., 2013 [32]	Retrospective, monocentric	Australia	2005–8	26	58.4 (24–82)	65.4	57.7	7.7		7.7 (3.8)	15.4	23.1 (19.2)	61.5	2
Pereira et al., 2014 [22]	Retrospective, monocentric	Portugal	2000–9	24	58.3 (17–89)	79.2	75.0	16.7	4.2	25.0 (8.3)	8.3	4.2 (0)	8.3	2
Ye and Ye, 2014 [31]	Retrospective, monocentric	Australia	2003–13	23	62.8 (30–89)	69.6	47.8	4.3	4.3	4.3 (4.3)	17.4	4.3 (0)	26.1	2
Cabalag et al., 2015 [18]	Retrospective, monocentric	Australia	2000–10	29	71 (38–92)	58.6	86.2	3.4	10.3	17.2 (6.9)	20.7	24.1 (6.9)	10.3	2

Table 1 continued

Study, year	Settings	Location	Period	No. of patients	Average (range) age, y	Female patients, %	Relevant comorbidity, %	UC, %	CD, %	Hematological (gammopathy), %	Solid malignancy, %	Arthritis (RA), %	Pathergy, %	NOS
Adışen et al. 2016 [39]	Retrospective, monocentric	Turkey	2004–15	27	48.6 (16–79)	63	29.6	7.4		3.7 (0)	11.1	7.4 (0)	14.8	2
Jockenhöfer et al., 2016 [28]	Retrospective, population based	Germany	2012	1227	NR	60.3	19.0	4.2	4.5	4.0 (2.5[g])	NR	6.3 (NR)	NR	2
Jockenhöfer et al., 2016 [26]	Retrospective, 3 centers	Germany	1999–2011	121	59.8 (18–96)	66.9	44.6	5.8	4.1	6.6 (0.8)	14.0	14.0 (12.4)	38.8	4
Inoue et al., 2017 [24]	Retrospective, 9 centers	Japan	1982–2014	62	50.2 (16–89)	53.2	74.2	32.3	1.6	16.1 (NR)	4.8	11.3 (6.5)	0	4
Vacas et al., 2017 [33]	Retrospective, monocentric	Argentina	2004–14	31	57[d] (39–76[g])	58	74.2	32.3		22.6 (NR)	0	16.1[h]	51.6	2

CD Crohn's disease, *MGUS* monoclonal gammopathy of unknown significance, *NOS* Newcastle–Ottawa Scale, *NR* not reported, *RA* rheumatoid arthritis, *UC* ulcerative colitis

[a]Solid malignancies were encountered but the precise prevalence was not reported

[b]Diabetes mellitus was not considered as an associated disease

[c]Prevalence of MGUS

[d]Median age

[e]Endocrine comorbidities and renal failure were not considered as associated diseases

[f]A combined prevalence of monoclonal gammopathy and myelodysplastic syndrome

[g]Interquartile range

[h]A combined prevalence of rheumatoid and seronegative arthritis

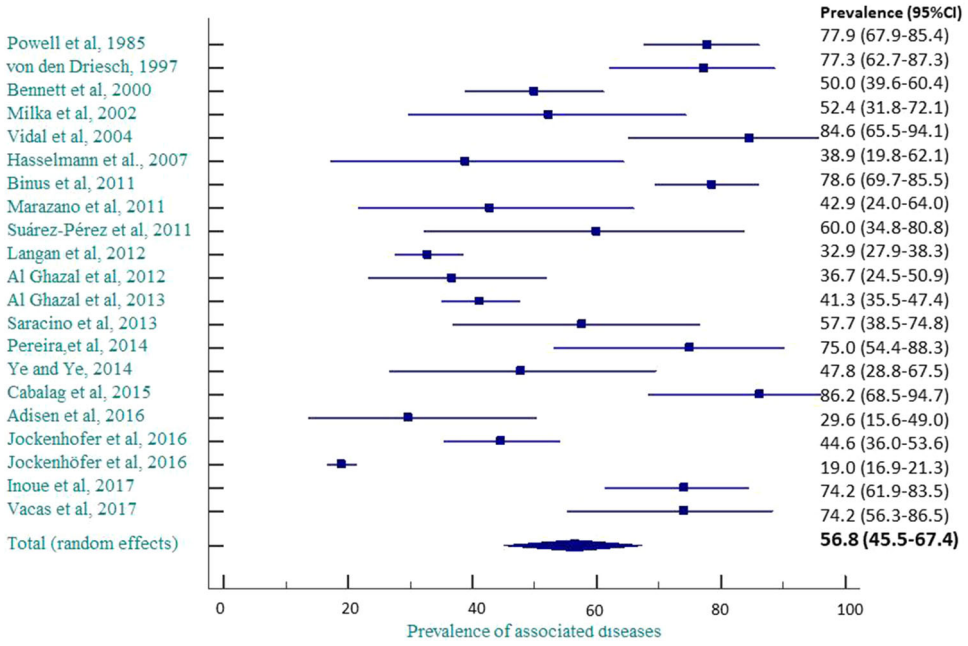

Fig. 2 Forest plot summarizing the prevalence of associated systemic diseases. The prevalence of the individual studies is represented by *squares*, through which the *horizontal lines* represent the 95% confidence intervals (CIs). The *diamond at the bottom* represents the pooled prevalence from these studies

3.7 Pathergy Phenomenon

In 16.3% (95% CI 7.7–27.1; $I^2 = 94.4\%$; $p < 0.001$) of patients with PG reported in the literature, the disease onset was attributed to the pathergy phenomenon. While two studies did not report the prevalence of this phenomenon [27, 28], its prevalence ranged between 0% [10, 17, 21, 23, 24] and 61.5% (95% CI 42.1–77.9) [32] in the remaining studies.

