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Advances in skin immunology

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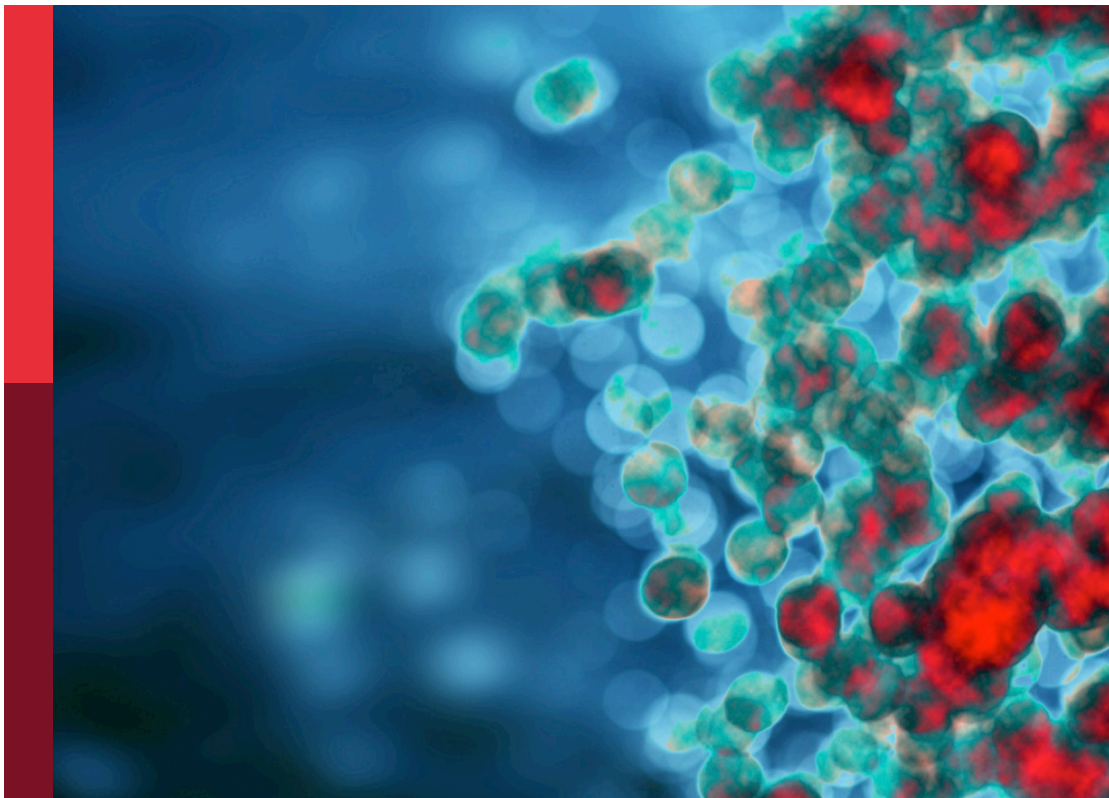

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Advances in skin immunology

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Editorial: Advances in skin immunology

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Editorial on the Research Topic
Advances in skin immunology

1 Introduction

The human skin does not fit the classic definition of a secondary lymphoid organ as it lacks lymphatic follicles, organised follicular dendritic cells and an architectural compartment containing T or B cells. However, functionally, it behaves like a secondary lymphoid organ and "immune orchestrator". It is equipped with stable memory cells (1) and is the site where adaptive responses begin (2). Furthermore, in inflammatory and/or autoimmune conditions such as psoriasis, eczema and chronic lupus erythematosus (LE), the local production of antibodies and the aggregation of T and B cells can be equated with tertiary lymphoid structures (3).

As guest editor of the special series "Advances in Skin Immunology ', I analysed papers that share a dermatological component, some of which report rare cases.

But the guiding thread of the edition the role of skin immunity as an 'orchestrator' in inflammation, metabolism and targeted therapies (4).

2 The skin's immune and metabolic balance

Patients with vitiligo can benefit from quitting tobacco and alcohol consumption, as well as taking vitamins E and B12, and the minerals copper (Cu) and zinc (Zn). (Liang et al.). The link between melanocyte survival and modulation of the immune response *via* vitamin D receptor (VDR) agonists suggests that these may be potential candidates for treating vitiligo (5).

Not only is the skin a self-regenerating organ, it also performs its own tissue repair in the event of injury. Fibrosis occurs as a defence mechanism *via* the involvement of macrophages in hypertrophic scarring. Type 1 macrophages intervene in early

inflammation, secreting proinflammatory cytokines (Shen et al.), while type 2 macrophages appear at a later stage, during tissue repair and fibrosis consolidation.

A meta-analysis of 116 studies examining autoimmune and metabolic comorbidities in *primary scarring alopecia* (Yongpisarn et al.) found significant associations with systemic lupus erythematosus (SLE), hypothyroidism, metabolic diseases and dermatological conditions.

3 Rare phenotypes with disrupted immune circuits are expressed in the molecular architecture of the skin

Although mucosal membrane involvement in patients with *Linear immunoglobulin A (IgA) bullous dermatosis (LABD)* is rare, Kowalewski and Wozniak demonstrate that severe scarring of the oesophagus and conjunctiva can occur in the presence of circulating IgG and IgA antibodies to the LAD-1 antigen. Clinicians should be aware that 'Linear IgA deposits in the Basement Membrane Zone (BMZ) detected by Direct ImmunoFluorescence (DIF) are not pathognomonic for LABD (Kowalewski and Wozniak).

Disrupted immune circuits are also found in other bullous diseases, such as immune pemphigus (6).

All interleukin 17 (IL-17) isoforms signal through IL17 receptor (IL-17R), the common subunit of all heteroreceptors of which IL-17RA is one (7). The presence of psoriasis and chronic mucocutaneous candidiasis in a five-year-old child born to consanguineous parents has been linked to a biallelic variant in the IL17 receptor A gene (Kadhi et al.).

Another important association is that between neonatal lupus, which is uncommon (8) and atopic dermatitis (AD) (Sun et al.). While the primary manifestations of neonatal lupus erythematosus (LE) are cutaneous and cardiac, due to the transplacental passage of maternal antibodies (anti-Ro/SSA or anti-La/SSB), it may be associated with AD, in a relationship that is unclear with perinatal factors. A retrospective cohort study reports that oral administration of probiotics in children with neonatal LE reduces the risk of AD (Sun et al.). This can be viewed as an example of maternal-foetal immune cross-talk, whereby disease is generated if maternal tolerance towards the foetus is disrupted.

Molecular analysis of checkpoint inhibitors associated with toxicities, such as polymorphic erythema in a patient with isolated brain metastases (melanoma) and erythema nodosum (Sun et al.), demonstrates how blocking immune regulation can reveal hidden inflammatory pathways. Immune checkpoint inhibitors (ICIs) block the interaction between programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) and their respective ligands, which are found on the surfaces of antigen-presenting cells (APCs) or tumour cells (PD-L1/2 and CD80/86) (9). On the other hand, erythema nodosum is not an autoimmune disease, but rather a reaction to superantigens (10).

This analysis shows that adverse reactions to treatment with checkpoint inhibitors differ from the tumour immune response due to the unique immune landscape of Erithema nodosum *like* immune-related adverse events (EN-like irAEs) (Sun et al.).

Another example of immunological mechanisms in rare cases is that of an 87-year-old female uremic patient undergoing peritoneal dialysis (Zhang et al.) who developed *psychogenic purpura*. This is a rare autoimmune vasculopathy also known as Gardner–Diamond syndrome or autoerythrocyte sensitisation syndrome (11). The pathology of purpura induced by psychological stress is not fully understood.

4 A "tailor-made" approach to modern immunological therapy, with a focus on the benefit-risk ratio

In recent years, *modern immunotherapy* has effectively transformed the approach to treating patients with oncological and inflammatory diseases (4). Depending on the geography and reimbursement system of each country, some molecules are included in national protocols, while others are not, as treatments are expensive. These neuro-immune signalling molecules require a personalised approach.

Thus, *treatment with anti-IL36 has been reported for generalized pustular psoriasis (GPP)* associated with Hallopeau's acrodermatitis after conventional therapies have failed (Hou et al.). Adverse reactions were not significant. IL-36 belongs to the IL-1 cytokine superfamily and is a cytokine whose signalling imbalance favours proinflammatory activity as a main driver of the pathogenesis of GPP (12). This explains the rapid impact of IL-36 inhibitors and why Spesolimab has been classified as a 'first-in-class medication' for treating acute GPP flares.

Vulgaris psoriasis, another form of psoriasis, was aggravated in a 61-year-old cancer patient who was treated with sintilimab for pulmonary metastases secondary to colon cancer (Ke et al.). In this case, guselkumab (also an IL-23 inhibitor) was introduced and there was a significant improvement in psoriasis symptoms, while the pulmonary condition remained stable during follow-up after standard cancer therapy was completed. *Combining two biological therapies in a frail cancer patient* is a modern approach based on interfering with systemic cancer-dermatology immune processes.

Proinflammatory cytokine profiles are distinct in patients with *nodular prurigo*, some of whom may have atopic dermatitis (Lee et al.). *Transcriptomic analysis* of these patients demonstrates that cytokine-mediated pathways play an important role in the

Abbreviations: VDR, vitamin D receptor; LABD, Linear immunoglobulin A (IgA) bullous dermatosis; LAD-1 antigen, 120-kDa protein; IgG, Immunoglobulin G; IgA, Immunoglobulin A; BMZ, Basement Membrane Zone; DIF, Direct ImmunoFluorescence; ASBDs, Autoimmune Subepidermal Blistering Diseases; HLA, Human Leukocyte Antigen; anti-Ro/SSA, Anti-SSA autoantibodies; anti-La/SSB, Anti-SSB autoantibodies; AD, atopic dermatitis; Ig, immunoglobulin; IL, interleukin; IL-17R, IL17 receptor; IL-17RA, IL17 receptor A gene; irAE, immune-related adverse events; GPP, generalized pustular psoriasis; x-Kit/SCF signalling pathway, the stem cell factor system; TNF-α, Tumour necrosis factor- α; IFN-γ, Interferon- γ.

pathogenesis of AD, highlighting the importance of identifying molecular targets. The pathogenesis of prurigo nodularis, which is still incompletely understood, involves cross talk between sensory nerve fibres, immune cells and the epidermis (13).

Iatrogenic vitiligo-like depigmentation (VDL) has been reported in cancer patients undergoing immunotherapy, with a notably high incidence in cases of melanoma and chronic myeloid leukaemia. In melanoma patients treated with pembrolizumab, the incidence of VDL was 2–25% due to an enhanced immune response destroying melanocytes via shared antigens (Wang et al.). In patients with chronic myeloid leukaemia treated with imatinib, vitiligo-like depigmentation occurs through the inhibition of the x-Kit/SCF signalling pathway, with an incidence of 40.9% (Wang et al.). The incidence of VDL was insignificant in cases of autoimmune inflammation (psoriasis, atopic dermatitis, inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis) treated with IL-17, IL-23, IL-4R or TNF-α inhibitors (Wang et al.).

Non-pharmacological neuroimmune modulation may be considered for *chronic spontaneous urticaria* (CSU) (Wei et al.). A meta-analysis of 1,867 patients and 22 randomised controlled trials (RCTs) by experts in traditional Chinese medicine showed that acupuncture is clinically effective and safe. It reduces the number and size of wheals, shortens the duration of flare-ups and reduces serum IgE, IFN-γ and IL-4 levels.

5 Discussions

'Advances in Skin Immunology' is a special series of papers exploring the role of skin immunity in specific inflammatory and neoplastic conditions. Present-day and future medicine (2025+) is evidence-based and precise. Although the skin is not a peripheral lymphoid organ, its behaviour is similar, with multiple integrative and dynamic levels.

A precise characterisation of skin immunity enables new immunological treatments to be applied, which require clinical and molecular integration. For this reason, it is imperative to thoroughly analyse the relationship between metabolism and skin immunity and the immune circuits disrupted in rare phenotypes. Last but not least, the benefit-risk ratio of modern immunological therapy must be considered, as each patient is unique.

Author contributions

OS: Conceptualization, Investigation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declared that this work 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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Healthy lifestyle choices: new insights into vitiligo management

Xin Liang[1†], Fei Guo[2†], Qian Fan[1], Xiaoce Cai[2], Jiao Wang[2], Jiale Chen[2], Fang Liu[1], Yuhua Du[1], Yan Chen[1*] and Xin Li[1,2,3*]

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Background: The treatment of vitiligo is complex, and providing guidance based on lifestyle habits is a good option that has not been summarized or analyzed.

Objective: To elucidate the relationship between vitiligo and lifestyle factors.

Methods: Four databases (PubMed, Embase, Cochrane, and China National Knowledge Internet) were searched for articles published between 1980 and December 2022. Keywords such as smoking, drinking, exercise, diet, and sleep were used.

Results: Based on the search strategy, 875 relevant studies were retrieved, and 73 were included in this study, of which 41 studies with 8,542 patients with vitiligo were included in the meta-analysis. Vitamin C [mean difference (MD), −0.342; 95% confidence interval (CI), −1.090−0.407; p >0.05), folic acid (MD, −1.463; 95% CI, −7.133−4.208; p >0.05), and selenium (MD, 0.350; 95% CI, −0.687−1.387; p >0.05) levels did not differ between the groups. Vitamin E (MD, −1.408; 95% CI, −2.611−−0.206; p <0.05), vitamin B12 (MD, −0.951; 95% CI, −1.672−−0.275; p <0.05), copper (MD, −0.719; 95% CI, −1.185−−0.252, p <0.005), and zinc (MD, −0.642; 95% CI, −0.731−−0.554; p <0.001) levels were lower in the vitiligo group than in the control group. The serum iron level of the vitiligo group was significantly higher than that of the control group (MD, 1.181; 95% CI, 0.390−1.972; p <0.005). Finally, more participants in the vitiligo group smoked and drank alcohol than those in the control group.

Limitations: Most studies are from Eastern countries; thus, extrapolating these results to Western populations is questionable. The significant heterogeneity may be attributed to the different stages, types, duration, center settings, population registries, etc., which seriously impair the validity of the results.

Conclusions: Patients with vitiligo should reduce smoking and alcohol consumption and take appropriate vitamin E, B12, copper, and zinc supplements. However, vitamin C, vitamin D, selenium, iron, and folic acid supplements are

unnecessary. Moreover, they should consider sun protection and avoid permanent hair dye use. Patients with vitiligo may experience sleep disturbances and sexual dysfunction, and these patients should seek help from a specialist if necessary.

Systematic review registration: https://www.crd.york.ac.uk/prospero/#recordDetails, identifier CRD42023480757.

KEYWORDS

lifestyle, systematic review, vitiligo, diet, exercise

Introduction

Vitiligo is an autoimmune skin disease associated with features such as chronic loss of melanocyte function and number and the formation of white patches or spots on the skin that impact one's esthetic appearance. The disease affects approximately 0.1%–2% of people worldwide and profoundly impact patients' quality of life.

Treatment options for vitiligo remain limited (1), as its pathogenesis remains unclear and may be related to oxidative stress, genetic, and environmental factors. Researchers have classified this disease as an autoimmune disease (2–5). Vitiligo is currently treated with narrow-band ultraviolet (UV) B-rays (UVB), 308-nm excimer lasers, calcium-regulated phosphatase inhibitors, glucocorticoids, Janus kinase inhibitors, surgical treatments, cosmetic covers, and others (6, 7). Owing to the limited treatment options for vitiligo, adopting a lifestyle approach to manage vitiligo symptoms and progression may be necessary. Although many studies have reported the influence of various lifestyle factors on vitiligo, no comprehensive literature review currently summarizes these factors to guide patients in their lifestyle choices. Therefore, in this study, we extensively reviewed the literature to summarize these findings for the first time. Our aim was to provide valuable information on vitiligo treatment and empower patients with better insights into managing their condition.

In this systematic review, we analyzed smoking, alcohol consumption, diet, exercise, light exposure, height, sleep, and permanent hair dye use data to provide more targeted, effective, and safe life coaching for patients suffering from this disfiguring disease. The summary of these studies may serve as a valuable resource for guiding future research in the field of vitiligo.

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GI, genital involvement; Hcy, homocysteine; MUFA, monounsaturated fatty acid; NOS, Newcastle–Ottawa Scale; PTH, parathormone; PUFA, polyunsaturated fatty acid; PUVA, psoralen ultraviolet A-ray; SFA, saturated fatty acid; UV, ultraviolet; UVB, ultraviolet B-rays.

Materials and methods

We performed a systematic review and meta-analysis to assess the association between vitiligo and lifestyle. This study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and registered with PROSPERO (CRD42023480757), an international registry of prospective systematic evaluations https://www.crd.york.ac.uk/PROSPERO/(Supplementary Tables S1, S2).

Data sources and searches

To explore the relationship between lifestyle and vitiligo, three reviewers (Xin Liang, Fei Guo, and Xin Li) systematically searched relevant publications from the EMBASE, PubMed, and Cochrane library electronic databases and the China National Knowledge Internet using the following keywords: "vitiligo," "sports," "smoking," "alcohol consumption," "insomnia," "diet," "vitamin C," "vitamin D," "vitamin E," "vitamin B12," "vitamin A," "folic acid," "zinc," "copper," "selenium," "iron," and "sunshine." Our comprehensive search encompassed articles written in English, spanning from January 1980 to December 2022. Additionally, the references of the retrieved articles were manually scanned.

Inclusion and exclusion criteria

Studies were selected based on the following criteria: (1) randomized controlled trials and observational studies, (2) human studies only, (3) studies describing the relationship between vitiligo and lifestyle habits, and (4) studies assessing the impact of lifestyle habits on the course of vitiligo. The exclusion criteria were as follows: (1) animal studies and (2) inability to contact the corresponding author for data. Initially, 706 publications were included (Figure 1). After a manual review of the reference lists of the included studies, three additional articles were identified. Then, these studies were carefully reviewed. Finally, 73 studies were included in this article. Figure 1 shows a flowchart of the screening process.

Data extraction and quality assessment

Three reviewers, including the first author, independently checked the data within each selected study against a predetermined data extraction form, encompassing study, participant, and outcome characteristics. The Newcastle–Ottawa scale (8) was used to assess the study quality.

Data synthesis and analysis

All analyses were performed using Stata software. The weighted mean difference/standardized mean difference and corresponding 95% confidence intervals (CIs) were aggregated to assess the association between serum vitamin E, C, zinc, copper, B12, and folic acid levels and vitiligo. Heterogeneity was tested using the I^2 statistic, with I^2 >50% considered highly heterogeneous. A random-effects model was employed owing to the observed heterogeneity, and Egger's test was used to assess publication bias. Finally, a sensitivity analysis was performed to explore the impact of potential sources of heterogeneity (Supplementary Figures S1-S4).

Results

Search results

A total of 875 articles were retrieved from PubMed, Cochrane Library, Embase databases, and China National Knowledge Infrastructure (CNKI) (Figure 1). In total, 539 duplicate items were excluded from further assessment. After screening the abstracts and titles, 106 studies remained. After a comprehensive review of the selected articles, 33 studies were excluded, and 73 studies were included in this systematic review, of which 41 studies with a total of 8,542 patients with vitiligo were finally included in the meta-analysis (Tables 1, 2).

Smoking

A meta-analysis of five studies (60–64) involving 552 patients indicated that the number of smokers in the vitiligo group was higher than in the control group [mean difference (MD), 1.240; 95% CI, 1.057–1.455; p <0.05; Table 3; Supplementary Figure S5).

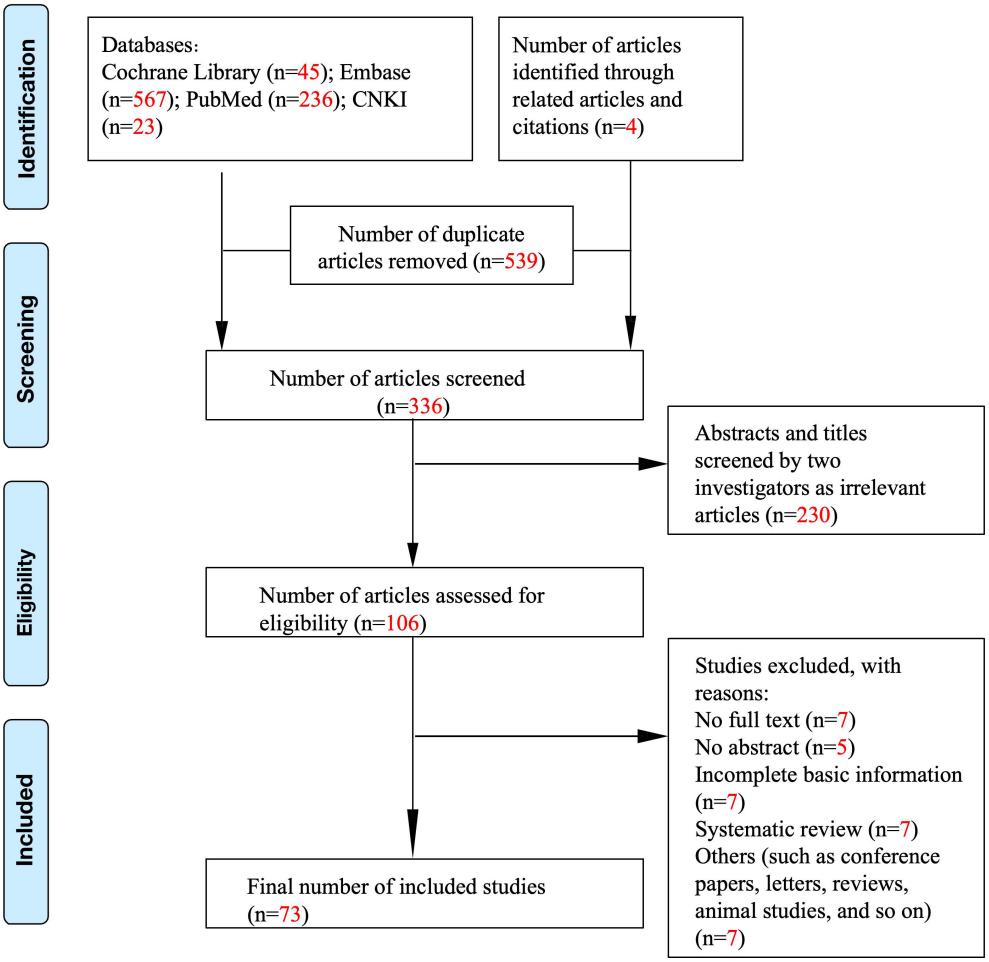

FIGURE 1
Literature search and study selection process.

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TABLE 1 Characteristics of the included studies and the Newcastle–Ottawa Scale (NOS) Quality Assessment Table.

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
Juhlin et al. (1997, Sweden) (9)	Improvement of vitiligo after oral treatment with vitamin B12 and folic acid and the importance of sun exposure	Patients with vitiligo, 100	Test: tablets containing vitamin B12 (1 mg cyanocobalamin) and folic acid (5 mg) should be taken twice daily for 3 months. Goal: to expose their skin to the sun in summer and UVB irradiation in winter	Single-arm study	NR	Repigmentation was clearly noted in 52 patients; 37 had been exposed to sunlight from April to September in Sweden, and six had been exposed to UVB lamps once or twice weekly in the winter. Repigmentation was most evident in sun-exposed areas, where 38% of the patients had previously noted repigmentation during the summer months. Total repigmentation was observed in six patients. The spread of vitiligo stopped in 64% of the patients after treatment.	2
Lajevardi et al. (2015, Providence) (10)	Vitiligo and associated pigmentation, sun exposure, and lifestyle factors in women	63,315 women	Pigmentation, sun exposure, and lifestyle factors	Cohort study	12 years	Women who had a painful burn/blistering skin reaction after 2 h of sun exposure as children/adolescents had a higher risk of vitiligo than those with no reaction or only redness after sun exposure. Women with strong tanning abilities had a higher risk of developing vitiligo compared to those without the ability to tan. In this study, no correlation was observed between the risk of vitiligo and body mass index, physical activity, or alcohol intake.	9
Kulkarni et al. (2016, India) (11)	A cross-sectional study to assess the incompatible dietary behaviors of patients suffering from skin diseases: A pilot study	32 patients with vitiligo aged 18–60 years with disease duration of up to 6 months, and 32 healthy controls	Incompatible diet	Case–control study	NR	The scores for consumption of incompatible diet and dietary habits in patients with vitiligo were similar to those of their respective controls.	7
Liu et al. (2021, China) (12)	Location, spreading, and oral corticosteroids are associated with insomnia in patients with vitiligo: a case–control study	Patients with vitiligo with insomnia, 204; patients with vitiligo without insomnia, 205	With or without insomnia	Case–control study	NR	Vitiligo on the face and neck, progression of vitiligo, and oral corticosteroids remained risk factors for insomnia in patients with vitiligo.	5
Lee et al. (2021, Korea) (13)	Height and risk of vitiligo: a nationwide cohort study	15,980,754 individuals	Height	Cohort study	Participants were followed until vitiligo diagnosis or until the end of 2015	Findings from this nationwide cohort study suggest that adult height positively correlates with the risk of vitiligo in Koreans. The association was stronger in the elderly population.	8

(Continued)

TABLE 1 Continued

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
Sanad et al. (2020, Egypt) (14)	Serum zinc and inflammatory cytokines in vitiligo	Patients with vitiligo, 50; healthy controls, 100	Zinc	Case–control study	NR	The mean serum levels of zinc were significantly reduced in patients with vitiligo	7
Lee et al. (2020, Korea) (15)	Association between vitiligo and smoking: a nationwide population-based study in Korea	Patients with vitiligo, 22,811	Smoking	Cohort study	NR	The results suggested there are suppressive effects of smoking on the development of vitiligo.	8
Derakhshandeh-Rishehri et al. (2019, Iran) (16)	Role of fatty acid intake in generalized vitiligo	Patients with vitiligo, 100; controls, 110	Total fat, PUFA, MUFA, SFA, linoleic acid, linolenic acid, oleic acid, EPA, DHA, and cholesterol	Case–control study	NR	Total fat intake was associated with an increased risk of vitiligo.	7
Hussein et al. (2019, Egypt) (17)	Role of vitamin B12, folic acid, and oxidative damage in the serum of patients with vitiligo	Patients with vitiligo, 42; controls, 36	Vitamin B12 and folic acid	Case–control study	6 months	The results declared significant decreases in vitamin B12 and folic acid levels in patients with vitiligo compared to those in controls.	8
Iraji et al. (2017, Iran) (18)	Comparing the improvement of unstable vitiligo in patients treated by topical PUVA therapy alone, topical PUVA therapy and oral vitamin D, and topical PUVA therapy and oral vitamin D and vitamin B12	60 patients with active vitiligo	Vitamin D and B12	Randomized controlled trial	6 months	The group receiving vitamin D demonstrated higher reductions in the extent and area of lesions compared to that in the control group.	6
Akhter et al. (2017, Pakistan) (19)	Estimation of serum vitamin B12, folic acid, homocysteine, and ferritin levels in subjects with vitiligo	Patients with vitiligo, 50; controls, 50	Vitamin B12 and folic acid	Case–control study	12 months	Serum vitamin B12 and folic acid levels were significantly lower in patients with vitiligo than in controls.	8
Dass (2016, India) (20)	Search for clinical and laboratory markers of severity and instability of vitiligo: a cross-sectional observational hospital-based study	Patients with vitiligo, 40; controls, 40	Vitamin B12, folic acid, and Hcy	A cross-sectional observational study		Elevated serum Hcy levels and reduced serum vitamin B12 levels were significantly associated with vitiligo. No significant association was observed with reduced serum folic acid levels.	6
Wu et al. (2015, Providence) (21)	Use of permanent hair dyes and risk of	254 incident vitiligo cases among	Permanent hair dyes	Cohort study	NR	After adjusting for multiple covariates, there was a borderline increased risk of vitiligo associated with using	8

(Continued)

TABLE 1 Continued

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
	vitiligo in women	68,176 participants				permanent hair dyes. This association was more pronounced in individuals who used hair dyes for a longer duration, initiated use before the age of 30, and had a longer usage period since their first use.	
Manisha et al. (2015, India) (22)	Epidemiological study of svitra (vitiligo) with special reference to viruddha ahara (incompatible diet)	Patients with vitiligo, 242	Incompatible diet	Observational studies	NR	The study observed that among the 242 patients with vitiligo, 100% had an incompatible combination of food, and 100% had an incompatible food sequence. In addition, 95.45% of patients exhibited an incompatible cooking method, and 71.90% reported an incompatibility of palatability. Based on the analysis of the data, the researchers concluded that incompatible food is the most potent etiological factor of vitiligo and should be avoided.	2
Ghiasi et al. (2015, Iran) (23)	Serum levels of vitamin B12, folic acid, and homocysteine in patients with vitiligo	Patients with vitiligo, 30; controls, 30	Vitamin B12 and folic acid	Case–control study	NR	No significant differences were observed in the levels of serum homocysteine, vitamin B12, and folic acid between patients with vitiligo and healthy controls. Moreover, there were no associations between these factors and age, body weight, or sex, nor with the extent, duration, and type of vitiligo.	7
Colucci et al. (2015, Italy) (24)	Evaluation of an oral supplement containing *Phyllanthus emblica* fruit extracts, vitamin E, and carotenoids in vitiligo treatment	Patients with vitiligo, 65; controls, 65	Group A included patients treated with oral antioxidants, and group B included individuals not treated with antioxidants. Group A patients took one tablet of an oral supplement containing *P. emblica* (100 mg), vitamin E (4.7 mg), and carotenoids (10 mg) three times a day for 6 months and were asked to stop the treatment in case of side effects. Both groups were treated at the same time with a comparable topical therapy and/or phototherapy	Case–control study	10 months	Group A patients showed significantly mild repigmentation in the head and neck region and on the trunk compared to other body sites. Although the repigmentation was not statistically significant for each individual body site, it was higher overall. Additionally, patients in Group A exhibited a higher level of disease stability.	6
Khurrum et al. (2014, Saudi Arabia) (25)	Is there a real relationship between serum levels of homocysteine and vitiligo?	Patients with vitiligo, 153; controls, 153	Vitamin B12, Hcy, and folic acid	Case–control study	NR	The results of this study revealed that there was no association between serum levels of Hcy and vitamin B12 and vitiligo. However, the folic acid levels were higher in patients with vitiligo than in controls.	6

(Continued)

TABLE 1 Continued

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
Kim et al. (2015, Korea) (26)	Childhood facial vitiligo: How intractable is it?	Medical data and photos of 111 children with facial vitiligo who were followed up for more than 1 year.	Nutritional education, vitamin E (α-tocopherol 100–400 IU/day), folic acid (1–2 mg/day), multivitamin intake, and antioxidant cosmetics are the mainstay of treatment. Conventional therapies, including oral, topical, and/or intralesional corticosteroids, topical macrolactam, excimer lasers, and epidermal grafts, were employed	Single-arm experiment	NR	9% of patients demonstrated no improvement regardless of treatment modality, whereas 91% showed improvement in lesions.	2
Araujo et al. (2014, Brazil) (27)	The relation between vitamin B12 levels and vitiligo repigmentation	Thirty-three patients were treated for vitiligo lesions using either 308 nm excimer light or NB UVB 311 nm (depending on the expansion of the lesion). They were given vitamin B12 before treatment began.	Vitamin B12	Single-arm experiment	NR	An association between vitamin B12 levels (upper than 365) and better repigmentation was not found in any of the subjects.	1
Finamor et al. (2013, Brazil) (28)	A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis	Serum 25(OH) D3, PTH	16 patients with vitiligo received vitamin D3 35,000 IU once daily for 6 months in association with a low-calcium diet (avoiding dairy products and calcium-enriched foods like oats, rice, or soy "milk") and hydration (minimum 2.5 L daily)	Before–after study in the same patient	NR	Following the treatment, there was a significant increase in the levels of 25(OH)D3 and a significant decrease in the levels of PTH among patients with vitiligo. The serum concentrations of PTH and 25 (OH)D3 were inversely correlated. Of the 16 patients with vitiligo, 14 achieved a repigmentation level ranging from 25% to 75%.	4
Yaghoobi et al. (2011, Iran) (29)	Original article title: "Comparison of therapeutic efficacy of topical corticosteroid and oral zinc sulfate-topical corticosteroid combination in the treatment of patients with vitiligo: a clinical trial"	35 patients with vitiligo were randomized into two groups, with the first group receiving topical corticosteroids and the second group receiving a combination of oral zinc sulfate-topical corticosteroids	Zinc	Randomized controlled trial	1 year	The mean response in the corticosteroid group was 21.43%, while in the zinc sulfate-corticosteroid combination group, it was 24.7%. However, there was no statistically significant difference between the two groups regarding therapeutic efficacy.	7
Silverberg et al. (2011, United States) (30)	Serum homocysteine is associated with the extent of vitiligo vulgaris	31 adult and 24 pediatric patients with vitiligo vulgaris	Homocysteine and vitamin B12	Cohort study	3 years	Active vitamin B12 supplementation may be beneficial for patients with vitiligo.	7

(Continued)

TABLE 1 Continued

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
Gonul et al. (2010, Turkey) (31)	Serum vitamin B12, folate, ferritin, and iron levels in Turkish patients with vitiligo	Patients with vitiligo, 42; controls, 36	Vitamin B12 and folic acid	Case–control study	NR	The vitamin B12 and folate levels in patients with vitiligo did not differ from those of controls.	7
Khan et al. (2009, India) (32)	Circulatory levels of antioxidants and lipid peroxidation in Indian patients with generalized and localized vitiligo	Patients with vitiligo, 30; controls, 30	Vitamin C and vitamin E	Case–control study	NR	The vitamin C and E levels of the patients with vitiligo were significantly lower compared to those in the controls.	7
Mouzas et al. (2008, Greece) (33)	Increased frequency of self-reported parasomnias in patients suffering from vitiligo	Group A, 116 patients with vitiligo; Group B, 52 patients suffering from other dermatological disorders without psychogenic involvement (such as acne). The control group (Group C) consisted of 48 partners and relatives of the patients without dermatological disorders	Nocturnal enuresis, sleepwalking, night illusions, sleep terrors, and nightmares	Case–control study	NR	Vitiligo sufferers reported significantly more sleep disorders compared to that in the controls, especially sleepwalking, nocturnal enuresis, night illusions, sleep terrors, and nightmares. In contrast, individuals with other dermatological diseases showed a statistically significant difference compared to that in the control group only in nightmares and nocturnal enuresis. Additionally, when comparing vitiligo sufferers to those with other dermatological diseases, significant differences were observed in nightmares, night illusions, and sleepwalking. However, these two groups had no statistically significant difference in sleep terrors and nocturnal enuresis.	6
Agrawal et al. (2004, India) (34)	Study on the antioxidant status of patients with vitiligo at different age groups in Baroda	Patients with vitiligo, 63; controls, 60	Vitamin E	Case–control study	NR	No significant change in plasma vitamin E levels was observed in vitiliginous patients compared to that in controls.	6
Akyol et al. (2002, Turkey) (35)	The effects of vitamin E on the skin lipid peroxidation and the clinical improvement in patients with vitiligo treated with PUVA	Patients were assigned to receive either only PUVA (first group: 15) or PUVA and vitamin E (900 IU daily perorally) (second group: 15) for 6 months	Vitamin E	Case–control study	6 months	Vitamin E may prevent oxidative distress caused by PUVA therapy. However, it does not have a significant impact on the clinical improvement of vitiligo lesions.	5

(Continued)

TABLE 1 Continued

Authors (publication year, country/ region)	Studies	Sample size	Intervention	Study design	Duration	Main results	NOS
TJIOE et al. (2002, Sweden) (36)	Erratum: Treatment of vitiligo vulgaris with narrow-band UVB (311 nm) for one year and the effect of the addition of folic acid and vitamin B12	Patients with vitiligo, 27	The first group received narrow-band UVB phototherapy, and the second group received vitamin B121000 mg sustained-release tablets and folic acid 5-mg tablets twice a day and received narrow-band UVB phototherapy.	Randomized controlled trial	12 months	The study reconfirmed the efficacy of narrow-band UVB phototherapy in vitiligo. However, it did not demonstrate any additional benefits from adding vitamin B12 and folic acid.	5
Picardo et al. (1994, Italy) (37)	Antioxidant status in the blood of patients with active vitiligo	Patients with vitiligo, 62; controls, 60	Vitamin E	Case–control study	NR	The blood levels of vitamin E in individuals with vitiligo were not significantly different from those of healthy age-matched controls.	6
Bashrahil et al. (2022, SAU) (38)	Association between vitamin D, zinc, and thyroid biomarker levels with vitiligo disease: a retrospective cohort study in a tertiary care center	Patients with vitiligo, 297	Vitamin D and zinc	Cohort study	NR	No significant association was observed between vitamin D or zinc levels and any of the characteristics or treatments of vitiligo.	5
Memon et al. (2021, Pakistan) (39)	Effect of vitamin B12 and folic acid in patients with vitiligo	Patients with vitiligo, 155	Vitamin B12 and folic acid	Cross-sectional study	6 months	Serum vitamin B12 and folic acid levels significantly affected the duration of vitiligo in patients.	5
Boisseau-Garsaud et al. (2002, France) (40)	Increase in total blood antioxidant status and selenium levels in black patients with active vitiligo	Patients with vitiligo, 11 Healthy controls, 11	Selenium	Case–control study	NR	Total blood antioxidant status and selenium levels were significantly increased in vitiligo patients, compared to those in sex- and age-matched controls	6

NR, not reported; NOS, Newcastle–Ottawa Scale; UVB, ultraviolet B-rays; Hcy, homocysteine; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PTH, parathormone.
NOS scores ranged from 0 to 9 points. A star scoring system was used to semi-quantitatively assess study quality. Each numbered item has been adjusted to a maximum of four stars in the selection and exposure categories. A maximum of two stars was assigned for comparison purposes. We considered studies achieving ≥7, 4–6, and <4 stars as having high, medium, and poor quality, respectively.

Additionally, a cohort study (15) involving 22,991,641 patients showed that smoking has an inhibitory effect on the development of vitiligo.

Alcohol consumption

We conducted a meta-analysis of two studies (60, 61) involving 255 patients, and the results showed that there was a significantly higher prevalence of alcohol dependence among vitiligo patients compared to the control group (MD, 1.474; 95% CI, 1.105–1.965; p <0.005; Table 4; Supplementary Figure S6).

Diet

Vitamin C

A meta-analysis of three studies (50, 65, 80) showed no significant differences in serum vitamin C levels between patients with vitiligo and controls (MD, 0.342; 95% CI, −1.090–0.407;

TABLE 2 Characteristics of the studies included in the meta-analysis and the Newcastle–Ottawa Scale (NOS) Quality Assessment Table.

Author (pub. year)	Study setting	Study period	Study design	Instruments used in the study	Controls: total number (M/F)	Cases: total number (M/F)	Classification of vitiligo	Mean age of controls, years, mean (SD)	Mean age of cases years, mean (SD)	Disease Duration, mean (SD)	NOS
Khoshdel et al. (2022) (41)	Iran	NR	Case–control study	zinc, copper	137 (62/75)	117 (48/69)	84% of patients had generalized/universal and 16% of localized/segmental stable vitiligo	47.19 (8.03)	37.64 (13.01)	9.57 (9.25)	8
Zaki et al. (2020) (42)	Egypt	1/2009–9/2009	Case–control study	zinc	50 (24/26)	50 (22/28)	Different types of vitiligo	31.19 (10.46)	33.64 (14)	NR	8
Wacewicz et al. (2018) (43)	Poland	NR	Case–control study	zinc, copper, selenium,	58 (17/41)	50 (21/29)	Active generalized vitiligo	40.12 (13.80)	44.76 (15.62)	NR	7
Mirnezami et al. (2018) (44)	Iran	4/2015–4/2016	Case–control study	zinc	103	103	Generalized, focal, and mucosal vitiligo	NR	NR	NR	7
Narang et al. (2017) (45)	India	NR	Case–control study	zinc, copper	8	29	NR	NR	NR	NR	6
Bagheri Hamidi et al. (2020) (46)	Iran	2/2017–4/2018	Case–control study	vitamin B12	100 (55/45)	104 (52/52)	Vulgaris, segmental, and universalis	35.97 (10.98)	35.63 (10.45)	11.66 (9.59)	7
Mogaddam et al. (2017) (47)	Iran	3/2012–4/2013	Case–control study	zinc	100 (54/46)	100 (54/46)	vulgaris	25.32 (2.47)	24.97 (2.58)	41.37 (26.41)	8
Dogan et al. (2016) (48)	Turkey	NR	Case–control study	zinc	52	52	NR	NR	NR	NR	5
Ataş et al. (2015) (49)	Turkey	2011–2013	Case–control study	folic acid, vitamin B12	60 (30/30)	60 (30/30)	Acrofacial, 8 Segmental, 3 Generalized, 48 Universal, 1	36.25 (7.8)	35.7 (11.2)	NR	7
Agrawal et al. (2014) (50)	Nepal	NR	Case–control study	vitamin C, vitamin E	80 (36/44)	80 (39/41)	Active and stable patients with vitiligo	32.61 (15.63)	32.66 (16.82)	8.76 (8.51)	7
Ramadan et al. (2013) (51)	Egypt	NR	Case–control study	vitamin E	15 (4/11)	15 (6/9)	the non-segmental type and only stable	33.47 (10.21)	30.53 (14.77)	6.27 (3.11)	7
Yasar et al. (2012) (52)	Turkey	NR	Case-control study	folic acid, vitamin B12	40 (22/18)	40 (23/17)	focal, segmental, acrofacial, and generalized	25.42 (4.48)	27.77 (13.44)	19.60 (13.39)	6
Karadag et al. (2012) (53)	Turkey	NR	Case–control study	vitamin B12, folic acid	52 (17/35)	69 (33/36)	NR	32.3 (16.7)	37.6 (8.6)	25.5 (35.3)	5
Balci et al. (2009) (54)	Turkey	NR	Case–control study	vitamin B12, folic acid	31 (14/17)	48 (27/21)	Vitiligo was clinically defined as localized, generalized, or universal, whereas disease activity was identified as stable or progressive	39.32 (13.15)	37.94 (16.27)	9.28 (9.32)	6

(Continued)

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TABLE 2 Continued

Author (pub. year)	Study setting	Study period	Study design	Instruments used in the study	Controls: total number (M/F)	Cases: total number (M/F)	Classification of vitiligo	Mean age of controls, years, mean (SD)	Mean age of cases years, mean (SD)	Disease Duration, mean (SD)	NOS
Jain et al. (2008) (55)	India	11/2006–11/2007	Case–control study	vitamin E	40 (20/20)	40 (20/20)	Generalized vitiligo	NR	NR	NR	6
Ines et al. (2006) (56)	Tunisia	NR	Case–control study	vitamin A, vitamin E, selenium	40 (25/15)	36 (22/14)	Active and stable patients with vitiligo	NR	NR	NR	7
Park et al. (2005) (57)	Korea	NR	Case–control study	vitamin B12, folic acid	80 (35/45)	77 (32/45)	Localized and generalized vitiligo	35.8 (11.8)	34.5 (18)	NR	7
Arora et al. (2002) (58)	India	9/1993–2/1995	Case–control study	zinc	24	15	NR	NR	NR	NR	6
Kim et al. (1999) (59)	Korea	NR	Case–control study	vitamin B12, folic acid	30 (14/16)	100 (50/50)	Eighty-seven patients had spreading vitiligo, and 13 were stable.	NR	NR	NR	6
Hussein et al. (2019) (17)	Egypt	1/11/2018–31/3/2019	Case–control study	vitamin B12, folic acid	36 (22/14)	42 (29/13)	Segmental, 30 non-segmental, 40	38.00 (4.81)	36.87 (11.09)	6.74 (0.80)	8
Sharma et al. (2017) (60)	India	NR	Case–control study	smoking, alcohol consumption	100 (64/36)	100 (66/34)	Non-segmental vitiligo	NR	NR	NR	8
Tanacan et al. (2020) (61)	Turkey	11/2014–3/2016	Cross-sectional study	smoking, alcohol consumption,	155 (84/71)	155 (83/72)	NR	37.37 (12.60)	37.04 (12.07)	NR	6
Dragoni et al. (2017) (62)	Italu	3/2012–3/2015	Case–control study	smoking	200 (92/108)	200 (92/108)	Non-segmental vitiligo	NR	NR	NR	6
Taneja et al. (2020) (63)	India	NR	Cross-sectional study	smoking	54 (22/33)	54 (19/35)	NR	32.4 (9.7)	30.7 (11.3)	10.3 (5.8)	7
Gorial et al. (2021) (64)	Iraq	9/2018–5/2019	Case–control study	smoking	63 (30/33)	63 (34/29)	Vulgaris, 45 Universal, 9 Focal, 7 Acrofacial, 2	39.9 (11.6)	38.7 (14.0)	13.3 (12.7)	7
Haider et al. (2010) (65)	Bangladesh	9/2007–7/2008	Case–control study	vitamin C, zinc	30 (12/18)	30 (10/20)	NR	NR	NR	NR	7
Barikbin et al. (2011) (66)	Iran	NR	Case–control study	selenium	45(15/30)	60 (26/34)	Active vitiligo vulgaris	31.28	31.83	NR	7
Ozturk et al. (2008) (67)	Turkey	NR	Case–control study	selenium	30 (12/18)	30 (19/11)	Generalized stable vitiligo	27.9 (7.1)	23.6 (7.4)	NR	7

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TABLE 2 Continued

Author (pub. year)	Study setting	Study period	Study design	Instruments used in the study	Controls: total number (M/F)	Cases: total number (M/F)	Classification of vitiligo	Mean age of controls, years, mean (SD)	Mean age of cases years, mean (SD)	Disease Duration, mean (SD)	NOS
Beazley et al. (1999) (68)	UK	NR	Case–control study	selenium	61 (19/42)	5932	Most of the group presented the clinical type of vitiligo vulgaris (n 44), and 13 patients had acrofacial vitiligo, two the segmental type, one the focal form, and one vitiligo totalis	NR	NR	NR	7
Yandong Wang et al. (2012) (69)	China	9/2010–9/2011	Case–control study	zinc, copper	120	120	NR	NR	NR	NR	7
Xuemin Wang (2011) (70)	China	NR	Case–control study	zinc, copper, iron	30	28	NR	NR	NR	NR	6
Aiping Yao (2011) (71)	China	1/2007–2009	Case–control study	zinc, copper, iron, selenium	50	90	Segmental vitiligo, 35 Localized vitiligo, 45 Generalized vitiligo, 10	36.7 (16.8)	35.6 (20.3)	NR	7
Jin Zhao et al. (2011) (72)	China	NR	Case–control study	selenium	16	36	Localized vitiligo, 6 Generalized vitiligo, 9 Disseminated vitiligo, 2 Segmental vitiligo, 1	28.45 (11.93)	36.4 (19.5)	NR	7
Zongping Li et al. (2001) (73)	China	NR	Case–control study	copper	30	96	NR	NR	NR	NR	6
Fei Wang et al. (1993) (74)	China	NR	Case–control study	zinc, copper, iron, selenium	34	34	NR	NR	NR	NR	8
Yi Wu et al. (2010) (75)	China	NR	Case–control study	zinc, copper	70	70	NR	NR	NR	NR	7
Xiaohua Wang et al. (1996) (76)	China	NR	Case–control study	zinc, copper	141	48	NR	NR	27.8 (9.7)	NR	7
Caixia Tu et al. (1991) (77)	China	NR	Case–control study	zinc, copper	36	27	Localized vitiligo generalized vitiligo	NR	NR	NR	7
Caixia Tu et al. (1998) (78)	China	NR	Case–control study	selenium	37	29	Segmental vitiligo, 5 Localized vitiligo, 13 Generalized vitiligo, 11	NR	NR	NR	7
Jialing Song et al. (2017) (79)	China	6/2013–1/2016	Case–control study	zinc, copper, selenium	63	63	NR	37.02 (5.91)	37.22 (5.63)	NR	7
Al-Hattab et al. (2020) (80)	Iraq	11/2019–3/2020	Case–control study	zinc, vitamin c	50 (24/26)	50 (28/22)	NR	26.30 (8.11)	28.60 (8.00)	NR	7

NOS, Newcastle–Ottawa Scale; NR, not reported; Pub, public. A star scoring system was used to semi-quantitatively assess study quality. Each numbered item was adjusted to a maximum of four stars in the selection and exposure categories. A maximum of two stars was assigned for comparison purposes. NOS scores ranged from 0 to 9 points. We considered studies achieving ≥7 stars as high quality, those with 4–6 stars as medium quality, and those with <4 stars as poor quality.

