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Immune-mediated inflammatory skin diseases

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Immune-mediated inflammatory skin diseases

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Table of contents

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SYSTEMATIC REVIEW
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The Efficacy and Effectiveness of Non-ablative Light-Based Devices in Hidradenitis Suppurativa: A Systematic Review and Meta-Analysis

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Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder that may be treated with non-ablative light-based devices; however, no systematic reviews on the topic exist to date. We conducted a systematic review and meta-analysis to determine efficacy of non-ablative light-based devices in treating HS. Specifically, a systematic review was conducted using MEDLINE, EMBASE, Web of Science and CINAHL. We analyzed the use of non-ablative light-based devices in the treatment of HS. At least two investigators performed title/abstract review and data extraction. Meta-analysis was conducted using comprehensive meta-analysis software. 5 RCTs and 11 case reports/series were included ($n = 211$ unique patients). No observational studies were found. For Nd:YAG laser, meta-analysis of 3 RCTs reported improvement in modified HS Lesion Area and Severity Index (HS-LASI) when compared to control subjects. In addition, three case reports/series reported HS-LASI, Physician Global Assessment (PGA) scores and number-of-lesion improvements in treated patients. For intense pulsed light (IPL), two RCTs reported HS-LASI and Dermatology Life Quality Index (DLQI) score improvements. For Alexandrite laser, one case report showed lesion improvement. In conclusion, meta-analysis of Nd:YAG laser in HS patients suggests significant improvement in HS-LASI scores. For IPL, evidence is limited, but suggests improvement in HS-LASI and DLQI scores. For Alexandrite laser, evidence precludes conclusions. Given small sample sizes and inconsistent reporting scales, larger RCTs are required to better determine the efficacy of these modalities in treating HS.

Keywords: hidradenitis suppurativa, lasers, hair removal, neodymium-doped yttrium aluminum garnet (Nd:YAG), alexandrite, intense pulse light (IPL), light-based devices

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease of intertriginous regions with a prevalence of 1 to 4% worldwide (1). It is thought to result from pilosebaceous unit occlusion and dilation, followed by follicular rupture, altered cytokine response, and abnormal microbiota in genetically predisposed individuals (2–4). Patients present with painful inflammatory papules and nodules that can progress to sinus tracts, hypertrophic, and keloid scars (5, 6). Lesions can be painful, disfiguring and malodorous leaving patients with depression and social isolation (7, 8). Smoking, obesity, and genetic factors are known risk factors for HS and likely play a role in its pathogenesis (2).

HS can be difficult to control depending on disease severity which is commonly classified by Hurley staging consisting of stages I (mild), II (moderate), and III (severe) (9). Mild disease is typically treated with topical and/or oral antibiotics (e.g., clindamycin). Moderate disease can be treated with intralesional corticosteroids, oral antibiotics (e.g., doxycycline, minocycline, rifamycin or clindamycin), retinoids (e.g., isotretinoin), hormonal medications (e.g., spironolactone) amongst other options. Advanced disease may require biologic therapies (e.g., high dose anti-TNF-alpha therapy), surgical deroofing or excision (10). The use of laser and other light-based devices in the treatment of HS has recently increased (11).

CO_2 laser was the first to be studied in HS patients and was used as a surgical tool for deroofing and excision of HS sinus tracts (12, 13). Its cutting and vaporization ability has allowed for scar reconstruction with minimal bleeding (14). While fractionated CO2 lasers are used to surgically excise nodules and sinus tracts, non-ablative lasers and light therapies including neodymium-doped yttrium aluminum garnet (Nd:YAG) 1,064 nm (15), Alexandrite 755 nm (16, 17) and intense pulse light (IPL) (18) have shown benefits by targeting the hair follicle directly, destroying the pilosebaceous unit. This is intriguing given that the hair follicle element and the follicular inflammation are central to the pathogenesis of HS (4). The long-pulsed Nd:YAG and Alexandrite are non-ablative lasers that destroy the hair follicle by targeting melanin and water chromophores (15, 16).

Lasers emit light by amplifying photons optically based on electromagnetic radiation, and each photon is delivered at a precise vibrational state and power (17). In contrast, IPL emits broad wavelengths, using filters to narrow the spectrum. Lasers and IPL target (a) melanin (found abundantly in hair follicles leading to follicular necrosis) and (b) water molecules in the dermis, making both suitable treatment options for lighter-skin phototype HS patients (19), but despite their potential efficacy in treating HS, evidence of their actual effectiveness in case reports, case studies, and small randomized controlled trial (RCTs) (20) supporting their usage is limited.

Currently, only one systematic review exists providing a general overview on all lasers (ablative and non-ablative) in treating HS. None specifically evaluated the role of non-ablative light therapies and no meta-analysis has ever been conducted (21). We conducted the first systematic review and meta-analysis examining the evidence behind non-ablative light therapies (mostly light-based hair removal devices) in the treatment of HS. Given the significant costs of non-ablative light therapy, physicians recommending their use have an obligation to ensure that the theoretical potential of these treatments is supported by evidence. The results of this review suggest that with regards to therapeutic impact, ablative light hair removal tools are not only efficacious (have the potential to improve HS) but also effective (positive results demonstrated). What remains to be determined is whether this can be shown also for cost effectiveness.

MATERIALS AND METHODS

Literature Search

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (22). MEDLINE, EMBASE, Web of Science and CINAHL were searched independently by two investigators (AJ, AS) from inception through April 2020. Search terms were "hidradenitis suppurativa," "acne inversa," "verneuil disease," and "laser," "intense pulse light," "light." No language restriction was applied.

Eligibility Criteria

All study designs were eligible for inclusion (RCTs, observational studies, case series, and case reports). Review articles and articles discussing the use of conventional (normal mode) or fractional CO2 lasers for scars or surgery were excluded.

Data Extraction

Data extraction was conducted by two independent reviewers (AJ, AS). Extracted data included: study design, number of patients, Fitzpatrick skin type, HS severity measured by Hurley staging, laser type [Nd:YAG 1,064 nm (15), Alexandrite 755 nm (16, 17), or IPL (18, 23)], laser characteristics (fluence (J/cm^2), spot size (mm), pulse duration (ms).

Quality Assessment

Risk-of-bias of included RCTs was assessed using the revised Cochrane risk-of-bias assessment version 2 (24), which is composed of five domains that assess risk of bias from initial randomization step through reporting step. Based on signaling questions, each domain was assigned an estimated risk-of-bias designated as "low," "high," or "some concerns."

Case reports and case series were assessed using a published methodological tool for case reports and case series that provided scores for selection, ascertainment, causality, and reporting (25). Studies scoring 50% or more (4 or more "yes" answers) were considered valid.

Outcomes Measures

The modified HS-LASI score (15) is composed of three physician-reported clinical components and four patient-reported symptoms. Clinical components were as follows: #1 lesion morphology: fistula 4 points, nodule 2 points, abscess and scar 1 point each; #2 distance between two lesions or size (if only one lesion): <5 cm, 2 points, 5–10 cm, 4 points, and >10 cm,

8 points; #3 lesions separated by normal skin: yes, 0 points, no, 6 points. The four patient-reported symptoms (erythema, edema, pain, purulent discharge) scored 0–3 points each. Additional endpoints, physician global assessment (PGA) (26) and dermatology quality of life index (DLQI) (27) were analyzed.

Statistical Analysis

Two independent investigators (AJ, AS) extracted primary outcome quantitative data, analyzing mean, standard deviation (SD) and sample size for both the control and intervention groups. In studies where range was mentioned, as a measure of dispersion, it was converted to SD using the formula SD = IQR/1.35, assuming the data followed a normal distribution. Studies were weighted using random effects proposed by DerSimonian and Laird (28). Heterogeneity across RCTs was estimated using the I^2 statistic, whereas a $I^2 > 50\%$ was considered significant (28). Publication bias was assessed by visualizing the Begg's funnel plot and Egger's regression analysis and was considered significant at $p < 0.10$ (29). In case of significant publication bias, Duval & Tweedie's Trim & Fill method adjusted the pooled effect size, improving the funnel plot's symmetry. The small number of patients studied meant subgroup analyses could not be performed. GRADE evidence profile was used to evaluate certainty of outcomes, assessed

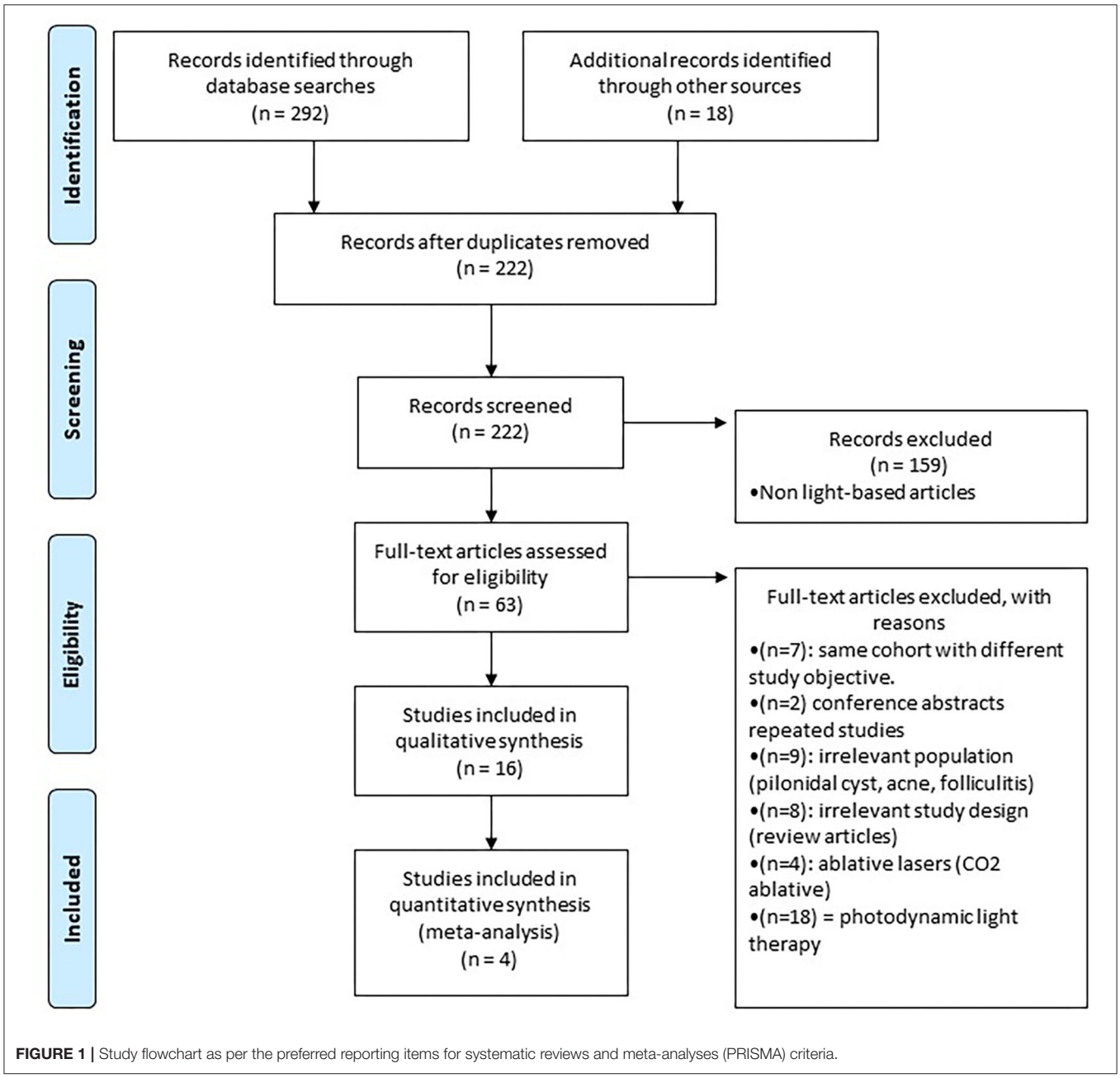

FIGURE 1 | Study flowchart as per the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria.

TABLE 1 | Detailed description of patient characteristics in the included studies.

	Patients characteristics					Intervention			
Study	**Sample**	**(M, F); age yrs. mean (range)**	**Fitzpatrick skin type (≤III vs. ≥IV)**	**Hurley stage I/II/III**	**Adjunctive therapies used**	**Laser (type) or IPL**	**Fluence (J/cm^2)/ Spot size (mm)/ Pulse duration (ms)**	**Number of sessions**	**Reported outcome result**
Randomized control trials (RCT)									
Highton et al. (23)	18	M (n = 3), F (n = 15); age = 34	NR	II–III	No systemic or topical therapies were allowed 2 weeks prior to and during enrollment	IPL	420 J/cm2/7–10 mm/30–50 ms	2/week × 4 weeks	HS-LASI: decrease by 56% at 3 months, decrease by 44% at 6 months −33% at 12 months on all sites
Mahmoud et al. (15)	22	M (n = 3), F (n = 19)	NR	II	No systemic or topical therapies were allowed 2 weeks prior to and during enrollment	Nd:YAG 1,064 nm	40–50 J/cm^2/10 mm/20 ms	1/month × 4 months	HS-LASI: decrease by 72.7% at 6 months all sites
Tierney et al. (31)	22	M (n = 3), F (n = 19); age = 41 (19–72)	≤III (n = 14), ≥IV (n = 8)	II–III	No systemic or topical therapies were allowed 2 weeks prior to and during enrollment	Nd:YAG 1,064 nm	40–50 J/cm^2 (Fitz ≤III), 25–35 J/cm^2 (Fitz ≥IV)/10 mm/20 ms (Fitz ≤III), 35 ms (Fitz ≥IV)	1/month × 3 months	HS-LASI: decrease by 65.3% all sites at 3 months
Wilden et al. (32)	43	M (n = 12), F (n = 31); age = 38 (23–57)	NR	I (n = 7), II (n = 23), III (n = 13)	Patients were not allowed to use topical or systemic therapy during the study (e.g. immunosuppressant, antibiotics, retinoids). Short-time rescue antibiotics, incisions of abscesses and the usage of disinfection were allowed.	IPL	4.4–6.0 J/cm^2 /8 mm/not avail.	2/week × 24 weeks	DLQI improved by 31% and 46% in patients treated with IPL + RF and RF only
Xu et al. (33)	20	M (n = 3), F (n = 17); age = 37 (23–54)	≤III (n = 11), ≥IV (n = 8)	II (n = 19)	Topical therapies were allowed but no systemic treatment 2 weeks prior to or during the enrollment	Nd:YAG 1,064 nm	40–50 J/cm^2 (Fitz ≤III), 25–35 J/cm^2 (Fitz ≥IV)/10 mm/20 ms (Fitz ≤III), 35 ms (Fitz ≥IV)	1/month × 2 months	HS-LASI: decrease by 31.6% all sites after 2 sessions
Case reports/Case series									
Abdel Azim et al. (34)	20	M (n = 9), F (n = 11); age= (20–35)	III–IV	I–II	No systemic or topical therapies were allowed 2 weeks prior to and during enrollment	Nd:YAG 1,064 nm	35 J/cm^2/10 mm/20 ms	1/2 weeks × 4 weeks	PGA score improvement (decrease by 70.68%)
Rucker et al. (35)	20	M (n = 3), F (n = 17); age = 41 (19–72)	II–IV	II	No systemic or topical therapies were allowed 2 weeks prior to and during enrollment	Nd:YAG 1064 nm	40–50 J/cm^2 (Fitz ≤ III), 25–35 (Fitz ≥ IV)/10 mm/20 ms (Fitz ≤ III), 35 ms (Fitz ≥ IV)	1/month × 3 months	HS-LASI: decrease in 20.5%
Theut et al. (20)	25	F (n = 25); age = 39.24 (16–63)	≤III (n = 23), ≥IV (n = 2)	I (n = 5), II (n = 19), III (n = 1)	Two patients were on metformin, 16 patients on topical risocinol and 11 patients were on topical clindamycin and systemic tetracycline.	IPL	18–34 J/cm^2/20 mm or 100 mm/not avail.	1–10 sessions/ 4–6 weeks	13/25 patients had a reduction in disease activity

(Continued)

TABLE 1 | Continued

Study	Patients characteristics					Intervention			
	Sample	**(M, F); age yrs. mean (range)**	**Fitzpatrick skin type (≤III vs. ≥IV)**	**Hurley stage I/II/III**	**Adjunctive therapies used**	**Laser (type) or IPL**	**Fluence (J/cm^2)/ Spot size (mm)/ Pulse duration (ms)**	**Number of sessions**	**Reported outcome result**
Tsai et al. (36)	1	M/19	IV	II	No topical or systemic therapies.	Alexandrite 755 nm	22–24 J/cm^2/18 mm/not avail.	1/month ×3 months	Improvement in pain and discharge
Vossen et al. (37)	15	M (n = 10), F (n = 5); age = 34.1 ± (10.1)	≤III (n = 15)	I	Three out of the 15 patients were on clindamycin 300 mg twice daily and rifampicin 600 mg once daily, minocy-cline 100 mg once daily, and acitretin 25 mg once daily, none of these treatments statistically affected the study outcomes).	Nd:YAG 1,064 nm	30–0 J/cm^2/7–12 mm/20–40 ms	1/month × 6 months	Decrease number of monthly flares

IPL, intense pulse light; Nd:YAG, neodymium-doped yttrium aluminum garnet; HS-LASI, hidradenitis suppurativa lesion, area, and severity index; PGA, physician global assessment.

TABLE 2 | GRADE evidence.

Certainty assessment							# of patients		Effect		Certainty	Importance
# of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[intervention]**	**[comparison]**	**Relative (95% CI)**	**Absolute (95% CI)**		
HS-LASI (assessed with: HS-LASI scale)												
3	Randomized control trials	Not serious	Serious[a]	Not serious	Serious[b]	Strong association	53	53	-	SMD **0.99 SD higher** (0.28 higher to 1.71 higher)	⊕⊕◯◯ LOW	CRITICAL

[a] *There was evidence for significant heterogeneity in reporting of HS-LASI scores; I squared= 65.37%.*
[b] *A wide confidence interval.*
CI, confidence interval; SMD, standardized mean difference.

across several domains: study design, risk-of-bias, imprecision, indirectness, inconsistency, publication bias, and strength of effect size (30). Evidence grade was rated from high to very low, with evidence downgraded by one level, where serious concerns pertaining to the aforementioned matrices existed. Meta-analysis was conducted using Comprehensive meta-analysis software (v. 3.0, New Jersey, USA).

RESULTS

Search Results

Study design is summarized in a flow diagram (**Figure 1**). A total of 310 articles were initially identified. After removing duplicates and screening titles, abstracts, and full-texts, 16 articles met the inclusion criteria, which consisted of 5 RCTs and 11 case report/series for a total of 211 unique HS patients. The most commonly investigated laser was Nd:YAG (three RCTs and three case series), followed by IPL (two RCTs and one case series) and Alexandrite (one case report).

Study and Patient Characteristics

Five RCTs and five valid case reports/series with a total of 206 patients treated with three light-based modalities (IPL, Nd:YAG 1,064 nm and Alexandrite 755 nm) were included. Most patients were females 159 (77%). **Table 1** summarizes study patient characteristics.

Quality Assessment

Five included RCTs were rated as having overall "low risk-of-bias" using Cochrane risk-of-bias two tool, and both investigator evaluations were concordant. Certainty of evidence was rated low due to imprecision and inconsistency noted in outcome as per the GRADE evidence profile (**Table 2**). Five of 11 case report/series were evaluated as valid and were included in the study (**Supplementary Table 1**).

Neodymium-Doped Yttrium Aluminum Garnet Laser (ND-YAG)

The Nd:YAG settings used by all three RCTs and 3 case series were 25–60 J/cm^2 fluence with 10 mm spot size and 20–35 s pulse duration. Two passes were done over inflamed lesions and one over unaffected skin, with treatments every 4–6 weeks (15, 31, 33–35, 37). Lower energy and higher pulse duration were applied in darker phototype skin (Fitzpatrick IV–VI) HS patients.

In the largest RCT of 22 patients treated with Nd:YAG, the percentage change in HS-LASI score after 3 months was −65.3% averaged over all anatomic sites, with the inguinal region having the greatest reduction by −73.4%, followed by −62.0% for the axillary region and −53.1% for the inframammary region (31).

Disease severity before and after use of Nd:YAG was rated on a numerical rating scale (NRS) ranging from 0 (no suffering) to 10 (extreme/unbearable suffering). Fourteen months after 8 to 10 monthly Nd:YAG sessions, revealed severity being reduced from NRS 6.4 ± 2.8 to NRS 3.6 ± 3.5 ($p = 0.010$) in a case series of 25 patients (37). This was a patient-based survey without physician assessment of outcomes. Hence, responses were subject to recall bias and possibly were impacted by the fluctuating nature of HS. Treated patients reported a 50% reduction in the number of flares and higher satisfaction after treatment completion compared to before Nd:YAG ($p = 0.019$). Additionally, 2 case series of 20 patients each reported improvement in PGA and HS-LASI respectively in all anatomical sites (34, 35). Patient follow-up was only 3 months, which is considered relatively short to assess improvement.

Intense Pulsed Light

An RCT of 17 patients found that twice-weekly IPL for 4 weeks at 420 nm, 7–10 J/cm^2, 30–50 ms (assessed at 12 months) significantly improved HS, with a 33% reduction in HS-LASI score (23). Another RCT of 43 patients compared IPL alone (three passes of 420–1200 nm, 4.4–6 J/cm^2 and 8 ms) to IPL with radiofrequency (RF), and reported that those receiving IPL plus RF experienced improvement in lesion count and DLQI of 44% ($p = 0.040$) at week 12 and 66% ($p = 0.014$) at week 24 compared to the IPL alone (32).

In a case series of 25 patients, a decrease in number of flares and hair reduction occurred after 1–10 sessions every 4–6 weeks with IPL (18–34 J/cm^2/20 or 100 ms) (20). Patients were mostly Fitzpatrick II–III skin type with the exception of two HS patients (Fitzpatrick type IV) with Hurley I/II, who received four sessions of IPL (500 nm and 550 nm, 9 J/cm^2, 5–10 ms) at intervals of 15–20 days (18). Both experienced complete resolution of the inflammatory, painful components of HS at 3 months follow up.

Alexandrite Laser

Our systematic review found no RCTs and only two case reports and one case series that investigated the use of Alexandrite laser for HS. These included a total of 4 HS patients with Hurley stage II disease and Fitzpatrick skin phototype II-III (16, 17, 36). Only one case report met inclusion criteria for this review (36). The setting used in all three studies was a wavelength of 755 nm (15–35 J/cm^2, 5–28 ms) with one session per 4 weeks. In one patient with Hurley stage III disease, the reported outcome of stopping oral antibiotic was provided without accompanying assessment of severity (16). In the other case (36), pain assessment was performed after only one session of Alexandrite, which is too early to assess treatment efficacy. Furthermore, the patient was on tetracycline for facial acne concomitantly, which is known to have a positive effect on HS and can be a confounder (11).

Meta-Analysis

Out of the five RCTs, three were included in the meta-analysis. These three employed the modified HS-LASI scale, as the measure of primary outcome (15, 23, 31, 33). One study did not provide enough statistical information for meta-analysis. Hence, only a qualitative assessment was performed (23). Another study measured primary lesion count and DLQI scores as outcomes for efficacy of laser treatment in patients with HS: due to a lack of a common reporting scale it was not included in the meta-analysis (32). Out of the studies included in the meta-analysis, one presented treatment effect size data for participants after

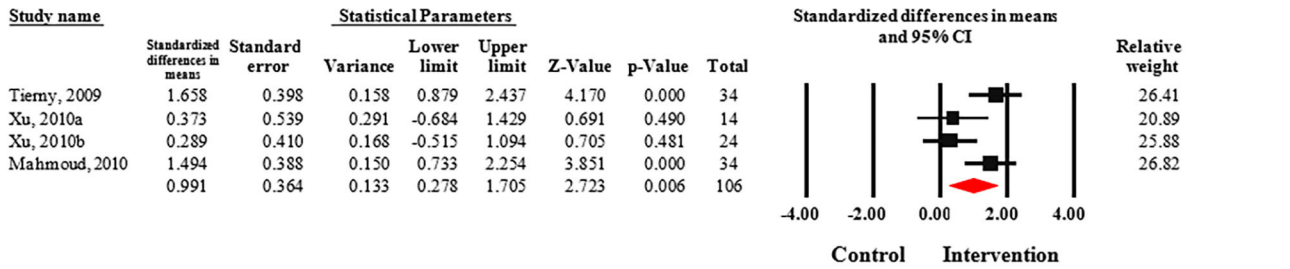

FIGURE 2 | Forest plot of standardized mean differences and confidence intervals of HS-LASI for HS patients treated with Nd:YAG laser compared to controls. It demonstrates that Nd:YAG laser treated patients ($n = 58$) had significantly improved HS-LASI scores compared to the control group.

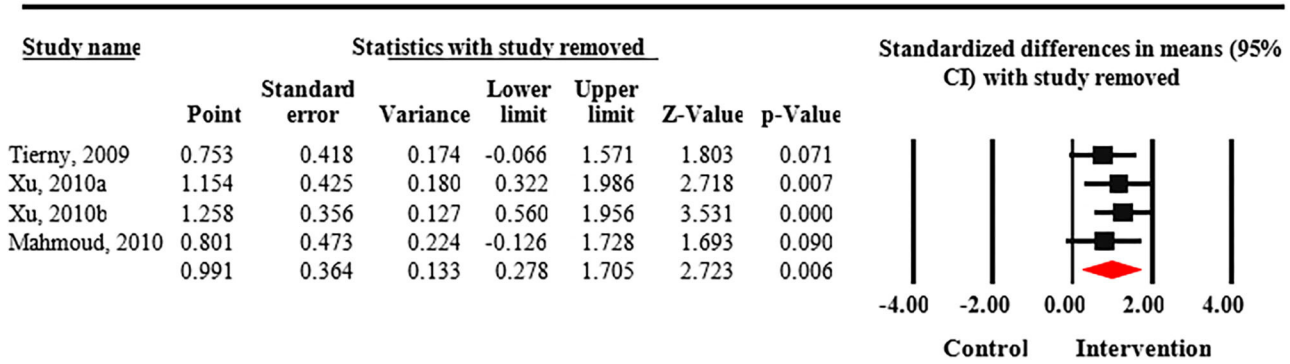

FIGURE 3 | Sensitivity analysis of included randomized control trials. Sensitivity analysis shows non-significant change in pooled effect size pertaining to laser therapy in Hidradenitis suppurativa (HS).

splitting them into one group with lesions in axilla and one with lesions in the groin, evaluating them as separate treatment groups (33).

In three studies with valid quantitative data, half intervention/half control study design was employed, with a total sample size of 106 patients with HS. Significant statistical heterogeneity in reporting of HS-LASI existed in these RCTs, where I^2 was measured at 65.37% ($P = 0.03$, $Q = 8.66$). Therefore, we used random effects for weighting them.

Meta-analysis revealed that treatment with Nd:YAG laser (58 patients) significantly improved HS-LASI scores compared to the control group with a standardized mean difference (SMD) of 0.99 (95% CI: 0.28 to 1.71, $p = 0.006$) (**Figure 2**). Sensitivity analysis showed non-significant change in pooled effect size pertaining to laser therapy in HS (**Figure 3**). There was no evidence of publication bias in this outcome (**Figure 4**). Egger's regression model was non-significant ($B = -6.99$, $P = 0.42$).

No unifying outcome was reported using case reports/series. Therefore, results could not be compared by statistical analysis, and only a qualitative assessment could be performed. For the RCTs, the scoring system of HS-LASI was used by 3/5 RCTs and the meta-analysis performed for those modalities had a common reported outcome (38).

DISCUSSION

Non-ablative light-based therapies targeting the hair follicle and/or water in the dermis can be considered as useful treatment options for patients with HS (39). This mechanism of action is particularly interesting given the role of follicular inflammation in HS pathogenesis. The use of long pulsed Nd:YAG laser resulted in significant improvement in HS lesions compared to the controls (95% CI: 0.28 to 1.71). Analysis of the Alexandrite laser 755 nm and IPL 420 nm also demonstrated improvement in clinical severity, however, given the lack of a uniform reporting scale, these results could not be compared quantitatively through a formal meta-analysis.

One of the possible reasons for Nd:YAG being the most commonly investigated hair removal device in HS is its higher efficacy and safety profile in darker skin patients given the higher likelihood of these individuals being affected by the disease (40). It is yet to be proven whether the earlier use of non-ablative light-based therapies such as Nd:YAG in HS can actually alter the natural history of the disease or delay the progression from Hurley I to stages II–III. Our report highlights the need for larger RCTs to assess the effectiveness of non-ablative lasers.

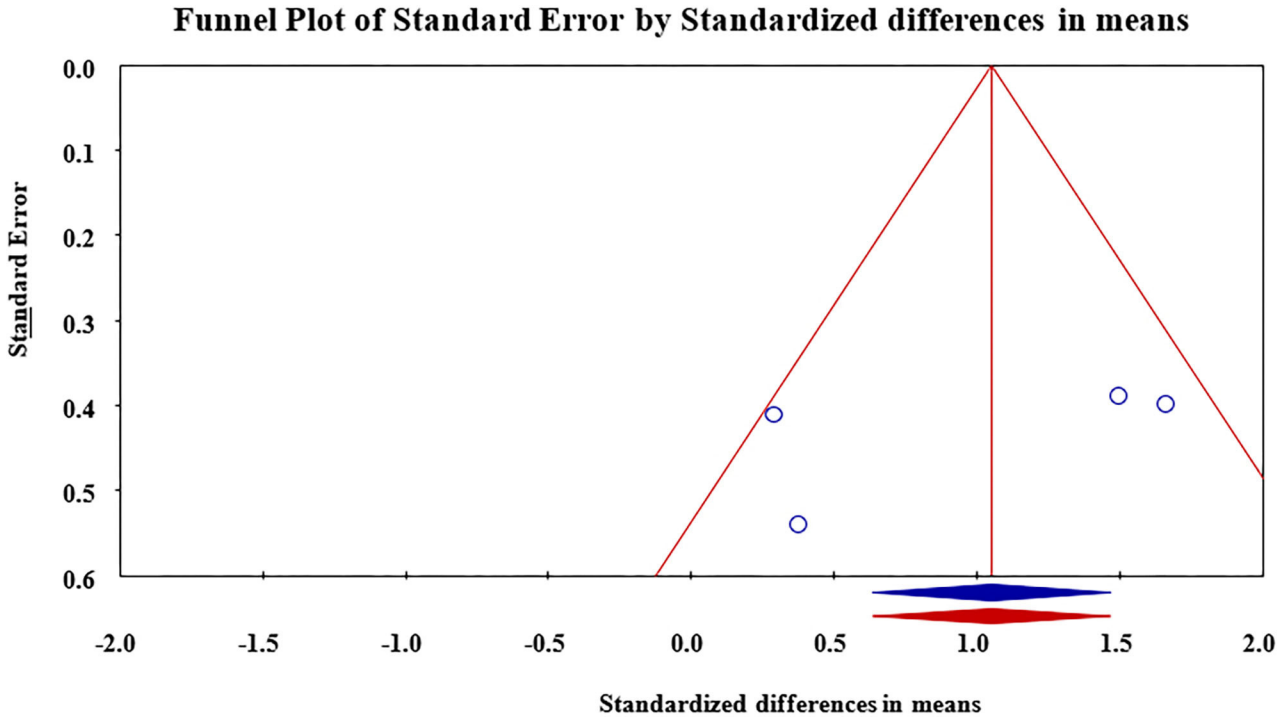

FIGURE 4 | Funnel plot for assessment of publication bias in reporting of outcomes. Publication bias was found to be non-significant.

One of the most significant limitations to recommending routine use of non-ablative light-based therapies remains the price. Importantly, given that non-ablative light devices are costly, not covered by most insurance plans in North America, and that multiple sessions are required, confirming their effectiveness in well-designed randomized trials prior to incorporating them into treatment algorithms remains essential. Future studies should examine dose-response effect and the number of sessions required for significant disease improvement and clinical end results in order to determine cost-effectiveness.

The assessment of effective hair removal is different in HS from other cosmetic treatments since the ultimate goal is to reduce the follicular load that triggers the inflammatory process rather than achieving a hairless skin. Hence, we and others emphasize the use of the modified HS-LASI measure that incorporates the patient's symptoms with the physical examination, when reporting efficacy of laser/IPL use in HS to facilitate future comparisons between studies (38).

LIMITATIONS AND STRENGTHS

This is the first systematic review specifically conducted to investigate the role of non-ablative light-based therapies in treating HS. The study's strengths include the use of the PRISMA guidelines and an extensive search including five databases with no restrictions on language, publication date, or study design. Additionally, all studies included in this systematic review were evaluated for quality using published quality assessment tools. Due to the small number of included studies and small sample size of patients overall, a meta-analysis could not be conducted for IPL and for Alexandrite laser. Given the lack of high-quality studies, RCTs and observational studies, firm conclusions about the efficacy and effectiveness of IPL and Alexandrite laser could not be drawn. Finally, the lack of common reporting scales, especially in case reports and case series, limited the ability to draw conclusions.

CONCLUSIONS

Our meta-analysis of Nd:YAG laser in HS patients suggests significant improvement in HS-LASI scores. For IPL, evidence is limited, but suggests improvement in HS-LASI and DLQI scores. For Alexandrite laser, evidence precludes conclusions. Given small sample sizes and inconsistent reporting scales, larger RCTs are required to better determine the efficacy of these modalities in treating HS.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: the data from respective papers can be accessed through www.pubmed.gov.

ETHICS STATEMENT

Since open source data were used for this study ethics review was not required for this systematic review and meta-analysis.

AUTHOR CONTRIBUTIONS

AJ and AS searched literature and analyzed included studies. AJ, AS, JR, EN, EO'B, DB, and IL—analyzed data. AJ, AS, and AB—prepared figures. AJ, AS, JR, EN, EO'B, DB, and IL—wrote the paper. JR, EO'B, DB, and IL—supervised the study. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.591580/full#supplementary-material

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Polyethylene Glycol Ointment Alleviates Psoriasis-Like Inflammation Through Down-Regulating the Function of Th17 Cells and MDSCs

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Objective: To explore the possible mechanism of improving the imiquimod (IMQ)-induced psoriasis-like inflammation by using polyethylene glycol (PEG) ointment.

Methods: We evaluated the appearance of psoriasis lesions by Psoriasis Area and Severity Index (PASI), observed the epidermal proliferation by histopathological staining and immunohistochemical staining, and explored the key molecules and signaling pathways of improving psoriasis-like inflammation treated with PEG ointment by RNA sequencing. Finally, we verified the expression of inflammatory cells and inflammatory factors by flow cytometry, immunohistochemical staining, and Q-PCR.

Results: PEG ointment could improve the appearance of psoriasis lesions and the epidermis thickness of psoriasis mouse, inhibit the proliferation of keratinocytes, and down-regulate the relative mRNA levels of IL-23, IL-22, IL-6, IL-17C, IL-17F, S100A7, S100A8, S100A9, CXCL1, CXCL2, and IL-1β in the skin lesions of psoriasis mouse by down-regulating the numbers of myeloid-derived suppressor cells (MDSCs) and T helper 17 (Th17) cells.

Conclusion: PEG ointment could improve the IMQ-induced psoriasis-like inflammation by down-regulating the functions of Th17 cells and MDSCs.

Keywords: psoriasis, IMQ, PEG, MDSCs, Th17

INTRODUCTION

Psoriasis is a chronic autoimmune disease affecting 0.09 to 5.1% of the general population worldwide (1–4). The mechanism of psoriasis is very complicated and has not been fully elucidated. Given that ∼80% of the patients with psoriasis are in mild-to-moderate states, topical physiotherapy can be used to control the condition, and therefore, the development of external medicine is the preferred option. Imiquimod (IMQ) is a ligand for Toll-like receptors (TLR7 and TLR8). IMQ has been used for the topical treatment of genital and perianal warts caused by human papilloma virus (5); unexpectedly, the patients who suffered from genital and perianal

warts developed psoriasis-like lesions at the affected areas after applying IMQ cream (6, 7). It has been proven that the IMQ-induced psoriasis-like skin lesions in mice, such as erythema, skin thickening, scaling, epidermal alteration (acanthosis, parakeratosis), inflammatory cell infiltration, and vascular proliferation, are very similar to psoriasis (8–10). The psoriasis mouse model is widely used in the screening of topical drugs for psoriasis. There have been an increasing number of studies in recent years focusing on the treatment of psoriasis using topical medicine, and the drugs that are currently being studied mainly concentrate on non-toxic and harmless natural Chinese herbal medicine extracts with anti-inflammatory and anti-proliferative effects (11). In our study, it was found that polyethylene glycol (PEG) (referring to a polymer or oligomer of ethylene oxide) as an ointment base could significantly improve the IMQ-induced psoriasis-like inflammation. PEGs with a molecular weight of 200–600 are in a liquid state at room temperature, while those with a molecular weight of >600 gradually enter a semi-solid state. PEGs with different molecular weights usually have different physical properties and applications, ranging from colorless, odorless viscous liquids to waxy solids. Most of the PEG chemistries are similar. PEGs with low molecular weights can be used as suppository base, eye drops, injections, and solvents, while PEGs with high molecular weights can be used for preparing tablets and film coats. Liquid and solid PEGs can be used as suppository base and ointment base at various ratios. Therefore, PEG has been widely used in the cosmetics and pharmaceutical industries. However, there was no report yet focusing on the therapeutic mechanism of PEG. In this study, we found that PEG ointment could improve the IMQ-induced psoriatic-like inflammation and epidermal keratinocyte proliferation, and we explored the possible mechanism of PEGs in the treatment of psoriasis by applying the RNA-seq method.

MATERIALS AND METHODS

Preparation of PEG Ointment

The PEG ointment is composed of 70% of PEG400 (SCRC, shanghai, China) and 30% of PEG4000 (SCRC, shanghai, China). Mix the PEG400 and PEG4000 ingredients and stir until well-distributed at 65°C, and then stir into a semi-solid state at room temperature.

Animals and Ethical Statement

A total of 18 male BALB/c mice (8 weeks) were purchased from Hunan Slack King Experimental Animal Co. During the experiment, mice were fed under specific pathogen-free conditions with controlled environmental conditions (12 h light/dark cycle, at 24°C) and provided with standard water and food *ad libitum*. All animal experiments were performed according to the principles specified in the "Guide for the Care and Use of Laboratory Animals in China" with approval from the Animal Ethics Committee of Central South University.

Animal Treatment

Mice at 8 to 11 weeks of age received a daily topical dose of 62.5 mg of commercially available IMQ cream (5%) (Aldara; 3M Pharmaceuticals) on the shaved back for 5 or 6 consecutive days to build a psoriasis mouse model. Besides, we can also extend the 6-day psoriasis model to 21 days by continuing to apply 62.5 mg of IMQ cream once every other day for 14 consecutive days (12, 13).

The 18 mice were randomly divided into three groups ($n = 6$): the Blank group, the IMQ group, and the PEG group. All mice were marked on the tail, and an area of 2 cm × 3 cm was shaved from the back of the mice. The mice in the Blank group were not given any intervention; the mice in the IMQ group were only applied with IMQ cream (62.5 mg/day); and the mice in the PEG group were applied with IMQ cream (62.5 mg/day) first, and then with PEG ointment (100 mg/day) 6 h later. The experimental period lasted for 6 days or 20 days. For the establishment of the 21-day psoriasis mouse models, 62.5 mg of IMQ cream was applied to each mouse in the IMG group once a day during the first 6 days and once every 2 days from day 7 to day 20; 100 mg of PEG ointment was applied to each mouse in the PEG group every day from day 1 to day 20 after applying IMQ cream. At the end point of the experiment, all the mice were weighed and sacrificed by breaking the neck. Skin lesions and spleens were collected for future investigation.

Scoring Severity of Skin Inflammation

An objective scoring system [Psoriasis Area and Severity Index (PASI)] was used to evaluate the severity of skin inflammation of the mouse model. Erythema, scaling, and infiltration were scored independently from 0 to 4 as follows: 0, none; 1, slight; 2, moderate; 3, marked; 4, very marked. The cumulative score (erythema plus scaling plus thickening) was calculated to indicate the severity of inflammation (scale 0–12).

Histology and Immunohistochemistry

The skin lesions from each mouse were fixed in 4% paraformaldehyde and then embedded in paraffin for 24–36 h. Sections (thickness 4 μm) were stained using hematoxylin and eosin (H&E). The tissue pathology was observed under a light microscope (Nikon, Beijing, China). As for immunohistochemistry, the section slides were heated at 60°C for 2 h first, and washed in xylene and hydrated with varying concentrations of alcohol. After repairing the antigen through high temperature addition, the sections were incubated in rabbit anti-Ki67 (Abcam, ab16667, USA) and rabbit anti-IL-17a (Seivicebio, GB11110, China) overnight at 4°C. Then, the secondary antibody was applied to detect the primary antibody following the manufacturer's instructions of the immunohistochemical general two-step test kit. Subsequently, the section slides were stained with DAB chromogen and counterstained with hematoxylin. The tissue pathology was observed under a light microscope (Nikon, Beijing, China).

Changes of Spleen in Mice

The mice were weighed before being sacrificed. Then, each spleen was weighed, and the spleen index was calculated accordingly [spleen index = 100 * spleen weight (mg)/body weight (g)].

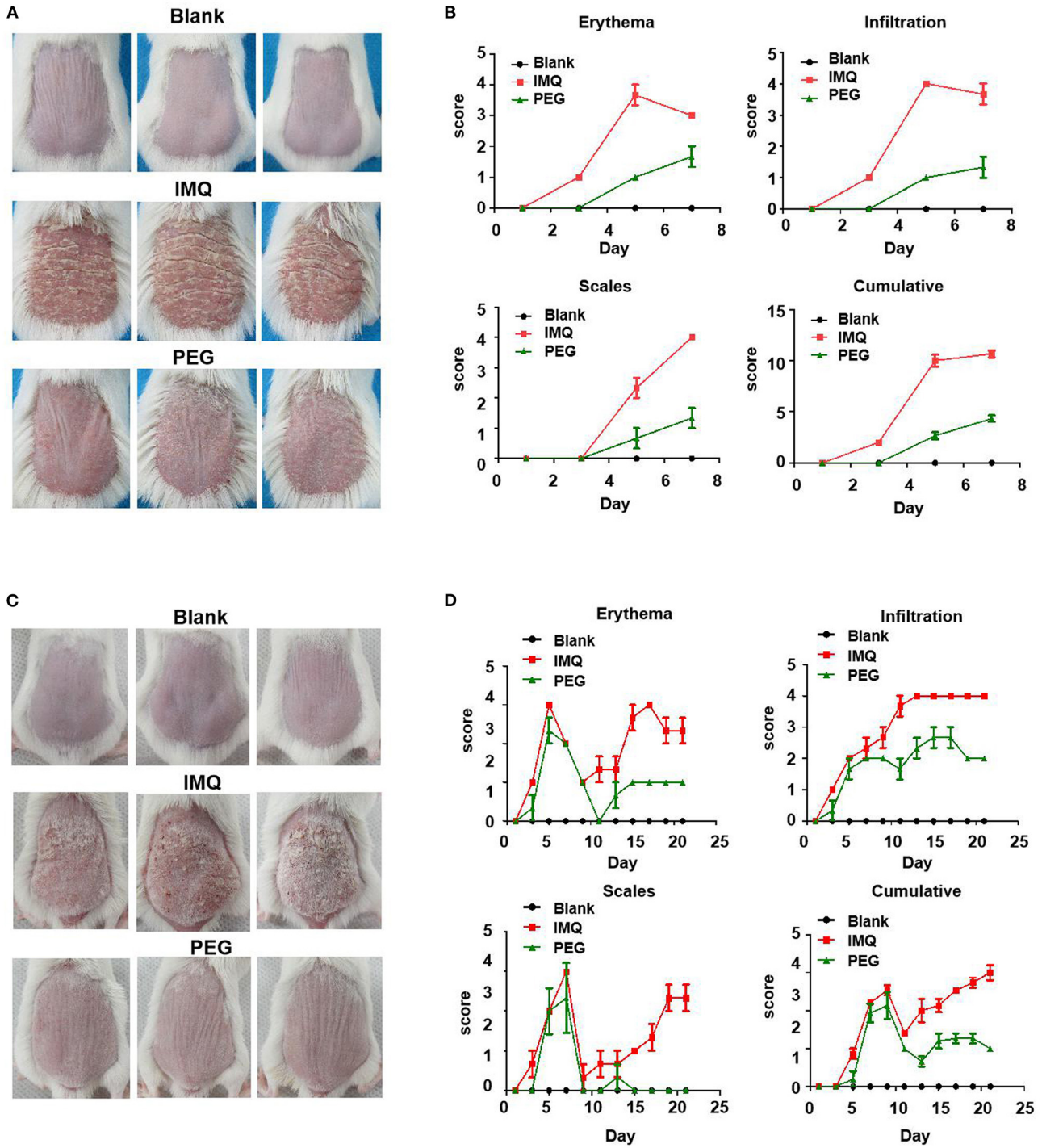

FIGURE 1 | Skin lesion appearance of the IMQ-induced psoriasis mouse model, PASI score graph. **(A)** At the end point of the psoriasis mouse model for 7 days, before all mice were killed, photos had been taken, with six mice in each group, and three images were selected for each group. **(B)** Scores of erythema, scales, and infiltration of skin lesions in each group at different time points. **(C)** At the end point of the psoriasis mouse model for 21 days, before all mice were killed, photos had been taken, with six mice in each group. **(D)** Scores of erythema, scales, and inltration of skin lesions in each group at different time pointsand three images were selected for each group. We have repeated the experiment more than three times.

