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ORIGINAL ARTICLE

The coexistence of pemphigus and psoriasis: a systematic review and meta-analysis

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Abstract

There is little consensus regarding the association between pemphigus and psoriasis. The aim of the current study is to synthesize existing data on the prevalence of psoriasis in patients with pemphigus and on the association between the two conditions. We performed a systematic review and meta-analysis of observational studies in Medline, Embase, and Web of Science (1900–2018). Reference lists of included studies were also searched for eligible studies. Quality of evidence was assessed using Newcastle-Ottawa scale (NOS). A meta-analysis was performed using random-effects models to estimate pooled prevalence rates and odds ratios (ORs) with 95% confidence intervals (CI). Subgroup and sensitivity analyses were also conducted. Twelve eligible studies comprising 12,238 patients with pemphigus were included in the quantitative synthesis. The overall random-effects pooled prevalence of psoriasis among patients with pemphigus was 2.4% (95% CI, 1.0–4.4) across all studies. The overall pooled multivariate OR for psoriasis in patients with pemphigus was significantly increased and estimated at 3.5 (95% CI, 1.6–7.6). In conclusion, a significant association was found between pemphigus and psoriasis. Physicians managing patients with pemphigus may be aware of this comorbidity. Further studies are warranted to establish the precise mechanisms underlying this relationship.

Keywords Pemphigus · Psoriasis · Association · Meta-analysis · Systematic review

Introduction

Pemphigus is a rare and chronic autoimmune, blistering disease that affects the skin and mucous membranes. It is mediated by IgG autoantibodies against both desmoglein 3 (pemphigus vulgaris) and desmoglein 1 (pemphigus foliaceus), transmembrane desmosomal glycoproteins that are cadherin-type cell-cell adhesion molecules. These autoantibodies inhibit the adhesive function of desmogleins and lead to loss of cell-cell adhesion of keratinocytes leading to the formation of vesicles and erosions through a process called acantholysis [1, 2]. Psoriasis is a T cell-mediated papulosquamous skin disorder resulting from dysregulation of the immune system with marked inflammatory and hyperproliferative changes [3, 4].

While psoriasis was typically associated with bullous pemphigoid—a subepidermal autoimmune bullous disease [5–7]—its association with pemphigus is less established and is based mainly on case reports and a handful of recent observational studies. No meta-analyses were previously conducted to summarize this association.

Given the gap in knowledge and the inconsistency of studies evaluating the prevalence of psoriasis among patients with pemphigus, there is a need to synthesize data across studies. In the current study, we aimed to review the existing literature and to assess the association between pemphigus and psoriasis

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quantitatively. We herein report the findings of a systematic review and meta-analysis with the following endpoints: [1] summarizing the prevalence of psoriasis among patients with pemphigus and [2] pooling the odds of having psoriasis in patients with pemphigus relative to control subjects.

Methods

Literature search

The literature review was conducted using Ovid-Medline (1946–present), Embase (1947–present), and Web of Science (1900–present) to identify eligible studies. Publications up to May 30, 2018 were searched independently and cross-checked by three researchers (KK, MK, and ADC). The search strategies are detailed in the Supplementary Table 1. 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. For inclusion, studies had to be published in English and contain original research with observational study design (e.g., case-control, cross-sectional, or cohort) which reported on pemphigus and the odds for and/or the prevalence of psoriasis. Studies were excluded based on the title, abstract, or both if there was no clear indication they were investigating comorbidities in patients with pemphigus. Editorials, reviews, and case studies were excluded.

Data extraction

Three researchers (KK, MK, and ADC) 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; number of patients and control participants; mean age of patients; percentage of females; pemphigus assessment method; crude prevalence estimates of psoriasis (number of cases divided by the sample size) and 95% confidence interval (CI); and the crude and multivariate odds ratios (OR)s to have psoriasis among pemphigus patients with 95% CI.

Methodological quality assessment

The quality of the studies was peer-reviewed by KK and GS using the Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis [9]. High-quality studies were defined as a score of at least 6 out of 9 total points on the NOS. Sensitivity analysis was performed for studies with NOS score higher than 6. This scoring system was applied only on controlled observational studies, whereas studies which did not enroll control participants had not been graded.