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TABLE 3 The number of people with smoking and alcohol consumption habits between the vitiligo and control groups.

Studies	Vitiligo group		Control group		RR [95% CI]	p-value
	Events	Total	Events	Total		
Smoking						
Sharma et al. (2017) (60)	25	100	19	100	1.316 [0.776–2.231]	
Tanacan et al. (2020) (61)	59	155	56	155	1.054 [0.788–1.408]	
Dragoni et al. (2017) (62)	72	180	58	200	1.379 [1.041–1.827]	
Taneja et al. (2020) (63)	8	54	9	54	0.889 [0.371–2.131]	
Gorial et al. (2021) (64)	43	63	31	63	1.387 [1.025–1.876]	
Meta-analysis (fixed, I^2 = 0%)					1.240 [1.057–1.455]	0.008#
Alcohol consumption						
Sharma et al. (2017) (60)	34	100	27	100	1.259 [0.825–1.921]	
Tanacan et al. (2020) (61)	50	155	30	155	1.667 [1.124–2.472]	
Meta-analysis (random, I^2 = 0%)					1.474 [1.105–1.965]	0.008#

CI, confidence interval; RR, risk ratio; #p <0.005.

TABLE 4 Serum zinc, vitamin B12, folic acid, vitamin E, and vitamin C levels between the vitiligo and control groups.

Studies	Vitiligo group		Control group		MD [95% CI]	p-value
	Mean	SD	Mean	SD		
1. Zinc						
Khoshdel et al. (2022) (41)	95.01	58.95	121.83	33.8	−0.570 [−0.821–−0.318]	
Zaki et al. (2020) (42)	50.93	11.02	77.09	12.16	−2.254 [−2.758–−1.751]	
Wacewicz et al. (2018) (43)	0.848	0.12	0.997	0.292	−0.650 [−1.038–−0.262]	
Mirnezami et al. (2018) (44)	85.4	14.1	91.8	16.2	−0.421 [−0.698–−0.144]	
Narang et al. (2017) (45)	20.05	7.89	32.72	0.68	−1.794 [−2.682–−0.905]	
Mogaddam et al. (2017) (47)	80.11	17.1	96.1	16.16	−0.961 [−1.254–−0.668]	
Dogan et al. (2016) (48)	92.84	15.51	88.94	13.43	0.269 [−0.117–0.655]	
Arora et al. (2002) (58)	97.3	26.6	105.3	30.1	−0.278 [−0.926–0.371]	
Haider et al. (2010) (65)	1.08	0.07	0.95	0.35	0.515 [0.000–1.030]	
Jialing Song et al. (2017) (79)	0.84	0.12	1.1	0.2	−1.576 [-1.980–−1.173]	
Caixia Tu et al. (1991) (77)	11.5	3.15	13.54	2.34	−0.751 [−1.268–−0.235]	
Xiaohua Wang et al. (1996) (76)	74.23	18.99	97.4	13.8	−1.517 [−1.879–−1.155]	
Yi Wu et al. (2010) (75)	6.416	1.758	7.193	1.412	−0.487 [−0.824–−0.151]	
Fei Wang et al. (1993) (74)	0.9	0.51	1.06	2.25	−0.098 [−0.574–0.378]	
Aiping Yao et al. (2011) (71)	0.88	0.26	1.07	0.31	−0.682 [−1.036–−0.327]	
Yandong Wang et al. (2012) (69)	12.79	2.31	13.02	3.53	−0.077 [−0.330–0.176]	
Xuemin Wang et al. (2011) (70)	9.9	0.51	15.62	2.94	−2.667 [−3.380–−1.953]	
Al-Hattab et al. (2020) (80)	82.49	23.92	98.78	36.62	−0.527 [−0.926–−0.128]	
Meta-analysis (random, I^2 = 91.3%)					−0.774 [−1.083–−0.466]	0.000*

(Continued)

TABLE 4 Continued

Studies	Vitiligo group		Control group		MD [95% CI]	p-value
	Mean	SD	Mean	SD		
1. Zinc						
1.1 Vitiligo type						
1.1 Generalized vitiligo						
Mirnezami et al. (2018) (44)	81.3	12.7	91.8	16.2	−0.701 [−1.024–−0.379]	
Khoshdel et al. (2022) (41)	93.11	59.33	121.83	33.8	−0.624 [−0.891–−0.357]	
Yi Wu et al. (2010) (75)	5.401	1.198	7.193	1.412	−1.306 [−1.859–−0.752]	
Meta-analysis (random, I^2 = 58.3%)					−0.799 [−1.121–−0.477]	0.000*
1.1.2 Focal vitiligo						
Mirnezami et al. (2018) (44)	92.1	13.8	91.8	16.2	0.019 [−0.349–0.388]	
Khoshdel et al. (2022) (41)	98.69	58.63	121.83	33.8	−0.610 [−1.075–−0.146]	
Yi Wu et al. (2010) (75)	6.767	1.793	7.193	1.412	−0.269 [−0.629–0.092]	
Meta-analysis (random, I^2 = 54.3%)					−0.264 [−0.601–0.073]	0.125
1.2 Sex						
1.2.1 Female						
Khoshdel et al. (2022) (41)	92.55	56.83	112.53	33.78	−0.438 [−0.769–−0.107]	
Wacewicz et al. (2018) (43)	0.812	0.101	0.987	0.281	−0.778 [−1.271–−0.284]	
Meta-analysis (fixed, I^2 = 20.3%)					−0.557 [−0.874–−0.240]	0.001*
1.2.2 Male						
Khoshdel et al. (2022) (41)	99.12	62.1	126.87	29.28	−0.597 [−0.982–−0.212]	
Wacewicz et al. (2018) (43)	0.897	0.129	1.021	0.325	−0.523 [−1.174–0.128]	
Meta-analysis (fixed, I^2 = 0.0%)					−0.578 [−0.909–−0.246]	0.0000*
1.3 Vitiligo disease activity						
1.3.1 Progressive						
Jialing Song et al. (2017) (79)	0.67	0.1	1.1	0.2	−2.556 [−3.089–−2.024]	
Yandong Wang et al. (2012) (69)	13.2	3.44	13.02	3.53	0.051 [−0.266–0.369]	
Meta-analysis (random, I^2 = 98.5%)					−1.243 [−3.798–1.312]	0.340
1.3.2 Stable						
Jialing Song et al. (2017) (79)	0.95	0.14	1.1	0.2	−0.804 [−1.306–−0.303]	
Yandong Wang et al. (2012) (69)	12.83	2.86	13.02	3.53	−0.057 [−0.361–0.246]	
Meta-analysis (random, I^2 = 84.8%)					−0.403 [−1.133–0.327]	0.279
2.Vitamin B12						
Bagheri Hamidi et al. (2020) (46)	384.62	198.63	434.1	177.86	−0.262 [−0.538–0.014]	
Ataş et al. (2015) (49)	372	142	348	121	0.182 [−0.177–0.541]	
Yasar et al. (2012) (52)	212.9	81.67	241.15	126.23	−0.266 [−0.706–0.175]	
Karadag et al. (2012) (53)	250.6	112.4	316.5	152	−0.504 [−0.869–−0.138]	
Balci et al. (2009) (54)	211.69	211.38	198.32	103.49	0.075 [−0.376–0.527]	
Park et al. (2005) (57)	668	290	875	302	−0.699 [−1.021–−0.376]	

(Continued)

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TABLE 4 Continued

Studies	Vitiligo group		Control group		MD [95% CI]	p-value
	Mean	SD	Mean	SD		
2.Vitamin B12						
Kim et al. (1999) (59)	630.25	230.94	627.16	251.35	0.013 [−0.395–0.421]	
Hussein et al. (2019) (17)	186	11.5	399.23	19	−13.751 [−16.012–−11.491]	
Meta-analysis (random, I^2 = 94.8%)					−0.951 [−1.672–−0.275]	0.006#
3. Folic acid						
Ataş et al. (2015) (49)	9.8	2.9	10.2	2.7	−0.400 [−1.403–0.603]	
Yasar et al. (2012) (52)	6.59	2.78	5.39	2.41	1.200 [0.060–2.340]	
Karadag et al. (2012) (53)	7.5	3.1	7	2.2	0.500 [−0.445–1.445]	
Balci et al. (2009) (54)	6.14	2.45	6.25	3.44	−0.110 [−1.505–1.285]	
Kim et al. (1999) (59)	6.31	2.82	6.11	3.11	0.200 [−1.043–1.443]	
Hussein et al. (2019) (17)	1.22	0.2	11.33	0.67	−10.110 [−10.337–−9.883]	
Meta-analysis (random, I^2 = 99.6%)					−1.463 [−7.133–4.208]	0.613
4.Vitamin E						
Ramadan et al. (2013) (51)	1.04	0.22	5.21	0.5	−10.796 [−13.712–−7.879]	
Jain et al. (2008) (55)	0.7	0.43	1.13	0.57	−0.852 [−1.310–−0.394]	
Ines et al. (2006) (56)	9.43	7.98	9.18	9.87	0.028 [−0.423–0.478]	
Agrawal et al. (2014) (50)	0.67	0.22	0.66	0.15	0.053 [−0.257–0.363]	
Meta-analysis (random, I^2 = 93.8%)					−1.408 [−2.611–−0.206]	0.022#
5.Vitamin C						
Haider et al. (2010) (65)	25.01	7.14	25.94	7.98	−0.123 [−0.629–0.384]	
Agrawal et al. (2014) (50)	0.65	0.15	0.63	0.14	0.138 [−0.172–0.448]	
Al-Hattab et al. (2020) (80)	6.27	2.65	10.83	5.52	−1.053 [−1.472–−0.634]	
Meta-analysis (random, I^2 = 90.2%)					−0.342 [−1.090–0.407]	0.371
6.Copper						
Khoshdel et al. (2022) (41)	113.57	59.43	138.9	38.14	−0.516 [−0.767–−0.265]	
Narang et al. (2017) (45)	31.7	10.28	22.52	1.95	0.994 [0.177–1.811]	
Wacewicz et al. (2018) (43)	1.099	0.273	1.038	0.336	0.198 [−0.181–0.577]	
Jialing Song et al. (2017) (79)	0.8	0.12	1.15	0.23	−1.908 [−2.334–−1.482]	
Caixia Tu et al. (1991) (77)	13.05	2.74	14.08	2.33	−0.410 [−0.914–0.094]	
Xiaohua Wang et al. (1996) (76)	107.6	10.16	109.2	16.7	−0.104 [−0.432–0.223]	
Yi Wu et al. (2010) (75)	1.46	0.471	1.536	0.345	−0.184 [−0.516–0.148]	
Fei Wang et al. (1993) (74)	0.88	0.17	1.13	0.21	−1.309 [−1.834–−0.783]	
Aiping Yao et al. (2011) (71)	0.69	0.15	1.12	0.2	−2.538 [−2.995–−2.080]	
Yandong Wang et al. (2012) (69)	13.1	2.56	14.78	2.4	−0.677 [−0.937–−0.417]	
Xuemin Wang et al. (2011) (70)	18.95	0.39	19.35	4.32	−0.128 [−0.644–0.387]	
Zongping Li et al. (2001) (73)	0.807	0.143	1.091	0.181	−1.859 [−2.330–−1.389]	
Meta-analysis (random, I^2 = 94.2%)					−0.719 [−1.185–−0.252]	0.003#

(Continued)

TABLE 4 Continued

Studies	Vitiligo group		Control group		MD [95% CI]	p-value
	Mean	SD	Mean	SD		
6.Copper						
6.1 Vitiligo disease activity						
6.1.1 Progressive						
Jialing Song et al. (2017) (79)	0.65	0.1	1.1	0.2	−2.675 [−3.219–−2.131]	
Yandong Wang et al. (2012) (69)	13.18	2.68	13.02	3.53	0.049 [−0.269–0.366]	
Meta-analysis (random, I^2 = 98.6%)					−1.304 [−3.973–1.365]	0.338
6.1.2 Stable						
Jialing Song et al. (2017) (69)	1.04	0.17	1.1	0.2	−0.311 [−0.800–0.177]	
Yandong Wang et al. (2012) (79)	12.9	3.28	13.02	3.53	−0.035 [−0.338–0.269]	
Meta-analysis (fixed, I^2 = 0.0%)					−0.112 [−0.369–0.146]	0.396
6.2 Sex						
6.2.1 Female						
Khoshdel et al. (2022) (41)	112.95	56.32	146.22	34.76	−0.718 [−1.055–−0.380]	
Wacewicz et al. (2018) (43)	1.128	0.317	1.118	0.348	0.030 [−0.446–0.505]	
Meta-analysis (random, I^2 = 84.2%)					−0.364 [−1.095–0.368]	0.330
6.2.2 male						
Khoshdel et al. (2022) (41)	114.65	63.88	135.46	25.13	−0.451 [−0.832–−0.069]	
Wacewicz et al. (2018) (43)	1.058	0.196	0.845	0.21	1.053 [0.369–1.737]	
Meta-analysis (random, I^2 = 92.9%)					0.273 [−1.199–1.745]	0.716
7. Selenium						
Wacewicz et al. (2018) (43)	51.3	13.99	79.42	18.97	−1.669 [−2.109–−1.229]	
Barikbin et al. (2011) (66)	1.021	0.04	0.909	0.01	3.616 [2.989–4.243]	
Ozturk et al. (2008) (67)	122.333	30.173	120.766	21.802	0.060 [−0.447–0.566]	
Beazley et al. (1999) (68)	1.27	0.32	0.93	0.2	1.687 [1.433–1.941]	
Caixia Tu et al. (1998) (78)	99.41	14.93	105.24	14.92	−0.391 [−0.881–0.100]	
Jialing Song et al. (2017) (79)	0.11	0.02	0.16	0.05	−1.313 [−1.702–−0.924]	
Fei Wang et al. (1993) (74)	0.1	0.02	0.13	0.14	−0.300 [−0.778–0.178]	
Jin Zhao et al. (2011) (72)	121.9	46.16	129.27	23.67	−0.181 [−0.771–0.409]	
Aiping Yao et al. (2011) (71)	0.09	0.03	0.14	0.07	−1.038 [−1.405–−0.671]	
Ines et al. (2006) (56)	1.37	0.19	0.93	0.07	3.138 [2.461–3.815]	
Meta-analysis (random, I^2 = 98.2%)					0.350 [−0.687–1.387]	0.508
7.1 Vitiligo disease activity						
7.1.1 Progressive						
Jialing Song et al. (2017) (79)	0.06	0.01	0.16	0.05	−2.529 [−3.059–−1.999]	
Jin Zhao et al. (2011) (72)	121.08	44.83	129.27	23.67	−0.225 [−0.900–0.451]	
Meta-analysis (random, I^2 = 98.0%)					−1.387 [−3.644–0.871]	0.229
7.1.2 Stable						

(Continued)

TABLE 4 Continued

Studies	Vitiligo group		Control group		MD [95% CI]	p-value
	Mean	SD	Mean	SD		
7. Selenium						
Jialing Song et al. (2017) (79)	0.12	0.03	0.16	0.05	−0.875 [−1.379–−0.370]	
Jin Zhao et al. (2011) (72)	122.72	48.74	129.27	23.67	−0.168 [−0.842–0.507]	
Meta-analysis (random, I^2 = 63.1%)					−0.558 [−1.247–0.131]	0.112
8. Iron						
Fei Wang et al. (1993) (74)	2.37	0.78	1.35	0.51	1.548 [1.004–2.092]	
Aiping Yao et al. (2011) (71)	2.28	0.61	1.37	0.46	1.621 [1.226–2.016]	
Xuemin Wang et al. (2011) (70)	25.67	7.92	23.09	6.8	0.350 [−0.169–0.870]	
Meta-analysis (random, I^2 = 89.8%)					1.181 [0.390–1.972]	0.003#

CI, confidence interval; RR, risk ratio; #p < 0.005; *p <0.001.

p >0.05; Table 4; Supplementary Figure S7). Another study (32) concluded that patients with vitiligo had significantly lower vitamin C levels than the controls.

Vitamin B12 and folic acid

One study (9) suggested combining folic acid and vitamin B12 supplementation with sunlight-induced repigmentation to be more effective than vitamin or sunlight exposure alone. In addition, two case–control studies (17, 19) reported that serum folic acid and vitamin B12 levels were significantly lower in patients with vitiligo than in controls.

A cross-sectional study (20) and a cohort study (30) showed that elevated serum homocysteine (Hcy) and reduced serum vitamin B12 levels were significantly associated with vitiligo. However, another two studies (23, 31) reported no significant differences in vitamin B12 and folic acid levels between patients with vitiligo and controls. In addition, one study (25) showed that patients with vitiligo had no significant difference in Hcy and vitamin B12 levels compared to that in controls. In contrast, those with vitiligo had higher folic acid levels.

An evaluation of 33 patients treated for vitiligo did not reveal an association between vitamin B12 levels and improved repigmentation (27). Tjioe et al. (36) reported that adding vitamin B12 and folic acid did not provide any therapeutic benefit in treating patients with vitiligo. Memon et al. (39) concluded that the serum levels of vitamin B12 and folic acid significantly affected the course of vitiligo.

A meta-analysis of eight studies (17, 46, 49, 52–54, 57, 59) showed that vitamin B12 levels were significantly lower in patients with vitiligo than in controls (MD, −0.951; 95% CI, −1.672–−0.275; p <0.05; Table 4; Supplementary Figure S8). In contrast, a meta-analysis of six studies (17, 49, 52–54, 59) showed no significant difference in the folate levels between patients with vitiligo and controls (MD, −1.463; 95% CI, −7.133–4.208; p >0.05; Table 4; Supplementary Figure S9).

Vitamin D

A randomized controlled trial (18) showed that vitamin D treatment resulted in a more significant reduction in the extent and size of lesions in patients with vitiligo than in controls, suggesting that vitamin D plays a role in preventing the progression of active vitiligo. Another study (28) concluded that high-dose vitamin D3 therapy (35, 000 IU once daily) is safe and effective for patients with vitiligo. A retrospective cohort study (38) reported no significant association between vitamin D and any feature or treatment of vitiligo. Among the studies, two research papers (18, 28) that found vitamin D treatment effective for vitiligo included a total of 76 patients. Meanwhile, one cohort study (38) that deemed it ineffective included 297 patients.

Vitamin E

Patients with vitiligo who received oral antioxidants (*Phyllanthus emblica*, vitamin E, and carotenoids) had significantly milder repigmentation of the head, neck, and trunk, along with a higher level of disease stability, compared to the corresponding patients who did not receive oral antioxidants (24).

A study (26) evaluated the long-term treatment of children with facial vitiligo. The study employed a combination of approaches, including nutrition education, vitamin E, folic acid, multivitamin intake, and antioxidant cosmetics, as the primary treatment. Additionally, conventional therapies were used as part of the treatment protocol. A total of 91% of patients demonstrated lesion improvement.

A case–control study (32) concluded that the serum vitamin E levels were significantly lower in patients with vitiligo than in controls. In contrast, two other case–control studies (34, 37) reported no significant difference in blood vitamin E levels in patients with vitiligo compared to age-matched healthy controls. Akyol et al. (35) concluded that vitamin E prevented oxidative distress caused by Psoralen UVA rays (PUVA) treatment; however, it did not affect the clinical improvement of vitiligo lesions. A meta-

analysis of four studies (50, 51, 55, 56) showed that the serum VE levels were significantly lower in patients with vitiligo than in controls (MD, −1.408; 95% CI, −2.611–−0.206; p <0.05; Table 4; Supplementary Figure S10).

Zinc

A retrospective cohort study reported no significant association between zinc and any feature or treatment associated with vitiligo (38). A randomized controlled trial showed that although the group that received oral zinc sulfate combined with topical corticosteroids responded better than the group that received topical corticosteroids alone, there was no statistical difference (29). Another study suggested that the average zinc level in the serum of patients with vitiligo was significantly lower (14). The meta-analysis of 18 studies (41–45, 47, 48, 58, 65, 69–71, 74–77, 79, 80) showed that the serum zinc levels were significantly lower in patients with vitiligo than in controls (MD, −0.774; 95% CI, −1.083–−0.466; p <0.001; Table 4; Supplementary Figure S11). Three studies showed that the serum zinc levels were significantly lower in patients with generalized vitiligo than in healthy controls (MD, −0.799; 95% CI, −1.121–−0.477; p <0.001; Table 4; Supplementary Figure S12), while the serum zinc levels in patients with localized vitiligo were not different from those in the control group (MD, −0.264; 95% CI, −0.601–−0.073; p >0.05; Table 4; Supplementary Figure S13). Both female (MD, −0.557; 95% CI, −0.874–−0.240; p <0.005; Table 4; Supplementary Figure S14) and male (MD, −0.578; 95% CI, −0.909–−0.246; p <0.001; Table 4; Supplementary Figure S15) patients with vitiligo had significantly lower serum zinc levels than those of healthy controls. However, the opposite was true for the serum zinc levels in patients with progressive (MD, −1.243; 95% CI, −3.789–1.312; p >0.05; Table 4; Supplementary Figure S16) and stable (MD, −0.403; 95% CI, −1.133–0.327; p >0.05; Table 4; Supplementary Figure S17) vitiligo.

Incompatible diet

Incompatible diets refer to incorrect combinations of food components in formulations, insufficient or excessive processing, inappropriate consumption amounts, and/or eating at incorrect times of the day and/or in the wrong seasons (11). A case–control study (11) concluded that the mean composite scores of two questionnaires for assessing incompatible dietary habits in patients with vitiligo were similar to those of controls. Additionally, a study (22) revealed that patients with vitiligo must avoid incompatible foods, as these are the most potent causative factors for vitiligo.

Total fat intake

A previous study (16) highlighted that the quantity of total fat consumed in the diet had a greater impact on the risk of vitiligo compared to specific subclasses of fat. The study suggested that a high-fat diet increases the risk of developing vitiligo.

Copper

The meta-analysis of 12 studies (41, 43, 45, 69–71, 73–77, 79) showed that the serum copper levels were significantly lower in patients with vitiligo than in controls (MD, −0.719; 95% CI, −1.185–−0.252; p <0.005; Table 4; Supplementary Figure S18). Whether progressive (MD, −1.304; 95% CI, −3.973–1.365; p >0.05; Table 4; Supplementary Figure S19) or stable (MD, −0.112; 95% CI, −0.369–0.146; p >0.05; Table 4; Supplementary Figure S20), and male (MD, 0.273; 95% CI, −1.199–1.745; p >0.05; Table 4; Supplementary Figure S21) or female (MD, −0.364; 95% CI, −1.095–0.368; p >0.05; Table 4; Supplementary Figure S22) patients, there were no significant differences in the serum copper levels in patients with vitiligo compared to those in controls.

Selenium

The meta-analysis of 10 studies (43, 56, 66–68, 71, 72, 74, 78, 79) indicated no significant difference in the serum selenium levels between patients with vitiligo and controls (MD, 0.350; 95% CI, −0.687–1.387; p >0.05; Table 4; Supplementary Figure S23). No significant difference was observed in the serum selenium level between the control group and the patients with progressive (MD, −1.387; 95% CI, −3.644–0.871; p >0.05; Table 4; Supplementary Figure S24) and stable (MD, −0.558; 95% CI, −1.247–0.131; p >0.05; Table 4, Supplementary Figure S25) vitiligo.

Iron

The meta-analysis of three studies (70, 71, 74) showed that serum iron levels were significantly higher in patients with vitiligo than in controls (MD, 1.209; 95% CI, 0.403–2.014; p <0.0055; Table 4; Supplementary Figure S26).

Exercise

No studies have examined the relationship between physical exercise and disease progression in patients with vitiligo.

Tanning ability

Women who had a painful burn/blistering skin reaction after 2 h of sun exposure as children/adolescents had a higher risk of vitiligo than those with no reaction or only redness after sun exposure. Women with strong tanning abilities had a higher risk of developing vitiligo compared to those without the ability to tan (10).

Sleeping

Two studies (12, 33) have examined the relationship between vitiligo and sleep disorders. One study indicated that patients with vitiligo reported significantly more sleep disturbances compared to that in controls, especially sleepwalking, nocturnal enuresis, nocturnal hallucinations, sleep fears, and nightmares. In addition, patients with vitiligo had statistically significant levels of nightmares, nocturnal hallucinations, and sleepwalking compared to those with other skin diseases; however, they did not have statistically significant levels of sleep phobias or nocturnal enuresis. Another study indicated that facial and neck vitiligo, vitiligo progression, and oral glucocorticoid use were risk factors for insomnia in patients with vitiligo.

Permanent hair dyes

The previous use of permanent hair dyes increased the risk of vitiligo. The association with vitiligo was more pronounced in those who had used hair dyes for a longer duration, initiated their use before the age of 30 years, and had a longer period of usage since their first use (21).

Height

A nationwide cohort study showed that height is positively associated with the risk of vitiligo in Korean adults. This association was stronger in the older adult population (age ≥65 years) (13).

Sexual dysfunction

In our previous study (96), we observed a higher risk of sexual dysfunction in patients with vitiligo, with the relationship being more prominent in women than in men.

Discussion

The importance of reviewing lifestyle habits (including smoking, alcohol consumption, diet, exercise, and sleep) lies in the provision of adjunctive measures for the treatment of vitiligo. Current treatments for vitiligo are abundant, with traditional approaches focusing on the autoimmune hypothesis through immunomodulatory and anti-inflammatory approaches. However, in recent years, new therapies, such as molecular targeted therapy, have become available (5–7). Despite the availability of various treatments, a few patients continue to experience unsatisfactory results with conventional therapies, and the effectiveness of newer treatments remains uncertain. This study carries several significant implications in this context.

We reviewed the smoking and alcohol consumption data of patients with vitiligo and observed that more patients with vitiligo smoked and drank alcohol compared to that in controls, which is contrary to the results of another cohort study (15), which suggested that smoking had a suppressive effect on the development of vitiligo. To date, there are no studies demonstrating the effect of smoking and alcohol consumption on the development of vitiligo.

Regarding diet, we focused on vitamins C, D, E, and B12, folic acid, zinc, copper, iron, selenium, incompatible diets, and total fatty acids. We observed no significant difference in the serum vitamin C levels between patients with vitiligo and controls, which refutes statements recommending vitamin C supplementation in patients with vitiligo. In addition, although the oxidative stress theory has been mentioned in studies on the pathogenesis of vitiligo, it is worth noting that vitamin C, as an antioxidant, may exert inhibitory effects on tyrosinase activity by inducing cytoplasmic acidification (95). This mechanism may contribute to a reduction in melanin content, offering a potential avenue for therapeutic intervention in vitiligo (58).

The results of this meta-analysis showed that vitamin B12 levels were low in patients with vitiligo. In contrast, the folic acid levels did not significantly differ from those of the controls. The folic acid and vitamin B12 levels are associated with homocysteine synthesis, inhibiting tyrosinase and reducing melanin production (81). Therefore, we recommend that vitamin B12 supplementation inhibits tyrosinase and reduces associated effects.

Decreased vitamin D levels play a role in the development of vitiligo by affecting Th1- and Th17-related immune responses (82). In contrast, studies have reported no role of circulating vitamin D in the pathogenesis of vitiligo. Although studies have suggested that vitamin D has a therapeutic effect on vitiligo, not all of these were single-drug studies, a few of these combined vitamin D with other therapeutic methods; therefore, the evidence for this is insufficient.

Our results suggested that vitamin E has a therapeutic effect on vitiligo; however, further studies are needed to confirm this hypothesis. Vitamin E, an antioxidant, inhibits tyrosinase activity, and its derivatives inhibit melanogenesis in epidermal melanocytes *in vitro*. In addition, vitamin E increases the expression of endosomal docking/fusion proteins, and melanosomes can be degraded within the lysosomal compartment by docking with lysosomes, decreasing the number of melanosomes (83, 84). Although the results of our meta-analysis identified low serum vitamin E levels in patients with vitiligo, these were inconclusive owing to the limited sample sizes and the observational nature of the included studies. Thus, whether vitamin E supplementation is beneficial for vitiligo needs to be confirmed in additional studies with larger sample sizes. Vitamin E supplementation is only appropriate for patients with vitamin E deficiency.

Copper, one of the trace elements, is a cofactor involved in the synthesis of melanin by tyrosinase and in the biosynthesis of superoxide dismutase, which plays an important role in protecting cells from oxidative stress (85, 86). Our study showed that patients with vitiligo had significantly lower serum copper levels than those of healthy controls. This indicates that copper may be involved in the pathogenesis of vitiligo, and further studies are needed to explain this.

Selenium is an essential immune nutrient for the human body, and the organic forms of selenium naturally exist in the human body: selenocysteine and selenoprotein. Glutathione peroxidase is the main selenium protein in the body, which helps control the excess production of free radicals at inflammatory sites (87). Our study did not find a difference in serum selenium between patients with vitiligo and healthy individuals. In the future, we can study the lesion site of vitiligo and observe whether the results have changed.

Toxic damage to melanocytes by redox-generated free radicals is one of the doctrines of the pathogenesis of vitiligo. Iron, an essential element for many important cellular functions in all organisms, catalyzes the formation of potentially toxic free radicals (88). Our research supports this view, although the results of two studies (31, 89) are diametrically opposed to ours.

Zinc is an antioxidant that inhibits apoptosis and may inhibit the apoptosis of melanocytes. Moreover, zinc plays an important role in the final stage of melanin formation. Therefore, zinc may

have an important effect on vitiligo (43). The results of this meta-analysis showed low serum zinc levels in patients with vitiligo.

The association between incompatible diets and vitiligo remains controversial and poorly understood. High-fat diets are thought to increase the risk of vitiligo, and diets high in saturated fats have deleterious effects on macrophage phagocytosis and natural killer cell activity in autoimmune diseases. Moreover, it has been well established that high-fat diets can contribute to the development of various diseases and have detrimental effects on the lifespan of animals (16).

The benefits of gluten-free diets for vitiligo have been reported in only two cases. Although chronic physical exercise can change the balance of inflammation to an anti-inflammatory state and improve the structure and function of the endogenous antioxidant system and mitochondria (90), thus improving the clinical symptoms and quality of life of patients with vitiligo, observational and experimental studies are still lacking. Moreover, vitiligo has been consistently linked to sleep disorders, and extensive research indicates the presence of a cyclic relationship between vitiligo and depression, in which sleep deprivation may play a contributing role (12).

Women with a strong ability to tan reportedly present at a higher risk of developing vitiligo. This association may be attributed to various factors, including the direct impact of UV rays on DNA, leading to the upregulation of the tyrosinase gene, and the direct influence of UV rays on melanin cell membranes. These mechanisms contribute to the overall tanning response observed in individuals (91). Therefore, tyrosinase seems to be a key player in the tanning response (92). A recent study (93) published in *The Lancet* indicated that regions with a higher overall prevalence of vitiligo are located in South Asia, including India, Bangladesh, Nepal, Pakistan, and Bhutan. This may be related to the greater visibility of vitiligo in individuals with darker skin tones.

Permanent hair dye contains many chemicals, including phenols such as p-aminophenol and resorcinol (94). Phenols act as tyrosinase analogs and interfere with melanin production, which may be associated with an increased risk of vitiligo caused by permanent hair dye use (21).

A national cohort study in South Korea identified a significant association between height and an increased risk of vitiligo in Korean adults (13). However, data from other countries in Asia, Europe, and the United States is lacking. In the future, large cohort and mechanistic studies on the relationship between height and vitiligo should be conducted to further explore this phenomenon.

Limitations

This study had certain limitations. First, the available literature on the lifestyle habits of patients with vitiligo is relatively limited, resulting in insufficient evidence in certain areas. Second, the studies in this review were highly heterogeneous. Third, most of the studies were conducted in Asian and African countries, and there is a lack of data from studies conducted in Europe and the United States. Fourth, there were limited data available for the meta-analysis and bias assessment. Fifth, most of the data came from non-segmental vitiligo cases, and the evidence for segmental vitiligo was weak. Moreover, the limited data in this study could not conduct a more in-depth analysis of differences in age, sex, and disease stage, among others. Further research is still needed to confirm these associations and clarify the underlying mechanisms.

Conclusion

Our review of lifestyle habits in relation to vitiligo provides several guiding suggestions. Additionally, it is recommended that both normal individuals and those with vitiligo refrain from smoking and excessive alcohol consumption. We recommend that every patient with vitiligo undergo blood tests for vitamin E, vitamin B12, zinc, and copper. If the test results indicate low levels of these nutrients, supplementation should be considered under the guidance of a doctor. However, supplementation with vitamin C, vitamin D, selenium, and folic acid may not be necessary. Furthermore, patients with vitiligo avoid high-fat diets, as these have been associated with negative health effects. Given the increased risk of sleep disorders and sexual dysfunction in individuals with vitiligo, seeking specialized help from healthcare professionals in these areas is advisable if necessary. Additionally, sun protection is crucial, particularly for women with high tanning abilities, as exposure to UV rays can have implications for the development and progression of vitiligo. Finally, regardless of the presence or absence of vitiligo, it is recommended to avoid the use of permanent hair dyes due to their potential association with an increased risk of vitiligo.

These guiding suggestions aim to provide individuals with vitiligo with lifestyle recommendations that may help manage their condition and improve their overall wellbeing. However, it is important to consult healthcare professionals for personalized advice and treatment plans based on individual needs and circumstances.

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

XLia: Data curation, Methodology, Writing – original draft. FG: Data curation, Methodology, Writing – original draft. QF: Data curation, Writing – original draft. XC: Formal analysis, Writing – original draft. JW: Validation, Writing – original draft. JC: Investigation, Resources, Writing – original draft. FL: Project administration, Writing – original draft. YD: Visualization, Writing – original draft. YC: Supervision, Writing – review & editing. XLi: Conceptualization, Methodology, Writing – review & editing.

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Conflict of interest

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1440705/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Sensitivity analysis of the serum zinc levels between patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 2
Sensitivity analysis of the serum vitamin B12 levels between patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 3
Sensitivity analysis of the serum copper levels between patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 4
Sensitivity analysis of the serum selenium levels between patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 5
Meta-analysis of smoking in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 6
Meta-analysis of alcohol consumption in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 7
Meta-analysis of the serum vitamin C levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 8
Meta-analysis of the serum vitamin B12 levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 9
Meta-analysis of the serum folic acid levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 10
Meta-analysis of the serum vitamin E levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 11
Meta-analysis of the serum zinc levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 12
Meta-analysis of the serum zinc levels in patients with generalized vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 13
Meta-analysis of the serum zinc levels in patients with localized vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 14
Meta-analysis of the serum zinc levels in female patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 15
Meta-analysis of the serum zinc levels in male patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 16
Meta-analysis of the serum zinc levels in progressive patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 17
Meta-analysis of the serum zinc levels in stable patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 18
Meta-analysis of the serum copper levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 19
Meta-analysis of the serum copper levels in progressive patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 20
Meta-analysis of the serum copper levels in stable patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 21
Meta-analysis of the serum copper levels in male patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 22
Meta-analysis of the serum copper levels in female patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 23
Meta-analysis of the serum selenium levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 24
Meta-analysis of the serum selenium levels in progressive patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 25
Meta-analysis of the serum selenium levels in stable patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY FIGURE 26
Meta-analysis of the serum iron levels in patients with vitiligo and controls 95% CI, 95% confidence interval.

SUPPLEMENTARY TABLE 2
Search strategy.

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Linear IgA bullous dermatosis–a fifty year experience of Warsaw Center of bullous diseases

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Linear IgA bullous dermatosis (LABD) is a rare subepidermal blistering disorder characterized by the presence of linear IgA deposits at the basement membrane zone (BMZ) by direct immunofluorescence (DIF). This entity was first described by Chorzelski and Jablonska from Warsaw Center of Bullous Diseases, Poland. The disease affects children and adults, whereby they differ in terms of clinical picture and course. Among polish patients with LABD mucous membrane involvement was exceptional, although, we reported a case presenting severe scarring of esophagus and conjunctivae with circulating IgG and IgA antibodies to LAD-1 antigen. Severe mucosal involvement was also observed in IgA-epidermolysis bullosa acquisita (EBA). Immunologically, LABD is characterized by circulating IgA antibodies directed to several epitopes of antigen BP180: LAD-1, 97kD, NC16A. Other BMZ antigens, like BP230, laminin 332, type VII collagen or p200 may be affected. We as a first published a case of anti-p200kD pemphigoid mediated by IgA. Our immunoelectron microscopic studies showed that the epitopes recognized by LABD sera are ultrastructurally localized in the lamina lucida. The antigenic heterogeneity, low titer of IgA antibodies and the lack of commercially available tests for some antigens (LAD-1, p200kD) makes the diagnosis challenging in many cases. It is under debate whether these cases are the subtypes of LABD or they represent a separate entities (IgA-p200 pemphigoid, IgA-MMP or IgA-EBA). Since, they differ in terms of clinical course, mucosal involvement, coexisting disorders, response to the treatment and prognosis, their differentiation is mandatory. In the literature there are many cases with undetectable circulating IgA antibodies in whom LABD was recognized based on DIF only. To avoid misdiagnosis, more sophisticated methods should be used, like direct immunoeletron microscopy (IEM), which is a time-consuming technique. The alternative for IEM may be: a) analysis of the BMZ serration pattern, b) immunofluorescence mapping of blister, c) direct salt split (patient's) skin, d) fluorescence overlay antigen mapping by laser scanning confocal microscopy. The two latter methods were established by the authors years ago and they allowed precise diagnosis (i.e., differentiation LABD from IgA-EBA), initiation of proper therapy and assessment of prognosis in many cases mediated by IgA.

KEYWORDS

linear IgA bullous dermatosis, IgA epidermolysis bullosa acquisita, direct immunofluorescence, direct split skin, fluorescence overlay antigen mapping by laser scanning confocal microscopy

Introduction

In 1976, Polish scientists Chorzelski and Jablonska reported nine cases in which IgA linear deposits were present at the basement membrane zone (BMZ) and named them "dermatitis herpetiformis and bullous pemphigoid - intermediate and mixed form" (1). Five years earlier, the same group studied the skin of 19 patients with dermatitis herpetiformis (DH) by direct immunofluorescence (DIF) and they found five unusual cases presenting with linear IgA deposits at the BMZ (2). Finally, the name of linear IgA bullous dermatosis (LABD) was proposed by them in 1979 (3).

The distinction between LABD and DH was crucial in terms of the pathomechanism of both diseases, especially given the relation of DH to gluten-sensitive enteropathy, which affects the treatment and prognosis. Further studies have also revealed differences regarding the characteristics of circulating antibodies. Patients with DH presented with IgA anti-endomysial antibodies (4) whereas some LABD patients had IgA anti-BMZ antibodies as determined by indirect immunofluorescence (IIF) (5).

Since the detection of circulating IgA antibodies in LABD using IIF was challenging due to its low serum concentration, it was widely accepted in the 20th century that the diagnosis of LABD could only be established based on the presence of linear IgA deposits in DIF. In the last 50 years, dozens of case reports recognized as LABD by DIF and original papers concerning the subject have been published showing different clinical pictures, prognoses, and responses to treatment.

The implementation of molecular techniques allowed the characterization of target BMZ antigens (6–10). It was found that in the majority of patients, the autoantibodies were directed to bullous pemphigoid (BP) antigens and their epitopes, which corresponded to the localization of IgA deposits in the lamina lucida (11, 12). In these cases, dermal-epidermal separation occurred in the lamina lucida (13–15). However, in some patients, circulating IgA anti-BMZ antibodies were directed to type VII collagen, which is an antigen of epidermolysis bullosa acquisita (EBA). In those patients, IgA deposits were located below the lamina densa, where dermal-epidermal separation occurs in the sublamina densa region (16, 17). Uncommonly, circulating IgA anti-BMZ antibodies may also be directed to other BMZ antigens (p200 antigen, laminin 332) (18–20).