Flow Cytometric Cell Staining

The mouse spleen was isolated and ground, and the red blood cells were lysed with 1× lysing buffer (BD, USA). Then, the spleen cells were resuspended with 1× PBS buffer for staining. The following Abs were used for surface staining: anti-mouse CD45-FITC (Biolegend, USA), anti-mouse CD4-PerCP/Cy5.5 (Biolegend, USA), anti-mouse CD11b-PE (Biolegend, USA), and anti-mouse Gr-1-FITC (Biolegend, USA). The anti-mouse IL-17-PE was used for intracellular staining. For reconstitution, pre-warm the kit to room temperature; add 100 μl of DMSO to one vial of Zombie Aqua™ dye (Biolegend, USA) and mix until fully dissolved. Dilute Zombie Aqua™ dye at 1:500 in PBS.

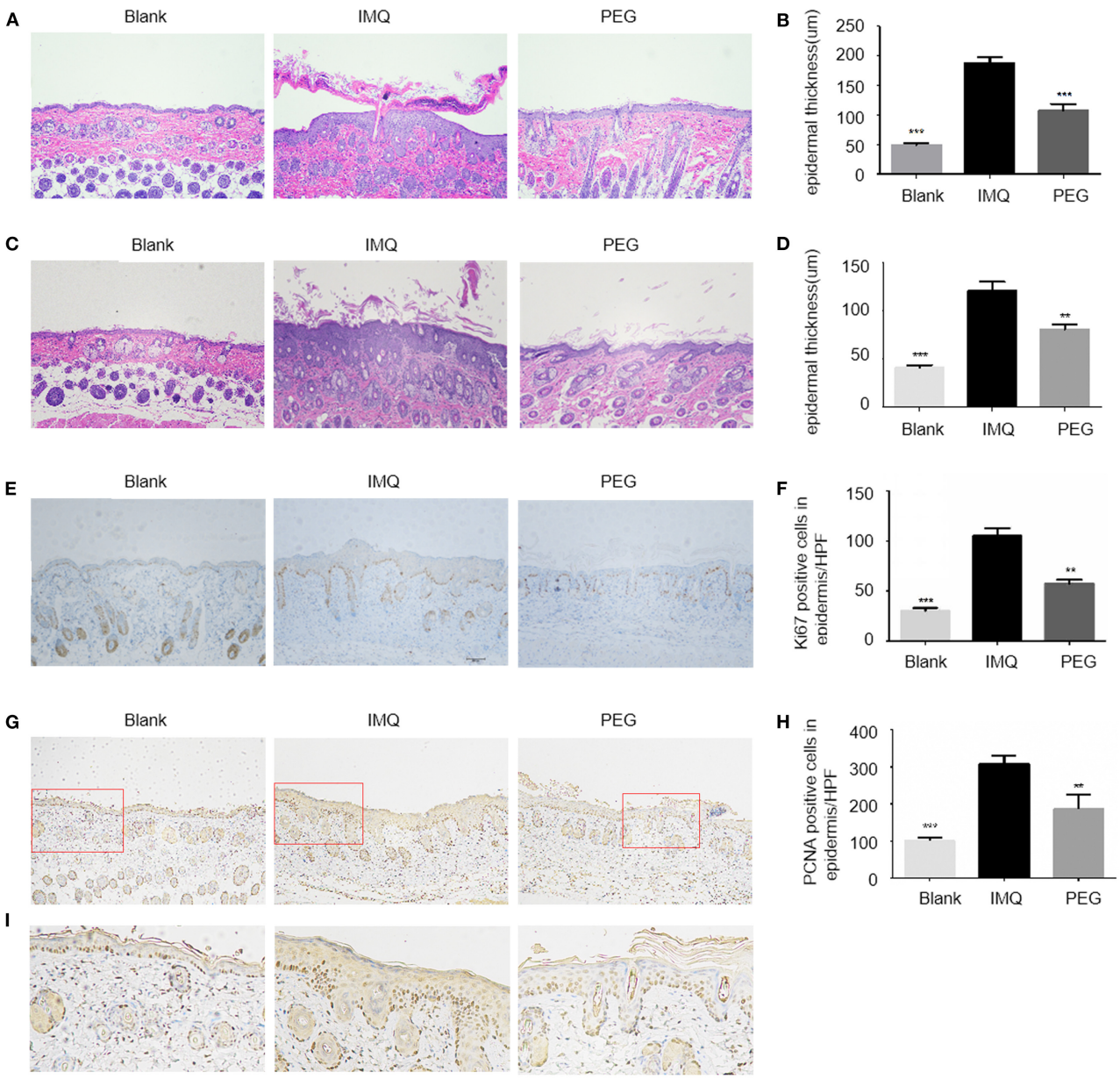

FIGURE 2 | (A,C) HE staining of lesion, with one representative for each group. **(A)** HE staining result of the 7-day model (100×). **(B)** The columnar statistical graph of the epidermal thickness of each group of the 7-day model (*compared with the IMQ group, ***$P < 0.001$). **(C)** HE staining result of the 21-day model (100×). **(D)** The columnar statistical graph of the epidermal thickness of each group of the 21-day model (*compared with the IMQ group, **$P < 0.01$, ***$P < 0.001$). **(E)** The immunohistochemistry staining of Ki67. It can be seen that the brown particles in the basal part of the epidermis are Ki67-positive expression (100×). **(F)** A bar graph of the number of Ki67-positive expressions/HPF in the basal part of the epidermis (*compared to the IMQ group, **$P < 0.05$, ***$P < 0.001$). **(G)** The immunohistochemistry staining of PCNA. It can be seen that the brown particles in epidermis are PCNA-positive expression (100×). **(H)** A bar graph of the number of PCNA-positive expressions/HPF in epidermis (*compared to the IMQ group, **$P < 0.05$, ***$P < 0.001$). **(I)** A partial enlarged view of PCNA staining from the red box in **(G)**. All statistical graph and data analysis were finished by GraphPad Prism 5 software. We have repeated the experiment more than three times.

Resuspend 10×10^6 cells in 100 µl of diluted Zombie Aqua™ solution. Incubate for 10–15 min at RT away from light. Add the cell surface antibody cocktail without washing the cells and incubate for another 30 min at 4°C away from light. Next, wash the cells with 1× PBS buffer. Last, stain the cells simultaneously with 4% paraformaldehyde for detection by flow cytometry. As for the intracellular staining of T helper 17 (Th17) cells, first cells were cultivated with 100 µl of PBS including 25 ng/ml of PMA, 1 µg/ml of ionomycin, and 10 µg/ml of brefeldin A for 6 h at 37°C away from light. Then, the cells were stained with the surface antibody mix (CD45/CD4) for 30 min at 4°C away from light and suspended with Fixation/Permeabilization solution for 30 min at 4°C away from light. Last, the cells were stained with the intracellular antibody for 30 min at 4°C away from light and detected by flow cytometry (FACSCalibur, BD, San Jose, CA).

Quantitative PCR

PCR was performed after reverse-transcribing the RNA with HiScript Q RT SuperMix for qPCR (Vazyme, R123-01, NanJing) by a Veriti 96-well Thermal cycler (Applied Biosystems) using the TaqMan primer sets purchased from Sangon Biotech. The sequences of these primers are shown in **Supplementary Table 1**. All values were normalized to the expression of the housekeeping gene GAPDH. Statistical significances were observed between Blank, IMQ, and PEG groups.

Transcriptomic Analysis

For microarray analysis, the gene expression profiles were generated using customized 4 x 44 k oligonucleotide microarrays (Agilent Technologies). Sample preparation, labeling, and hybridization were performed according to the manufacturer's protocol. The microarray expression profiles were generated using Agilent's Feature Extraction software (Version 9.5.1). For RNA sequencing, the Dynabeads® mRNA Purification Kit (Invitrogen) was used to purify mRNA from total RNA, and ERCC RNA spike-in was added according to the user guide. Then, library construction was performed according to the non-stranded TruSeqs™ protocol, and clusters were generated according to the TruSeq PE cluster Kit v3 reagent preparation guide (for cBot-HiSeq/HiScanSQ). The high-throughput shotgun sequencing was performed on the Illumina HiSeq 2000 platform. Paired-end reads with lengths of 90 and 100 nucleotides were generated for 12 samples and 486 samples, respectively.

Statistical Analyses

All experiments were repeated three times at least. Statistical analyses were carried out using the unpaired two-tailed Student's *t* test and one-way analysis of variance (ANOVA). Statistical significance was accepted at the level of $P < 0.05$. Photographs were captured and processed using GraphPad Prism 5 software and Adobe Photoshop CS5 software. All the statistical analyses were performed using GraphPad Prism 5 software and IBM SPSS Statistics 23 software.

RESULTS

PEG Ointment Improves the Appearance of IMQ-Induced Psoriasis-Like Lesions

The skin lesions of the IMQ-induced psoriasis mouse model exhibited the following symptoms: erythema, scales, and infiltration. The effect of PEG ointment on psoriasis mice was observed. In the two different duration models, the back skin of IMQ mice showed obvious erythema, scales, and infiltration, indicating that we successfully induced a psoriasis mouse model. The PASI scores of the lesions were scored during the experiment. At the end of the experiment, the mice were photographed using a camera to record the appearance of the lesion (**Figures 1A,C**). **Figure 1A** shows the 7-day model, and **Figure 1C** shows the 21-day model. We found that IMQ mice showed obvious erythema, scales, and infiltration, However, the PEG group showed slight erythema, scales, and infiltration, indicating that the psoriasis-like inflammation was significantly alleviated after treatment with PEG ointment. The analysis of PASI score was shown in **Figures 1B,D**. During the psoriasis mouse model for 6 days (**Figures 1A,B**), we observed that the erythema and infiltration scores of the psoriasis mice increased rapidly from day 3, reached the peak on the 5th day, and then slightly decreased on the 7th day. The scales turned up from day 3 and reached the peak on the 7th day. Meanwhile, the 21-day psoriasis mouse model also demonstrated that PEG ointment could improve the appearance of the IMQ-induced psoriasis-like lesions (**Figures 1C,D**), and we found that the PASI score experienced two cycles of exacerbation-reduction-heaviness of skin lesions.

PEG Ointment Down-Regulates the High Expression of Ki67 in Epidermis

The main pathological manifestations of lesions in psoriasis patients are hyperkeratosis with parakeratosis, and the

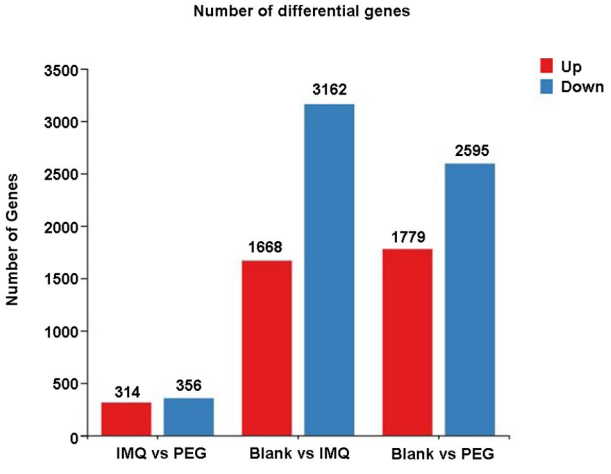

FIGURE 3 | A statistical graph of differential gene expression among the three groups. Red represents up-regulated genes and blue represents down-regulated genes.

pathological tissue of the psoriasis mouse model has similar manifestations. At the end of the experiment, the lesions were collected, fixed, and stained using the H&E method (**Figures 2A–D**). The results showed that the epidermal thicknesses of the mice in the IMQ group were significantly increased compared with that in the Blank group, while the epidermal thicknesses of the mice in the PEG group were significantly reduced compared with that in the IMQ group. The immunohistochemical staining of the epidermal basal nucleus Anti-Ki67 antibody and Anti-PCNA was used to compare the proliferation of keratinocytes among three groups (**Figures 2E,F**). There were a larger number of brown Ki67-positive cells in the basal part and PCNA-positive cells of the epidermis of the mice in the IMQ group; however, the number of brown Ki67-positive cells and PCNA-positive cells was less in the PEG group than in the IMQ group. It can be seen from **Figures 2G,H** that PEG ointment significantly down-regulated the high expression of Ki67 and PCNA in the psoriasis mice induced by IMQ cream. In order to facilitate observation, we zoomed in on the partial staining of PCNA in the red box (**Figure 2I**).

TABLE 1 | 12 candidate genes and information.

Gene	IMQFPKM	PEGFPKM	log2 (PEG/IMQ)	*P*-value (IMQ vs. PEG)
Cc13	145.436	66.603	−1.110483116	1.17E-257
Cc14	76.57	27.51	−1.444101609	3.47E-172
Cxcl2	491.093	212.14	−1.19719882	0
Cxcl3	126	59.626	−1.064298513	1.72E-266
Egf	6.98	3.173	−1.157795634	1.25E-73
Il12a	0.983	0.38	−1.373554963	2.90E-05
Il17a	1.01	0.2	−2.35009599	2.08E-09
Il17f	1.47	0.466	−1.672699662	6.93E-09
Illb	463.503	185.713	−1.304860538	0
1122	0.583	0.156	−2.004321154	8.51E-05
Ly6g	1.643	0.333	−2.280201881	9.13E-11
Ptes	26.136	11.82	−1.134363715	3.58E-277

Gene is the gene name, FPKM is the average expression level, and log2 (PEG/IMQ) < 0 represents the gene down-regulated in the PEG group compared with the IMQ group.

Differentially Expressed Genes

From the results above, it can be seen that PEG ointment could significantly improve the IMQ-induced psoriasis-like inflammation. However, the underlying mechanism has not been fully elucidated, so we performed RNA sequencing to discover the differential genes in skin lesions. It was found that 314 genes were up-regulated and 356 genes were down-regulated in the PEG group compared with the IMQ group (**Figure 3**). Then, we selected 12 inflammation-related genes (**Table 1**) for cluster analysis and KEGG Pathway enrichment analysis from the 356 down-regulated genes (**Figure 4**) and found that these differential genes mainly concentrated on the "Cytokine–Cytokine receptor interaction," "IL-17 signaling pathway," "Th17 cell differentiation," and "Chemokine signaling pathway." Given that the pathogenesis of psoriasis is closely related to the IL23/Th17 axis, we focused on the IL-17 signaling pathway. Besides, the gene Ly6g is the marker of myeloid-derived suppressor cells (MDSCs), and MDSCs can regulate the Th17 cell differentiation by IL-1β, so we also followed MDSCs.

PEG Ointment Reduces the Expression Level of Inflammatory Factor mRNA in the Epidermis of the Psoriasis Mouse Model

The results of RNA sequencing suggested that the genes related to the functions of Th17 cells and MDSCs were

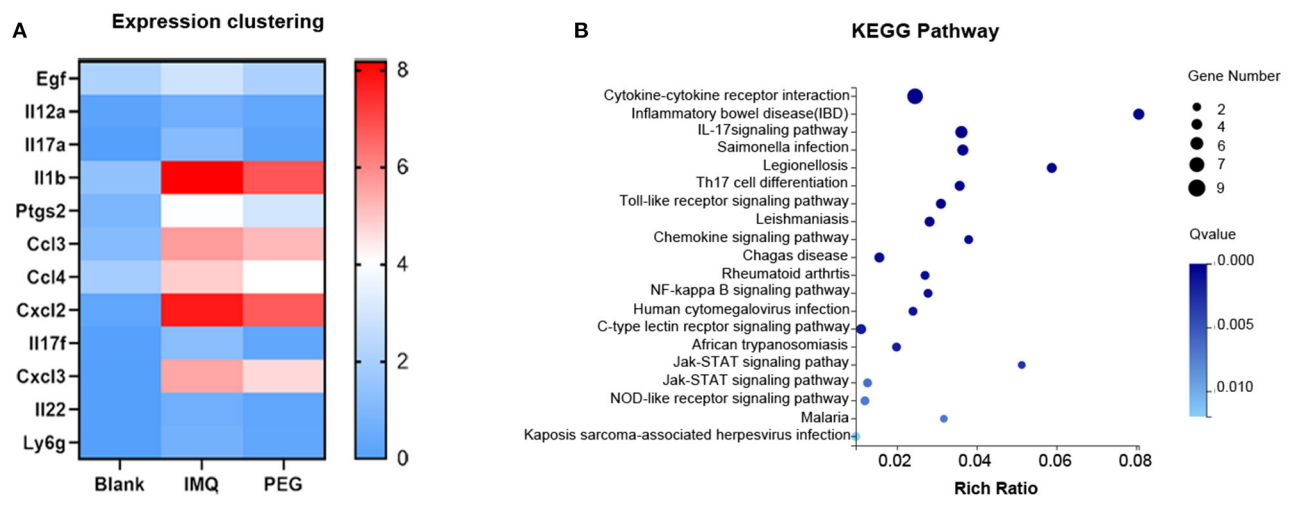

FIGURE 4 | (A) Expression clustering heat map; the horizontal axis represents the log2 (FPKM+1) of the sample, and the vertical axis represents the gene. Under the default color scheme, the redder the color, the higher the expression level, and the bluer the color, the lower the expression level. **(B)** KEGG Pathway enriches the bubble chart; the *X*-axis is the enrichment ratio, and the *Y*-axis is the KEGG Pathway. The size of the bubble indicates the number of genes annotated to a KEGG Pathway. The color represents the enriched *Q* value. The darker the color, the smaller the *Q* value.

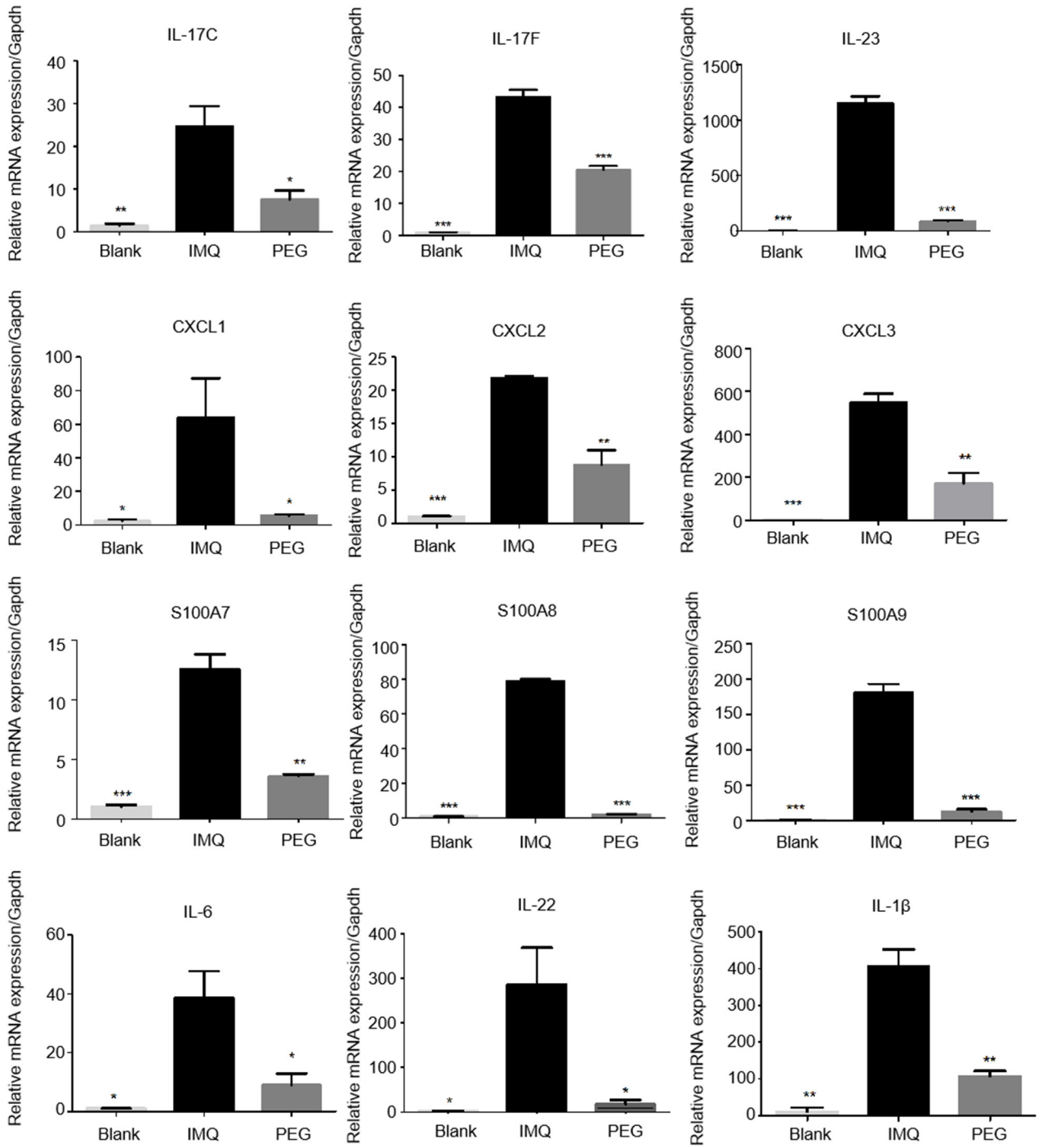

FIGURE 5 | The mRNA expression levels of IL-23, IL-17C, IL-17F, IL-22, S100A7, S100A8, S100A9, CXCL1, CXCL2, CXCL3, IL-1β, and IL-6 in the skin lesions of each group (*compared to the IMQ group, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). We have repeated the experiment more than three times.

significantly down-regulated. Therefore, we detected the relative mRNA levels of these genes of Th17 cells and MDSCs in the lesional tissues by Q-PCR. The results showed that PEG ointment could down-regulate the mRNA levels of genes IL-23, IL-17C, IL-17F, IL-22, S100A7, S100A8, S100A9, CXCL1, CXCL2, CXCL3, IL-1β, and IL-6 induced by the psoriasis mouse model (**Figure 5**).

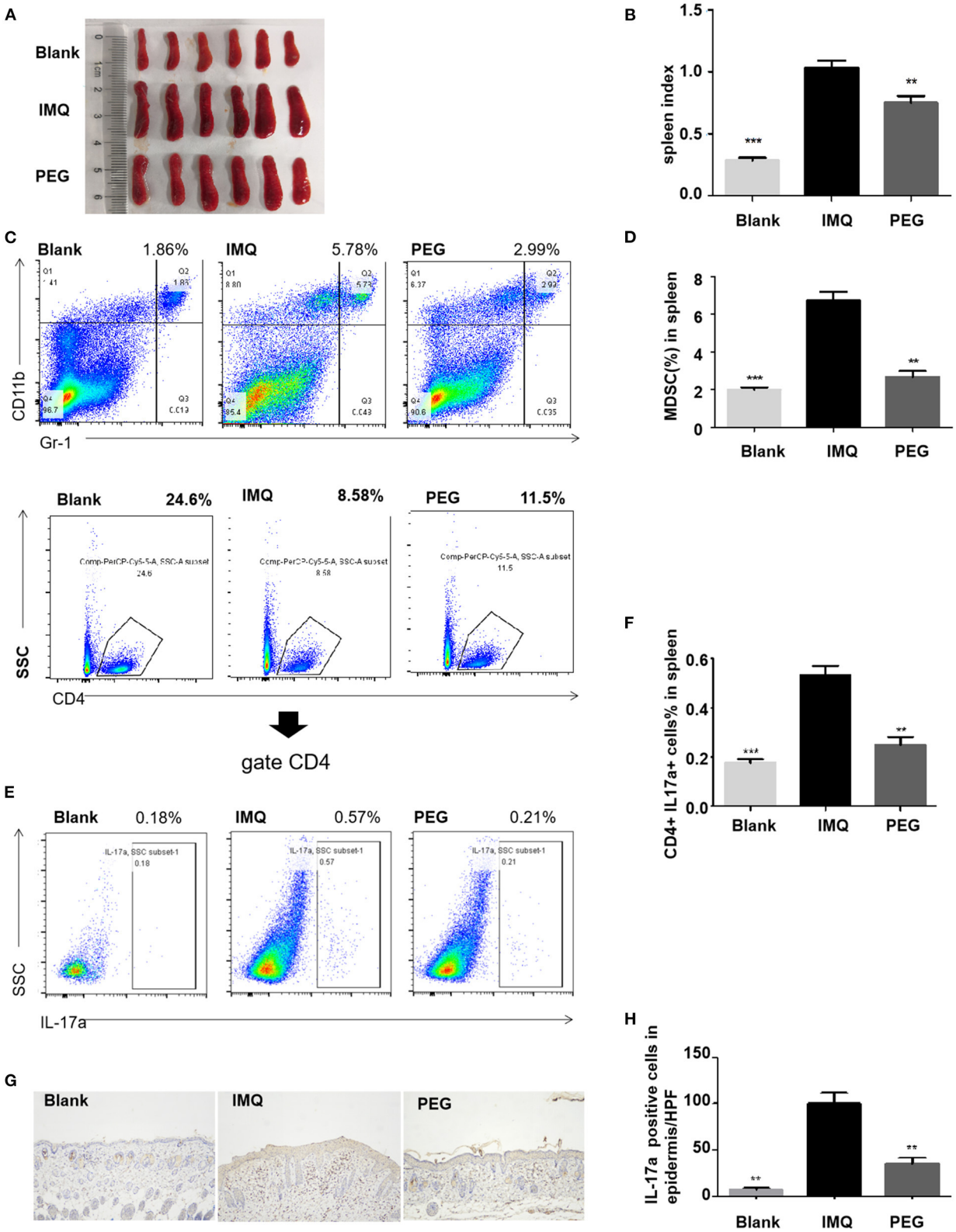

FIGURE 6 | (A,B) Spleen and statistical graph of all mice. **(C–F)** Flow analysis chart of spleen and statistical graph. **(C,D)** Percentage of MDSCs in the spleen of each group of mice and statistical graph. **(E,F)** Percentage of Th17 cells in the spleen of each group of mice and statistical graph. **(G,H)** Infiltration of IL-17A cells in dermal superficial of each group of mice and statistical graph. (*compared with the IMQ group, $^{**}P < 0.01$, $^{***}P < 0.001$). All statistical graph and data analysis were finished by GraphPad Prism 5 software. We have repeated the experiment more than three times.

PEG Ointment Down-Regulates the Number of Immune Cells in the Spleen of Psoriasis Mice

Psoriasis is an immune-mediated disease, which is closely related to the IL-23/Th17 axis. In clinical practice, anti-IL-17 treatment can significantly improve psoriasis. The IMQ-induced psoriasis mice are also related to the IL-23/Th17 axis. We found that PEG ointment improved the signaling pathway in the psoriasis mice associated with Th17 cells and MDSCs by RNA sequencing. The results of Q-PCR were consistent with that of RNA sequencing, so we further analyzed the numbers of Th17 cells and MDSCs in the spleen by flow cytometry. It was found that PEG ointment could reduce the spleen index of the psoriasis mouse model (**Figures 6A,B**). In addition, the numbers of MDSCs and Th17 cells were increased in the spleen of the psoriasis mouse model compared with the Blank group. However, the numbers of MDSCs and Th17 cells were down-regulated after the treatment of PEG ointment (**Figures 6C–F**). Meanwhile, we performed immunohistochemical staining for the dermal cytoplasmic anti-IL-17A antibody in order to compare the Th17 cells infiltration inside the dermis among various groups (**Figures 6G,H**). It was found that the number of IL-17A cells with a positive expression increased significantly in the IMQ group compared to that in the Blank group and the number of IL-17A cells with a positive expression decreased significantly in the PEG group compared to that in the IMQ group. These results suggest that PEG ointment may improve the IMQ-induced psoriasis inflammation by reducing the numbers of Th17 cells and MDSCs, but the specific mechanism warrants further research.

DISCUSSIONS

Psoriasis is a disease that requires lifelong treatment, which imposes a great economic burden to the affected patients (14–16). At present, the first-line external medicine for the clinical treatment of psoriasis includes steroids, vitamin D_3 derivatives, retinoic acid, and calcineurin inhibitors (17–20), which can inhibit the proliferation and differentiation of keratinocytes, the activation of T cells, and the release of inflammatory factors. In recent years, a growing number of studies have focused on the development of new drugs for psoriasis, including JAK inhibitors, Stat3 inhibitors, PDE4 inhibitors, TRK inhibitors, and AhR agonists (21–24). However, there was no report yet on the treatment of PEG. The pharmaceutical application of PEG mainly targets at the modification of PEG, that is, the combination of PEG with therapeutic protein drugs. PEGylated drugs can effectively overcome some shortcomings of traditional drugs, such as improving the pharmacokinetic behavior, reducing the excretion and administration frequency of the drug to maintain a stable concentration in the blood, and releasing the drug at the targeted site (25–27). PEGylated protein drugs have significantly improved the treatment outcomes of several chronic diseases such as hepatitis C, leukemia, severe combined immunodeficiency disease, RA, and Crohn's disease (28).

In this study, we observed that PEG ointment was effective for the IMQ-induced psoriatic-like inflammation. The PASI scores showed that PEG ointment could significantly improve the appearance of psoriasis-like lesions such as erythema, scales, and epidermal thickening. The pathological tissue staining showed that PEG ointment could improve the IMQ-induced keratinocyte hyperkeratosis, parakeratosis, acanthosis thickening, and inflammatory cell infiltration. The immunohistochemical staining showed that PEG ointment could down-regulate the high expression of Ki67. The RNA sequencing showed that the genes IL-17A, IL-17F, IL-22, CXCL2, and Ly-6G, which are closely related to Th17 cells and MDSCs, were down-regulated in the PEG group. We verified our results by Q-PCR. Specifically, we detected the mRNA expression level of the factors related to Th17 cells and MDSCs and found that the mRNA expression levels of IL-17C, IL-17F, IL-22, S100A8, S100A9, CXCL1, CXCL2, IL-6, and IL-1β were down-regulated after the treatment of PEG ointment in the mice of the IMQ group. The flow cytometry experiments indicated that PEG ointment could down-regulate the numbers of MDSCs and Th17 cells of the psoriasis model induced by IMQ cream. The immunohistochemical staining also showed that PEG ointment could reduce the infiltration of Th17 cells inside the dermis of psoriasis mice. In short, PEG ointment could improve the IMQ-induced psoriatic-like inflammation by down-regulating the numbers of MDSCs and Th17 cells and the secretion of inflammatory factors.

MDSCs are a group of heterogeneous cells from bone marrow origin. As the precursor cells of dendritic cells (DCs), macrophages, and granulocytes, MDSCs can significantly suppress immune cell responses. It is well known that the number of MDSCs in cancer patients is higher than that in the healthy population (29–31). This is because MDSCs in the peripheral blood increase and accumulate locally in the tumor and will release active substances to suppress the immune response and promote tumor growth. MDSCs are generally considered to be a poor prognosis signal for cancer (32), and what roles MDSCs play in psoriasis is of a great concern. It has been reported that MDSCs in the peripheral blood of psoriasis are increased and exhibit an immunosuppressive effect; however, the specific mechanism has not been clarified (33, 34). In recent years, the relationship between MDSCs and Th17 cells has been studied by many researchers. In tumor and rheumatoid arthritis (RA), the increase in the number of MDSCs is usually accompanied by the increase of Th17 cells. Zhang et al. reported that MDSCs promoted the differentiation of naïve $CD4^+$ T cells into Th17 cells in an IL-1β-dependent manner (35). Wen et al. (36) found that MDSCs could secrete IL-1β to directly or indirectly promote the proliferation and differentiation of Th17 cells and also secrete IL-6 and TGF-β to indirectly promote the differentiation of naïve $CD4^+$ T cells into Th17 cells. However, the interaction between MDSCs and Th17 cells still needs to be further explored.

It is well known that the IL-23/IL-17 axis is the key pathway leading to the pathogenesis of psoriasis. In the dermis, the IL-23 secreted by DCs induces the activation of Th17 cells, which subsequently releases various cytokines including IL-17A, IL-17F, and IL-22 to promote epidermal hyperplasia (37, 38). In addition, Th17 cells can also induce keratinocytes to produce IL-8 and antimicrobial peptides (e.g., S100A8 and S100A9) for the recruitment of neutrophils, the activation of vascular endothelial growth factor, and angiogenesis (39). Combined with

our experimental results, we speculated that the number of MDSCs and the secretion of IL-1β and IL-6 in the psoriasis mice would decrease after treatment with PEG ointment, the ability of MDSC to promote Th17 proliferation and differentiation would be weakened, and, consequently, the Th17 function would be down-regulated. Eventually, the inflammatory reaction of psoriasis mice was alleviated. PEG ointment may improve the psoriasis-like inflammation by down-regulating the functions of Th17 cells and MDSCs.

CONCLUSION

PEG ointment could improve the IMQ-induced psoriasis-like inflammation by down-regulating the functions of Th17 cells and MDSCs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of Central South University, China.

AUTHOR CONTRIBUTIONS

Thanks to all authors for their contributions to this work. WZ provided the funding. Y-HK designed the research, modified the manuscript, and also provided some funding. YLu performed the research, analyzed data, and wrote the manuscript. YX helped with statistical analysis. M-ZY participated in the design of the research. X-CZ instructed the production of ointment. L-SW, W-QC, and YLuo also made some contributions to the research.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.560579/full#supplementary-material

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frontiers in Medicine

SYSTEMATIC REVIEW
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Comparison of Efficacy of Anti-interleukin-17 in the Treatment of Psoriasis Between Caucasians and Asians: A Systematic Review and Meta-Analysis

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Background: Interleukin-17 (IL-17) monoclonal antibody drugs have been increasingly significant in the treatment of psoriasis, but it is not clear whether the efficacy is equivalent across ethnicities.

Objective: To explore the differences of short-term efficacy of IL-17 inhibitors between Caucasians and Asians.

Methods: The pooled log risk ratio (logRR) between the groups was estimated. The meta-regression analysis on the logRR was performed, with the proportion of Caucasian patients as the covariate. The subgroup analysis was performed by specific IL-17 inhibitors.

Results: Of the 1,569 potentially relevant studies, sixteen randomized controlled trials (RCTs) were included. For the Psoriasis Area and Severity Index 75 (PASI 75) response at week 12, the pooled logRR of the Asian group and the Caucasian group was 2.81 (95% CI: 2.27–3.35, $p < 0.001$) and 2.93 (95% CI: 2.71–3.16, $p < 0.001$), respectively, indicating no significant difference of efficacy between Asians and Caucasians. The meta-regression analysis did not show an association of the proportion of Caucasians with the effect size ($\beta = 0.3203$, $p = 0.334$). In the subgroup analysis, the comparison results of secukinumab were consistent with the main analysis.

Limitations: Only the short-term efficacy was explored. The data from Asian countries were limited.

Conclusions: The short-term efficacy of IL-17 inhibitors in the treatment of psoriasis has no significant difference between Caucasians and Asians.

Systematic Review Registration: PROSPERO, identifier CRD42020201994, https://www.crd.york.ac.uk/prospero/.

Keywords: psoriasis, secukinumab, brodalumab, ixekizumab, Asian, Caucasian

INTRODUCTION

Psoriasis is a chronic inflammatory disease driven by proinflammatory cytokines (1), affecting 2–3% of the population of the world (2). Although psoriasis presents in all the ethnic groups, there are variances in the incidence that Asian countries are significantly lower than European countries (3–5). The psoriasis phenotype is also different among ethnicities. Chronic plaque psoriasis is the most common form of psoriasis, accounting for about 90% of cases (6). Patients with psoriasis in western countries are more likely to present large plaque psoriasis, while small and intermediate plaque psoriasis is more common in Asian psoriasis patients (7, 8). Although the prevalence of moderate-to-severe psoriasis is relatively low in Asia, its severity is significantly higher than in Caucasians (9).

At present, interleukin-17 (IL-17) pathway antagonists in the market are mainly secukinumab (AIN457), ixekizumab (LY2439821), and brodalumab (AMG827), which were approved by the US Food and Drug Administration (FDA) in 2015, 2016, and 2017, respectively, for the treatment of moderate-to-severe psoriasis (10, 11). Secukinumab and ixekizumab are human monoclonal antibodies against IL-17A, while brodalumab antagonizes the IL-17A receptor (IL-17RA) and disrupts the signal transduction of IL-17A, IL-17C, (12) IL-17F, and IL-17A/F heterodimer (13).

In previous studies, three IL-17 inhibitors have shown excellent efficacy in regional clinical trials (14–16). However, a study showed that molecular phenotypes of small (Asian) and large (Western) plaque psoriasis show co-activation of genes in the IL-17 pathway, while with different regulatory gene sets. IL-17A and IL-17-regulated proinflammatory cytokines were highly expressed in Asian small plaque psoriasis, but lower in Western large plaque psoriasis (7). Moreover, one study suggested better clinical efficacy of secukinumab, brodalumab, and ixekizumab in the Japanese groups compared to Western subjects (17). We hypothesize that there may be a difference in the efficacy of IL-17 inhibitors between Asians and Caucasians. This study aims to integrate and analyze the efficacy of IL-17 inhibitors on psoriasis from randomized controlled trials (RCTs) obtained by systematic retrieval and strict screening to explore the differential efficacy between Asian and Caucasian patients.

METHODS

Data Searches and Sources

The systematic literature search was conducted in the PubMed, Embase, and Cochrane databases, the Wanfang Database, and the Chinese National Knowledge Infrastructure Data of Chinese Journals from inception up to November 29, 2020. No restrictions by language were employed. The analysis included the full-study population of the randomized, double-blind, and placebo-controlled trials of secukinumab, brodalumab, and ixekizumab. We also reviewed abstracts and presentations from all the major conference proceedings.

The keywords used in the search strategy included "psoriasis or psoriatic," "secukinumab or cosentyx," "brodalumab or siliq," "ixekizumab or taltz," and "randomized controlled trials." The search strategy adjusted to a controlled vocabulary for each database. The full search terms and strategies are given in **Supplementary File 1**.

This study was registered on the PROSPERO (registration number #CRD42020201994). Changes from the protocol were mentioned in supplementary methods.

Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review and meta-analysis were: (1) patients: moderate-to-severe plaque psoriasis; (2) intervention: IL-17 antagonists (secukinumab, brodalumab, and ixekizumab); (3) comparator: placebo; (4) outcomes: 75% or greater and 90% or greater improvement in the Psoriasis Area and Severity Index score from baseline (PASI 75 and PASI 90) as primary outcome; and (5) study design: double-blind, randomized placebo-controlled trials.

We excluded: (1) nonrandomized placebo-controlled trials; (2) observational studies, case reports/series, or review articles; (3) studies that did not provide the proportion of Caucasian patients; and (4) outcome data could not be extracted.

Study Selection

Titles and/or abstracts of all the relevant studies were screened independently by two reviewers (DZ and JQ) to identify studies that met the above inclusion criteria. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by two investigators. Any disagreement between the two reviewers regarding the eligibility of a study was resolved through discussion with a third reviewer (XL).

Data Extraction

The extracted data included the following: the name of the author; year of publication; the characteristics of the study population (including number, sex ratio, the races or the Caucasian proportion, the average of age and body mass index (BMI), the baseline PASI, and previous therapy history); dosing schedule; week of evaluation of response; and study outcomes at the endpoint (including PASI 75, PASI 90, sPGA0/1, IGA0/1, and DLQI0/1 response rates). We also collected the incidence of adverse event (AE), serious AE (SAE), discontinuations due to AE, and some most common adverse effects (e.g., infections, nasopharyngitis, headache, and upper respiratory tract infection).

Two reviewers (DZ and JQ) extracted data independently; discrepancies were identified and resolved through discussion [with a third reviewer (XL) when necessary].

Quality Assessment

To assess the risk of bias within each included study, we used the Cochrane risk-of-bias tool, which includes the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The judgment of authors is categorized as "low risk," "high risk," or "unclear risk" of bias. We also used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system to assess the

quality of evidence for every outcome. Two independent reviewers assessed eligibility criteria and extracted data and any disagreements were resolved by discussion.

Statistical Analysis

Extracted data were combined for the meta-analysis using the STATA version 16.0 (StataCorp LLC, 4905 Lakeway Drive, College Station, Texas, USA). We chose the PASI 75 response at week 12 as the primary outcome. Dichotomous data were pooled as the log risk ratios (logRRs) with the respective 95% CIs using the Mantel–Haenszel fixed effects method. The data of ethnically Asian patients and the Caucasian patients were classified and pooled separately. The meta-regression analysis was performed to investigate the association of the basal PASI and proportion of Caucasian patients with the efficacy, as the basal PASI seemed to be slightly higher in the Asian group and some studies included a variety of ethnicities (but still Caucasian predominant). The subgroup analysis was performed by specific agents and doses. Sensitivity analysis was conducted to examine whether one or more studies deviated from the overall results. Heterogeneity between studies was assessed using the Q-statistic (significance level at $p = 0.050$) and I^2 statistic (significant heterogeneity, $I^2 > 50\%$; insignificant heterogeneity, $I^2 < 40\%$). A Z-test was performed to assess the combined statistical outcomes. The funnel plot analysis was used for the detection of potential publication bias.

RESULTS

Study Selection

Our search identified 1,569 records through database search: PubMed ($n = 306$), Embase ($n = 659$), Cochrane library ($n = 604$) databases, the Wanfang Database ($n = 0$), and the Chinese National Knowledge Infrastructure data of Chinese journals ($n = 0$). After removing duplicates, 880 records were screened and 779 were excluded (which were not RCTs, not related to psoriasis, or not related to IL-17 antagonists, etc.). After a full-text review of the remaining 101 references, we excluded 87 studies according to the exclusion criteria. Finally, 14 studies with a total of 16 double-blind, randomized placebo-controlled trials that met the inclusion criteria were included in this meta-analysis (**Figure 1**) (18–31).