Statistical analysis

Due 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 (inverse variance methods) or random (DerSimonian and Laird) effects 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 less than 0.05, I^2 statistic greater than 50%, or both. A two-sided P value of 0.05 was taken as significant. Egger's test and funnel plot regression were used to assess for potential publication bias. In the meta-analysis of prevalence, we conducted the quantitative synthesis with prevalence estimates that had been transformed using the double arcsine method. The final pooled result and 95% CIs were back-transformed for ease of interpretation [10].

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 (hospital-based vs. population-based vs. self-reported registry-based), [2] sample size (≥ or < the median number of patients [256]). Statistical analyses were conducted by using Comprehensive Meta-Analysis software (version 3.3, 2014), Englewood, NJ, USA.

Results

The literature search yielded 241 manuscripts. Eleven additional articles were identified from other sources. Seventy-two articles were duplicates, and 143 were not related to the coexistence of pemphigus and psoriasis. Full-text review was performed on the remaining 37 articles. Overall, 12 studies fulfilled the eligibility criteria and were included in the quantitative synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram is demonstrated in Fig. 1.

Study characteristics

The 12 eligible studies comprised a total of 12,238 patients with pemphigus from 8 countries, encompassing participants of all ages, both males and females. Published years of studies ranged from 1998 to 2017, and the follow-up