Therefore, it is still a matter of discussion whether LABD is one disorder with a heterogeneous clinical and immunological description (21) or whether the observed cases are examples of different entities mediated by IgA anti-BMZ antibodies (22–25).

Here, we present findings based on the experience of the Warsaw Center for Autoimmune Blistering Disorders and on a review of the literature on the correlation of clinical symptoms with immunological findings in disorders mediated by IgA anti-BMZ antibodies. Due to the lack of commercially available techniques allowing fast and easy detection of IgA anti-BMZ antibodies, the diagnostics of these cases is challenging. Based on the presented findings, we propose a diagnostic management protocol using techniques that enable the localization of IgA deposits within different BMZ structures.

Epidemiology

LABD is a rare autoimmune bullous disease that most often occurs in adults, with a slightly higher prevalence in women than men (11, 23–25). There is also a pediatric form of this disease that usually has a milder presentation than the adult form. There is a considerable variation in the incidence of LABD between countries, i.e., in Germany, it is 0,25%/million/year (23), whereas in South Korea, it is 4 times higher (26).

The age of the onset of adult LABD differs between Asian and European countries. In Japan and Korea, adult LABD appears between 60 and 65 years of age (26–28), whereas a study performed in Lubeck, Germany on more than 220 LABD cases, indicated an age of onset of over 70 (23). In contrast to Germany, patients in France and Denmark developed LABD at the age of 56 years on average (29, 30), which is similar to Poland. Several reports published in the 20th century by the Warsaw Center of Autoimmune Blistering Disorders on a small number of cases showed that Polish patients with adult LABD were younger than those from Germany (1, 5, 11, 31). Of the 19 well-documented LABD patients described by Wozniak in 2013, four cases were children, and only three out of the 15 adults were aged 70 to 81. The remaining 12 adult patients were aged 29-68 but it is noteworthy that three adult patients were aged 29, 34, and 35 (32). Thus, young patients with LABD seem to be a rather common phenomenon in Poland. Such a difference between Poland, France, and Germany, which are neighboring countries, seems to indicate a need for further analysis.

Pediatric LABD was separated from the chronic bullous dermatosis of childhood (CBDC) group by Chorzelski and Jablonska in 1979 (3). In children, LADB occurs mainly between 1 and 11 years of age and has a peak incidence at 4-5 years (33). It is essential to emphasize that there are also several unusual cases described in the literature as neonatal LABD, which are characterized by severe mucosal involvement and a worse prognosis, unlike in cases of older children with LABD (34, 35).

Genetics

A British study showed that adult LABD in the Caucasian population was significantly associated with human leucocyte antigen (HLA) Cw7, B8, and DR3 (36), whereas the cases of LABD in children were mostly associated with HLA B8. Additionally, it has been suggested that the presence of the HLA B8 haplotype was associated with a good prognosis (36). In patients expressing the TNF2 haplotype, the duration of LABD appeared to be longer than in those expressing the TNF1 allele (36). In African patients, similarly to Caucasian patients, LABD is also significantly associated with HLA B8, but in Japanese patients that association has not been found (37). In Tunisia, HLADR3 haplotypes were found to be present in 80% of childhood LABD patients (38). In the Chinese population, a Celiac Gene HLA-DQB1∗02:01 seems to be associated with linear IgA bullous dermatosis (39).

Genetic differences between different ethnic groups in LABD may in part explain the different incidences of this disease and the differences in its clinical presentation.

Pathogenesis

Target antigens

Circulating IgA anti-BMZ antibodies in patients with autoimmune subepidermal blistering disease (ASBD) are directed to various antigens of the BMZ (Table 1). This determines not only the level of dermal-epidermal separation but also the clinical picture and the response to treatment. Both in the cases of childhood and adult LABD, circulating IgA autoantibodies bind to proteolytic products of the extracellular domain of the BP180 antigen, i.e., a 97-kDa protein and/or a 120-kDa protein, which are called LABD97 and LAD-1 respectively (6–8, 50). It is calculated that up to 40% of LABD sera react with full-length BP180 or the NC16A domain of BP180 (9, 10). It has also been observed that some LABD sera concurrently react with several epitopes of the same antigen, which can probably be explained by the intermolecular epitope spreading phenomenon (10). Less frequently, a circulating IgA antibody in LABD binds to an intracellular hemidesmosomal protein—BP230 (43). In some patients, circulating IgA antibodies are accompanied by equally strong IgG anti-BMZ antibodies and they are directed to the same LAD-1 antigen (40). Those patients seem to display a different clinical picture than pure LABD, and they are therefore categorized into a subgroup of so-called LA(G)BD (41, 44, 45, 51–59). Between 5% and 10% of patients with linear IgA deposits in the BMZ present with circulating IgA antibodies directed to type VII collagen—EBA antigen (47, 48). However, it is a matter of debate whether those patients represent the so-called sublamina densa type of LABD (48) or IgA-EBA (22, 23). In Europe, it is postulated that this type of disorder should be named IgA-EBA (25), however, Hashimoto provided a number of historical and immunological arguments supporting the classification of diseases dependent on IgA antibodies as different subtypes of LABD (21). Despite the controversy, there is a general agreement that the above-mentioned cases differ regarding the clinical picture and the response to treatment.

In rare cases, sera may react with another BMZ antigens, such as p200 (18) or gamma laminin1, as we showed previously, or else with laminin 332 as presented by Hashimoto (20). Therefore, according to the recently published recommendations, the final diagnosis in patients with IgA anti-BMZ antibodies should be based on the characterization of target antigen(s) (25).

TABLE 1 Target antigens recognized by circulating anti-BMZ antibodies.

References	Antigens recognized by IgA antibodies	Proposed diagnosis
(6, 24, 32, 40, 41)	LAD-1 (fragment of BP180)	LABD
(7, 8)	LABD97 (fragment of BP180)	LABD
(9, 10, 32, 42)	BP180 (full length)	LABD
(9, 10, 32)	BP180-NC16a epitope	LABD
(32)	BP180- C-terminal fragment	LABD
(43)	BP230	LABD
(18, 32, 44–46)	p200 antigen	LABD or Anti-p200 pemphigoid mediated by IgA
(19, 20)	Laminin 332	LABD or anti-laminin 332 MMP
(11, 22, 32, 47–49)	Type VII collagen	IgA-EBA or sublamina densa type of LABD

LABD, linear IgA bullous dermatosis; MMP, mucous membrane pemphigoid; IgA-EBA – epidermolysis bullosa acquisita mediated by IgA.

Ultrastructural localization of antigens recognized by IgA anti-BMZ antibodies

In 1995, we used the pre-embedding immunoperoxidase indirect immunoelectron microscopic (IEM) technique to establish the localization of epitopes of the antigens recognized by IgA anti-BMZ antibodies (11).

The study was performed on 27 sera in total: 21 collected from patients with adult LABD, four from those with childhood LABD, and two from patients with MMP mediated by IgA for comparison. Of the 27, 24 sera [19 from the cases of adult LABD, four from those of childhood LABD, and one from the IgA-mucous membrane pemphigoid (MMP-IgA)] reacted on the epidermal side of salt split skin (SSS)-IIF. Those sera reacted in the lamina lucida and/or in the hemidesmosomes on immune electron microscopy (IEM) performed on normal human skin as a substrate. The remaining two sera reacted with the dermal side on SSS-IIF. On the ultrastructural level, they decorated the sublamina densa region, presenting with non-continuous labeling referring to anchoring fibrils. Further studies have revealed that one serum was negative by IB, while the second one reacted with type VII collagen, pointing to the diagnosis of IgA-EBA, not MMP-IgA.

Interestingly, the 24 sera that recognized epitopes of antigen(s) in the upper part of the BMZ presented with four different labeling patterns: a) intercellular labeling of hemidesmosome plaques combined with staining of the underlying portion of the lamina lucida; b) non-continuous labeling of the lamina lucida; c) continuous labeling of the lamina lucida related to the presence of hemidesmosomes; d) mixed labeling pattern of linear lamina lucida and non-continuous lamina lucida and hemidesmosome plaque, suggesting the binding of IgA antibodies to the several epitopes concurrently (11). These findings were further confirmed using an image analysis technique, which made it possible to distinguish specific immune reactions from the background (60).

In the next step, indirect post-embedding immunogold studies were performed on lowicryl K11M-embedded human skin using six selected LABD sera, which strongly reacted with the epidermal side of split skin. All sera recognized antigens localized ultrastructurally

in hemidesmosomal plaques and the adjacent lamina lucida. Most of the immunogold particles were found in a linear distribution within the basal cells, directly over the hemidesmosomal portions of the plasma membrane; some extracellular labeling was also noticed (12). In turn, Ishiko et al., using post-embedding immunogold on cryosection and purified IgA anti-BMZ directed against 97kD LABD antigen, found its linear distributions within the upper part of the lamina lucida (61).

Thus, studies conducted using indirect electron immunomicroscopy indicate that IgA anti-BMZ antibodies are directed against various epitopes of the bullous pemphigoid minior antigen 180 (BP180) in LABD patients. Moreover, a mixed labeling pattern, often observed in IEM, suggests that sera from some LABD patients recognize several epitopes of the BP180 concurrently and less frequently; an additional antigen bullous pemphigoid major antigen 230 (BP230) is also present within the hemidesmosomal plaque (11, 12, 60, 61).

The pathogenic character of IgA antibodies directed to anti-LAD-1 and anti-LABD97

The binding of IgA to a specific Fc alpha receptor, also known as CD89, present on granulocytes has been shown to induce chemotactic migration of those cells to IgA deposits in the skin of LABD patients (62). Blister formation is the result of granulocyte activation and subsequent degranulation, as demonstrated after the passive transfer of an IgA monoclonal antibody to LABD97 antigen in an immunodeficient mouse model (63). The role of granulocyte activation in the pathomechanism of LABD was also demonstrated in further studies on genetically modified mice, which expressed human CD89 after an injection of human IgA anti-BP180 antibodies (64). The separation of the epidermis from the dermis occurs as a result of the activation of proteases, including plasmin and neutrophil elastases, and reactive oxygen species originating from neutrophils, eosinophils, and mast cells (64–66).

Using an *in vitro* LABD model on cryosections of normal human skin treated with anti-BMZ antibodies and then granulocytes, it has been shown that blocking Fc alpha R resulted in inhibition of dermal and epidermal detachment (62). Furthermore, administration of anti-Fc alpha R monoclonal antibodies to a murine LABD model prevented chronic inflammation and tissue damage (62–68). It is worth mentioning that recombinant human IgA1 and IgA2 autoantibodies to type VII collagen induced subepidermal blistering *ex vivo* by a similar mechanism (69).

Clinical picture of LABD

LABD in adults

In adults, the skin lesions of LABD are usually polymorphic with associated pruritus. In some cases, the clinical picture is dominated by vesicles, papules, and erythematous patches with a herpetic pattern, resembling DH; however, most patients have large blisters located on the trunk and extremities sitting on inflamed or healthy skin, similar to BP (1, 5, 70, 71). Cases of LABD with a severe clinical picture resembling erythema multiforme, toxic epidermal necrolysis, or erythema annulare centrifugum have also been described (72–76).

The course of LABD in adults is generally chronic with a tendency toward relapses and remissions that last from 6 months to several years; spontaneous remissions occur in approximately 10% of patients (1, 5, 77, 78).

LABD in children

LABD is the most common autoimmune skin disease in childhood (3, 23, 24, 78–80).

The most common clinical picture of LABD contains blisters and/or vesicles that form a garland-like arrangement, the so-called "clusters" which are most often located on the face around the mouth, in the genital area, and on the hands and feet (3, 78–80). The skin lesions may be accompanied by pruritus. For years, it was thought that such a clinical picture was pathognomonic for children's LABD, however, recent publications report children presenting with similar characteristics and distribution of skin lesions but being diagnosed with BP (81). Additionally, among our patients, we can report a female pediatric patient with IgA-EBA who initially presented with clusters, suggesting LABD, but a few months later developed milia, typical for EBA (32). Therefore, one should be aware that, at the beginning, ASBDs in children may be indistinguishable. Interestingly, some children with LABD present with erythematous papules or even excoriated plaques resembling allergic disorders. Since the disease usually resolves within 4 years on average and has a good prognosis in the majority of cases, it is classified as a self-limiting disease (3, 23–25, 78–80, 82).

In contrast, LABD in newborns may have an unfavorable course. As has already been reported in publications, the severe course of the disease in this age group was associated with mucous membrane involvement and is usually provoked by drugs (34, 83)—see the section below.

Mucous membrane involvement

There are significant differences in the literature regarding the occurrence of mucosal lesions in patients with LABD. In the pioneering articles by Chorzelski and Jablonska who described 13 patients with adult LABD (1) and 27 cases of pediatric LABD (3), no mucosal involvement was observed. In subsequent studies from the same center, conducted by the authors of this paper on a well-documented group of 45 patients in whom the recognized antigens and/or ultrastructural localization of IgA deposits at the BMZ were thoroughly described, mucous membrane involvement was found only in three patients. In those three cases, sera recognized type VII collagen in immunoblot or anchoring filaments in the sublamina densa region on IEM (11, 32). Another research group from northern Poland reported 22 LABD cases, which included six patients who presented with mucous membrane involvement

(84). Interestingly, eight out of the 22 patients showed reactivity with the dermal side of SSS-IIF, typical for IgA-EBA.

A study performed by a Tunisian research group in a cohort of 31 children showed the occurrence of mucous membrane involvement in 13% (80). A Japanese research group studied 213 cases of LABD and found 26 patients with mucosal lesions, among which 25 were adults and only one was a child. The authors showed that the incidence of mucosal involvement mainly referred to the IgA/G type (27).

In contrast to the above-mentioned papers, a British research group, in their first publication on 25 adult LABD patients and 25 patients with CBDC, found mucosal lesions in 80% and 64% of patients respectively (78). Further studies published by the same authors on a group of 10 patients in whom an LABD diagnosis was based on IgA deposits along the BMZ in DIF performed on the patients' skin, showed that all of them had oral erosions and 6 also had conjunctival lesions (85). Interestingly, in the biopsies taken from the conjunctiva, only linear IgG deposits were present in DIF, thus conjunctival involvement in those patients depended on IgG, but not on IgA. This observation raises the question of whether such patients present with LABD with mucosal involvement or rather MMP. It is worth noting that conjunctival involvement is the symptom most frequently observed in MMP, whereas in LABD it is not evident. Therefore, such cases require thorough research, especially in terms of target antigens and the precise localization of IgA and IgG deposits.

The vast majority of single cases of LABD described in the literature in which very severe mucosal involvement was shown, including scarring of the esophagus, conjunctivitis, or airway obstruction, were diagnosed based only DIF and histology, without antigen characterization (86–89). However, there are well-documented cases with IgA deposits at the BMZ and conjunctival involvement that in the end fulfilled immunological criteria for IgA-EBA (47, 49, 90, 91).

In turn, we have described a patient with mucosal involvement (critical esophageal stricture and scarring conjunctivitis) in whom circulating IgA and IgG antibodies were directed to the LAD-1 antigen (40). It is still under debate whether such cases should be identified as MMP or IgG/IgA LABD.

Particular attention should be paid to neonatal LABD which occurs in the first weeks, or even days, of life. Only several such cases have been published so far in the form of case reports (34, 83, 92, 93). They are characterized by very severe mucosal lesions, including in the gastrointestinal tract, and sometimes result in fatal outcomes. In all cases but one the diagnosis of LABD was established exclusively based on DIF. Only in one patient was LAD-1 identified as a target antigen, however, in this particular case mucous membranes were not involved and the clinical course was mild and similar to older children (94). Therefore, further research is necessary to understand the pathogenesis of neonatal LABD and to assess the relationship between the target antigen and the clinical course.

In summary, the differentiation in the frequency of mucous membrane involvement in LABD between countries may be a result of ethnic differences but generally is more common in cases of IgA-EBA and LA(G)BD than in the lamina lucida type of LABD.

Atypical manifestations and course

Single cases of LABD with erythroderma or prurigo nodularis-like lesions have been described (95). The patients presented with nodules instead of blisters, which were accompanied by intense pruritus. Due to an atypical clinical picture, a proper diagnosis was delayed in those cases and they required long-term treatment (96). Atypical LABD may also manifest as different variants of erythema multiforme, including toxic epidermal necrolysis (97). Such reports referred to adults and were usually associated with drug induction, mainly by vancomycin (98).

Atypical cases of LABD may also refer to the course of the disease. We had the opportunity to observe a 3-year-old boy with LABD presenting with vesicobullous eruptions located on the face, around the mouth, on the lower part of the abdomen, and on the genitals, who initially responded well to sulfones and low doses of prednisone. However, despite the systematic treatment, the disease did not disappear and changed its clinical image and course. At the age of 11, the patient developed large, hemorrhagic blisters on the traumatized areas mainly affecting the feet, which resolved leaving scars and milia. Fluorescence overlay antigen mapping using laser scanning confocal microscopy (FOAM-LSCM) performed on the patient's skin revealed the presence of linear IgA deposits below type IV collagen (32). Analysis of the clinical course of this patient raises the question of whether the sublamina densa type of LABD may not in fact be the same as IgA-EBA.

Another interesting case was initially seen in our department 30 years ago when a 5-year-old boy was admitted with typical manifestations of pediatric LABD mediated by IgA anti-BMZ antibodies directed to the BP180 antigen (32). He responded well to sulfones combined with low doses of prednisone, however, recently, as a 35-year-old man, he visited our department again due to disseminated vesiculobullous lesions resembling a string of pearls. This time, the diagnosis of recurrent LABD was confirmed by DIF. Repeated treatment with disulone in combination with a low dose of prednisone cleared the skin lesions promptly. There is one other case report in the literature of a case of childhood LABD which recurred after puberty (99).

Associated diseases

Cancers

A British research group was one of the first to analyze the occurrence of cancer in adult LABD patients. They found nine non-lymphoid and three lymphoid malignant neoplasms in the group of 70 patients. The malignancy rate of non-lymphomatoid neoplasms was almost identical to that which would be expected in an age- and sex-matched population, whereas the frequency of lymphoproliferative diseases among their cases was significantly higher (100). A similar malignancy rate was found in the most recent report on 81 LABD patients. Ten of them had comorbid malignancy (77). Other studies have also confirmed the association of LABD with lymphoproliferative neoplasms (101), most

frequently with non-Hodgkin lymphoma (102), chronic lymphocytic leukemia (103, 104), and T-cell lymphoma (105).

LABD may also coexist with visceral malignancy of the urinary bladder (106), esophagus, breast, thyroid gland, and colorectum (28). In most of the above-mentioned cases, the diagnosis of LABD was based only on the presence of linear IgA deposits in DIF.

The retrospective analysis of 58 well-described LABD patients from the city of Kurume, Japan revealed malignancy in 10 of them (28). Other authors from Japan studied a unique group of 32 cases of sublamina densa LABD with a humoral autoimmune IgA response to COL7. In this cohort, they did not find any malignancy (107).

In our center, we also have not noticed any association between LABD and malignancy (11, 32).

The differences in this aspect between countries worldwide might once again be explained by ethnic and genetic diversity. Only an analysis of larger cohorts of patients, well defined in terms of clinical and immunological characterization and subjected to a long follow-up, may lead to a better understanding of the relationship between LABD and malignancies.

Inflammatory bowel diseases

Kanda et al. reviewed the international literature and reported 35 cases of ulcerative colitis (UC) in patients with well-characterized LABD. The sera of these patients reacted with the roof of IIF-SSS, indicating the localization of those target antigens in the lamina lucida. In the vast majority of those cases, UC preceded the onset of LABD, therefore, the authors suggested a pathogenic relationship between these entities via modification of intestinal antigens due to chronic inflammation, through the production of IgA antibodies and their subsequent cross-reaction with the cutaneous BMZ (108). Several other reports also pointed to an association between LABD and UC (109–111). Less frequently, an association between LABD and Crohn's disease, another inflammatory bowel disease (IBD), has been reported (112, 113).

However, it has been reported that drugs used in the treatment of UC, such as infliximab, may induce LABD (114). However, in contrast to this finding, we published a case of EBA with coexisting UC, in which infliximab resulted in the long-lasting remission of both diseases (115).

Agents that provoke LABD

Drugs

It is worth highlighting that skin eruptions in drug-induced LABD may occur as soon as a few days after the introduction of the offending drug (116, 117). This is opposite to BP or anti-p200 pemphigoid, the diseases mediated by IgG anti-BMZ antibodies directed to the same antigens, in which the time between the introduction of the offending drug and skin lesions development is 6 weeks or even longer (46, 118). It is clear from the point of view of pathology: first, BMZ antigens are modified by the drug and they are then detected by the immune system, leading to the subsequent production of autoantibodies and their binding to the BMZ and followed by chemotactic attachment of leukocytes and enzymatic digestion of the BMZ and blister formation (64). We have described a case of anti-p200 pemphigoid with a clinical picture of Stevens–Johnson syndrome which appeared several days after the introduction of penicillin (46). The DIF performed at the time was negative but when repeated 6 weeks later revealed a strong linear IgG reaction along the BMZ. This particular patient shows that in cases with a clinical picture of AIBD provoked by drugs, DIF may not be positive from the beginning. Therefore, on the basis of our experience in different AIBD, DIF should be repeated with an interval of 4-6 weeks, especially if the skin lesions do not disappear and tend to persist.

In several publications on the subject of drug-induced LABD, skin lesions occurred as early as 2 days after the introduction of the offending drug, but there is no precise information on how long after the appearance of skin lesions the DIF test result was positive (116, 117). Although the current literature lacks satisfyingly comprehensive information on this subject, drug-related LABD may occur soon after the initiation of drug administration, and the immunological mechanism of this phenomenon requires further investigation.

The list of drugs that may cause LABD in both adults and children is long, including antibiotics, non-steroidal anti-inflammatory drugs, antiepileptics, antihypertensive, phenytoin, trimethoprim, immunosuppressive drugs, and even anti-TNF antibody or infliximab (25, 114, 117, 119–122).

It is particularly important to mention vancomycin, which is responsible for more than half of the drug-induced LABD cases (25, 116, 117, 123–126). In most of them, the diagnosis was based on the detection of linear IgA deposits in the BMZ. An interesting study was published by a Japanese research group which proved that circulating anti-BMZ IgA antibodies reacted with vancomycin-modified type VII collagen (123, 127).

From a medical point of view, it is important to note that in some cases of vancomycin-induced LABD, the clinical picture corresponded to TEN with a positive Nikolsky's sign (124–126). Disruption of type VII collagen in vancomycin-induced LABD suggests the diagnosis of drug-induced IgA-EBA and determines the formation of blisters below the basal lamina, similar to TEN.

In the literature, there are reports on drug-induced LABD with a clinical manifestation of TEN that were caused by drugs other than vancomycin, such as penicillin, phenytoin, diclofenac, and verapamil (25, 123, 128). It should be assumed that the mechanism leading to the formation of those skin lesions is analogous to the mechanism of vancomycin-induced LABD. In such cases, in order to understand the pathogenesis, it is necessary to determine the target antigen recognized by circulating IgA anti BMZ antibodies or alternatively to determine the ultrastructural location of IgA bound in the patient's skin.

Vaccinations

Before the COVID-19 pandemic era, cases of vaccine-induced LABD were reported infrequently and mainly referred to children.

In these cases, LABD was provoked by vaccines against mumps, measles, or HPV. The time of development of blisters ranged from several days to weeks, similar to drug-induced LADB (129, 130). At that time, only a single case report was published on adult LABD after an influenza vaccination (131).

In the past, the role of vaccines in LABD provocation was thought to be limited to children, however, it seems that they also play a role in adults due to the increase in the use of vaccines against influenza and COVID-19 in this age group (132–134).

Sunburn and burns

Ten years ago, we described a case of LADB induced by ultraviolet radiation (UV) and discussed five other such cases described in the literature. In three of the six published cases, the diagnosis of LABD was established on the basis of the reactivity of circulating IgA antibodies, with LAD-1 in two cases, and with BP180 in our case, using immunoblotting. In our case, the diagnosis of LABD was additionally supported by FOAM-LSCM showing IgA deposits above laminin 332 and type IV collagen (42). All the patients presented with blisters located on the sun-exposed areas. Among the patients who underwent phototesting, only our case showed hypersensitivity to UVB. The prognosis of LABD induced by UV radiation is good. All patients but one responded well to the treatment and stayed in remission at least for a few years (42).

A case of a 43-year-old Caucasian man with LABD induced by chemical and thermal burns was described but the diagnosis of LABD was based solely on DIF (135).

Therapy and prognosis

In most LABD cases in children, favorable results are obtained with dapsone in doses of 50-100mg/d (5), during the use of which it is necessary to control the morphology and liver function occasionally. In cases of side effects or contraindications to dapsone, other derivatives of sulfones should be considered, such as sulfapyridine and sulfasalazine (25, 111, 136, 137), which may be better tolerated than dapsone. In isolated cases, it is necessary to add prednisone alongside dapsone to achieve remission (3, 5). Due to the high risk of serious side effects of prednisone in mild cases, local corticosteroids or tacrolimus are worth consideration as a first line of treatment, with or without dapsone or antibiotics (i.e., erythromycin) (138, 139). Cyclosporine has also been suggested as a treatment for severe LABD, however, this drug by itself may induce LABD (119–121, 123, 125, 140).

In cases refractory to dapsone and prednisone, intravenous immunoglobulins or mycophenolate mofetil (23, 25) may be used. If conventional immunosuppressants are not effective, biologicals, such as rituximab or infliximab may be helpful (141–143).

In the treatment of adults with LABD, dapsone at a dose of 100mg/d in monotherapy has been shown to be highly effective, although some patients require higher doses of sulfones (12, 17). In some cases, it is necessary to include low doses of prednisone. In the literature, there are reports on the efficacy of azathioprine, colchicine, methotrexate, tetracycline, or mycophenolate mofetil in LABD (25, 144, 145).

It is not clear why some LABD cases respond to conventional treatment and others require more sophisticated regimens. It has been suggested that it may be in part related to circulating IgA antibodies directed against lamina lucida or sublamina densa antigens (23).

Studies are ongoing on the role of FcαRI as a promising new therapeutic target in LABD (68). Moreover, there is a clinical study in progress in Poland that could lead to the potential registration of anti-CD89 monoclonal antibodies as a treatment for LABD (Eudra CT, number: 2023-508661-33).

Diagnostics of LABD and other ASBD mediated by IgA anti-BMZ antibodies

Histology

The histopathological picture of LABD is not uniform (25). In some cases, it shows features characteristic of DH with the presence of clusters of multinucleated granulocytes, arranged mainly in the dermal papillae. In other patients, a subepidermal blister and infiltrates composed of multinucleated granulocytes and eosinophils along the BMZ are observed, similar to BP. In rare cases, the histological picture of LABD combines the phenomena observed in both BP and DH.

Serology

Indirect immunofluorescence

Circulating IgA-anti BMZ autoantibodies in LABD are directed mainly to LAD-1, but also to NC16A of BP180 and BP230, all expressed in the upper part of the BMZ. Therefore, IIF on SSS shows the reactivity of circulating IgA-anti BMZ autoantibodies with the roof of SSS (11, 23, 24, 28, 32, 70, 146). If circulating IgA anti-BMZ antibodies are directed to type VII collagen expressed in the sublamina densa region, they react with the floor of SSS (11, 27, 28, 32, 70, 146). Similarly, circulating IgA or IgG antibodies directed to p200 or laminin 332 antigens also react with the floor of SSS since these antigens are localized in the upper part of the lamina densa (18–20). It is a matter of controversy whether the antibodies that react with the antigens present at the floor of SSS represent a special subset of LABD or are separate entities (21, 25).

Recently, BIOCHIP, a novel diagnostic tool, was introduced for diagnostics of ASBD (146). This is an IIF technique on several substrates in a single incubation field of a laboratory slide including SSS and monkey esophagus for the demonstration of anti-BMZ antibodies and transfected cells expressing the BP230-gC (C-terminal globular domain) recombinant antigens encompassing the NC16a portion of the extracellular domain of BP180 (BP180-NC16a). This technique is mainly used for the detection and characterization of circulating IgG anti-BMZ antibodies, but it is also possible to use it to examine circulating IgA anti-BMZ antibodies, as was recently shown (147).

Enzyme-linked immunosorbent assay

Progress in molecular biology has allowed for the synthesis of recombinant antigens, which significantly improved the diagnostics of ASBD. The enzyme-linked immunosorbent assay (ELISA) method, especially multivariant ELISA containing a battery of recombinant antigens (BP180 NC16A, BP230, type VII collagen, envoplakin, and desmogleins 1 and 3) enables the rapid detection of circulating antibodies. The method is characterized by very high specificity and sensitivity (70, 148). Commercially available ELISA is intended for the detection of IgG antibodies. ELISA method kits can also be adapted for the detection of IgA antibodies, however, it requires extensive laboratory experience (70).

Western immunoblot

Currently, there is no commercially available test allowing for the detection of IgA circulating antibodies to LAD1/LABD97 and LABD antigens. The detection of these antigens is enabled by immunoblot and is possible only in a few laboratories around the world (7–10, 24, 52, 70). Thus, the detection of IgA anti-BMZ antibodies is challenging even if using a battery of methods and the detection rate ranges from 20% to 75%, depending on the cohorts of studied patients, technical capabilities, and experience of diagnostic laboratories (24, 70, 79, 80).

Direct immunofluorescence

Direct immunofluorescence performed in a patient's skin shows the presence of linear IgA deposits along the BMZ in all or nearly all patients, therefore, in cases with negative DIF but clinical characteristics of LABD, the biopsy should be repeated (23, 25). A study published by Becker disclosed only one patient out of 220 examined LABD cases was negative in DIF (23).

The fluorescence pattern of IgA in DIF is varied; in some patients it is thin and linear, but more often it forms a thick, linear, or even fibrillar staining, therefore the assessment of DIF in LABD may sometimes lead to confusion with granular staining, especially when observed under low magnification (2, 3, 149). It is likely that this characteristic thick band is the result of the concurrent reactivity of IgA anti-BMZ antibodies with different epitopes of BP180 and BP230 as presented by Kowalewski with the use of indirect IEM (11, 60). Interestingly, DIF stays positive in LABD from the onset of the disease, during the entire treatment and for many years after the therapy was finished (5). Therefore, in contrast to pemphigus and pemphigoid, positive DIF in the remission of LABD should not be, in our opinion, recommended as a decision criterion for continuing or ending the therapy.

In the majority of LABD patients, IgA in the BMZ is a single component but in 30% of the cases, it can be accompanied by C3 linear deposits (1–3, 5). In some of the patients, IgG linear deposits could also be detected (1, 2, 5, 23, 25, 28). If IgG is equally as strong as IgA, the diagnosis of LA(G)BD has been suggested by Hashimoto (41, 43), and it would be a diagnosis of an entity overlapping with LABD and pemphigoid in terms of clinical and immunological features (23, 40, 52).

Linear IgA deposits observed in DIF are not a hallmark for the diagnosis of LABD, since IgA deposits along the BMZ are also observed in IgA-EBA (22, 23, 32, 47) and anti-p200 pemphigoid (18, 44). Thus, in each case the diagnostics process should be supported by other techniques, allowing for the identification of the target antigen or for precise localization of IgA deposits in the BMZ.

Techniques allowing precise localization of IgA deposits in the BMZ

Serration pattern of linear IgA deposits

More than 20 years ago, Vodegel et al. introduced a method for differentiating BP from EBA based on the serration immunofluorescence pattern of IgG deposits in the patient's skin. Subsequently, the same research group and others confirmed the possibility of distinguishing between IgA deposits in the BMZ using the same methodology (150). It has been shown that an n-serrated pattern corresponded to the localization of either IgG or IgA deposits in the hemidesmosomes, lamina lucida, or lamina densa on the ultrastructure level, whereas an u-serrated pattern referred to the ultralocalization of type VII collagen in the sublamina densa (25, 70, 146, 150).

The analysis of n- and u-serrated patterns requires high-quality IF slides, a high-resolution lens, and extensive experience of the IF reader(s) (150). In cases where thick or fibrous IF staining is present, the analysis of the serration pattern is more challenging compared to BP or EBA. At the moment, a multi-center European program (the MAXISPA study), the objective of which is to research this method, is being conducted under the EADV grant to improve the ability in diagnostics of SBD.

Immunofluorescence mapping of lesioned patient's skin

Immunofluorescence mapping (IFM) on a patient's blister is a widely recognized diagnostic method, originally described for the differentiation of hereditary epidermolysis bullosa (151). The method allows the localization of blister formation using appropriate BMZ markers (i.e., antibodies against laminin 332 as a marker of the lamina lucida-lamina densa border and/or type IV collagen as a marker of lamina densa (151).

The same method may be used to determine the location of blister formation in patients with ASBD mediated by IgA. The presence of both markers in the floor of the blister indicates separation of the epidermis from the dermis within the lamina lucida (lamina lucida type of LABD), whereas the presence of both reactants in its roof indicates separation below the lamina densa (sublamina densa type of LABD or IgA-EBA).

The advantage of the IFM technique is the possibility to perform retrospective analyses of paraffin-embedded tissues in search of immunostaining with type IV collagen antibody (152). Diagnostics using IFM are limited to the patients presenting with fresh blisters.

Direct salt split skin performed in patients' own tissue

Direct salt split skin (DSSS) may be helpful for diagnosis in cases with undetectable circulating antibodies. DSSS was originally described by Kowalewski in his doctoral thesis in 1989 (153) and subsequently by Gammon and Kowalewski in 1990 (154).

Originally, the authors showed the presence of IgG deposits in the epidermal side of the blister or in both epidermal and dermal sides in BP, which corresponded to its ultrastructural localization in the entire lamina lucida. Whereas in EBA, IgG deposits were located at the bottom of the artificial blister, which corresponded to its ultrastructural localization in the sublamina densa (154).

In LABD, IgA deposits were located on the epidermal side of the separation (153). Here, we present a case of LABD in which IgA deposits were located on the epidermal side of the artificial blister (Figure 1A) and a case of IgA-EBA with linear IgA deposits at the bottom of the blister in DSSS (Figure 1B). The blister formation within lamina lucida in DSSS was confirmed by dermal staining of laminin 332 antibodies using IFM (Figures 1C, D).

In 2019, a French group studied two patients with linear IgA deposits on DSSS and found these deposits on the epidermal side of the blister in one case and on the dermal side of the blister in the second patient (142). Thus, DSSS allows one to distinguish between IgA deposits located in the lamina lucida and those located in the sublamina densa (142, 153). The great advantage of DSSS is that it is easy to apply in all patients. The limitation of the method is that dermal pattern has to be differentiated from those present in anti-p200 pemphigoid and anti-laminin 332 pemphigoid mediated by IgA.

Ultrastructural localization of IgA deposits at the BMZ

Direct immunoelectron microscopy

Direct immunoelectron microscopy using the pre-embedding immunoperoxidase technique (DIEM) performed on skin biopsies from patients with linear IgA deposits in the BMZ, showed the presence of IgA deposits in the lamina lucida of the BMZ in the majority of cases (13–15). Less frequently, IgA deposits were found in the sublamina densa region (16, 17).

Interestingly, there is only one study revealing a so-called "mirror image pattern", referring to the concurrent localization of IgA deposits in the lamina lucida and sublamina densa (155). Thus far, the nature of this phenomenon has not been explained.

Though IEM has a high resolution, it is not a routine technique in the diagnostics of ASBD due to the time-consuming nature and demanding procedure.

Fluorescence overlay antigen mapping with the use of laser scanning confocal microscopy

Alternatively to IEM, in 2003, we developed a method named fluorescence overlay antigen mapping using laser scanning confocal microscopy for practical differentiation of subepidermal bullous diseases mediated by IgG anti-BMZ antibodies (BP, MMP and EBA) (156). This is a method of choice for cases in which circulating anti-BMZ antibodies are not detectable and characterization of the target antigens is impossible. Originally, we compared the localization of linear IgG deposits to the localization of different BMZ markers: laminin 332 and type IV collagen (156). Our study disclosed that, in BP, the patients' IgG deposits were located above type IV collagen and laminin 332 whereas in EBA, IgG deposits were localized below type IV collagen. In MMP patients, IgG deposits were located between laminin 332 and type IV collagen (156).

In 2013, we applied this method for the differentiation of the diseases mediated by IgA anti-BMZ. FOAM-LSCM was

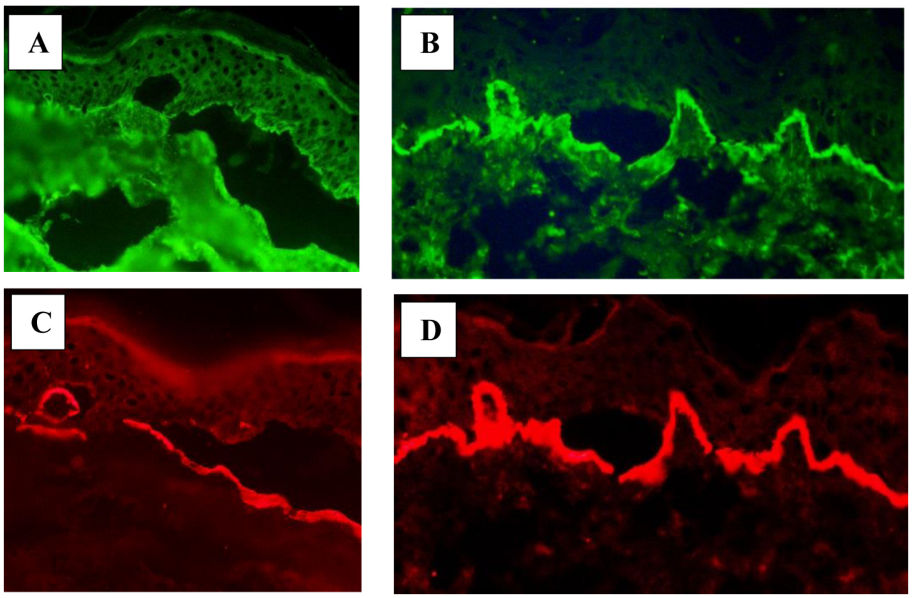

FIGURE 1
Direct salt split skin. **(A)** IgA deposits (green) located on the epidermal side of the blister in a patient with LABD. **(B)** IgA deposits (green) located on the dermal side of the blister in a patient with IgA-EBA. Antibodies against laminin 332 (red) proving dermal-epidermal separation in the lamina lucida located on the dermal side of the blister in LABD **(C)** and IgA-EBA **(D)**.

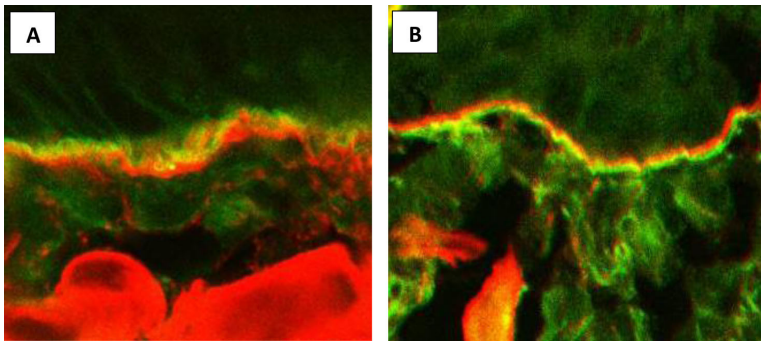

FIGURE 2
Fluorescence overlay antigen mapping by laser scanning confocal microscopy. **(A)** IgA deposits (green) located above type IV collagen (red) in a patient with LABD. **(B)** IgA deposits (green) located below type IV collagen (red) in a patient with IgA-EBA.

performed in 19 patients with disseminated tense blisters, who presented with *in vivo* bound and circulating IgA anti-BMZ in immunofluorescence tests (32). FOAM-LSCM disclosed IgA deposits above type IV collagen in 14 of the 19 cases, characteristically of the lamina lucida type LABD, whereas in the remaining five patients, IgA deposits were located below type IV collagen, suggestive of sublamina densa LABD or IgA-EBA (Figure 2). FOAM-LSCM studies were supplemented by immunoblotting showing that IgA antibodies in 11 of the 14 patients with deposits above type IV collagen reacted with different epitopes of BP180, but mainly with LAD-1, which is the target antigen in LABD. In one patient with IgA, deposits above type IV collagen serum reacted with the 200kD antigen. Among the five patients with deposits below type IV collagen, one had antibodies to the 290-kDa type VII collagen by immunoblot, whereas another three patients were positive with recombinant type VII collagen by ELISA (32).

It is worth mentioning that, thanks to FOAM-LSCM, we were able to diagnose anti-p200 pemphigoid mediated by IgA on the basis of co-localization of IgA deposits with laminin 332 (18). The results of our research have proven that it is possible to differentiate the lamina lucida type of LABD from the sublamina densa type of LABD and IgA-EBA.

It is also possible to assess the binding site of circulating IgA antibodies in the BMZ using FOAM-LSCM, if characterization of target antigens has failed (157, 158).

Conclusions

Linear IgA deposits in the BMZ detected by DIF are not pathognomonic for LABD and may also be present in other ASBD mediated by IgA-anti BMZ antibodies. These diseases differ in terms of clinical course and response to treatment even though they may present clinical similarities at the onset of the disease. In LABD, circulating antibodies are directed to various epitopes of the BP180 antigen located in the hemidesmosomes and lamina lucida. For practicing dermatologists, it is very important to distinguish LABD from other diseases in which IgA antibodies recognize antigens of the lower part of the BMZ—mainly type VII collagen, characteristic in IgA-EBA, and less frequent diseases such as IgA-anti p200 pemphigoid. The final diagnosis should be established on the basis of the clinical picture and the characteristics of the target antigen(s), if possible.

However, in cases in which circulating antibodies are not detectable, it is mandatory to establish the location of IgA deposits in the patient's skin using accessible methods, i.e., immunofluorescence mapping of the patient's lesioned skin, serration immunofluorescence pattern, or direct split of patient's skin, which clarifies the diagnosis in almost all cases, and FOAM-LSCM, which can precisely distinguish LABD from IgA-EBA.

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Conflict of interest

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Deciphering the role of IL17RA in psoriasis and chronic mucocutaneous candidiasis: shared pathways and distinct manifestations

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Introduction: Psoriasis and chronic mucocutaneous candidiasis (CMC), although distinct in their clinical manifestations, often coexist within specific patient cohorts. Despite this intriguing clinical observation, their genetic etiologies have been studied separately, neglecting the shared inflammatory mediator, interleukin 17A-F (IL17A-F). Consequently, the immunogenetic foundations underlying these conditions have remained enigmatic.

Methods: In this study, we analyzed the case of a 5-year-old female born to consanguineous parents who presented with concomitant psoriasis and CMC phenotypes. Utilizing whole exome and transcriptomic sequencing, we meticulously investigated the genetic underpinnings and molecular pathways underlying these complex pathologies. RNA sequencing was performed on a skin biopsy to confirm transcriptomic profiles associated with these conditions.