Study Characteristics

In total, 6,765 patients (4,843 patients with IL-17 antagonists and 1,922 patients with placebo) were involved in this study. Of the 14 studies included, ten studies were phase III and four studies were phase II. Among them, six studies specifically recruited Asian patients (Japanese, Indian, or Chinese) including four studies for secukinumab, one study for brodalumab, and one study for ixekizumab. Eight studies predominantly recruited Caucasian patients including four studies for secukinumab, two studies for brodalumab, and two studies for ixekizumab. All the included studies had at least the two intervention groups, and the one placebo group and reported the PASI 75, from baseline at week 12. All the studies involved in this meta-analysis shared similar baseline characteristics and inclusion criteria. Fourteen studies reported the average age, the baseline PASI score, and prior treatment history and nine studies reported averaged BMI (**Supplementary File 2**).

Risk-of-Bias Assessment

The risk-of-bias among the included studies was rated as "low risk," "unclear risk," or "high risk" (**Supplementary File 3**; **Supplementary Figures 1, 2**). 10 studies (62.5%) reported an adequate randomization method of all the sixteen studies, while allocation concealment was sufficient in 8 studies (50%). In all of these studies, the blinding of participants and personnel was ensured. The risk of attrition bias in 1 (6.25%) trial was unclear and in another trial was high. The risk of reporting bias was low in all of these studies. Two (12.5%) studies published a high risk of other bias. The funnel plot showed slight asymmetry (**Supplementary File 3**; **Supplementary Figure 3**), but Egger's test ($\beta = 0.511$, $p = 0.522$) and Begg's test (score $= 22.211$, $p = 0.685$) indicate no publication bias.

Main Analysis

As shown in **Figure 2**, the pooled estimate of the Asian group favored IL-17 inhibitors over placebo for the PASI 75 response at week 12 (logRR = 2.81,95% CI: 2.27 to 3.35, $p < 0.001$). As shown in **Figure 3**, the pooled estimate of the Caucasian group also favored IL-17 inhibitors over placebo for the PASI 75 response at week 12 (logRR = 2.93, 95% CI: 2.71 to 3.16, $p < 0.001$). The results showed that there is no significant difference in the efficacy between the groups, as the 95% CIs overlapped. Evidence quality was evaluated on each outcome index. The results of the GRADE evaluation showed that both the Asian group PASI 75 and the Caucasian group PASI 75 outcome the quality of evidence were high (**Table 1**).

Meta-Regression Analysis

Because some of the included studies also recruited a proportion of non-Caucasian patients, we performed the meta-regression analysis. As shown in **Figure 4**, the proportion of Caucasian patients was not significantly associated with the efficacy of IL-17 inhibitors ($\beta = 0.3203$, $p = 0.334$). We also noticed that the basal PASI seemed to be a little higher in the Asian group, but the meta-regression analysis indicates that the basal PASI was not significantly associated with the efficacy of IL-17 inhibitors ($\beta = -0.0692$, $p = 0.11$) (**Figure 5**).

Subgroup Analysis

To examine possible effect modification by drug and dose, we performed the subgroup analysis by specific agents and doses (**Table 2**). For secukinumab 150 and 300 mg, the pooled logRR was approximate between Caucasians and Asians. But, for brodalumab and ixekizumab, there is a difference between Caucasians and Asians.

Sensitivity Analysis

After removing each independent study and combining the remaining research data, sensitivity analysis was conducted for the meta-analysis. The results were consistent and stable (**Supplementary File 4**).

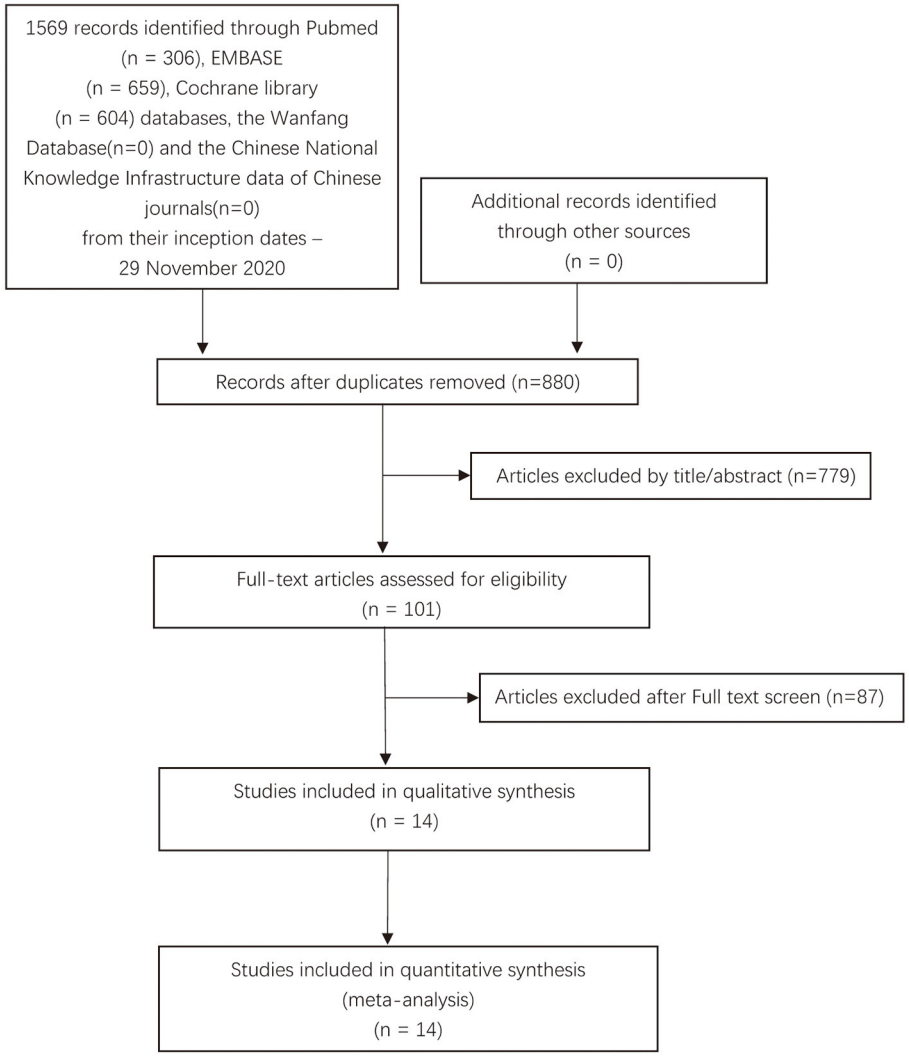

FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search strategy for the present studies.

DISCUSSION

Summary of Evidence

So far, to the best of our knowledge, there is still no clear evidence to clarify the heterogeneity in the efficacy of IL-17 antagonists that is attributable to ethnicity or race. We found out that there is no significant difference in the PASI 75 response between the Asian group and the Caucasian group after a 12-week treatment with IL-17 inhibitor and the meta-regression analysis did not show the association of the proportion of Caucasians with the efficacy of IL-17 inhibitors. For the subgroup analysis, the results of secukinumab 150 and 300 mg showed a consistency of the main analysis. But, for brodalumab and ixekizumab, the result is opposite. In brodalumab, the Caucasian group has better efficacy and in ixekizumab, the Asian group seems a little better. That might be a result from the limited included studies. In Asian RCTs, the basal PASI is slightly higher, which is consistent with the study of Abrouk M. But, the meta-regression analysis did not show association of the basal PASI with the short-term efficacy of IL-17 inhibitors.

The heterogeneity among the included studies was relatively low and might be attributable to the diverse treatment history prior to the enrollment of patients, different-sex ratio, and diverse BMI (some did not provide BMI data). Similarly, methodological differences in study design may also lead to the heterogeneity. For example, the frequency of secukinumab administration is unequal across the studies.

The prevalence of psoriasis is higher in Caucasians than that in Asians and other ethnicities (7, 32). Genome-wide association studies (GWASs) identified multiple psoriasis-associated susceptibility loci, among which HLA-Cw6 was one of the most important alleles in psoriasis (33). The global frequency of the HLA-Cw6 allele varies widely, but is generally higher in Caucasians than in Asians (34, 35).

Of note, three studies (two studies conducted in Italy and one study conducted in Switzerland) showed that HLA-C*06:02

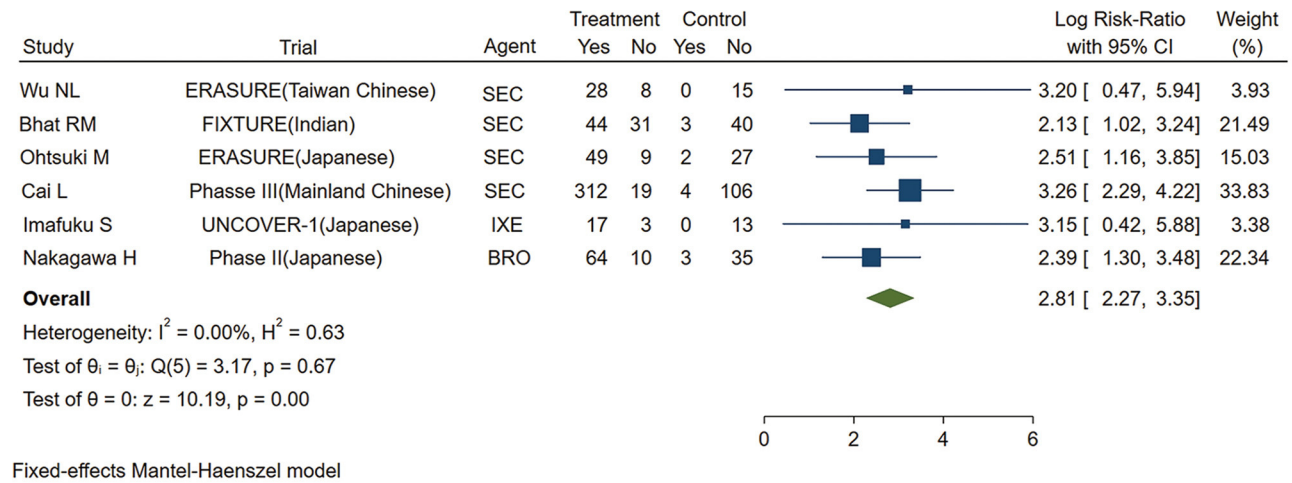

FIGURE 2 | Meta-analysis of Asian patients treated with IL-17 inhibitors or placebo for the PASI 75 response at week 12. RR, risk ratio; SEC, secukinumab; BRO, brodalumab; IXE, ixekinumab; Q4W, every 4 weeks; Q2W, every 2 weeks; IL-17, interleukin-17; PASI, Psoriasis Area and Severity Index 75.

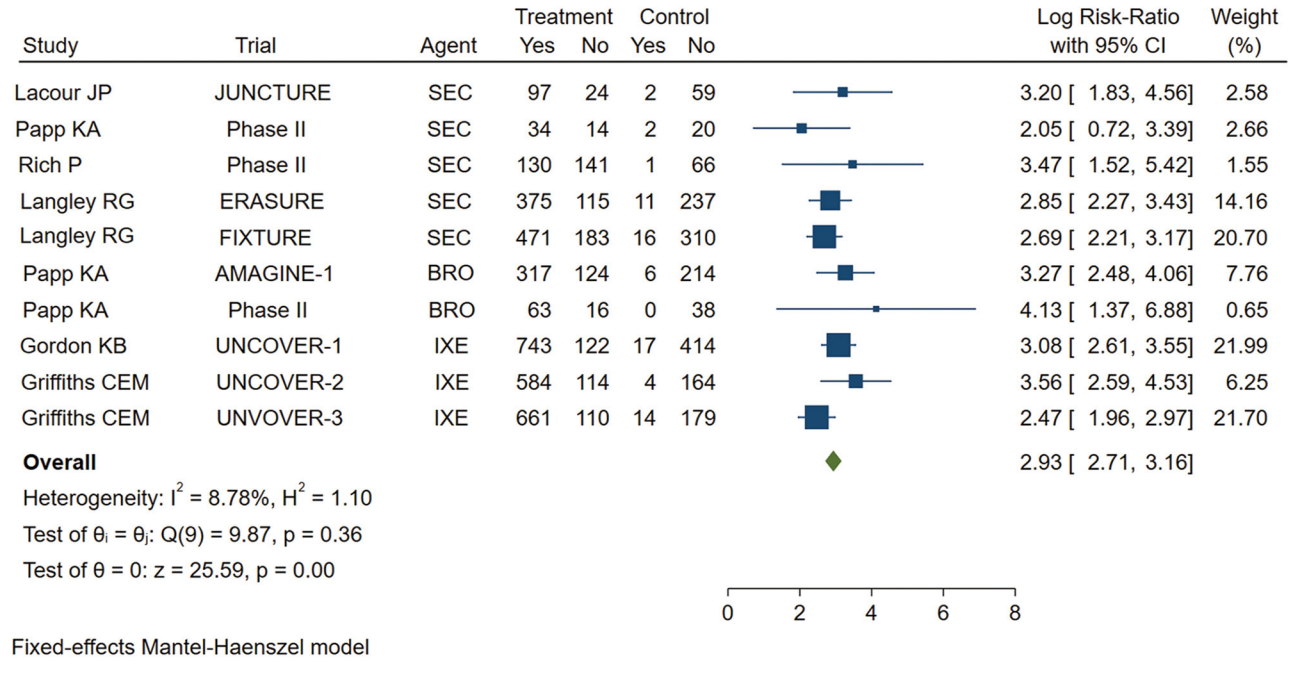

FIGURE 3 | Meta-analysis of Caucasian patients treated with IL-17 inhibitors or placebo for the PASI 75 response at week 12. RR, risk ratio; SEC, secukinumab; BRO, brodalumab; IXE, ixekinumab; Q4W, every 4 weeks; Q2W, every 2 weeks; IL-17, interleukin-17; PASI, Psoriasis Area and Severity Index 75.

TABLE 1 | Quality of evidence in included systematic reviews with the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE).

Research Indicators	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Included RCTs (patients)	Quality of evidence
PASI 75 at week 12 (Asian group)	Not serious	Not serious	Not serious	Not serious	Not serious	5(402)	High
PASI 75 at week 12 (Caucasian group)	Not serious	Not serious	Not serious	Not serious	Not serious	10(6,212)	High

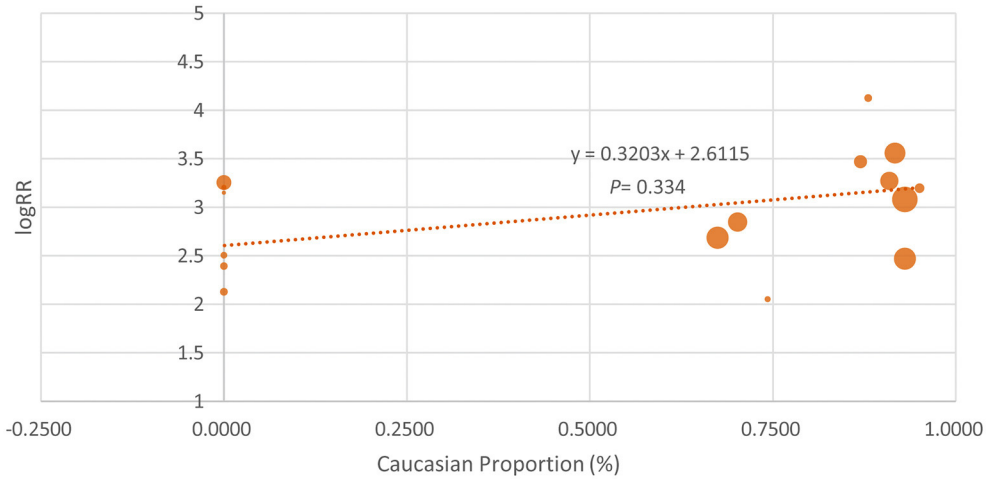

FIGURE 4 | The meta-regression analysis investigating the association of Caucasian proportion and the log risk ratio (logRR) treatment effect across studies (the PASI 75 response at week 12).

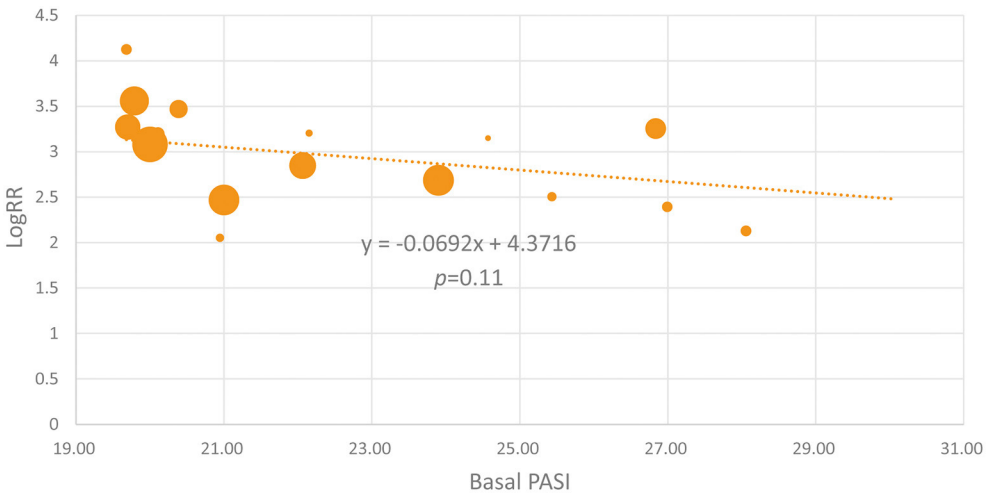

FIGURE 5 | The meta-regression analysis investigating the association of the basal PASI and the logRR treatment effect across studies (the PASI 75 response at week 12).

TABLE 2 | Pooled estimates in the subgroup analysis.

Subgroups	Caucasian				Asian			
	No. of studies	I^2	Pooled LogRR (95% CI)	*P*	No. of studies	I^2	Pooled LogRR (95% CI)	*P*
SEC 150 mg	6	0.00%	2.78 (2.44, 3.12)	<0.001	4	0.00%	2.82 (2.19, 3.45)	<0.001
SEC 300 mg	3	0.00%	2.86 (2.50, 3.22)	<0.001	4	0.00%	2.96 (2.31, 3.61)	<0.001
BRO 140 mg	2	0.00%	3.22 (2.45, 3.99)	<0.001	1	…	2.30 (1.20, 3.39)	<0.001
BRO 210 mg	2	0.00%	3.50 (2.74, 4.26)	<0.001	1	…	2.48 (1.39, 3.57)	<0.001
IXE 80 mg Q2W	3	70.86%	2.99 (2.34, 3.64)	<0.001	1	…	3.28 (0.55, 6.00)	<0.001
IXE 80 mg Q4W	3	57.94%	2.91 (2.38, 3.45)	<0.001	1	…	3.02 (0.28, 5.76)	<0.001

RR, risk ratio; SEC, secukinumab; BRO, brodalumab; IXE, ixekinumab; Q4W, every 4 weeks; Q2W, every 2 weeks.

was not associated with the response to secukinumab in Caucasians (36–38). Another study conducted in European countries showed that the response to secukinumab and ixekizumab cannot be explained by genetic variation in the *IL-17A* gene (39). However, a pharmacogenomic study by Morelli et al. evaluated the influence of the presence/absence

of genetic variants of psoriasis-related loci on the response to secukinumab in Caucasians. They found out that eight single nucleotide polymorphisms (SNPs) in HLA-C and upstream region, including one in HLA-Cw6 and three in *MICB-DT*, *DDX58*, and *TYK2* genes, were associated with a better response to secukinumab (40). After searching for the National Center of Biotechnology Information database, we noticed that for some SNPs which allele positively associated with the better achieved PAS I75 according to a study by Morelli M, the differences of mutant allele frequency (MAF) between Asians and Caucasians are quite small. For example, Koreans have an MAF of 0.047, and Vietnamese have an MAF of 0.037 in rs4406273, an HLA-Cw6 psoriasis classical allele. Similarly, Northern Swedes have an MAF of 0.045. But, there are also inconsistent findings. The MAF of some SNPs mentioned in a study by Morelli M was different between Asians and Caucasians. Few studies investigated the pharmacogenetics of IL-17A inhibitors in Asians and the MAF data is quite limited. More study is warranted to investigate the genetic factors for IL-17 inhibitors to individualize the treatment.

For the subgroup analysis, we noticed that in brodalumab, the Caucasian group seems to have better efficacy and in ixekizumab, the result seems reverse. Except for the difference in the targets of brodalumab and ixekizumab, *IL-17/IL-17RA* genes polymorphisms which tend to occur in different ethnicity may also contribute to the different response degrees (41, 42). However, it should be pointed out that the number of studies on brodalumab and ixekizumab included in the Asian group was small as well as the sample size. The true efficacy difference of brodalumab and ixekizumab between Asian and White patients remains to be further explored.

In recent years, with the deepening study on the pathogenesis of psoriasis, the important role of interleukin-23 (IL-23)/IL-17 axis in promoting the occurrence and continuation of psoriasis has attracted more and more attention and the studies on the development of IL-23 inhibitors and IL-17 inhibitors and their clinical application are also being carried out continuously. Except for IL-17 monoclonal antibodies, bimekizumab, a new agent targeting IL-17A and IL-17F, has just been reported in phase III clinical trials, showing high efficacy and good safety (43, 44). Since ethnicity-related data were not available for comparison, it was not included in this study.

LIMITATIONS

There are limitations of this study. First, the "Caucasian group" defined in this study also included a small proportion of non-Caucasian patients. Because the individual data were not available, we alternatively used the proportion of Caucasians to perform the meta-regression analysis. Moreover, the Asian group only included Japanese, Indian, and Chinese, while data from other Asian regions, such as Korea, Thailand, and Vietnam, were not available. Therefore, more studies are needed to further identify the differences in the efficacy and safety of IL-17 antagonists between ethnicities. It is also a pity that as far as we know, no statistics of the efficacy of IL-17 inhibitors in Asians living in European and American countries was reported, so we did not analyze the data of these Asians. Besides, the number of included studies was small and the duration of the study was short. For each IL-17 antagonist, the included studies were limited. The rate of the PASI 75 at week 12 was synthesized as the only outcome in this study, since most studies regrouped the patients with different strategies at week 12. The ethnicity-related differences in the long-term efficacy should be tested in real-world settings.

CONCLUSION

In summary, based on the currently available data, the short-term efficacy of IL-17 monoclonal antibodies for psoriasis has no significant difference between Caucasians and Asians. Long-term observations in real-world settings in addition to the pharmacogenetic investigations with respect to the ethnicity-related differences in the efficacies of emerging biological agents are warranted for precision medicine.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DZ, JQ, MS, and YX involved in the concept and design of this study. DZ did the literature search, performed data analysis, and drafted the manuscript. JQ contributed to the literature search and data analysis. XL edited the tables and figures. DJ and YD critically revised the manuscript. All the authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.814938/full#supplementary-material

Supplementary File 1 | Search terms and strategies.

Supplementary File 2 | Supplementary Table 1. Characteristics of included studies. Summary of the design and findings of included studies **(a)** and baseline characteristics of enrolled patient in included studies **(b)**.

Supplementary File 3 | Supplementary Figure 1, **Supplementary Figure 2**, and **Supplementary Figure 3**.

Supplementary File 4 | Sensitivity analysis in the Asian group and the Caucasian group.

Supplementary File 5 | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Supplementary File 6 | Supplementary Methods.

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CASE REPORT
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Case Report: The Application of Dupilumab in Atopic Dermatitis Children Complicated With Nephrotic Syndrome

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Nephrotic syndrome (NS) tends to be more common in patients with history of allergies. Atopic dermatitis (AD) is one of the most common allergic diseases in children. Dupilumab, a dual IL-4 and IL-13 inhibitor, has been widely used to treat AD patients. However, the efficacy and safety of Dupilumab in NS is unclear. We reported two AD patients with NS comorbidities treated with Dupilumab. The outcomes showed the good control of NS and less systemic steroids and/or immunosuppressive agents use during the Dupilumab treatment period, accompanied by significant relief of AD symptoms. We suggest prospective pilot studies and randomized controlled trials could be carried out to validate the efficacy and safety of Dupilumab in the treatment of NS patients.

Keywords: case report, Dupilumab, atopic dermatitis, nephrotic syndrome, efficacy and safety

INTRODUCTION

Atopic dermatitis (AD) is one of the most common allergic diseases in children, with a prevalence of more than 20% in high-income countries, which seriously affects the life quality of children (1). In China, the prevalence of AD also reached 14% in the general population and nearly 13% in children (2, 3). Nephrotic syndrome (NS) is a rare pediatric kidney disease, with an average incidence of 2–16.9 per 100,000 children worldwide (4).

There are reports that the risk of nephrotic syndrome in children with AD is seven times higher than those without AD (5). Many studies suggest that the pathogenesis of NS might be correlated to Th2 activation and resulted in a Th1/Th2 imbalance. The activated Th2 cells produce signatured type 2 cytokines such as IL-4 and IL-13, which will promote the synthesis and secretion of immunoglobulin E (IgE) through B cells. This may be one of the mechanisms for the conjecture that NS and allergic diseases are correlated (6, 7). Clinical trials and real-world studies have confirmed the efficacy and safety of Dupilumab (a human monoclonal antibody against interleukin (IL)-4Rα and a dual inhibitor of IL-4 and IL-13 signaling) in the treatment of pediatric AD (8–12). However, it is unclear whether Dupilumab can be used in NS complicated with AD children. We treated patient #1 and patient #2 with Dupilumab at Tongji Hospital, Tongji Medical College of Huazhong University of science and technology, and reviewed the relationship between AD and NS.

TABLE 1 | Sera antibodies levels before and after Dupilumab treatment.

	Before				After			
	IgG	IgM	IgA	IgE	IgG	IgM	IgA	IgE
Patient 1#	7.7	1.51	1.83	>5,000	8.9	1.61	1.91	3,135
Patient 2#	11.7	0.79	2.05	492	11.1	0.84	1.88	223

IgG, IgM, IgA: g/L; IgE: KU/L.

CASE DESCRIPTION

The first patient was a 9-year-old boy who suffered from recurrent erythema and papules over body and diagnosed as infant AD after birth. The manifestation of AD included a long history of intense pruritus, dry skin, recurrent erythema and papules, lichenized and excoriated plaques of the skin, mostly appearing on the limbs and affecting flexor surfaces in a symmetrical distribution. His AD symptoms were worsened in summer especially after perspiration. He was given topical glucocorticoids and oral antihistamines irregularly to control the AD symptoms, but didn't respond well to the treatments. He developed allergic rhinitis (AR) when he was 7 years old. His mother also had AR history. When he was 5 years old, he suffered from anasarca and proteinuria (urinary albumin excretion rate >1,500 mg/day) and was diagnosed with NS. He received prednisone 1 mg/kg daily to control the NS comorbidity and gradually tapered to 2.5 mg daily according to urine albumin level. The patient had a height of 137 cm, weight of 32 kg and the body mass index of 17.05 kg/m^2 when he presented to our department. Investigator's global assessment (IGA; ranging from "0" to "5", "0" for none, "5" for very severe), the body surface area (BSA) (ranging from "0%" to "100%") and the eczema area and severity index (EASI) (ranging from "0" to "72", "0" for none, "72" for very large area involved and very severe) were used to assess the severity of skin symptoms. The score of IGA was 4, BSA was above 50%, EASI was 32 at the first visit. The level of serum total IgE was above 5,000 KU/L. We initiated treatment with Dupilumab, 600 mg at first dosage and then 300 mg every 2 weeks. After 8 weeks, the IGA score decreased to 1, BSA to 5% and EASI to 2.5. The Dermatology Life Quality Index (DLQI) score decreased from 16 at baseline to 5 at week 8. The serum total IgE level also decreased to 3,135 KU/L at week 12 (**Table 1**). In addition, the indicators related to NS, such as serum creatinine, serum albumin, urinary protein, urinary creatinine, and urine protein/creatinine ratio were within normal range, and the prednisone dosage decreased to 1.25 mg daily.

The second patient was a 13-year-old boy who also suffered from AD after birth. The manifestation of AD was similar to that of patient #1. Similarly, he didn't respond well to the treatment with topical glucocorticoids and oral antihistamine. He was diagnosed with AR and asthma when he was 3 years old, His father had AD and asthma history. He was diagnosed with NS 3 years ago and received oral prednisone and tacrolimus because of refractory proteinuria. When the patient presented to our department, he had a height of 155 cm, weight of 40 kg and the body mass index of 16.65 kg/m^2. He received prednisone 10 mg every 2 days and Tacrolimus 2 mg/day to treat the NS comorbidity. His urinary protein test was negative at the dosage but turned to be positive when we tried to reduce the medication dosage. The score of IGA was 4, BSA was 40%, EASI was 21.4 at the first visit. The level of serum total IgE was 492 KU/L at baseline. We initiated treatment with Dupilumab, 600 mg at first dosage and then 300 mg every 3 weeks. After 8 weeks, the IGA score decreased to 1, BSA to 4%, EASI to 2.4 and total IgE to 223 KU/L (**Table 1**). The DLQI score was decreased from 17 at baseline to 4 at 8 weeks. The indicators related to NS were within normal range, and the prednisone dosage decreased to 7.5 mg every 2 days and Tacrolimus dosage decreased to 1.5 mg/day at week 8. The peripheral blood mononuclear cells were further collected for T cell subsets analysis. Interestingly, the proportion of IL-4 and IL-13 producing Th2 cells were increased after Dupilumab treatment (**Figure 1**, **Table 2**).

The statutory guardians of patient #1 and patient #2 had given written informed consent to the publication of their case details. The study was conducted according to the Declaration of Helsinki.

DISCUSSION

Taken together, in the course of Dupilumab treatment, the AD symptoms of both patients were relieved significantly. Meanwhile, the dosages of prednisone or Tacrolimus for NS were also reduced, and no adverse reactions were found.

NS is an abnormal kidney condition marked by excretion of albumin in the urine and hypoalbuminemia due to altered permeability of the glomerular basement membranes (13). Although NS can affect people of any age, it's usually first diagnosed in children aged between 2 and 5 years old. Systemic steroids are the core treatment for NS with protocols based on seminal researches of the International Study of Kidney Disease in Children. However, there are still unmet needs for the management of NS in children. For example, most patients will relapse, with approximately half becoming frequently relapsed or steroid dependent, and it is well known that long term steroid use is associated with many side-effects including obesity, hypertension,Cushing syndrome, growth disorder, ocular complications, and osteoporosis (13).

Several studies showed that NS was closely related to allergic diseases (5, 14, 15) and type 2 inflammation (16–19). From an epidemiological aspect, Fanconi et al. (20) first linked atopy to NS in 1951. Many studies have shown that pediatric NS had a higher incidence of allergic diseases, including AD, allergic rhinitis, asthma, recurrent urticaria and hay fever (20). These patients also presented a higher serum IgE level (5, 15). Meanwhile, a large-population retrospective cohort study which enrolled 192,295 pediatric AD and 769,169 non-AD children showed the incidence of NS was significantly higher in the AD children compared with non-AD group, and the severity of AD also showed a

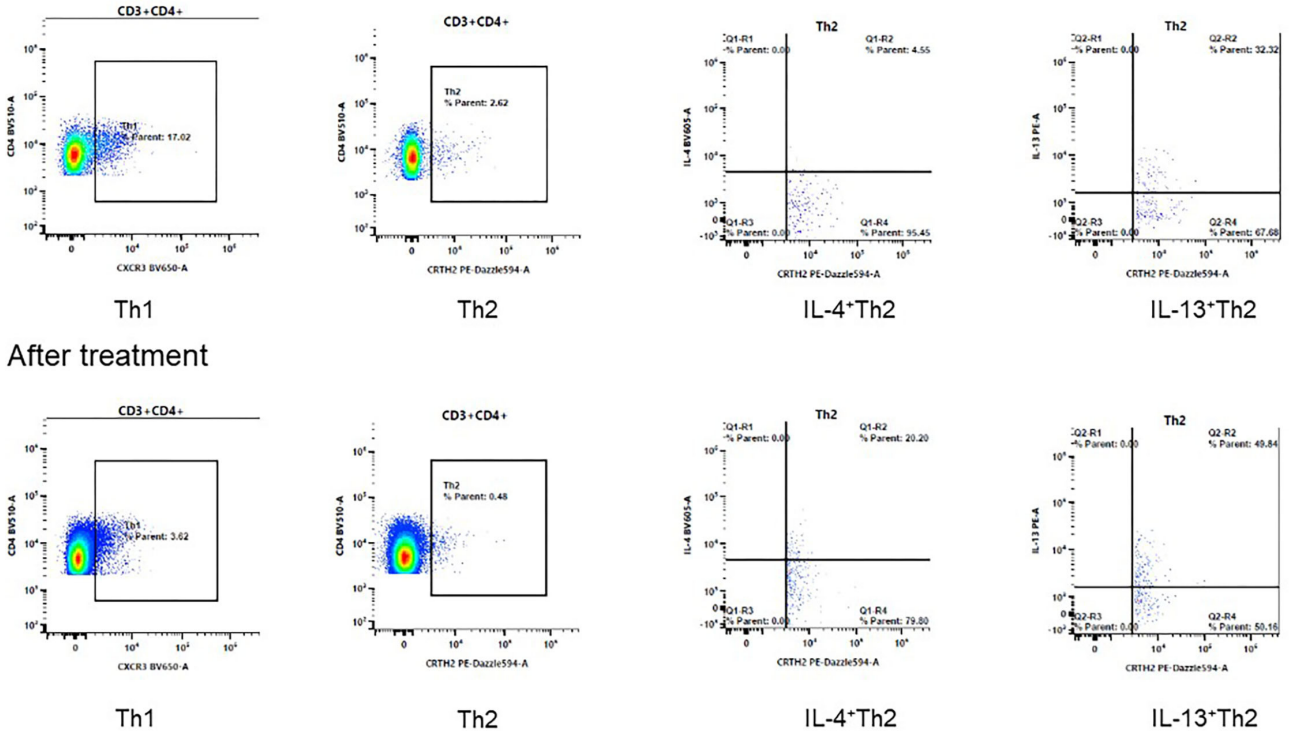

FIGURE 1 | The changes of Th1 and Th2 cells after 8 weeks treatment of Dupilumab. The proportion of IL-4+Th2 cells increased from 4.55% to 20.20%, IL-13+Th2 cells increased from 32.32% to 49.84% after treatment in patient #2.

positive correlation to NS incidence (5, 15). From pathogenesis aspect, there are also evidences implying the correlation between allergic diseases and NS. As the key mechanism of allergic diseases is the chronic inflammation mediated by T helper type-2 (Th2) cells (12, 21), allergic diseases are characterized by elevated levels of cytokines such as IL-4 and IL-13, which may play important roles in the pathogenesis of NS (16–19). Previous studies showed the levels of IL-4, IL-13 and IL-18 were significantly higher during the active stage of steroid sensitive nephrotic syndrome (SSNS) than remission stage and control group (17, 19). The percent of IL-13 producing $CD3^+$ cells was significantly higher in the nephrotic relapse with steroids group compared with the nephrotic remission with steroids group (22). Animal studies also showed that IL-13 was involved in the pathogenesis of minimal-change nephrotic syndrome, and that the overexpression of IL-13 may lead to renal injury (23). There are emerging data suggested NS and AD might share similar pathogenesis (7). Thus, inhibition of type 2 inflammatory mediators such as IL-4/IL-13 may be a potentially effective therapy for NS (24).

Dupilumab is a human monoclonal antibody that can inhibit the signaling pathway induced by IL-4 and IL-13. It has shown convincing efficacy and good safety for the treatment of type 2 inflammatory diseases including AD, asthma, and chronic rhinosinusitis with nasal polyposis (24). Currently, there are no reports of the efficacy and safety of Dupilumab in patients with NS. Based on the epidemiological and basic research data of AD and NS, we hypothesize that Dupilumab may be a potential therapeutic medication for NS patients, at least not a contraindication. In addition, some studies suggested that Th2 and related cytokines IL-4 and IL-13 also involved in other kidney diseases, such as idiopathic focal segmental glomerulosclerosis and correlated with lower cortico-resistance (25). Theoretically, Dupilumab might be an alternative option if the patients are reluctant or intolerant to long-term corticosteroid treatment.

Our hypothesis was preliminarily validated in the two cases which both showed good control of NS and less

TABLE 2 | Sera cytokines levels before and after Dupilumab treatment.

	Before				After			
	IL-4	**IL-13**	**IFN-γ**	**IL-10**	**IL-4**	**IL-13**	**IFN-γ**	**IL-10**
Patient 1#	13.5	15.2	59.4	13.4	15.4	17.1	59.7	12.6
Patient 2#	13.5	11.6	59.9	12.9	13.0	11.2	59.5	12.9

IL-4, IL-13, IFN-γ, IL-10: pg/ml.

systemic steroids and/or immunosuppressive agents use during the Dupilumab treatment period, accompanied by significant relief of AD symptoms. The $CD4^{+}$T cell subsets analysis in one patient showed the proportion of IL-4 and IL-13 producing Th2 cells were increased after Dupilumab treatment. In contrast to the decreased IgE level, we hypothesize the increased IL-4 and IL-13 producing Th2 cells may be a response to suppressed IL-4 and IL-13 functions. However, serum IL-4 and IL-13 levels of the two patients didn't change significantly after Dupilumab treatment. We also found the other antibodies such as IgG/IgA/IgM and cytokines such as IFN-γ/IL-10 were not changed. Thus, more data is needed to validate our findings and elucidate the exact mechanisms of Dupilumab in NS. We suggest prospective pilot studies and randomized controlled trials could be carried out to validate the efficacy and safety of Dupilumab in the treatment of NS patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the participants' statutory guardian for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

R-FZ and L-RQ conceived the idea and prepared and revised the manuscript. Y-QY and HC collected the data. All authors contributed to the article and approved the submitted version.

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Psoriasis and medical ramifications: A comprehensive analysis based on observational meta-analyses

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Purpose: Based on a large number of systematic reviews and meta-analyses exploring the relationship between psoriasis and various health outcomes, we conducted an comprehensive analysis to assess the strength and evidence for the association between psoriasis and medical end-point ramifications in patients.

Methods: We searched related meta-analyses, investigating the links between psoriasis and medical ramifications from three databases. All summary effect sizes, 95% CIs, heterogeneity, and small-study effects in the included meta-analyses were recalculated. We assessed the methodological quality of included articles with the AMSTAR 2 tool and graded the epidemiological evidence. Subgroup analysis based on the severity of psoriasis and study design were also performed.

Results: A total of 38 articles comprising 85 unique meta-analyses were included in this study. Although 69 outcomes were statistically significant, only 8 outcomes (nonvascular dementia, ulcerative colitis, pediatric dyslipidemia, gestational diabetes, gestational hypertension, fracture, multiple sclerosis, and schizophrenia) showed a high quality of epidemiological evidence.

Conclusion: We found that psoriasis increased the risk of 69 health outcomes, and 8 outcomes were graded as high-quality evidence. No evidence was found that psoriasis was beneficial for any medical end point. However, to verify our results, more large-sample, multi-center prospective cohort studies are needed.

KEYWORDS

psoriasis, medical ramifications, meta-analysis, epidemiological evidence, quality

Introduction

Psoriasis, which can affect the skin, nails, and scalp, is a chronic, noncommunicable, painful disfiguring, and disabling disease, involving hyperproliferative keratinocytes and infiltration of T cells, dendritic cells, macrophages, and neutrophils (1, 2). So far, even with the proper treatments, psoriasis is still not cured but controlled (3). Affecting

approximately 125 million adults and children all over the world, psoriasis results in serious global health issues and burdens (4). The overall prevalence of psoriasis ranges from 0.5 to 11.4% (5) and is higher in adults than in children. However, the majority of data on psoriasis prevalence are focused on a small number of countries (the U.K, the USA, and some European countries), causing that the prevalence of psoriasis is only known in 19% of countries worldwide (6). The psychosocial health of most patients with psoriasis may also receive a substantial and negative effect. Depression seems to be more common in patients with psoriasis (up to 20%) and even shows suicidal ideation extending to suicidal behavior when compared with the general population (7). The possibility of future development of psoriasis arthritis (PsA), another comorbidity of psoriasis, cannot be completely protected against the use of biological drugs (8). Therefore, psoriasis imposes a heavy burden on patients.

Until now, a large body of systematic reviews and meta-analyses investigated the association between psoriasis and certain medical ramifications. Except for psychiatric disorders, psoriasis seems to be linked with other comorbidities, including metabolic syndrome, uveitis, cardiovascular diseases (CVDs), and chronic kidney disease (9–12), which may further lead to impaired quality of life. However, most of the studies focused on a single health-related outcome, and to the best of our knowledge, no study has systematically summarized the strength of these relationships between psoriasis and multiple medical ramifications. A comprehensive analysis focuses on a specific topic and has the potential to provide the highest quality of evidence if performed and interpreted properly (13).

Consequently, we conducted this comprehensive analysis to gain a comprehensive overview of the existing published studies that investigated the association between psoriasis and health end point and assess its strength and validity. Our study shows that psoriasis has a major harmful effect on human health and can raise awareness of psoriasis.

Methods

We have registered the protocol in PROSPERO (CRD42022306771). The study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) regulations (14).

Abbreviations: PsA, psoriasis arthritis; CVD, cardiovascular disease; ACM, all-cause mortality; RR, relative risk; NAFLD, nonalcoholic fatty liver disease; CKD, chronic kidney disease; VTE, venous thromboembolism.

Literature search

Using "psoriasis" AND "meta-analysis" OR "meta-analyses" OR "systematic review" as search terms, we searched PubMed, Web of Science, and Embase for relevant studies from the initiation to January 2022 with no other restrictions. We also screened the references in each selected article in order to avoid missing the potential meta-analyses.

Study selection

Two authors selected independently the full texts for potentially eligible articles. Any discrepancies were discussed and resolved with ST. Studies were included if they met the following criteria:

(1) Meta-analysis was based on observational studies with quantitative analysis.

(2) Meta-analysis reported the association between psoriasis and the direct results on human health (risk of disease and mortality).

Studies were excluded if they met the following criteria:

(1) Meta-analysis only reported the relationship between psoriasis and indirect indicators (e.g., lipid levels and blood pressure).
(2) Studies were protocols, letters, and conference abstracts.
(3) Studies were only reviews.
(4) Psoriasis was not the exposure of interest.

When multiple meta-analyses investigated the same medical ramifications, we selected the one with the largest number of included primary studies.

Data extraction

For each included meta-analysis, two authors (YZ and LZ) independently extracted the following information: name of the first author, publication year, health outcomes, severity of psoriasis, study design (case-control, cross-sectional, or cohort studies), number of studies included in each meta-analysis, number of participants and events, metric-type (OR, odds ratio; RR, relative risk; HR, hazard ratio), summary effect size, 95% confidence interval (CI) of the results, *P*-values for statistically significant level, Q-test, and Egger's test. All differences were discussed and resolved by consensus with a third person (ST).

Data analysis

We used the extracted data obtained from the eligible studies to reanalyze each meta-analysis. The summary effect size and

its 95% CI were all reestimated. We used the I^2 metric and Cochran's Q-test to evaluate the heterogeneity. When the I^2 is >50%, we choose the random effect model; otherwise, we choose the fixed effect model. Egger's regression test was used to evaluate the publication bias. A P-value of < 0.1 for heterogeneity and publication bias was considered statistically significant. If a meta-analysis reported the severity and type of study of psoriasis, we performed subgroup analyses on basis of these data.