3.8 Exploration of Heterogeneity

Potential sources of heterogeneity were explored using a stratified analysis of the included studies. Pooling of estimates according to the study settings suggests an increase in the prevalence of associated diseases in monocenter (61.4%; 95% CI 50.1–71.7; $I^2 = 78.4\%$; $p < 0.001$) and multicenter (58.2%; 95% CI 42.8–72.2; $I^2 = 92.2\%$; $p < 0.001$) studies relative to population-based studies (25.2%; 95% CI 14.0–41.0; $I^2 = 96.4\%$; $p < 0.001$; Table 2).

3.9 Publication Bias

Publication bias was not detected as judged by the non-significant Begg rank correlation or funnel plot regression for the main outcome of the study (the prevalence of overall associated comorbidities; $p = 0.314$; Fig. 5 of the ESM).

4 Discussion

This is the first systematic review and meta-analysis aiming to summarize the prevalence of underlying diseases in PG. This study suggests that more than half of patients with PG present with a relevant underlying systemic disease, with IBD being the leading associated disease, followed by arthritis and hematological and solid malignancies. The pooled prevalence of the triggering pathergy phenomenon was as high as 16.3%.

The current knowledge about associated comorbidities in PG is severely hampered by the paucity of well-designed large-scale studies. The common teaching textbooks and expert reviews report an association with underlying diseases between 50 and 70% of the patients [34–36]. Older textbooks reported such an association in up to 80% of the patients [37]. Although our pooled synthesis lends weight to the current knowledge with regard to the overall prevalence of associated diseases, the distribution of these diseases is discordant [36]. While the prevalence of inflammatory arthritis and hematological malignancies were evaluated in a recent textbook at 20 and 15–25% [36], respectively, the corresponding pooled estimates of these conditions in our study were 12.8 and 8.9%. The tendency of the current literature to overestimate the prevalence of arthritis and hematological malignancies is paralleled with a tendency to underestimate the prevalence of solid malignancies. Intriguingly, the pooled prevalence of solid malignancies was as high as 7.4%. The pathergy phenomenon has previously been reported in about 30% of patients with pre-existing PG [36, 38]. The pooled prevalence of pathergy in our analysis (16.3%) reflects only

Table 2 Results of subgroup analyses based on the study setting, sample size, and quality of evidence score

	No. of studies	Pooled prevalence of associated comorbidities	I^2, %	Pooled prevalence of IBD	I^2, %	Pooled prevalence of arthritis	I^2, %	Pooled prevalence of hematological malignancies	I^2, %
Settings									
Monocenter	14	61.4 (50.1–71.7)	78.4	18.1 (12.2–26.0)	66.1	13.7 (9.0–20.3)	57.4	14.0 (10.9–17.8)	5.8
Multicenter	5	58.2 (42.8–72.2)	92.2	19.4 (10.5–33.0)	90.9	17.7 (12.7–24.0)	67.5	8.4 (5.1–13.5)	67.8
Population based	2	25.2 (14.0–41.0)	96.4	13.4 (5.6–28.5)	96.8	8.6 (4.5–15.6)	90.8	4.0 (3.1–5.1)	0.0
Sample size									
≥ 31	11	55.2 (40.2–69.3)	97.1	18.3 (12.2–26.6)	92.4	14.8 (10.0–21.4)	90.0	8.3 (5.6–12.2)	79.8
< 31	10	58.3 (45.2–70.4)	70.5	16.9 (10.5–26.2)	53.8	15.2 (10.6–21.3)	34.5	14.6 (10.3–20.4)	13.0
Modified NOS									
≥ 3	7	60.8 (46.9–73.2)	91.6	22.0 (13.5–33.6)	89.1	18.8 (13.3–26.0)	75.3	9.4 (6.4–13.7)	59.6
< 3	14	54.4 (40.6–67.6)	93.7	15.3 (10.3–22.1)	81.3	11.4 (8.0–16.0)	65.2	9.7 (5.9–15.4)	76.9

IBD inflammatory bowel disease, *NOS* Newcastle–Ottawa Scale

patients in whom the onset of PG was attributed directly to this phenomenon. This may explain the lower estimate relative to the literature.

In a stratified analysis, the prevalence of associated systemic diseases was higher in hospital-based studies (both monocenter and multicenter studies) as compared with population-based studies. This observation may be attributed to ascertainment bias, as individuals in a tertiary-care setting may be more likely to be diagnosed with PG in a setting of concurrent disease, or equally might be more likely to have a minor manifestation of an associated disease or asymptomatic disease investigated once they are diagnosed with PG [27]. In addition, a selection bias in hospital-based studies leading to overestimation of underlying diseases is highly probable.

This study has several limitations to consider. The majority of studies in this review were retrospective and observational, with several methodological limitations. Moreover, the pooled studies had different inclusion/exclusion criteria, sample sizes, sampling approaches, and geographic locations. Owing to the high level of heterogeneity among most of the comparisons, results should be interpreted with caution. Although the funnel plot did not reveal the existence of publication bias in the current study, this test is difficult to understand in an observational study of prevalence.

5 Conclusions

Underlying systemic disease is present in approximately 57% of patients with PG. IBD, arthritis, and hematological and solid malignancies are the leading associated diseases. Relative to the current literature, the pooled prevalence of arthritis and hematological diseases is lower, while the prevalence of solid malignancies is higher than believed. These findings confirm the association of PG with solid malignancies.

Compliance with Ethical Standards

Funding No funding was received for the conduct of this study or the preparation of this article.

Conflict of interest Khalaf Kridin, Arnon D. Cohen, and Kyle T. Amber have no conflicts of interest directly relevant to the content of this article.

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