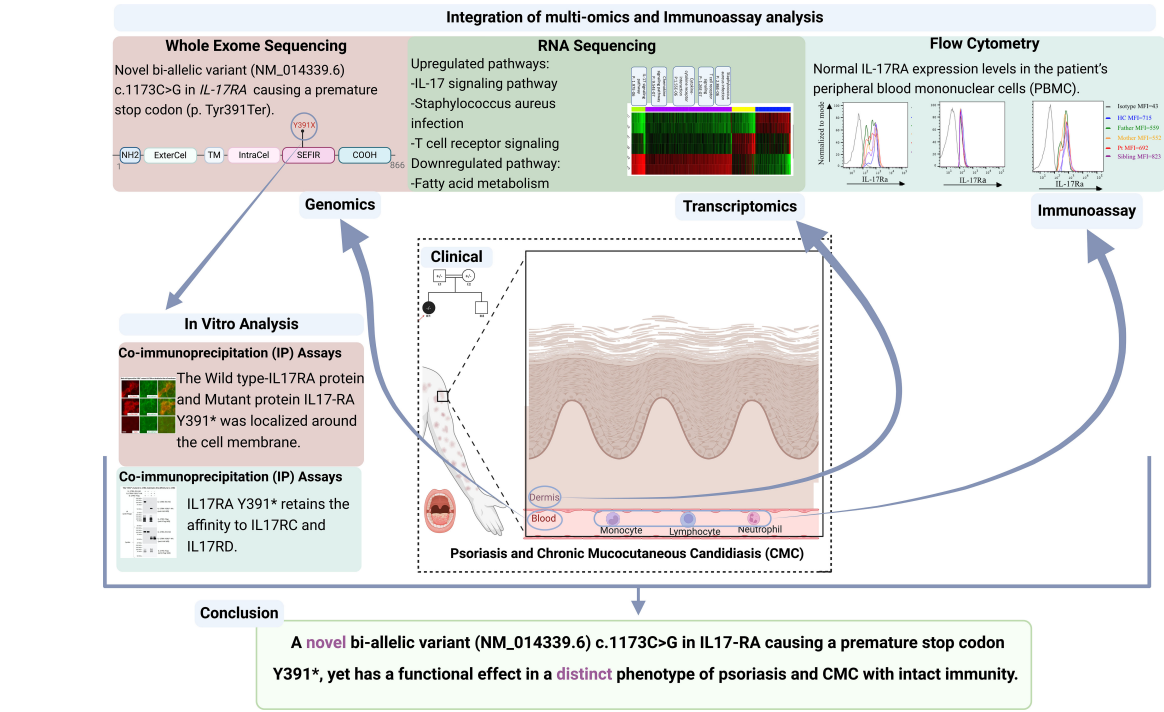
Results: We identified a novel bi-allelic variant (NM_014339.6, c.1173C>G A) within the interleukin 17 receptor type A (IL17RA) gene, resulting in a premature stop codon (p. Tyr391Ter). Despite the truncation, our investigations revealed that this variant produces a fully functional IL17RA protein. This was evident from the presence of IL17RA in the patient's peripheral blood mononuclear cells (PBMCs) and the ability of the mutant IL17RA to dimerize with both wild-type protein and its partners IL17RC and IL17RD. Transcriptomic analysis of the skin biopsy showed a distinct psoriasis-associated signature intertwined with inflammatory pathways, including responses to fungal infections.

Discussion: This report unveils an unprecedented genetic link serving as a common denominator for psoriasis and CMC. The novel IL17RA variant highlights the pivotal role of this receptor in the shared inflammatory pathways underlying these conditions. Our findings bridge a critical knowledge gap and

provide insights into the molecular mechanisms connecting these diseases. This discovery not only advances our understanding of their pathophysiology but also lays the groundwork for personalized therapeutic strategies, heralding a new era of precision medicine for patients with intertwined psoriasis and CMC.

KEYWORDS

IL17RA, psoriasis, oral candidiasis, multi-omics, flow cytometry



GRAPHICAL ABSTRACT

Highlights

- Novel pathogenic biallelic nonsense variant (NM_014339.6) c.1173C>G identified in the *IL17RA* gene by Whole Exome Sequencing in a 5-year-old child with psoriasis and chronic mucocutaneous candidiasis, expanding the range of IL17RA variant-associated phenotypes.
- The identified variant (NM_014339.6) c.1173C>G results in a premature stop codon with an amino acid change (p. Tyr391Ter). Despite that, the variant retains its functionality; it is expressed around the cell membrane, interacts with IL17RC and IL17RD partners like the wild type, and shows similar expression of IL17RA in peripheral blood mononuclear cells (PBMC) between the affected child and non-affected family members.
- Transcriptome analysis reveals signature pathways linked to psoriasis, and candidiasis, with IL17 identified as an upstream regulator.
- IL17/IL17RA axis SNPs potentially contribute to variable responses to IL17 inhibitors, warranting further investigation.

Introduction

Psoriasis and chronic mucocutaneous candidiasis (CMC) represent distinct yet interconnected inflammatory conditions, exerting a profound impact on affected individuals' quality of life.

Chronic mucocutaneous candidiasis (OMIM#615527, CMC) is a rare immunodeficiency disorder, characterized by recurrent and persistent fungal infections affecting the oral mucosa primarily (1). Psoriasis (OMIM: 614204), a chronic inflammatory skin disorder, is characterized by the presence of red plaques anywhere in the body, excessive keratinocyte proliferation, and immune cell infiltration driven by dysregulated T helper 17 (Th17), which are defined by their production of Interleukin-17 (IL-17) in response to Interleukin-23 (IL-23) (2). IL-23 promotes the survival and proliferation of Th17 cells, which in turn secrete pro-inflammatory cytokines such as IL-17A and IL-22. These cytokines contribute to the inflammatory response and keratinocyte proliferation seen in psoriatic lesions (3).

Interestingly, psoriasis exacerbations have been associated with *Candida albicans* infections, as individuals with psoriasis are shown to have higher rates of *Candida* colonization, particularly in saliva and sometimes on the skin and in feces, often without a clear etiology (4–7).

The interleukin-17 axis serves as a crucial defense mechanism against *Candida* albicans, while simultaneously playing a pivotal role in psoriasis immunopathogenesis (8, 9).

The role of Interleukin receptor A (IL17RA), a critical component of the IL17 receptor family is particularly significant, as genetic mutations in *IL17RA* have been linked to CMC (8, 10, 11). On the other hand, the association between IL17RA and psoriasis has been explored through association studies only, identifying a single nucleotide polymorphism (SNP) in *IL17RA* (rs4819554) that increases psoriasis risk in Spanish and Egyptian populations (9, 12).

Thus, IL17 inhibitors, often hailed as a breakthrough in the treatment of psoriasis for their precision in targeting the IL17 pathway come with a caveat.

Inhibiting the IL17 response may inadvertently promote fungal colonization, potentially aggravating the IL17 response and exacerbating psoriasis in a vicious cycle. This is exemplified by the common occurrence of oral candidiasis as a significant side effect of IL17 inhibitors (7). Of note, Brodalumab, the only approved anti-IL17RA drug for psoriasis, demonstrated superiority over ustekinumab in achieving Psoriasis Area Severity Index (PASI) 100 at week 12 in AMAGINE-2 and AMAGINE-3 clinical trials and a multicenter study involving 606 patients further showed that 91.3% of patients achieved a PASI score of 2 or less after 3 years of Brodalumab treatment (13, 14). However, the long-term use of Brodalumab was associated with a significantly higher rate of Candida infections compared to ustekinumab and other IL-17 inhibitors (13, 14).

Indeed, it is plausible that genetic mutations in the *IL17RA* gene could exacerbate this effect, an area that remains unexplored to our knowledge.

This study marks an unprecedented advancement in the understanding of these conditions by reporting the first mutation in *IL17RA* bridging psoriasis and CMC immunogenetic elements. Through comprehensive analysis, we aim to unravel the intricate immunogenetic underpinnings shared by these two conditions and potentially serve as a foundational cornerstone for deciphering the complex interactions shaping psoriasis and CMC pathogenesis and potentially pave the way for novel therapeutic strategies.

Materials and methods

Patients' recruitment and DNA samples

Patients and their families were recruited at the Genodermatoses unit, department of dermatology at the American University of Beirut Medical Center (AUBMC, Beirut, Lebanon) under the ethical approval Institutional Review Board (IRB) from AUBMC (Protocol Number: IRB: DER.MK.01). Approval and written informed consents were obtained from patients or their parents (if minors) for obtaining blood sample and pictures. The sibling did not participate, and his genetic data was not available. Clinical phenotypes were provided by the referring physician. Peripheral blood samples were collected from the participating individuals and kept at 4 degrees Celsius. DNA was extracted within 1 hour after blood collection from specimens and stored at 4°C.

Whole exome sequencing, annotation, and filter

Whole Exome Sequencing was performed for the patient and her parents at Macrogen Laboratory (https://dna.macrogen.com/) (Seoul, South Korea). 4 µg DNA of each sample was processed. One-hundred fifty-one base pair(bp-paired-end) reads were sequenced using the Illumina NovaSeq6000 platform. The library preparation was performed according to the manufacturer's protocol (Twist Human core exome). The Phred quality value was assigned to Q30, which means that the base call accuracy was 99.9%. Supplementary Table S1 shows the raw data statistics and quality scores. The generated FASTQ files were mapped to the Human GRCh37/hg19 reference assembly. Annotation and filtering processes for curated potential variants were performed as previously described (15).

RNA extraction and sequencing

Punch biopsies were obtained from the lesion of the affected patient (MK384) and controls (MK391 and MK392), individuals without skin autoimmune or chronic inflammatory diseases who are around the same age as the patient. Samples were processed directly for total RNA extraction using the Invitrogen Life Technologies TRIzol reagent following the manufacturer's protocol. RNA quantification was performed using the Nanodrop 1000 spectrophotometer (Thermo Scientific) at AUB. All samples, from both the patient and controls, were processed in technical duplicates, and the fragments per kilobase of exon per million mapped fragments (FKPM) values represent the mean of these duplicates. Further experimental details were performed as previously described (16).

Differential expression analysis

Htseq-count was used to summarize the read counts at the gene level. The differentially expressed genes (DEGs) were identified using DESeq2 after filtering out genes with low counts in all samples from the expression matrix. A gene was considered differentially expressed if its adjusted P-value (false discovery rate or FDR) was less than 0.01, and the absolute Log2 fold change was greater than or equal to 1, which corresponds to a 2-fold change threshold. Differential expression analyses compared the gene-expression profiles between the patient and the controls. Data analysis was conducted using iDEP.91 for generating heatmaps, scatterplots, and boxplots. Hierarchical clustering with the top 1000 most variable genes used a correlationbased distance metric, with linkage determined by an average cut-off score of 4. Gene expression values were centered by subtracting their mean value. Additionally, k-mean clustering with four clusters was performed using the top 2000 variable genes to identify biological processes. Gene normalization was achieved using the mean-center pathway database for GO biological processes within iDEP. 91.

Functional annotation analysis

The lists of DEGs were imported to the Ingenuity Pathway Analysis (IPA) software package (Ingenuity Systems, Redwood City, CA) to identify top enriched canonical pathways, upstream regulators, mechanistic networks, disease and functions' annotations. The analysis followed a methodology similar to the description reported by (17). In brief, the probe sets were mapped to the Ensemble and HUGO gene symbols within IPA software. Probe sets that did not map to any HUGO/Ensemble genes were discarded. Pathways were ranked according to p-values, with the most significantly impacted pathways displayed at the top. The analysis included genes with log2 fold changes of < -4.4 and >+ 4.7 and FDR less than or equal to 0.05. These criteria were used to identify genes with the most pronounced differential expression, which were subsequently selected for functional annotation.

Flow cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll-Paque PLUS gradient (GE Healthcare; IL, USA). Anti-human antibodies for surface makers, with isotype-matched controls, were used to stain CD3 (UCHT1) and CD14 (M5E2) from Biolegend (CA, USA), and IL-17RA (W23-251) from BD Biosciences (NJ, USA). In brief, T cells were identified by gating on the lymphocytes in the forward vs. side scatter plots using the CD3 marker, a pan marker for T lymphocytes. Monocytes were identified by gating on the monocytes in the forward vs. side scatter and using the CD14 marker, which is expressed on all monocytes and is part of the TLR4 signaling complex. Neutrophils were not specifically gated using a marker; instead, granulocytes, primarily composed of neutrophils, were gated in the forward vs. side scatter plots. Cells were sorted using a BD FACS Aria cell sorter (BD Biosciences, NJ, USA), and analyzed with FlowJo software (Tree Star Inc.; OR, USA).

Generation of expression vectors

The vectors were generated at Yamaguchi University Graduate School of Medicine, Japan by Dr. Yutaka Shimomura. Tags were introduced into the C-terminus. Using skin cDNA from a healthy control individual, expression vectors were constructed for an N-terminal HA-tagged IL17RA (IL17RA-HA), IL17RA-Y391*-HA, and Il17RC-FLag. For wild-type (Wt) IL17RA, the coding sequences were amplified by polymerase chain reaction (PCR) using a forward primer (IL17RA-F-EcoRI: 5'-CTCTGAATTCTCAGAACGTTCGTTCGCTGC-3') and a reverse primer (IL17RA-Wt-R-HA-SalI: 5'AAAAGTCGACTAGG CGTAGTCGGGCACGTCGTAGGGGTATGCAC TGGGCCCCTCTGACT-3') which introduced the HA-tag. The amplified PCR product was digested with EcoRI & SalI enzymes and subcloned into the pCXN2.1 vector at EcoRI and XhoI sites.

For the IL17RA-Y391*-HA vector, PCR was performed using the forward primer to amplify its sequence (IL17RA-F-EcoRI: 5'-CTCTGAATTCTCAGAACGTTCGTTCGCTGC-3') and reverse primer (IL17RA-Y391*-R-HA-KpnI: 5'AAAGGTACCT AGGCGTAGTCGGGCACGTCGTAGGGGTAGAGGG GGTGGTCGGCT-3') that introduced the reverse primer. The amplified product was digested with EcoRI and KpnI enzymes and subcloned into the mammalian pCXN2.1 vector at EcoRI and KpnI sites. The mutation c.1173C > G (p. Tyr391Ter) was introduced into the pCXN2.1- HA-IL17RA-Wt vector using the Quick-Change site-directed mutagenesis kit (Agilent Technologies). Similar to the cloning of IL17RA, cDNA sequences encoding the intracellular domain (IC) of IL17RC and IL17RD were amplified by PCR using forward and reverse primers. For IL17RC-Flag, the forward primer (IL17RC-F-EcoRI:5'CTCGAATTCGCCACCA TGCCTGTGCCCTGGTTCTT-3') and reverse primer (IL17RC-R-Flag-NheI): 5'AAAGCTAGCTACTTATCGTCGTCATC CTTGTAATCAGTCCCGTCCCCCGCCCCA-3') were used. The HA-tag nucleotide sequences were introduced into the reverse primer. For all tags, it was introduced into the C-terminus. The PCR products were digested with EcoRI and NheI enzymes and subcloned into pCXN2.1 vector at EcoRI and NheI sites (pCXN2.1-IL17RC/D-HA).

Cell culture, indirect immunofluorescence, co-immunoprecipitation assays

Human embryonic kidney (HEK293T) cells were used according to the manufacturer's instructions. 0.6 μg of vectors encoding N-terminal HA-tagged IL17RA (Wt or p. Tyr391Termutant [Mut]) or an empty pCXN2.1 vector, were transfected into wells.

For immunofluorescence (IIF) studies, HEK293T cells were transfected with expression vectors for IL17RA-Wt-HA, IL17RA-Y391*-HA, or an empty vector (50 ng each). Cells were stained with rabbit polyclonal anti-HA antibody (diluted 1:1,000; Abcam) and

mouse monoclonal antipan-cadherin antibody (diluted 1:1,000; Abcam). For Co-IP assays, HEK293T cells were transfected with IL17RA-HA and IL17RC-Flag, as well as IL17RA-HA and IL17RD-Flag (1.0 µg each), using Lipofectamine 2000 (Life Technologies). Immunoprecipitation was performed using mouse anti-DDDDK (flag) agarose gels (MBL International). Cell culture, transfection, IIF, and Co-IP were performed as previously described (16).

Results

Clinical diagnosis of two traits

The proband II.1 is a 5-year-old female child, the offspring of first-cousin consanguineous Lebanese parents (Figure 1A). She presented to the dermatologist at the age of one year with psoriasis on her scalp but no hair loss (Figure 1B), along with recurrent erythematous. At the time of presentation, she was not receiving any medical treatment; yet, she had persistent oral mucosal candidiasis, confirmed by a KOH smear showing *candida albicans* growth (Table 1). She did not have any other infections, and her immune workup showed unremarkable findings, her White Blood Cell(WBC) count and Automated Differential were within the reference range [Neutrophils[0.8-7.2x10(9)/L], Lymphocytes [1.3-8x10(9)/L], Monocytes [0.1-1.1x10(9)/L], Eosinophils [0-0.7x10(9)/L], Basophils [0-0.2x10(9)/L]. The patient's parents and brother underwent clinical assessment, which did not reveal any features of psoriasis or oral candidiasis, prompting a genetic workup.

Exome sequencing: a novel bi-allelic deleterious variant in *IL17RA*

The whole exome sequencing results of the patient and her parents yielded an average of 85,000 variants per sample. After applying a stringent filtering approach (see material and methods), 1,882 variants were retained for further analysis. Segregating with the phenotypes and assuming a recessive mode of inheritance, only homozygous variants were included in the first filter, yielding 206 homozygous variants (Supplementary Figure S1, see methods). Amongst these, a novel homozygous variant was detected on chromosome 22 (NM_014339.6 c.1173C>G, g.23439C>G) mapping to the *IL17RA* gene, resulting in a premature stop codon (p. Tyr391Ter). This variant was found in a homozygous form in the proband and in a heterozygous manner in her parents (Figures 1C, D) (ClinVar#SCV002520326). The variant is classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) classification (18), with a Combined Annotation Dependent Depletion (CADD) score of 36 (19). It is predicted to have a deleterious effect with a tree vote score of (184|16), which may cause nonsensemediated decay NMD (-476 AA/more than 10% missing) according to MutationTaster (20). This variant is absent from gnomAD (21), ExAC (22), and our in-house database of 300 Lebanese exomes. While additional variants in *HLA-DRB1* and *NLRP3* genes (Table 1, Figure 1E) may influence the phenotype(s), we focused on this variant to gain insights into its consequences on IL17RA protein function, as it is implicated in both phenotypes observed in the affected child. Of note, potentially

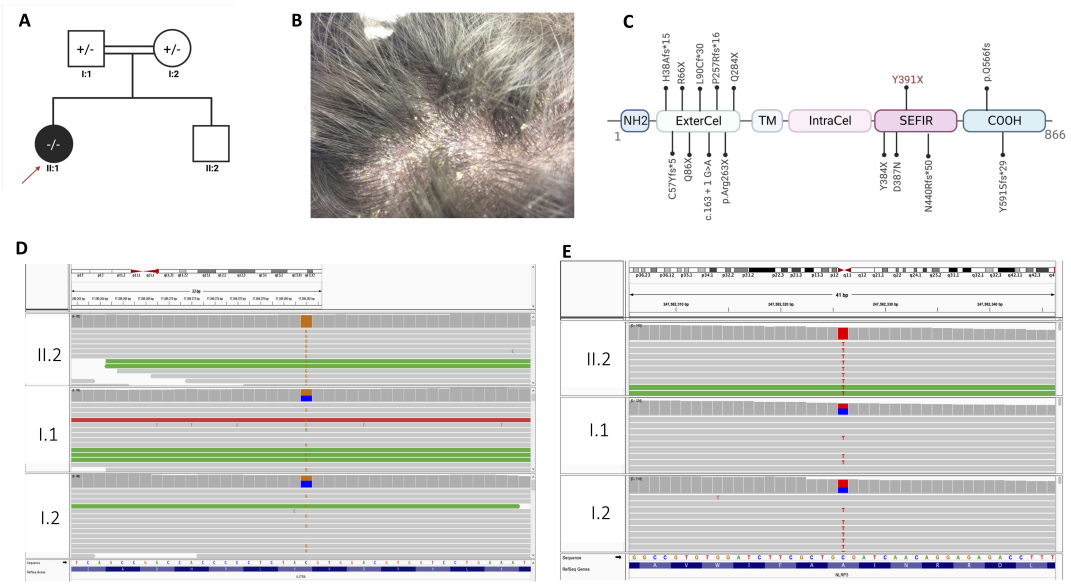


FIGURE 1
Characterization of the genetic causes of concomitant psoriasis and chronic mucocutaneous candidiasis. **(A)** The pedigree of the family, consanguineous marriage; all members are healthy (highlighted with white color), the proband affected with psoriasis and oral candidiasis is highlighted with red arrowhead. **(B)** Well defined scaly plaques on the scalp of the proband. **(C)** IL17RA protein structure, position of mutation is shown (Y391X) NH2- N terminal domain, ExterCel – Extracellular domain, TM - Transmembrane domain, IntraCel - intracellular domain, SEFIR domain – COOH-C terminal domain. **(D)** IGV visualization of IL17RA; the G > C variant change in the homozygous form for the patient (II.1) and heterozygous form in the mother and father (I.1 and I.2). **(E)** IGV visualization of NLRP3 showing T > C variant change in the homozygous form for the patient (II.1) and heterozygous form in the mother and father (I.1 and I.2). +/- heterozygous -/- homozygous.

TABLE 1 Genetic and clinical findings of the potential disease-causing variant in the proband.

Genetic Findings												Clinical Findings			
Gene Variants	**c.DNA Position**	**Protein Domain**	**Coding Impact**	**CADD Score**	**Sift**	**PolyPhen**	**Predicted Effect (ACMG/ MutationTaster)**	**MAF (gnomAD v2.1.1)**	**gnomAD Mean Depth Coverage (v2.1)**	**MAF (ExAC v1.0)**	**MAF (Lebanese Exomes and other Population Exomes)**	**Skin**	**CMC**	**Auto-immunity**	**Treatment**
IL17RA p.Tyr391Ter	c.1173C>G	SEFIR	Nonsense	36	NA	NA	Likely Pathogenic (PVS1)/ Deletrious (184| 16)	0/ 141,456 (exomes)	Exomes 69.5 Genomes 32.1	0/ 60,706	0/72	Psoriasis (scalp, no hiar loss)	KOH smear (*candida albicans*: oral)	–	–
Other Potential disease-causing variants in the Proband															
HLA-DRB1 p.Gln39Ter	c.115C>T	Beta-1	Nonsense	53	NA	NA	Likely Pathogenic (PVS1)/ Deletrious (17| 183)	0/ 72246 (exomes)	Exomes 15.9 Genomes 17.7	1/ 23358	1)Lebanese28/72 2) KRGDB 708/2852 3)SGDP 16/48				
NLRP3 p.Ala77Val	c.230C>T	Pyrin	Missense	18.3	Deleterious (0.04)	Possibly damaging (0.533)	Benign/ Benign 23|77	29/249554 (exomes) 2/ 31326 (genomes)	Exomes 74.9 Genomes 29.2	8/ 119986	0/72				

CADD, Combined Annotation Dependent Depletion; ACMG, American College of Medical Genetics and Genomics; MAF, Minor Allele Frequency; HGVS, Human Genome Variation Society; KRJBD, Korean Reference Genome Database; SGDP, Simons Genome Diversity Project.
NA, not applicable.

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pathogenic variants in genes previously associated with psoriasis such as *PSORS1-13*, MHC, I, *TNF*, and *TRAF3IP2* (23–26), and genes implicated in CMC, including *STAT1*, *AIRE*, *IL17F*, *IL17RC*, and *RORC* (27–29) were absent in our patient.

Genome-wide transcriptomics identify upregulated pathways related to IL17 pathway

To further elucidate the molecular mechanisms underlying both phenotypes and ascertain the diagnosis, RNA-seq was conducted on lesional skin biopsies from the indexed patient (II.1) and two non-lesional skin samples from healthy controls. The data distribution and sample correlation of the FPKM values are shown in Supplementary Figures S2A-C. We detected 1,136 differentially expressed genes (DEGs) with 967 upregulated and 169 genes downregulated when defined by a fold change (FCH) >2 and a false discovery rate (FDR) <0.01 (Supplementary Table S2, Supplementary Figures S2D-F). Tables 2A, B show the top 15 upregulated and downregulated DEGs, respectively. The top upregulated genes include those encoding the S100 calcium-binding proteins (*S100A8, S100A7/A*, and *S100A9*) which exhibited the most significant increase in expression with a log2 fold change of 8.17. Additionally, proteolysis regulation molecules (*SERPINB4, SERPINB3, PI3*), matrix metalloproteinases (*MMP1* and *MMP3*) and chemokines (*CCL18*) were highly upregulated. Conversely, the top downregulated genes include PPAR-fatty acids and lipid metabolism-related genes such as *FADS2*, which exhibited the most substantial decrease in expression, along with *FABP7*, *ACSBG1*, *ELOVL3*, *PM20D*, and *DGAT2L6*, keratinocyte related genes *KRT79 and KRT2*, Serpin Family A Member 12(*SERPINA12*), and (*C1ORF68*).

We identified 39 enriched pathways with an adjusted p-value (adj.p-value) of <0.05 (Figure 2A; Supplementary Table S3). Among the top 15 enriched pathways (Table 3), T cell receptor signaling (adj.p-value 1.26E-07), chemokine signaling (adj.p-value 9.54E-07), cytokine-cytokine receptor (adj.p-value 1.55E-06), Staphylococcus aureus infection (adj.p-value 2.86E-06), and notably the IL17 signaling pathway (adj.p-value 1.97E-06) were upregulated (Figure 2B).

Interestingly, we found that the most significant canonical pathway is IL17A in Psoriasis [pvalue: 2.65E-08, -log (p-value: 7.58)] amongst 16 canonical pathways identified by IPA with a p-value of ≤ 0.05 (Figure 2B; Supplementary Table S4).

IL17R emerged as the master upstream regulator (p-value 3.29E-10) with a predicted activation in the pathway indicated by a z-score of 2, among 566 upstream regulators with a of p-value ≤ 0.05. (Figures 2C, D; Supplementary Table S5).

In terms of diseases categories, dermatological diseases (with a p-value between 1.44E-17 and 4.21E-02) were among the second top categories out of 73 identified (Figures 2D, E; Supplementary Table S6). Among these, 877 disease function annotations were identified with a p-value ≤ 0.05 (Supplementary Table S7). Strikingly, under the "dermatological diseases" category, psoriasis emerged as the top annotated disease function with a p-value of 2.94E-12, involving 9 corresponding molecules (Supplementary Table S7). We conducted additional analysis to identify and annotate molecules and biological functions that are common to psoriasis, fungal infection (associated with CMC), and inflammatory response. This analysis is detailed in Figure 2G and Supplementary Table S8.

Detection of normal levels of IL17RA proteins in the patient

Moreover, to gain better insight into this increased IL17 pathway activity, we quantified the presence of the protein in the patient's PBMCs.

We used flow cytometry on PBMCs from the patient, her sibling, and her parents, using a specific monoclonal antibody against the IL17RA protein. Results showed that the patient (II.1) expresses normal levels of IL17RA on her T lymphocytes, monocytes, and neutrophils (Figure 3). This suggests that the mutation produces a stable truncated protein, which may be capable of homodimerizing and potentially enhancing the IL17RA downstream pathway. These findings prompted us to assess the structure and function of the mutated protein *in vitro*.

The IL17RA mutant protein is localized at the cell membrane and maintains the interation with IL17RC and IL17RD

To assess the impact of the Y391* variant on the structural and functional properties of IL17RA, site-directed mutagenesis was performed on human *IL17RA* cDNA cloned into an HA-tagged expression vector. The generated plasmid was transfected into HEK293 and HaCat cells to examine the localization of the mutant protein and compared to the wild-type IL17RA (Wt).

Immunofluorescence studies revealed that both Wt-IL17RA protein and mutant protein IL17RA Y391* were localized to the cell membrane in both HEK293 and HaCat cells (Supplementary Figures S2A, B). To assess the physical interaction with IL17RC/D, Co-immunoprecipitation (IP) assays were performed. The results showed that the mutant p.Y391* retained its capability to bind to both IL17RC and IL17RD proteins. This finding confirms a potential deregulated signaling pathway that could contribute to the underlying psoriatic phenotype (Figures 4A, B).

Discussion

Psoriasis and CMC share an intriguing undercurrent immune dysfunction, chronic inflammation, and susceptibility to perturbations in IL17-mediated signaling. The IL17RA plays a pivotal role in Th17 cell differentiation and downstream signaling, significantly influencing the inflammatory pathways in both conditions. In this study, we have detected a novel deleterious mutation in *IL17RA* causing a dual phenotype, resulting in a functional receptor and demonstrating the complexity of receptor-ligand interaction in the IL17 family.

Mutations in the *IL17RA* gene have been previously linked to CMC and, in some cases, other skin abnormalities (Table 4) (10). However, our indexed patient developed psoriasis and CMC from

TABLE 2 The top 15 up/downregulated differentially expressed genes (DEGs).

(a) Upregulated genes										
Symbol	log2 FC	adj. p-value	Chr	Type	Control 1a	Control 1b	Control 2a	Control 2b	Patient a	Patient b
S100A9	8.17693416	0.00021902	1q21.3	protein_coding	3.05837711	3.14590729	2.42068989	2.34885277	10.9267556	10.9140263
ELK2AP	7.96511871	0.00026016	14q32.33	processed_pseudogene	0	0	0.55341359	0.84963104	8.37384393	8.25791579
S100A8	7.49793854	0.00021095	1q21.3	protein_coding	3.22297299	3.20427534	2.6238809	2.56471959	10.4047052	10.3990963
S100A7	6.93517774	6.57E-05	1q21.3	protein_coding	2.83854239	3.31321392	3.16031356	3.20389492	10.1060394	10.0222985
VTRNA1-3	6.8120407	0.00186493	5q31.3	misc_RNA	0	0	0	0	7.9109245	5.7131569
IGLL5	6.52670759	6.94E-05	22q11.22	protein_coding	0.59614896	0.69694372	0.27226929	0.68431516	7.04923868	7.12901506
SERPINB4	6.37927495	5.37E-05	18q21.33	protein_coding	0.22126214	0.51586482	0.16459451	0.14284079	6.67788874	6.60294229
MMP1	5.74151243	5.26E-06	11q22.2	protein_coding	0	0.0746686	0.03089737	0.05283209	5.83466824	5.72755565
CCL18	5.60475791	8.16E-05	17q12	protein_coding	0.24229519	0.10285025	0.44665536	0.50068582	5.97321634	5.88254279
LTF	5.15417654	0.00021095	3p21.31	protein_coding	0.10276682	0.2364816	0.58886788	0.54759987	5.5730412	5.47316997
PI3	5.03872063	1.29E-03	20q13.12	protein_coding	1.40923342	1.35995965	0.35130154	0.47774674	5.8541453	6.02241664
SERPINB3	4.949767	7.71E-06	18q21.33	protein_coding	1.22196367	1.30615139	1.21966728	1.38209172	6.23305783	6.23141321
MMP3	4.63021645	5.26E-06	11q22.2	protein_coding	0	0.0394714	0.06380926	0.08192422	4.71856986	4.63446549
S100A7A	4.57798229	7.71E-06	1q21.3	protein_coding	0.05000666	0.16952099	0.04585433	0.02278808	4.64543075	4.65461884
FABP4	4.36353074	2.00E-02	8q21.13	protein_coding	0.99413001	1.00093745	3.33112332	3.28017687	6.59375861	6.43648669
(b) Downregulated genes										
Symbol	log2 FC	adj. p-value	Chr	Type	Control 1a	Control 1b	Control 2a	Control 2b	Patient a	Patient b
Symbol	log2FC	adj. p-value	Chr	Type	control 1a	control1b	control2a	control2b	Patient a	Patient b
FADS2	-4.7703907	8.16E-05	11q12.2	protein_coding	5.86522105	5.86800763	6.17982352	6.063999	1.23146313	1.21628102
FABP7	-4.3232274	0.00413127	6q22.31	protein_coding	3.93966854	4.10798073	5.39283601	5.26774178	0.25457107	0.45308767
KRT79	-4.1937686	0.0003437	12q13.13	protein_coding	5.40251413	5.10090618	5.70980619	5.52887445	1.24925722	1.23425605
PM20D1	-4.1594922	0.00104106	1q32.1	protein_coding	4.2813941	4.26530186	5.04146641	4.94963298	0.41955291	0.53036045
ALOX15B	-3.5086781	0.00039423	17p13.1	protein_coding	4.28209132	4.27326224	4.62182917	4.69598825	0.92222602	0.9970033
GAL	-3.3676949	0.00101649	11q13.2	protein_coding	3.57618349	3.41043202	4.00452836	4.08137372	0.48013481	0.3207342
THRSP	-3.2907684	8.16E-05	11q14.1	protein_coding	4.79466019	4.64582845	4.87170568	4.76263584	1.51639343	1.43948484
C1orf68	-3.1050519	0.00052195	1q21.3	protein_coding	4.17594769	4.30013837	3.91141356	3.95247336	1.13255052	0.82733208

(Continued)

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TABLE 2 Continued

(b) Downregulated genes										
Symbol	log2 FC	adj. p-value	Chr	Type	Control 1a	Control 1b	Control 2a	Control 2b	Patient a	Patient b
DGAT2L6	-3.0635369	0.01422656	Xq13.1	protein_coding	2.41673978	2.3046483	3.78686815	3.81767442	0	0.03589145
ACSBG1	-3.0386056	0.00021902	15q25.1	protein_coding	3.89762767	3.72908503	4.02575528	3.92523991	0.76281993	0.94882284
AADACL3	-3.021471	1.67E-04	1p36.21	protein_coding	2.88022708	2.95466534	3.13082711	3.12016446	0	0
SERPINA12	-2.9762025	2.92E-03	14q32.13	protein_coding	4.68048752	4.66440319	3.89239103	3.85887618	1.29767859	1.29799546
ELOVL3	-2.8620087	8.67E-03	10q24.32	protein_coding	3.06764216	2.91597018	4.13341557	4.05660954	0.50638766	0.85641368
AWAT2	-2.856141	2.64E-04	Xq13.1	protein_coding	2.71101026	2.8964288	3.03151695	3.01427316	0.08591463	0.02841794
KRT2	-2.8135481	3.42E-03	12q13.13	protein_coding	7.72292363	7.73023915	8.49033346	8.5499502	5.27465304	5.34497404
IL37	-2.6347421	2.01E-03	2q14.1	protein_coding	2.9632614	3.2455489	2.47201459	2.60986604	0.25289398	0.12296739

RNAseq performed in technical duplicates.

the age of one, effectively ruling out medication-induced side effects as a cause, given the absence of systemic medication use.

While this is the first report linking a mutation in *IL17RA* to psoriasis in humans, a psoriasis-like skin alteration phenotype and immunodeficiency has been reported in cattle caused by recessively inherited frameshift variant in *IL17RA* (XP_015316220.2: p. Cys61AlafsTer62), resulting in a loss-of-function LOF effect (30). The reported loss of function *IL17RA* mutation in cattle might suggest a phenotype like psoriasis. One could argue, however, that alternative splicing might generate an N-terminal truncated form with potentially greater potency, a hypothesis we propose for our truncated protein.

Our mutation results in a presumably truncated receptor lacking the SEFIR domain, an essential component for its downstream activity (Figure 1C). This domain is required for docking to the nuclear factor activator protein 1 (ACT1), encoded by *TRAF3IP2*, thereby activating proinflammatory pathways (Figure 5) involving the different players mainly MAPK, NF-κB, and C/EBP (31, 32).

The complexity of ascertaining a mode of action is intimately related to the broad spatiotemporal expression of IL17RA and its network of intracellular and extracellular partners. We have previously shown that a missense mutation in *TRAF3IP2* resulted in a partial defect of physical interaction with IL17RA but would preserve or potentially enhance its interaction with TRAF6. This pleiotropic and wide effect spans from scarring alopecia to folliculitis decalvans in affected patients (16). Others have highlighted a seemingly contradictory effect between innate and adaptive immunity in a *TRAF1* polymorphism, which is associated with reduced expression of the protein but paradoxically leads to a gain of function that leads to rheumatoid arthritis (33). This model proposes that distinct TRAF1 partners are present in T-cells and monocytes, leading to a differential contextual effect that shapes the phenotype. It has been proposed that TRAF1's role in restraining innate immune inflammatory signaling surpasses its function in maintaining TNFR superfamily signaling in T-cells (34). It was also demonstrated that IL17RA mobilizes, attracts, and triggers neutrophils (35). This connection between innate and adaptive immunity might provide additional insight into the intricacies of the observed phenotype.

Our findings show preserved expression of the IL17RA variant in the patient's PBMCs and *in vitro* analysis, along with normal membrane localization and functional heterodimerization with IL17RC and IL17RD (Figures 3, 4). Paradoxically, despite harboring this truncated form of the protein, transcriptomic analysis showed a strong activation of the IL17A/RA axis, bearing the signature of a psoriatic phenotype (Figure 2B). Notably, we discovered that IL17R serves as a unifying genetic factor, linking these seemingly disparate conditions by modulating immune responses, inflammation, and tissue integrity (Figures 2C, D). A loss of function of *IL17RA* in keratinocytes could trigger a feedback mechanism resulting in hyperproduction of IL17 in the skin and recruitment or expansion of more Th17 cells, as observed in mice. Indeed, it was previously shown that *Il17ra* knockout mice exhibit significantly elevated levels of Th17- and IL17A-producing dermal γδ T cells in the skin, indicating the role of IL17RA in regulating the size of these populations in the skin (36).

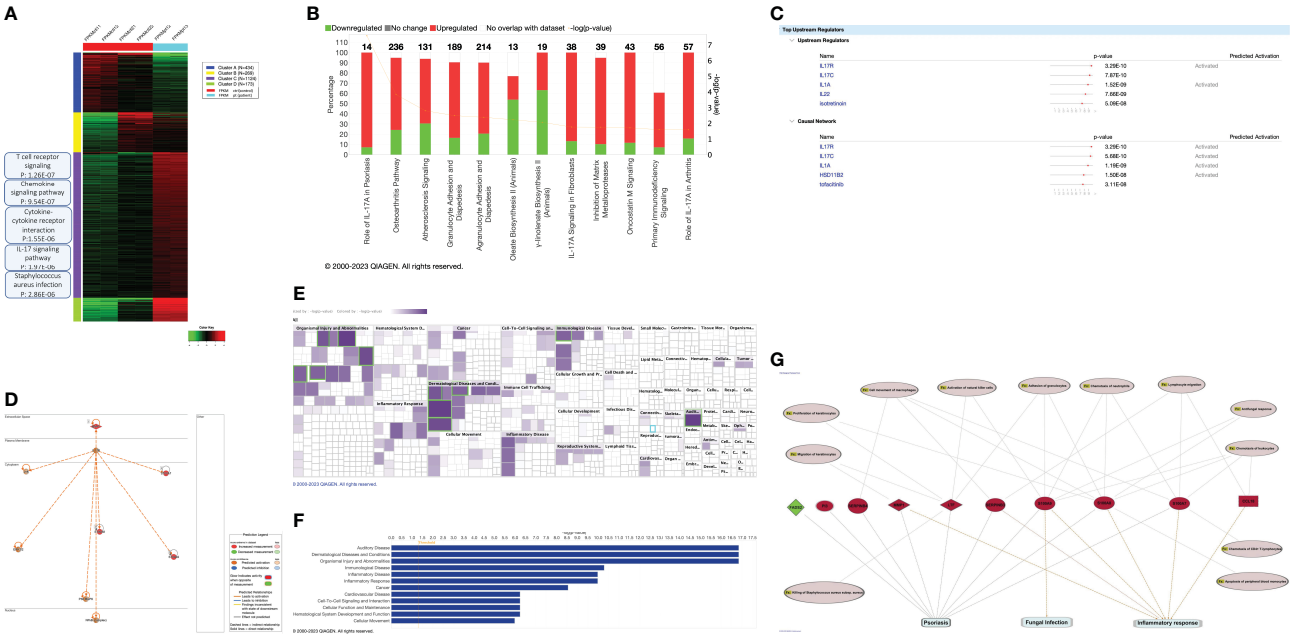

FIGURE 2
Transcriptional profiling of the affected psoriatic skin biopsy. **(A)** Heatmap of different enriched clusters in distinct biological pathways (based on kmeans and GO biological process (patient vs control). **(B)** The Top 12 Canonical pathways ranked from the most significant according to the – log(p-value). For the complete list, check Supplementary Table S4. **(C)** The top 5 upstream regulators and casual network in the dataset (patient vs control). For the complete list, check Supplementary Table S5. **(D)** The master upstream regulator: IL17R. **(E)** Heatmap of the top disease and function categories. The top 5 categories (based on the p-value) are highlighted with green boxes. **(F)** The top 12 disease and function categories are shown as a bar chart. **(G)** Shared molecules and disease function annotation between psoriasis and CMC. Psoriasis, fungal infection, and inflammatory shares 9 molecules depicted in red, LTF, MMP1, S100A7, S100A8, S100A9, SERPINB3, SERPINB4. Each molecule is associated with disease function annotation in pink circles.

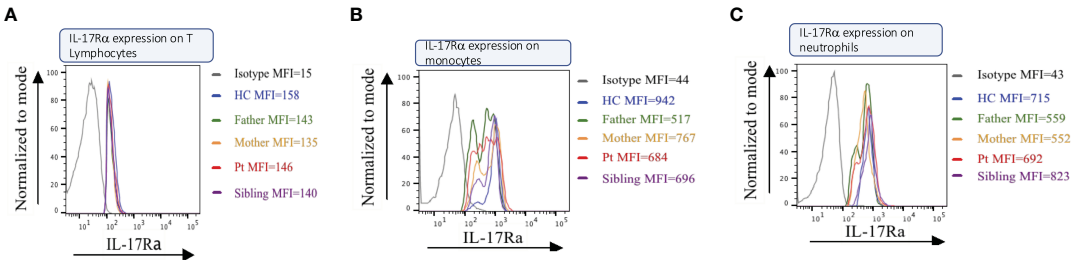

FIGURE 3
IL17RA expression in the patient/parents/sibling's peripheral blood mononuclear cells (PBMC). Cell sorting in Lymphocytes **(A)**, Monocytes **(B)**, and Neutrophils **(C)** show similar expressions between the patient and her non-affected family members.

TABLE 3 The top 15 enrichment clustered genes based on k- means (patient vs control).