Evaluation of methodological quality and epidemiological evidence quality

We applied A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR2), a robust and validated tool, to assess the methodological quality of each included study. AMSTAR2 contains 16 items, seven of which are key items, and it classifies the study quality into four ranks as follows: critically low, low, moderate, and high (15). To evaluate the evidence quality of the association between psoriasis and each medical end point, grading parameters that have been adapted in various studies (16–19) were used in this study. According to the criteria (precision of the estimate, number of cases, heterogeneity, and small-study effects), the strength of epidemiological evidence was categorized into high, moderate, weak, or not applicable. Two authors independently finished the above evaluations.

Results

Search result

Figure 1 shows the flowchart of the selection process. Overall, a total of 3,893 articles were identified from three databases (1,068 articles from Web of Science, 646 from PubMed, and 2,179 from Embase). After excluding 1,508 duplicates, we carefully screened for the inclusion and exclusion criteria and finally found 38 eligible articles with 85 unique medical end points in this study. The remaining articles were all published between 2012 and 2021. The characteristics of these meta-analyses are all shown in Supplementary Table 1. Medical end points related to psoriasis were involved in the following categories of diseases: mortality ($n = 8$), cancer ($n = 17$), cardiovascular system disease ($n = 7$), nervous system disease ($n = 4$), gastrointestinal system disease ($n = 6$), respiratory system disease ($n = 3$), metabolic disease ($n = 9$), pregnancy outcomes ($n = 14$), and other outcomes ($n = 17$) (Figure 2).

Mortality

A meta-analysis of 6 cohort studies showed that psoriasis and all-cause mortality (ACM) exhibited a positive correlation, with a RR of 1.21 (1.14–1.28) (20). Psoriasis was found to increase the mortality in CVD, liver disease, respiratory disease, kidney disease, and infections (20). But no significant associations between psoriasis and mortality in malignancy (20) and cancer (21) were found (Figure 3).

Cancer

Psoriasis increased the incidence of total cancer (21). Compared with people without psoriasis, those with psoriasis had an increased risk of respiratory tract cancer (22), upper aerodigestive tract cancer (22), urinary tract cancer (22), colorectal cancer (23), colon cancer (23), nonmelanoma skin cancer (24), and squamous cell carcinoma (22). Except for total hematological malignancy, we found that psoriasis was significantly correlated to evaluate the risk of lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and leukemia (25). In addition, we found no relationship between psoriasis and rectal cancer (23) and melanoma (22) (Figure 4).

Cardiovascular system

In Figure 4, the adverse effects of psoriasis on cardiovascular system diseases are presented. We observed that 7 CVDs were linked to psoriasis. Previous data revealed that psoriasis evaluated the incidence of CVD (26), myocardial infarction (26), stroke (27), hypertension (28), pediatric hypertension (29), pediatric ischemic heart disease or heart failure (30), and atrial fibrillation (31) (Figure 5).

Nervous system

Compared with individuals without psoriasis, those with psoriasis were more likely to develop a dementia (32), nonvascular dementia (32), vascular dementia, (32) and Parkinson's disease (33) in our study (Figure 5).

Gastrointestinal system

Our data indicated that psoriasis can enhance the likelihood of developing Crohn's disease (34), ulcerative colitis (34), nonalcoholic fatty liver disease (NAFLD) (35), helicobacter pylori infection (36), hepatitis C (37), and celiac (38) (Figure 5).

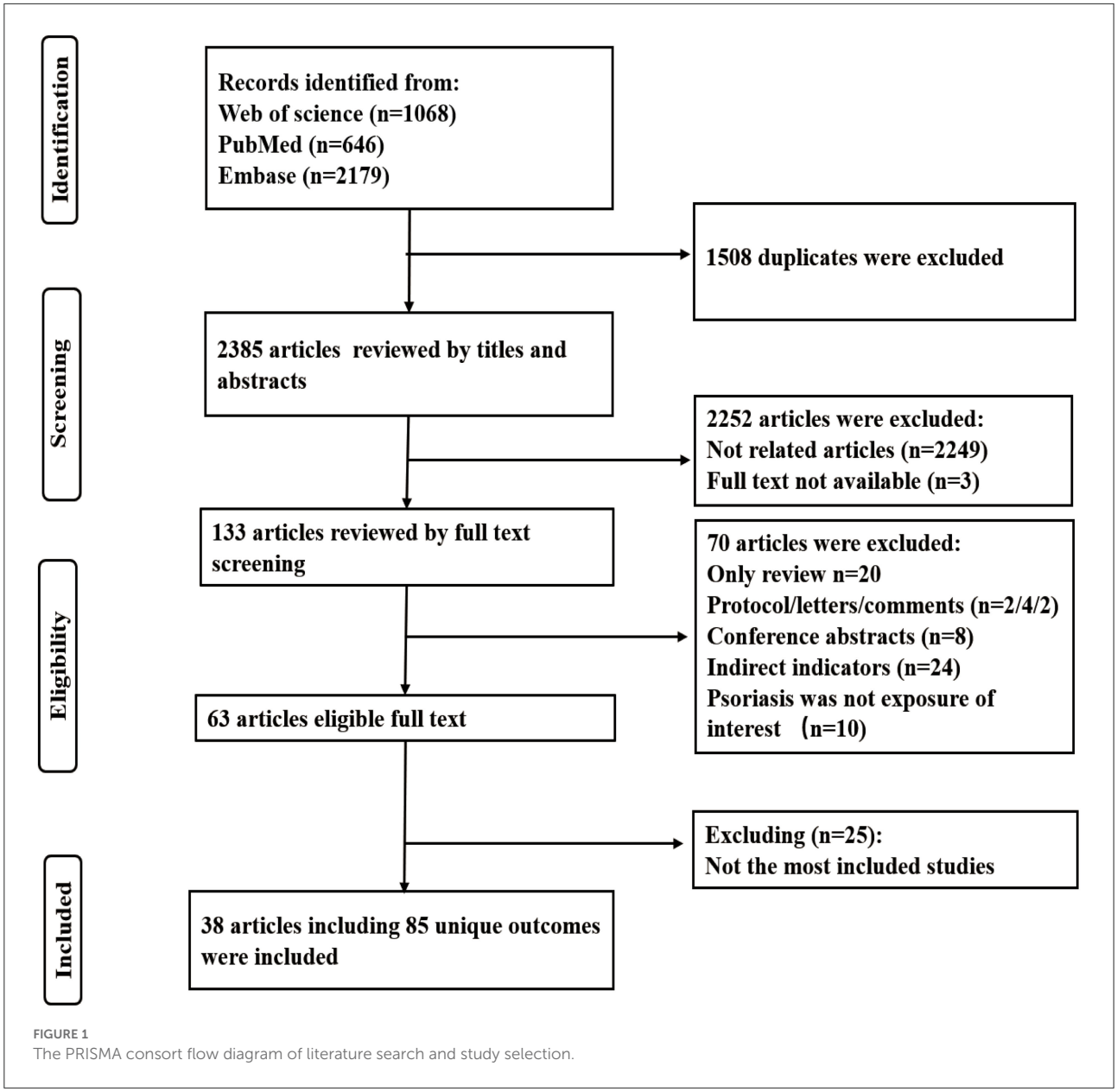

FIGURE 1
The PRISMA consort flow diagram of literature search and study selection.

Respiratory system

As shown in Figure 5, only three medical ramifications (39–41) (i.e., chronic obstructive pulmonary disease, obstructive sleep apnea, and asthma) of the respiratory system were rated as psoriasis with an evaluated incidence.

Metabolic diseases

Psoriasis had an adverse effect on metabolic disease in both adults and children. There were statistically significant associations found between psoriasis and incidence of obesity (42), diabetes (43), and metabolic syndrome (44) in adults. Sincerely, psoriasis also increased the risk of developing overweight (30), hyperlipidemia (30), metabolic syndrome (30), obesity (29), diabetes, (29) and dyslipidemia (29) in children (Figure 6).

Pregnancy-related outcomes

A study assessed the possible association between psoriasis and pregnancy medical end points (45). Compared with pregnant women without psoriasis, those pregnant women with psoriasis seemed more likely to have harmful

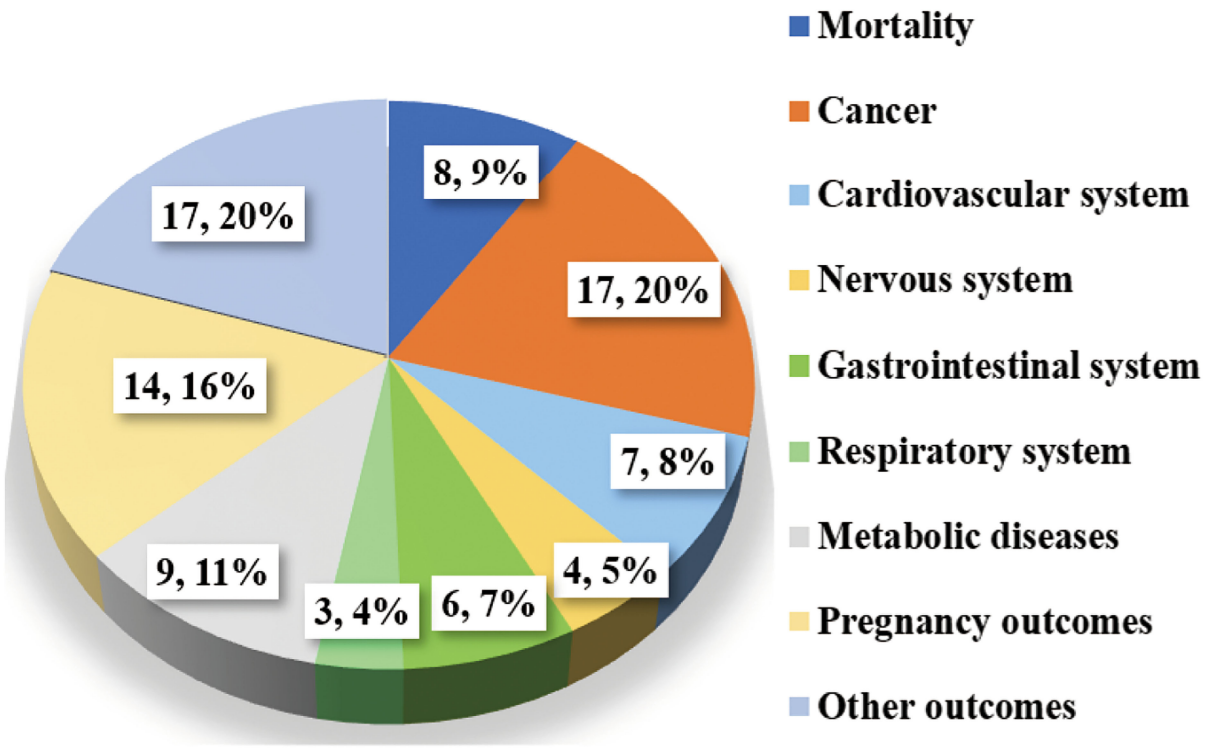

FIGURE 2
Map of medical end points associated with psoriasis.

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Mortality								
ACM	Dhana et al, 2019	6	19262		RR: 1.21 (1.14-1.28)	90.2	0.108	Moderate
CVD mortality	Dhana et al, 2019	5	6131		RR: 1.14 (1.09-1.21)	65.9	0.508	Moderate
Mortality in liver disease	Dhana et al, 2019	3	51		RR: 2.31 (1.61-3.31)	NA	NA	Weak
Mortality in respiratory disease	Dhana et al,2019	3	542		RR: 1.12 (1.02-1.22)	41.0	NA	Weak
Mortality in kidney disease	Dhana et al, 2019	3	29		RR: 2.16 (1.37-3.40)	NA	NA	Weak
Mortality in infections	Dhana et al,2019	3	810		RR: 1.23 (1.15-1.32)	12.1	NA	Weak
Mortality in malignancy	Dhana et al, 2019	3	2465		RR: 1.03 (0.99-1.08)	0.0	NA	NA
Mortality in cancer	Trafford et al, 2019	2	2455		RR: 1.05 (0.96-1.16)	30.5	NA	NA

FIGURE 3
Associations between psoriasis and mortality.

pregnancy-related outcomes such as cesarean delivery, preterm birth, (pre)eclampsia, gestational diabetes, gestational hypertension, premature of membranes, and prematurity; however, psoriasis was not associated with an increased risk of congenital malformations, neonatal mortality, stillbirth, spontaneous abortion, antepartum or postpartum

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Cancer								
Cancer incidence	Trafford et al, 2019	7	9485		RR: 1.18 (1.06-1.31)	90.2	0.328	Weak
Respiratory tract cancer	Pouplard et al, 2013	7	>310		RR: 1.36 (1.11-1.68)	53.1	0.014	Weak
Upper aerodigestive tract cancer	Pouplard et al, 2013	5	>90		RR: 3.05 (1.74-5.32)	0.0	0.230	Moderate
Urinary tract cancer	Pouplard et al, 2013	5	>205		RR: 1.30 (1.08-1.55)	7.2	0.527	Weak
Colorectal cancer	Fu et al, 2020	8	5871		HR: 1.16 (1.08-1.25)	2.6	0.024	Moderate
Colon cancer	Fu et al, 2020	5	4880		HR: 1.14 (1.05-1.24)	6.4	0.029	Weak
Hematologic malignancy	Bellinato et al, 2021	5	297		HR: 1.55 (1.24-1.94)	0.0	0.431	Moderate
Lymphoma	Bellinato et al, 2021	10	858		HR: 1.33 (1.09-1.64)	60.0	0.578	Weak
Hodgkin lymphoma	Bellinato et al, 2021	4	41		HR: 1.74 (1.13-2.69)	49.7	0.773	Moderate
Non-Hodgkin lymphoma	Bellinato et al, 2021	10	791		HR: 1.33 (1.09-1.64)	60.0	0.469	Weak
Cutaneous T-cell lymphoma	Bellinato et al, 2021	3	21		HR: 5.45 (3.49-8.50)	92.5	0.180	Weak
Multiple myeloma	Bellinato et al, 2021	2	932		HR: 1.32 (1.03-1.69)	0.0	NA	Weak
Leukemia	Bellinato et al, 2021	6	1583		HR: 1.51 (1.10-2.08)	64.5	0.254	Weak
Non-melanoma skin cancer	Wang et al, 2020	16	>551939		RR: 1.72 (1.46-2.02)	96.8	0.324	Moderate
Squamous cell carcinoma	Pouplard et al, 2013	7	449		RR: 5.31 (2.63-10.71)	95.0	0.562	Weak
Rectal cancer	Fu et al, 2020	3	125		HR: 1.18 (0.99-1.41)	0.0	0.492	NA
Melanoma	Pouplard et al, 2013	6	253		RR: 1.07 (0.85-1.35)	39.0	0.231	NA

FIGURE 4
Associations between psoriasis and cancers.

hemorrhage, low birth weight, and small for gestational age (Figure 7).

Other medical conditions

We observed that psoriasis also evaluated the risk of CKD (46), end-stage CKD (46), uveitis (47), fracture (48), geographic tongue (49), multiple sclerosis (50), erectile dysfunction (51), aortic aneurysm (52), schizophrenia (53), prevalence and incidence of depression (54), and prevalence of anxiety (54). However, meta-analyses also reported the lack of significant correlation between psoriasis and osteoporosis (55), osteopenia (55), suicide (56), suicide attempt (56), and venous thromboembolism (VTE) (57) (Figure 8).

Subgroup analysis

In a subgroup analysis of 22 meta-analyses that reported the severity of psoriasis, we found that only 6 outcomes were affected by the severity of psoriasis, while the remaining 16 outcomes were not (Table 1). We also conducted a subgroup analysis of 19 meta-analyses that concluded with cohort studies and case-control studies. The result showed that 16 medical end points were not influenced by the study design, whereas 3 medical end points were affected by the type of study (Table 2).

Heterogeneity

Among 85 included meta-analyses, we could not reanalyze the heterogeneity for 2 meta-analyses due to the lack of detailed data from the original studies. A total of 33 meta-analyses

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Cardiovascular system								
CVD	Gaeta et al, 2013	13	567569		RR: 1.24 (1.18-1.31)	93.4	0.017	Weak
MI	Gaeta et al, 2013	8	105088		RR: 1.25 (1.11-1.39)	83.2	0.429	Moderate
Stroke	Raaby et al, 2017	5	16110		HR: 1.17 (1.07-1.28)	78.5	0.343	Moderate
Hypertension	Duan et al, 2020	16	126838		OR: 1.46 (1.28-1.66)	94.1	0.043	Weak
Pediatric hypertension	Cho et al, 2021	8	61384		OR: 2.73 (1.79-4.17)	72.0	0.638	Moderate
Pediatric IHD or heart failure	Phan et al, 2020	3	7145		OR: 3.14 (1.08-9.10)	83.7	0.687	Weak
Atrial fibrillation	Upala et al, 2016	4	12755		HR: 1.42 (1.22-165)	68.5	0.255	Moderate
Nervous system								
Dementia	Liu et al, 2020	7	69414		RR: 1.16 (1.06-1.27)	56.0	0.685	Weak
Non-vascular dementia	Liu et al, 2020	3	63464		RR: 1.13 (1.11-1.16)	0.0	0.468	High
Vascular dementia	Liu et al, 2020	2	601		RR: 1.41 (1.09-1.82)	0.0	NA	Weak
Parkinson's Disease	Ungprasert et al, 2016	4	46827		OR: 1.38 (1.15-1.53)	35.0	0.72	Weak
Gastrointestinal system								
Crohn's disease	Fu et al, 2018	9	>19322		OR: 1.93 (1.52-2.47)	85.9	0.977	Moderate
Ulcerative colitis	Fu et al, 2018	8	>26985		RR: 1.77 (1.66-1.88)	24.3	0.614	High
NAFLD	Candia et al, 2014	6	1994		0R: 2.15 (1.57-2.94)	74.0	0.710	Moderate
Helicobacter pylori infection	Yu et al, 2019	11	787		OR: 1.70 (1.15-2.52)	60.0	0.154	Weak
Hepatitis C	Zhang et al, 2019	8	3577		OR: 1.70 (1.12-2.57)	84.2	0.632	Weak
Celiac disease	Acharya et al, 2019	7	136536		OR: 2.10 (1.66-2.66)	52.3	0.202	Moderate
Respiratory system								
COPD	Ungprasert et al, 2015	7	>19098		OR: 1.53 (1.29-1.83)	81.1	0.352	Moderate
Obstructive sleep apnea	Ger et al, 2020	3	834		OR: 2.60 (1.07-6.32)	89.3	0.193	Weak
Asthma	Wang et al, 2018	6	35933		OR: 1.33 (1.21-1.46)	52.5	0.739	Moderate

FIGURE 5
Associations between psoriasis and cardiovascular diseases (CVDs), nervous system, gastrointestinal system disease, and respiratory system disease.

showed low heterogeneity, while the remaining 50 showed high heterogeneity in our study.

Strength of epidemiological evidence and AMSTAR2 results

According to the criteria (Supplementary Table 2), the assessment of epidemiological evidence was not applicable for 16 (19%) medical ramifications because the *P*-values for their summary effects were >0.05. Among 69 significant medical ramifications, 8 (9%), 23 (27%), and 38 (45%) medical ramifications were rated as high, moderate, and weak epidemiological evidence, respectively (Figure 9).

We observed that there was no high/moderate methodological quality according to the strict AMSTAR2 tool. Only 4 (11%) articles were rated as low, and the other 34 (89%) articles were rated as critically low (Figure 9). The detailed information of 16 items in AMSTAR2 and the results of specific quality scores are shown in Supplementary Table 3.

Discussion

Main findings and possible explanation

Based on the existing evidence from 38 articles that covered 85 unique medical end points, our study showed

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Metabolic diseases								
Obesity	Armstrong et al, 2012	16	230248		OR: 1.66 (1.46-1.89)	97.3	0.653	Moderate
Diabetes	Mamizadeh et al, 2019	38	464990		OR: 1.69 (1.51-1.89)	98.5	0.087	Weak
Metabolic syndrome	Qiao et al, 2021	22	25917		OR: 2.02 (1.67-2.43)	83.6	0.119	Moderate
Pediatric overweight	Phan et al, 2020	8	398		OR: 1.54 (1.21-1.95)	40.8	0.628	Moderate
Pediatric hyperlipidemia	Phan et al, 2020	6	14594		OR: 1.84 (1.65-2.04)	28.8	0.060	Moderate
Pediatric metabolic syndrome	Phan et al, 2020	5	310		OR: 2.35 (1.75-3.16)	38.2	0.044	Weak
Pediatric obesity	Cho et al, 2021	13	77086		OR: 2.40 (1.60-3.59)	91.1	0.808	Moderate
Pediatric diabetes	Cho et al, 2021	8	25656		OR: 2.01 (1.09-3.73)	89.7	0.985	Weak
Pediatric dyslipidemia	Cho et al, 2021	7	12592		OR: 1.67 (1.42-1.97)	0.0	0.114	High

FIGURE 6
Associations between psoriasis and metabolic diseases.

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Pregnancy outcomes								
Caesarean delivery	Xie et al, 2021	10	>1148489		OR: 1.35 (1.14-1.60)	87.1	0.105	Moderate
Preterm birth	Xie et al, 2021	10	>475541		OR: 1.45 (1.21-1.74)	76.6	0.007	Weak
(Pre)eclampsia	Xie et al, 2021	8	>245519		OR: 1.28 (1.10-1.49)	54.7	0.202	Weak
Gestational diabetes	Xie et al, 2021	5	>276483		OR: 1.21 (1.12-1.31)	0.0	0.349	High
Gestational hypertension	Xie et al, 2021	4	>2261		OR: 1.28 (1.17-1.40)	2.7	0.989	High
Premature rupture of membranes	Xie et al, 2021	3	>693		OR: 1.17 (1.06-1.29)	64.9	0.373	Weak
Prematurity	Xie et al, 2021	2	>4		OR: 1.12 (1.01-1.25)	0.0	NA	Weak
Congenital malformations	Xie et al, 2021	4	>40432		OR: 1.02 (0.91-1.14)	0.0	0.207	NA
Neonatal mortality	Xie et al, 2021	3	>1155		OR: 1.14 (0.90-1.43)	0.0	0.518	NA
Still birth	Xie et al, 2021	5	>3630		OR: 1.23 (0.93-1.47)	35.8	0.665	NA
Spontaneous abortion	Xie et al, 2021	4	>288		OR: 1.44 (0.95-2.17)	77.3	0.274	NA
Ante- or postpartum hemorrhage	Xie et al, 2021	3	>2392		OR: 1.12 (0.71-1.76)	91.2	0.785	NA
Low birth weight	Xie et al, 2021	5	>841		OR: 1.15 (0.93-1.42)	70.0	0.94	NA
Small for gestational age	Xie et al, 2021	7	>257327		OR: 1.05 (0.99-1.12)	15.6	0.725	NA

FIGURE 7
Associations between psoriasis and pregnancy outcomes.

a broad overview of the association between psoriasis and other medical end points. The results covered mortality, cancer, cardiovascular system disease, nervous system disease, gastrointestinal system disease, respiratory system disease, metabolic disease, pregnancy outcomes, and other outcomes. We found that psoriasis had no beneficial effects on medical end points, while it was associated with an increased risk of 69 medical outcomes. However, the epidemiological evidence was graded as high only for 8 medical end points (i.e., nonvascular dementia, ulcerative colitis, pediatric dyslipidemia, gestational diabetes, gestational hypertension, fracture, multiple sclerosis, and schizophrenia).

Outcome	Study	Total studies	No of events	Risk Estimates (95%CI)	Estimates (95%CI)	I^2	Small-study effects	Quality of evidence
Other outcomes								
CKD	Ungprasert et al, 2018	4	199808		RR: 1.34 (1.14-1.58)	95.8	0.044	Weak
End-stage CKD	Ungprasert et al, 2018	3	151729		RR:1.29 (1.05-1.60)	12.6	0.427	Weak
Uveitis	Li et al, 2020	4	>15004		RR: 1.50 (1.08-2.08)	91.0	0.466	Weak
Fracture	Chen et al, 2020	5	67233		OR: 1.09 (1.06-1.11)	0.0	0.674	High
Geographic tongue	Alvarez et al, 2019	11	784		OR: 3.31 (2.66-4.11)	48.2	0.198	Weak
Multiple sclerosis	Islam et al, 2019	9	53863		RR: 1.67 (1.46-1.91)	0.0	0.443	High
Erectile dysfunction	Wu et al, 2018	9	87545		OR: 1.93 (1.51-2.46)	86.0	0.036	Weak
Aortic aneurysm	Yu et al, 2020	3	24864		HR: 1.30 (1.10-1.55)	53.5	0.426	Weak
Schizophrenia	Ungprasert et al, 2018	5	405421		OR: 1.35 (1.20-1.53)	33.1	0.345	High
Prevalence of depression	Zusman et al, 2020	4	>178		OR: 1.69 (1.37-2.08)	96.7	0.911	Weak
Incidence of depression	Zusman et al, 2020	4	>5270		RR: 1.44 (1.20-1.73)	94.7	0.759	Moderate
Prevalence of anxiety	Zusman et al, 2020	2	>122		OR: 1.48 (1.34-1.64)	0.0	NA	Weak
Osteoporosis	Sepehri et al, 2021	7	1672184		OR: 1.28 (0.86-1.90)	99.2	0.483	NA
Osteopenia	Sepehri et al, 2021	2	309110		OR: 1.50 (0.74-3.02)	99.5	0.601	NA
Suicide	Chi et al, 2017	2	1074		RR: 1.13 (0.87-1.46)	57.0	NA	NA
Suicide attempt	Chi et al, 2017	3	2102		RR: 1.25 (0.89-1.75)	92.7	0.339	NA
VTE	Hillary et al, 2021	5	86830		RR: 1.29 (0.92-1.80)	96.8	0.281	NA

FIGURE 8
Associations between psoriasis and other outcomes.

The remaining 61 associations were rated as moderate/weak in our study.

The management and treatment of psoriasis are complex, and there are currently data showing that Risankizumab, a biological agent, can improve psoriasis (58, 59). In particular, elderly patients represent an increasing proportion of patients with psoriasis. Biologics and small molecules seem to be a valuable option (60). In addition, anti-interleukin (IL)-23 therapies are assessed as safe and effective options for elderly patients (61). Therefore, early selection of appropriate drugs for psoriasis-related diseases is also very important.

Psoriasis is a complex disease involving many pathogeneses. The main pathogenesis of psoriasis highlighted the crosstalk between the innate and adaptive immune system, the central role of IL-23 and helper T cell type 17 responses, the role of TNFα and interferons, and the link to genetics (62). Our analysis found that psoriasis offers a harmful effect on nonvascular dementia, including Alzheimer's disease, with high epidemiological evidence. Another meta-analysis included eight observational studies that were consistent with our findings (63). Psoriasis and nonvascular dementia may share some genetic, immune, and inflammatory pathways. Ulcerative colitis, associated with psoriasis, also involves immune and inflammatory diseases and is of concern. In our study, the epidemiological evidence was graded as high for the association between them. There also exists common genetic abnormalities (chromosomal locus 6p21, IL23R, and IL12B) (64–66), immune dysfunction, and inflammation (IL17) (67, 68), or gut dysfunction (69) of disease progression both in both psoriasis and ulcerative colitis.

Dyslipidemia, hypertension, and diabetes in psoriasis are receiving more and more attention. We found that psoriasis increased the risk of pediatric dyslipidemia, gestational diabetes, and gestational hypertension with high-quality evidence. The correlation between cardiovascular risk factors (obesity, dyslipidemia, hypertension, and diabetes) and psoriasis has been arousing awareness and, consequently, with CVDs. In 2018, the American Heart Association and American College of

TABLE 1 Subgroup analysis results by severity of psoriasis.

Outcome	References	Total studies	Estimates	Mild (studies)	Mild	Severe (studies)	Severe
Consistent effect							
ACM	(20)	6	RR: 1.21 (1.14–1.28)	4	1.13 (1.09–1.16)	6	1.52 (1.35–1.71)
CVD mortality	(20)	5	RR: 1.14 (1.09–1.21)	3	1.05 (0.92–1.20)	4	1.38 (1.09–1.74)
Mortality in liver disease	(20)	3	RR: 2.31 (1.61–3.31)	1	2.00 (1.34–2.99)	3	3.97 (2.87–5.50)
Mortality in infections	(20)	3	RR: 1.23 (1.15–1.32)	1	1.41 (1.11–1.79)	3	1.58 (1.24–2.02)
Mortality in malignancy	(20)	3	RR: 1.03 (0.99–1.08)	1	1.02 (0.93–1.12)	3	1.21 (0.98–1.50)
Hodgkin lymphoma	(25)	4	HR: 1.74 (1.13–2.69)	1	1.42 (1.00–2.02)	1	3.18 (1.01–10.01)
Cutaneous T-cell lymphoma	(25)	3	HR: 5.45 (3.49–8.50)	2	3.70 (2.73–5.01)	2	9.67 (4.89–19.12)
Non-melanoma skin cancer	(24)	16	RR: 1.72 (1.46–2.02)	7	1.61 (1.25–2.09)	8	1.82 (1.38–2.41)
Stroke	(27)	5	HR: 1.17 (1.07–1.28)	5	1.10 (1.01–1.19)	5	1.38 (1.20–1.50)
Atrial fibrillation	(31)	4	HR: 1.42 (1.22–1.65)	2	1.22 (1.15–1.30)	2	1.51 (1.22–1.87)
Aortic aneurysm	(52)	3	HR: 1.30 (1.10–1.55)	3	1.23 (1.10–1.37)	3	1.55 (1.21–1,97)
Obstructive sleep apnea	(20)	3	OR: 2.60 (1.07–6.32)	1	1.36 (1.21–1.53)	1	1.53 (1.08–2.18)
Asthma	(41)	6	OR: 1.33 (1.21–1.46)	2	1.34 (1.14–1.57)	2	1.36 (1.03–1.80)
Obesity	(42)	16	OR: 1.66 (1.46–1.89)	4	1.46 (1.17–1.82)	5	2.23 (1.63–3.04)
Suicide	(56)	2	RR: 1.13 (0.87–1.46)	2	1.05 (0.84–1.31)	2	0.78 (0.45–1.35)
Suicide attempt	(56)	3	RR: 1.25 (0.89–1.75)	3	1.01 (0.51–2.01)	3	1.69 (1.00–2.84)
Inconsistent effect							
Mortality in kidney disease	(20)	3	RR: 2.16 (1.37–3.40)	1	2.20 (1.36–3.56)	3	2.28 (0.95–5.46)
Mortality in respiratory disease	(20)	3	RR: 1.12 (1.02–1.22)	1	1.36 (1.07–1.74)	3	1.06 (0.52–2.19)
Lymphoma	(25)	10	HR: 1.33 (1.09–1.64)	1	1.15 (0.97–1.36)	1	0.73 (0.28–1.90)
Non-Hodgkin lymphoma	(25)	10	HR: 1.33 (1.09–1.64)	1	1.15 (0.97–1.36)	1	0.73 (0.28–1.90)
Leukemia	(25)	6	HR: 1.51 (1.10–2.08)	1	0.95 (0.85–1.06)	1	0.88 (0.57–1.36)
Hypertension	(28)	16	OR: 1.46 (1.28–1.66)	4	1.09 (0.98–1.22)	5	1.13 (1.03–1.25)

ACM, all-cause mortality; CVD, cardiovascular disease.

Cardiology identified that chronic inflammatory diseases, such as psoriasis, act as a risk factor for CVD (70). It is not uncommon that psoriasis happens in children and adolescents as well as pregnant women. According to current screening guidelines, clinicians should screen for dyslipidemia from 9 years of age for psoriatic children and adolescents (71). Pregnant women with psoriasis had a higher risk to develop hypertension and diabetes than pregnant women without psoriasis in this study. For pregnant women, early treatment of psoriasis seems to be more important in order to avoid adverse pregnancy outcomes as well as CVD events. However, the underlying mechanism of the relationship between psoriasis and these cardiovascular risk factors remains unclear, and genetic susceptibility, cellular mediators, and the common inflammatory pathways seem to link these together.

Our study found a significant positive correlation between psoriasis and fracture with high epidemiological evidence, with a pooled RR of 1.09 (1.06–1.11). The following aspects might explain the mechanism. Long-term increased expression of inflammatory factors affects bone metabolism and exacerbates systematic bone loss (72). From the point of view of medicine, psoriatic patients taking methotrexate or ciclosporin can directly damage bone structure (73). Multiple sclerosis, which is considered to be an immune-mediated inflammatory disorder, has been reported as a comorbidity in psoriatic patients and vice versa (50, 74). With the high-quality evidence, psoriasis significantly increased the risk of multiple sclerosis in this study. These two diseases seem to have some biological similarities, involving common genes, immunity factors, and tumor necrosis factor, and these may mediate the inextricable link between them. Another notable correlation is between mental diseases and psoriasis. There has high epidemiological evidence that psoriasis enhanced the risk of schizophrenia in our study. Few possible interpretations can explain the result. T helper (Th17) is dysregulated in both diseases, which may share underlying etiology (75, 76). The proximity of chromosomes 6p21.3 and 6p22.2 to psoriasis and schizophrenia, respectively, may lead to the simultaneous transmission of these two susceptibility genes (77, 78). Both conditions are more likely to happen to the same person. Therefore, in the treatment of psoriasis, in addition, to pay attention to the treatment of the disease itself, it also needs to pay attention to these comorbidities.

In this study, the heterogeneity between studies has been observed in 50 meta-analyses. We think that the following

TABLE 2 Subgroup analysis results by study design.

Outcome	References	Total studies	Estimates	Cohort (studies)	Cohort	Case-control (studies)	Case-control
Consistent effect							
CVD	(26)	13	RR: 1.24 (1.18–1.31)	4	1.18 (1.09–1.29)	4	1.24 (1.11–1.39)
MI	(26)	8	RR: 1.25 (1.11–1.39)	3	1.17 (0.99–1.38)	2	1.19 (1.05–1.36)
Hypertension	(28)	16	OR: 1.46 (1.28–1.66)	1	1.37 (1.29–1.45)	10	1.37 (1.14–1.64)
Dementia	(32)	7	RR: 1.16 (1.06–1.27)	5	1.13 (1.11–1.16)	1	1.25 (1.09–1.43)
Crohn's disease	(34)	9	OR: 1.93 (1.52–2.47)	4	2.53 (1.65–3.89)	5	1.70 (1.20–2.40)
Ulcerative colitis	(34)	8	OR: 1.77 (1.66–1.88)	4	1.72 (1.56–1.90)	4	1.75 (1.50–2.05)
Celiac	(38)	7	OR: 2.10 (1.66–2.66)	3	1.71 (1.48–1.98)	4	3.09 (1.92–4.97)
Asthma	(41)	6	OR: 1.33 (1.21–1.46)	3	1.34 (1.19–1.51)	3	1.26 (1.00–1.58)
Diabetes	(43)	38	OR: 1.69 (1.51–1.89)	12	1.40 (1.24–1.60)	15	1.89 (1.47–2.35)
Pediatric overweight	(30)	8	OR: 1.54 (1.21–1.95)	1	1.42 (0.44–4.53)	6	1.65 (1.05–2.60)
Pediatric hyperlipidemia	(30)	6	OR: 1.84 (1.65–2.04)	5	1.84 (1.65–2.04)	1	2.21 (0.33–14.64)
Cesarean delivery	(45)	10	OR: 1.35 (1.14–1.60)	8	1.28 (1.08–1.50)	2	2.22 (0.68–7.22)
Multiple sclerosis	(50)	9	RR: 1.67 (1.46–1.91)	5	1.55 (1.24–1.95)	4	2.01 (1.22–3.34)
Osteoporosis	(55)	7	OR: 1.28 (0.86–1.90)	2	1.04 (1.03–1.09)	3	1.38 (0.95–1.99)
Erectile dysfunction	(51)	9	OR: 1.93 (1.51–2.46)	1	1.27 (1.12–1.450	2	3.94 (2.87–5.41)
Schizophrenia	(46)	5	OR: 1.35 (1.20–1.53)	1	1.37 (1.01–1.86)	4	1.35 (1.19–1.54)
Inconsistent effect							
Parkinson's Disease	(33)	4	OR: 1.38 (1.15–1.53)	3	1.38 (1.20–1.58)	1	1.25 (0.51–3.06)
Hepatitis C	(37)	8	OR: 1.70 (1.12–2.57)	2	2.01 (1.67–2.42)	2	0.92 (0.14–6.00)
Helicobacter pylori Infection	(36)	11	OR: 1.70 (1.15–2.52)	3	1.64 (0.73–3.70)	4	1.20 (0.55–2.65)

CVD, cardiovascular disease; MI, myocardial infarction.

confounding factors may be the causes of heterogeneity: age, severity of psoriasis, study design, geographical regions, and follow-up period. The methodological quality of studies included in this comprehensive analysis was all rated as low/critically low, and none was graded as high/moderate based on the AMSTAR2 criteria. We concluded that lack of protocol, list of excluded studies, founding source of primary studies, and the bias risk assessment were the main reasons for affecting the methodological quality. Only eight medical end points showed high-quality evidence. We observed that remarkable heterogeneity and small-study effects might contribute to the evidence rating downgrade in this study.

Strength and limitations

To the best of our knowledge, this is the first time to systematically clarify the relationship between psoriasis and various medical end points. We applied robust search terms to identify eligible articles in three important databases to ensure the research result was as reliable as possible. Then, two authors independently screen the articles and extract the data from eligible studies. In the meanwhile, the AMSTAR2 tool and a strong evaluation method of evidence were used to assess the quality of the methodology of included studies and the epidemiological evidence. We suggest that this study can provide scientific evidence for arousing the awareness of psoriasis.

Inevitably, there are some limitations in our study. We included studies that focused on direct health-related outcomes, and thus we may have missed some data on indirect health-related results. We conducted the review based on the published studies with the largest number of included primary studies, and some individual studies might be missed, which could affect the results through selection bias. In the meanwhile, due to a lack of raw data, most of the meta-analyses failed to be conducted in subgroup analyses. Both prevalence and incidence of psoriasis are lower in children than in adults (79, 80). A systematic review conducted by Iskandar et al. suggests that there is a clear bimodal age pattern in psoriasis onset, showing the first and second peaks at around 30–39 and 60–69 years, respectively (81). Psoriasis occurs earlier in women than men, with a bimodal onset at the ages of 16–22 and 55–60 years (82). But the prevalence of psoriasis did not differ significantly between genders. Except for age, the prevalence of psoriasis is unequally distributed across a geographical area. According to some studies, the prevalence of psoriasis is unequally distributed across geographical regions, with the highest prevalence in high-income countries and prevalence ranging from 0.1% in east Asia to 1.5% in western Europe (6). Unfortunately, many of the included meta-analyses lacked data on these two aspects, and

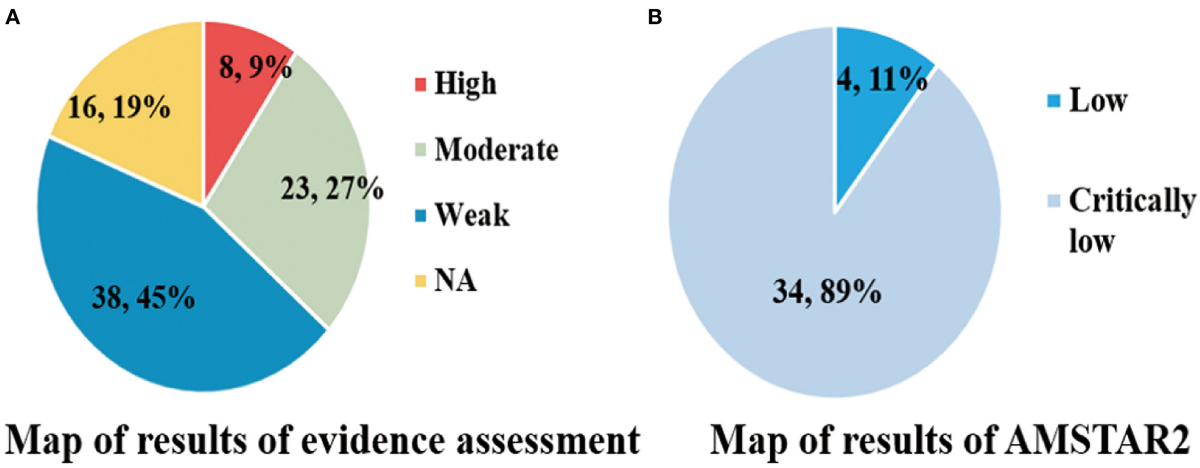

FIGURE 9
(A,B) Map of results of evidence assessment and AMSTAR 2.

there was no way to perform subgroup analyses across age and geographic regions to provide more reliable and accurate results in our study.

Conclusion

We found high-quality evidence showing that psoriasis is adverse for nonvascular dementia, ulcerative colitis, pediatric dyslipidemia, gestational diabetes, gestational hypertension, fracture, multiple sclerosis, and schizophrenia. No evidence was found to be beneficial for medical end points in our comprehensive analysis. Nonetheless, more large-sample, multi-center prospective cohort studies are needed to verify our results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YZ, LZ, LS, and ST were involved in the conception and design of the study and drafted the manuscript. YZ, LZ, LS, SC, QZ, and LL contributed to the acquisition and analysis of the data. YZ and LZ interpreted the results. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.998815/full#supplementary-material

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Exposure to silica and systemic sclerosis: A retrospective cohort study based on the Canadian Scleroderma Research Group

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Introduction: Systemic sclerosis (SSc) is thought to be induced by an environmental trigger in genetically predisposed individuals. This study assessed the demographic and clinical characteristics and disease severity of silica exposed SSc patients.

Methods: Data was obtained from the Canadian Scleroderma Research Group (CSRG) cohort, containing 1,439 patients (2004–2019). Univariate and multivariate logistic regression analyses were performed, to determine the phenotype and severity of silica-exposed SSc patients. Mortality was assessed using Cox Survival Regression and Kaplan-Meier analyses.

Results: Among 1,439 patients (86.7% females), 95 patients reported exposure to silica. Those exposed were younger, of male sex and with more severe disease. Sex differences were observed where male patients exposed to silica were more likely to be Caucasian and smokers whereas female patients were younger at SSc diagnosis compared to unexposed. Multivariate regression, controlled for multiple confounders, showed that silica exposure was associated with a younger age at diagnosis and worse disease severity and mortality.

Conclusion: Exposure to silica was reported in ∼7% of CSRG cohort and ∼20% of male patients and was associated with a worse prognosis in terms of age of diagnosis, organ involvement and mortality. Hence, screening for silica exposure among higher risk individuals may be beneficial and these patients may require closer monitoring for systemic disease.

KEYWORDS

systemic sclerosis, silica, environmental triggers, occupation, mortality, gastrointestinal disease, interstitial lung disease, scleroderma

Introduction

Systemic sclerosis (SSc) is a chronic, fibrosing systemic autoimmune rheumatic disease (1). Most commonly affected organs are the skin, gastrointestinal (GI) tract, and lungs, which have the most contact to the outside world, and their involvement leads to significant morbidity and mortality (2). The prevalence of SSc in Canada in 2003 was estimated to be 74.4/100,000 females and 13.3/100,000 males (2). While SSc is more common in females, the prognosis has been consistently shown to be worse in male patients including more diffuse cutaneous SSc (dcSSc), more interstitial lung disease (ILD) and higher mortality (3, 4). It is not known whether this different SSc phenotype and prognosis seen in males is mediated by biological/hormonal influences or whether exposure/occupation related factors in males contribute to the process. As disease-modifying treatment options are limited, determining triggers and elucidating preventive strategies is of significant importance (3).