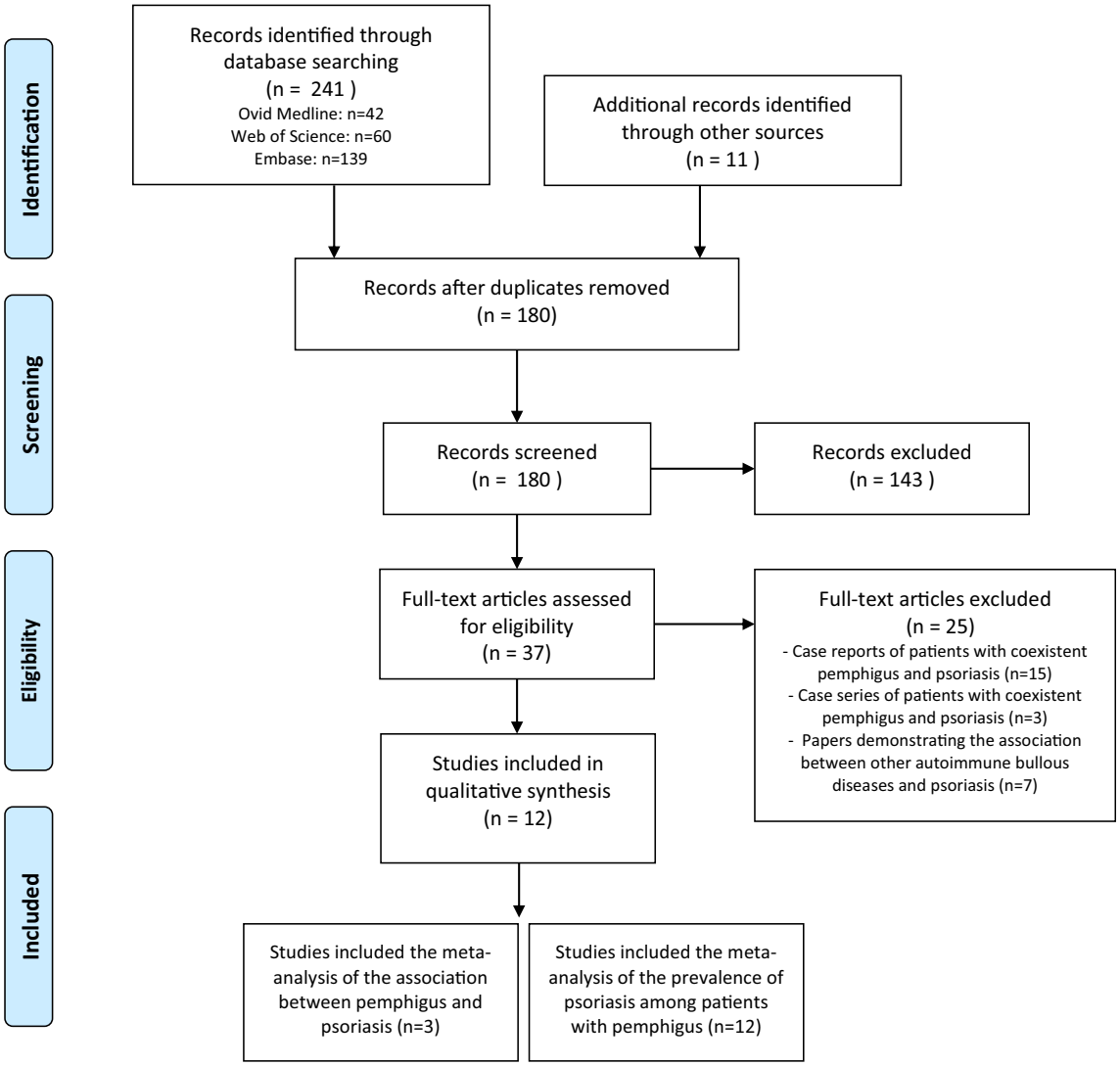

Fig. 1 PRISMA flow diagram of literature search and study selection for meta-analysis

period covered the years 1982–2015. The mean age of psoriasis patients in the different study cohorts ranged between 30.4 years in Peru [11] and 72.4 years in Israel [12]. Apart from two studies from Taiwan [13] and Peru [11], a female predominance was reported in all the remaining cohorts, with the female percentage ranging between 57.4% [14] and 71.8% [15]. Three studies were controlled cross-sectional studies [12, 13, 16], thus enabling the estimation of the OR for psoriasis among patients with pemphigus. Three additional studies were uncontrolled cross-sectional studies [15, 17, 18], whereas the remaining six were retrospective cohort studies [11, 14, 19–22]. With regard to the setting of the studies, seven were hospital-based [11, 14, 17, 19–22], three were population-based [12, 13, 16], and two were self-reported registry-based [15, 18]. The characteristics of the eligible studies are demonstrated in Table **1**.

Meta-analysis of the prevalence rates of psoriasis among patients with pemphigus

All the 12 eligible studies reported the prevalence of psoriasis among patients with pemphigus, and therefore were included in the quantitative synthesis of prevalence. The overall random-effects pooled prevalence of psoriasis among pemphigus patients was 2.4% (95% CI, 1.0–4.4; $I^2 = 96.3\%$; $P < 0.001$) across the 12 studies. The prevalence of psoriasis ranged between 0.7% (95% CI, 0.5–1.0) in the USA[16] and Turkey[14] and 8.6% (95% CI, 7.4–9.9) in Taiwan[13] **(**Fig. 2**)**.

Potential sources of heterogeneity were explored using stratified analysis of the included studies. Pooling of estimates according to the study settings suggests lower prevalence of psoriasis in hospital-based (2.0%; 95% CI, 1.2–2.9; $I^2 = 18.9\%$; $P = 0.286$) [11, 14, 17, 20–23] and self-reported registry-based (2.1%; 95% CI, 1.1–3.5; $I^2 = 0.0\%$; $P = 0.821$)