Cluster	adj. p-value	nGenes	Pathways	Genes
C	4.82E-40	58	Systemic lupus erythematosus	HIST2H3C CTSG FCGR2A FCGR3B HIST1H2AE HIST1H2AD H2AFZ HIST1H2BB HIST2H3A HIST2H2BF HIST2H4B HIST2H3D C1R C1S HIST2H2AA4 HIST1H4I HIST1H2AI HIST1H2AJ HIST1H2AL HIST1H2AB HIST1H2AM HIST2H2AA3 HIST1H2BG HIST1H2BL HIST1H2BN HIST1H2BM HIST1H2BF HIST1H2BE HIST1H2BH HIST1H2BI HIST1H2BC HIST1H2BO HIST1H3A HIST1H3D HIST1H3C HIST1H3E HIST1H3I HIST1H3G HIST1H3J HIST1H3H HIST1H3B HIST1H4A HIST1H4D HIST1H4F HIST1H4K HIST1H4J HIST1H4C HIST1H4H HIST1H4B HIST1H4L HIST1H2AH ACTN1 HIST1H3F HIST1H2AG HIST1H2BJ CD28 CD80 CD86
C	1.88E-30	57	Alcoholsim	HIST2H3C FOSB GNG5 GNG10 HIST1H2AE HIST1H2AD H2AFZ HIST1H2BB HDAC1 HIST2H3A MAOB HIST2H2BF HIST2H4B HIST2H3D HIST2H2AA4 CALM1 CALM2 HIST1H4I HIST1H2AI HIST1H2AJ

(Continued)

TABLE 3 Continued

Cluster	adj. p-value	nGenes	Pathways	Genes
				HIST1H2AL HIST1H2AB HIST1H2AM HIST2H2AA3 HIST1H2BG HIST1H2BL HIST1H2BN HIST1H2BM HIST1H2BF HIST1H2BE HIST1H2BH HIST1H2BI HIST1H2BC HIST1H2BO HIST1H3A HIST1H3D HIST1H3C HIST1H3E HIST1H3I HIST1H3G HIST1H3J HIST1H3H HIST1H3B HIST1H4A HIST1H4D HIST1H4F HIST1H4K HIST1H4J HIST1H4C HIST1H4H HIST1H4B HIST1H4L HIST1H2AH HIST1H3F HIST1H2AG HIST1H2BJ CREB5
C	1.42E-16	44	Viral carcinogenesis	CDK4 CDKN1A YWHAQ CCR5 EGR3 GTF2A2 HIST1H2BB HDAC1 JAK3 JUN LYN HIST2H2BF PMAIP1 HIST2H4B VDAC3 HIST1H4I HIST1H2BG HIST1H2BL HIST1H2BN HIST1H2BM HIST1H2BF HIST1H2BE HIST1H2BH HIST1H2BI HIST1H2BC HIST1H2BO HIST1H4A HIST1H4D HIST1H4F HIST1H4K HIST1H4J HIST1H4C HIST1H4H HIST1H4B HIST1H4L PIK3R3 ACTN1 CCNA2 CCND2 HIST1H2BJ ATP6V0D1 CREB5 CDK1 CDC20
B	4.44E-09	16	Influenza A	IRF9 HLA-DRA HLA-DRB1 HLA-DRB5 CXCL10 CIITA MX1 OAS1 OAS2 OAS3 EIF2AK2 IFIH1 STAT1 STAT2 TNFSF10 RSAD2
C	4.91E-09	28	Cell adhesion molecules (CAMs)	CDH3 CD226 CLDN4 VCAN CTLA4 TIGIT CD274 ICOS ICAM1 ITGA4 ITGAL ITGB2 PDCD1 SDC2 SELE SELL SELP SELPLG VCAM1 PDCD1LG2 MPZL1 CD4 CD6 CD8A CD8B CD28 CD80 CD86
C	1.93E-08	21	Rheumatoid arthritis	TCIRG1 TNFSF13B CTLA4 CTSK ICAM1 IL1B ITGAL ITGB2 JUN ATP6V0B ACP5 CCL2 CCL5 CCL20 TLR2 ATP6V0E1 ATP6V0D1 ATP6V1F CD28 CD80 CD86
C	3.70E-08	27	Phagosome	TCIRG1 TUBA1B SEC61B CORO1A CTSS FCGR2A FCGR2B FCGR3B SEC61G CD209 ITGB2 M6PR MRC1 ATP6V0B ACTB NCF1 THBS1 TLR2 C1R CALR TUBB6 TUBA1C MARCO ATP6V0E1 ATP6V0D1 ATP6V1F CD36
C	4.07E-08	28	Necroptosis	ALOX15 FTH1 FTL GLUL PYCARD HIST1H2AE HIST1H2AD H2AFZ BIRC2 HSP90AA1 IFNGR1 IFNGR2 IL1B JAK3 PYGL BID TNFAIP3 HIST2H2AA4 VDAC3 HIST1H2AI HIST1H2AJ HIST1H2AL HIST1H2AB HIST1H2AM HIST2H2AA3 CASP1 HIST1H2AH HIST1H2AG
C	5.83E-08	15	Malaria	HBA1 HBA2 ICAM1 IL1B ITGAL ITGB2 KLRB1 CCL2 SDC2 SELE SELP THBS1 TLR2 VCAM1 CD36
C	1.26E-07	21	T cell receptor signaling pathway	RASGRP1 CDK4 CTLA4 ICOS ITK JUN LCK NFKBIE PDCD1 VAV1 ZAP70 CARD11 PIK3R3 BCL10 CD3G CD247 CD4 CD8A CD8B CD28 GRAP2
C	9.54E-07	28	Chemokine signaling pathway	CXCR6 CCL27 CCR1 CCR5 DOCK2 FGR PIK3R5 GNG5 GNG10 CXCL2 HCK ITK JAK3 LYN ARRB2 PLCB2 PREX1 CXCL16 RAP1B CCL2 CCL5 CCL17 CCL20 NCF1 CCR2 VAV1 WAS PIK3R3
C	1.55E-06	36	Cytokine-cytokine receptor interaction	CXCR6 TNFSF13B CCL27 IL17F CCR1 CCR5 CSF2RA CSF2RB IL36RN TNFRSF21 CXCL2 IFNGR1 IFNGR2 IL1B IL1RN IL2RA IL4R IL10RA IL12RB2 IL13RA1 IL21R TNFRSF12A CXCL16 CCL2 CCL5 CCL17 CCL20 CRLF2 TNFRSF1B CCR2 TNFRSF4 TNFRSF6B IL1RL1 CD4 CD27 IL27RA
D	1.97E-06	9	IL-17 signaling pathway	FOS CXCL1 MMP1 MMP3 MMP9 S100A7 S100A8 S100A9 FOSL1
C	2.86E-06	15	Staphylococcus aureus infection	FCGR2A FCGR2B FCGR3B FPR1 ICAM1 ITGAL ITGB2 DEFB103B MASP1 PTAFR SELP SELPLG C1R C1S C3AR1
B	3.53E-06	13	NOD-like receptor signaling pathway	IRF9 GBP4 GBP5 GBP1 GBP2 GBP3 ITPR1 OAS1 OAS2 OAS3 STAT1 STAT2 PSTPIP1

TABLE 4 Reported mutations in *IL17RA* associated with CMC or skin anomalies.

Mutation	Pediatric Patient	Country	Consanguinity	Phenotype	Institution
H38Afs*15	Yes	Saudi Arabia	Yes	Oral Mucosal Candidiasis	IMAGINE
C57Yfs*5	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE

(Continued)

TABLE 4 Continued

Mutation	Pediatric Patient	Country	Consanguinity	Phenotype	Institution
R66X	Yes	Japan	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
Q86X	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
L90Cf*30	Yes	Saudi Arabia	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
c.163 + 1 G>A	Yes	Algeria	Yes	Oral Mucosal Candidiasis	IMAGINE
P257Rfs*16	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
p.Arg263X	Yes	Turkey	Yes	Oral Mucosal and genital Candidiasis+Eczema	Hacettepe University School of Medicine
Q284X	Yes	Morocco	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
Y384X	Yes	Argentina	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
D387N	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
Y391X (This study)	Yes	Lebanon	Yes	Oral Mucosal Candidiasis+Psoriasis	AUB
N440Rfs*50	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE
p.Q566fs	Yes	N/A	No	Mucocutaneous Candidiasis+ Eczema	The Hospital for Sick Children
Y591Sfs*29	Yes	Turkey	Yes	Oral Mucosal Candidiasis +Skin Folliculitis	IMAGINE

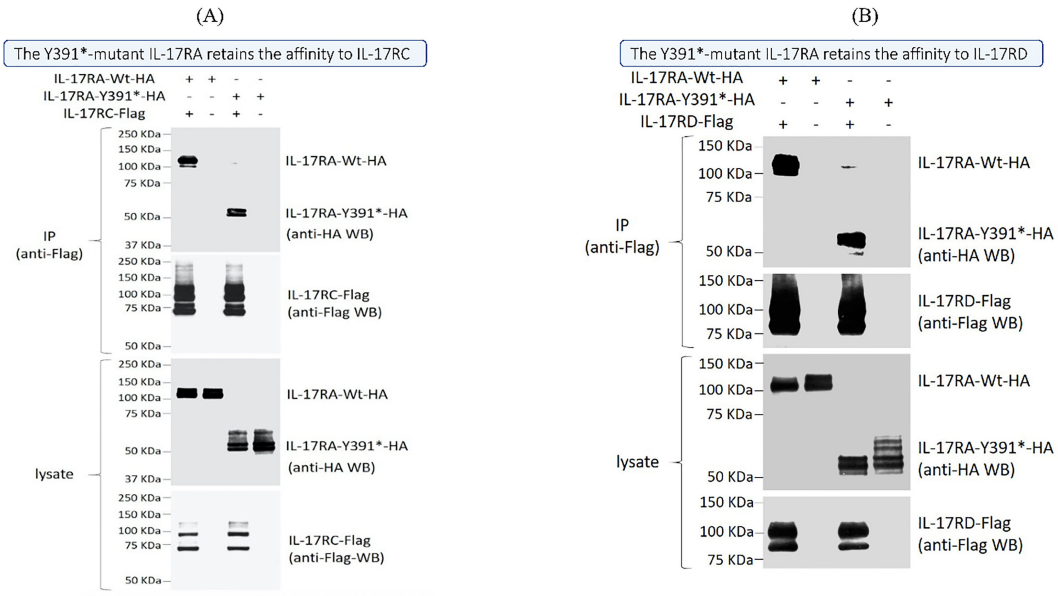

FIGURE 4
Physical interaction between the IL17RA wild type and mutated protein and their partners IL17RC and IL17RD. Co-immunoprecipitation assays using transiently expressed Flag-tagged IL17RC **(A)** or IL17RD **(B)** along either an HA-tagged wild-type (Wt) or mutant IL17RA (IL17RA Y391*) showed similar levels of interaction. Immunoprecipitations (IP) were done using an anti-Flag antibody, and both anti-HA and anti-Flag antibodies are sued to reveal the bands on western blots.

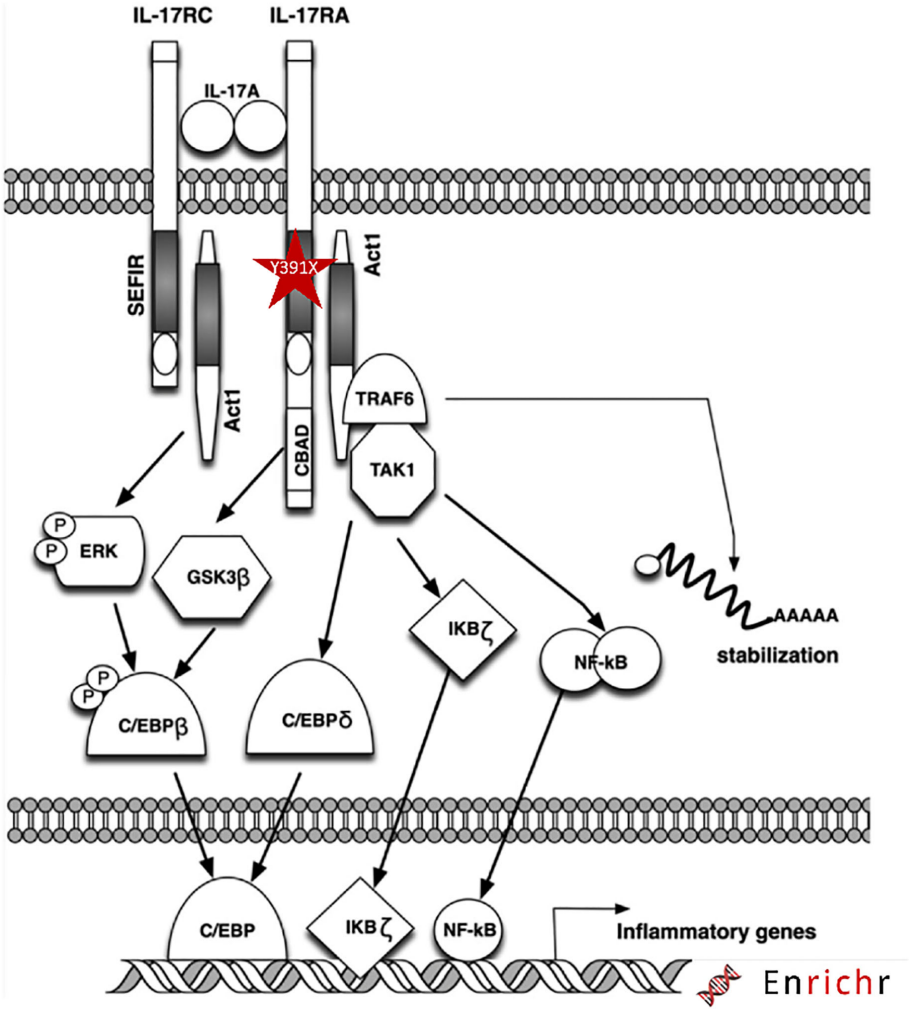

FIGURE 5
Schematic diagram of the IL17RA mutation and downstream signaling pathway. The mutation is highlighted with red star within the SEFIR domain of IL17RA.

Moreover, recent insights into the structure and function of the IL17 signaling pathway have highlighted the formation of a hexametric complex and a two-faced cytokine signature with unique receptor recognition properties. This includes IL17A or F binding to receptors IL17RA/C or ILRA/D, respectively. These structural considerations may provide a plausible explanation for the dual phenotype observed in our indexed patient (37). The hyperactivity of the IL17A pathway in our study results in overstimulation of inflammatory responses, typical of conditions like psoriasis, where excessive IL17 signaling leads to chronic skin inflammation. In CMC, the hyperactivity could be paradoxical: while IL17 normally confers protection against *Candida*, excessive or dysregulated signaling might disrupt the delicate balance of immune regulation, potentially contributing to immune exhaustion, impaired recruitment of effective immune cells, or altered antimicrobial responses, allowing Candida to persist.

Thus, treatments targeting IL-17 pathway have gained prominence in managing psoriasis. Brodalumab's stands out among IL-17 inhibitors due to its unique approach of targeting IL-17RA directly, unlike other IL-17 inhibitors like secukinumab and ixekizumab that target individual cytokines. By binding to the receptor itself, Brodalumab prevents the activity of several IL-17 cytokines, including IL-17A, IL-17E, and IL-17F, thereby disrupting downstream inflammatory signals at its source (13, 14, 38).

However, the broader inhibition achieved by Brodalumab carries a greater risk of side effects like Candida infections. This is because IL-17 plays a critical role in immune defense against fungal pathogens. Remarkably, inhibiting IL-17 signaling with brodalumab might lead to changes in the production or activity of IL-22. Since IL-22 is involved in maintaining epithelial barrier integrity and defending against extracellular pathogens often in collaboration with IL-17, any modulation in the Th17 pathway could influence these processes indirectly. Brodalumab's effect on IL-22 activity could theoretically weaken mucosal immunity, resulting in fungal infections like *Candida albicans* (39). Indeed, mice lacking both IL-17 and IL-22 receptors exhibit significantly higher fungal loads and more severe symptoms compared to those lacking only one of the receptors, indicating that these cytokines work together to enhance

antifungal defenses (40). This warrants the importance of further investigation of the relationship between IL-17 and IL-22.

As a result, treatments are now shifting focus toward IL-23 inhibitors, as studies have shown that the incidence of Candida infections is higher in patients treated with IL-17 inhibitors compared to those receiving IL-23 inhibitors. IL-23 inhibitors act upstream in the inflammatory cascade and do not directly suppress IL-17 activity. This indirect modulation allows for the preservation of mucosal immunity, resulting in a lower likelihood of Candida infections (3, 41).

Finally, the complexity in deciphering a genotype/phenotype correlation is further exacerbated by the findings of additional SNPs in other genes involved in the immune response. The NLRP3 inflammasome, a hallmark of the innate immune sensing pathway, and as such could be relevant to the CMC phenotype observed in our indexed patient. Previous reports have linked mutations in *NLRP3* to familial cold autoinflammatory syndrome 1 (CAIS1) and muckle-wells syndrome (MWS), both inherited in an autosomal dominant manner (42). In our case, the bi-allelic variant NP_001073289.1: p. Ala77Val in *NLRP3* exhibits an exceptionally low minor allele frequency (MAF). Loss-of-function mutations in *NLRP3* are associated with increased susceptibility to infections, potentially linking this variant to the CMC phenotype. In contrast, gain-of-function mutations have been associated with susceptibility to auto-immune diseases like arthritis and psoriasis (43). Nevertheless, a detailed mechanistic understanding of *NLRP3* mutations in human disease remains unclear, highlighting the need for an in-depth investigation of protein interactions. We also identified a variant p. Gln39Ter in *HLA-DRB1*, but we excluded as it was detected in normal individuals within our in-house exome database and in two other large-scale genome population studies (Korean and African projects, last accessed in May 2024 (https://www.ncbi.nlm.nih.gov/snp/rs9269957#seq_hash) (44, 45).

In summary, our study uncovers a novel deleterious mutation in *IL17RA* that maintains a functional receptor, highlighting the intricate interactions within the IL17 family. By identifying psoriasis as a novel phenotype alongside CMC for being associated with *IL17RA* variants, our findings expand the current understanding of IL17RA's diverse roles in health and diseases. The strength of this study lies in being the first case to document this phenomenon with an in-depth analysis. Nonetheless, the results require validation through larger patient cohort for broader applicability. Comprehensive insights into IL17RA signaling pathways could pave the way for developing more effective IL17 receptor inhibitors with higher efficacy and reduced side effects, facilitating individualized therapy and overcoming treatment resistance.

Data availability statement

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

Ethics statement

The studies involving humans were approved by American University of Beirut (AUB). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

AK: Data curation, Formal analysis, Methodology, Software, Validation, Writing – original draft, Conceptualization, Investigation, Project administration, Supervision, Visualization, Writing – review & editing. EE: Investigation, Methodology, Writing – review & editing. MM: Methodology, Validation, Writing – review & editing. IE: Methodology, Validation, Writing – review & editing. DK: Methodology, Writing – review & editing. YS: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. NR: Investigation, Methodology, Writing – review & editing. MK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. GN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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 constructed as a potential conflict of interest.

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Supplementary material

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SUPPLEMENTARY FIGURE 1
Dataflow chart of the variant curation.

SUPPLEMENTARY FIGURE 2
Results of RNASeq analysis (Data distribution and sample correlation of transformed data and expression in technical duplicate). **(A)** Scatter plot of transformed expression in patient and controls line represent R:0.995 **(B)** Distribution of transformed data in controls and patients shown in boxplot **(C)** Density of transformed data in respect to expression values in the patient and controls **(D)** Number of differentially expressed genes (1136 genes:967 d 169 downregulated) **(E)** Volcano plot of differentially expressed genes **(F)** Heatmap of hierarchical clustering of the most 1000 variable genes.

SUPPLEMENTARY FIGURE 3
Results of expression studies (Wild-type-Wt) or p.Y391* mutant (Mut) of IL17RA protein in HEK293 and HaCat cultured cells. (A)Wild-type (Wt) and p.Y391* mutant (Mut) IL17RA protein with an N-terminal HA-tag was overexpressed in HEK293T cells, the expression patterns were analyzed by indirect immunofluorescence (IIF) with anti-HA and anti-pan-cadherin antibodies. The results showed that both the Wt-IL17RA protein and Mut IL17RA p.Y391* protein were localized around the cell membrane. (B) Wild-type (Wt) and p.Y391* mutant (Mut) IL17RA protein with an N-terminal HA-tag was overexpressed in HaCat cells. The expression patterns were analyzed by indirect immunofluorescence (IIF) with anti-HA and Hoechst staining. Both the wild type-IL17RA and mutant IL17RA p.Y391* proteins were localized around the cell membrane.

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Molecular analysis of immune checkpoint inhibitor associated erythema nodosum-like toxicity

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Purpose: Immune checkpoint inhibitors (ICIs) are increasingly used to treat advanced malignancy but can induce immune-related adverse events (irAE). The mechanisms behind these sporadic and sometimes life-threatening irAEs remain largely unexplored. Here, we present a case report and in-depth molecular analysis of an erythema nodosum (EN) like irAE occurring in a melanoma patient with isolated brain metastasis, aiming to explore the potential mechanism of this irAE.

Methods: We performed RNA and T cell receptor (TCR) sequencing on the patient's resected brain metastasis and biopsy of EN-like irAE. Single cell RNA/TCR sequencing was conducted on the patient's peripheral blood mononuclear cells (PBMC) at baseline, 3 weeks after ipilimumab and nivolumab combination therapy, during EN toxicity and after resolution.

Results: The site of EN-like irAE showed a distinct accumulation of pro-inflammatory immune cells, accompanied by the upregulation of inflammatory and interferon response signatures. In addition, clonal expansion and activation of irAE-associated CD8 T cells and upregulation of monocyte-specific interferon signatures occurred concurrently with irAE onset.

Conclusion: The unique immune landscape at the EN-like irAE could indicate that this irAE is distinct from anti-tumor immune and analogous non-ICI autoimmune milieus. Our data also suggests that systemic immune activation induced by ICI treatment, as reflected in PBMC, may help monitor the patient's treatment response and access irAE risk.

KEYWORDS

immunotherapy, melanoma, irAE, erythema nodosum (EN), autoimmunity

Background

Immune checkpoint engagement is a key component in limiting autoimmune inflammation, maintaining fetal tolerance during pregnancy, and preventing the rejection of transplanted organs; however, it is also a common immune suppression mechanism that tumor cells can hijack to avoid immune surveillance. Immune checkpoint inhibitors (ICI), such as anti-PD-1/PD-L1 or anti-CTLA-4, can bind co-inhibitory immune checkpoint receptors and reactivate anti-tumor immunity. Currently, ICI has profoundly changed the treatment in 20 different cancer types, increasing response rate from 10-50% across various solid tumors (1, 2).

ICI can also cause immune-related adverse events (irAEs). Common ICI-induced irAEs include dermatitis, endocrinopathies, colitis, hepatitis, and pneumonitis, which are all thought to arise from aberrant activation of autoreactive T cells (3, 4). The rate of irAEs and severity vary by treatment regimen. From previous clinical experience in melanoma, CTLA-4 inhibition results in a high incidence of dose-dependent toxicities (high-grade toxicities in 38.6% and 57.9% of patients with metastatic melanoma receiving ipilimumab 3 mg/kg or 10 mg/kg, respectively) (5), while only 10-15% of patients receiving PD-1/PD-L1 experienced high-grade toxicity (6). Concurrent ICI use, such as combined anti-CTLA-4 +anti-PD-1, also augments the risk of autoimmune toxicities, resulting in almost two-fold increased incidences of high-grade irAEs (7).

The molecular and cellular mechanisms of irAEs remain largely unclear, with a few limited studies on lichenoid and bullous pemphigoid irAEs (8, 9). To gain insights into these mechanisms, we describe a case of erythema nodosum (EN)-like irAE from a patient treated with combination ipilimumab and nivolumab and apply deep molecular analysis of the tumor, the EN-like toxicity, and longitudinal analysis of peripheral blood.

Results

Case report

A man in his 40s without a history of known cutaneous melanoma presented with headaches and seizures and was found to have a hemorrhagic right parietal lobe mass. He underwent surgical resection which showed metastatic melanoma, and post-operative radiation therapy. Imaging showed no other intra- or extra-cranial disease. The patient received a combination of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) complicated by hypothyroidism and elevated liver enzymes after his second dose, which was treated by levothyroxine and prednisone, followed by mycophenolate mofetil, respectively. Following the resolution of liver enzymes, he received maintenance therapy with a single agent, nivolumab, without worsening liver function and with no evidence of a new metastatic disease (Figure 1A).

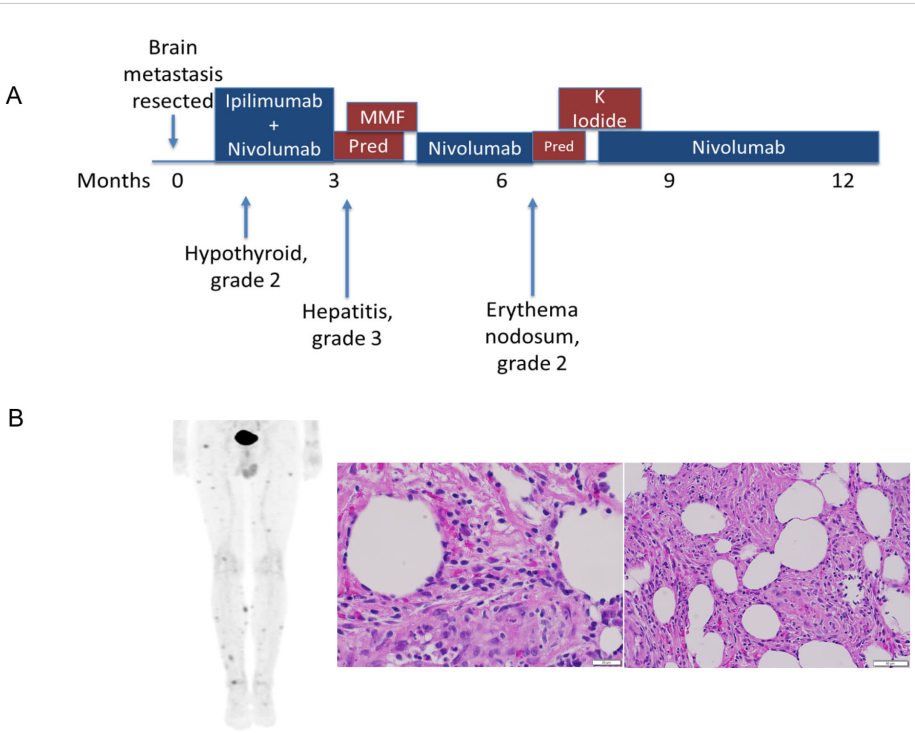

FIGURE 1
Clinical course of anti-PD-1-induced erythema nodosum. **(A)** The patient developed Erythema nodosum-like irAE approximated 6 months after metastasis resection and ICI treatment **(B)** PET-CT imaging demonstrating multiple FDG-avid subcutaneous nodules, which were biopsied and identified as erythema-nodosum-like panniculitis, as demonstrated by increased immune infiltration.

Approximately 4 months after resuming nivolumab, the patient developed an EN-like irAE. He developed painful subcutaneous nodules on his lower extremities and trunk. Although clinical pictures are not available for this patient, the irAE's clinical presentation was similar to previously reported EN-like irAEs (10, 11). PET-CT showed multifocal FDG avid subcutaneous lesions concerning for metastatic disease. Biopsies of two different lesions both demonstrated adipose tissue with acute and chronic inflammation and panniculitis consistent with an EN-like reaction. IHC showed a mixture of CD4+ and CD8+ T cells, negative CD56, and rare CD20+ B cells (Figure 1B). The condition was effectively managed with potassium iodide treatment. Since EN-like irAE is not life-threatening toxicity and half of the patients experiencing irAEs do not have irAE recurrence on ICI rechallenge (12, 13), the nivolumab therapy was subsequently resumed, and the patient carefully monitored. The patient stopped therapy after approximately two years and has had no additional recurrences of tumor or irAEs approximately 5.5 years after the initial presentation. As EN is a rarely reported irAE (10, 11, 14, 15), we sought to elucidate the pathogenesis by conducting an extensive examination of samples from the patient's blood, resected brain metastasis, and a tissue biopsy from the EN toxicity site.

Profound immune cell infiltration and immune activation in EN nodules

We performed bulk RNA sequencing on the patient's irAE biopsy, resected brain metastasis, and four cases of non-ICI-related skin autoimmune disease samples (three EN and one granulomatous disease [GD]) as non-ICI-induced skin condition comparators.

Compared to all other samples, the EN-like irAE demonstrated enrichment of pro-inflammatory leukocytes RNA signatures, including CD8+ T cells, memory-activated CD4+ T cells, M1 macrophages, and resting NK cells (Figure 2A). Notably, immunosuppressive M2 macrophages, which were abundant in tumor and non-ICI related EN, were nearly undetectable in the EN-like irAE (Figure 2A). Furthermore, we observed enrichment of immune activation signatures at the toxicity site, evidenced by elevated enrichment scores for Hallmark pathways "inflammatory response", "interferon response", and "allograft rejection" when compared to tumor and non-ICI autoimmune skin disorders (Figure 2B). Since the response to anti-PD-1 therapy has been linked to type-II interferon responses (16, 17), these findings suggest that the toxicity site is characterized by an ICI-associated immune activation pattern reminiscent of anti-tumor immune responses.

Distinct TCR clonal expansion patterns in toxicity sites and peripheral blood

One proposed mechanism for ICI-induced irAE is that the site of toxicity and the tumor share a common antigen(s), leading to T cells indiscriminately attacking healthy tissue upon the loss of negative modulation by immune checkpoints (18). To test whether the EN-like irAE and the patient's original tumor harbored T cells that shared similar T cell repertoire, which could support this hypothesis, we extracted and compared T cell receptor (TCR) -beta sequences across these sites. There was minimal overlap in TCR clones between these sites (Figure 3A). Given that the brain metastasis was removed nearly six months before the onset of EN toxicity, it remains possible that the T cells had experienced clonal evolution during ICI treatment, resulting in novel TCRs.

Previous research demonstrated that clonal expansion of peripheral T cells is associated with the development of irAE (19).

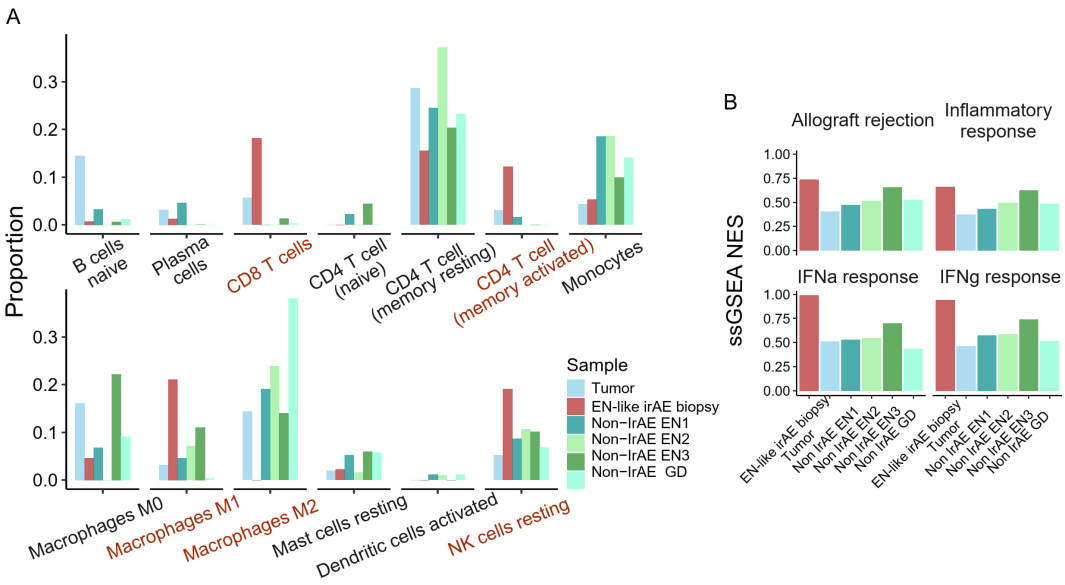

FIGURE 2
Site of ICI-induced erythema nodosum harbors pro-inflammatory immune cells. **(A)** CibersortX immune cell deconvolution using LM22 reference of the site of toxicity, tumor, and non-ICI induced skin autoimmune disease. **(B)** Enrichment score of Hallmark immune-related pathways.

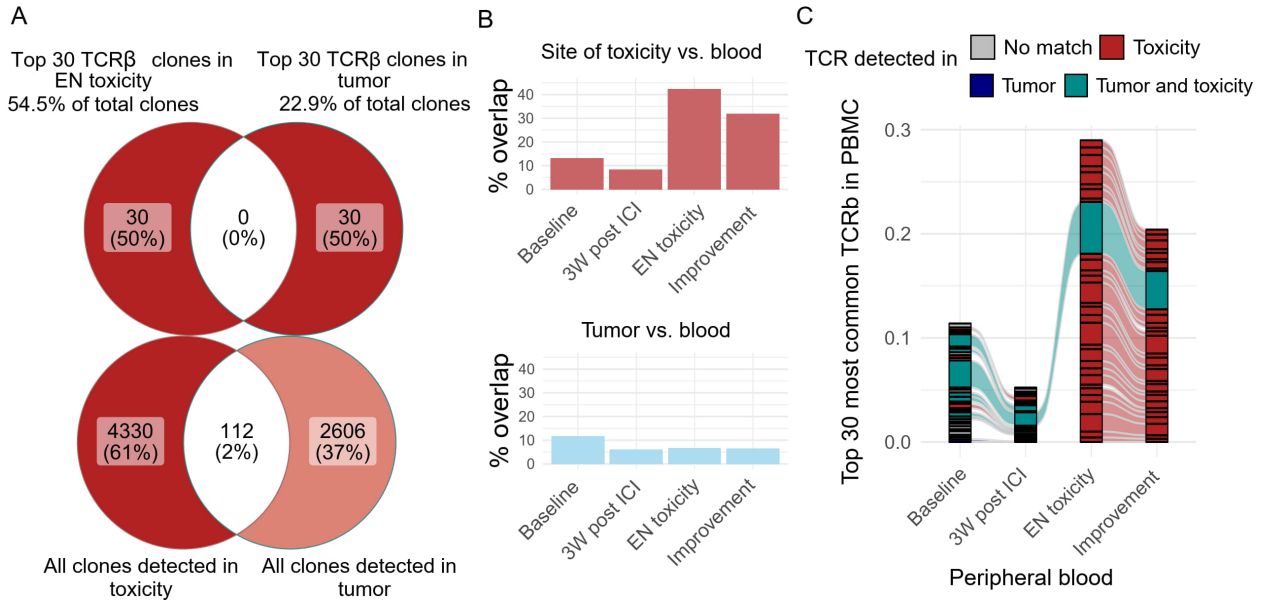

FIGURE 3
Toxicity-associated TCRs were enriched in peripheral blood. **(A)** Venn diagram depicting overlapping TCR beta clones between the site of toxicity and the patient's original tumor mass. **(B)** The percentage of peripheral blood TCRb that overlaps with clones detected on the site of toxicity(red) or tumor(blue). **(C)** Flow diagram of the top 30 most abundant TCRb clones detected in the longitudinal blood samples, colored by the site where the clone was detected.

Next, we tested whether toxicity-associated TCRs could be detected in the peripheral blood and if they expanded during ICI-EN. TCR-beta sequences were extracted from longitudinal peripheral blood samples collected post-brain metastasis removal (Baseline), 3 weeks post-ICI (3W post-ICI), during EN toxicity, and after symptom improvement (Improvement). Overall, 11.6% of TCR-beta clonotypes in the baseline blood sample overlapped with the tumor. The proportion of tumor-overlapping clonotypes decreased post-surgical resection and with the initiation of ICI (Figure 3B). During EN toxicity, 42% of the clonotypes detected in the blood overlapped with those at the toxicity site. The proportion of overlapping clones slightly decreased after symptom improvement (Figure 3B). Additionally, we observed clear clonal replacement in the blood, with previously undetected, toxicity-associated clones becoming heavily enriched during the onset of toxicity (Figure 3C). Overall, the TCR data suggests that the systemic clonal dynamics in the blood may reflect the onset and resolution of irAE.

Systemic immune dynamics during irAE onset

To further characterize the changes in systemic immunity during irAE onset, we performed single-cell RNA/TCR sequencing on the patient's longitudinal PBMC samples. We observed a decrease in peripheral classical monocyte (cMono) abundance concurrent with an expansion of CD8+ T cells during EN-like irAE (Figure 4A). Differential gene expression analysis revealed a downregulation of myeloid signature genes, such as *LYZ*, *S100A8*, and *S100A9*, during EN-like irAE compared to pre- and post-toxicity timepoints (Figure 4B). In contrast, genes associated with CD8+ T cell cytotoxicity, such as *GZMB, NKG7, and PRF1*, were upregulated during EN-like irAE (Figure 4B). Additionally, our ssGSEA analysis showed an upregulation of interferon response and inflammatory response-related genes post-ICI treatment, indicating a systemic immune response induced by ICI (Figures 4C, D).

Sub-clustering of the CD8+ T cells resulted in eight functionally distinct clusters, including naïve/central memory, newly activated, cytotoxic, and effector memory T cells (Figure 5A). There was a dominant population of GZMB+ cytotoxic CD8 T cells, carrying TCRs that were also detected at the site of EN-like irAE (Figure 5B), alongside a smaller subset that shared nearly identical functional markers but was uniquely enriched for specific TRBV and TRAV sequences; these T cells had TCRs that were detected in both the tumor and EN-like irAE biopsy (Figure 5B). Longitudinal analysis of CD8+ T cells revealed that ICI treatment induced a significant expansion of GZMK+ early activated CD8+ T cells (Figure 5C), potentially reflecting early T cell priming. As EN toxicity developed, GZMB+ cytotoxic CD8+ T cells became the dominant phenotype (Figure 5C), indicating peripheral CD8+ T cell activation and potential clonal expansion. Furthermore, during EN toxicity, most clonal T cells in the peripheral blood carrying EN associated TCRs were the activated, GZMB+ cytotoxic subtype (Figure 5D). This suggests that the clonal expansion and activation of CD8+ T cells, particularly the GZMB+ cytotoxic subtype, are closely associated with the development of EN toxicity.

Since the proportion of cMono decreased after EN toxicity, we decided to further investigate whether the development of EN-like irAEs also coincides with a change in monocyte phenotype. Monocytes were further divided into six clusters based on their transcriptomic

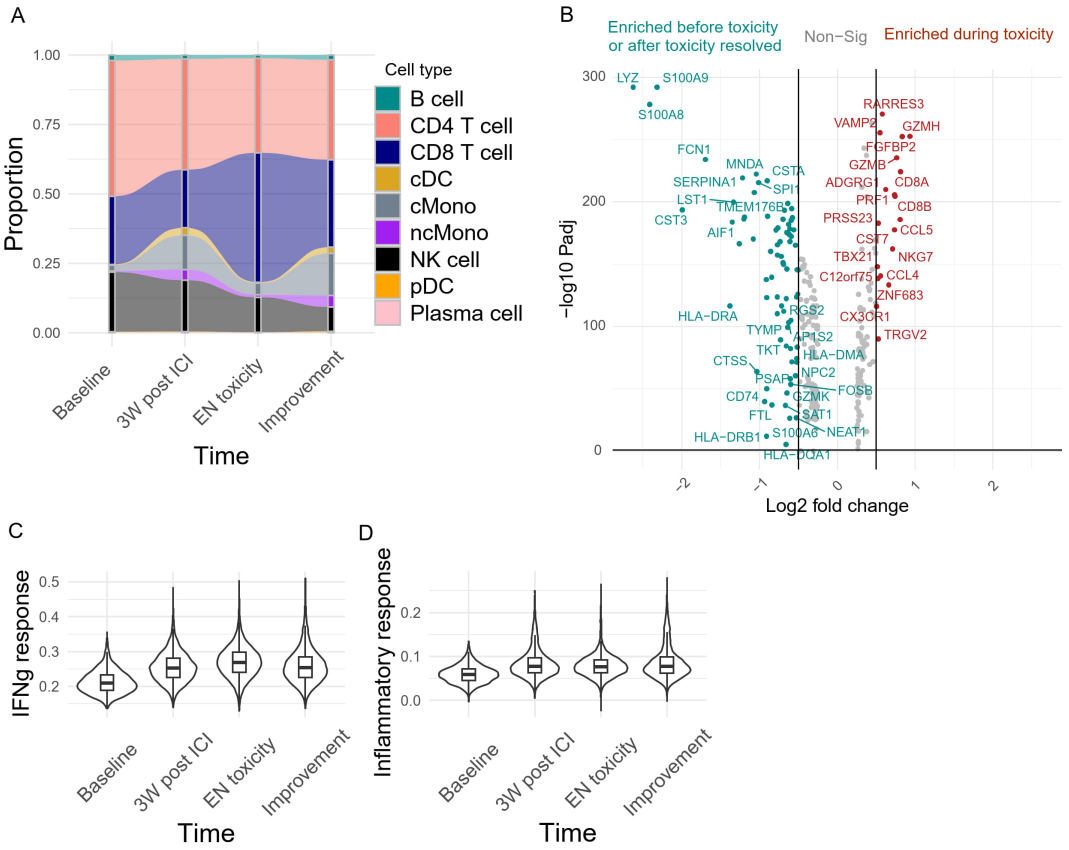

FIGURE 4
Systemic immune dynamics during irAE onset **(A)** Peripheral blood immune cell abundance monitored longitudinally. **(B)** Differential gene expression analysis of the peripheral blood capturing genes upregulated during EN toxicity (right, red) and pre/post-toxicity (left, green). Adjusted P value <0.01 and absolute log2 fold change >0.5. The per-cell enrichment score of **(C)** Hallmark interferon gamma response, and **(D)** Inflammatory response pathway across 4 different time points in the peripheral blood.

features, specifically by the expression of MHC-II transcripts, S100s, and interferon response genes (Figure 6A). Two clusters also expressed T cell-associated genes, which may represent monocyte-T cell doublets or physiological interacting cells. Apart from the increase in T cell-bound monocytes during toxicity, no significant changes were observed in other monocyte subclusters (Figure 6B). However, differential gene expression analysis revealed a reduction in S100 gene expression, which was previously reported to be a marker of immunosuppressive phenotypes (20, 21), and a concurrent increase in interferon response element expression (Figure 6C). Further GSEA analysis supported the observation of increased interferon and cytokine responses during EN toxicity (Figure 6D). These findings suggest a shift in the monocyte landscape towards a more pro-inflammatory state, potentially contributing to the pathogenesis of ICI-induced EN.

Discussion

The mechanism behind ICI-induced irAEs remains largely case-specific. While theoretically, these toxicities can affect nearly every organ, dermatologic cases are among the most common irAEs for ICI-treated patients (22, 23). Here, we report our observations on the clinical and molecular features of ICI-induced EN in a melanoma patient. A detailed description of the patient's peripheral immune signature during irAE highlights the role of systemic immunity during this rare cutaneous toxicity.

Several cases of EN-like irAE have been reported in ICI treated melanoma patients, with isolated cases in clear cell carcinoma, esophageal cancer, and renal cell carcinoma (10, 11, 14, 15). irAE onset ranges from 4 weeks to a year after ICI treatment. Among most cases, increased lymphocytes, histiocytes, and neutrophils were observed with no sign of infection, similar to the immune infiltration pattern observed in our case (10). In addition, prior or concomitant hypothyroidism was found in two EN toxicity cases (10), hinting at a potential association between these conditions. Although sparse HLA typing data were available for prior reported cases, upon comparing the patients' HLA typing, our case shared HLA-B*35 and HLA-DPB1*04, two frequently carried alleles, with a previously reported EN-like irAE patient who had a prior medical history of hypothyroidism (10), suggesting the association between HLA genotype and the toxicity pathogenesis.

The basic cancer immunity cycle suggests that antigens released from tumors during cell turnover and in response to therapies drain to the lymph node, where they are acquired by professional antigen presenting cells and presented to T lymphocytes for priming.

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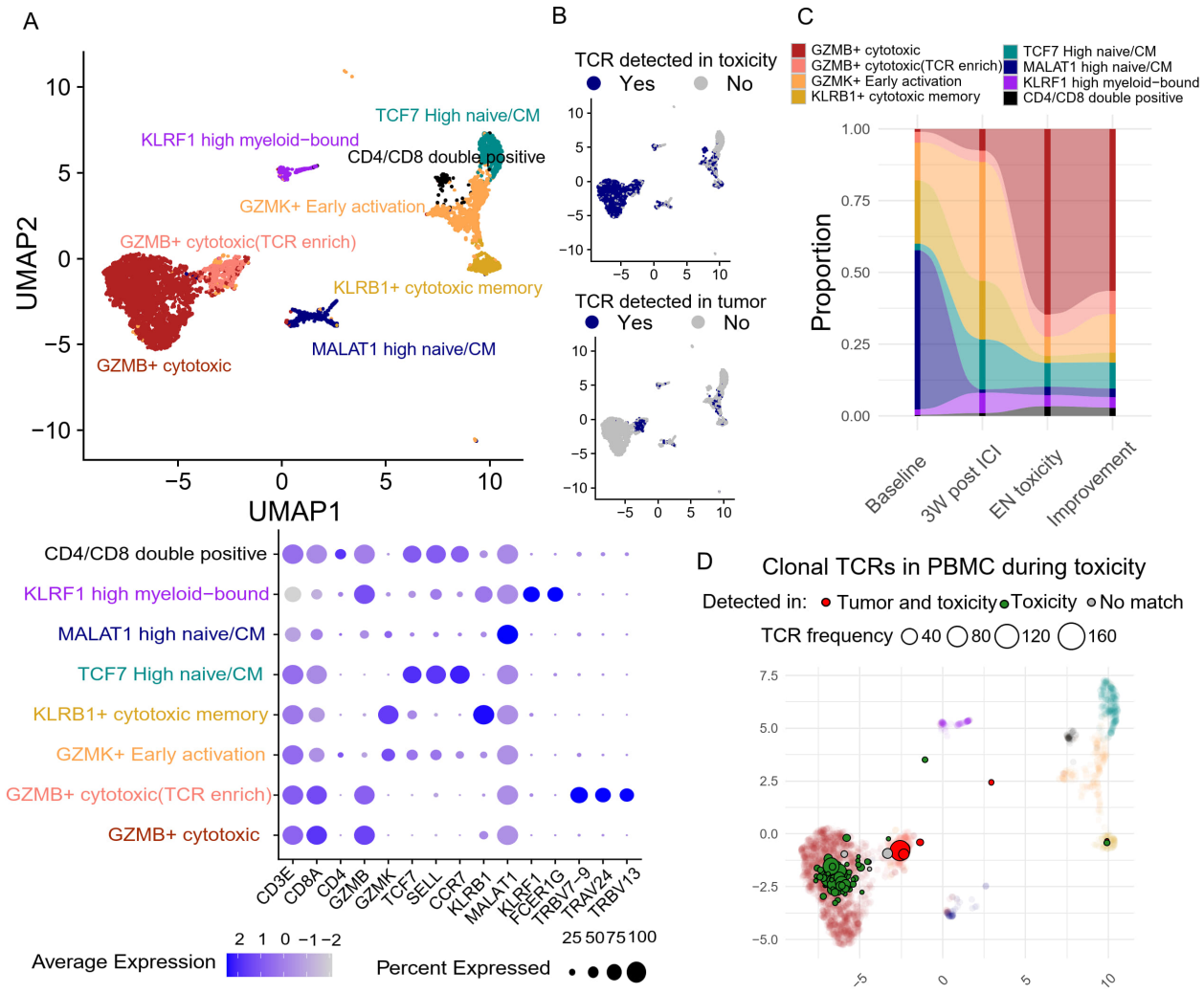

FIGURE 5
Peripheral blood CD8+ T cell dynamics and their association with tumor and site of toxicity based on TCR clone overlap **(A)** Unsupervised clustering based on transcriptomic features generates eight distinct CD8 T cell clusters, with their corresponding gene features presented in the dot plot. **(B)** TCR clones of each T cell are compared against tumor and site of toxicity to identify overlapping clones. **(C)** The abundance of each CD8 T cell cluster was tracked longitudinally. **(D)** The center location of each clonal (>3 T cell sharing same TCR) TCR clones on the Umap during toxicity onset. Toxicity-overlapping TCRs are colored green, and tumor+toxicity-overlapping TCRs are colored red.