The pathogenesis of SSc, while not fully understood, is believed to be induced by environmental triggers in genetically predisposed hosts (3, 4). The nature of such triggers and factors accounting for disease severity/prognosis remain poorly understood. A recent review highlighted the environmental factors studied to date for association with SSc (5). The strongest evidence was observed for environmental or occupational exposure to silica and organic solvents. Specifically, a meta-analysis of cohort studies focusing on workers (often male) exposed to silica demonstrated an 18-fold increased incidence of SSc (5).

While there is evidence to suggest that occupational exposure to silica may be associated with an increased risk of SSc and a more severe phenotype, the proportion of SSc patients with history of occupational or other exposure to silica in North America remains to be clarified. It is unclear whether certain patient characteristics should prompt assessment for prior silica exposure and whether these patients have a more severe SSc than unexposed SSc patients and may require a different clinical/screening approach for comorbidities and complications. Hence, using the Canadian Scleroderma Research Group (CSRG) (6), we aimed to assess the frequency of occupational exposure to silica among Canadian SSc patients, define the demographic and clinical characteristics of SSc patients exposed to silica, and study whether occupational exposure to silica confers a worse disease severity and mortality.

Materials and methods

Study population

The CSRG is the largest multi-center registry of Canadian SSc patients, extensively described elsewhere (7–10). Patients with a diagnosis of SSc followed in one of the 15 rheumatology centers (across Canada and Mexico), who accepted to participate in the registry, were prospectively recruited between 2004 and 2019. Detailed demographic, clinical, laboratory and imaging data were collected at study enrollment (first visit) and at subsequent visits (usually annually) thereafter, for up to 15 study visits. SSc diagnosis was verified by an experienced rheumatologist and over 98% of the patients met the 2013 ACR/EULAR classification criteria for SSc (11). Ethics approval for this study was obtained at the Jewish General Hospital, Montreal, Canada and at all participating CSRG study sites.

Design

This retrospective cohort study included SSc patients with $\geq$ 1 registry visit between January 2004 and September 2019. Patients were asked to complete a detailed questionnaire at inception into the cohort which included yes/no questions regarding certain occupational exposures. Patients were categorized into silica exposed vs. silica unexposed based on their response. The following was indicated on the form "Please check the box if you have ever worked in environments that commonly involve the following substances or if you have ever been exposed to the medications or other exposures

mentioned below. If you are not sure or would like to comment, please use the space provided." A patient was considered to be exposed to silica if they answered yes to any of the following exposures: silica dusts, hard rock mining, and/or coal mining. Patients also had an optional field to enter their current occupation title.

Socio-demographic and clinical characteristics

The following variables were extracted from the first patient's visit for all exposure groups: age, sex, ethnicity, smoking status (never or ever smoked), and disease duration (defined as the time between the onset of first non-Raynaud manifestation and recruitment date into the study). SSc subtype was reported as limited cutaneous (lcSSc) and dcSSc, defined as skin fibrosis involving the proximal limbs and/or trunk at any time (8). Severity of skin involvement was measured using the modified Rodnan skin score (mRSS) (score range 0–51) (8). Presence of abnormal nailfold capillaroscopy and history of finger necrosis/gangrene/amputation were recorded.

Presence and severity of internal organ involvement (cutaneous, cardiac, pulmonary, renal, and GI), SSc-specific and SSc-related antibodies and treatment were collected at baseline. Systemic organ involvement was defined as follows (ILD defined below). Pulmonary hypertension corresponds to a systolic pulmonary artery pressure of $>$ 45 mmHg on right heart echocardiogram. SSc-specific renal involvement was defined as a history of renal crisis. Gastrointestinal (GI) involvement was defined based on the median gastrointestinal (GI)-14 score (12). Other variables recorded by recruiting physicians at the first visit included presence of inflammatory arthritis, myositis, and history of cancer. Mean Medsger disease severity scale (DSS) (13), assessing the presence and severity of 9 individual organs, was also evaluated to corroborate results (14). Categories in this scale included a general domain, peripheral vascular, joint/tendon, muscle, GI, pulmonary, cardiac, renal, and the skin domain. Detailed definition and grading of Medsger DSS are explained elsewhere (14).

Antibody profiles including anticentromere (ACA), anti-topoisomerase 1 (ATA), anti-RNA polymerase III antibodies (anti-RNAP), anti-Ro52, and anti- nucleolus organizer region 90 (Nor90), anti-Ku, anti-Th/To, fibrillarin, anti-PM75, and anti-PM100 were detected by Euroline SSc profile LIA (Euroimmun GmbH, Luebeck, Germany) according to manufacturer's instructions. Antibody against anti-U1 ribonucleoproteins (U1RNP) was assessed by addressable laser bead immunoassays (ALBIA) (QUANTA PlexTM SLE8, INOVA Diagnostics, Inc.). All measurements were obtained from the initial registry visit. Antibodies were reported as negative or weak positive (considered absent) and moderate or strong positive (considered present) based on the accepted lab cut off point and numerical values were not available. Antibodies with nucleolar patterns were considered to be fibrillarin, anti-Th/To, Anti RNAP, PM75 and PM100 (15).

Medication history, including mycophenolate mofetil (MMF) or cyclophosphamide (CYC), was recorded by recruiting physicians as past use, current use, or never used. This was dichotomized for statistical analysis into exposed (past or current use) and never exposed.

Disease severity definition(s)

The following disease severity outcomes were considered: dcSSc phenotype, SSc-specific antibodies, younger age at SSc diagnosis, worse GI disease (GI-14 score) and higher risk and worse ILD. ILD was defined as present if a High Resolution Computerized Tomography (HRCT) of the lungs was interpreted by an experienced radiologist as showing ILD or chest x-ray findings of increased interstitial markings (not due to congestive heart failure) or fibrosis, and/or if a study physician reported findings indicative of ILD on physical examination based on a previously published decision rule (16). Patients with ILD were stratified into Forced Vital Capacity (FVC) of $\geq$ 70% for mild disease and $<$ 70% for moderate-to-severe based on their spirometry findings on the first visit.

Mortality

Mortality data was collected during annual visits using a standardized death case report form (17). Follow up was started at date of first registry visit and end of follow up was considered when mortality occurred. Patients were censored at the last available registry visit if they were lost to follow up and no mortality data was recorded.

Statistical analysis

Baseline patient characteristics were compared across the two groups (silica exposure vs. no silica exposure) using Chi-square or Fisher's exact test for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables. Univariate and multivariate logistic regression was used to predict patients' characteristics associated with silica exposure, where silica exposure was considered as the outcome.

Additional univariate logistic regression models, where silica exposure was considered to be a predictor, were used for categorical variables and linear regression for the continuous variable (i.e., GI-14) to determine whether silica exposure was associated with SSc severity (as defined above). The multivariate model was adjusted for possible confounders.

Cox regression analysis for mortality was performed adjusting for age, sex, smoking, and disease duration. R Studio (version 1.4.1106) and SAS studio software was used to conduct all statistical analyses.

Subgroup analyses

As silica exposure is more common in males, separate analyses for silica exposure were performed by sex. Data on gender was not available.

TABLE 1 Baseline patient characteristics.

Variables	Exposure to silica (*N* = 95)	No exposure to silica (*N* = 1,344)	*P*
Demographics			
Age ≥ 50 years, *N* (%)	25 (27.5)	546 (41.5)	**0.016**
Male sex, *N* (%)	43 (45.3)	149 (11.1)	**<0.001**
Caucasian, *N* (%)	88 (92.6)	1,204 (89.7)	0.626
Disease duration ≥ 5 years, *N* (%)	47 (51.6)	773 (58.9)	0.207
Smoking, *N* (%)	67 (70.5)	786 (58.7)	0.065
Clinical characteristics			
Diffuse disease, *N* (%)	48 (51.6)	470 (35.3)	**0.003**
Treatment with CYC or MMF, *N* (%)	14 (14.9)	110 (8.3)	0.082
ILD, *N* (%)	36 (38.3)	393 (30.0)	0.157
FVC < 70, *N* (%) (*n* = 1,244)	18 (21.7)	130 (11.2)	**0.016**
Pulmonary arterial hypertension, *N* (%) (*n* = 909)	8 (15.4)	140 (16.3)	0.208
Rodnan score, median (IQR)	10.00 [4.00, 17.50]	6.00 [2.00, 14.00]	**0.011**
Digital ulcer/pitting scars, *N* (%)	45 (47.9)	556 (41.8)	0.516
Necrosis/gangrene/amputation, *N* (%)	32 (34.0)	473 (35.6)	0.957
Nailfold capillaroscopy, *N* (%)	67 (71.3)	1,017 (76.5)	0.513
GI_14, Median (IQR) (*n* = 1,343)	4.00 [2.00, 7.00]	3.00 [1.00, 6.00]	**0.014**
Joint impairment, *N* (%)	23 (24.5)	377 (28.3)	0.721
History of renal crisis, *N* (%)	7 (7.4)	48 (3.6)	0.174
Cancer, *N* (%)	8 (8.5)	108 (8.1)	0.991
Antibody profile			
ACA antibody, *N* (%) (*n* = 1,244)	24 (28.3)	458 (39.5)	0.075
ATA antibody, *N* (%) (*n* = 1,244)	18 (21.8)	172 (14.8)	0.189
U1RNP, *N* (%) (*n* = 1,276)	6 (7.0)	63 (5.3)	0.758
Ro52, *N* (%) (*n* = 1,244)	22 (25.8)	309 (26.7)	0.664
Ku, *N* (%) (*n* = 1,244)	0 (0.0)	9 (0.7)	0.477
Nor90, *N* (%) (*n* = 1,244)	1 (1.1)	26 (2.2)	0.54
Nucleolar antibodies, *N* (%) (*n* = 1,243)	18 (21.4)	232 (20.0)	0.795
Medsger severity scores			
Medsger—general, mean (*SD*)	1.06 (1.37)	0.89 (1.18)	0.172
Medsger—peripheral vascular,Mean (*SD*) (*n* = 1,156)	1.88 (1.21)	1.63 (1.24)	0.097
Medsger—skin, mean (*SD*)	1.36 (0.77)	1.21 (0.70)	0.05
Medsger—joint/tendon,Mean (*SD*) (*n* = 1,095)	0.96 (1.32)	0.68 (1.18)	0.055
Medsger—muscle, mean (*SD*)	0.33 (0.90)	0.23 (0.72)	0.185
Medsger—GI tract, mean (*SD*)	2.07 (0.85)	1.91 (0.78)	**0.049**
Medsger—lung, mean (*SD*)	1.57 (1.21)	1.30 (1.11)	**0.02**
Medsger—heart, mean (*SD*)	0.56 (1.17)	0.46 (0.95)	0.354
Medsger—kidney, mean (*SD*) (*n* = 1,266)	0.16 (0.65)	0.11 (0.61)	0.473

IQR, interquartile range; SD, standard deviation; CYC, cyclophosphamide; MMF, mycophenolate mofetil; ACA, anticentromere antibody; ATA, anti-topoisomerase I antibody; U1RNP, anti-U1 Ribonucleoproteins antibody; ILD, interstitial lung disease; FVC, forced vital capacity; Unless a different denominator (n) is indicated, the missing number for remaining variables was < 5%.

Chi-square or fisher exact test for categorical variable. ANOVA or Kruskal-Wallis test for continuous variables.

N provided where > 5% of data was missing.

Bold indicates statistically significant values.

Results

Patient characteristics

In total, 1,439 patients were included in this study, 86.7% were females with mean age at SSc diagnosis of 46.5 ± 13.7 years. Average disease duration at baseline was 9.83 ± 9.23 years.

Ninety-five patients (6.6%) reported exposure to silica with female-male ratio of ∼1:1 among exposed vs. 8:1 among unexposed patients (6.5:1 in the entire CSRG cohort). Specifically, 22.4% of CSRG males vs. 4.2% females were exposed to silica ($p < 0.0001$) (Table 1).

Baseline patient characteristics (Table 1) showed that SSc patients exposed to silica were significantly more likely to be younger at diagnosis (median age 44.9 vs. 47.2 years old; $p = 0.016$), males (45.3 vs. 11.1%; $p < 0.001$), have a dcSSc phenotype (51.6% vs. 35.3%; $p = 0.003$), more severe ILD (with higher proportion of low FVC (< 70%) 21.7% vs. 11.2%; $p = 0.016$; higher Medsger score for lung disease 1.57 vs. 1.30; $p = 0.02$), worse skin fibrosis based on mRSS, 10 vs. 6; $p = 0.011$), and worse GI disease (median GI-14 score, 4 vs. 3; $p = 0.014$ and Medsger GI score 2.07 vs. 1.91; $p = 0.049$) compared to the non-exposed group. Furthermore, consistent with dcSSc phenotype, silica-exposed patients had higher ATA positivity (21.8% vs. 14.8%), lower ACA positivity (28.3% vs. 39.5%), higher prevalence of ILD (38.3% vs. 30.0%), and were more likely to be treated with cyclophosphamide (CYC) and/or MMF (14.9% vs. 8.3%), albeit statistical significance was not reached.

Results of the univariate logistic regression were similar. Silica-exposed patients were younger at diagnosis (OR 0.53; 95% CI: 0.33–0.84), males (OR 6.63; 95% CI: 4.27–10.28), and smokers (OR 1.69; 95% CI: 1.08–2.69) with worse disease phenotype, notably dcSSc (OR 1.96; 95% CI: 1.28–2.99), treatment with CYC and/or MMF (OR 1.95; 95%CI: 1.03–3.45), lower ACA positivity (OR 0.60; 95% CI: 0.36–0.97), more severe ILD (FVC < 70% predicted, OR 2.20; 95% CI: 1.23–3.74 and higher mean lung Medsger severity score, OR 1.24; 95%CI: 1.03–1.48), worse skin fibrosis (mRSS, OR 1.03; 95%CI: 1.01–1.04), and worse GI disease (higher GI-14 and Medsger GI scores). All significant variables were considered in the multivariate model (Table 2). Co-linearity assessment between the included variables in the multivariate model did not identify high collinearity ($r > 0.7$) (data not shown). The results showed that younger age (OR 0.42; 95%CI: 0.22–0.75), male sex (OR 7.87; 95%CI: 4.51–13.84), severe ILD (FVC < 70%) (OR 2.08; 95%CI: 1.00–4.27) and severe GI disease (GI-14) (OR 1.11; 95%CI: 1.01–1.21) were significant demographic and clinical characteristics of silica exposed patients.

Multivariate regression analyses stratified by sex and adjusted for confounders (all significant variables identified in the univariate model), female patients exposed to silica were diagnosed younger (OR 0.40; 95%CI: 0.16–0.90) whereas male patients were more likely to be Caucasian (OR 12.06; 95% CI: 1.83–250.88), smokers (OR 4.70; 95% CI: 1.10–33.72), and had more severe ILD (OR 5.72; 95% CI: 1.51–24.27) (Table 3).

TABLE 2 Univariate and multivariate logistic regression model for factors associated with exposure to silica among all study sample.

	Univariate logistic regression	Multivariate logistic regression
	Silica ($N = 95$)*	Silica
Variables	**OR (95% CI)**	**Adjusted OR (95% CI)**
Age ≥ 50 years	**0.53 (0.33–0.84)**	**0.42 (0.22–0.75)**
Male sex	**6.63 (4.27–10.28)**	**7.87 (4.51–13.84)**
Caucasian	1.15 (0.71–3.51)	–
Disease duration ≥ 5 years	0.75 (0.49–1.14)	–
Treatment with CYC or MMF	**1.95 (1.03–3.45)**	1.11 (0.45–2.48)
Smoking	**1.69 (1.08–2.69)**	1.05 (0.60–1.89)
Diffuse disease	**1.96 (1.28–2.99)**	1.49 (0.75–2.94)
Digital ulcer/ pitting scars	1.28 (0.84–1.94)	–
Necrosis/gangrene/ amputation	0.94 (0.60–1.44)	–
Nailfold capillaroscopy	0.76 (0.48–1.23)	–
Pulmonary arterial hypertension	0.93 (0.40–1.92)	–
Joint impairment	0.82 (0.49–1.31)	–
History of renal crisis	2.15 (0.87–4.60)	–
Cancer	1.05 (0.46–2.10)	–
ACA antibody	**0.60 (0.36–0.97)**	0.91 (0.48–1.66)
ATA antibody	1.54 (0.87–2.60)	–
U1RNP	1.36 (0.51–3.00)	–
Ro52	0.96 (0.57–1.56)	–
PDGFR	–	–
Ku	–	–
Nor90	0.52 (0.03–2.49)	–
Nucleolar antibodies	1.09 (0.62–1.83)	–
ILD	1.45 (0.93–2.22)	–
FVC < 70	**2.20 (1.23–3.74)**	**2.08 (1.00–4.27)**
GI_14	**1.08 (1.02–1.15)**	**1.11 (1.01–1.21)**
Rodnan score	**1.03 (1.01–1.04)**	1.00 (0.96–1.03)
Medsger—General	1.12 (0.95–1.31)	–
Medsger—Peripheral Vascular	1.18 (0.97–1.43)	–
Medsger—Skin	1.31 (0.99–1.72)	–
Medsger—Joint/Tendon	1.19 (0.99–1.41)	–
Medsger—Muscle	1.17 (0.90–1.47)	–
Medsger—GI tract	**1.33 (1.01–1.79)**	0.99 (0.69–1.43)
Medsger—Lung	**1.24 (1.03–1.48)**	1.08 (0.82–1.42)
Medsger—Heart	1.10 (0.89–1.33)	–
Medsger—Kidney	1.12 (0.77–1.48)	–

* Reference group no exposure to silica.
– Defines not available/not applicable.
Bold signifies significant values; Variable definitions as above.

TABLE 3 Univariate and multivariate logistic regression model for factors associated with exposure to silica among male and female patients.

	Univariate logistic regression		Multivariate logistic regression	
	Males	Females	Males	Females
	OR (95% CI)*	OR (95% CI)*	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age ≥ 50 years	0.60 (0.29 201.21)	**0.37 (0.17 200.72)**	0.37 (0.12 201.03)	**0.40 (0.16 200.90)**
Male sex	–	–	–	–
Caucasian	**3.94 (1.10 25.15)**	1.00 (0.43 202.93)	**12.06 (1.83 250.88)**	0.95 (0.37 202.97)
Disease duration ≥ 5 years	0.87 (0.43 201.74)	0.88 (0.50 201.59)		
Treatment with CYC or MMF	1.39 (0.51 203.48)	1.89 (0.76 204.07)	0.75 (0.16 203.08)	2.20 (0.66 206.32)
Smoking	**3.22 (1.19 11.26)**	0.89 (0.51 201.57)	**4.70 (1.10 33.72)**	0.68 (0.34 201.35)
Diffuse disease	0.87 (0.44 201.72)	**2.22 (1.25 203.93)**	1.57 (0.48 205.19)	1.50 (0.60 203.67)
Digital ulcer/pitting scars	1.03 (0.52 202.06)	1.04 (0.58 201.83)	–	–
Necrosis/gangrene/amputation	0.63 (0.28 201.32)	1.27 (0.71 202.23)	–	–
Nailfold capillaroscopy	1.00 (0.48 202.19)	0.71 (0.39 201.36)	–	–
Pulmonary arterial hypertension	1.54 (0.39 205.18)	0.79 (0.23 202.08)	–	–
Joint impairment	0.50 (0.19 201.16)	1.15 (0.61 202.08)	–	–
History of renal crisis	2.03 (0.60 206.25)	1.20 (0.19 204.06)	–	–
Cancer	0.93 (0.20 203.17)	1.22 (0.41 202.86)	–	–
ACA antibody	0.95 (0.37 202.22)	0.74 (0.39 201.37)	1.95 (0.59 206.43)	0.65 (0.28 201.45)
ATA antibody	1.63 (0.67 203.76)	1.24 (0.53 202.57)	–	–
U1RNP	2.29 (0.29 14.31)	1.59 (0.47 204.10)	–	–
Ro52	0.76 (0.30 201.75)	1.19 (0.61 202.23)	–	–
PDGFR	–	–	–	–
Ku	–	–	–	–
Nor90	0.80 (0.04 205.63)	–	–	–
Nucleolar antibodies	0.72 (0.29 201.67)	1.17 (0.54 202.31)	–	–
ILD	**2.20 (1.11 204.45)**	0.74 (0.37 201.40)	2.10 (0.80 205.70)	**0.25 (0.08 200.64)**
FVC < 70	**2.88 (1.14 207.12)**	1.75 (0.74 203.67)	**5.72 (1.51 24.27)**	1.75 (0.58 205.05)
GI_14	**1.13 (1.01 201.26)**	1.10 (1.02 201.20)	1.10 (0.93 201.31)	1.10 (0.98 201.23)
Rodnan score	0.99 (0.96 201.02)	**1.03 (1.00 201.05)**	0.98 (0.92 201.04)	1.01 (0.97 201.06)
Medsger—General	1.10 (0.85 201.4)	1.06 (0.93 201.60)	–	–
Medsger—Peripheral vascular	0.98 (0.72 201.34)	1.21 (0.93 201.60)	–	–
Medsger—Skin	0.80 (0.51 201.22)	1.40 (0.94 202.02)	–	–
Medsger—Joint/Tendon	0.97 (0.73 201.27)	1.19 (0.92 201.50)	–	–
Medsger—Muscle	1.65 (0.99 202.75)	1.10 (0.75 201.48)	–	–
Medsger—GI tract	1.16 (0.79 201.75)	**1.47 (1.01 202.21)**	0.77 (0.44 201.33)	1.39 (0.81 202.36)
Medsger—Lung	**1.37 (1.02 201.86)**	1.07 (0.83 201.37)	1.03 (0.65 201.63)	1.15 (0.79 201.65)
Medsger—Heart	1.09 (0.79 201.48)	1.01 (0.72 201.33)	–	–
Medsger—Kidney	1.02 (0.68 201.61)	0.89 (0.34 201.45)	–	–

*Reference group: no exposure to silica.
Bold indicates statistically significant values.

To assess whether exposure to silica may predict a worse disease prognosis, linear and logistic regression was performed (Table 4). SSc patients with reported silica exposure were significantly more likely to be diagnosed before age 50 (OR 0.53; 95% CI: (0.33–0.84) and have a worse disease. Notably, higher risk of dcSSc phenotype (OR 1.95; 95% CI: 1.28–2.99), more severe GI disease (β 0.85; 95% CI: 0.19–1.51), and a lower likelihood of ACA antibody positivity (OR 0.60; 95% CI: 0.37–0.98) were seen. A trend toward more ILD and more severe ILD was also observed, however this was not statistically significant. Multivariate model confirmed that SSc patients with silica exposure were significantly more likely to be diagnosed with both Raynaud's phenomenon (OR 0.48, 95% CI: 0.29–0.78) or SSc before 50 years of age (OR 0.47; 95% CI: 0.29–0.77) when adjusted for sex, ethnicity, smoking status and dcSSc disease phenotype. A strong trend for increased risk of ILD,

severe ILD (OR 2.05; 95% CI: 0.96–5.36) and worse GI disease (β 0.67; 95% CI: -0.03 to 1.36) was observed when adjusting for multiple confounders including sex (Table 4). Similarly, an important trend toward dcSSc phenotype (OR 1.54; 95% CI: 0.99–2.42), higher prevalence of ATA antibodies and lower prevalence of ACA antibodies was seen after adjusting for age, sex, smoking, and ethnicity.

Mortality

Over the follow up period, 237 patients (of 1,439) were excluded for loss to follow up and/or missing data and 260 died (21.6%). Mortality rate of 71.4 (95% CI: 47.4–103.2) per 1,000 person-years (103.7 per 1,000 person-years in males and 50.5 per 1,000 person-years in females) was seen in silica exposed patients vs. 43.4 (95% CI: 38.0–49.4) (76.1 per 1,000 person-years in males and 39.9 per 1,000 persons-years in females) in the unexposed group (Table 5). Additionally, mortality in patients exposed to silica with disease duration of < 5 years was 86.1/1,000 person-years compared to 41.5/1,000 person years in the unexposed group. Unadjusted Kaplan Meier curve shows a significantly increased mortality rate in the silica-exposed group compared to the unexposed [Hazard Ratio (HR) 1.58, 95%CI: 1.07–2.35; p = 0.0217] (Figure 1). When the hazard ratio was adjusted for age, sex, smoking, and disease duration, a non-statistically significant trend for increased mortality was observed (HR 1.45, 95%CI: 0.96–2.19; p = 0.0911).

Discussion

Occupational exposure to silica has been strongly correlated with a higher risk of developing SSc and possibly confers a worse disease phenotype, however prior studies were limited by patient number and hence additional research were needed (5). Occupations with highest risk of exposure are reviewed elsewhere (5), but these include coremaker, bench molder, mineral-crushing machine operator, stone and gem cutter and finisher, concrete-mixer operator, and miners (5). Not surprisingly these occupations commonly employ male patients and males have been consistently shown to exhibit a worse SSc-related prognosis (3).

We showed that 6.6% of the CSRG participants reported exposure to silica and higher chance of reporting silica-exposure was associated with younger age (at diagnosis), male sex and more severe disease phenotype. These findings are aligned with previous reports where Marie et al. also showed that the 18 SSc patients exposed to silica vs. 82 patients not exposed to either silica nor organic solvents in their study were more often males with severe disease (18). Our results are also aligned with a recent Australian SSc cohort study, which also found that patients exposed to silica were more likely to be male, smokers with worse disease features such as dcSSc, ILD, lower frequency of ACA (3). One study reported the dose dependent relationship between silica exposure and SSc although this could not be assessed in our cohort. The overall risk was found to increase with cumulative exposure from the time of entering

TABLE 4 Association between health outcomes and exposure to silica (yes vs. no).

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted β (95% CI)	Adjusted β (95% CI)
ILD (yes vs. no) (N = 1,371)[a]	1.44 (0.94–2.23)	1.21 (0.73–1.99)	–	–
Severe ILD* (vs. mild ILD) (N = 370)[b]	1.60 (0.74–3.50)	2.05 (0.96–5.36)	–	–
Diffuse disease (yes vs. no) (N = 1,397)[c]	**1.95 (1.28–2.99)**	1.54 (0.99–2.42)	–	–
GI-14 (N = 1,397)[d]	–	–	**0.85 (0.19–1.51)**	0.67 (-0.03–1.36)
ATA (yes vs. no) (N = 1,222)[e]	1.54 (0.89–2.66)	1.47 (0.82–2.64)	–	–
ACA (yes vs. no) (N = 1,222)[f]	**0.60 (0.37–0.98)**	0.76 (0.45–1.29)	–	–
Earlier age of onset of disease ≥ 50 years (N = 1,395)[g]	**0.53 (0.33–0.84)**	**0.47 (0.29–0.77)**	–	–
Age of onset of Raynauds ≥ 50 years (N = 1,397)[h]	**0.53 (0.33–0.85)**	**0.48 (0.29–0.78)**	–	–

[a]Model adjusted for age, sex, diffuse disease, immunosuppressive medication, disease duration, ethnicity, smoking and organic solvents.
[b]Model adjusted for age, sex, diffuse disease, immunosuppressive medication, disease duration, ethnicity, smoking and organic solvents.
[c]Model adjusted for age, sex, smoking, and ethnicity.
[d]Model adjusted for age, sex, disease duration, diffuse disease, immunosuppressive medication, smoking and organic solvents.
[e]Model adjusted for age, sex, smoking, and ethnicity.
[f]Model adjusted for age, sex, smoking, and ethnicity.
[g]Model adjusted for sex, smoking, ethnicity, and diffuse disease.
[h]Model adjusted for sex, smoking, ethnicity, and diffuse disease.
*Defined as presence of ILD and FVC < 70. ILD, interstitial lung disease; ACA, anticentromere antibody; ATA, anti-topoisomerase I antibody.
Bold indicates statistically significant values.

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TABLE 5 Mortality case count and incidence rate per 1,000 person years.

	Number of deaths	Person-years	MR per 1,000 person-year (95% CI)
Exposure to silica (N = 81)	28	391	71.4 (47.4–103.2)
No exposure to silica (N = 1,121)	232	5,340	43.4 (38.0–49.4)
Male patients (N = 162)			
Exposure to silica (N = 38)	16	154	103.7 (59.3–168.4)
No exposure to silica (N = 124)	40	527	76.1 (54.3–103.6)
Female patients (N = 1,040)			
Exposure to silica (N = 43)	12	237	50.5 (26.1–88.2)
No exposure to silica (N = 997)	192	4,813	39.9 (34.4–45.9)
Young patients < 50 years (N = 712)			
Exposure to silica (N = 59)	14	305	45.9 (25.1–77.0)
No exposure to silica (N = 653)	110	3,211	34.2 (28.1–41.3)
Older patients ≥ 50 years (N = 490)			
Exposure to silica (N = 22)	14	87	161.2 (88.1–270.3)
No exposure to silica (N = 468)	122	2,129	57.4 (47.6–68.4)
Disease duration < 5 year (N = 493)			
Exposure to silica (N = 39)	13	151	86.1 (45.8–147.3)
Not exposure to silica (N = 454)	85	2,046	41.5 (33.2–51.4)
Disease duration ≥ 5 year (N = 709)			
Exposure to silica (N = 42)	15	241	62.2 (34.8–102.7)
Not exposure to silica (N = 667)	147	3,294	44.6 (37.7–52.4)

The whole study sample contained 1,202 patients. MR, mortality rate.

the workforce for males [Incidence Rate Ratio (IRR) 1.07 (1.05–1.09) per 50 mg/m^3 -years] and females [IRR 1.04 (0.99–1.10) per 50 mg/m^3 -years] (19).

We found that exposure to silica in SSc patients confers a twofold increased risk of being diagnosed with Raynaud's phenomenon and SSc before age 50, despite adjusting for multiple confounders, including sex. Furthermore, silica exposure increased the risk of dcSSc and ATA positivity by almost 50% and increased the risk of severe ILD by twofold, with a confidence interval near statistical significance despite adjusting for multiple confounders. Previous literature supports the association between ILD, dcSSc phenotype and silica exposure (5, 20, 21). As expected, ACA positivity was lower in silica exposed patients as this antibody profile is typically associated with lcSSc phenotype and has been consistently shown to be protective against ILD and SSc related mortality in both lcSSc and dcSSc.

A robust trend toward worse GI disease was seen in patients exposed to silica in our study. While previous studies have shown the association between occupational silica exposure and gastric cancer, GI symptoms secondary to silica exposure in SSc patients have not yet been reported. Silica can come into contact with the GI tract as a result of ingestion following clearance from the lungs (22, 23) and can lead to chronic local injury and inflammation in the GI tract (24). Thus, this area warrants further evaluation and assessment.

Sex is an important determinant of SSc prognosis. In our study, almost a quarter of male SSc patients reported silica exposure as opposed to only 4.2% of female SSc patients. This is also aligned with the Australian SSc cohort where 7.5% of SSc patients and 31.6% of male SSc patients reported silica exposure (3). These rates of silica exposure are much higher than rates expected in general population where ∼1.1% of working Canadians may be exposed to silica in the workplace (25). The profile of SSc patients exposed to silica differed by sex. Male patients were more likely to be younger, Caucasian and smokers whereas female SSc patients exposed to silica were more likely to be younger at diagnosis compared to silica unexposed group. Despite adjusting for sex and multiple other covariates, we showed that silica exposure was associated with adverse outcomes.

Almost 35% of silica exposed and ∼20% of unexposed SSc patients died over 14-year follow up with a mortality rate of 71.4 per 1,000 person-years in silica exposed vs. 43.4 in unexposed patients. As expected, mortality rate was higher for males and older patients. While significance was lost after adjustment, we believe the strong trend toward excess mortality needs further research.

Our study has several limitations. Missing data for individual variables usually ranged from 0 to 5% (**Table 2**). The exposure to silica was based on self-report and coded as Yes/No. Timing, duration, and intensity of exposure were not available, although this is similar to other studies in the literature. Hence, it was not possible to evaluate dose dependent response and development/severity of SSc. Additionally, exposure misclassification and recall bias are possible. However, we believe that both under- and overreporting of silica exposure are more likely to bias toward not finding any association. Few patients reported their occupation and industry type, which was used to verify likelihood of exposure to silica. However, different industry types and occupations may lead to low vs. high risk of silica exposure which could not be assessed in this study. While this is one of the largest studies assessing the association between silica exposure and SSc, the absolute number of patients with reported exposure to silica remains relatively low (95 patients, 6.6% in this registry). Finally, we did not have gender data and hence it remains to be confirmed whether

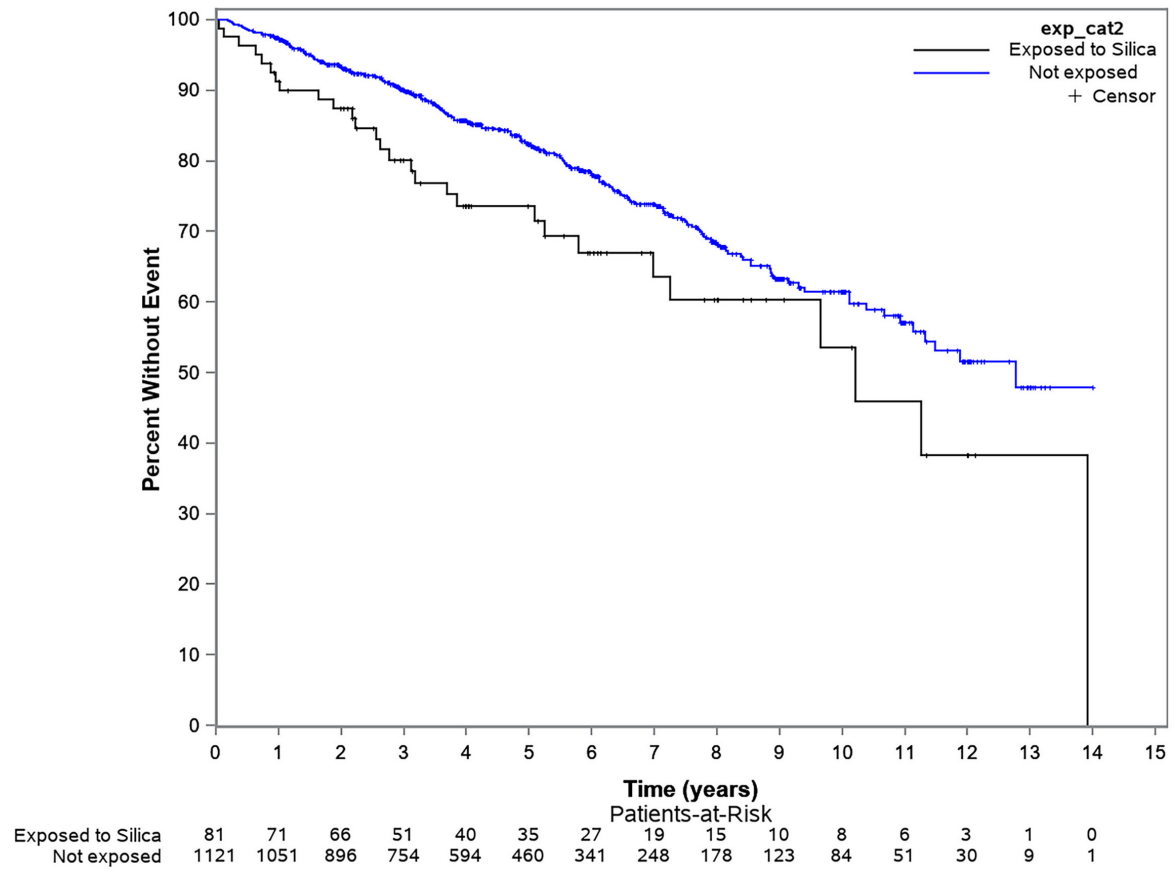

FIGURE 1
Kaplan-Meier curve evaluating mortality over time in silica exposed vs. unexposed groups.

the worse disease features seen in males with SSc are driven by biological factors (i.e., sex) or occupational/sociocultural exposures (i.e., gender).

Exposure to silica was seen in ∼7% of the CSRG cohort and was more common patients younger at diagnosis, males, smokers and patients with a more severe disease. Differences by sex were observed where male patients exposed to silica were more often smokers and Caucasian vs. silica-exposed female patients were younger at SSc diagnosis. Furthermore, silica exposure was associated with worse SSc outcomes in these patients such as younger age at SSc diagnosis and a strong trend toward higher risk of dcSSc, ATA antibodies, more severe GI disease, ILD, and mortality. Hence, our results suggest that prior silica exposure among SSc patients in North America is common, particularly among males and younger females and these patients are at risk of worse outcomes. Patients with occupational silica exposure who present with new onset Raynaud's phenomenon should be thoroughly assessed for Very Early Diagnosis Of SSc (VEDOSS) through physical examination (e.g., puffy fingers), nailfold capillaroscopy (using dermoscopy or videocapillaroscopy), and antibody testing (i.e., antinuclear and/or SSc-specific antibodies). Earlier diagnosis of SSc could lead to counseling about discontinuation of silica exposure as well as earlier screening for systemic involvement and prompt treatment initiation. For patients diagnosed with SSc, ILD is considered to be an early complication often occurring in the first 3–5 years of disease onset. While there are no clear guidelines, experts usually suggest baseline ILD screening with high resolution CT scan and PFTs with DLCO and regular monitoring by spirometry for the first 3–5 years. SSc patients with silica exposure could benefit from regular follow up during the first 5 years and beyond. As any SSc patients, clinical signs or features of ILD should prompt an early specialist referral to minimize complications. Unfortunately, there is no specific treatment available for SSc associated with silica exposure aside from discontinuing exposure, smoking cessation and SSc management. Large prospective studies with detailed exposure/occupational questionnaires and job matrices are needed to further study the association between silica exposure and prognosis of patients with SSc.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Canadian Scleroderma Research Group has the dataset. Requests to access these datasets should be directed to MB.

Ethics statement

The studies involving human participants were reviewed and approved by Jewish General Hospital, Montreal, Canada and at all participating CSRG study sites. The patients/participants provided their written informed consent to participate in this study.

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AM, RM, ER, MB, and EN designed the study. AM and LO collected and organized the data. AM prepared the manuscript. RM performed the statistical analyses with input from ER. AL, MC, IL, and MH provided feedback on the design, analyses, and manuscript. EN guided and supervised the study. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Liver fibrosis prevalence and risk factors in patients with psoriasis: A systematic review and meta-analysis

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Background: Patients with psoriasis are more likely than matched controls in the general population to have advanced liver fibrosis; however, our understanding of these patients is limited. There is currently no systematic evaluation of the prevalence and risk factors of liver fibrosis in psoriasis patients.

Objective: To evaluate the prevalence of psoriasis patients who are at high or low risk for advanced liver fibrosis and determine the risk factors for developing liver fibrosis.

Methods: Electronic searches were conducted using the PubMed, Embase, Scopus, and Cochrane Library databases from the dates of their inception till May 2022, using the PubMed, Embase, Scopus, and Cochrane Library databases. Any observational study describing the prevalence and/or risk factors for liver fibrosis in patients with psoriasis was included.

Results: Patients with psoriasis at high risk for advanced liver fibrosis had a pooled prevalence of 9.66% [95% confidence interval (CI): 6.92–12.75%, I^2 = 76.34%], whereas patients at low risk for advanced liver fibrosis had a pooled prevalence of 77.79% (95% CI: 73.23–82.05%, I^2 = 85.72%). Studies that recruited methotrexate (MTX)-naïve patients found a lower prevalence of advanced liver fibrosis (4.44, 95% CI: 1.17–9.22%, I^2 = 59.34%) than those that recruited MTX-user cohorts (12.25, 95% CI: 6.02–20.08%, I^2 = 82.34%). Age, sex, BMI, PASI score, psoriasis duration, MTX cumulative dose, and the prevalence of obesity, MTX users, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome were not identified as sources of heterogeneity by meta-regression analysis. The pooled odds ratios for age >50 years, BMI > 30, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome were 2.20 (95% CI: 1.42–3.40, I^2 = 0%), 3.67 (95% CI: 2.37–5.68, I^2 = 48.8%), 6.23 (95% CI: 4.39–8.84, I^2 = 42.4%), 2.82 (95% CI: 1.68–4.74, I^2 = 0%), 3.08 (95% CI: 1.90–4.98, I^2 = 0%), and 5.98 (95% CI: 3.63–9.83, I^2 = 17%), respectively.

Conclusion: Approximately 10% of the population with psoriasis is at high risk for advanced liver fibrosis, while 78% are at low risk. Patients over the age of 50 with obesity, diabetes, hypertension, dyslipidemia, and/or metabolic syndrome have an increased risk of developing liver fibrosis, necessitating monitoring.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022303886], identifier [CRD42022303886].

KEYWORDS

cirrhosis, hepatic fibrosis, hepatotoxicity, liver toxicity, NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

Introduction

Liver disease is a leading cause of mortality and morbidity worldwide (1). When liver fibrosis reaches an advanced stage, patients are at increased risk of developing hepatocellular carcinoma, hepatic decompensation, and liver-related mortality (1). Patients with psoriasis are more likely to have advanced liver fibrosis than matched controls in the general population (2). They are predisposed to liver fibrosis for a variety of reasons, one of which is non-alcoholic fatty liver disease (NAFLD), a prevalent liver disease affecting approximately 25% of the general population (3). NAFLD has been found to be strongly associated with psoriasis in previous meta-analyses (4–6).

Recent scientific breakthroughs have significantly advanced our understanding of psoriasis pathophysiology, resulting in the development of targeted biologic therapies such as anti-TNF, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors. Furthermore, the efficacy of biologic treatments for psoriasis has been validated by numerous real-world studies (7–9), which is significant because, in a real-life situation, some patients are not typically included in clinical trials, such as those with multiple comorbidities, elderly patients, erythrodermic or pustular psoriasis, and previous history of biologic treatment failure. Moreover, paradoxical adverse effects, such as the development of hidradenitis suppurativa and vitiligo, have been linked to biologics in psoriasis patients and require to be monitored (10, 11).

Methotrexate (MTX) is among the most frequently prescribed non-biologic medications for psoriasis. In addition to its standard indications, such as psoriatic arthritis, MTX can be prescribed in conjunction with biologic therapy to minimize the occurrence of anti-drug antibodies (12). The extent of the association between MTX and liver fibrosis in psoriasis patients is disputed. A histology-based study discovered a similarity between the histopathologic features of MTX-induced liver toxicity and non-alcoholic steatohepatitis (NASH), a severe form of NAFLD, implying that MTX may exacerbate pre-existing NASH (13). As a result, psoriasis patients who have NASH risk factors such as diabetes or obesity are also classified as having a high risk of hepatotoxicity by psoriasis guidelines (14, 15), as they can develop liver fibrosis as a result of MTX toxicity at a lower cumulative dose.

Screening for liver fibrosis is critical because it identifies patients at risk, allowing elimination of hepatotoxic risk factors from those individuals proactively (such as by switching off hepatotoxic medications). Previous psoriasis guidelines recommend monitoring hepatotoxicity with routine blood sampling and liver biopsy (14, 15). However, a liver biopsy may be deemed excessively invasive, and many studies stated that routine liver enzyme tests are not sensitive enough to detect advanced liver fibrosis (16).