Table 1 Eligible study characteristics

Study	Setting	Design	Location	Period	*N* of patients	*N* of control subjects	Average age, y	% Female patients	Pemphigus assessment	Prevalence of psoriasis (95%CI)	Crude OR (95%CI)	Multivariate OR (95%CI)	NOS
Hsu et al.[16], 2016	Population-based	Controlled cross--sectional	USA	2002–2012	6406	87,033,305	68.2	59.1	Diagnostic codes from database	0.7 (0.6–1.0)	2.8 (2.0–3.9)	2.2 (1.5–3.2)[d]	3
Chiu et al.[13], 2017	Population-based	Controlled cross--sectional	Taiwan	1997–2010	1998[a]	7992	58	47.7	Diagnostic codes from database	8.6 (7.5–9.9)	7.7 (6.0–9.9)	7.2 (5.6–9.3)[e]	6
Kridin et al.[12], 2017	Population-based	Controlled cross--sectional	Israel	2004–2014	1985	9874	72.4	59.8	Diagnostic codes from database	3.3 (2.6–4.2)	2.8 (2.1–3.9)	2.6 (1.9–3.6)[f]	7
Micali et al.[21], 1998	Monocenter hospital-based	Retrospective cohort[c]	Italy	1982–1996	84	–	55.0	61.9	Clinical, immuno-pathological	2.4 (0.7–8.3)	–	–	–
Uzun et al.[14], 2006	Bicenter hospital-based	Retrospective cohort[c]	Turkey	1998–2004	148	–	43.0	57.4	Clinical, immuno-pathological	0.7 (0.1–3.7)	–	–	–
Gupta et al.[18], 2011	Virtual registry	Cross-sectional[c]	International	NR	171[a]	–	51.8	68.4	Self-reporting	2.3 (0.9–5.9)	–	–	–
Ramos et al.[11], 2012	Multicenter hospital-based	Retrospective cohort[c]	Peru	2003–2007	67[b]	–	30.4	43.3	Clinical, immuno-pathological	3.0 (0.8–10.3)	–	–	–
Zhu et al.[22], 2014	Monocenter hospital-based	Retrospective cohort[c]	China	2001–2010	221	–	44.2	58.4	Clinical, immuno-pathological	3.6 (1.9–7.0)	–	–	–
Shah et al.[15], 2015	Virtual registry	Cross-sectional[c]	International	2010–2011	393[a]	–	45.7	71.8	Self-reporting	2.0 (1.0–4.0)	–	–	–
Heelan et al.[17], 2015	Monocenter hospital-based	Cross-sectional[c]	Canada	2012-2013	295	–	56.6	59.3	Clinical, immuno-pathological	1.0 (0.3–3.0)	–	–	–
Baum et al.[20], 2016	Monocenter hospital-based	Retrospective cohort[c]	Israel	1980–2009	290	–	49.7	60.7	Clinical, immuno-pathological	2.8 (1.4–5.4)	–	–	–
Kridin et al.[23], 2016	Monocenter hospital-based	Retrospective cohort[c]	Israel	2000–2015	180	–	54.7	64.3	Clinical, immuno-pathological	1.7 (0.6–4.8)	–	–	–

The first three studies were included in the meta-analysis of odds ratio. All studies were included in the meta-analysis of prevalence

[a] PV

[b] 60 with endemic pemphigus foliaceus and 7 with endemic pemphigus vulgaris

[c] Uncontrolled study lacking recruitment of control subjects

[d] Adjusted for age and sex

[e] Adjusted for age, sex, and other comorbid diseases

[f] Adjusted for age, sex, ethnicity, drug abuse, alcohol abuse, healthcare utilization, and other comorbid diseases

N number, *OR* odds ratio, *CI* confidence interval, *NOS* Newcastle-Ottawa scale, *NR* not reported

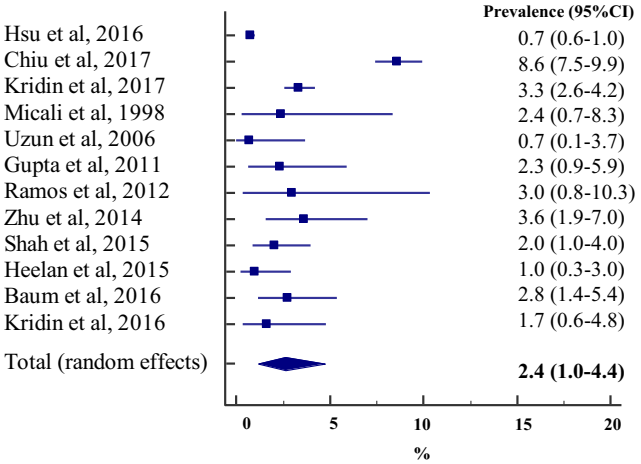

Fig. 2 Forest plot summarizing the prevalence of psoriasis among patients with pemphigus. The prevalence of the individual studies is represented by squares, through which the horizontal lines represent the 95% CIs. The diamond at the bottom represents the pooled prevalence from these studies

[15, 18] relative to population-based studies (3.5%; 95% CI, 0.4–9.7; $I^2 = 99.3\%$; $P < 0.001$) [12, 13, 16]. Larger studies [12, 13, 16, 15, 18] observed higher prevalence of psoriasis (2.7%; 95% CI, 0.7–5.9; $I^2 = 98.3\%$; $P < 0.001$) relative to small studies [15, 18, 11, 14, 17, 20–23] (2.2%; 95% CI, 1.3–3.2; $I^2 = 0.0\%$; $P = 0.456$).