Appropriately primed T cells are 'licensed' to leave the lymph node and seek out sources of inflammation, whereby they must pass through the systemic peripheral circulation as a conduit (24). Similarly, irAE induced by bystander effects from activated T-cells or T cells targeting healthy organ-tumor overlapping antigens could use a similar adaptive immune response cycle (19, 25). Previous studies have shown that peripheral activated CD4 memory T cell abundance and TCR diversity are strongly associated with irAE onset (25). Using longitudinal peripheral blood, we showed that expansion of cytotoxic CD8 T cells and increased monocytic interferon response were also strongly associated with EN toxicity onset. Together, those data suggest that systemic immune activation induced by ICI treatment may also reflect the risk of irAE, providing a potential method to monitor the patient's treatment response and irAE risk assessment. However, these results also suggest that differential mechanisms (for example dominated by CD4 or CD8 T cell responses) may exist among irAEs.

One popular mechanistic explanation of irAE is that shared antigens between the tumor and the affected organ may cause a break in self-tolerance during anti-tumor immune responses (18, 26). In this unique case, however, the TCRs detected were not shared between the site of irAE and the original brain metastasis that was resected 6 months prior. It is still possible that the TCRs we detected in the site of toxicity may target potential micrometastases that we were not able to detect and/or sample. It is important to note that the development of irAEs has been correlated with anti-tumor immunity and response to ICI (27–29). The T cell activation signatures observed in the peripheral blood support the idea that ICI could induce long-term constant immune surveillance against cancer, even when the patient appears to be disease free.

Previous analysis demonstrated that clonal T cell activation in tumors and peripheral blood is associated with better ICI treatment response in melanoma. As demonstrated by our data and other studies (19, 25, 30, 31), systemic T cell expansion is also associated with the

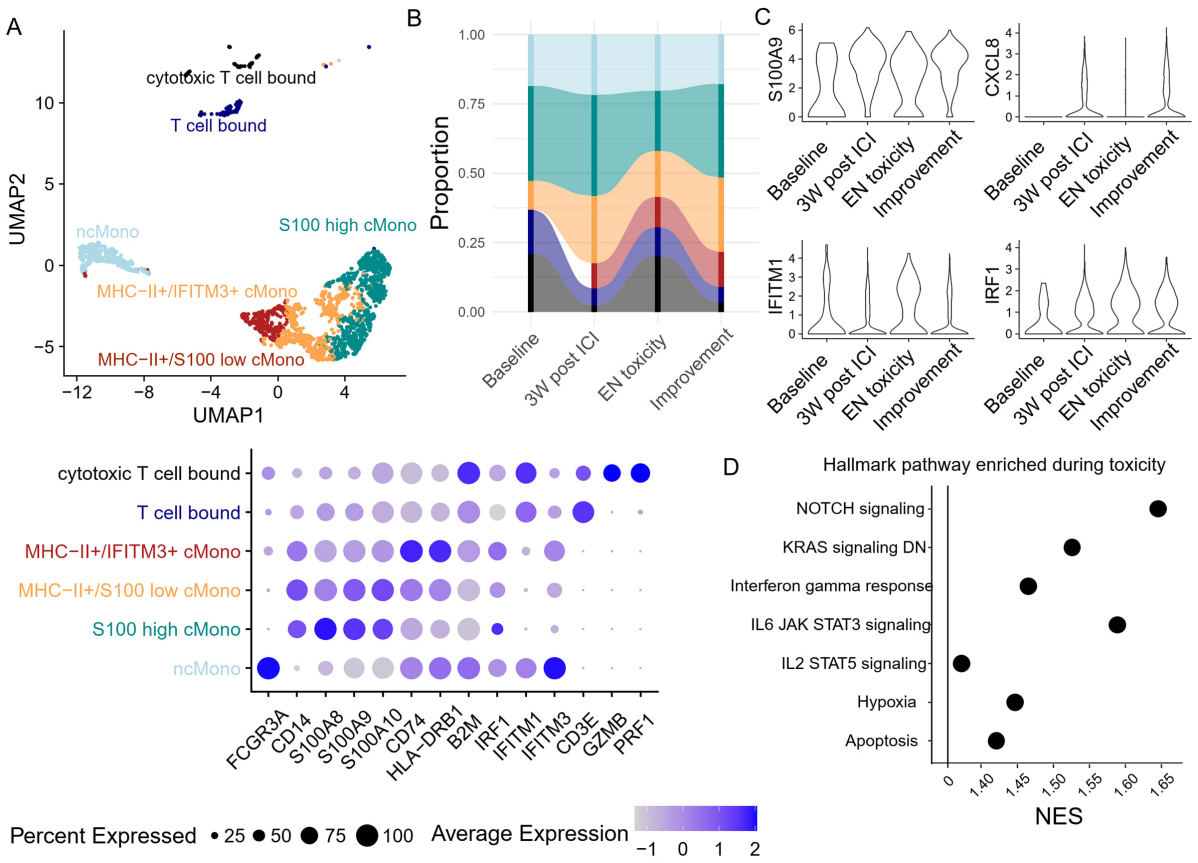

FIGURE 6
Peripheral blood monocyte dynamics and transcriptomic changes during toxicity onset **(A)** Unsupervised clustering based on transcriptomic features generates six monocyte clusters, with their corresponding gene features in the dot plot. **(B)** The abundance of each monocyte cluster was tracked longitudinally. **(C)** The expression of S100A9, CXCL8, and two interferon response-related genes in monocytes was monitored longitudinally. **(D)** Gene set enrichment analysis based on the differentially expressed genes between toxicity onset vs. pre/post toxicity. Only pathways with adjusted p-values <0.05 are presented.

development of irAE. Currently, one of the challenges of irAE management is early detection and biomarker development. Using peripheral biomarkers such as T cell clonality and T cell activation, it may be possible to detect patients experiencing systemic immune responses and enhance patient monitoring to mitigate potential severe irAEs. Nonetheless, further research is needed to determine whether such markers can be used to monitor patients for development of potential irAEs.

In conclusion, we present a deep molecular analysis of ICI-induced EN. In addition, the observation of systemic inflammation during toxicity onset further strengthens the importance of systemic immunity during ICI and the development of irAEs.

Methods

Patient information

The patient was treated at Vanderbilt University Medical Center and consented to the clinical and biospecimen repository (IRB#100178). Peripheral blood samples were taken at baseline, early on treatment, and at time of toxicity per our protocol. FFPE samples from resected brain metastasis and skin biopsies were obtained from pathology. Samples from patients non-ICI autoimmune disorders were obtained from pathology (IRB# 150754).

RNA sequencing and data analysis

Total RNA was isolated from FFPE tumor, ICI-EN and non-ICI skin autoimmune disease biopsy samples using the Promega Maxwell 16 FFPE RNA kits per the manufacturer's protocol. mRNA enrichment and cDNA library were prepared utilizing the stranded mRNA (polyA-selected) library preparation kit. Sequencing was performed at Paired-End 150 bp on the Illumina NovaSeq 6000 targeting an average of 50M reads per sample. Demultiplexed FASTQ files were next aligned using STAR with a genome index generated from human Hg38. FeatureCount was next applied to create gene count matrix. Subsequent MultiQC was performed to ensure sample homogeneity. Raw count generated by FeatureCount was imported to R. Genes that were expressed in less than 50% of the samples were excluded from the analysis. The filtered gene count matrix was next used to generate DESeq2 objects with corresponding metadata. Raw gene counts were transformed using VST

transformation followed by GSVA enrichment analysis which assigns enrichment scores of the Hallmark pathways to each sample. The transformed gene sets were deconvoluted with CIBERSORTx using the LM22 matrix to obtain immune cell composition in each biopsy.

TCR sequencing

Using the whole RNA extracted from FFPE biopsies, TCRs were sequenced using the TCR Immunoverse all chain assay per the manufacturer's protocol (Invitae/ArcherDX). Sequencing results were evaluated using Archer Immunoverse analyser. CDR3 sequences and frequency tables were extracted from the manufacturers' analysis platform. TCR beta sequence was extracted to identify matching clones among tumor biopsy, ICI-EN site, and peripheral blood.

Single cell RNA sequencing and data analysis

Each sample (targeting 5,000–15,000 cells per sample) was processed for single-cell 5′ RNA and TCR sequencing utilizing the 10x Chromium system. Libraries were prepared following the manufacturer's protocol. The libraries were sequenced using NovaSeq 6000 with 150 bp paired-end reads. RTA (v.2.4.11; Illumina) was used for base calling, and analysis was completed using 10x Genomics Cell Ranger software. Data were analyzed in R using the filtered h5 gene matrices in the Seurat package (32). In brief, samples were subset to include cells with >200 but <3,000 unique transcripts to exclude probable non-cellular RNA reads and doublets. Cells with >15% of reads coming from mitochondrial transcripts were also excluded as probable dying cells. General immune cell subtypes were imputed using *scPred* (33). CD8 T cell clusters were generated with *FindClusters* function after removing all CD8 T cell without TCR information. Monocyte clusters were generated in by setting FindClusters. Detailed cell subtype identify was given based on top10 differentially expressed genes in each cluster.

Differential gene expression analysis was performed across all cells using FindMarkers function between different timepoints. Gene set enrichment analysis was performed to obtain pathway enrichment score by taking the log2 fold change and p-value from differential gene expression results. Besides pair-wise comparison, enrichment scores for each Hallmark pathways is generated for each cell using Escape (34).

HLA typing

We performed four-digit class I and II typing of HLA (with Illumina MiSeq) for the HLA antigens ABC, DR, DQ, and DP on DNA extracted from peripheral blood.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Vanderbilt University Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XS: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. MA: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. PG-E: Conceptualization, Data curation, Investigation, Writing – review & editing. VS: Data curation, Investigation, Writing – review & editing. YW: Data curation, Formal Analysis, Investigation, Writing – review & editing. JC: Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. EP: Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. YX: Data curation, Formal Analysis, Investigation, Writing – review & editing. DJ: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. JB: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

JB receives research support from Genentech/Roche and Incyte Corporation, has received advisory board payments from AstraZeneca and Mallinckrodt and is an inventor on patents regarding immunotherapy targets and biomarkers in cancer.

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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The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Risk of infantile atopic dermatitis in neonatal lupus erythematosus: a retrospective cohort study

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Objectives: The onset and progression of atopic dermatitis (AD) are closely linked to autoimmune status. While AD has been observed in children with neonatal lupus erythematosus (NLE), its relationship with perinatal factors remains unclear. This study aimed to identify early-life risk factors for the development of AD in children with NLE within their first two years of life.

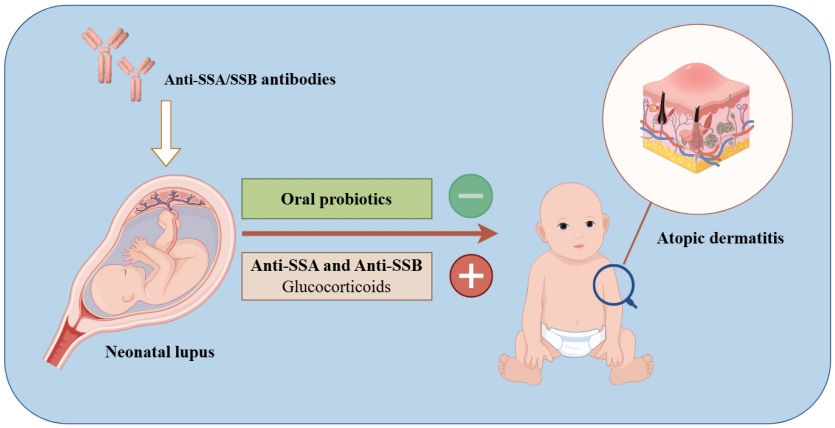
Methods: We conducted a multicenter, retrospective cohort study using electronic medical records and follow-up data from patients in the NLE cohort. Children were categorized into AD and non-AD groups based on whether they developed AD by age two. Univariate and multivariate analyses were performed to compare general and clinical data between the two groups.

Results: AD incidence in NLE patients was 27.27 (21/77). Compared to the non-AD group, the AD group had significantly lower use of oral probiotics and intravenous gamma globulin, but higher rates of small-for-gestational-age (SGA) status, hypocomplementemia, thrombocytopenia, anti-SSA, anti-SSB, double antibody (anti-SSA, anti-SSB) positivity, antibiotic use, and systemic glucocorticoid (GC) treatment. Logistic regression analysis revealed that oral probiotics were a protective factor against AD, while double antibody positivity and systemic GC were risk factors.

Conclusion: In children with NLE, oral probiotics were associated with a reduced risk of AD, while double antibody positivity and systemic GC administration significantly increased the risk of AD within the first two years of life. However, the limited sample size in this study warrants further findings.

KEYWORDS

lupus erythematosus, neonate, atopic dermatitis, autoantibody, glucocorticoid, probiotics



GRAPHICAL ABSTRACT
Exogenous probiotic supplementation early in life serves as a protective factor, while double antibody positivity (anti-SSA/SSB) and the systemic use of glucocorticoids increase the risk of developing atopic dermatitis in children with neonatal lupus erythematosus.

1 Introduction

Neonatal lupus erythematosus (NLE) is an acquired autoimmune condition caused by the transplacental transfer of maternal immunoglobulin G (primarily anti-SS-A and anti-SS-B antibodies) into the fetal circulation. This transfer targets fetal autoantigens, resulting in transient multiorgan involvement in the fetus (1, 2). Clinical symptoms of NLE typically appear at birth or within 4–6 weeks of life and may affect multiple organs, with skin manifestations being the most common, followed by hematological, hepatobiliary, and cardiac involvement (3, 4). These symptoms usually resolve within 6–12 months as maternal antibodies wane (4).

Atopic dermatitis (AD), or atopic eczema, is a chronic, recurrent inflammatory skin disease with a genetic predisposition, affecting 15–30% of children worldwide (5). Characterized by persistent itching and polymorphic skin lesions, AD is often the first stage in the "allergy march" and significantly impacts a child's physical and mental development. The recurrent nature of AD leads to sleep disturbances and reduced quality of life, making it a particularly challenging condition to manage in childhood (6, 7).

During clinical studies and follow-up of patients with NLE, we observed a significantly higher rate of late-onset AD compared to its normal prevalence. While the pathogenesis of NLE and AD differs, autoimmune diseases are primarily mediated by Th1 cells, and allergic diseases are mediated by Th2 (8, 9). However, both are now understood to result from complex interactions between genetic, environmental, and other unknown factors (10). Recent evidence suggests a bidirectional relationship, with patients who have allergic diseases being at increased risk for autoimmune conditions (11, 12). Based on this, we hypothesized that certain clinical variables in patients with NLE may contribute to an elevated risk of developing AD. This study aimed to identify early-life risk factors for the development of AD in children with NLE within their first two years of life.

2 Material and methods

2.1 Study design and ethics approval

This is a multicenter retrospective cohort study analyzing early-life risk factors for AD development in patients with NLE. Patients with NLE hospitalized between January 1, 2011, and January 1, 2021, at the Children's Hospital of Soochow University, the Affiliated Suzhou Hospital of Nanjing Medical University, Yangzhou Maternal and Child Health Hospital, and Huai'an Maternal and Child Health Hospital were included as study participants. Data were collected by reviewing electronic medical records from both inpatient and outpatient visits, supplemented by telephone and outpatient follow-up visits. The study was approved by the Ethics Committee of all Hospital (No. 2023CS024). Written informed consent was obtained from the guardians of all patients.

2.2 Study outcome

The primary outcome was whether NLE patients were diagnosed with AD before the age of 2. Clinical data and diagnostic information for all patients were reviewed and evaluated by specialized allergists to ensure diagnostic accuracy.

2.3 Diagnosis and definitions

The diagnosis of NLE was based on positive serum anti-SSA/SSB/U1RNP antibodies in pregnant women with autoimmune diseases or neonates with clinical manifestations of NLE (13). AD was diagnosed with reference to the Williams Clinical Diagnostic Criteria (14). Oral probiotics were counted from postpartum to 3 months after birth.

2.4 Exclusion criteria

Patients were excluded if they had significant deficiencies in clinical data that could introduce substantial bias, if their families declined participation, or if they had confirmed genetic defects or inherited metabolic diseases.

2.5 Data collection

Data were obtained from electronic medical records, outpatient clinics, and telephone follow-ups. Collected information included maternal history of rheumatologic diseases, parental history of allergic conditions, demographic characteristics, clinical presentations, laboratory and imaging results, and follow-up data. Demographic data included sex, gestational age (GA), and birth weight (BW). Laboratory investigations included routine blood counts, biochemical tests, and rheumatology-related serological tests. Imaging tests included ultrasonography, echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI).

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 26.0. Categorical data are presented as n (%) and were compared using chi-square or Fisher's exact tests. Continuous data, which were non-normally distributed continuous data, are presented as medians with interquartile ranges (P25, P75) and analyzed using non-parametric tests. Logistic regression analysis was conducted with the occurrence of AD as the dependent variable, using significant indicators as independent variables. A P-value of < 0.05 was considered statistically significant.

3 Results

3.1 Clinical baseline characteristics

A flowchart of the study is provided in Figure 1. A total of 82 patients with NLE were hospitalized between January 1, 2011, and January 1, 2021. After excluding four cases due to loss to follow-up and one case with a confirmed inherited metabolic disease, 77 patients were finally included in the analysis. The cohort consisted of 31 males and 46 females, with a mean GA of 37^{+2} (35^{+4}, 37^{+6}) weeks, and a mean birth weight of 2425 (1795–2910) g. Among the patients, 38 had a GA ≥37 weeks, 28 had a GA between 32 and 37 weeks, and 11 had a GA <32 weeks. In terms of birth weights (BW), 38 patients weighed >2500 g, 27 weighed between 1500–2500 g, and 12 weighed <1500 g. Thirteen cases were younger than their gestational age. There were 34 cesarean deliveries and 43 vaginal deliveries. A history of allergic diseases was reported in 20 mothers and 15 fathers. Additionally, 47 patients had a history of oral probiotic, and 24 were breast feeding. By the age of two, 21 out of 77 patients with NLE were diagnosed with AD. See Table 1.

There were no significant differences between the AD and non-AD groups regarding sex, BW, GA, extremely preterm birth, SGA status, mode of delivery, exposure to pets during pregnancy, parental history of allergic disease, maternal history of autoimmune disease, days of oral probiotic or breast feeding (P>0.05). Compared to the control group, the percentage of preterm births was significantly higher in the AD group, the percentage of oral probiotic in the neonatal period was significantly lower (P<0.05). See Table 1.

3.2 Clinical manifestations and laboratory tests

The percentage of patients with hypocomplementemia, thrombocytopenia, anti-SSA antibodies, anti-SSB antibodies, and double-positivity for anti-SSA and anti-SSB antibodies was significantly higher in the AD group compared to the non-AD group (P<0.05). However, no significant difference was observed between the two groups in terms of cutaneous manifestations (rash), anemia, neutropenia, coagulation abnormalities, congenital heart block, structural cardiac abnormalities, gastrointestinal involvement, or neurological involvement (P>0.05). Additionally, no significant differences were observed in anti-U1-RNP levels, antibody triple positivity (anti-SSA, Anti-SSB, Anti-U1-RNP), or serum eosinophil counts between the two groups (P>0.05). See Table 2.

3.3 Main treatment during hospitalization

Compared with patients in the non-AD group, those in the AD group had a significantly higher percentage of antibiotic and systemic GC applications and a lower percentage of intravenous (IV) immunoglobulin applications (P<0.05). There were no significant differences in platelet counts, suspended oligoerythrocytes, or virus-inactivated plasma transfusions between the two groups (P>0.05). See Table 3.

3.4 Independent risk factor analysis

Logistic regression analyses were performed with the occurrence of AD as the dependent variable, using indicators of significant differences between the AD and non-AD groups as independent variables. The results revealed that oral probiotics (OR: 0.235, 95%CI: 0.059–0.942) served as a protective factor against the development of AD within the first two years of life in patients with NLE. Conversely, double positivity for anti-SSA and anti-SSB antibodies (OR: 4.213, 95%CI: 1.034–17.165) and systemic GC application (OR: 4.408, 95% CI: 1.248–15.568) were identified as risk factors. See Table 4.

4 Discussion

The microecology of the human gastrointestinal tract plays an important role in the onset and progression of allergic conditions by

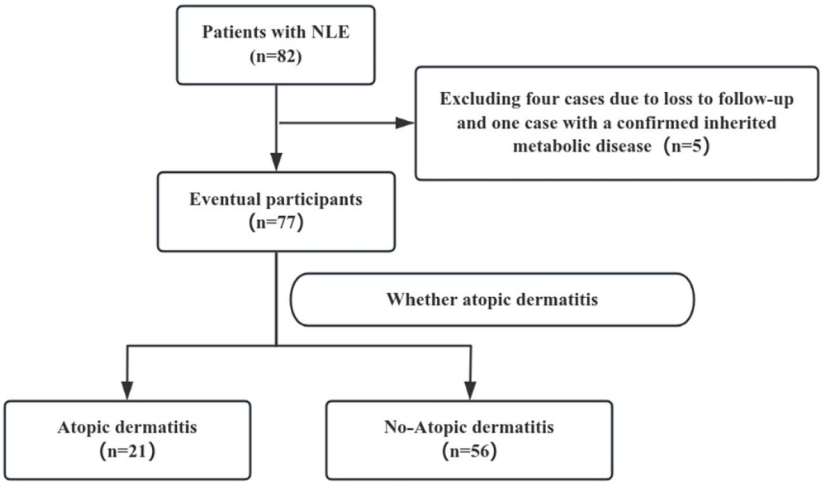


FIGURE 1
Flow chart of the study population. NLE, neonatal lupus erythematosus.

influencing anti-allergic mechanisms such as Th1 immunity, TGF signaling, and IgA production (15). Early colonization and development of the gut microbiota are thought to be closely linked to the risk of allergies in infancy, childhood, and adulthood (16). A large number of studies have confirmed that prenatal and postnatal probiotic supplementation may be an effective means of preventing AD in children, but there is heterogeneity in the results of the existing studies, and further confirmation is still needed (17–19). In this study, the percentage of patients in the AD group who used oral probiotics was significantly lower than that in the non-AD group, while the use of intravenous antibiotics was significantly higher. In addition, among the children with NLE in this study, the number of days of oral administration of probiotics was higher in non-AD children than in children in the AD group, although there was no statistical difference between the two groups, which may be related to the smaller sample size. Although the study population was limited to patients with NLE, our findings suggest that early probiotic supplementation may help

TABLE 1 Clinical baseline characteristics (n, %).

		AD (n=21)	No-AD (n=56)	*P-value*	NLE (n=77)
Sex	Male	9 (42.86)	22 (39.29)	0.776	31 (40.26)
	Female	12 (57.14)	34 (60.71)		46 (59.74)
Gestational age					
Term infant	≥37 weeks	7 (33.33)	31 (55.36)	0.085	38 (49.35)
Premature infant	<37 weeks, ≥32 weeks	12 (57.14)	16 (28.57)	0.020	28 (36.36)
Extremely preterm infant	<32 weeks	2 (9.52)	9 (16.07)	0.465	11 (14.29)
Birth weight					
Normal birth weight	>2500 g	8 (38.10)	30 (53.57)	0.642	38 (49.35)
Low birth weight	1500–2500 g	9 (42.86)	18 (32.14)	0.921	27 (35.06)
Very low birth weight	<1500 g	4 (19.05)	8 (14.29)	0.873	12 (15.58)
SGA		5 (23.81)	8 (14.29)	0.223	13 (16.88)
Mode of delivery	Cesarean section	9 (42.86)	25 (44.64)	0.888	34 (44.16)
	Vaginal delivery	12 (57.14)	31 (55.36)		43 (55.84)
Pet exposure during pregnancy		5 (23.81)	13 (23.21)	0.956	18 (23.38)
Mother allergic disease		6 (28.57)	14 (25.00)	0.750	20 (25.97)
Father allergic disease		4 (19.05)	11 (19.64)	0.953	15 (19.48)

(Continued)

TABLE 1 Continued

		AD (n=21)	No-AD (n=56)	*P-value*	NLE (n=77)
Maternal autoimmune disease					
	SLE	11 (52.38)	32 (57.14)	0.708	43 (55.84)
	Photosensitivity symptoms	2 (9.52)	5 (8.93)	1.000	7 (9.09)
	MCTD	1 (4.76)	2 (3.57)	1.000	3 (3.90)
	Sjogren's syndrome	2 (9.52)	5 (8.93)	1.000	7 (9.09)
	Autoantibody abnormalities	2 (9.52)	4 (7.14)	1.000	6 (7.79)
	—	3 (14.29)	8 (14.29)	1.000	11 (14.29)
Oral probiotic		8 (38.09)	39 (69.64)	0.011	47 (61.04)
Days of oral probiotic		0 (17.50, 0)	14 (21, 0)	0.059	14 (21, 0)
Breast feeding		5 (23.81)	19 (33.93)	0.393	24 (31.17)

AD, atopic dermatitis; SGA, smaller than gestational age; SLE, systemic lupus erythematosus; MCTD, mixed Connective Tissue Disease.

maintain a balanced gut microbiota, potentially serving as a therapeutic strategy to prevent the development of allergic diseases.

Relevant studies have shown that anti-SSA/SSB/U1RNP antibodies are associated with rashes in children with NLE, with double positivity for anti-SSA and anti-SSB, as well as triple positivity (Anti-SSA/SSB/U1RNP antibody), greatly increasing the incidence of rashes in patients with NLE (20). Histological examinations have revealed granular IgG deposits at the dermal-epidermal junction and vesicular changes at the skin's interface and adnexal structures (21). Additionally, many studies have confirmed that immune complex deposition plays an important role in the development of NLE rash. However, to our knowledge, no studies have directly linked autoimmune antibodies to the development of AD. In our study, we found that children with NLE who developed AD had significantly higher rates of anti-SSA, anti-SSB, and anti-SSA/SSB double antibody positivity compared to the non-AD

TABLE 2 Clinical manifestations and laboratory tests (n, %).

		AD (n=21)	No-AD (n=56)	*P-value*	NLE (n=77)
Cutaneous	Total	18 (85.71)	47 (83.93)	0.977	65 (84.42)
Hematological	Total	16 (76.19)	36 (64.29)	0.368	52 (67.53)
	Anemia	9 (42.86)	28 (50.00)	0.530	37 (48.05)
	Hypocomplementemia	13 (61.90)	17 (30.36)	0.013	30 (38.96)
	Neutropenia/deficiency	6 (28.57)	18 (32.14)	0.727	24 (31.17)
	Thrombocytopenia	13 (61.90)	16 (28.57)	0.003	29 (37.66)
	Coagulation abnormalities	6 (28.57)	12 (21.43)	0.536	18 (23.38)
Cardiac	Total	12 (57.14)	26 (46.43)	0.442	38 (49.35)
	Congenital heart block	4 (19.05)	7 (12.50)	0.737	11 (14.29)
	Structural cardiac abnormalities	10 (47.62)	20 (35.71)	0.369	30 (38.96)
Gastrointestinal	Total	11 (52.38)	39 (69.64)	0.978	50 (64.94)
Neurological	Total	7 (33.33)	15 (26.79)	0.602	22 (28.57)
Antibodies	Anti-SSA	19 (90.48)	36 (64.29)	0.029	55 (71.43)
	Anti-SSB	16 (76.19)	24 (42.86)	0.011	40 (51.95)
	U1-RNP	7 (33.33)	14 (25.00)	0.492	21 (27.27)
	Anti-SSA and Anti-SSB	13 (61.90)	18 (32.14)	0.021	31 (40.26)
	Anti-SSA, Anti-SSB, Anti-U1-RNP	3 (14.29)	6 (10.71)	0.992	9 (11.69)
Eosinophil count×10^9/L, IQR)		0.20 (0.13, 0.31)	0.18 (12, 0.28)	0.321	

AD, atopic dermatitis.

TABLE 3 Main treatment during hospitalization (n, %).

	AD (n=21)	No-AD (n=56)	*P-value*
Antibiotic	15 (71.43)	25 (44.64)	0.043
Platelet	5 (23.81)	8 (14.29)	0.338
Red blood cell	7 (33.33)	21 (37.50)	0.695
Virus-inactivated plasma	4 (19.05)	8 (14.29)	0.897
Intravenous immunoglobulin	4 (19.05)	24 (42.86)	0.047
Systemic application of GC	17 (80.95)	23 (41.07)	0.002

AD, atopic dermatitis; GC, glucocorticoids.

group, identifying double antibody positivity as a risk factor for AD. This may be due to NLE-associated antibodies on processes such as apoptosis, inflammatory responses, T-cell activation and proliferation, and pro-inflammatory interleukin production—mechanisms that are also central to the pathogenesis of AD (22–24).

The use of GC in patients with NLE is common, with intravenous GC administered to 40 patients in our study. The rate of IV GC use was significantly higher in the AD group compared to the non-AD group, identifying it as a risk factor for the development of AD in patients with NLE by age 2. While GCs are typically used to regulate skin homeostasis and are the first-line topical treatment for AD (25, 26), studies on the impact of early-life intravenous GC administration on AD risk are limited. Fetuses and newborns are particularly sensitive to GC, and therapeutic doses have lasting effects on growth, organ function, and immune function (27, 28). Early exposure to GC may increase immune reactivity to foreign antigens and compromise the skin's natural barrier, both of which increase the risk of allergic diseases.

Epidemiological studies have consistently shown that children exposed to antibiotics in the first months or years of life have a significantly increased risk of developing AD and asthma (16, 29–31). The use of antibiotics early in life disrupts the normal evolution and colonization of gut microorganisms, which, in turn, alters the host's immune status, thus increasing the susceptibility to AD (16). This was corroborated by the significantly higher percentage of patients in the non-AD group who were taking oral probiotics. In this study, the percentage of antibiotic use in patients in the AD group was significantly higher than that in the non-AD group; however, after multifactorial regression analysis, it was not found to be an independent risk factor for AD development in patients with NLE. Most of these studies, including ours, were observational, and patients on antibiotics often have bacterial infections and varying underlying immune statuses; therefore, more confounding factors may be involved.

TABLE 4 Independent risk factor analysis.

	P-value	HR(95%CI)
Oral probiotics	0.041	0.235 (0.059-0.942)
Hypocomplementemia	0.380	0.561 (0.154-2.041)
Thrombocytopenia	0.557	0.629 (0.134-2.958)
Anti-SSA	0.125	4.183 (0.673-26.010)
Anti-SSB	0.289	1.890 (0.582-6.135)
Anti-SSA and Anti-SSB	0.045	4.213 (1.034-17.165)
Antibiotic	0.863	1.186 (0.171-8.221)
Intravenous immunoglobulin	0.078	0.341 (0.103-1.13)
Systemic application of GC	0.021	4.408 (1.248-15.568)

GC, glucocorticoids.

This study is the first to establish a correlation between perinatal factors and the occurrence of AD within the first two years of life in patients with NLE. Although the study included patients from four clinical centers, the rarity of NLE resulted in a relatively small final sample size. To reduce bias, we utilized electronic case retrieval, along with outpatient and telephone follow-ups, ensuring all relevant information was collected and cross-checked by specialized physicians in pairs to. In addition, it is important to note that, based on the retrospective of this study, whether relevant factors, including oral probiotics in NLE patients, are associated with the development of AD needs to be further verified. Previous studies have shown that dupilumab or oral JAK inhibitors have good therapeutic effects and a high safety profile in patients with moderate-to-severe AD. Among them, dupilumab can significantly reduce related comorbidities in pediatric AD patients (32, 33). In the future, we need to conduct large-scale, multicenter prospective studies to further explore and confirm the long-term risk factors for developing AD in NLE patients, as well as the corresponding treatment strategies.

Our results indicate that early exogenous probiotic supplementation may be a protective factor against the development of AD in patients with NLE by age 2, while anti-SSA/SSB double positivity and intravenous GC use are risk factors. However, further research and prospective clinical trials are required to elucidate the causal relationships of these associations.

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.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Children's Hospital of Soochow University, the Affiliated Suzhou Hospital of Nanjing Medical University, Yangzhou Maternal and Child Health Hospital, and Huai'an Maternal and Child Health Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent has been obtained from the patient's family, granting permission for the publication of their child's clinical data.

Author contributions

WS: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. YL: Conceptualization, Investigation, Writing – original draft. XJ: Writing – original draft. HL: Data curation, Writing – original draft. ZS: Data curation, Writing – original draft. HW: Data curation, Writing – original draft. XL: Formal Analysis, Software, Writing – original draft. JHH: Data curation, Writing – original draft. LL: Data curation, Writing – original draft. JH: Data curation, Writing – original draft. XZ: Funding acquisition, Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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The role of macrophages in hypertrophic scarring: molecular to therapeutic insights

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Hypertrophic Scar (HS) is a common fibrotic disease of the skin, usually caused by injury to the deep dermis due to trauma, burns, or surgical injury. The main feature of HS is the thickening and hardening of the skin, often accompanied by itching and pain, which seriously affects the patient's quality of life. Macrophages are involved in all stages of HS genesis through phenotypic changes. M1-type macrophages primarily function in the early inflammatory phase by secreting pro-inflammatory factors, while M2-type macrophages actively contribute to tissue repair and fibrosis. Despite advances in understanding HS pathogenesis, the precise mechanisms linking macrophage phenotypic changes to fibrosis remain incompletely elucidated. This review addresses these gaps by discussing the pathological mechanisms of HS formation, the phenotypic changes of macrophages at different stages of HS formation, and the pathways through which macrophages influence HS progression. Furthermore, emerging technologies for HS treatment and novel therapeutic strategies targeting macrophages are highlighted, offering potential avenues for improved prevention and treatment of HS.

KEYWORDS

hypertrophic scar, macrophages, inflammation, signaling molecules, M1, M2

1 Introduction

Hypertrophic scar (HS) is a fibrotic disease of the skin, usually caused by abnormal tissue repair after burns, trauma, or surgery (1). The clinical manifestations of HS are bright red skin surface, protruding from the surrounding normal skin tissues, and localized thickening. Itching, localized numbness, and sensory abnormalities produced by HS have a severe impact on the quality of life and mental health of patients (1, 2). HS formation is a complex and challenging clinical problem that affects about 100 million patients in developed countries alone. The incidence of post-burn HS has been reported to range from 32% to 72% (3, 4). Although many studies have been devoted to exploring the mechanisms of HS, its exact pathophysiologic processes are still not fully characterized.

The formation of HS is a complex and multistage process that usually includes hemostasis, inflammation, proliferation, and remodeling phases. Macrophages are an essential component of the innate immune system. They play a crucial role in tissue repair and scar formation. Macrophages exhibit different phenotypes and functions at different stages of HS formation. M1 macrophages, also known as classically activated macrophages, primarily mediate pro-inflammatory and antimicrobial responses, producing cytokines such as TNF-α, IL-6, and IL-1β, which amplify inflammation and recruit additional immune cells (5, 6). As the inflammatory response subsides, macrophages transition to the M2 phenotype, which promotes tissue repair, extracellular matrix remodeling, and fibrosis through the secretion of anti-inflammatory cytokines and growth factors (7, 8). However, macrophage-targeted therapies for HS face significant challenges, including the complex plasticity of macrophage phenotypes, their dynamic changes during the different stages of HS formation, and the need for specific delivery systems to target macrophages without affecting surrounding tissues. Precision therapy targeting macrophages has made significant progress in tumors and rheumatic diseases (9, 10). However, the exact mechanism of macrophage action in HS remains under-revealed.

In this review, we summarize the pathological process of HS formation and the phenotypic changes that occur in macrophages at various stages of HS formation. In addition, we explore macrophage-influenced pathways in HS. Finally, we summarize the therapeutic strategies for HS, including emerging technologies and macrophage-targeted treatment approaches, and discuss the specific challenges associated with these strategies. This review systematically integrates research findings spanning from molecular mechanisms to therapeutic strategies, based on comprehensive searches of databases such as PubMed and Web of Science, to identify critical gaps and highlight potential advancements in the treatment of HS. We hope that it will help develop drugs of potential treatment value for HS and provide theoretical support for developing more effective therapeutic strategies.

2 Methods

This review is based on a systematic literature search conducted in the PubMed and Web of Science databases using keywords such as “hypertrophic scar,” “macrophages,” “fibrosis,” and “therapeutic strategies,” combined with Boolean operators (AND/OR). The search was performed on August 24, 2024. The inclusion criteria were as follows: (1) studies focusing on the role of macrophages in the mechanisms of HS and therapeutic strategies for HS; (2) original research, including *in vivo*, *in vitro*, and clinical studies; and (3) studies published in English to ensure accessibility and practical usability. The exclusion criteria were as follows: (1) studies unrelated to HS; (2) conference abstracts, pathological reports, or review articles; and (3) articles with insufficient data quality or poor study design. The screening process consisted of two steps: title and abstract screening followed by full-text evaluation. These steps were implemented to ensure the relevance, reliability, and quality of the included studies.

3 Pathological mechanisms of HS formation

Routine wound healing consists of four phases: hemostasis, inflammation, proliferation, and remodeling, each of which overlaps and differs in time and space (1).The formation of HS is the result of an abnormally active and dysregulated event during the wound healing phase, leading to an abnormal accumulation of extracellular matrix (ECM). Next, we will explore the characteristics of HS at different stages of formation.

3.1 Hemostasis

Hemostasis is the first step in wound repair (11). Damaged endothelial cells release substances such as endothelin to constrict vascular smooth muscle and reduce bleeding (12, 13). Generally, forming a blood clot involves primary and secondary hemostatic processes. During initial hemostasis, platelet receptors interact with ECM proteins, such as fibronectin and collagen, to form platelet plugs that promote adhesion to the vessel wall (14). Secondary hemostasis depends on a coagulation factor cascade reaction that activates thrombin (15). Thrombin induces the conversion of fibrinogen to fibrin, which results in the formation of a stable fibrin network. This fibrin network and fibronectin, vitronectin, and thrombospondin form an insoluble clot (16).

During hemostasis, platelet activation and release of growth factors, the intensity and duration of the inflammatory response, and deposited fibrin are closely related to the formation of HS (17). The initial hemostatic event occurs when platelets produce pro-fibrotic growth factors such as PDGF, VEGF, TGF-β1, and CTGF. Moderate release of these factors promotes hemostasis (11). Overproduction of pro-fibrotic factors can lead to excessive cell proliferation and fibrous tissue production. Previous studies have found that the use of platelet-rich plasma (PRP) for treating various types of scars is increasing. PRP attenuates the fibrotic process by decreasing the levels of pro-fibrotic markers Transforming Growth Factor Beta 1 (TGF-β1), smooth muscle actin α (α-SMA), Collagen Type I (COL-I), and Matrix Metalloproteinase-9 (MMP-9) (18, 19). In addition, these pro-fibrotic molecules may induce excessive inflammation. This may lead to the overproduction of ECM, abnormal fibroblast differentiation, and inappropriate matrix remodeling, which may promote the formation of HS (1). Overall, the release of abnormal pro-fibrotic molecules during the hemostatic phase, and the sustained inflammatory response lead to excessive fibrin network formation in HS (Figure 1A), which ultimately promotes HS (20).

3.2 Inflammation

HS is formed due to skin damage in the reticular dermis (21). The inflammatory response in the reticular dermis begins immediately at the time of injury and varies in duration depending on the degree of injury (12). The study suggests

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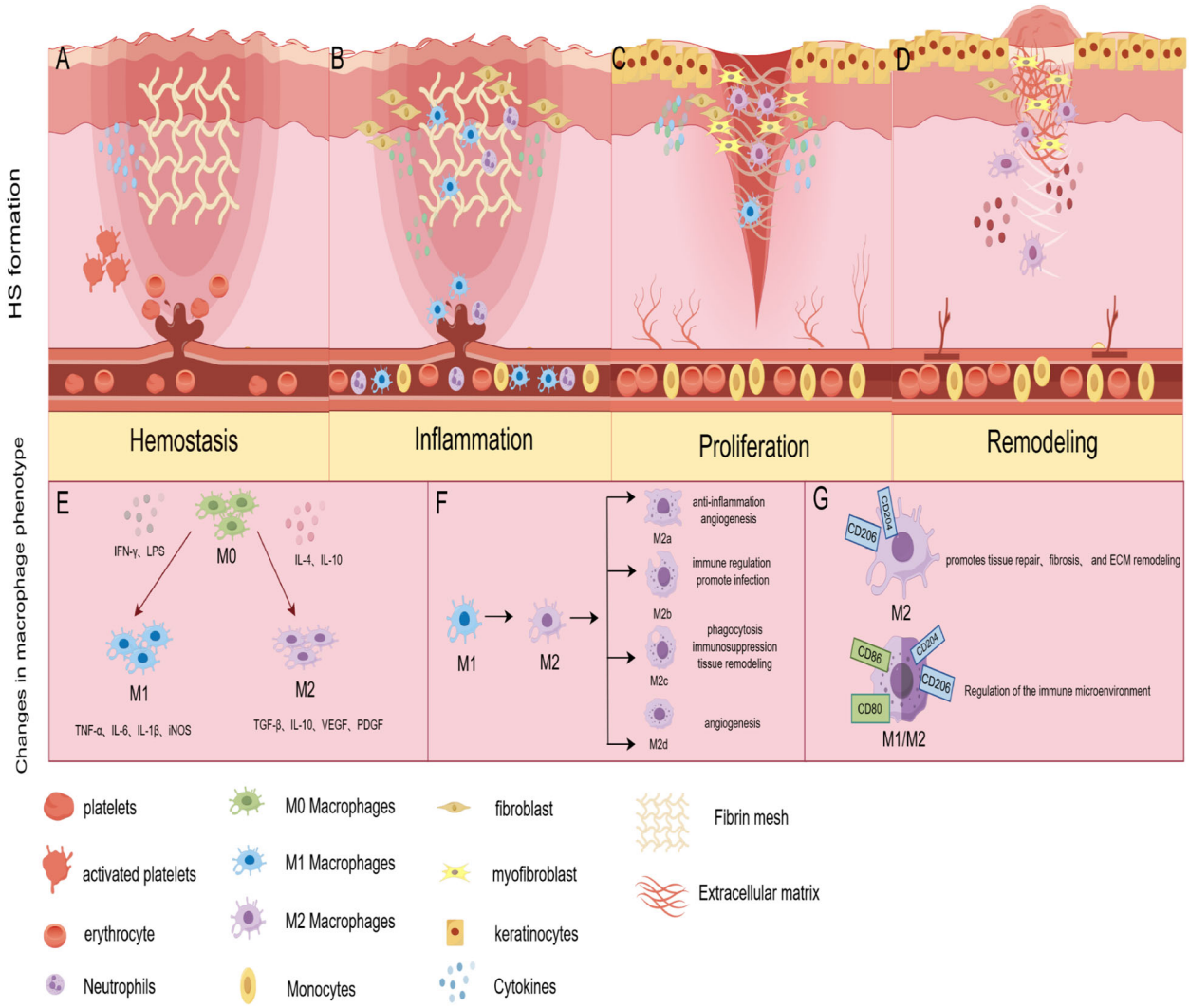

FIGURE 1
Pathological mechanisms of HS formation and phenotypic changes in macrophages during the HS formation phase. **(A)** Hemostasis: aberrant release of pro-fibrotic molecules leads to a sustained inflammatory response and excessive fibrin network formation. **(B)** Inflammation: high levels of inflammatory infiltrate leads to fibroblast activation. **(C)** Proliferation: overactive keratinocytes, dermal fibroblasts, and macrophages promote ECM deposition and excessive angiogenesis. **(D)** Remodeling: fibroblasts remodel the deposited ECM, myofibroblasts cause overall wound contraction; MMPs regulate fibroblast proliferation and are involved in ECM degradation. fibroblasts cause overall wound contraction; MMPs regulate fibroblast proliferation and participate in ECM degradation. **(E)** During HS formation, M0 macrophages respond to an initial stimulus to polarize to M1 and M2 phenotypes, with the M1 phenotype playing a significant role in the early stages. **(F)** Macrophages undergo an M1 to M2 phenotypic transition, or conversion of the M2 subtype, in the intermediate stages of HS formation; **(G)** Macrophages are dominated by the M2 phenotype in the later stages of injury and may develop a mixed M1/M2 phenotype. (By Figdraw).

excessive inflammation is the pathologic basis for HS formation (22). Increased expression of interleukins, interferons, and growth factors released by immune cells, such as neutrophils and macrophages, can activate fibroblasts (Figure 1B), which are involved in the formation of HS (23, 24).