Recent research has demonstrated that non-invasive tests (NITs) are extremely beneficial in clinical practice, as they can reliably rule out the presence of advanced fibrosis in NAFLD patients (17). Patients classified as having a high risk of advanced fibrosis may be referred for additional testing, while those classified as having a low risk of advanced fibrosis may be offered lifestyle modifications and annual re-evaluation (17). NIT has been incorporated into the most recent AAD guidelines for MTX hepatotoxicity screening (18). NIT is recommended for a baseline evaluation of liver fibrosis; if NIT reveals a low risk of liver fibrosis, MTX can be initiated, and annual evaluations are recommended (18).

Liver stiffness measurement (LSM) by transient elastography (TE) is the most extensively used and verified non-invasive technique to date, and is frequently referred to as the NIT of choice by many. However, the tests to be used (serum biomarkers or imaging-based techniques) should be determined by local availability and usage context. For example, because TE performs poorly in obese individuals, alternative techniques such as magnetic resonance elastography or point shear wave elastography may be considered depending on local availability. While in resource-limited settings, liver fibrosis

scores calculated from simple laboratory values such as the Fibrosis-4 index (FIB-4) may be used to identify patients who require additional testing such as TE and liver biopsy (19).

The prevalence of advanced liver fibrosis in patients with psoriasis is not well established, which contributes to a lack of awareness regarding the risk of advanced liver fibrosis in psoriasis patients. To the best of our knowledge, no meta-analysis has been conducted to determine the prevalence or risk factors for liver fibrosis in patients with psoriasis. The objectives of this meta-analysis were to determine the prevalence of patients with psoriasis who were at a high or low risk of having advanced liver fibrosis, as well as to determine the risk factors for developing liver fibrosis. Our research, we believe, will inform future clinical decision-making regarding risk assessment, screening, and treatment of psoriasis patients in daily practice, thereby promoting more tailored care and improving patient outcomes.

Materials and methods

Study design

The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42022303886). The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (20) (Supplementary document). Electronic searches were conducted from database's inception to May 2022, using the PubMed, Embase, Scopus, and Cochrane Library databases. Using keywords and a controlled vocabulary, the search strategy was designed to retrieve all studies on psoriasis and NITs for liver fibrosis. There were no restrictions on the language or publication period of the searches. Conference abstracts were excluded. **Supplementary Table 1** provides details about the search strategy.

Study selection

Each article was reviewed independently by two reviewers (TY and AN), both at the title/abstract and full-text levels. Disagreements between the two reviewers regarding the studies' eligibility were resolved *via* discussion with a third reviewer (WI). Any observational study describing the prevalence and/or risk factors for liver fibrosis in patients with psoriasis or containing sufficient data to calculate the respective prevalence or odds ratio was included. We excluded studies in which more than 10% of patients had a known cause of liver fibrosis (except NAFLD), such as chronic viral hepatitis, or consumed excessive amounts of alcohol (more than 20 g/day). We also excluded studies on special populations such as pregnant patients, duplicate studies from the same cohort, and studies with a small sample size of fewer than 10.

Data extraction

Data were extracted from the included studies using a standardized format. The following data were collected: study type, study characteristics (primary author, country, publication year), patient characteristics [number of psoriasis patients, age, female percentage, weight, BMI, severity of psoriasis (PASI), age of onset, disease duration, type of psoriasis, presence of joint involvement, systemic treatment with duration and accumulative dosage, relevant laboratory data, alcohol intake, comorbidity], investigations [tests for liver fibrosis with associated cutoff(s), liver biopsy], and outcomes (prevalence of liver fibrosis detected, sensitivity and specificity, risk ratios of associated factors for significant fibrosis). Corresponding investigators were contacted *via* email if there was missing data. Two independent reviewers (TY and AN) extracted data, and discrepancies were resolved with the assistance of a third reviewer (WI).

Quality assessment

TY and AN independently assessed the quality of cohort and case-control studies using the adapted version of the Newcastle-Ottawa Scale (NOS) (21). The original NOS is a scoring tool comprised of seven items with nine scores that assesses how well the investigators selected their participants (score ranges from 0 to 4), the comparability of their results (score ranges from 0 to 2), and the applicability of the outcomes (score ranges from 0 to 3). We assigned up to one point for the sample size element of the selection score since smaller studies are prone to sampling bias; hence we had to lower the outcome score from 3 to 2. The higher the score, the higher the study's quality and the lower the likelihood of bias. Therefore, we classified studies as having high quality if they received a total score of 7 or more, fair quality if they received a score of 4–6, and low quality if they received a score of 4. Any discrepancies between reviewers regarding the risk of bias in specific studies were resolved through discussion with a third reviewer (PR).

Statistical analysis

Primary analysis assessed the prevalence of psoriasis patients with low and high risk of advanced liver fibrosis. The odds ratios for variables associated with liver fibrosis were also pooled using the inverse variance method. The "metaprop" and "metan" commands were used in Stata to summarize prevalence

and odds ratios, respectively (22). As significant heterogeneity across studies was expected, the DerSimonian–Laird random-effects model was used. Heterogeneity between studies was estimated using Higgins' and Thompson's I^2-statistics derived from Cochran's *Q*-test, with an I^2 value > 50% representing substantial heterogeneity (23).

The prevalence analyses were based on previously established cutoffs for low risk (LSM < 8 kPa, FIB-4 < 1.3, NFS < −1.455, FibroTest/FibroSure < 0.3) and high risk (LSM ≥ 10 kPa, FIB-4 > 3.25, NFS > 0.672, ELF > 9.8, FibroTest/FibroSure > 0.7) of advanced liver fibrosis (17, 24, 25). When different cutoffs were utilized in the included studies, we selected those closest to the established cutoffs and categorized them accordingly. Because TE is the current test of choice, it was chosen to represent the cohort's prevalence in studies that included multiple tests. When multiple NITs were used to determine the prevalence of a cohort and none of the NITs were TE, the NIT with the highest performance in detecting advanced fibrosis and cirrhosis was selected to represent the cohort's prevalence (17, 26). We could not locate any study demonstrating that an abnormal level of procollagen III amino-terminal peptide (PIIINP) is associated with an increased risk of advanced liver fibrosis; instead, all such studies were conducted regardless of fibrosis stage, and thus PIIINP studies were excluded from the quantitative analysis. Additionally, studies that lacked data specifically on psoriasis patients were excluded from the quantitative analysis.

To compare the prevalence estimated between groups and investigate the source of heterogeneity, subgroup analyses by the geography of research origin, type of NIT, and percentage of MTX users were conducted. We also conducted univariable meta-regression analyses on variables with at least ten observations to determine the effect of specific moderators on the prevalence of liver fibrosis across studies (e.g., age, sex, and BMI). Deeks funnel plots of the outcomes were created to assess for publication bias. Due to the possibility of bias revealed by funnel plots, the Egger linear regression test was used. All statistical analyses were conducted using STATA 16.0 (StataCorp LLC, College Station, TX, USA).

Results

Study characteristics

After removing duplicates, 2,619 references were screened by title/abstract. At the full-text stage, 128 full articles met our predefined selection criteria and were sought, 123 were retrieved, and we further excluded 82 references for the following reasons: conference abstract (n = 55), insufficient data (n = 9), wrong population (n = 8), review articles (n = 5), and editorial or comment (n = 5) (**Figure 1**). Forty-one studies, enrolling a total of 3,868 patients with psoriasis between 1988 and 2022, were included in the review (**Table 1**) (**Supplementary Table 2**).

We included thirty-seven studies in the quantitative analysis (19, 27–62), and twelve studies were only used qualitatively (55–66). Nine types of NIT were included: twenty-two TE (27, 29–34, 36–42, 44–46, 48, 49, 51–53, 66) (n = 2222), thirteen PIIINP (36, 54–65) (n = 947), six FIB-4 (19, 27, 28, 32, 34, 35) (n = 689), five NAFLD fibrosis score (NFS) (28, 32, 34, 35, 47) (n = 477), four FibroTest/FibroSure (34, 43, 50, 66) (n = 285), two AST to Platelet Ratio Index (APRI) (27, 34) (n = 180), two Enhanced Liver Fibrosis score (ELF) (54, 65) (n = 297), one Forns Index (34) (n = 63), one FibroMeter (34) (n = 64), one Hepascore (34) (n = 64), and one Fibrosis Probability Index (34) (n = 64) studies. Formulae of NITs mentioned in this review are shown in **Supplementary Table 3**.

Prevalence of high risk of advanced liver fibrosis

The pooled prevalence of 9.66% [95% confidence interval (CI): 6.92–12.75%, I^2 = 76.34%, **Figure 2A**] was found for psoriasis patients with a high risk of having advanced liver fibrosis. Studies conducted in Asian countries (6.64, 95% CI: 3.92–9.94%, I^2 = 59.08%) were found to have lower prevalence, compared to European countries (10.99, 95% CI: 7.66–14.79%, I^2 = 64.45%). Fifteen of the 18 studies that used NIT with a high-risk cutoff for advanced liver fibrosis performed TE as their NIT, and the prevalence was 9.36% (95% CI: 6.35–12.82%, I^2 = 76.34%). Subgroup analyses based on other NITs were not performed due to a limited number of studies. A lower prevalence (4.44, 95% CI: 1.17–9.22%, I^2 = 59.34%) was also found among studies that recruited MTX-naïve patients, compared to MTX-user cohorts (12.25, 95% CI: 6.02–20.08%, I^2 = 82.34%) (67) (**Supplementary Figure 1**).

Prevalence of low risk of advanced liver fibrosis

The pooled prevalence of 77.79% (95% CI: 73.23–82.05%, I^2 = 85.72%, **Figure 2B**) was found for psoriasis patients with a low risk of advanced liver fibrosis. Studies conducted in Europe (74.61, 95% CI: 68.88–79.96%, I^2 = 80.49%) were found to have lower prevalence than studies originated in Asia (84.02, 95% CI: 76.48–90.39%, I^2 = 88.04%). Twenty-one of the 27 studies that used NIT with a low-risk cutoff for advanced liver fibrosis used TE as their NIT, and the prevalence was found to be 78.51% (95% CI: 78.51–83.36%, I^2 = 85.97%). Whereas, in the studies that used FIB-4 (3 studies) and FibroTest/FibroSure (2 studies) as their NIT, the prevalences were 73.88 and 84.39%,

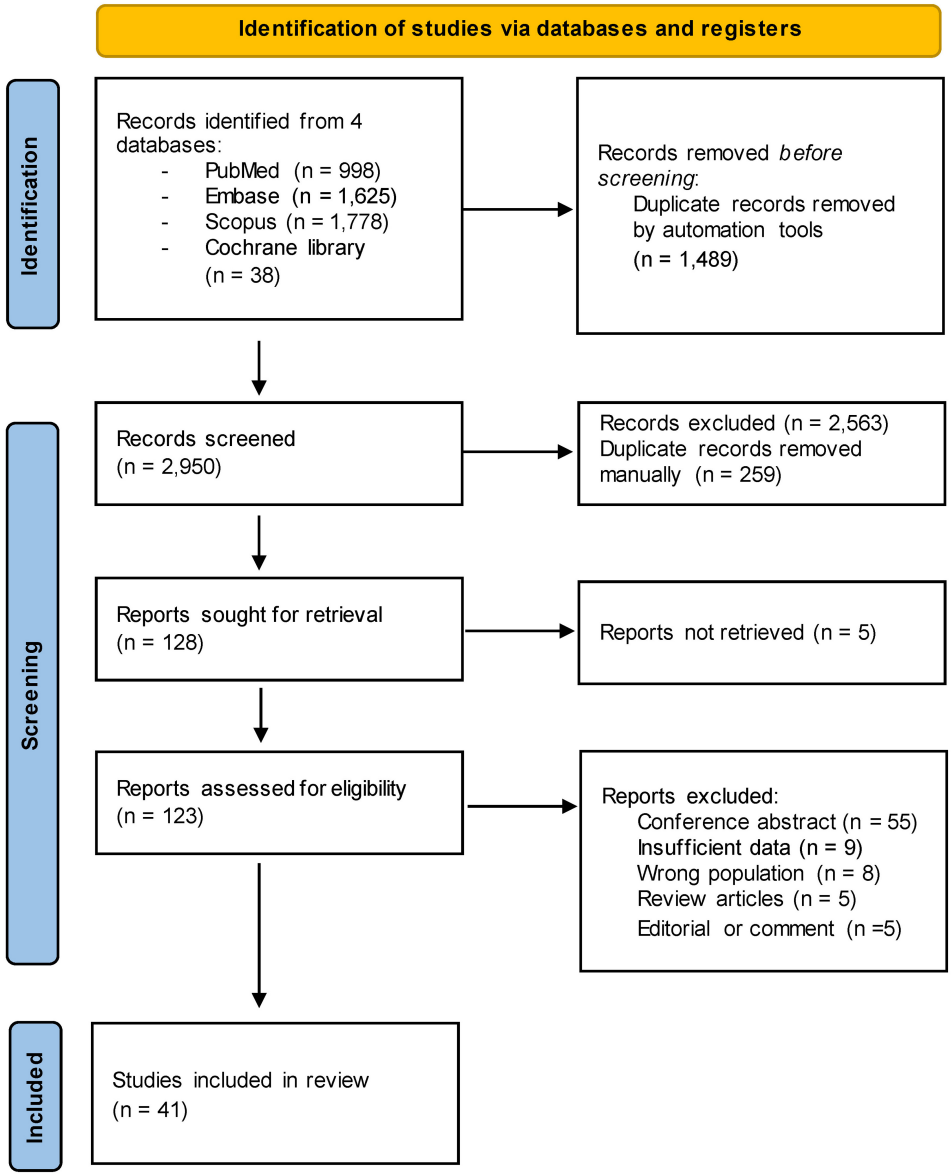

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of search strategy and included studies.

respectively. Similar prevalence was found for MTX-naïve and MTX-user cohorts, with pooled prevalence of 79.98% (95% CI: 65.79–91.23%, I^2 = 90.89%) and 71.95% (95% CI: 64.70–78.69%, I^2 = 83.54%) (Supplementary Figure 2).

Meta-regression

Meta-regression analysis did not identify age, BMI, PASI score, psoriasis duration, MTX cumulative dose, and the proportion of females, obesity, MTX user, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome as sources of heterogeneity. Supplementary Table 4 provides a summary of the meta-regression analysis.

Factors associated with liver fibrosis

The pooled odds ratios of 2.20 (95% CI: 1.42–3.40, I^2 = 0%), 3.67 (95% CI: 2.37–5.68, I^2 = 48.8%), 6.23 (95% CI: 4.39–8.84, I^2 = 42.4%), 2.82 (95% CI: 1.68–4.74, I^2 = 0%), 3.08 (95% CI: 1.90–4.98, I^2 = 0%), and 5.98 (95% CI: 3.63–9.83, I^2 = 17%) were found for age > 50 years, BMI > 30, diabetes mellitus, hypertension, dyslipidemia,

TABLE 1 Characteristics of included studies.

References	Country	Number of patients, age (years), female	Prevalence of patients with high and low risk of advanced liver fibrosis NIT and cutoff
Lee et al. (27)	Malaysia	**MTX group:** 61 patients, age 52.98 ± 15.5, female 29 (47.5%)	• **Low risk:** LSM < 6.5 kPa = 39 (63.9%), FIB-4 < 1.45 = 48 (78.7%), APRI < 0.7 = 54 (88.5%) • **High risk:** LSM > 11.5 kPa = 7 (11.5%), FIB-4 > 3.25 = 2 (3.3%), APRI > 1.0 = 5 (8.2%)
		MTX-naïve group: 56 patients, age 52.2 ± 15.1, female 24 (42.9%)	• **Low risk:** LSM < 6.5 kPa = 45 (80.4%), FIB-4 < 1.45 = 46 (82.1%), APRI < 0.7 = 49 (87.5%) • **High risk:** LSM > 11.5 kPa = 4 (7.1%), FIB-4 > 3.25 = 2 (3.6%), APRI > 1.0 = 6 (10.7%)
Mahajan et al. (30)	India	61 patients, age 47.5 ± 13.8, female 18 (29.5%)	• **Low risk:** LSM < 7.6 kPa = 61 (100%)
Takamura et al. (28)	Japan	65 patients, age 46 (range 40–54.5), female 16 (24.6%)	• **Low risk:** NFS < −1.455 = 75.4%, FIB-4 < 1.3 = 76.9%
Rattanakaemakorn et al. (31)	Thailand	132 patients, age 52, female 68 (51.5%)	• **Low risk:** LSM < 8 kPa = 123 (93.2%) • **High risk:** LSM ≥ 10 kPa = 7 (5.3%)
Belinchoìn-Romero et al. (32)	Spain	91 patients (87 with valid TE), age 53 (IQR 45.5–61.5), female 32 (35.2%)	• **Low risk:** LSM < 7.8 kPa = 72 (82.8%)
Brunner et al. (33)	Hungary	52 patients, age 54.0 ± 13.4, female 26 (50%)	• **Low risk:** LSM < 8.2 kPa = 72 (82.8%) • **High risk:** LSM > 9.7 kPa = 14 (26.9%)
Cervoni et al. (34)	France	66 patients (49 TE, 63 Forns index, 65 APRI, 65 FIB-4, 64 FPI, 64 Hepascore, 64 NFS, 64 Fibrometer, 61 FibroTest), age 54 ± 2, female 39%	• **Low risk:** LSM < 7.1 kPa = 90.5%, FibroTest < 0.49 = 88.6%, Hepascore < 0.5 = 92.2%, Forns Index < 6.9 = 90.5%, FPI < 0.8 = 87.5%, FibroMeter < 0.49 = 78.1% • **High risk:** FIB-4 > 3.25 = 4.6%, NFS > 0.676 = 6.3%, APRI > 1.5 = 3.1%
Yim et al. (19)	Spain	39 patients, age 49.8, female 24 (61.5%)	• **Low risk:** FIB-4 < 1.45 = 26 (66.7%) • **High risk:** FIB-4 > 3.25 = 1 (2.6%)
Rivera et al. (35)	Spain	457 patients (280 NFS, 392 FIB-4), age 53.3 ± 14.0, female 199 (43.5%)	• **Low risk:** FIB-4 < 1.3 = 73.8%, NFS < −1.455 = 62.8%
Koch, (36)	New Zealand	66 patients, age 51.2 ± 14.0, female 34 (51.5%)	• **Low risk:** LSM < 7.1 kPa = 37 (56.1%) • **High risk:** LSM > 9 kPa = 23 (34.8%) • PIIINP > 4.2 μg/L = 29 (43.9%)
Mahajan et al. (29)	India	134 patients, age 44.13 ± 13.86, female 40 (30.3%)	• **Low risk:** LSM < 7 kPa = 101 (75.4%) • **High risk:** LSM ≥ 9 kPa = 16 (6.7%)
Magdaleno-Tapial et al. (37)	Spain	71 patients, age 46.7 ± 14 years, female 24 (33.8%)	• **Low risk:** LSM < 7.7 kPa = 61 (85.9%) • **High risk:** LSM ≥ 9.5 kPa = 6 (8.5%)
Kumar and Ganapathi, (38)	India	102 patients, age 42.12, females 61 (59.8%)	• **Low risk:** LSM < 7.5 kPa = 83 (81.3%) • **High risk:** LSM ≥ 10 kPa = 8 (7.8%)
Neema, (39)	India	82 patients, age 47.04 ± 12.45, female 20 (24.4%)	• **Low risk:** LSM < 7 kPa = 59 (72.0%)
Ortolan et al. (40)	Italy	**PsA group:** 43 patients, age 60.2 ± 8.4, female 11 (25.6%)	• **Low risk:** LSM < 7 kPa = 69%
		without PsA group: 33 patients, age 54.5 ± 19.6, female 12 (36.4%)	• **Low risk:** LSM < 7 kPa = 72%
Ben Lagha et al. (41)	Tunisia	88 patients, age 45.6 ± 14.3, female 48 (42.9%)	• **Low risk:** LSM < 7 kPa = 71 (80.7%) • **High risk:** LSM > 9.5 kPa = 5 (5.7%)
Maybury et al. (42)	United Kingdom	400 patients (333 TE), age 49.5 ± 13, female 108 (27.2%)	• **Low risk:** LSM < 7 kPa = 265 (79.6%) • **High risk:** LSM 8.7 kPa = 47 (14.1%)
Van den Reek et al. (55)*	Netherlands	**Elevated PIIINP:** 41 patients, age 55.9 ± 16.5, female 20 (48.8%)	• Elevated PIIINP = 41 (22.4%)
		No elevated PIIINP: 142 patients, age 55.9 ± 16.5, female 20 (48.8%)	

(Continued)

TABLE 1 (Continued)

References	Country	Number of patients, age (years), female	Prevalence of patients with high and low risk of advanced liver fibrosis NIT and cutoff
Van der Voort et al. (54)	Netherlands	**PsA group:** 151 patients, age 52.8 ± 11.7 years, female 70 (46.3%)	• **High risk:** ELF > 9.8 = 20 (13.2%) • PIIINP > 12.2 μg/L = 7 (6%) · PIIINP > 15.3 μg/L = 6 (5.2%)
		Without PsA group: 119 patients, age 49.8 ± 14.3, female 45 (37.8%)	• **High risk:** ELF > 9.8 = 25 (21%) • PIIINP > 12.2 μg/L = 9 (6%) • PIIINP > 15.3 μg/L = 2 (1.3%)
Bauer et al. (43)	United States	107 patients (69 FibroSure), age 83.3 ± 13.5, female 57 (53.2%)	• **Low risk:** FibroSure < 0.21 = 50 (71.5%)
Talme et al. (44)	Sweden	**Biologic group:** 32 patients, age 48 (range 18–76), female 6 (18.8%)	• **Low risk:** LSM < 6.5 kPa = 20 (62.5%) • **High risk:** LSM > 11.5 kPa = 1 (3.1%)
		MTX duration > 24 months group: 122 patients, age 60 (range 22–82), female 52 (41.9%)	• **Low risk:** LSM < 6.5 kPa = 76 (62.3%) • **High risk:** LSM > 11.5 kPa = 11 (9%)
		MTX duration ≤ 24 months group: 47 patients, age 50 (range 20–76), female 17 (34.7%)	• **Low risk:** LSM < 6.5 kPa = 32 (68.1%) • **High risk:** LSM > 11.5 kPa = 3 (6.4%)
Rongngern et al. (45)	Thailand	41 patients, age 51.2 ± 11.6, female 17 (41.5%)	• **Low risk:** LSM < 7.1 kPa = 31 (75.6%) • **High risk:** LSM ≥ 10 kPa = 3 (7.3%)
Pongpit et al. (46)	Thailand	165 patients, age 49.2 ± 14, female 90 (54.5%)	• **Low risk:** LSM < 7 kPa = 147 (89.1%) • **High risk:** LSM > 9.5 kPa = 11 (6.7%)
Gisondi et al. (47)	Italy	124 patients (55 NFS), age 55 ± 12, female 55 (44%)	• **Low risk:** NFS < −1.455 = 30 (54.5%) • **High risk:** NFS > 0.676 = 4 (7.3%)
Van der Voort et al. (53)	Netherlands	74 patients, age 71.2 ± 6.5 years, female 33 (44.6%)	• **High risk:** LSM > 9.5 kPa = 6 (8.1%)
Martyn-Simmons et al. (65)*	United Kingdom	27 patients, age 56 ± 2.7 years, female 9 (33%)	NR
Lynch et al. (48)	Ireland	77 patients (50 TE, 70 FibroTest, 51 PIIINP), age 51 (range 22–85), female 36 (46.8%)	• **Low risk:** LSM < 7 kPa = 41 (82%), FibroTest < 0.31 = 59 (84.3%) • Serial PIIINP (1 year before TE) > 4.2 μg/L = 9/51 (17.6%) • Serial PIIINP (1 year before FibroTest) > 4.2 μg/L = 3/34 (8.8%)
Bray et al. (49)	United Kingdom	21 patients (10 TE), age 59 (range 41–83), female 9 (42.9%)	• **Low risk:** LSM < 8 kPa = 6 (60%) • **High risk:** LSM ≥ 10 kPa = 3 (30%)
Madanagobalane and Anandan, (50)	India	58 patients, age 46.9 ± 1.15, female 12 (20.7%)	• **Low risk:** FibroTest stage < F2–F3 = 94.9%
Seitz et al. (51)	Switzerland	**TNF-naïve group**: 20 patients, age 51.9 ± 14.1, female 6 (30.0%)	• **Low risk:** LSM < 8 kPa = 14 (70%)
		TNF group: 23 patients, age 51.3 ± 10.9, female 7 (30.4%)	• **Low risk:** LSM < 8 kPa = 22 (95.7%)
Laharie et al. (52)	France	111 patients, age 56.2 ± 12.2, female 30 (27%)	• **Low risk:** LSM < 7.9 kPa = 99 (89.2%)
Lindsay and Gough, (56)*	United Kingdom	48 patients, age 54.4 ± 11, female NR	• Elevated PIIINP = 16 (33.3%)
Berends et al. (66)*	Netherlands	24 patients, age 55 (range 34–73), female 13 (54.2%)	NR
Khan et al. (64)*	United Kingdom	15 patients, age 56.4 ± 12.8, female 7 (46.7%)	NR
Zachariae et al. (57)*	Denmark	70 patients, age NR, female 31 (44.3%)	• PIIINP > 4.2 μg/L = 6 (8.6%)
Zachariae et al. (59)*	Denmark	11 patients, age NR, female NR	• PIIINP > 4.2 μg/L = 0
Boffa et al. (60)*	United Kingdom	87 patients, age NR, female NR	• PIIINP > 4.2 μg/L = 41 (47.1%)
Oogarah et al. (63)*	United Kingdom	22 patients, age 42.6 (22–72), female 8 (36.4%)	• Elevated PIIINP (first assay) = 6/11 (54.5%) • Elevated PIIINP (second assay) = 4/22 (18.2%)

(Continued)

TABLE 1 (Continued)

References	Country	Number of patients, age (years), female	Prevalence of patients with high and low risk of advanced liver fibrosis NIT and cutoff
Zachariae et al. (58)*	Denmark	170 patients, age NR, female NR	• PIIINP > 4.3 μg/L = 24 (21.8%)
Mitchell et al. (61)*	United Kingdom	51 patients, age 47 (range 22–69), female NR	• PIIINP > 11.8 μg/L = 35 (68.6%)
Risteli et al. (62)*	Denmark	24 patients, age 50 (range 32–75), female 10 (41.7)	• PIIINP > 4.2 μg/L = 8 (33.3%)

APRI, aspartate aminotransferase to platelet ratio index; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; FPI, fibrosis probability index; LSM, liver stiffness measurement; MTX, methotrexate; NFS, non-alcoholic fatty liver disease fibrosis score; NR, not reported; PsA, psoriasis arthritis; PIIINP, procollagen III amino-terminal peptide; TE, transient elastography; TNF, tumor necrosis factor alpha blockers; UK, United Kingdom; USA, United States. *These studies are not included in the quantitative analysis.

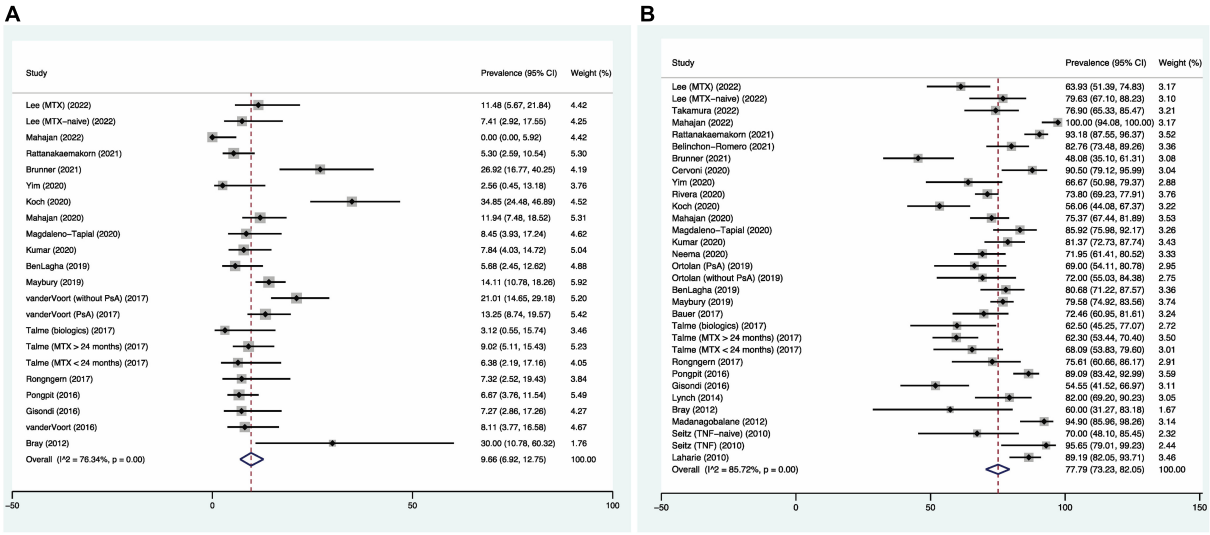

FIGURE 2
Forest plots for pooled prevalence of psoriasis patients with high risk **(A)** and low risk **(B)** of advanced liver fibrosis.

and metabolic syndrome, respectively. Pooled odds ratios of 1.10 (95% CI: 0.87–1.39, I^2 = 3.2%), 1.67 (95% CI: 0.94–2.95, I^2 = 37%), 1.30 (95% CI: 0.82–2.06, I^2 = 30.6%), and 1.58 (95% CI: 0.91–2.75, I^2 = 0%) were found for male, PASI > 10, psoriatic arthritis, and cumulative MTX dose > 1500 mg, respectively. **Supplementary Figure 3** depicts the forest plots, and **Table 2** summarizes the details.

Quality assessment and publication bias

Supplementary Table 5 summarizes the quality assessment scores for the included studies. The mean quality assessment score was 8.1 (range: 4–9), with 34 high-quality studies and seven of moderate quality. Publication bias was assessed through funnel plots, which were found to be slightly asymmetric (**Figure 3**), but Egger's tests (p = 0.86 and 0.33) indicate no publication bias.

Discussion

In this systematic review and meta-analysis, we discover that 9.66% of people with psoriasis are at high risk of having advanced liver fibrosis, necessitating further investigation and management. While 77.79% of the population is considered low risk, the remaining 22.21% requires further testing. Subgroup analysis revealed a lower prevalence of advanced liver fibrosis in Asian studies (6.64%), compared to European studies (10.99%). It is highly improbable to be the result of NAFLD alone, as a recent meta-analysis (68) discovered comparable prevalence of NAFLD in Asia (30.5%) and Europe (30.9%). Further investigation of the factors that contribute to geographic disparity may provide additional insights on risk factors for advanced liver fibrosis in patients with psoriasis.

We are able to identify significant risk factors for liver fibrosis, including advanced age, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome. On the other hand, disease-related factors such as severe psoriasis

TABLE 2 Summary of pooled odds ratios of variables associated with significant liver fibrosis.

Variables	Pooled OR (95% CI)	I^2	References	Number of patients
Age	2.20 (1.42–3.40)	0%	(31, 38, 44, 45)	344
Male	1.10 (0.87–1.39)	3.2%	(27, 29, 31, 35, 36, 38, 39, 41, 42, 44–46)	1,851
PASI > 10	1.67 (0.94–2.95)	37%	(27, 31, 41, 46)	500
Psoriatic arthritis	1.30 (0.82–2.06)	30.6%	(27, 35, 36, 46)	738
Cumulative MTX dose >1500 mg	1.58 (0.91–2.75)	0%	(29, 39, 45, 46)	422
BMI > 30	3.67 (2.37–5.68)	48.8%	(27, 31, 36, 41, 44)	602
Diabetes mellitus	6.23 (4.39–8.84)	42.4%	(27, 31, 35, 36, 41, 44–46)	1,200
Hypertension	2.82 (1.68–4.74)	0%	(27, 41, 45, 46)	409
Dyslipidemia	3.08 (1.90–4.98)	0%	(27, 31, 41, 45, 46)	541
Metabolic syndrome	5.98 (3.63–9.83)	17%	(35, 39, 41, 45, 46)	768

BMI, body mass index; MTX, methotrexate; OR, odds ratio; PASI, psoriasis area severity index.

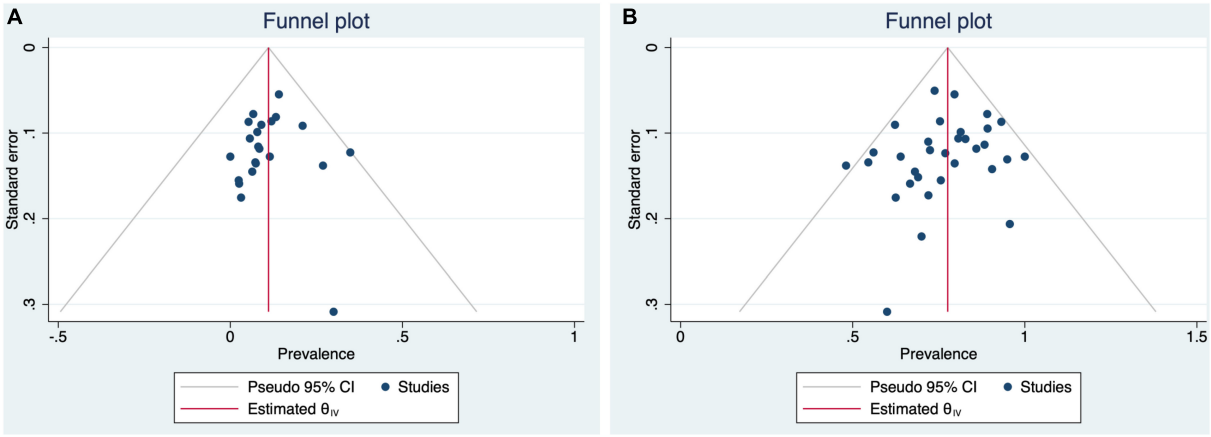

FIGURE 3
Funnel plots for pooled prevalence of psoriasis patients with **(A)** high risk and **(B)** low risk of advanced liver fibrosis analyses.

and psoriatic arthritis were not found to have a statistically significant association with liver fibrosis. Our findings are consistent with previous meta-analyses (4–6) which found that NAFLD was associated with the development of liver fibrosis in patients with psoriasis. Furthermore, a previous study by Ortolan et al. also reported that insulin resistance was the main determinant of liver fibrosis, and psoriatic arthritis, a disease-related inflammation, was not a significant predictor (40). As the evidence for MTX-induced liver fibrosis is anecdotal and based on poorly controlled data, metabolic syndrome and its risk factors, such as insulin resistance, could be considered a more significant risk factor for liver fibrosis than MTX use (69–75).

Since the introduction of NITs, routine liver biopsy on psoriasis patients has become unethical. The most recent joint AAD-NPF guideline does not recommend a baseline liver biopsy, regardless of the presence of risk factors for liver fibrosis (18). Liver biopsies are now reserved for patients who have been classified non-invasively as having a high risk of advanced liver fibrosis and who have been advised to undergo the procedure by a gastrointestinal specialist (18).

There is limited evidence regarding the performance of different NITs in detecting advanced liver fibrosis in the psoriasis population, which may contribute to their underutilization. Only three studies using TE reported sensitivity and specificity values ranging from 50% (45, 66) to 100% (49) and 67 (49) to 88% (66), respectively, for detecting significant liver fibrosis in psoriasis patients. Previous meta-analysis (16) reported a pooled sensitivity and specificity for TE of 60 and 80%, respectively; however, the number of patients included was limited (two studies, $n = 34$).

In the past, PIIINP was used to detect liver fibrosis in patients with psoriasis taking MTX and was found to have a pooled sensitivity and specificity of 74 and 77% (16), respectively, for any stage of liver fibrosis. In addition to not being widely available in many countries, including the United States (18), it is well-established that PIIINP has other

significant limitations, including the fact that it only measures active fibrogenesis and may be falsely elevated in inflammatory conditions such as arthritis (76–82). We observed that the majority of PIIINP studies were small, old, and received lower scores by NOS. Since the introduction of other NITs, the number of published PIIINP studies has decreased. In the last decade, only four studies (36, 48, 54, 55) involving PIIINP have been conducted, and none of them have recommended PIIINP over other tests. More studies on PIIINP are needed to justify its usage, particularly on how a particular level of PIIINP would be associated with high risk of advanced liver fibrosis. In the meantime, we concur with Patel that other NITs, such as FIB-4, may be preferred because they are more consistent with current recommendations (83).

There is an urgent need for a safe, non-invasive, and efficient screening test to aid in the diagnosis or exclusion of advanced liver fibrosis in psoriasis patients. Many studies (19, 27, 34, 37) attempted to assess the risk of liver fibrosis without performing a biopsy; however, we felt that the efficacy of NITs had not been established in the psoriasis population. Future large-scale, prospective, histologically based studies comparing the performance of various tests for the detection of liver fibrosis are necessary to determine which tests are the most effective and safe non-invasive screening tools for liver fibrosis.

Methotrexate is one of the most frequently prescribed systemic medications for psoriasis patients due to its affordability and efficacy. In the past, the AAD recommended a routine liver biopsy for psoriasis patients who had received 3.5 to 4 g of MTX cumulative dosage due to the long-held belief that drug accumulation directly causes liver injury (84). In high-risk patients, it was recommended that liver biopsy be performed at a lower cumulative MTX dose of 1.0 to 1.5 g. The relationship between cumulative MTX dose and the risk of liver fibrosis in psoriasis patients remains controversial. A previous meta-analysis of histology-based studies found that MTX-induced liver toxicity is associated with total cumulative dose (85). In contrast, a recent systematic review of eight observational studies involving 429 psoriasis patients reported no clear association between cumulative MTX dose and liver fibrosis (69). Additionally, many observational studies (27, 33, 46, 48, 52, 66, 86) did not find any association between MTX cumulative dose and the risk of liver fibrosis. Lynch et al. discovered an association between MTX cumulative dose and abnormal FibroTest results, but not with TE (48). Bauer et al. discovered that a higher cumulative MTX dose was associated with a higher FibroSure score in women, but not in men (43). In our meta-analysis, we found that MTX-naive cohorts (4.44%) have a lower prevalence of patients at high risk for advanced liver fibrosis than MTX-using cohorts (12.25%). However, no statistically significant association between cumulative MTX doses greater than 1,500 mg and an increased risk of liver fibrosis was found. Additional research into the association between MTX use and liver fibrosis would aid in determining how strict a fibrosis screening protocol should be following MTX prescription.

The present results should be interpreted in the light of some limitations. First, there was substantial heterogeneity found in some of our analyses, specifically in the pooled prevalence analyses. Through multiple subgroup analyses and meta-regression, we investigated the source of the heterogeneity; however, we were unable to determine its source. Additionally, there are limitations to the fibrosis assessment. In contrast to previous reviews (69, 85) that included studies that assessed liver fibrosis through liver biopsies, we chose to examine the prevalence of patients at risk for liver fibrosis and the risk factors for liver fibrosis using NITs, as these are the method of choice when evaluating liver fibrosis for the first time in clinical practice.

Conclusion

This meta-analysis sheds light on the burden of advanced liver fibrosis in psoriasis patients. We hope to inform practitioners and future researchers about the high prevalence of advanced liver fibrosis in psoriasis patients, as well as the critical need for liver fibrosis screening. Approximately 10% of the psoriasis population is at high risk of having advanced liver fibrosis, while only around 78% are at low risk. Patients over the age of 50 with comorbidities such as obesity, diabetes mellitus, hypertension, dyslipidemia, and/or metabolic syndrome are at an increased risk of developing liver fibrosis, necessitating surveillance. Further research is required to determine why the prevalence of patients at high risk for advanced liver fibrosis is higher in European countries, the performance of NITs for the detection of advanced liver fibrosis in patients with psoriasis, and the extent of association between MTX use, particularly its cumulative dose, and liver fibrosis.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

WI, PR, and PS: conceptualization. PS, TY, and AN: methodology. PS and PR: validation. TY and WI: formal analysis. TY, AN, and WI: investigation. TY: data curation. TY, AN, WI, and PR: writing – original draft preparation. PS: writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1068157/full#supplementary-material

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Bloodletting cupping combined with conventional measures therapy for psoriasis: A systematic review and meta-analysis of randomized controlled trials

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Background: Psoriasis is an immune-mediated inflammatory disease prone to recurrence. Some studies indicated that bloodletting cupping combined with conventional measures therapy had been proposed as a treatment strategy for psoriasis. Therefore, we performed a systematic review and meta-analysis to assess the effectiveness of this combination therapy in reducing the severity of disease in patients with psoriasis.

Methods: The following electronic databases were searched for articles from January 1, 2000 to March 1, 2022: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), Wan-Fang Database, and China National Knowledge Infrastructure (CNKI). The language was not restricted while performing the search. The quality of articles was evaluated using Rev. Man 5.4 software (provided by the Cochrane Collaboration), comparing bloodletting cupping combined with conventional measures therapy to conventional measures treatments. The studies obtained randomized controlled trials (RCTs) of bloodletting cupping combined with conventional standard treatment for treating psoriasis. Two trained researchers (Xiaoyu Ma and Jiaming He) independently reviewed the literature, extracted data based on exclusion and inclusion criteria, and assessed the quality of the included studies. We estimated the aggregate data using a random effects model.

Findings: We identified 164 studies. Ten studies met the inclusion criteria for the meta-analysis. The primary outcome indicator was the total number of effective individuals. Secondary outcomes included the Psoriasis Area and Severity Index (PASI), adverse effects, and the Dermatology Life Quality Index (DLQI). Compared with conventional treatments, bloodletting cupping combined with conventional medicine yielded an improved total effective number of persons (RR=1.15, 95%CI: 1.07 to 1.22, $p<0.00001$), PASI (MD=−1.11, 95%CI: −1.40 to −0.82, $p<0.00001$) and DLQI scores (MD=−0.99, 95%CI: −1.40 to −0.59, $p<0.0001$). We found no significant difference in adverse reactions (RR=0.93, 95%CI: 0.46 to 1.90, $p=0.85$). The heterogeneity test showed the total effective numbers ($p<0.00001$, $I^2=43\%$) and PASI ($p<0.00001$, $I^2=44\%$) and DLQI scores ($p<0.00001$, $I^2=0\%$).

Interpretation: Bloodletting cupping combined with conventional treatment can achieve the ideal treatment for psoriasis. However, the combined treatment in psoriasis needs to be further evaluated in high-quality RCTs with large sample sizes to enable future studies in clinical use.

KEYWORDS

psoriasis, bloodletting cupping, total effective numbers, PASI, randomized controlled trials, meta-analysis

1. Introduction

Psoriasis is a common, chronic, and inflammatory disorder characterized by a strong genetic predisposition and autoimmune pathogenic traits associated with many other medical conditions (1, 2). The worldwide prevalence varies from approximately 0.14% in East Asia to 1.99% in Oceania, with incidence and prevalence closely related to age but varying by region (3). In 2014, the WHO passed a resolution recognizing psoriasis as an incurable, chronic, non-contagious, painful, disfiguring, and debilitating disease (4). The expression of psoriasis depends on gene interaction with the environment (5). In addition, psoriasis is associated with many diseases, such as hypertension, obesity, psoriatic arthritis, depression, type 2 diabetes, and cardiovascular disease (2). In terms of medication, treatment options for psoriasis include the topical use of vitamin D analogs, glucocorticoids, keratolytics, and phototherapy. Traditional oral therapy includes cyclosporine, amitriptyline, and methotrexate. When the disease is moderate to severe, psoriasis usually requires systemic treatment (5). Patients with moderate-to-severe psoriasis have a high risk of death, mainly attributed to cardiovascular disease (6–8). Despite the availability of safe and effective treatment options for moderate-to-severe psoriasis, there is dissatisfaction with the efficacy of the treatment, underutilization, and poor adherence (9–12). A study has reported that methotrexate is associated with a high incidence rate of hepatotoxicity (13). Despite the proven efficacy of corticosteroids in treating psoriasis, studies have shown that it has potential side effects, particularly skin atrophy and adrenal suppression associated with prolonged and widespread use (14, 15). In addition, to avoid long-term immunosuppressive effects, many drugs are not allowed to be used in children, and some experts use etretinate as the treatment of choice, but long-term use can also cause skeletal changes in children (16). The presence of hepatic and renal impairment in the elderly increases the incidence of adverse reactions to cyclosporine and methotrexate (17). In addition, in patients with metabolic syndrome, drugs such as etretinate, methotrexate, and cyclosporine have been shown to have adverse effects on hypertension and liver injury (18). Biological therapies are currently emerging in the treatment of psoriasis, and Interleukin (IL)-23 inhibitors are the latest class of biological agents available for the treatment of psoriasis, which has shown good results, including showing sustainable efficacy and tolerable side effects (19, 20). Despite this, there are some safety issues or the induction of new diseases due to the diversity of patients' conditions during the treatment (21, 22). Available Current therapies have not been shown to reverse this natural damage reliably. However, the cost is also an issue of concern. Thus, there is a pressing need for a more effective, less toxic, and cost-effective treatment to alternative therapy for psoriasis.