Publication bias was not detected for this outcome as judged by non-significant Egger's regression test of the funnel asymmetry ($P = 0.278$; Supplementary Fig. 1).

Meta-analysis of the association between pemphigus and psoriasis

Only three eligible studies enrolled control subjects and were able to investigate the odds to have psoriasis in patients with pemphigus as compared to control subjects [12, 13, 16]. These studies comprised a total of 10,389 patients with pemphigus and 87,057,577 control participants. Study publication dates ranged from the years 2016 to 2017, and follow-up periods covered the years 1997–2014. Quality assessment using the NOS scale revealed that two of the three included studies had scores of 6 or greater [12, 13] (Table 1).

Multivariate ORs for psoriasis among patients with pemphigus ranged from 2.2 (95% CI, 1.5–3.2) in the USA to 7.2 (95% CI, 5.6–9.3) in Taiwan [13]. The pooled multivariate OR was 3.5 (95% CI, 1.6–7.6; $I^2 = 94.6\%$; $P < 0.001$) across all studies (Fig. 3). In a sensitivity analysis excluding the study with low NOS [16], the pooled OR increased (OR, 4.4; 95% CI, 1.6–11.8; $I^2 = 95.8\%$; $P < 0.001$).

Publication bias was not identified for this outcome, as seen by the non-significant result of the Egger's test or funnel plot regression ($P = 0.104$; Supplementary Fig. 2).

Discussion

This is the first systematic review and meta-analysis aiming to summarize the association between pemphigus and psoriasis. This study suggests that the pooled odds of having psoriasis is 3.5-times higher in patients with pemphigus as compared to control participants. In addition, the pooled prevalence of psoriasis in patients with pemphigus is 2.4% across all published studies.

The current literature

Several case reports and case series have reported the coexistence of psoriasis with the different variants of pemphigus, primarily pemphigus foliaceus [24–33], but also pemphigus vulgaris [34–38], IgA pemphigus [39], and pemphigus herpetiformis [40, 41]. A recent Japanese case series consisting of 145 patients with concomitant psoriasis and autoimmune bullous diseases revealed that pemphigus foliaceus was observed in 2.8% of the cases [42]. The coexistence of the two entities was substantiated by three controlled cross-sectional studies providing evidence that patients with pemphigus were collectively greater than three times more likely to have psoriasis [12, 13, 16]. In a recent Taiwanese case-control study consisting of 51,800 patients with psoriasis, the prevalence of pemphigus was greater in cases than in control participants (OR, 41.8; 95% CI, 12.4–140.9) [8]. This study further lends credibility to the mutual association between the two inflammatory conditions.

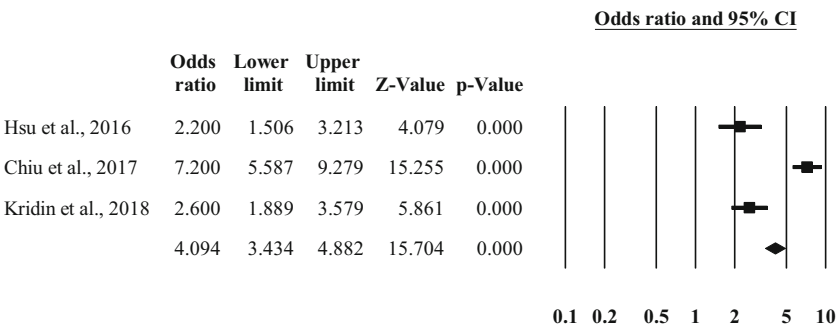

Fig. 3 Forest plot summarizing the OR for psoriasis in patients with pemphigus. The OR of the individual studies is represented by cycles, through which the horizontal lines represent the 95% CIs. The diamond at the bottom represents the pooled OR of these studies

Our quantitative synthesis revealed that the pooled prevalence of psoriasis in different cohorts of patients with pemphigus was 2.4%. A recent comprehensive worldwide systematic review of the epidemiology of psoriasis was undertaken to inform WHO Global report on psoriasis [43]. The prevalence rates of psoriasis in studies of all ages ranged from 0.09 to 5.1%, with only 5 studies out of 34 reporting values higher than 2.4% [44]. This further substantiates the findings of our study suggesting a higher burden of psoriasis among patients with pemphigus.