Previous studies have shown the most apparent effect of IL-6 in promoting human HS formation. IL-6 levels were significantly elevated in burned HS fibroblasts (25). IL-6 enhances VEGF expression in macrophages, keratinocytes, and fibroblasts, ultimately leading to scarring (26). In addition to IL-6, inflammatory factors such as IL-1β, IL-4, IL-17, and IL-13 were highly expressed in HS (27, 28). Interestingly, another point was made that pro-inflammatory cytokines contribute to wound healing. Inadequate pro-inflammatory responses slow the wound-healing process (29, 30). This delay in the inflammatory response during the acute phase of early healing and its role in HS formation deserves further investigation.

In contrast to IL-6, the expression of IL-10, IL-18, and IL-37 was lower in HS. IL-10 was found to regulate the TLR4/NF-κB pathway in dermal fibroblasts via the IL-10R/STAT3 axis. Through this mechanism, IL-10 attenuated the deleterious effects of LPS on wound healing, further reducing scar formation and skin fibrosis (31). This suggests that IL-10 may mediate the TLR4/NF-κB pathway to exert anti-scarring effects.IL-18 and IL-37 are members of the IL-1 family (32). The available evidence indicates that IL-18 and IL-37 have the potential as new treatments for

pathologic scarring (33, 34). However, further research is required to fully ascertain their potential and elucidate these cytokines' optimal targeting.

3.3 Proliferation

Overactive keratinocytes, dermal fibroblasts, vascular endothelial cells, and macrophages promote HS progression during proliferative (Figure 1C). The standard proliferative period of wound healing begins about three days after injury and may last 2 ~ 3 weeks. Indeed, from 12 hours after injury, keratinocytes are activated by changes in the microenvironment of hydrogen peroxide, pathogens, growth factors, and cytokines, which result in a high degree of activation, hyperproliferation, and aberrant differentiation in the HS (35). In this process, keratinocytes produce pro-fibrotic molecules such as TGF-βand PDGF (36). These molecules induce fibroblasts to respond to the pro-fibrotic environment by producing more extracellular matrix (ECM) proteins or differentiating into myofibroblasts, accelerating scar formation (11). Fibroblasts in the upper and deeper dermis have different functions (37). Where fibroblasts in the upper dermis contribute to re-epithelialization, fibroblasts in the deeper spectrum contribute to ECM deposition. In HS proliferative events, endothelial dysfunction and altered expression of angiogenic genes such as endothelin and angiopoietin can lead to excessive angiogenesis (38). Studies have shown that excessive angiogenesis can increase collagen deposition (39). Macrophages play an essential role in this process by participating in the remodeling of neovascularization, phagocytosis of excess blood vessels, and inhibition of the angiogenic response (40).

3.4 Remodeling

The main event during the HS remodeling phase is the dysregulation of the balance between ECM collagen synthesis and degradation (41). This is accomplished by regulating key MMPs (42). MMPs are expressed by macrophages, fibroblasts, and keratin-forming cells (43). Previous studies have found that MMP2 and MMP9, enzymes essential for remodeling the ECM, are significantly elevated in the pathological microenvironment of HS (44, 45). MMP1 and MMP7 are downregulated during HS formation (46). A study observed that fibroblast proliferation and migration can be inhibited by reducing MMP-9 expression, thereby reducing fibrotic scar formation (47). Altered expression of these MMPs results in reduced degradation of ECM components, including COL-1, COL-3, and fibronectin (48). Additionally, macrophage signaling pathways play a crucial role in regulating HS remodeling. The Notch signaling pathway controls the expression of Smad, α-SMA, and collagen in HS fibroblasts to some extent (49, 50). A study using RBP-J knockout mice demonstrated that inhibition of Notch signaling in macrophages suppresses the inflammatory response and reduces collagen deposition, leading to better wound healing and reducing fibrosis (51). The above studies suggest macrophage-derived MMPs and their intracellular signaling control tissue remodeling during skin wound repair (Figure 1D). However, the precise role of macrophages in scar formation remains insufficiently understood.

4 Phenotypic changes in macrophages during the HS formation phase

4.1 Initial response and early phenotype

In response to initial stimuli such as pathogens, cytokines, or injury signals, macrophages typically polarize rapidly into either a classically activated (M1-type) or alternatively activated (M2-type) phenotype (52) (Figure 1E). This initial response typically occurs within a few hours to a few days, representing a rapid immune reaction to injury (53). M1-type macrophages are typically activated by IFNγ, either alone or in combination with LPS (54). Macrophages with the M1 phenotype highly express CD80, CD86, and CD16/32 (55), and are capable of producing pro-inflammatory cytokines such as IL-6, IL-12; chemokines such as CXCL9 and CXCL10; and NO (56). IL-4 and IL-13 induce the M2 macrophage phenotype, which is distinguished by its ability to produce vasoactive substances, exhibit anti-inflammatory properties, and promote tissue repair (57, 58). At the initial stage of HS formation, the phenotype of macrophages is predominantly of the M1 type. Under normal circumstances, the pro-inflammatory factors secreted by M1 macrophages function to clear pathogens and necrotic tissue in the initial wound environment. However, in HS, the overexpression of pro-inflammatory factors promotes the proliferation and differentiation of fibroblasts. Increasing evidence suggests that, during the early stages of wound healing, it is crucial to shift macrophages from the M1 pro-inflammatory phenotype to the M2 anti-inflammatory phenotype (59, 60).

Notably, the M1 and M2 classification model of macrophages is a simplified model for describing the different functional properties exhibited by macrophages during polarization. In addition, macrophages responding to the initial stimulus may exhibit a mixed phenotype between M1/M2, Mregs, and CXCL4-induced M4 type (53, 61, 62). However, these phenotypes have not been intensely studied in HS.

4.2 Medium-term trends and phenotypic shifts

As the inflammatory response develops or environmental factors change, the macrophage phenotype shifts in the medium term, a process that usually occurs within a few days to a week (63). At this point, macrophages can shift from M1 to M2 type or between M2 subtypes (Figure 1F). M2-type macrophages express specific surface markers, such as CD206 and CD204, and secrete anti-inflammatory factors, thereby inhibiting inflammation and promoting tissue regeneration and repair. M2 macrophages can

be further categorized into M2a, M2b, M2c, and M2d subtypes (64, 65) (Figure 1F). Although current data suggest that different phenotypes of M2 macrophage subpopulations play different roles, no reports have evaluated the role of M2 macrophage subtypes in HS, and further studies are warranted.

Interestingly, one study suggests that tumors are somehow characteristic of unhealed wounds. Significant similarities exist between many tumor markers and the wound-healing process's biological markers (66). In the tumor microenvironment, macrophages typically exhibit specific phenotypes associated with tumor progression. Tumor-associated macrophages (TAMs), which are highly plastic, can adopt either an M1-like phenotype, contributing to anti-tumor immunity, or an M2-like phenotype, promoting tumor growth and immune escape (67, 68). This mixture of phenotypes and their dynamic changes reflect the complex response of macrophages in different environments. Recent advances in cancer immunotherapy have demonstrated that targeting TAMs can effectively modulate their function. For instance, PD-1+ TAMs exhibit impaired phagocytic capacity, which can be rescued by PD-1/PD-L1 blockade, leading to a reduction in tumor burden (69, 70). Given the functional plasticity of macrophages in both tumor progression and wound healing, it is plausible that a similar immunomodulatory approach could be relevant to HS treatment. Future research should explore whether macrophages undergo a TAM-like phenotypic shift during HS formation and whether targeting immune checkpoints such as PD-1/PD-L1 could regulate macrophage activity to control excessive fibrosis and pathological scar formation. Investigating these mechanisms may provide novel insights into macrophage-targeted therapies for HS.

4.3 Late phenotype and persistence

Under prolonged inflammation lasting weeks to months, macrophages tend to adopt a phenotype suited to the specific tissue or pathological state, facilitating tissue stabilization and functional recovery. In this process, M2-type macrophages predominate (Figure 1G). By secreting anti-inflammatory cytokines, M2-type macrophages inhibit inflammatory responses and prevent tissue damage caused by excessive immune responses. In addition, M2-type macrophages secrete VEGF and PDGF during the recovery phase after injury, which promotes neovascularization and collagen production to support new tissue generation and repair. This M2-type phenotype tends to be persistent during the remodeling phase of HS formation. This results in excessive scar tissue formation via mechanisms such as prolonged anti-inflammatory response, fibrosis promotion, and ECM remodeling.

Besides, in long-standing chronic inflammatory or tumor environments, macrophages can also exhibit a mixture of M1 and M2 phenotypes (71) (Figure 1G). This mixed phenotype can sustain the fight against pathogens while modulating the local immune microenvironment to avoid excessive damage to normal tissues. Overall, the phenotypic changes of macrophages during the formative stages of HS further reflect their complex roles in maintaining immune homeostasis and regulating pathological states. Modulation of macrophage phenotypic switching is expected to be a new strategy for treating disease.

5 Macrophages affect HS through different pathways

5.1 Effect of M1-type macrophage-associated signaling molecules on HS

5.1.1 TNF-α

TNF-α is a pleiotropic cytokine secreted by various immune cells, including monocytes, T cells, dendritic cells, natural killer cells, and macrophages. M1-type macrophages are one of the significant sources of TNF-α (72). TNF-α regulates inflammatory responses and plays a crucial role in biological processes such as apoptosis, cell proliferation, and autophagy (73–75). A 16S rRNA sequencing showed that the expression of TNF-α was significantly higher in HS tissues than in normal tissues (76). TNF-α is involved in HS through the activation of relevant inflammatory pathways. The NF-kB pathway was shown to be activated in HS fibroblasts (77). Studies have shown that TNF-α induces ROS production in human dermal fibroblasts and upregulates the transcription factor NF-κB (78). *In vitro* experiments demonstrated that TNF-α induced up-regulation of MMP-1 and MMP-3 expression in human dermal fibroblasts. Resveratrol significantly inhibited this effect through the NF-κB pathway (79). Another study showed that blocking TNF-α interaction with TNFR effectively inhibits TNF-α-induced NF-κB activation (80). These studies suggest that TNF-α activates the NF-κB signaling pathway by TNFR, which alters the biological behavior of human dermal fibroblasts and may play a role in HS formation (Figure 2A).

In addition, TNF-α interacts with neutrophils to promote HS formation (Figure 2A). Research suggests that TNF-α activates neutrophils via IL-8, p55, secretory vesicles, and specific granules, enhancing their bactericidal activity and releasing inflammatory mediators (81, 82). In the early stages of infection and inflammation, TNF-α regulates the activity of neutrophil surface receptors, inhibits apoptosis, and prolongs the lifespan of neutrophils through signaling pathways such as JNK and NF-κB (83, 84). Notably, TNFR1 and TNFR2 initiate pro-inflammatory signaling, but only TNFR1 triggers a pro-apoptotic response (85). Moreover, TNF exhibits dual properties that activate neutrophil apoptosis under specific conditions (86, 87).

Although the mechanism of TNF-α has been extensively studied, TNF-α inhibitors are widely used in treating psoriasis, rheumatoid arthritis, and other immune-related diseases (88, 89). However, their specific role in HS lacks support from large-scale research data. Understanding the interactions between TNF-α and other inflammatory factors and cell types could help clarify its overall role in HS formation and potentially optimize treatment strategies.

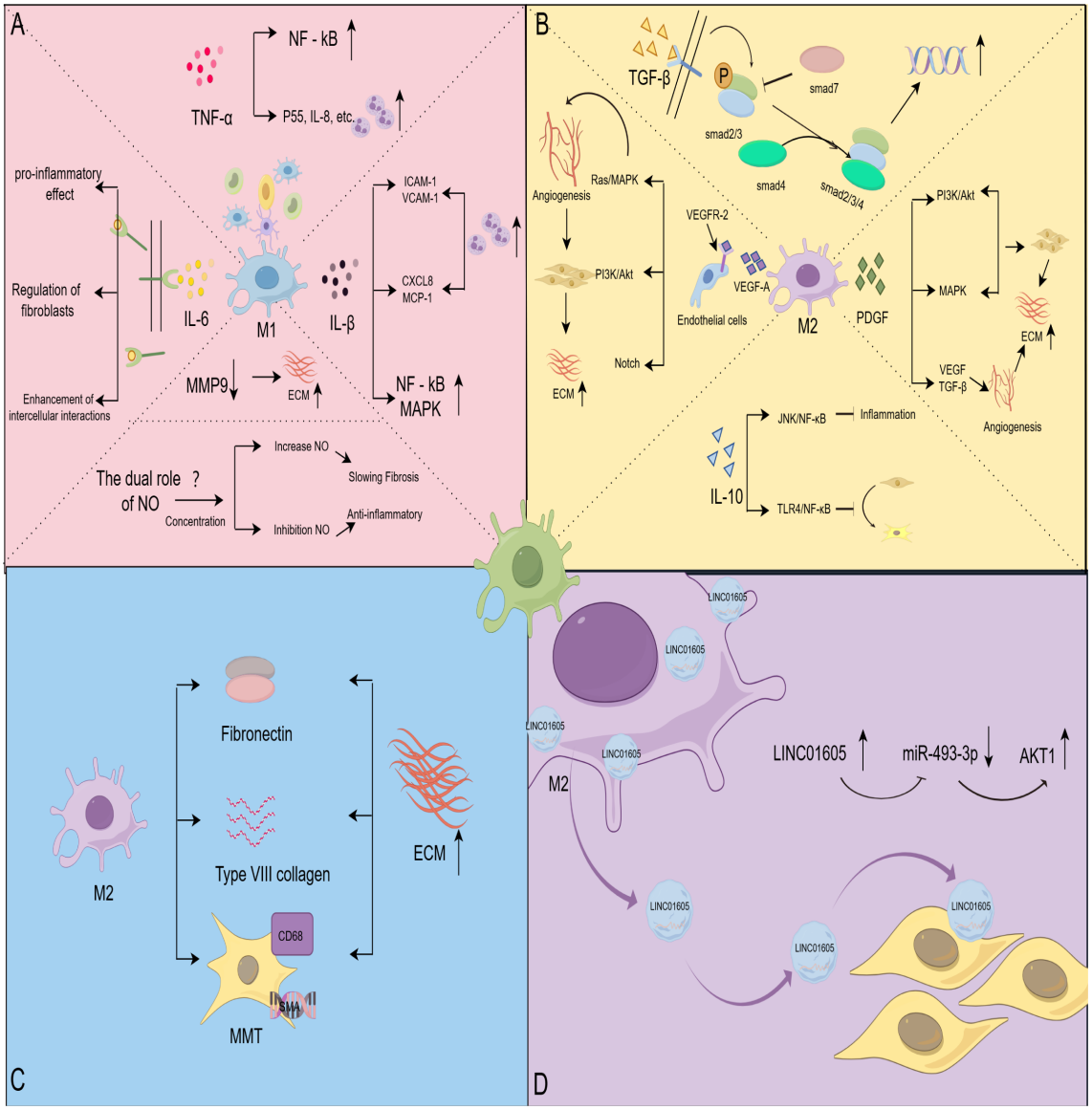

FIGURE 2
Macrophages affect HS through different pathways. **(A)** Effect of M1-type macrophage-associated signaling molecules on HS; TNF-α activates NF-κB and promotes inflammatory cell infiltration; IL-6 exhibits pro-inflammatory activity, regulates fibroblast behavior, and interacts with macrophages, fibroblasts, and endothelial cells; IL-1β recruits immune cells and activates the NF-κB and MAPK signaling pathways; NO regulates fibrotic disease in a concentration-dependent manner; MMP9 reduces ECM deposition. **(B)** Effect of M2-type macrophage-associated signaling molecules on HS; over-activation of the TGF-β pathway promotes fibroblast value-addition and differentiation, and Smad7 negatively regulates TGF-β signaling; IL-10 inhibits inflammatory responses and fibroblast differentiation through the JNK/NF-κB and TLR4/NF-κB pathways; VEGF activation Ras/MAPK, PI3K/Akt and Notch signaling pathways, which regulate the behavior of vascular endothelial cells and promote angiogenesis overgrowth; PDGFPI3K/Akt, MAPK and other signaling pathways enhance the secretory activity of fibroblasts, and synergistically act with VEGF and TGF-β to promote angiogenesis and promote the development of HS. **(C)** Macrophages were directly involved in matrix remodeling; macrophages secreted fibronectin and collagen type VIII and differentiated into myofibroblasts to directly intervene in ECM remodeling. **(D)** Macrophages mediate HS via exosome formation; exosomes derived from M2 macrophages were enriched in LINC01605, and high levels of LINC01605 caused a decrease in miR-493-3p and activated AKT to enhance the inflammatory response. (By Figdraw).

5.1.2 IL-6

IL-6 is a multifunctional cytokine that affects the fibrotic process by promoting monocyte recruitment, M2-type macrophage polarization, and increased ECM deposition (90). After binding to its receptor, IL-6 exerts its biological effects primarily through three signaling modes: cis, trans, and cluster signaling (91). Studies indicate that IL-6 is one of the most significant cytokines promoting human HS formation, highlighting its critical role in fibrotic pathology (25). Trans signaling by IL-6 exhibits pro-inflammatory activity and is associated with various pathological changes (92). Previous studies have demonstrated that activation of trans IL-6 signaling accelerates fibrosis (93). Inhibition of IL-6 and its downstream pathways positively impacts the clinical management of fibrotic diseases (94, 95). Interestingly, a study of renal scarring found no significant

differences in trans IL-6 signaling markers between patients with renal scarring and those without scarring (96). This suggests that there may be some degree of dysfunction in the trans-IL-6 signaling pathway during scarring that deserves further investigation.

IL-6 regulates fibroblast behavior through autocrine mechanisms. *In vitro* experiments demonstrated that IL-6 autocrine activity drove scar fibroblasts to exhibit significant anisotropy and altered ECM arrangement, resulting in a directional matrix structure (97). This change in matrix structure and orientation may contribute to the rigid and irregular morphology of scar tissue. This study suggests that IL-6 not only promotes HS formation via its pro-inflammatory effects but also influences ECM structure by modulating fibroblast behavior. This highlights the importance of IL-6 signaling in inhibiting fibrosis progression as a potential therapeutic target.

Additionally, elevated IL-6 levels promote HS formation through intercellular interactions. Specifically, IL-6 stimulates macrophage polarization towards the M2 type, upregulates TGF-β and promotes fibroblast differentiation towards myofibroblasts (98). Furthermore, IL-6 amplifies the inflammatory response in vascular endothelial cells, regulating angiogenesis and immune cell recruitment. These effects are mediated by classical and trans signals activating PI3K-Akt, ERK1/2, and gp130 signaling pathways (99, 100). In summary, IL-6 plays a key role in HS formation through multiple signaling pathways and intercellular interactions (Figure 2A). However, the complexity of the IL-6 signaling pathway has not been fully clarified. Exploring the causes of dysregulation of the IL-6 signaling pathway and its specific role in the fibrosis process will help develop more precise therapeutic strategies.

5.1.3 IL-1β

IL-1β is also highly expressed in HS (27). IL-1β belongs to the IL-1 family, which consists of 11 cytokines.IL-1β is one of these ligands with proinflammatory activity and is produced mainly by macrophages. In the early stages of scar formation, IL-1β attracts immune cells to migrate to the damaged site by activating the inflammatory response. It has been shown that IL-1β enhances vascular permeability and promotes the aggregation of inflammatory cells to the area of injury by upregulating the expression of ICAM-1 and VCAM-1, adhesion molecules of vascular endothelial cells (101, 102). IL-1β also stimulates endothelial cells to secrete CXCL8 and monocyte chemotactic protein-1, which further attracts immune cells, such as neutrophils and monocytes, to the site of infection or injury (103). In addition, IL-1β activates the NF-κB and MAPK signaling pathways, amplifying the inflammatory response and exacerbating tissue fibrosis (104, 105). Studies have shown that anti-IL-1β therapy is effective in inhibiting the course of chronic progressive fibrosis. This effect may be attributed to its inhibition of IL-1β-mediated pro-inflammatory responses (106, 107).

Overall, IL-1β exacerbates tissue fibrosis by enhancing the inflammatory response and attracting immune cell aggregation (Figure 2A). Although some preliminary studies have suggested a possible role for anti-IL-1β therapy in organ fibrotic diseases (107, 108), more clinical studies and trials are needed to determine the efficacy and applicability of anti-IL-1β therapy.

5.1.4 iNOS

Endogenous nitric oxide (NO) is produced by three different types of enzymes: neuronal NOS (nNOS; NOS1), inducible NOS (iNOS; NOS2), and endothelial NOS (eNOS; NOS3) (109). Of these, iNOS plays a critical role in the fibrotic process. iNOS activity is upregulated by cytokines, such as IFN-γ and LPS, secreted by M1-type macrophages. This leads to the production of large amounts of NO, which is involved in regulating fibrosis and the inflammatory response. Recent studies have found that NO exhibits different effects in various fibrotic diseases through different concentrations and mechanisms (110) (Figure 2A). NO inhibition of myofibroblast activation and collagen I production in renal fibrosis, using nanocarrier-delivered NO, slows the progression of renal fibrosis (111). In a phase 2 clinical trial, pulsed inhaled NO demonstrated favorable safety and tolerability in treating interstitial lung disease and improved patients' physical activity (112). These studies suggest the potential benefit of NO supplementation in fibrotic diseases.

In contrast, other studies have demonstrated that inhibiting NO production in LPS-stimulated RAW 264.7 macrophages exerts an anti-inflammatory effect (113). Huseyin Gungor's study supports the notion that inhibiting NO production helps improve liver fibrosis (114). Another *in vitro* study showed that p53 knockdown mesenchymal stem cells (MSCs) promoted fibroblast proliferation by increasing NO production. This phenomenon was reversed by inhibiting NO production (115). It is thus clear that the role of NO in fibrotic diseases is dual, and its specific effect depends mainly on the concentration level of NO. Further research on the application of NO in fibrotic diseases is of critical significance for guiding HS treatment.

5.1.5 MMPs

MMPs are a class of metal ion-dependent proteases capable of degrading a wide range of components in the ECM. The human genome contains 24 MMP genes, two of which encode the MMP23 protein, resulting in 23 distinct MMPs. Under normal conditions, MMP activity is low, but it increases significantly during tissue repair and inflammation. MMPs regulate tissue degradation and remodeling by cleaving ECM components such as collagen, fibronectin, laminin, and gelatin (116). Among MMPs, MMP-9 plays a crucial role in HS formation (Figure 2A). Previous studies have found that upregulated gene expression of MMP-2, MMP-9, and TIMP-1 is strongly associated with proliferative scarring (117). In experiments with a rabbit ear scar model, elevated MMP-2 and MMP-9 expression significantly reduced the Scar Elevation Index, Epidermal Thickness Index, and collagen deposition (118). Recent *in vitro* studies have demonstrated that capacitive resistive electro transfer therapy alters MMP-9 expression in human myofibroblast cultures, potentially benefiting fibrotic pathology treatment (119). These findings suggest that the activity of MMP-9 has a critical role in tissue repair. The mechanism of macrophage-MMP-ECM interactions warrants further investigation. Targeted interventions against this interaction may offer new strategies for treating HS.

5.2 Effect of M2-type macrophage-associated signaling molecules on HS

5.2.1 TGF-β

TGF possesses the ability to induce a transformed phenotype in untransformed cells, and it was first discovered by De Larco and Todaro in 1978. Mammalian cells express three isoforms of TGF: TGF-β1, TGF-β2, and TGF-β3. These isoforms are widely involved in biological processes, such as inflammation, matrix generation, matrix remodeling, cell proliferation, and the regulation of apoptosis, all of which play an important regulatory role in HS formation (120, 121).

Recent studies have confirmed that TGF-β, especially the TGF-β1 isoform, significantly promotes HS formation. Specifically, TGF-β1 promotes fibroblast activation by activating the downstream Smad protein signaling pathway (Figure 2A). Simultaneously, it induces fibroblasts to secrete large amounts of collagen and fibronectin, which leads to the excessive accumulation of scar tissue (122). Studies have shown that inhibition of the activation of the TGF-β1-Smad2/3/4 signaling pathway promotes apoptosis of fibroblasts, thereby alleviating HS production (123). In addition, TGF-β1 promotes the differentiation of fibroblasts into myofibroblasts by regulating the expression of α-SMA, further enhancing contractility and fibrosis at the trauma site (124).

Several studies have shown that moderate TGF-β signaling during the early stages of wound repair helps maintain the tissue repair balance and promotes wound healing. In contrast, when TGF-β signaling is overactivated, it leads to fibrosis formation. Smad7 is an inhibitory factor in the TGF-β signaling pathway and plays a key role in the negative regulation of fibrosis. It inhibits the excessive transmission of TGF-β signaling by competitively inhibiting the phosphorylation and nuclear translocation of Smad2/3, thereby limiting the progression of fibrosis (125) (Figure 2B). These findings highlight the complex role of TGF-β signaling in wound repair, including its positive role in promoting wound healing but also the risk of fibrosis. Previous studies have shown that the critical role of TGF-β in scar formation has been extensively researched, and that TGF-β inhibitors have demonstrated potential efficacy in preclinical studies (126). However, since the TGF-β signaling pathway is critical for various normal physiological processes, such as wound healing and immune regulation, treatments directly targeting TGF-β may lead to significant side effects. Therefore, future studies may need to develop more selective TGF-β inhibitory strategies to minimize side effects while preserving therapeutic efficacy.

5.2.2 IL-10

IL-10 is an anti-inflammatory cytokine, mainly secreted by M2-type macrophages, and it is involved in scar formation and fibrosis-related diseases. However, the anti-fibrotic molecular mechanism of IL-10 in skin scarring remains unclear. Early studies found that a lack of IL-10 in fetal skin triggered scar formation. This intrinsic lack of IL-10 may lead to a sustained amplification of inflammatory cytokines, persistent stimulation of fibroblasts, and abnormal collagen deposition (127). Other studies have demonstrated that IL-10 is highly expressed in fetal skin during mid-gestation and is absent in human skin after birth (128). These findings tentatively suggest that IL-10 is involved in wound healing and scar formation. Recently, several studies have shown that IL-10-modified BMSCs inhibited inflammatory progression through the JNK/NF-κB pathway and prevented the formation of HS in a rabbit ear model (129). This suggests that IL-10 may mediate the JNK/NF-κB pathway to exert an anti-scarring effect. The study by Xie Fang et al. demonstrated that IL-10-modified Adipose-Derived Mesenchymal Stem Cells prevented HS formation by modulating fibroblast biology and inflammation (130). Another *in vitro* study demonstrated that IL-10 regulates the TLR4/NF-κB pathway in dermal fibroblasts via the IL-10R/STAT3 axis, which in turn reduced ECM deposition and fibroblast-to-myofibroblast transformation, thereby attenuating LPS-induced HS formation (31).

In summary, IL-10 may take on an anti-scarring role through various mechanisms, such as reducing the inflammatory response and modulating the biological behavior of fibroblasts (Figure 2B). Although IL-10 has the potential to inhibit HS formation, it is poorly stable *in vivo* and requires an effective delivery system to ensure adequate concentration in target tissues. Existing delivery systems (e.g., nanocarriers, hydrogels, and other methods) are effective, but their effectiveness and safety must be further validated. Future research may focus on developing controlled-release IL-10 systems that can be combined with antifibrotic drugs, laser therapy, or other cytokines to develop a combination therapy strategy for preventing HS.

5.2.3 VEGF

The process of HS formation is closely related to dysregulated angiogenesis. VEGF is the major pro-angiogenic factor, generating different mRNA variants through alternative splicing. These variants are translated to produce protein subtypes of different lengths and biological functions (131). Specifically, VEGF-A binds to VEGFR-2, forming a dimer and activating the receptor's tyrosine kinase activity. This process triggers the autophosphorylation of tyrosine residues on the receptor. The phosphorylated tyrosine residues become binding sites for various downstream signaling molecules, activating multiple signaling pathways such as Ras/MAPK, PI3K/Akt, and Notch (132, 133) (Figure 2B). These pathways act synergistically to regulate the behavior of vascular endothelial cells and ultimately promote angiogenesis. However, overactivation of these signaling pathways can lead to excessive angiogenesis. The overproduced blood vessels provide sufficient nutritional support for the abnormal proliferation of fibroblasts and collagen deposition, thus exacerbating scarring. Numerous studies have shown that downregulation of VEGF signaling can alleviate HS formation (134, 135). Moreover, VEGF signaling also upregulates the expression of MMPs, promoting endothelial cell migration in the stroma and neovascularization (136, 137). Thus, VEGF and its associated signaling pathways play a multifaceted role in the formation of HS, making it an essential target for understanding and treating pathological scarring.

5.2.4 PDGF

The PDGF family consists of PDGF-aa, PDGF-bb, PDGF-ab, PDGF-cc, and PDGF-dd, which are composed of five members that form disulfide-linked homo- or heterodimers (138). The primary sources of PDGF are platelets and fibroblasts, and M2 macrophages can secrete small amounts of PDGF during the proliferation phase of wound healing. PDGF regulates cell proliferation, migration, and differentiation by initiating downstream signaling pathways through binding to its specific receptor, PDGFR (139).

PDGF's ability to promote fibroblast activity plays a crucial role in HS formation. Studies have shown that PDGF expression in HS tissue is significantly higher than in normal skin, which correlates directly with the hyperactivation of fibroblasts (140). The overexpression of PDGF leads to abnormal proliferation and migration of fibroblasts, resulting in collagen production exceeding normal levels and causing thickened and hardened scar tissue. Another *in vitro* study found that adding PDGF-BB to fibroblasts cultured *in vitro* significantly increased the proliferation rate of the cells (141). This effect was more pronounced in HS fibroblasts (142), suggesting an essential role of PDGF in promoting cell proliferation in this process.

PDGF also enhances the secretory activity of fibroblasts by activating the PI3K/Akt, MAPK, and other signaling pathways (Figure 2B). This results in the overproduction of collagen, fibronectin, and other ECM components, ultimately leading to the persistent and abnormal proliferation of scar tissue (143, 144). In addition, PDGF promotes HS generation through synergistic effects with VEGF and TGF-β (145, 146) (Figure 2B). This suggests that PDGF affects scar formation by directly acting on fibroblasts and also indirectly contributes to the development of HS by regulating angiogenesis. Inhibiting the PDGF/PDGFR signaling pathway can effectively block the aberrant signal transduction of various growth factors, thereby preventing the onset and progression of diseases such as fibrosis (147). Given the critical role of PDGF in HS, targeting the PDGF/PDGFR pathway is a promising therapeutic strategy.

5.3 Direct involvement of macrophages in matrix remodeling

Macrophages are not only indirectly involved in HS formation by secreting signaling molecules but also directly influence HS formation by remodeling the ECM. Macrophages directly intervene in ECM remodeling by both secreting collagen and differentiating into myofibroblasts (Figure 2C). As early as 1999, Weitkamp et al. used fluorescence techniques to demonstrate that macrophages can synthesize type VIII collagen themselves (148). Another study found that macrophages secrete fibronectin and collagen type VIII to promote ECM formation and express almost all known collagen and collagen-related mRNAs (149). These findings suggest a direct role for macrophages in HS formation.

Notably, macrophages undergo macrophage-to-myofibroblast trans differentiation (MMT) in chronic inflammation and fibrotic pathological environments. A study collected human liver specimens at different stages of hepatic fibrosis and found MMT cells, which co-expressed macrophage (CD68) and myofibroblast (a-SMA) markers. Moreover, this result was validated in an animal model of liver fibrosis (150). In another study, researchers found that macrophages are involved in the formation of subretinal fibrosis through MMT changes (151). This suggests that MMT is involved in the progression of multiple fibrotic diseases. However, current research on direct collagen secretion by macrophages has primarily focused on organ fibrosis. Therefore, there is an urgent need to improve the understanding of macrophage-secreted ECM components in skin scarring.

5.4 Macrophages mediate HS formation via exosomes

Macrophages secrete different extracellular vesicles, including Exosomes, Microvesicles, and Apoptotic Bodies. Exosomes are important extracellular vesicles that contain various bioactive molecules such as microRNA, proteins, and lipids, which can regulate intercellular communication and influence the behavior of recipient cells.

Exosomes are secreted by prokaryotic and eukaryotic cells, with a diameter of about 30-150 nm, and are essential carriers of paracrine signaling (152). Macrophages initiate the process through membrane endocytosis, forming endosomes. Subsequently, the endosomes generate intraluminal vesicles in the cytoplasm, which transform into multivesicular bodies (MVBs). Finally, the MVBs fuse with the cell membrane, releasing exosomes (152, 153). A study co-culturing M2 macrophages with human dermal fibroblasts found that exosomes derived from M2 macrophages promoted the proliferation and migration of human dermal fibroblasts by delivering LINC01605 (154) (Figure 2D). Another study showed that M2 macrophage-derived exosomes were enriched in long-stranded noncoding RNA, specifically lncRNA-ASLNCS5088. This lncRNA can be efficiently transferred to fibroblasts, increasing α-SMA expression (155). Interestingly, recent studies have shown that macrophage filamentous pseudopods can produce filopodia tip vesicles. Such vesicles detach from the tips of the cell's filamentous pseudopods and deliver many molecular signals to fibroblasts (156). These studies suggest that macrophage-derived exosomes play a role in HS formation by influencing fibroblast behavior.

Although studies of macrophage-mediated HS formation via exosomes have shown potential, their high cost and shortcomings in delivery efficiency and specificity have limited their application. In the future, new breakthroughs in therapeutic HS should be achieved by studying standardized production and optimizing delivery systems.

6 Treatment strategies for HS

6.1 Emerging technologies for HS treatment

6.1.1 Photomedical therapy technology

Compared with traditional conservative treatments, such as local drug injections and physical pressure therapy, photoelectric technology offers non-invasiveness, high precision, a rapid onset of action, and shorter treatment durations. Common photoelectric therapy modalities used in clinical practice include laser therapy (ablative and non-ablative), microplasma radiofrequency technology, and photodynamic therapy (PDT).Recently, PDT has emerged as a promising non-surgical strategy for treating HS in both cellular studies and animal models. PDT primarily relies on the cytotoxic effects of photosensitizers to achieve its therapeutic action. When photosensitizers accumulate around proliferating fibroblasts, laser irradiation triggers the production of reactive oxygen species (ROS).ROS exert cytotoxic effects on fibroblasts, inducing apoptosis and ultimately leading to the necrosis of scar tissue (157, 158). However, the detailed mechanism underlying PDT's scar-inhibitory effects remains unclear. In clinical applications, PDT is often combined with microneedling techniques, which enhance drug penetration while amplifying PDT's anti-scarring effects (159, 160). There is no doubt that PDT is an effective strategy for the prevention and treatment of HS. Notably, the selection of photosensitizers, the presence of side effects such as pain during treatment and how to effectively combine photodynamic therapy with other therapies are current challenges.

6.1.2 New drug delivery systems

6.1.2.1 Controlled release materials

Controlled-release materials significantly enhance the continuity and efficacy of therapy due to their unique drug slow-release properties. Hydrogel is a network structure composed of hydrophilic polymer chains linked by various chemical bonds and forces, featuring diverse cross-linking modes. In recent years, it has been used as a bioscaffold to promote wound healing, demonstrating promising therapeutic effects in the treatment of HS. Zivari-Ghader T et al. showed that hydrogel wound dressings made of chitosan/alginate scaffolds loaded with HPCE effectively prevented HS formation. This hydrogel exhibited antimicrobial, antioxidant, and anti-inflammatory properties, effectively inhibiting excessive collagen deposition and reducing inflammation (161). Similarly, numerous studies support these findings (162–164). Fu et al. demonstrated that hydrogels possess tension-shielding capabilities, which reduce wound tension via shape fixation and ultimately minimize HS formation (165). Zhang et al. utilized a bioglass/alginate composite hydrogel, which significantly inhibited scar formation in a rabbit ear scar model. The main mechanism involves stimulating the expression of the integrin subunit Alpha 2 in dermal fibroblasts, which accelerates wound healing and modulates fibroblast behavior (166). This indicates that different functional hydrogels can inhibit HS formation through multiple mechanisms (Table 1).

Microspheres are small spherical multiparticulate drug delivery systems with diameters ranging from 1 to 1,000 μm, capable of enhancing the bioavailability, stability, and efficacy of traditional drugs while ensuring good safety. Zhang et al. constructed asiaticoside microspheres to achieve efficient drug loading and sustained release, providing regenerative healing and anti-scarring effects (167). Another study prepared hemostatic porous microspheres, which demonstrated high fluid absorption capacity and excellent coagulation properties, accelerating wound healing and highlighting their potential in scar treatment (168).

Microsponges are porous structures composed of polymerized particles, typically ranging from 5 to 300 μm in diameter. The porous structure of microsponges enables controlled drug release. In a study investigating a microsponge gel of silver sulfadiazine for burn wound treatment, loading silver sulfadiazine into a microsponge incorporated in a gel matrix enhanced drug potency, enabled sustained drug release, reduced dosing frequency, improved adherence in burn patients, and minimized cytotoxicity (169). Furthermore, incorporating microsponges into a hydrogel allows for sustained drug delivery to the wound site, while the gel matrix maintains a moist environment and enhances cell adhesion, promoting wound healing and offering a novel approach for HS treatment (170).

6.1.2.2 Enhanced penetration materials

The stratum corneum is the primary barrier to drug delivery through the skin to the scar tissue. Both liposomes and ethosomes possess bilayer membrane structures that resemble biological membranes. This structure enables them to mimic the properties of biological membranes, facilitating their fusion with cell membranes, penetration of the stratum corneum, and enhancement of drug permeation. SHI et al. developed an anti-VEGF antibody-modified liposome gel containing salvinorin. It exhibited excellent skin permeability, delayed drug release, and promoted high drug accumulation in the dermis. *In vivo* studies demonstrated that it reduced VEGF, TGF-β1, and TNF-α levels, inhibited cell proliferation, and exhibited therapeutic effects on HS in a rabbit ear model (171). Xie et al. developed new statin-loaded liposomes with enhanced skin penetration, which were successfully delivered topically and significantly reduced HS formation in a rabbit ear model (172). Zhang et al. prepared 5-FU-encapsulated ethosomes for HS treatment in combination with CO2 fractional laser therapy. The nanoscale ethosomes penetrated scar tissue through narrow and tightly connected cellular gaps. Fractional laser reduces the required drug dose, facilitating drug penetration into deeper skin layers, achieving higher local concentrations, and effectively inhibiting HS formation (173). Similarly, Yu et al. utilized the transdermal delivery capability of ethosomes to prepare an IR-808-loaded nanoethosome system as a novel photosensitizer for HS treatment with transdermal photodynamic therapy (174).

6.1.2.3 Bioactive materials

The exceptional biocompatibility and functionality of bioactive materials facilitate the effective repair of scar tissue. Exosomes, as critical mediators of intercellular communication, can deliver

TABLE 1 Novel drug delivery systems for HS.

Material Type	Category	Name	Model	Mechanism	References
Controlled Release Materials	Hydrogel	Chitosan-Alginate Hydrogel with Hypericum perforatum Callus Extract	Mouse wound healing model/ Normal human fibroblast cell	Inhibited E. coli and K. pneumoniae, MRSA, and MR-CoNS/accelerated re-epithelialization, neovascularization, and collagen deposition while reducing inflammation	(161)
		GelMA/PEGDA Hydrogel Microneedle Patch	Rabbit Ear HS Model/ HS fibroblasts	Inhibition of HS fibroblasts/ decreased the protein expression of collagen I/III and TGF-β1	(162)
		polysaccharide hydrogel	Rabbit Ear HS Model/Human keloid fibroblasts	Reducing the expression of α-SMA expression	(163)
		Tough, antibacterial, and antioxidant hydrogel	MRSA-infected rat full skin defect model/MRSA-infected rabbit ear HS model	Decreased inflammatory reactions, reduce collagen deposition, regulate collagen type and down-regulate α-SMA production	(164)
		Shape-fixing hydrogel	Mouse HS model	Reduces mechanical tension on wounds, optimizing the healing environment to promote scarless repair	(165)
		Bioglass/alginate composite hydrogels	Rabbit Ear HS Model/ HS fibroblasts	Inducing scar fibroblasts apoptosis	(166)
	Microspheres	Porous microspheres loaded with asiaticoside	Epithelial cells, Dermal fibroblast cell models/Rat full-skin excision model	Accelerating re-epithelization, regulating the synthesis and disposition of different types of collagens	(167)
		Cellulose nanocrystal/calcium alginate-based porous microspheres	Mouse full thickness skin wound	Inhibited the activities of Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa	(168)
	Microsponges	Silver sulfadiazine-loaded microsponge gel	Epidermal keratinocyte and mouse embryonic fibroblast cell/Second degree burn wound model in mice	Enhanced the efficacy of the drug by reducing the cytotoxicity towards the keratinocytes and fibroblasts without altering the antimicrobial properties	(169)
		Resveratrol-loaded microsponge gel	Excision wound model in rats	Influenced cell adhesion	(170)
Enhanced Penetration Materials	Liposomes	anti-VEGF antibody-modified Paeonol liposome gels	Rabbit Ear HS Model	Inhibition inflammation	(171)
		Liposome-encapsulated statins	Rabbit Ear HS Model/Human foreskin fibroblasts	Decreased type I/III collagen content	(172)
	Ethosomes	ethosomes encapsulated with 5-florouracil	Rabbit Ear HS Model	CO2 fractional laser promote the permeation of 5-fluorouracil encapsulated ethosomes	(173)
		IR-808 loaded nanoethosomes	HS fibroblast/Rabbit Ear HS Model	promoting HSF apoptosis and remodeling collagen fibers	(174)
Bioactive Materials	Exosomes	LINC01605-enriched exosomes from M2 macrophages	Human dermal fibroblast	LINC01605 promoted fibrosis of human dermal fibroblast by directly inhibiting the secretion of miR-493-3p, and miR-493-3p down-regulated the expression of AKT1	(154)
		lncRNA-ASLNCS5088-enriched exosomes from M2 macrophages	Fibroblast	Inhibition fibroblast activation	(155)
		Exosome derived from mesenchymal stem cells	HS fibroblast	Inhibition the TNFSF-13/HSPG2 signaling pathway	(175)

(Continued)

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TABLE 1 Continued

Material Type	Category	Name	Model	Mechanism	References
		Exosomes from miR-29a-modified adipose-derived mesenchymal stem cells	Mouse scalded skin model/ HS fibroblasts	Inhibition the TGF-β2/Smad3 signaling pathway	(176)
		Exosome from adipose-derived mesenchymal stem cells	Mice skin incision model/ Fibroblasts model	Regulation of microRNA-181a/ SIRT1 axis	(177)
		Exosomes from hypertrophic scar fibroblasts	Normal human keratinocytes	Changed molecular patterns of proliferation, activation, differentiation and apoptosis of NHKs and proliferation/ differentiation regulators and EMT markers	(178)
		Exosomes derived from human hypertrophic scar fibroblasts	HS fibroblasts	Increased cell proliferation and migration,induces smad and TAK1 signaling	(179)
	Nanoparticles	Verteporfin-loaded bioadhesive nanoparticles	HS fibroblasts	Inhibition the collagen deposition and angiogenesis	(180)
		Resveratrol-laden mesoporous silica nanoparticles	HS fibroblasts	Induce the apoptosis and autosis via the ROS -mediated p38-MAPK/ HIF-1α/p53 signaling axis	(181)
		DNA-Fe nanoparticle	Rabbit Ear HS Model/Human fibroblast cells	Remodeling collagen fibers and promoting human fibroblast cells apoptosis	(182)
		Cu2Se@LYC (CL) composite	Rabbit Ear HS Model/ HS fibroblasts	Induce the generation of reactive oxygen species and mitochondrial damage in hypertrophic scar fibroblasts	(183)
		Cuprous oxide nanoparticles	Rabbit Ear HS Model/ HS fibroblasts	Inhibiting HSFs proliferation and inducing HSFs apoptosis	(184)
	Nanofiber Membranes	Palmatine-loaded poly (ε-caprolactone)/gelatin nanofibrous scaffolds	Rabbit Ear HS Model/ L929 Fibroblasts	Facilitate the adhesion, spreading and proliferation of L929 fibroblasts	(185)
		ginsenoside Rg3-loaded electrospun PLGA fibrous membranes	Rabbit Ear HS Model	Decreased collagen I, VEGF expression	(186)
		Random composite nanofibers	Rat whole skin defect model	Promote re-epithelialization and angiogenesis and reduce excessive inflammation	(187)
		Electrospun Naringin-Loaded Fibers	Normal Human Dermal Fibroblasts/Hypertrophic Human Fibroblasts	Decreased Normal Human Dermal Fibroblasts TGF-β1, COL1A1, α-SMA	(188)
		Electrospun Fibers Loaded with Pirfenidone	HS fibroblasts	Modulates the gene expression of TGF-β1 and α-SMA	(189)

biologically active substances and have demonstrated significant therapeutic potential in the treatment of HS. Recent research on adipose stem cell exosomes (ADSC-exos) has yielded increasing evidence that ADSC-exos not only promote wound repair but also possess therapeutic potential for HS. By carrying specific microRNAs, ADSC-exos regulate target gene expression, suppress fibrosis-related signaling pathways such as TGF-β/Smad, reduce fibroblast proliferation, migration, and collagen deposition, and promote HS tissue repair. This demonstrates the great potential of ADSC-exos in the treatment of HS (175–177). Moreover, fibroblast exosomes have shown a beneficial role in HS treatment. They affect HS formation by regulating fibrotic signaling pathways, promoting cell proliferation migration and epithelial-mesenchymal transition (178, 179). Notably, lncRNAs enriched in M2-type macrophage-derived exosomes were found to influence HS formation through a mechanism potentially linked to fibroblast activation (154, 155).