Bloodletting cupping, also known as blood cupping or blood-letting puncture and cupping therapy, referring to a superficial needle prick in the skin, followed by cupping, is a substantial part of complementary alternative medicine (CAM). Cupping after bloodletting can enhance the therapeutic effect of blood cupping. It treats diseases by unblocking the meridians and Qi and Blood (23). Moreover, the mechanism of cupping therapy is to influence local soft tissue microcirculation through mechanical pressure under a vacuum, which enhances capillary vascular permeability, increases regional blood circulation flow, improves metabolism, and stimulates the body's immune response for feedback regulation (24, 25). During cupping, the most common is the appearance of cupping marks, which often appear as red petechiae or purple petechiae. Based on the above, eliminating a certain amount of blood through cupping can eliminate the accumulated harmful substances and facilitate the infusion of fresh blood. The ideal treatment would be one that can combine the ability to control the condition with a low tendency to cause adverse effects and unstable therapeutic efficacy. The further action of cupping can promote the further increase of metabolism, thus producing local and systemic regulatory results. It is mainly used to treat low back pain, soft tissue injuries or sprains, pain caused by external rheumatism, etc. Blood-letting puncture and cupping are widely used to treat psoriasis because of their relatively faster and superior effectiveness, simple manipulation, short duration of treatment, fewer adverse effects, and lower medical expenses. However, applying the method to patients with anemia, those susceptible to bleeding, or where big blood vessels lie is inadvisable (26).

Since ancient times, CAM has played an irreplaceable role in treating disease and human health and has been recognized by various countries (27). In this case, there is considerable interest in the potential benefits of bloodletting cupping combined with conventional measures therapy for psoriasis. Moreover, there is a robust clinical rationale to support such a strategy. However, its ideal role in clinical treatment strategies of effectiveness and safety on psoriasis has not been established due to the low qualities of these studies. We recognized that individual studies alone might not provide sufficient data to influence clinical practice; we attempted to assess this therapy's potential role objectively. Therefore, we conducted a systematic review and meta-analysis of RCTs to determine the impact of combination therapy on critical outcomes such as overall effectiveness and Psoriasis Area and Severity Index (PASI) in patients with psoriasis.

2. Methods

We report this systematic review and meta-analysis by the PRISMA 2020 statement (28) and have registered with Prospero (number CRD42022314260).

2.1. Search strategy

Two researchers (Xiaoyu Ma and Minghui Zhao) independently selected comprehensive articles published between January 1, 2000 and March 31, 2022 by searching the following online databases: Embase, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), Wan-Fang Database, Chinese Scientific Journal Database (VIP database), and China National Knowledge Infrastructure (CNKI). The analysis included the total study population of the randomized, blind,

and placebo-controlled trial using bloodletting cupping combined with conventional measures therapy for treating psoriasis. Two researchers (Xiaoyu Ma and Jiaming He) independently reviewed the literature against inclusion and exclusion criteria and extracted data to assess the quality of included studies. The complete detailed search string is as follows: ((("Psoriasis"[Mesh]) OR (((((Psoriasis[Title/Abstract]) OR (Psoriases[Title/Abstract])) OR (Pustulosis Palmaris et Plantaris[Title/Abstract])) OR (Palmoplantaris Pustulosis[Title/Abstract])) OR (Pustular Psoriasis of Palms[Title/Abstract] AND Soles[Title/Abstract]))) AND (((((bloodletting cupping[Title/Abstract]) OR (blood cupping[Title/Abstract])) OR (acupuncture cupping[Title/Abstract])) OR (blood-letting puncture[Title/Abstract] AND cupping[Title/Abstract])) OR (pricking[Title/Abstract] AND cupping[Title/Abstract]))) AND (((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])).

2.2. Study selection and data extraction

2.2.1. Study selection

We regarded studies as eligible for inclusion:

- I randomized controlled trials (RCTs)
- II at least 2 weeks duration of intervention
- III receiving bloodletting cupping combined with conventional measures therapy strategies
- IV comparing with conventional measures therapy strategies
- V outcomes including at least adverse reactions, the total effective number of people, and PASI and DLQI scores
- VI adult humans with diagnosed psoriasis of any type

The exclusion criteria were as follows:

- I involved a non-RCT design
- II participants were children
- III outcome measures were not comprehensive
- IV compared bloodletting cupping combined with conventional therapy to other treatment options

2.2.2. Data extraction

First, two reviewers (Minghui Zhao and Dilong Li) independently read the title and abstract and conducted a preliminary review of the article. At the same time, a third reviewer (Jingyan Kong) decided in the event of a difference of opinion. Two researchers (Xiaoyu Ma and Jiaming He), according to the inclusion and exclusion criteria, independently examined the study by reading the full text, and a third researcher (Fang Yang) performed the assessment. Data extraction is completed by using the established extraction table. We extracted the characteristics of the following data from each eligible study: ① the first author, ② year of publication, ③ the number of cases in the treatment groups and control groups, ④ intervening measures, ⑤ treatment period (days), and ⑥ outcome indicators.

2.3. Assessment of risk of bias

Two researchers assessed the risk of bias according to the 7-item criteria of Rev. Man 5.4 (The Cochrane Collaboration). Two trained reviewers (Xiaoyu Ma and Dilong Li) independently assessed each included study based on its methodological quality, and disagreements were resolved through the discussion with a third author (Fan Yang). The main content of the assessment included some of the following: random allocation method, allocation options hidden, blind process, completeness of result data, selective or non-selective reporting of study results, and availability of other sources of bias (Figure 1). In the aforementioned case, a "yes" response meant a low risk of bias, a "no" response meant a high risk of bias, and an "uncertain" answer meant an unclear risk of bias (Table 1).

2.4. Statistical analysis

All RCTs were conducted with Rev. Man 5.4 software. Random effects models were used to calculate relative ratios (RR) and 95% confidence intervals (CI) for the primary outcome (dichotomous data), and mean differences (MD) and 95% CI were used to assess continuous variables. The I^2 test assessed the heterogeneity of the included data if the I^2 value was <50%, indicating a low statistical heterogeneity among the studies, and was accepted. Otherwise, if the I^2 value was >50%, it shows a high statistical heterogeneity among the studies. The random effects model was considered for all data analysis. A funnel plot was conducted to identify the publication bias when the number of the included studies for one outcome was more than 10. We consider the primary outcome for each study was the total number of influential individuals. Secondary outcomes were adverse effects, PASI, and DLQI scores.

3. Results

3.1. Literature search results

We identified 164 pieces of initial literature of which 98 duplicate references were excluded and 66 were included. A total of 56 articles were excluded, screening titles and abstracts identified 33, and 23 records were excluded by reading the full text, and the screening process of the 10 included studies (29–38) is shown in Figure 2. A total of 833 patients were eligible for inclusion in the meta-analysis. Of these, 422 patients were in the treatment groups, and the other 411 patients were in other groups. In our included studies, participants in the 10 studies that met the criteria were Chinese. The study period of three studies (29–31) was 28 days, that of three studies (32–34) was 14 days, that of three studies (35, 36, 38) was 30 days, and that of only one study (37) was 90 days. We used first authors, year of publication, duration of treatment, number of cases, interventions in treatment and control groups, and outcomes as basic information for inclusion in meta-analyses. For more details, see Table 2.

3.2. Quality assessment

3.2.1. Total effective numbers

A total of 10 studies, with 411 participants in the control groups and 422 in the experimental groups, reported the efficacy of bloodletting puncture and cupping in combination with conventional measures for treating psoriasis. Figure 3 shows a low statistical heterogeneity ($p < 0.00001$, $I^2 = 43\%$) between the control and

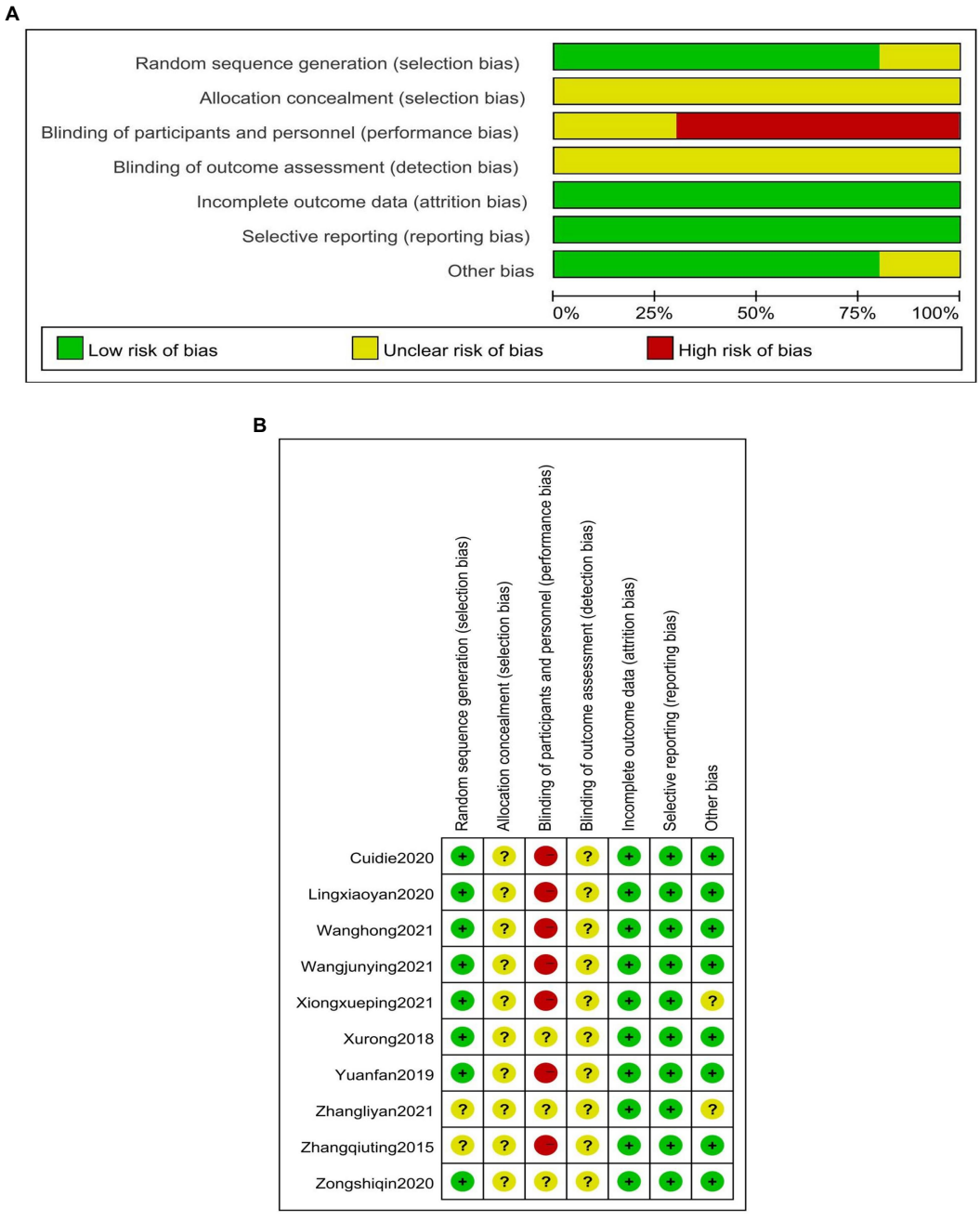

FIGURE 1
(A) Methodological quality assessment of the included studies. **(B)** Methodological quality assessment of the included studies.

treatment groups. The aggregated results indicated a clear difference in the two groups (RR = 1.15, 95%CI: 1.07 to 1.22, $p < 0.00001$). Figure 3 shows the meta-analysis of efficiency between the treatment and control groups ($p < 0.00001$, $I^2 = 43\%$). Pooled results showed a significant difference between the control and treatment groups (RR = 1.15, 95% CI: 1.07 to 1.22, $p < 0.00001$). Figure 3 shows the results of the meta-analysis of the total effective numbers between the treatment and control groups.

3.2.2. Psoriasis area and severity index

The Psoriasis Area and Severity Index (PASI) is a combination of the severity of the lesions (including erythema, infiltrates, and scaling) and the area of the lesions for psoriasis. A specific formula is used to calculate the final score, often used to assess the severity of psoriasis, and is an internationally accepted scale for scoring the severity of psoriatic lesions (39). Of the 10 included studies, five studies involved the application of the PASI. It consisted of 208 patients in the treatment groups and 205 patients in the control groups. The I^2 test was used to test for heterogeneity. We used the random effects model. The results show a low statistical heterogeneity between the two groups ($p < 0.00001$, $I^2 = 44\%$), as shown in Figure 4. The pooled results indicated a significant difference between the control and treatment groups (MD = −1.11, 95%CI: −1.40 to −0.82, $p < 0.00001$). The results are shown in Figure 4.

TABLE 1 Methodological quality evaluation of the included studies.

Studies	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cui Die, 2020 (30)	No	Unclear	Yes	Unclear	No	No	No
Ling Xiaoyan, 2020 (30)	No	Unclear	Yes	Unclear	No	No	No
Wang Hong, 2021 (30)	No	Unclear	Yes	Unclear	No	No	No
Wang Junying, 2021 (37)	No	Unclear	Yes	Unclear	No	No	No
Xiong Xueping, 2021 (32)	No	Unclear	Yes	Unclear	No	No	Unclear
Xu Rong, 2018 (34)	No	Unclear	Unclear	Unclear	No	No	No
Yuan Fan, 2019 (29)	No	Unclear	Yes	Unclear	No	No	No
Zhang Liyan, 2021 (35)	Unclear	Unclear	Unclear	Unclear	No	No	Unclear
Zhang Qiuting, 2015 (38)	Unclear	Unclear	Yes	Unclear	No	No	No
Zong Shiqin, 2020 (36)	No	Unclear	Unclear	Unclear	No	No	No

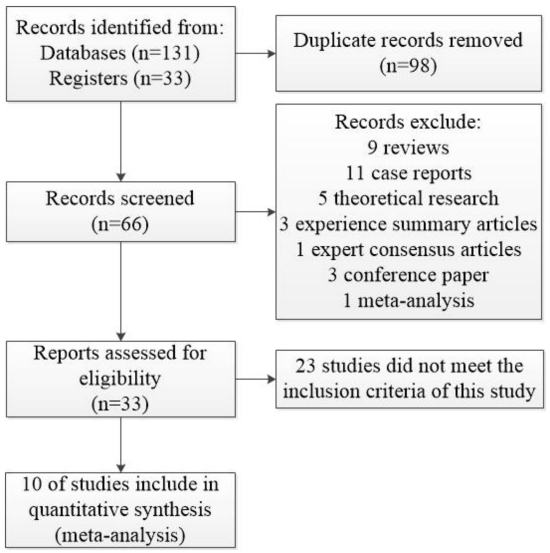

FIGURE 2
Literature selection flow chart.

3.2.3. Adverse reactions

Only two studies reported the occurrence of adverse effects. As shown in Figure 5, no significant heterogeneity is established between the two groups ($p = 0.85$, $I^2 = 0\%$). The meta-analysis showed that the statistics were not statistically significant. Therefore, fixed effects models were used to analyze our data. The results showed a substantial difference between the control and test groups (RR = 0.92, 95% CI: 0.45 to 1.86, $p < 0.81$).

3.2.4. Dermatology life quality index scores

For non-life-threatening psoriasis, treatment goals should focus on the patient's perceived health-related quality of life, usually measured by the Dermatology Life Quality Index (DLQI) (40). Two studies mentioned the DLQI score, and there were 74 patients in experimental groups and 73 patients in control groups. As shown in Figure 6, significant heterogeneity is not established between the two groups ($p < 0.00001$, $I^2 = 0\%$). Meta-analysis results showed that the results were statistically significant. The combined results showed a remarkable difference between the control and test groups (MD = −0.99, 95%CI: −1.40 to −0.59, $p < 0.00001$).

3.3. Publication bias

The funnel plot for the total effective numbers is symmetric, indicating no significant publication bias, as presented in Figure 7.

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TABLE 2 The basic characteristics of the included articles ① Blood-letting puncture and cupping therapy ② conventional measures therapy.

Author	Publication year	Group	Number of patients	Interventions	Treatment period (days)	Outcome indicators
Cui Die (30)	2020	Experimental group	32	①+②	28	Total effective numbers, PASI, Traditional Chinese medicine symptom scores, DLQI Scores, Recurrence rates
		Control group	31	②	28	Number of adverse reactions
Ling Xiaoyan (30)	2020	Experimental group	45	①+②	14	PASI, Total effective numbers, Recurrence rates
		Control group	45	②	14	
Wang Hong (30)	2021	Experimental group	38	①+②	28	PASI, Total effective numbers, Number of adverse reactions
		Control group	38	②	28	
Wang Junying (37)	2021	Experimental group	42	①+②	90	Total effective numbers, SDS Scores, SAS Scores, DLQI Scores, QOL Scores
		Control group	42	①	90	
Xu Rong (34)	2018	Experimental group	43	①+②	14	PASI, Total effective numbers, Number of adverse reactions, Symptom scores
		Control group	41	②	14	
Yuan Fan (29)	2019	Experimental group	32	①+②	28	Total effective numbers
		Control group	25	②	28	
Zhang Liyan (35)	2021	Experimental group	34	①+②	30	Number of adverse reactions, Total effective numbers
		Control group	34	②	30	
Zhang Qiuting (38)	2015	Experimental group	38	①+②	30	Total effective numbers
		Control group	37	②	30	
Zong Shiqin (36)	2020	Experimental group	50	①+②	30	PASI, PQOLS scores, Number of adverse reactions, Total effective numbers
		Control group	50	②	30	
Xiong Xueping (32)	2021	Experimental group	68	①+②	14	Total effective numbers, Patient satisfaction rates
		Control group	68	②	14	

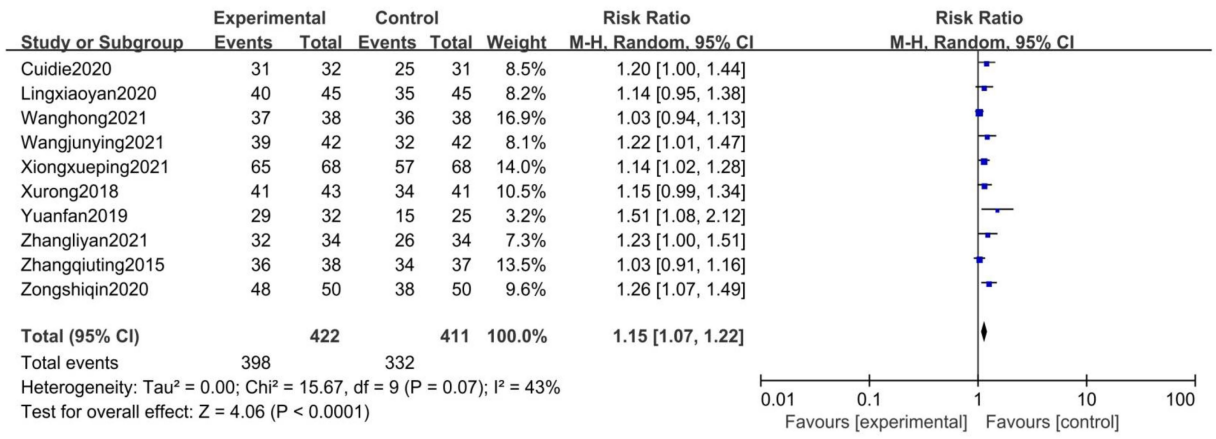

FIGURE 3
Meta analysis of total effective number between the treatment group and control group.

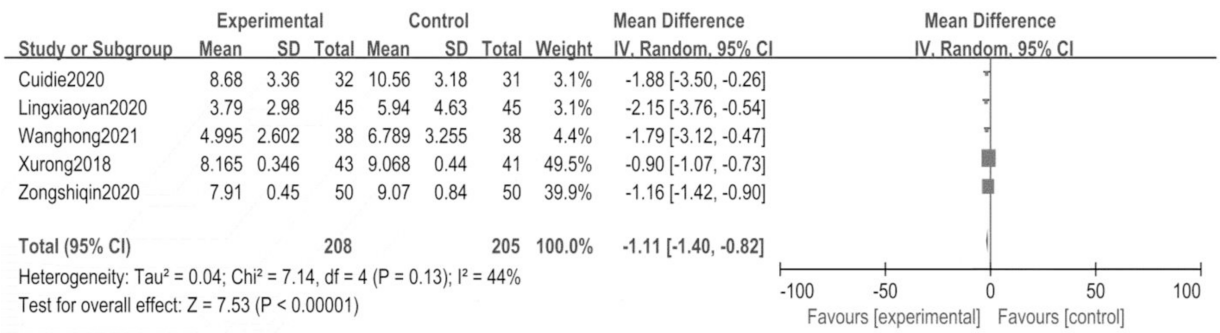

FIGURE 4
Meta analysis of PASI between the treatment group and control group.

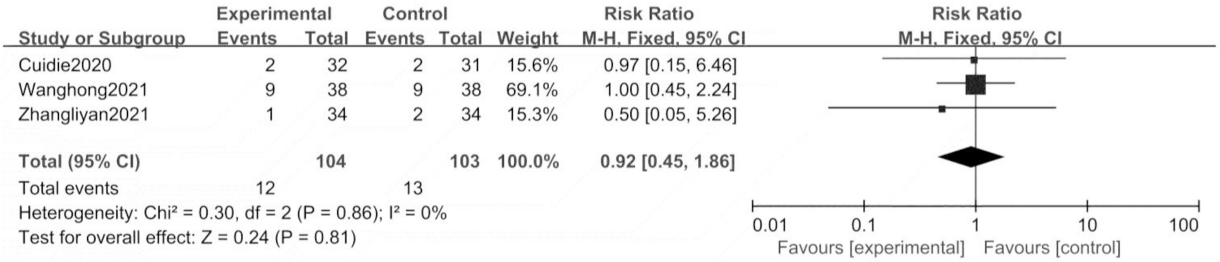

FIGURE 5
Meta analysis of number of adverse reactions between the treatment group and control group.

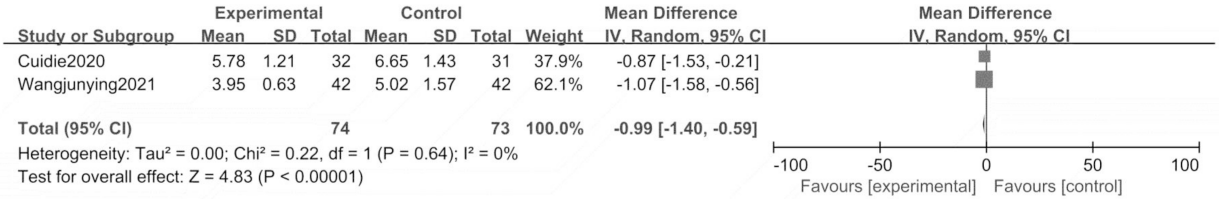

FIGURE 6
Meta analysis of DLQI score between the treatment group and control group.

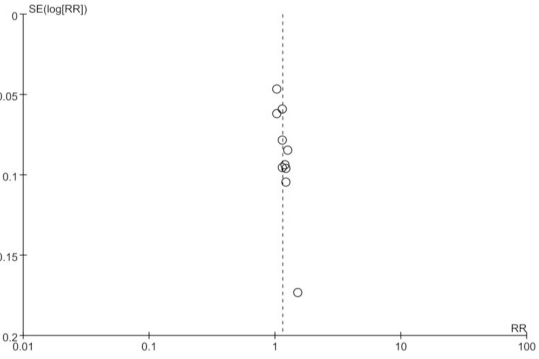

FIGURE 7
Funnel plot analysis.

4. Discussion

As far as we know, psoriasis, one of the most joint immune-mediated disorders, a papulosquamous skin disease, is distinctive, not enough to be recognized by clinicians (1). Psoriasis already possesses a substantial psychosocial barrier to patients and seriously affects their quality of life and physical and mental health (41). Frequent and long-term relapses of psoriasis have been of great concern to clinicians and healthcare professionals. The side effects of various treatments available and the unaffordable high cost of medical care mean that many patients are less satisfied with the treatment they receive. Biological therapies represent an important advance in the management of moderate-to-severe forms of plaque psoriasis, and their efficacy of them in the treatment of psoriasis has been universally recognized, specifically targeting key cytokines involved in psoriasis pathogenesis, resulting in a huge improvement of cutaneous manifestations, and with a generally safe profile. Both clinical trials and real-life studies showed impressive results for their safety and efficacy profiles. Particularly, real-life studies included patients who are typically excluded by the rigid inclusion and exclusion criteria of the clinical trials, showing significant PASI75, PASI90, and PASI 100 responses, even in more fragile patients (42–46). Despite the good performance of biological preparations, there are still some patients with poor or no efficacy. Dermatologists

should identify the causes and treat them in a timely manner according to the patient's own condition, thus making the treatment of psoriasis with biologics more professional and precise (47). Therefore, it is not surprising that in recent years, bloodletting cupping combined with conventional measures has been widely used in the treatment of psoriasis, and years of clinical experience and reports in the literature have concluded that its efficacy in psoriasis is definite, and the incidence of adverse reactions is lower compared with that of western medicine. On the one hand, trials used blood cupping therapy to unblock the meridians so that the Qi and blood flow unimpeded. On the other hand, the warm stimulation of cupping can make the pores open, and traditional Chinese medicine is called the "sweat method" so that the Qi can flow to get rid of the unhealthy trend.

In this study, a meta-analysis of the results of the combination of acupuncture cupping with other therapies compared with other therapies in the control group showed that the combination of acupuncture cupping with other therapies further reduced the PASI score and the incidence of adverse reactions compared with other control groups, and increased the total number of effective clinical patients and the DLQI score, which are indices suggesting that the medication is effective and safe.

Therefore, to provide information on the effectiveness of bloodletting cupping combined with conventional measures for psoriasis, this review was written to evaluate the currently published studies. Based on the meta-analyses, the 10 included randomized controlled trials involving 833 participants. Moreover, the results of this meta-analysis showed that, compared with conventional measures therapy alone, blood-letting puncture and cupping combined with conventional measures treatment had increased the number of clinically effective people. Meanwhile, the PASI decreased more obvious, and the Dermatology Life Quality Index (DLQI) decreased significantly. As for adverse reactions, the test groups included one case of mild diarrhea, one case of itching at the acupuncture site, nine instances of dry mouth, and one case of burning skin; the control groups had two cases of mild diarrhea, nine cases of dry mouth, and two cases of skin erythema. In addition, we found a substantial outcome difference between the control and treatment groups in terms of adverse events using a fixed effects model ($p < 0.81$), suggesting that combining the two treatments reduced the risk of adverse events. It is possible that the beneficial effects of blood-letting puncture and cupping combined with conventional measures were maybe overvalued. Most of the current clinical research literature outcome indicators are too simple and have different reference indicators, and some studies only list the total clinical effective rate, the number of adverse reactions, and PASI values. Single data cannot be meta-analyzed, so after combining all data, the total effective number, PASI, adverse reaction rate, and DLQI were finally used as valid data for the analysis.

This study has several limitations as well as relative shortcomings. First, the duration of the included trials ranged from 14 to 90 days, and no longer was efficacy observed, so it was not known whether this treatment was long-lasting. Second, the quality of the included articles was uneven. Only Chinese patients were included in the included randomized controlled trials, so there may be a potential risk of bias. Third, differences in interventions (including twice–daily versions, once–weekly versions, and twice–weekly versions) may influence the optimal choice of combination therapy. Fourth, the grey literature did not search, and publication bias may exist. Fifth, the differences in blooding and cupping techniques used by doctors, such as the amount of blood released, the strength of the cupping, and the depth of the needles, can also impact the efficacy to some extent. In addition, patient satisfaction, recurrence rates, and other issues related to the bloodletting puncture and cupping with conventional treatment measures have been up in the air. Finally, it is unknown when in the course of clinical treatment is the best time to start this treatment.

Although more robust evidence is needed to determine the best way and method to apply this integrative treatment approach in clinical practice, our findings support the use of bloodletting cupping combined with conventional measures therapy during the clinical trial in patients with psoriasis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

FY and XM proposed and designed this study. XM, MZ, and DL retrieved and selected the data. XM and JH were responsible for the extraction of data and the quality assessment of all study data. XM then performed a statistical analysis and summarized. XM drafted the manuscript and then FY and JK revised it. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Beyond skin white spots: Vitiligo and associated comorbidities

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Vitiligo is a common depigmentation disorder of an unknown origin characterized by the selective loss of melanocytes, resulting in typical white macules and patches. However, vitiligo is now recognized as more than just a skin disease, what a dermatologist observes as a white spot of skin is just the "tip of the iceberg" of the condition. We attempt to clarify the classification of comorbidities associated with vitiligo from various reviews and reports, and describe their possible pathogenesis. In conclusion, the literature provides evidence of an association between vitiligo and ocular and auditory abnormalities, autoimmune disorders, other dermatological diseases, metabolic syndrome and related disorders, and psychological diseases. These associations highlight the importance of a multidisciplinary approach in managing vitiligo patients.

KEYWORDS

Vitiligo, comorbidities, etiology, pathogenesis, melanocytes

1. Introduction

Vitiligo is a chronic inflammatory autoimmune condition that results in skin depigmentation due to the loss of melanocytes (1, 2). Globally, the prevalence ranges from 0.5 to 2.0% and varies geographically (3). The pathogenesis of vitiligo is not completely understood. Many theories, such as genetic background, autoimmune responses, oxidative stress, melanocyte adhesion, and neuronal involvement, have been proposed for the pathogenesis of vitiligo (2, 4). However, vitiligo is now recognized as more than just a skin disease, some studies have found that vitiligo is associated with several organ-specific or systemic disorders, including ocular or otologic diseases, autoimmune disease, metabolic syndrome (MetS) and psychological diseases (5–8). In this review, we clarify the classification of comorbidities associated with vitiligo and describe their possible pathogenesis (Figures 1, 2).

We searched the electronic database PubMed, Web of Science, Embase and Cochrane Library from inception to April 30, 2022 and analyzed the relevant literature related to vitiligo and associated comorbidities, including case–control, cross-sectional, and cohort studies, as well as systematic reviews and meta-analyses. A combination of medical subject headings (MeSH) and free terms were used in the search. The MeSH terms included "vitiligo," "eye diseases," "ear diseases," "autoimmune diseases," "metabolic syndrome" and "mental disorders."

2. Related to melanocyte distribution

Epidermal melanocyte damage is one of the causes of vitiligo. However, in addition to the skin, melanin and melanocytes are also present in the eyes, cochlea, leptomeninges, heart, and even inhospitable environments, such as adipose tissue (9). Therefore, some comorbidities

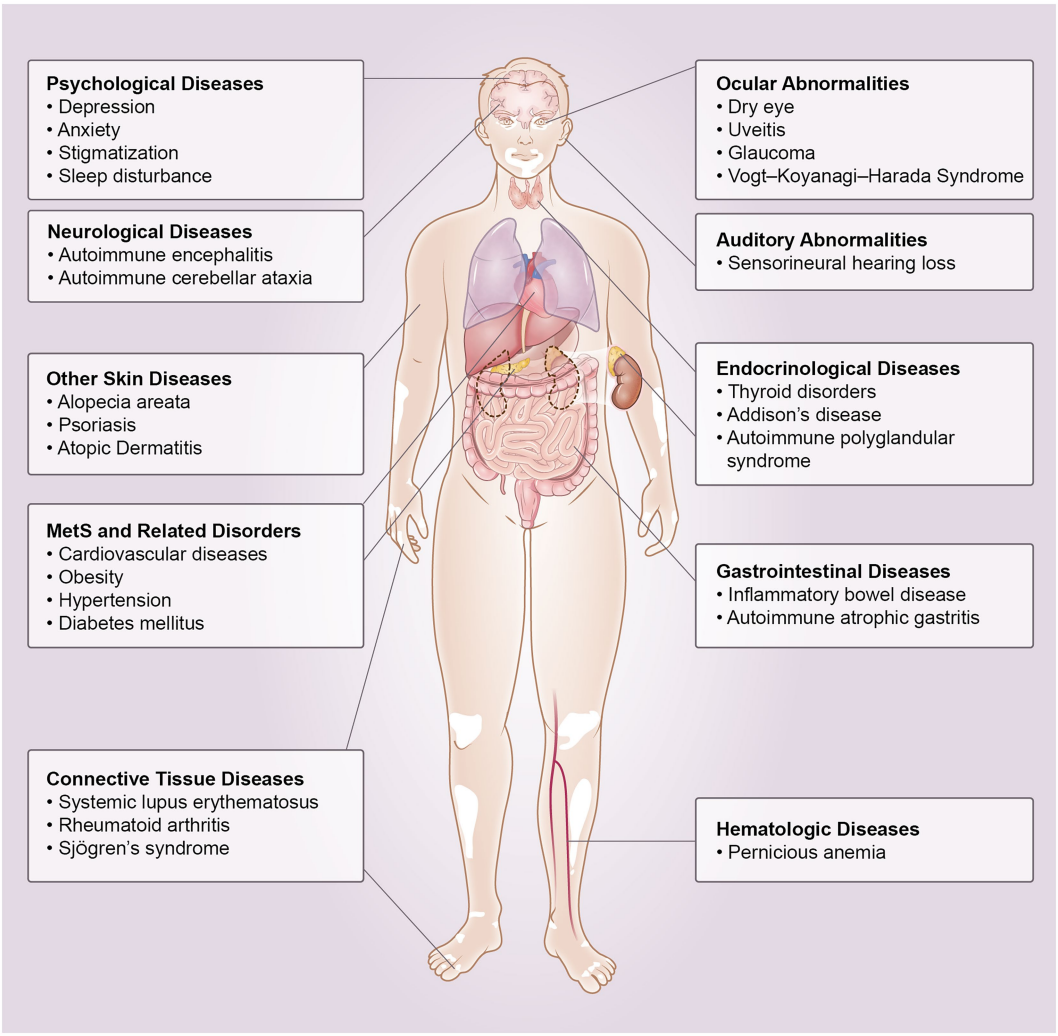

FIGURE 1
Comorbidities associated with vitiligo. MetS: metabolic syndrome.

associated with vitiligo may be related to melanocyte damage at different locations.

2.1. Ocular abnormalities

Melanocytes are found in both the retinal pigment epithelium (RPE) and the choroid of the eye, with the RPE originating from the neural ectoderm and the latter from the neural crest (10). Melanocytes in the RPE are crucial for the metabolism of rod outer segments and retinoids and photoprotection of the retina, whereas melanocytes in the choroid contribute to eye pigmentation and UV protection (9, 11). Damage to these melanocytes and reduced melanogenesis may result in ocular abnormalities and even vision impairments.

Prabha et al. (12) found various ocular abnormalities, such as hypopigmented trabecular meshwork, pigment clumps, uveitis, and RPE atrophy, in patients with vitiligo, and periorbital depigmentation was associated with eye abnormalities. Another cross-sectional study by Genedy et al. (13) revealed a significantly higher prevalence of ocular abnormalities in patients with vitiligo but no significant differences in visual acuity, which may be because ocular melanocytes are not directly involved in detecting or transferring visual information. There have also been reports of vitiligo comorbidities that cause loss of vision. For example, Dertlioğlu et al. (14) found that among 49 patients with vitiligo, 9 patients (18.4%) had normal-tension glaucoma (NTG), whereas there were no signs of NTG in the control group. In the absence of treatment, NTG can cause permanent loss of vision because it is a chronic progressive neuropathy that damages the optic nerve. Moreover, Rogosić et al. (15) confirmed primary open-angle glaucoma in 24 of 42 patients (57%) with vitiligo suspect of glaucoma. Multivariate logistic regression revealed that advanced age and a long vitiligo duration were risk factors for primary open-angle glaucoma.

According to one study by Ma et al. (7), patients with vitiligo had significantly reduced tear production, shorter tear film break-up time, and more symptoms related to dry eyes, which may be attributed to localized autoimmunity, such as T-helper (Th) 17 cells and related cytokines, concomitant rheumatologic diseases and adhesion defect theory (16–19). Additionally, subfoveal choroidal thickness was significantly thinner in the vitiligo group, possibly reflecting

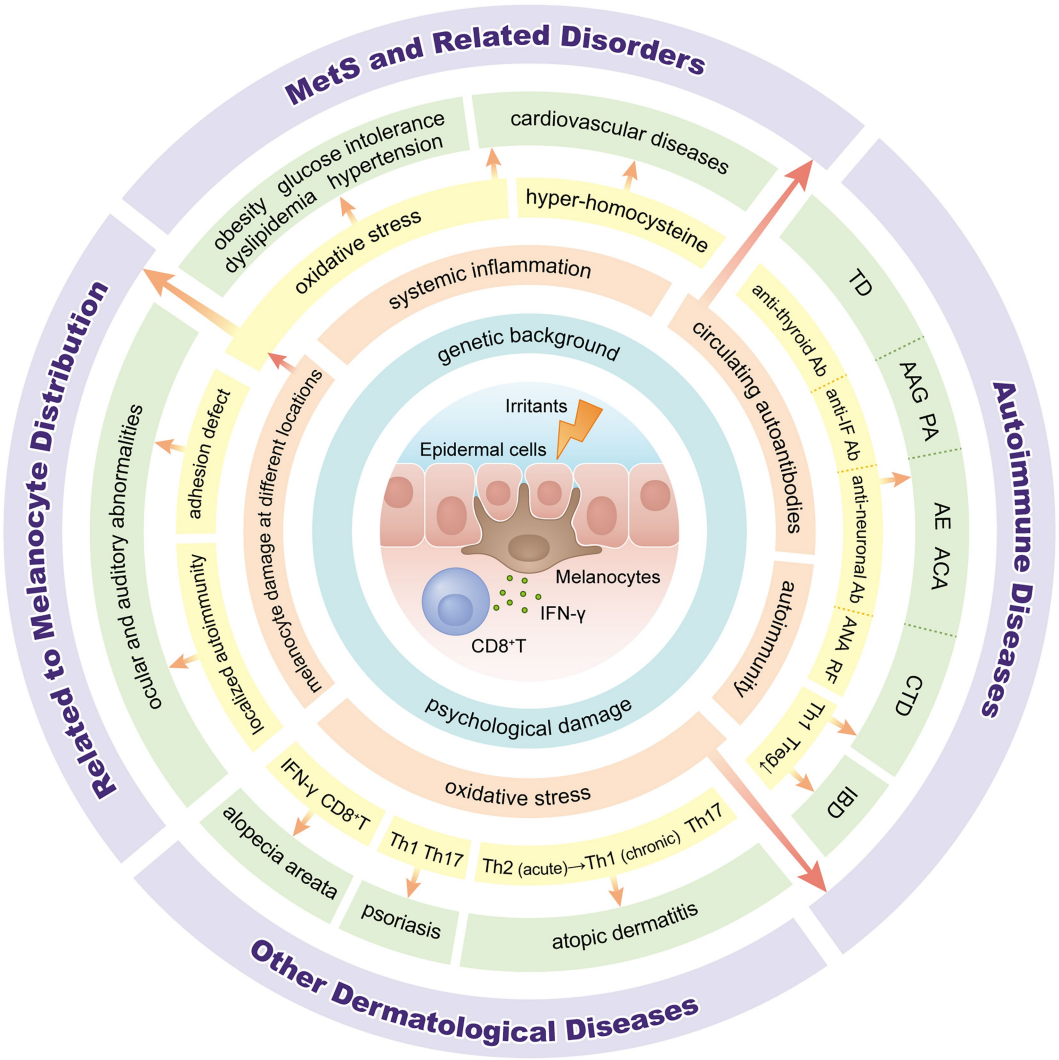

FIGURE 2
Overview of pathogenesis between vitiligo and associated comorbidities. IFN: interferon; Ab: antibody; IF: intrinsic factor; ANA: anti-nuclear antibody; RF: rheumatoid factor; Th: T-helper; Tregs: regulatory T cells; TD: thyroid disease; AAG: autoimmune atrophic gastritis; PA: pernicious anemia; AE: autoimmune encephalitis; ACA: autoimmune cerebellar ataxia; CTD: connective tissue diseases; IBD: inflammatory bowel disease; MetS: metabolic syndrome.

melanocyte depletion within this structure. Several external irritants, such as trauma, toxic chemical agents, ultraviolet radiation, and infection, can trigger oxidative stress, resulting in excessive reactive oxygen species production, autoimmune reactions, and melanocyte death (4, 20). It is also evident from the Köebner phenomenon that friction and trauma play critical roles in the pathogenesis of vitiligo (21). These stress signals spread to melanocytes in other parts of the body, potentially increasing their comorbidity risk.

2.2. Auditory abnormalities

In the auditory system, melanocytes are distributed in the stria vascularis and spiral ligament of the cochlea, which are required for maintaining the endocochlear electrical potentials that play an essential role in normal hearing (22). Melanin has been demonstrated to reduce oxidative stress by scavenging free radicals, and oxidative stress is considered one of the most important factors underlying sensorineural hearing loss (23, 24).

Accordingly, numerous studies have examined the relationship between vitiligo and hearing impairment but with varying results (25–28). A recent systematic review indicated that patients with vitiligo had a 6.02-fold increased risk of developing sensorineural hearing loss compared with the control group, but the definition of hearing loss was heterogenous between included studies (29). Lien et al. (6) conducted a similar analysis, and only studies meeting the criteria that examined hearing loss by assessing the pure-tone thresholds (PTTs) were included. According to their research findings, patients with vitiligo had significantly elevated PTTs only at high frequencies, including 2,000, 4,000, and 8,000 Hz, not at low frequencies ranging from 250 to 1,000 Hz. Since most of the sound in our daily life are at low and intermediate frequencies, we are generally not sensitive to hearing damage in the high frequency region. As a result, most cases of hearing loss among patients with vitiligo are

subclinical. Furthermore, Anbar et al. (30) conducted a study to compare cochlear function in patients with nonsegmental vitiligo (NSV) and segmental vitiligo (SV), and the results showed that bilateral cochlear dysfunction was common in both disease subtypes. Regarding the age of onset, one study revealed a tendency towards an increased severity of sensorineural hearing loss in the older group and patients with late-onset vitiligo (28). In contrast, another study found that late-onset vitiligo was not statistically associated with abnormalities of the auditory system (27).