In a stratified analysis, the prevalence of psoriasis was higher in population-based studies relying on computerized datasets as compared to hospital-based and self-reported registry-based studies. This observation may be attributed to ascertainment bias, as the former tends to report the lifetime prevalence of psoriasis whereas other studies usually report point prevalence or period prevalence rates.

Biologic plausibility of the association

The mechanism of the existence of pemphigus and psoriasis in a single individual has not been fully elucidated. However, several interpretations of the biologic plausibility underlying this association have been proposed. The pathogenesis might be ascribed to the "epitope spreading phenomenon," a process in which a primary autoimmune or inflammatory process may cause damage to the tissue. Hence, certain protein components that were previously concealed from the immune system become exposed, thus inducing a secondary autoimmune response [45]. It has also been suggested that altered regulation of T cells with rising production of autoantibodies may be a conceivable link between the clinical manifestations of these two diseases in the same patient [33]. Another potential hypothesis is that inflammation from other skin diseases could create a favorable environment for the expression of intraepidermal antigens and improve the activity of pathogenic autoantibodies [26, 33]. Furthermore, plasminogen activation is known to play a role in acantholysis in pemphigus, and elevated levels of plasminogen activator have been recognized in psoriatic lesions [28, 30, 33]. The role of genetics might be considered on the grounds that HLA DRB1 alleles have been reported to be associated with both psoriasis [46] and pemphigus [23]. Further genetic studies might help to elucidate the exact mechanism of this clinical observation.

Another explanation for the concomitant development of pemphigus and psoriasis is UV irradiation. It has been well documented in the literature that sunlight and heat may be exacerbating factors in pemphigus [25, 31, 32, 36, 37]. UV radiation has been shown to induce acantholysis and epidermal instability in nonlesional skin in patients with pemphigus, which may account for the development of pemphigus after treatment with phototherapy in psoriatic patients [37]. Clarification of the temporal relationship between the appearance of pemphigus and psoriasis (whether pemphigus precedes or follows psoriasis) may help to confirm or refute this hypothesis.

Strengths and limitations

The large sample size and the inclusion of studies stemming from different geographical regions are the major strength of the current study. The conglomeration of various studies substantiates the statistical power and allows more accurate quantification of the odds for psoriasis among patients with pemphigus. This study has several limitations that should be addressed. The eligible controlled studies in this review were cross-sectional and lacked the temporal relationship between the conditions, which hinders drawing meaningful conclusions regarding the existence of a causal relationship. Moreover, the pooled studies had different inclusion/exclusion criteria, sample sizes, sampling approaches, geographic locations, and follow-up durations. High level of heterogeneity was observed among most of the investigated comparisons, which may make the results more difficult to interpret and generalize on typical pemphigus patients. To treat heterogeneity among the studies, we used the random-effect model, and we further provided plausible biological mechanisms that may account for the association between the two conditions. Other limitations stem from the design of eligible studies. Although the validation of their diagnoses is of high reliability, hospital-based studies, constituting the majority of eligible studies, are more susceptible to referral and inclusion biases. Additionally, population-based studies depended on diagnostic codes from databases, and thus are prone to non-differential misclassification that may embody another putative source of bias. The self-reporting in registry-based studies renders them liable to recall bias. It should be noted that estimation of publication bias in the second meta-analysis may be hindered by the inclusion of only three studies.

In conclusion, this meta-analysis provides epidemiological evidence that patients with pemphigus are significantly more likely to have coexistent psoriasis. Although epidemiological and experimental evidence supporting this association is emerging, it is yet to be clarified whether this observation is a causal effect or the result of some unmeasured confounding variables. More prospective cohort studies are necessary to shed light on a potential cause and effect relationship. Awareness of this association could be valuable to physicians treating patients with pemphigus.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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