Based on the findings of the above studies, we recommend regular evaluation of patients with vitiligo to detect ocular and auditory abnormalities and to treat these conditions in the early stage. Melanocyte destruction in patients with vitiligo can affect melanocytes that share a common embryological origin, ultimately affecting the function of the organs in which they reside. However, small sample sizes and heterogeneous definitions have led to conflicting results between these studies. Further large-scale studies are required to clarify the disease burden and the associated pathogenesis of ocular and auditory abnormalities in patients with vitiligo.

2.3. Vogt–Koyanagi–Harada syndrome

Vogt–Koyanagi–Harada syndrome (VKH) is an autoimmune disease that mainly affects melanocyte-containing systems, such as the eyes, ears, meninges, skin, and hair follicles (31). It is characterized by granulomatous uveitis with varying degrees of extraocular manifestations, such as headache, meningismus, hearing loss, poliosis, and vitiligo (32). According to the current theory, VKH is an exacerbated response by melanocytes and their precursor cells compared with vitiligo. The study by Egbeto et al. (33) supports the theory that T cell responses (particularly cytotoxic CD8+ T cells), type 1 cytokines, memory T cell responses, and chemokines are involved in the development of VKH and vitiligo.

Melanocytes are also located in the brain and leptomeninges, possibly with neuroendocrine and detoxification functions (9). Melanocytes are also present in the heart, where they may play a role in electrical signaling (34). However, there are few clinical studies of diseases associated with melanocyte destruction in these regions, and the correlation between these diseases and vitiligo requires further study.

3. Autoimmune diseases

There is an extensive correlation between vitiligo and other organ-specific or generalized autoimmune disorders. A 10-year retrospective study involving 3,280 patients showed that comorbid autoimmune conditions occur in approximately 23% of vitiligo patients, including thyroid disease (TD), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and type 1 diabetes mellitus (35). Of note, a cross-sectional study showed that patients with at least one comorbid autoimmune disease tended to have more extensive vitiligo compared with those without comorbid autoimmune disease (36).

As mentioned above, the exact pathogenesis of vitiligo remains complicated and unclear, but the most accredited hypothesis is the autoimmune theory, which may help explain how the disease manifests systemic alterations. First, vitiligo patients show circulating autoantibodies directed toward melanocyte antigens. Clinical studies also found that a significant number of patients tested had elevated anti-nuclear antibody titers, rheumatoid factor positivity, and increased anti-thyroid antibodies compared to the general population (35, 37–41), which imply potential cross-talk between vitiligo and associated diseases. Second, C-X-C motif chemokine ligand 10 (CXCL10), a marker of Th1-mediated immune responses, is elevated in peripheral liquids from vitiligo patients (42). Recent studies have shown that serum and tissue CXCL10 expression are increased in organ-specific autoimmune diseases, such as autoimmune thyroiditis, Graves' disease, type 1 diabetes, and systemic rheumatological disorders (RA, SLE, systemic sclerosis, mixed cryoglobulinemia), underlining the importance of a common immunopathogenesis of these disorders characterized by a Th1-prevalent autoimmune response (43, 44). Third, regulatory T cells (Tregs) play a critical role in the augmentation of peripheral immune tolerance, thereby protecting the human body from autoimmune damage (45). Accumulating data suggests that patients with vitiligo have a reduced number of Tregs; decreased Treg suppression; and reduced levels of Treg-associated suppressive cytokines, such as interleukin (IL)-10 and transforming growth factor-β (46, 47). Likewise, quantitative and functional deficiencies in Tregs have been reported in a variety of autoimmune diseases, including RA, SLE, type 1 diabetes mellitus, multiple sclerosis, and myasthenia gravis, among others, which might contribute to the elevated frequency of various associated autoimmune diseases in patients with vitiligo (48). Fourth, vitiligo lesions tend to recur at the same location of previous depigmented patches after treatment cessation, suggesting a potent role of non-recirculating tissue-resident memory T (TRM) cells in the pathogenesis of vitiligo (49, 50). TRM cells respond rapidly to the secondary exposure of known antigens *in situ* and provide efficient protection. They also respond to autoantigens in other barrier tissues, including the lungs, gastrointestinal tract, and reproductive tract, as well as in non-barrier tissues, including the brain, pancreas, and joints, which may be involved in the pathogenesis of organ-specific autoimmune disorders, such as IBD, multiple sclerosis, and type 1 diabetes mellitus (51). Finally, through genetic studies, over 50 vitiligo-associated genes and loci have been discovered, and many have also been found to be associated with other autoimmune diseases (52). Thus, these genetic associations may confirm the shared underlying genetic predisposition between vitiligo and other autoimmune diseases. In summary, patients with vitiligo are more likely to suffer from autoimmune conditions than the general population.

3.1. Endocrinological diseases

3.1.1. Thyroid disorders

Among all autoimmune diseases associated with vitiligo, TD is one of the most common and widely studied (5). Conversely, recent research has demonstrated that vitiligo is one of the most prevalent autoimmune diseases among patients with autoimmune thyroiditis (53). The British guidelines suggest that dermatologists should be aware of the increased risk of TD or autoimmune thyroid disease (ATD) in vitiligo patients, and routine examination of thyroid function and antibodies should be considered (54).

A recent meta-analysis of 37 studies with 78,714 vitiligo patients showed that in all patients with vitiligo, the prevalence of TD, ATD, thyroid peroxidase antibodies (TPOAbs), and thyroglobulin antibodies (TGAbs) was 15.7, 1.9, 16.8, and 11.4%, respectively, which was significantly higher than that in healthy controls (40). Another systematic review involving 77 studies reported by Yuan et al. (55) assessed the prevalence of six thyroid disorders in vitiligo patients, including subclinical hyperthyroidism, overt hyperthyroidism, subclinical hypothyroidism, overt hypothyroidism, Graves' disease, and Hashimoto thyroiditis. The highest prevalence was in subclinical hypothyroidism, and the lowest was in subclinical hyperthyroidism or Graves' disease. In addition to serum thyroid autoantibodies (TPOAbs, TGAbs, and thyroid-stimulating hormone receptor antibodies), which are closely associated with thyroid autoimmune disease, Colucci et al. (56) evaluated thyroid hormone antibodies (THAbs) against triiodothyronine and/or thyroxine and found surprisingly high levels in patients with vitiligo. Furthermore, they suggested that THAbs may act as a "bridge of vicious cycles" between melanocytic and thyroid systems. Moreover, a cohort study involving 700 patients summarized the clinical characteristic of generalized vitiligo patients with TDs (57). According to their results, the affected body surface area (BSA) was significantly higher in patients with vitiligo combined with TD. Notably, these patients also had a typical distribution pattern of lesions; the most common depigmentation areas were the hands, wrists, ankles, and elbows, which are susceptible to friction (classified as Köebner phenomenon type 2A).

An increasing number of studies focusing on the type and onset of vitiligo or gender and race of patients aim to identify the confounding factors based on subgroup analyses. Many studies have confirmed that NSV patients are more susceptible to TD than SV patients, possibly because SV is more associated with neural mechanisms (58). Some studies divided vitiligo patients into early-onset and late-onset groups and defined the former as onset before 12 years of age (59). They found that early-onset vitiligo patients exhibited a lower prevalence of TD compared with the late-onset group, potentially because the latter might be more associated with acquired autoimmunity (40, 60). Sexual dimorphism of the immune system exists between men and women (61, 62). van Geel et al. (57) reported that female patients with vitiligo more frequently have TD compared with male patients, and this phenomenon might be associated with stimulation of the autoimmune system by estrogen in women.

3.1.2. Addison's disease

A significant correlation was found between vitiligo and Addison's disease. Alkhateeb et al. (63) reported that the prevalence of Addison's disease was 0.38% among Caucasian vitiligo probands and 0.087% among their relatives, which is substantially higher than the prevalence in the general population. Similarly, in another study involving 113 family members of Addison's disease patients, 3.5% were diagnosed with vitiligo, which was significantly more frequent than the proportion of controls (64).

Autoimmune polyglandular syndrome (APS) occurs when two or more endocrine glands in the same individual become hypofunctional because of autoimmune inflammation, either sequentially or simultaneously (65). It can also affect the non-endocrine system. APS-1 is a rare recessive inherited disease caused by autoimmune regulator gene mutations and characterized by chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and Addison's disease (66). A recent study analyzed autoimmune conditions associated with autoantibodies in 158 Italian APS-1 patients. At the end of follow-up, 17% had vitiligo, and melanin-producing cell autoantibodies were found in 10/18 tested patients (67). APS-2 is characterized by adrenal insufficiency (Addison's disease), ATD, or type 1 diabetes mellitus and has also been reported to be significantly associated with vitiligo (68).

3.2. Gastrointestinal diseases

3.2.1. IBD

IBD is an immune-mediated chronic intestinal inflammatory disease and includes Crohn's disease (CD) and ulcerative colitis (UC). Some large-scale studies found a higher frequency of IBD among vitiligo patients, but the prevalence varies according to country and ethnicity. Hadi et al. (69) reported that 1.1% of their vitiligo patients had IBD, which is 2.13-fold higher than the incidence in the general population. Sheth et al. (35) reported a considerably higher prevalence of IBD in their 3,280 vitiligo patients in the USA. Among the 2.3% of patients with IBD, 1.4% had UC, 0.6% had CD, and 0.3% were unspecified. Furthermore, Alkhateeb et al. (63) showed that the frequency of IBD was elevated by 2-fold, with 0.67% among adult Caucasian vitiligo probands compared with a population frequency of 0.37%. Conversely, Jo et al. (70) analyzed 64,837 patients with IBD in the Korean population, and after adjusting for age and insurance type, patients with IBD had a higher risk of vitiligo than non-IBD subjects.

3.2.2. Autoimmune atrophic gastritis

Autoimmune atrophic gastritis (AAG), characterized by the development of antibodies against parietal cells and intrinsic factor, leads to mucosal destruction that primarily affects the corpus and fundus of the stomach (71). Vitiligo has been described in association with AAG, but most studies were case reports (71, 72). Only one retrospective study involving 138 AAG patients showed that vitiligo was present in 2.8% of patients (73). Further studies are required to understand the associations between vitiligo and AAG.

3.3. Hematologic diseases

Several observational studies have found an increased prevalence of pernicious anemia (PA) in the vitiligo population. A 10-year cross-sectional retrospective study of 1,487 vitiligo patients in urban USA showed that an estimated 0.4% of patients have combined PA (69). Another study in 1,098 patients in the USA suggested a similar incidence of approximately 0.5% (36). It is worth noting that the prevalence of PA was significantly increased in a study conducted in Canada, with 1.3% of 300 vitiligo patients reporting the disease (74), which was higher than the general population prevalence of 0.15%. However, in a similar population-based study that enrolled 14,883 vitiligo patients in Taiwan, no statistically significant association of PA with vitiligo was revealed (57). This lower prevalence may be responsible for the differences in comorbidity profiles between Easterners and Westerners.

PA occurs in the later stage of AAG with severe gastric intrinsic factor deficiency and consequent vitamin B12 deficiency (75). PA is linked to but different from AAG. Anti-parietal cell antibodies

(APCAs) are a serum biomarker of AAG present in most patients with AAG and 85–90% of individuals with PA (76), and APCAs are more frequent among individuals with vitiligo (77). Hence, associations of vitiligo with AAG and PA indicate a common immunopathogenic pathway.

3.4. Connective tissue diseases

The most commonly reported comorbid connective tissue diseases (CTD) in vitiligo patients are SLE and RA. Other associated CTDs include Sjögren's syndrome (SS), systemic sclerosis (SSc), and dermatomyositis/polymyositis (DM/PM).

Choi et al. (78) performed a large-scale cross-sectional study and indicated that 86,210 patients with vitiligo were at an increased risk of SLE, SSc, SS, and RA. Subgroup analysis showed an increased risk of DM/PM for males and ankylosing spondylitis for female vitiligo patients. Research conducted by Gill et al. (36) in a US population found a statistically significant higher prevalence of SLE (0.3%), SS (0.2%), discoid lupus (0.2%), and linear morphea (0.2%) in vitiligo patients, and SLE was observed only in Black patients. Another similar study in vitiligo patients in the United States reported a considerably higher prevalence, with 2.2% for SLE and 2.9% for RA. Stratified analyses based on race/ethnicity suggested that these two comorbidities were more common in the African-American/Black population, which is consistent with the previous study (35). In Taiwan, a case–control study also showed a significant association of vitiligo with SLE and SS. In the age- and gender-stratified analysis, only patients with onset between 60 and 79 years of age were found to display an increased risk of SLE (79). In summary, age-, sex-, or ethnicity-specific approaches for comorbid CTDs in vitiligo patients will assist in the proper management of these disorders by clinicians.

3.5. Neurological diseases

Recent studies have suggested an observational link between vitiligo and neuroimmune disorders involving the peripheral and central nervous systems. According to a cross-sectional analysis of 1,098 patients with vitiligo, three had Guillain-Barré syndrome (0.2%), two had multiple sclerosis (0.2%), and two had myasthenia gravis (0.2%) (36). Considering that both the skin and the nervous system originate from the ectoderm, the underlying pathogenesis may be related to the fact that the epitopes of the neuronal cell surface are more likely to be attacked by autoantibodies induced by exposure to antigens triggered by vitiligo.

Autoimmune encephalitis is a group of disorders characterized by antibodies reacting with the extracellular epitopes of neuronal cell membranes or synaptic proteins (80). Of the three cases reported by Ren et al. (81), two suffered from anti-leucine-rich glioma-inactivated 1 encephalitis, and one had anti-IgLON5 encephalopathy. A Mayo Clinic cohort study showed that in a series of 62 patients with anti-glutamate decarboxylase 65 antibody-positive autoimmune cerebellar ataxia (ACA), 10 patients (16%) had vitiligo (82). In addition, Han et al. (83) reported a patient with ACA with anti-delta/notch-like epidermal growth factor-related receptor antibodies who suffered from vitiligo for more than 20 years. Most published studies on the association of vitiligo with neurological disease are case series or small sample studies. Therefore, further studies are warranted to investigate the cross-links between them.

Based on the above, we speculate that vitiligo may be a clue to understanding the diagnosis or autoimmune etiology of other autoimmune disorders. Patients with vitiligo are prone to disruption of autoimmune tolerance and autoimmune attack, thereby increasing their risk of concomitant autoimmune diseases. Similarly, if vitiligo lesions are observed in patients with diseases of other tissues, autoimmunity may be responsible for the pathogenesis. A diagnosis based on this information may be more accurate. Several large cross-sectional or retrospective studies have also noted that these diseases often occur alongside one another, which implies that their pathologies are inextricably linked. As a result, vigilance should be exercised when searching for possible concomitant diseases, and patients should be referred to specialists where necessary. Nevertheless, further studies are required to determine whether therapies for vitiligo can slow the progression of concomitant autoimmune disorders.

4. Other dermatological diseases

4.1. Alopecia Areata

Vitiligo and alopecia areata (AA) are common autoimmune conditions characterized by white spots on the skin (vitiligo) and bald spots on the scalp (AA) (84). A retrospective study of 1,098 patients with vitiligo showed that AA is the second most common autoimmune disease associated with vitiligo after ATD, occurring in 3.8% of patients with vitiligo (36). Notably, a relatively high AA prevalence of 5.3% was observed in a study involving 133 NSV patients in Japan (85). Conversely, a Danish nationwide register-based cohort study showed that a diagnosis of AA was significantly associated with a higher risk of vitiligo (86), and the same phenomenon has been reported in pediatric patients (87).

Oxidative stress and autoimmunity with genetic susceptibility are associated with the pathogenesis of AA and vitiligo (88). Both conditions are characterized by a prominent interferon (IFN)-γ + signature and cytotoxic CD8 + T cell attack, selectively targeting the anagen hair follicle bulbs in AA and the epidermal melanocytes of the basal layer in vitiligo (84). Additionally, Tomaszewska et al. (89) found elevated levels of the oxidative stress markers IFN-γ, IL-1β, and IL-6 in the serum of both NSV and AA patients. In clinical practice, oral Janus kinase inhibitors are a promising treatment with demonstrated effectiveness in AA and vitiligo patients (90, 91). Together, these facts indicate a similar pathogenesis of both diseases.

4.2. Psoriasis

Psoriasis is a relatively common disease with an estimated prevalence ranging from 0.51 to 11.43% in adults (92). A recent systematic review showed that compared with controls, psoriasis patients were 2.29-fold more likely to have vitiligo, and vitiligo patients were 3.43-fold more likely to be diagnosed with psoriasis (93). However, regarding its incidence in vitiligo patients, there is a large heterogeneity across studies. In a descriptive and cross-sectional study, 7.79% of 154 vitiligo patients simultaneously had psoriasis (94).

However, in a similar study in 712 vitiligo patients, only 3% of the vitiligo group had associated psoriasis (95). In another cross-sectional study, in addition to the current comorbidities, Canu et al. (96) evaluated the history of psoriasis, and the results showed that 16.9% of 463 vitiligo patients had a past and/or current personal history of psoriasis. Remarkably, a case–control study demonstrated that inflammation or pruritus in vitiligo macules and a family history of cardiovascular disease were the most significant predictors of patients having both psoriasis and vitiligo (97).

Shared cell-mediated immune pathogeneses, including Th1 and Th17 pathways activated by IFN-γ, may play a role in the similar patterns of autoimmune inflammation in both diseases (98). Moreover, genome-wide association studies have provided extensive evidence that psoriasis and vitiligo share common genetic variants with similar effect sizes, including allelic variations in genes related to immune responses, such as *AIS1*, *PSOR7* (99), and the major histocompatibility complex (100).

4.3. Atopic dermatitis

Increasing evidence suggests that vitiligo is associated with atopic dermatitis (AD). A meta-analysis of 16 studies showed that patients with vitiligo had a 7.82-fold increase in AD compared with control patients without these disorders. Intriguingly, the odds of having AD were higher in those with early-onset vitiligo than in those with adult-onset vitiligo (101). Similarly, the results of a recent population-based cohort study of 173,709 patients newly diagnosed with AD showed that people with AD had a higher incidence of vitiligo compared with the general population, particularly when AD is more severe (102). In addition, Roh et al. (103) conducted a study to characterize the real-world comorbidities associated with adult AD. They also found that AD was associated with increased odds (odds ratio = 4.44) of vitiligo, and the same findings were confirmed in another identical study in a pediatric population (104). Furthermore, AD prevalence was stratified by vitiligo BSA, and the results showed that a BSA of 76% or higher was associated with an increased risk of AD (105).

There are a few possible explanations for the pathomechanism linking AD and vitiligo. Campione et al. (106) suggested that although AD is associated with a Th2-mediated immune response in its acute phase, its chronic phase is predominantly Th1-mediated with remodelling and fibrosis of the tissues. In addition, Th17 cells, which produce IL-17A and IL-17F, seem to play a role in AD by interacting with eosinophils and triggering the Th2 response, which are also involved in the development of vitiligo (107). What's more, Silverberg et al. (105) proposed that the proinflammatory state of AD may lead to melanocyte destruction, while scratching of pruritic AD lesions may köebnerize vitiligo.

Vitiligo and other associated dermatological diseases are characterized by a complex combination of factors, including genetic predisposition and the immune response triggered by exogenous stimulation. Vitiligo can precede or co-occur with other skin comorbidities, or emerge at different stages of the development of other skin comorbidities. Despite these obvious clinical differences, skin diseases share much in common, and understanding their similarities may help us to better determine their pathogenesis and develop common therapeutic approaches to treat them in a more efficient way, such as biological agents or Janus kinase inhibitors.

5. MetS and related disorders

MetS is described as the clustering of obesity, hypertension, hyperglycemia, and dyslipidemia in an individual, ultimately leading to diabetes mellitus, cardiovascular diseases, or other chronic diseases (108). Several clinical or fundamental studies have investigated the association of vitiligo with MetS or its components.

Recently, Chuang et al. (8) conducted a meta-analysis and revealed a significant association between vitiligo and MetS (odds ratio = 1.648). Furthermore, in subgroup analyses based on the type and activity of vitiligo, MetS prevalence was not significantly different. Another recent meta-analysis of 30 studies found significant associations between vitiligo and MetS components, including diabetes mellitus, obesity, and hypertension. Kang et al. (109) found that patients with vitiligo had a 3.30-fold increased risk of developing diabetes mellitus and a 2.08-fold increased risk of suffering from obesity compared with controls, and the prevalence of hypertension was 19.0% in vitiligo patients. A meta-analysis conducted by Chang et al. (110) demonstrated that vitiligo was significantly associated with type 1 and type 2 diabetes mellitus. These meta-analysis findings are consistent with the results of some previous case–control studies. Tanacan et al. (111), Ataş et al. (112), and Sharma et al. (113) found that the frequency of MetS was higher in patients with vitiligo compared with that in control groups. Furthermore, Tanacan et al. (111) and Ataş et al. (112) reported a higher rate in patients with the active or severe form of the disease, whereas Sharma et al. (113) showed that MetS remained unaffected by the severity of vitiligo.

MetS and its components are important risk factors for cardiovascular disease. Carotid ultrasound measurements, including carotid intima media thickness (CIMT), are used for the assessment of subclinical atherosclerosis and can be independent predictors of cardiovascular events (114). A hospital-based, case–control study among Egyptians by Azzazi et al. (115) showed that a significantly higher proportion of vitiligo patients had hypercholesterolemia and borderline high, high, or very high levels of low-density lipoprotein. Atherosclerotic plaques and increased CIMT were detected significantly more in patients than in controls. In addition, the CIMT was significantly correlated with the Vitiligo Area Severity Index and duration of vitiligo (116). Intriguingly, another study by Karadag et al. (117) demonstrated higher levels of homocysteine in vitiligo patients than in controls. Homocysteine inhibits tyrosinase, an enzyme involved in melanin synthesis and a marker for cardiovascular diseases.

There are some similarities in the underlying pathophysiology of vitiligo, MetS, and atherosclerosis, including genetic background, pro-inflammatory signaling pathways, and increased oxidative stress. Genetically, a genome-wide association study identified susceptible loci in vitiligo patients and found that these genes also have a strong association with diabetes mellitus, including *IFIH1, BACH2, BTNL2, IL2RA, SH2B3,* and *ZMIZ1* (118). Additionally, it has been revealed that elevated levels of the serum pro-inflammatory cytokines TNF-α, IL-1, and IL-6 play a role in the pathogenesis of vitiligo (119). The increase in these pro-inflammatory cytokines in serum and adipose tissue is also associated with insulin resistance and atherosclerosis. Furthermore, as mentioned above, melanocytes have been detected in adipose tissue. In vitiligo, lipid peroxidation causes a deterioration in reactive oxygen species, leading to a reduction in melanocytes in adipose tissue (108). Excessive reactive oxygen species contribute to adipogenesis by facilitating the proliferation and differentiation of

pre-adipocytes and obesity (109), and decreased melanocyte numbers and melanogenesis impair their anti-inflammatory and antioxidative functions. These changes may predispose patients to develop MetS.

Recently, the association between vitiligo and MetS has attracted the attention of researchers, which further confirms that vitiligo not only affects the skin, but also that it has several systemic manifestations. MetS is an alarming health problem that increases the risk of type 2 diabetes mellitus and cardiovascular diseases, which can result in serious complications, such as myocardial infarction or stroke. Therefore, dermatologists should recognize the possibility of MetS in patients with vitiligo and refer patients to other specialists for further evaluation. Additionally, controlling risk factors, including obesity, high blood glucose, and high blood pressure, as well as maintaining a healthy lifestyle, may be beneficial for patients with vitiligo.

6. Psychological diseases

To the best of our knowledge, vitiligo greatly affects psychosocial well-being. Vitiligo patients experience a higher level of burden compared with healthy people, as reflected by quality-of-life (QoL) indicators. Morrison et al. (120) conducted a meta-analysis of 12 studies and demonstrated QoL impairment in patients with vitiligo, and subgroup analysis showed that those with darker skin or from Southern Asian cultures were more likely to suffer from reduced QoL. Additionally, psychosocial comorbidities were more prevalent in patients with vitiligo than in those with acne, AA, atopic dermatitis, and urticaria (121). One study reported that QoL impairments were even comparable to those observed in non-dermatologic diseases, such as chronic lung disease, arthritis, and cancer, according to SF-36 mental component scores (122).

Depression and anxiety are the most commonly reported psychosocial comorbidities. Wang et al. (123) showed that the prevalence of clinical depression was 8% and that of depressive symptoms increased to 33% among vitiligo patients. In addition, the patient group was 4.96 times more likely to suffer from depression symptoms compared with healthy people. Regarding anxiety, Kussainova et al. (124) suggested that the general incidence of anxiety in vitiligo patients was 35.8%, and the incidence was substantially higher among female patients.

Ezzedine et al. (121) also investigated the relationship between vitiligo and other psychological disorders. The most prevalent psychosocial comorbidities included feelings of stigmatization, sleep disturbance, adjustment disorders, avoidance or restriction behavior, and relationship difficulties, including sexual dysfunction. Moreover, several factors were associated with significantly higher psychological burden, including female sex, visible or genital lesions, age < 30 years (particularly adolescents), and extensive BSA involvement. Vitiligo affects not only the patient themself but also their caregivers. Parents of affected children were found to suffer from moderately reduced QoL and higher risks of depression and anxiety than parents of unaffected children (125). Intriguingly, a Korean multicenter, cross-sectional, prospective survey suggested that the willingness to pay was highest in vitiligo patients compared with that in subjects with other chronic skin conditions, including psoriasis, AD, AA, rosacea, chronic urticaria, and seborrheic dermatitis (126).

In summary, vitiligo can increase the psychological burden of patients and cause several psychological problems. Simultaneously, mental and psychological stress can further aggravate the progression of vitiligo, thus creating a positive feedback effect. Moreover, the degree of inflammation may be enhanced under emotional stress, which in turn contributes to the development of other comorbidities associated with vitiligo (109). Therefore, regular assessments of QoL and psychosocial state should be incorporated in routine clinical evaluation.

7. Conclusion

There is evidence in the literature that vitiligo is associated with several comorbid disorders (Figures 1, 2). However, more prospective studies and basic mechanism studies are needed to confirm these findings. These associations highlight the importance of a multidisciplinary approach in managing vitiligo patients. Dermatologists should consider these diseases associated with vitiligo to identify and screen potential co-morbidities in patients in a timely manner.

Author contributions

ZH performed the literature search and drafted the first version of the manuscript. TW provided expert guidance and critically revised the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Canakinumab leads to rapid reduction of neutrophilic inflammation and long-lasting response in Schnitzler syndrome

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Interleukin-1 (IL-1)-blocking therapies are effective in reducing disease severity and inflammation in Schnitzler syndrome. Here, we present a patient with Schnitzler syndrome treated successfully using canakinumab for over 10years. Complete clinical response was associated with a decrease in dermal neutrophil number and expression of the pro-inflammatory cytokines IL-1β, IL-8, and IL-17 as assessed by immunohistochemical studies.

KEYWORDS

Canakinumab, Schnitzler syndrome, neutrophilic inflammation, immunohistochemical, autoinflammatory disorders

Introduction

Schnitzler syndrome is a rare autoinflammatory disorder, defined by an urticarial rash associated with a monoclonal immunoglobulin (Ig) M gammopathy and at least two additional minor criteria, such as fever, arthralgia, lymphadenopathy, hepatomegaly, splenomegaly, increased markers of systemic inflammation, or abnormal findings on bone imaging (1). Approximately 20% of all cases with Schnitzler syndrome develop a lymphoproliferative disorder, such as Waldenström macroglobulinemia (1, 2). Treatment options for Schnitzler's syndrome are limited and include nonsteroidal anti-inflammatory drugs, fluoroquinolones, oral glucocorticoids, and immunosuppressive drugs, which often fail to provide long-term remission and have safety issues (1). Ample evidence exists indicating a critical role of the interleukin-1 (IL-1) pathway in the pathogenesis of Schnitzler's syndrome, which is substantiated by the beneficial response with an IL-1 blockade (3). Here, we present a case with excellent long-term response to canakinumab, which was associated with a rapid decrease in neutrophils and pro-inflammatory cytokines.

Case report

A 71-year-old woman presented with eruptions consisting of rose to red macules and slightly raised plaques affecting the trunk and limbs as well as bone pain, recurrent fever, night sweats, and weight loss in recent years. Light microscopy studies of a skin biopsy specimen (Hematoxylin and eosin staining) revealed a mixed inflammatory cellular dermal and

perivascular infiltrate of lymphocytes and neutrophils. Extensive work up with serum protein electrophoresis and immunofixation as well as a bone marrow biopsy revealed an IgM monoclonal gammopathy of undetermined significance (MGUS; serum IgM monoclonal protein, 12.8 g/l). Blood tests showed elevated systemic inflammatory signs: high erythrocyte sedimentation rate (ESR), 55 mm/h; C-reactive protein (CRP), 30 mg/l (range < 5 mg/l); and leukocytes, 9 G/l (range 3.5–10.5 G/l). Based on these clinical and laboratory findings, the diagnosis of Schnitzler syndrome was made. The disease was controlled using oral prednisolone (1 mg/kg body weight daily). However, attempts to reduce the doses to 20 mg or less led to recurrences of the rash, fever, and bone pain. Further regimens including colchicine and pefloxacine were also ineffective to control the clinical manifestations. Therefore, canakinumab 150 mg subcutaneously was initiated, which led to a rapid improvement of the symptoms within 24 h. The extent of involvement calculated using the body surface area (BSA), reduced from 34 to 12% after 3 months of therapy (Figures 1A–E). Hematological and inflammatory (ESR and CRP) parameters also normalized after 3–4 months. Canakinumab was administered twice at 3-month intervals. Thereafter, the intervals were prolonged to every 6 months since disease activity was minimal (BSA between 2 and 4%). Usually at the end of each 6-month period, mild urticarial rashes and night sweats reappeared, but immediately disappeared within 1–2 days after the injection of canakinumab. Therapy using canakinumab 150 mg every 6 months is ongoing since over 10 years with no adverse effects, especially during the coronavirus disease 2019 (COVID-19) pandemic.

Methods

To investigate the effect of canakinumab, we performed an immunohistochemical analysis of the cellular infiltrate from a skin biopsy specimen obtained before and 1 month after initiating treatment with canakinumab using the avidin–biotin complex-alkaline phosphatase method with the following primary antibodies:

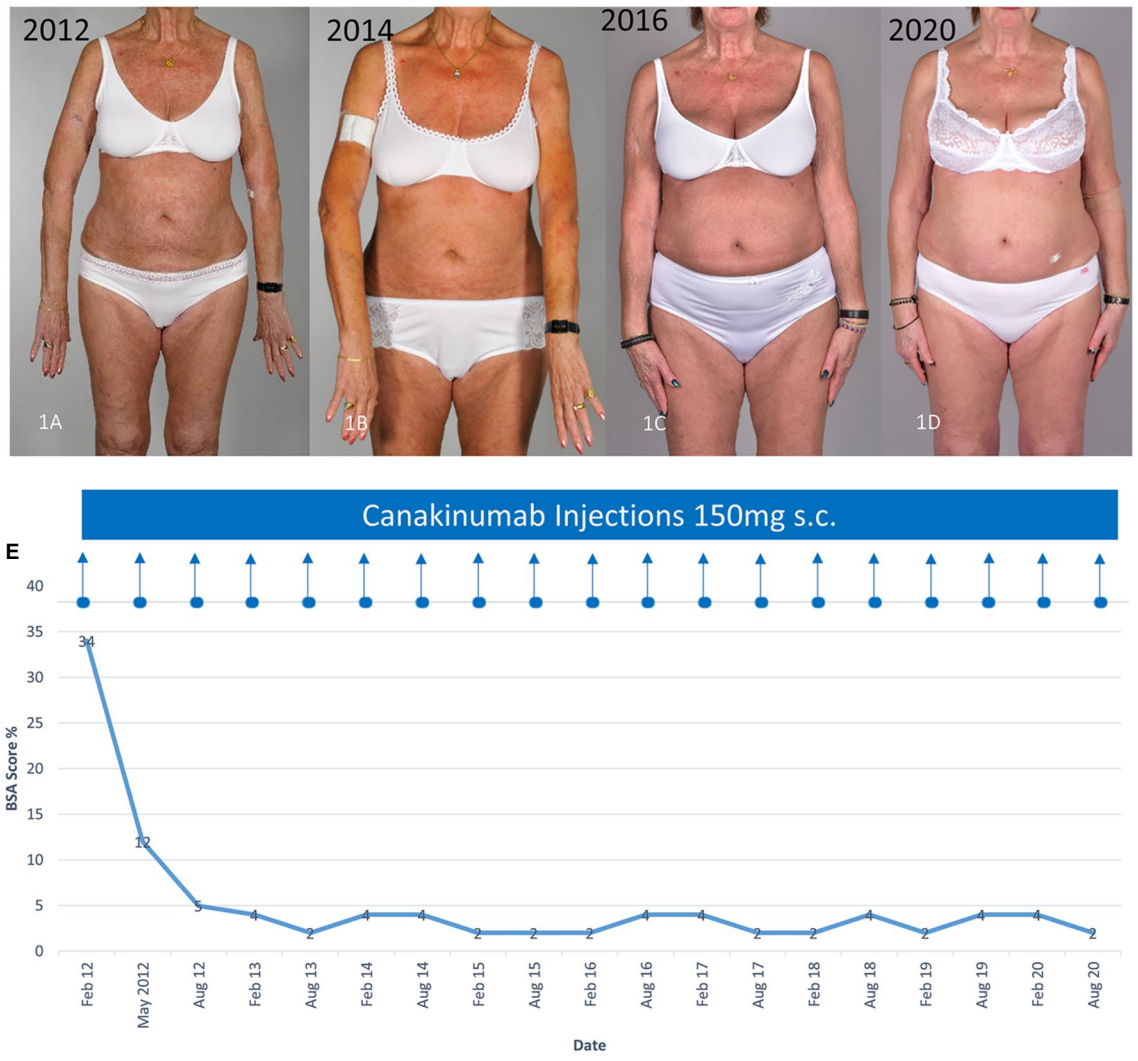

FIGURE 1
Clinical improvement of the characteristic urticarial eruption using canakinumab. **(A)** Before canakinumab, **(B–D)** during therapy with canakinumab 150mg every 6months **(E)** Clinical response assessed using the body surface area (BSA). The time course of the treatment with canakinumab and BSA affected with the urticarial rash are shown.

CD1a (clone 10; DakoCytomation, Glostrup, Denmark), CD4 (clone MT310, DakoCytomation), CD8 (clone C8/144B; DakoCytomation), CD11c (clone KB90, DakoCytomation), CD32 (KB61, Dakocytomation), CD68 (clone EBM11, Dakocytomation), CD163 (clone EDHU-1; Serotec MCA, Oxford, United Kingdom), CD206 (clone 19.2, BDPharmingen, Allschwil, Switzerland), inducible nitric oxide synthase (iNOS; clone EPR16635, Abcam, Cambridge, United Kingdom), tryptase (clone AA1, DakoCytomation), neutrophil elastase (clone NP57, DakoCytomation), IL-1β (clone 11E5; Abcam), IL-8 (clone 807; Abcam), and IL-17 (polyclonal, AF-317-NA, R&D Systems, Minneapolis, MN, United States). Irrelevant IgG subclass-matched antibodies were used as negative control. Quantitative analysis of positively stained cells was performed using the digital image analysis system NIS-Elements Software BR 2.30 (Nikon, Tokyo, Japan).

Results

Immunohistochemical analysis showed a marked decrease in neutrophil elastase, a marker for neutrophil granulocytes, within 1 month after the first canakinumab injection. Furthermore, a substantial decrease in the expression of the proinflammatory cytokines IL-1β, IL-8, and IL-17 was observed. The latter are involved in neutrophil recruitment and activation. With regard to the dermal inflammatory infiltrate, there was a marginal decrease in cells positive for the markers of myeloid dendritic cells ($CD11c^+$) and macrophage subsets, i.e., M1-like ($iNOS^+$, $CD68^+$, and $CD32^+$) macrophages. In contrast, a slight increase was seen in Langerhans cells ($CD1a^+$) and M2-like ($CD206^+$ and $CD163^+$) macrophages as well as for both T cell subsets ($CD4^+$ and $C8^+$). No difference was noted for tryptase-positive mast cells after canakinumab administration (Figures 2A,B).

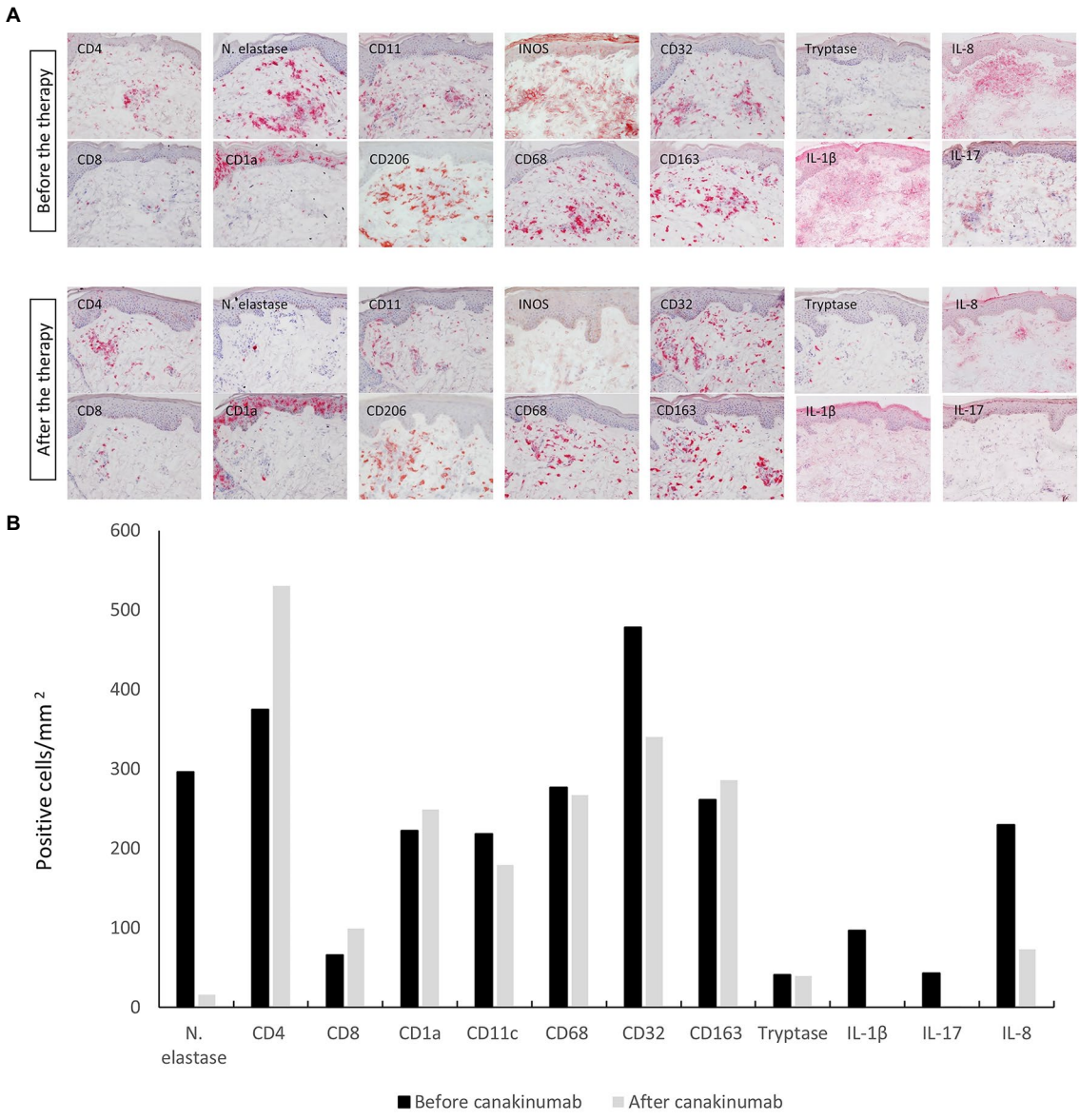

FIGURE 2
(A) Immunohistochemical staining of the cellular infiltrate with different leucocyte populations and proinflammatory cytokines from a skin-biopsy specimen obtained before and 1month after initiating treatment with canakinumab. Original magnification 200×. **(B)** Quantification of the number of stained cells in the infiltrate (cells/mm^2) before and 1month after the initiation of canakinumab.

Discussion

Our observation illustrates the long-lasting sustained positive effect of canakinumab for over 10 years in a patient with Schnitzler syndrome, confirming the key role of blocking IL-1β in the disease management.

IL-1β is a proinflammatory cytokine that not only acts as a mediator of the peripheral immune response to infections and inflammation but also plays an important role in acute and chronic autoimmune diseases, diabetes, pain, and neurological disorders. A dysregulated activity of IL-1β is characteristic in autoinflammatory diseases, which may be caused either due to abnormally elevated cytokine levels or a qualitative or quantitative deficiency of the endogenous antagonist of IL-1 receptor type 1 (4).

In cryopyrin-associated periodic syndromes, there is an uncontrolled activation of caspase-1 and subsequent abnormal IL-1β secretion by a mutation in the cryopyrin-coding gene for nucleotide-binding domain, leucine-rich repeat containing gene family, pyrin domain containing protein 3 (*NLRP3*). In patients with Schnitzler's syndrome, in whom *NLRP3* somatic mosaicism has been anecdotally identified, IL-1β secretion is up-regulated (5). The latter is thought to directly contribute to the clinical manifestations (6). In line with this notion, we observed a strong staining for IL-1β as well as for IL-8 and IL-17 together with a dense infiltrate particularly of neutrophils, dendritic cells, and macrophages in the skin lesion of our patient.

Canakinumab was developed as a human IgGκ monoclonal antibody targeting IL-1β for the treatment of immune and autoinflammatory disorders. This specific inhibition of IL-1β efficiently suppresses the neutrophil-driven inflammation and often results in a quick and effective reduction of disease activity (4, 7). We were able to demonstrate this mechanism clinically and immunohistochemically with a remarkable decrease in the proinflammatory cytokines 1β, IL-8, IL-17 and particularly of neutrophils in the skin lesions within 1 month after initiation of canakinumab. This effect has now lasted for over 10 years and the therapy is well tolerated without any side effect.

Canakinumab is generally well tolerated; however, upper respiratory tract infections are known to be the most common side effect during therapy (7, 8). In our case, the therapy with canakinumab was continued during the COVID-19 pandemic, as IL-1β together with IL-6 and tumor necrosis factor-α plays an important role as key interleukin in SARS-CoV-2-induced cytokine storm. The latter accounts for a significant part of the negative consequences of SARS-CoV-2 infection (9). Therefore, inhibition of IL-1β may be able to inhibit this excessive immune response (9, 10).

Approximately 15% of all cases of Schnitzler syndrome develop a lymphoproliferative disorder, such as Waldenström macroglobulinemia (11). Our patient showed a decrease in IgM gammopathy to 4 g/l after 1 year. Over the past years, stable values between 3.6 and 4 g/l were observed.

In brief, our case provides evidence for an excellent long-term efficacy of canakinumab in Schnitzler syndrome. There was no impact on the MGUS or its potential progression into a higher-grade lymphoproliferative disease as well as no increased susceptibility to infections. Follow-up of a large cohort of patients with Schnitzler syndrome is however necessary to better assess the response and safety of canakinumab in the long-term management of this condition.

Data availability statement

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Ethical approval was not provided for this study on human participants because Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for the publication of the images or data included in this article. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SB, SS, KH, KY, LF, LB, and NY designed the study and performed the acquisition, analysis, and interpretation of data. SB, SS, and NY wrote the manuscript. KH, KY, LF, and LB performed critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

NY has served as a consultant for Novartis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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