Bioactive nanomaterials exhibit tremendous potential for treating proliferative scarring. Studies have utilized nanoparticles as encapsulants, effectively inhibiting scar tissue formation. For example, Rerteporfin, Resveratrol, and Doxorubicin hydrochloride

were encapsulated into nanoparticles to enhance drug stability and targeting, reduce side effects, and inhibit scar fibroblast proliferation effectively (180–182). Additionally, nanoparticles have been used to deliver photosensitizers in combination with near-infrared light therapy to induce mitochondrial damage and cell death (183). Furthermore, nanoparticles have been found to regulate the proliferation and apoptosis of HS fibroblasts, providing a scientific basis for developing novel therapeutic strategies for HS (184). Beyond nanoparticles, nanofiber membranes play a critical role in HS treatment. One study prepared Palmatine-loaded electrospun poly(ε-caprolactone)/gelatin nanofibrous scaffolds. These scaffolds exhibited strong antimicrobial and antioxidant activities, significantly inhibited scar formation, and accelerated wound healing (185). Another study developed ginsenoside Rg3-loaded electrospun PLGA fibrous membranes using electrostatic spinning and pressure-driven infiltration techniques. These membranes promoted tissue repair during the early stage of wound healing and inhibited scar formation during the later stage (186). In addition, nanofibrous membranes can influence scar formation by regulating macrophage function and promoting macrophage polarization. In a study, dendritic mesoporous bioglass nanoparticles loaded with VR23 were blended with poly (ester-curcumin-urethane) urea to prepare random composite nanofibers with bi-directional modulation. The dressing effectively promoted scarless healing of chronic wounds (187).

In addition to serving as drug carriers, the structural and mechanical properties of nanofiber membranes play a crucial role in scar treatment. One study developed electrospun fibers loaded with naringin. The fibers featured an innovative rounded texture, which effectively minimized HS formation during early wound healing (188). Another biofiber loaded with Pirfenidone exhibited outstanding elongation and toughness, enabling it to effectively treat HS during the established wound healing phase (189).

Clinical treatment of HS has made significant progress fueled by advancements in optoelectronics and novel drug delivery systems, but these emerging technologies still face multiple challenges in practical application. With its non-invasive and minimally invasive characteristics, photofacial technology provides an innovative and promising approach to treating scarring. However, the technical complexity, high equipment costs, and stringent requirements for operator expertise have restricted its widespread adoption. Moreover, the efficacy of photoelectric treatment is often unpredictable due to patient-specific variability, and its long-term effects require further validation. Therefore, reducing treatment costs, improving operational simplicity, and ensuring treatment efficacy have become pressing challenges for the application of photoelectric technology in HS therapy.

On the other hand, novel drug delivery systems offer a more targeted and efficient method of administering drugs for HS therapy. However, the complex preparation processes of these novel delivery systems impose higher requirements on the biocompatibility, targeting, and stability of the materials. Poor biocompatibility may trigger immune responses, while inadequate targeting can result in non-specific drug distribution in normal tissues, raising the risk of side effects. Additionally, the stability of novel delivery systems *in vivo* is a critical determinant of their therapeutic efficacy. Therefore, optimizing the preparation process and enhancing delivery efficiency while ensuring material safety and efficacy have become major challenges for novel drug delivery systems in HS therapy.

6.2 Strategies for targeting macrophages in the treatment of HS

Current treatment of HS focuses on controlling the inflammatory response with steroids and NSAIDs, as well as managing scar tissue through physical interventions such as surgery (190, 191). Although these methods are effective to a certain extent, they still have the limitations of significant side effects and high recurrence rates. Therefore, the development of new treatment modalities is urgently necessary. The role of macrophages in scar formation is gaining attention. Macrophages play a dual role in tissue repair, promoting both the inflammatory response and facilitating tissue remodeling. Therefore, therapeutic strategies targeting macrophages have emerged as a potential approach to mitigate proliferative scar formation. This review will discuss the strategies and prospects of targeting macrophages to treat proliferative scarring from four aspects (Figure 3, Table 2).

6.2.1 Regulation of macrophage polarization

Dysregulation of the macrophage M1/M2 phenotypic transition is one of the major causes of HS formation. Thus, regulating the polarization state of macrophages is expected to inhibit fibroplasia and reduce scar formation. A study used nanogels as carriers to deliver tretinoin and 5-fluorouracil subcutaneously to a rabbit ear HS model. The results showed that this method effectively modulated macrophage phenotypic switching and had an antifibrotic effect, providing a promising therapeutic strategy for HS (192). Other studies have shown that a single dose of a two-layer microneedle system enhances the therapeutic effect against HS. The mechanism may be related to the anti-inflammatory drug dexamethasone, released from the outer layer, which inhibits the polarization of macrophages into a pro-inflammatory phenotype (193). Research by Tianya Li et al. also demonstrated that inhibiting the excessive polarization of M2 macrophages can effectively reduce scar formation (194) (Figure 3A). These findings suggest that therapeutic strategies targeting the modulation of macrophage polarization status have significant potential for preventing and treating HS. This provides new ideas for developing more effective anti-scarring therapies in the future.

6.2.2 Inhibition of macrophage proliferation

Macrophage proliferation and accumulation have been noted as critical factors in the formation of HS (195). Therefore, inhibition of macrophage proliferation is considered a promising therapeutic strategy. Multiple studies have explored the effects of different drugs

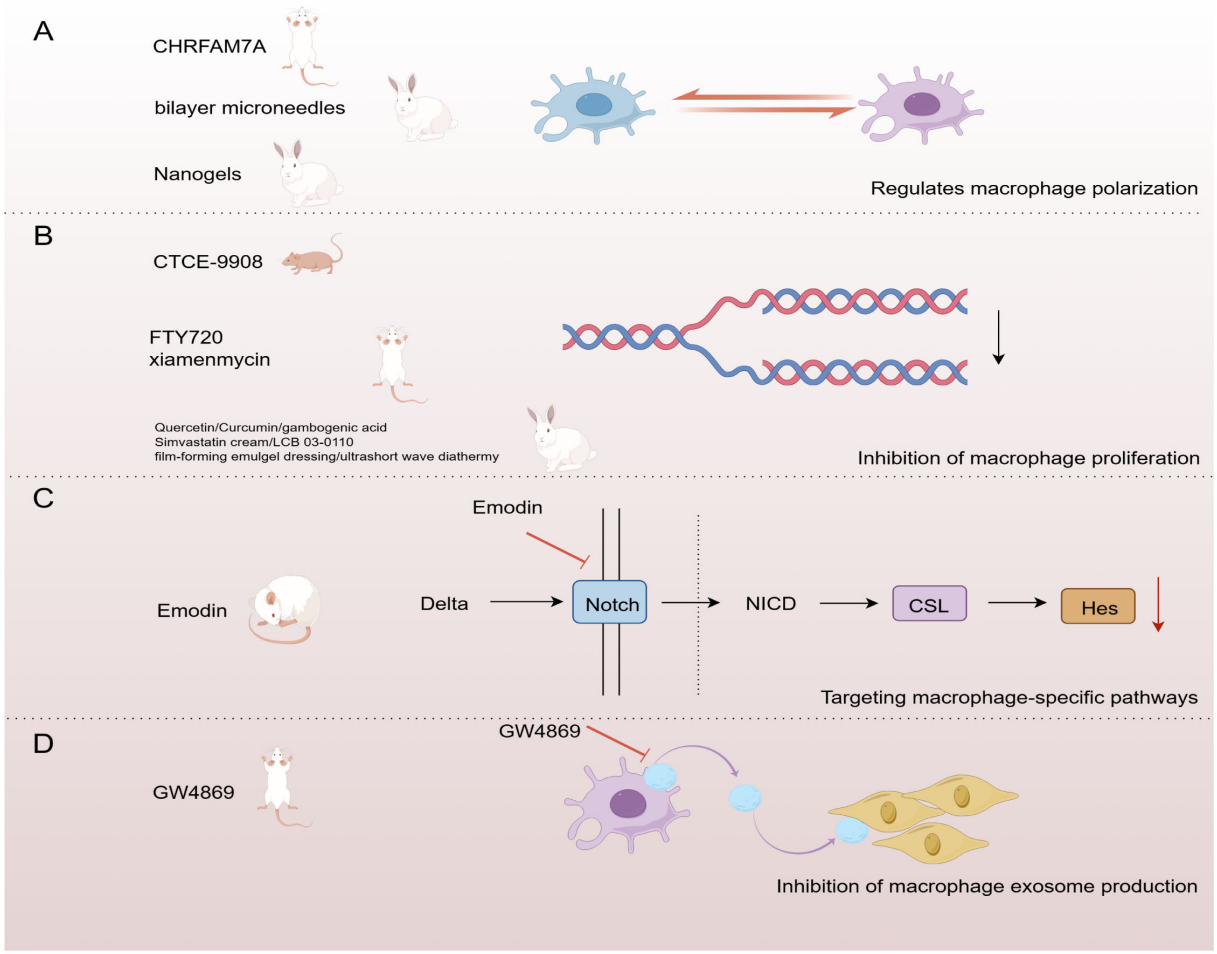

FIGURE 3
Strategies for targeting macrophages in the treatment of HS. **(A)** Regulation of macrophage polarization **(B)** Inhibition of macrophage proliferation **(C)**Targeting macrophage-specific pathways **(D)** Inhibition of macrophage exosome production. (By Figdraw).

on macrophage proliferation and accumulation using a rabbit ear HS model. SFN/ASA-containing gel dressing and quercetin have been shown to inhibit scar formation by reducing macrophage numbers in a rabbit ear HS model (196, 197). In addition, ultrashort-wave hyperthermia reduced the macrophage ratio, while gambogenic acid decreased macrophage infiltration. Both demonstrated significant anti-scarring effects in this model (198, 199). Finally, simvastatin cream, curcumin, and LCB 03-0110 in a rabbit ear HS model also showed that reducing macrophage accumulation significantly inhibited fibrosis (200–202).

In a mechanical force-induced mouse model of HS, FTY720 significantly inhibited scar formation by reducing M2 -dominant macrophages (203). Xiamenmycin showed sound anti-scarring effects in this model by reducing macrophage retention (204) (Figure 3B).

Another study used a nude mouse model of HS generated by human xenografts and found that CTCE-9908 effectively controlled scar formation by reducing macrophage accumulation (205). These studies suggest that HS formation can be effectively controlled by targeting macrophage proliferation and accumulation, providing a new direction for future anti-scarring therapies.

6.2.3 Targeting macrophage-specific pathways

Targeting macrophage-specific pathways is one of the critical strategies for treating HS. The Notch signaling pathway plays a role in dermal fibrosis by regulating fibroblast proliferation and activation, influencing inflammatory responses, and controlling ECM remodeling (206). It was shown that emodin significantly attenuated HS formation in the rat tail by inhibiting macrophage recruitment and polarization, an effect associated with inhibition of the Notch signaling pathway. This study revealed that down-regulation of Notch1, Notch4, and Hes1 could inhibit macrophage polarization and attenuate HS formation (207) (Figure 3C). This suggests that targeting the Notch pathway may be an effective intervention strategy for HS formation.

6.2.4 Inhibition of macrophage exosome production

Therapeutic strategies to inhibit exosome production have shown potential in various diseases, including cancer, neurodegenerative diseases, and cardiovascular diseases (208, 209). GW4869 is a selective neutral sphingomyelinase inhibitor widely used to study the role of exosomes in disease by blocking

TABLE 2 Strategies for targeting macrophages in the treatment of HS.

Modes of action	Drugs/Methods	Model	Mechanisms of action	References
Regulation of macrophage polarization	CHRFAM7A	Mouse HS model of human skin grafts	Modulates macrophage phenotype and attenuates M2 macrophage activation	(194)
	Integrated bilayer microneedles	Rabbit Ear HS Model	Inhibition of macrophage M1 polarization	(193)
	Transdermal Transfersome Nanogels	Rabbit Ear HS Model	Promoting macrophage phenotype switching	(192)
Inhibition of macrophage proliferation	Film-forming emulgel dressing	Rabbit Ear HS Model	Decreased number of macrophages	(196)
	Quercetin	Rabbit Ear HS Model	Decreased number of macrophages	(197)
	Ultrashort wave diathermy	Rabbit Ear HS Model	Reduced macrophage ratio	(198)
	FTY720	Mechanical force induced HS model in mouse	Reduced M2-dominant macrophage frequency	(203)
	CTCE-9908	Nude mouse HS model of human xenografts	Decreased number of macrophages	(205)
	Simvastatin cream	Rabbit Ear HS Model	Reduced macrophage density	(201)
	Curcumin	Rabbit Ear HS Model	Decrease in the number of M2-type macrophages	(200)
	Gambogenic acid	Rabbit Ear HS Model	Reduced macrophage infiltration	(199)
	xiamenmycin	Mechanical force induced HS model in mouse	Decreased number of macrophages	(204)
	LCB 03-0110	Rabbit Ear HS Model	Decreased number of macrophages	(202)
Targeting macrophage-specific pathways	Emodin	Tail HS model in rats	Inhibition of macrophage recruitment and polarization/inhibition of Notch pathway	(207)
Inhibition of macrophage exosome production	GW4869	Mouse wound splint HS model	Blockade of lncRNA-ASLNCS5088-enriched exosome production in M2 macrophages	(155)

their production (210). Studies have shown that GW4869 successfully inhibited the activation of fibroblasts by M2 macrophages by blocking the production of exosomes enriched with the long-chain lncRNA ASLNCS5088 from M2 macrophages. This mechanism was validated in an *in vitro* macrophage-fibroblast co-culture model and a mouse wound splint HS model, demonstrating its potential therapeutic value in inhibiting scar formation (155) (Figure 3D). These findings suggest that inhibition of exosome production may be a new direction for treating HS.

In summary, therapeutic strategies targeting macrophages demonstrate significant potential in managing HS. Modulating macrophage polarization status, inhibiting their proliferation, targeting specific signaling pathways, and inhibiting macrophage exosome production effectively reduce scar formation. Future studies should optimize strategies for targeting macrophages through further research and technological improvements to achieve more effective scar management in clinical practice.

7 Summary and outlook

HS formation is a complex pathological process involving the interaction of multiple cell types and signaling pathways. Macrophages play a key role at different stages as an important part of the innate immune system. This paper reviews the phenotypic changes of macrophages during HS formation, the effects of key signaling molecules on HS, and the potential of macrophages as therapeutic targets, revealing the importance of macrophages in forming and regulating scarring. However, there are still some questions about the role of macrophages in HS.

First, most studies have shown that M1-type macrophages promote the maintenance and expansion of the inflammatory response, while M2-type macrophages drive the formation and remodeling of scar tissue. However, the diverse roles of macrophages in HS are influenced by various factors, including the severity of the condition and variations in disease models. Currently, there is a lack of a standardized model for HS. Therefore, standardizing the methods for HS modeling is necessary to study the role of macrophages in HS better. Our review emphasizes the complex role of macrophages in HS formation, highlighting their dynamic phenotypic changes and their interactions with the scar microenvironment. These findings provide valuable guidance for the development of physiologically relevant and standardized HS models. By simulating the phenotypic changes of macrophages at different stages and their effects on the scar microenvironment, the physiological relevance of HS models and the translational value in preclinical research can be significantly enhanced. This not only

facilitates the study of HS pathophysiological mechanisms but also provides new directions for the evaluation and optimization of emerging therapeutic strategies.

Second, this paper reviews the direct effects of macrophages on HS formation through various signaling molecules. However, macrophage-associated signaling molecules such as TNF-α, IL-6, TGF-β, and IL-10 may play dual roles in different pathological settings. Therefore, further studies on the mechanisms by which macrophage-associated signaling molecules function are necessary.

Third, macrophage-targeted therapies are considered a promising strategy for managing HS due to their critical role in scar formation and remodeling. By precisely regulating macrophage polarization and function, these therapies can reduce scar formation and improve wound healing outcomes. The integration of macrophage-targeted therapies into existing HS management practices has the potential to enhance treatment efficacy. For instance, combining macrophage-targeted therapies with laser therapy or novel delivery systems can provide more precise, localized, and sustained therapeutic effects while minimizing the systemic side effects commonly associated with traditional treatments. However, successful clinical application still requires addressing individual variability in patient responses, challenges related to cost-effectiveness and affordability, and rigorous clinical trials to validate their efficacy and safety. Overall, targeting macrophages is expected to be a new and effective therapeutic strategy for preventing HS.

Author contributions

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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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Spesolimab in generalized pustular psoriasis complicated by acrodermatitis continua of Hallopeau: a case report and mechanistic insights

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A 62-year-old Chinese woman presented to the hospital for help with generalized pustular psoriasis (GPP) and acrodermatitis continua of Hallopeau (ACH). While conventional treatments failed to achieve significant improvement, the patient received two doses of spesolimab, and the effect was remarkable. No adverse reactions were observed in the follow-up period.

KEYWORDS

spesolimab, generalized pustular psoriasis, acrodermatitis continua of Hallopeau, IL-36 pathway, IL-1

Highlights

- A patient who suffered from generalized pustular psoriasis (GPP) coexisting with acrodermatitis continua of Hallopeau (ACH) exhibited no significant clinical improvement following conventional therapies, however, an effect was observed in the patient after the injection of spesolimab for the first time and signs and symptoms were quickly brought under control.
- Spesolimab, by directly blocking the receptor with a therapeutic antibody, is the first biologic agent that works via the IL-36 pathway, which is associated with the pathogenesis of GPP. Thus, spesolimab delivers more precise treatment.
- The patient remained free of adverse reactions during the post-treatment observation period until 10 March 2025.
- There are few reports about the use of spesolimab in patients with ACH coexisting with GPP. Our report provides a case reference for such patients, which has practical significance.

Introduction

Generalized pustular psoriasis (GPP) is an uncommon and intractable variant of the disorder characterized by diffuse erythematous rashes and recurrent pustular flares (1). It is hard to treat this disease because of a paucity of reliably efficacious therapeutics. It has been indicated that the interleukin (IL)-36 pathway plays an important role in the occurrence and development of this disease (2). Thus, IL-36 receptor antagonists are emerging as a promising therapy for pustular psoriasis, providing a rapid and efficacious response. Herein we share our experience with spesolimab in a Chinese patient with GPP and acrodermatitis continua of Hallopeau (ACH) who was heavily treated with other common methods with poor response.

Case report

A 62-year-old female patient presented to our department in August 2024 with the symptom of a generalized pustular eruption that appeared 20 days previously. The patient had a past medical history of ACH for 16 years. The rash of the patient progressed rapidly, with severe skin tenderness. She was admitted to the inpatient department. At the time of hospital admission, the symptoms of ACH remained persistent.

The physical examination was notable for widespread, red plaques studded with pustules, many coalescing into broad areas of erythema, scaling, and pustules on the trunk and extremities. Swelling and deformity could be observed in the finger joints and toe joints. The nails and toenails were deformed, and there were

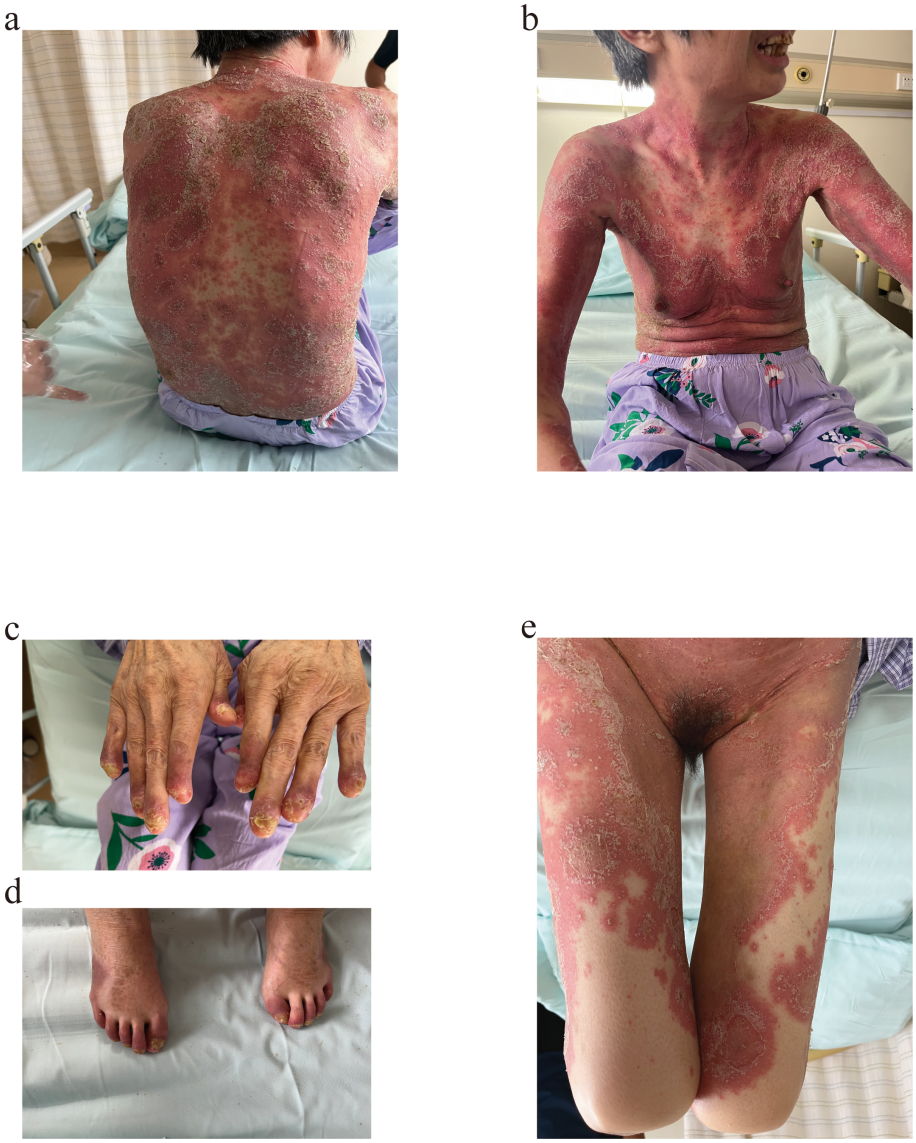

FIGURE 1
Skin lesions of the patient at first admission, the lesions manifest as erythematous plaques covered with pustules, with extensive confluence leading to widespread erythema, scaling, and pustular lakes. Nail plates are dystrophic, showing subungual pustules. **(a, b)** Trunk. **(c, d)** Distal extremities. **(e)** Perineum and bilateral lower limbs.

pustules under the nail plate and tenderness on the skin, which was especially obvious when walking (Figure 1). Standardized scoring systems were utilized to assess disease severity. The score for Pustular Psoriasis Area and Severity Index (GPPASI) was 64.8, Nail psoriasis Area and Severity Index (NPASI) was 8, Dermatology Quality of Life Index (DLQI) was 30, BSA was 80%, and Pustular Psoriasis Physician's Global Assessment (GPPGA) was 4.

A complete study was performed with blood and skin cultures. No evidence of infectious diseases, such as syphilis and human immunodeficiency virus (HIV), was found by blood testing. Leukocytosis and neutrophilia with elevated phase reactants were revealed. There was no specific abnormality in the results of her echocardiogram and a body CT scan. Skin biopsies were reported as diagnostic for pustular psoriasis (Figure 2). Microbiological samples were negative.

The diagnosis of GPP was definitively established based on the patient's medical history, clinical presentation, and histopathological findings. The patient was administered polyene phosphatidylcholine, aminopeptide, and acitretin for 1 month, however, the medication treatment failed to achieve a significant improvement. In order to further improve the patient's health, she was treated with a single intravenous infusion of 900mg of spesolimab. A remarkable response to spesolimab with an almost complete resolution of pustules in 6 hours in the patient was observed. There were no adverse reactions in the follow-up period. After 2 weeks, at the patient's follow-up in an outpatient dermatology clinic, there were no visible lesions but patchy pigmentation. Another 2 weeks later, the patient was readmitted to the hospital for treatment with spesolimab in order to consolidate the effects and prevent GPP recurrence (Figure 3). During the 6-month follow-up period, no recurrence was observed, and no adverse events were reported. The long-term efficacy still needs further observation.

Discussion

As an autoinflammatory skin disease, the notable features of GPP are eruption of sterile pustules with or without severe systemic symptoms, such as organ failure and sepsis. ACH, a rare dermatological disorder, presents as a sterile pustular eruption localized to one or more digits and is characterized by a chronic clinical progression. In terms of classification, ACH is classified as a localized pustular psoriasis (3). ACH demonstrates a characteristically chronic and treatment-resistant clinical course, with spontaneous remission seldom documented in medical literature (4). It is difficult to achieve significant results in both of these diseases with treatment.

GPP coexisting with ACH is hard to treat because the condition is so rare, resulting in an absence of standardized treatment guidelines. Current therapeutic strategies for ACH largely mirror those employed for other psoriasis subtypes, reflecting shared pathogenic mechanisms within the psoriasis spectrum (5). Methotrexate, cyclosporine, and acitretin are systemic drugs commonly used in GPP and ACH. However, the effects of these treatments are often not significant and can be associated with a multitude of adverse effects, including hypertension, renal toxicity, and teratogenicity (6), and patients often relapse.

A lack of extremely effective therapies poses serious challenges for GPP and ACH management for physicians. The fundamental reason is that the etiology of GPP and ACH remains to be fully elucidated. The development of GPP and ACH is complex, and there is a significant overlap in the pathogenic mechanisms between GPP and ACH. The IL-36 pathway has been identified to play a key role in the pathogenesis of the disorder (7). GPP and ACH may occur due to overexpression of IL-36 and the loss-of-function mutation in the IL-36 receptor antagonist (IL-36RA), which leads to increased levels of pro-inflammatory cytokines and activation of IL-36 receptors in skin cells (8–10). IL-36RN, a negative regulator of the IL-36 pathway, encodes the IL-36RA, and in some sporadic and familial cases of GPP, an IL36RN gene mutation has been detected (1, 11, 12), mainly in those not associated with plaque psoriasis (PP). Thus, anti-IL-36R drugs, such as spesolimab, can be effective in treating GPP coexisting with ACH. Spesolimab is a humanized monoclonal antibody that inhibits the ability of IL-36 to bind and initiate proinflammatory cascades by blocking the IL-36 receptor (6). Treatment guidelines have indicated that the recommended grade for IL-36 receptor antagonists, such as spesolimab, is C. Spesolimab has had the broadest clinical development with five phase-I and three phase-II trials. In phase I, spesolimab completed clearance at week 4, and this was maintained at week 12 regardless of the presence of IL36RA mutation (2), which proved good efficacy. In phase II, 54% of patients were free of pustules at week 1, and 60% had complete clearance after

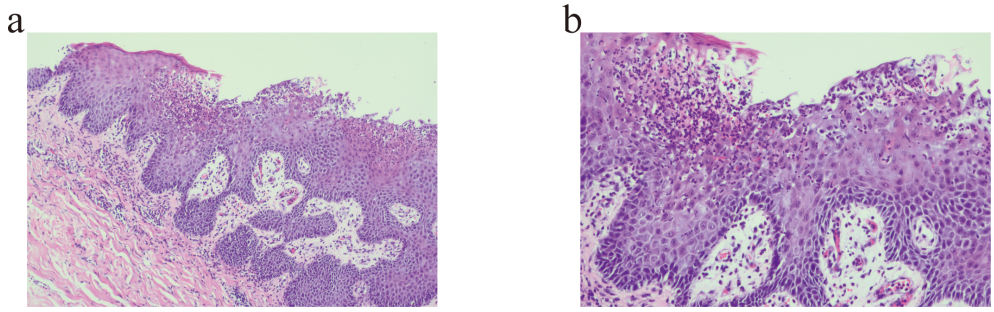

FIGURE 2
Pustule formation was observed in the epidermis, and numerous neutrophil infiltrations were observed. **(a)** Haematoxylin and eosin, original magnification ×100. **(b)** Haematoxylin and eosin, original magnification ×200.

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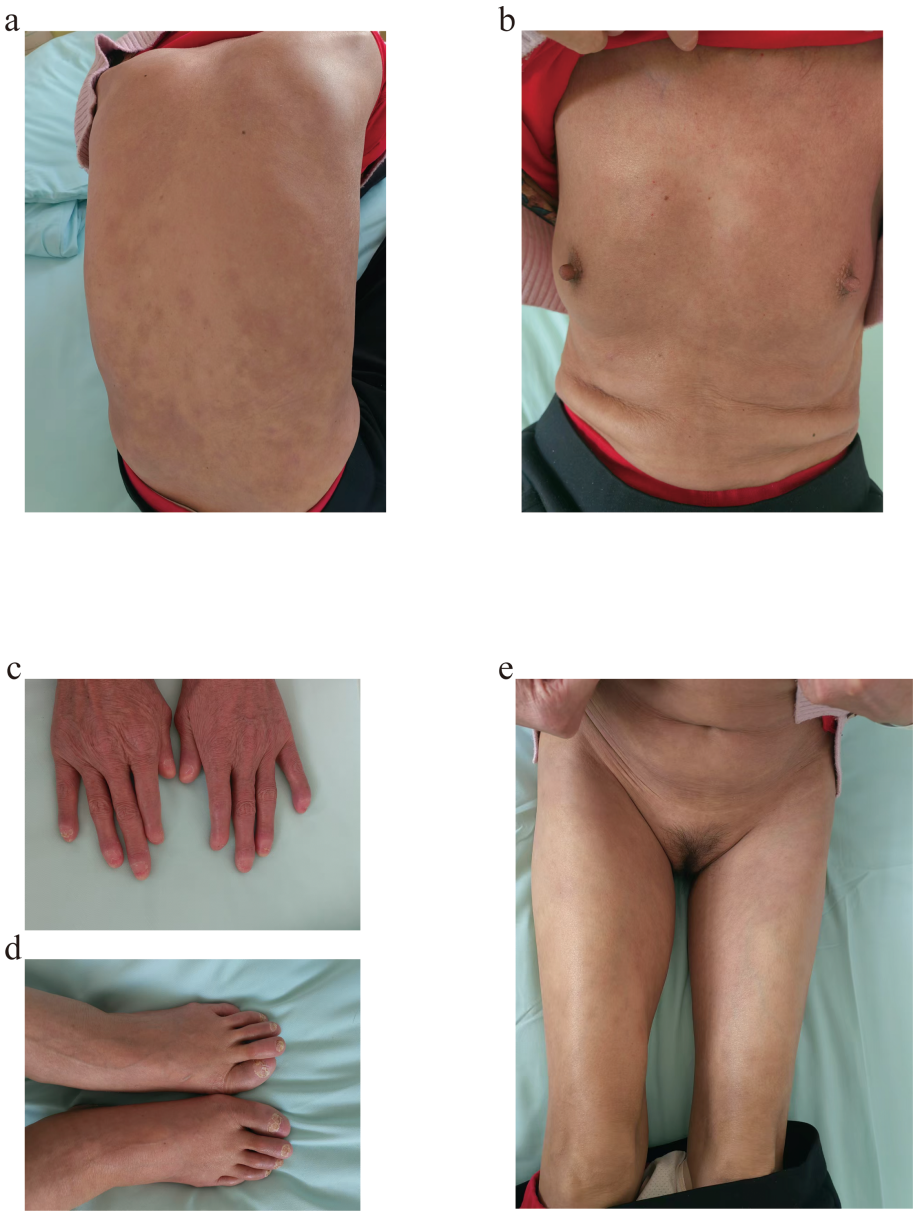

FIGURE 3
Before using Spesolimab for the second time,notable resolution of the skin lesions was documented. **(a, b)** Trunk. **(c, d)** Distal extremities. **(e)** Perineum and bilateral lower limbs.

1–2 doses, with some patients having a complete clearance in less than 24 h. Furthermore, a sustained response and a favorable safety profile were found at week 12 of treatment (13). In previous reports, most of the patients using spesolimab achieved the desired treatment results, however, a small number of patients showed adverse drug reactions. Common adverse reactions are rash, nasopharyngitis, headache, and acne (14).

Although our study highlights the central role of IL-36 signaling in this patient, the interplay between the IL-1 and IL-36 pathways in GPP pathogenesis merits attention. The release of excessive amounts of IL-1 and IL-36 results in an inflammatory response in the skin, which leads to the development of pustules in pustular psoriasis. Targeted therapies, such as IL-1 antagonists, have demonstrated definitive efficacy in improving the prognosis of pustular eruptions following COVID-19 vaccination (15). However, further research is required to elucidate the mechanistic interplay between IL-1 and IL-36 in pustule formation, thereby providing critical insights to guide future investigative directions.

Although there have been many cases of spesolimab treating GPP, there are few reports on the use of spesolimab in GPP coexisting with ACH. The patient in this case report suffered from GPP with ACH for a long period of time. She received many treatments; however, clinical improvement was not remarkable. An effective manifestation was observed in the patient after the injection of spesolimab for the first time. Her signs and symptoms were quickly brought under control, the rash

disappeared except for the lesions on the fingers and toes, and no adverse effects were observed. We evaluated the disease severity again after the first treatment with spesolimab, and the score of GPPASI was 0, NPASI was 4, DLQI was 5, BSA was 0, and GPPGA was 0. To improve the treatment effect, she received the treatment with spesolimab again after 1 month; however, the long-term benefit of the therapy needs further observation, including safety and tolerability profile.

Conclusion

When a generalized pustular eruption emerges, the diagnosis of GPP should be considered. This case highlights the efficacy of IL-36 inhibitors, such as spesolimab, for GPP coexisting with ACH. The approach of targeting proinflammatory cytokines not only shows a rapid and effective response but also minimizes the adverse effects. This is a potential treatment modality that should be considered when other treatments are not effective.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

X-YH: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing, Data curation, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Writing – original draft. H-LX: Data curation, Investigation, Writing – original draft. J-YW: Data curation, Investigation, Writing – original draft. JZ: Investigation, Writing – original draft, Data curation. BR: Investigation, Writing – original draft, Data curation. C-cN: Investigation, Writing – original draft, Data curation. F-FL: Investigation, Writing – original draft, Data curation. BL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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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Clinical efficacy and safety of acupuncture in the treatment for chronic spontaneous urticaria: a systematic review and meta-analysis

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Objective: This study aims to systematically evaluate the clinical efficacy and safety of acupuncture in treatment for chronic spontaneous urticaria (CSU) and provide evidence to inform clinical decision-making.

Methods: A comprehensive search of eight Chinese and English databases was carried out. The search period spanned from the inception of the database up to 20 August 2024, and the search included randomized controlled trials (RCTs) on acupuncture for CSU, without language restrictions. Two independent researchers screened the resulting studies, evaluated their quality, and cross-checked their results. The extracted data were subjected to meta-analysis using RevMan 5.4 and Stata 15.

Results: A total of 22 RCTs involving 1,867 patients were included. Meta-analysis showed that acupuncture significantly improved the overall response rate, reduced the recurrence rate, decreased the urticaria activity score, and improved the Dermatology Life Quality Index, Hamilton Depression Scale, VAS itching score, and the Chronic Urticaria Quality of Life Questionnaire scores. Acupuncture also resulted in a reduced number and size of wheals, shortened duration of flare-ups, and reduced serum IgE, IFN-γ, and IL-4 levels. In addition, it led to significantly reduced traditional Chinese medicine syndrome scores, all with statistical significance. Furthermore, acupuncture did not significantly increase the incidence of adverse events, which indicates good safety. However, moderate to high bias and heterogeneity were observed in the included RCTs. Based on the Grading of Recommendations, Assessment, Development, and Evaluation evidence, this study provides a moderate to low recommendation for acupuncture in the treatment for CSU although the results remain promising.

Conclusion: Acupuncture appears to be an effective and safe treatment for CSU. However, further high-quality RCTs are needed to confirm its clinical efficacy and safety.

KEYWORDS

acupuncture, chronic spontaneous urticaria, urticaria, meta-analysis, systematic review

1 Introduction

Urticaria (1) is a common dermatological condition that is primarily driven by mast cells (MCs) and characterized by wheals of varying sizes and associated itching. If these wheals appear intermittently or daily for more than 6 weeks, the condition is diagnosed as chronic spontaneous urticaria (CSU). The prevalence of CSU in China is approximately 0.75%, with women being affected twice as likely as men (2). The pathogenesis of CSU is complex, with frequent relapses, severely impairing the quality of life of patients. Unlike other forms of urticaria, CSU occurs spontaneously without requiring physical or inducible triggers such as temperature changes, pressure, and exercise (3). According to national and international guidelines (1, 2), first-line treatment for CSU involves initiating standard doses of second-generation non-sedating H1 antihistamines (sgAH), with recommendations for dose escalation if an inadequate response is observed. However, despite the overall safety profile of sgAH (e.g., loratadine and cetirizine), mild fatigue or drowsiness may still occur in some patients during long-term management of CSU (4). To improve treatment adherence and address individualized needs, acupuncture therapy and other traditional Chinese medicine (TCM) interventions have emerged as valuable complementary methods in recent years. Recent studies suggest that acupuncture may modulate humoral and cellular immunity, regulate multiple signaling pathways, inhibit MC activation, and modulate gene expression and resting-state brain function, thus reducing allergic responses and alleviating itching symptoms (5, 6). Thus, acupuncture is considered a potential alternative therapy for CSU. However, the efficacy and safety of acupuncture in the treatment for CSU remain unclear, which warrants an updated and comprehensive systematic review. This review aims to systematically analyze the existing literature and conduct a meta-analysis to evaluate the efficacy and safety of acupuncture in the treatment for CSU and provide reliable evidence for clinical practice.

2 Materials and methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered on PROSPERO (CRD42024557552), titled "The efficacy and safety of acupuncture for chronic spontaneous urticaria: A systematic review and meta-analysis of randomized clinical trials."

2.1 Literature search

A comprehensive search of both Chinese and English databases was conducted to identify randomized clinical trials (RCTs) investigating acupuncture treatment for CSU. Chinese databases included CNKI, VIP, WanFang, and CBMDisc, whereas English databases included PubMed, Cochrane Library, Embase, and Web of Science. The search period spanned from the inception of each database until 20 August 2024, with no language restrictions. Additional searches of reference lists and grey literature were carried out to avoid missing relevant studies. Chinese search terms included "针刺" (acupuncture), "针灸" (acupuncture), "皮肤针" (dermal needling), "荨麻疹" (urticaria), and "随机对照试验" (randomized controlled trial). English search terms included "Acupuncture," "Urticarias," and "Urticarial Wheals." Both subject terms and free-text terms were used in the search strategies, which were adapted to the characteristics of each database. A cross-search was performed to avoid omissions. For example, the search strategy for PubMed is shown in Table 1, with additional search strategies provided in Supplementary material 1.

2.2 Inclusion and exclusion criteria (PICOS principle)

The inclusion and exclusion criteria for this study were based on the PICOS principle:

1. Study type: This systematic review and meta-analysis included RCTs in which acupuncture was the sole intervention. Non-randomized trials, observational studies, clinical protocols, animal experiments, case reports, and expert opinions were excluded. In the case of duplicate publications, only one study was included.
2. Participants: The participants were required to be diagnosed with CSU according to established international or domestic guidelines or expert consensus. There were no restrictions on nationality, ethnicity, gender, and age. However, patients in the acute phase or with severe liver, kidney, cardiovascular, cerebrovascular, or immune system diseases were excluded.
3. Interventions: The intervention in the treatment group was acupuncture as the primary therapy, with no restrictions on acupuncture type, course of treatment, acupoint selection, and frequency. Studies involving acupuncture, together with point injection, thread embedding, or non-acupuncture treatments such as oral medications, were excluded. Control group interventions included standard clinical medications, sham acupuncture, or placebo.
4. Outcome measures: The primary outcome measures included clinical efficacy, recurrence rate, TCM symptom scores, clinical symptom improvement, immune indicator changes, and adverse events, with the aim of evaluating the effectiveness and safety of acupuncture in the treatment for CSU.

TABLE 1 PubMed search strategy.

Steps	Retrieval formula
#1	"Acupuncture"[Mesh] OR "Pharmacopuncture"[All Fields]
#2	"Urticaria"[Mesh] OR "Urticarias"[All Fields] OR "Hives"[All Fields] OR "Urticarial Wheals"[All Fields] OR "Urticarial Wheal"[All Fields] OR "Wheals, Urticarial"[All Fields] OR "Wheal, Urticarial" [All Fields]
#3	"Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [All Fields] OR "Clinical Trial" [All Fields] OR "Clinical Study" [All Fields] OR "Randomized" [All Fields]
#4	#1 AND #2 AND #3

2.3 Literature screening

All studies retrieved from Chinese and English databases were input into EndNote 20 for automatic deduplication. Two researchers independently screened the deduplicated studies. Initially, titles and abstracts were reviewed, and then, the full text of potentially eligible studies was further assessed. Reasons for exclusion were recorded, and any disagreements were resolved through discussion or adjudicated by a senior researcher. The screening results were cross-checked.

2.4 Data extraction

Two researchers independently extracted data from the included studies using a predefined extraction form. The extracted data included: (1) basic information: first author and publication year; (2) participant characteristics; (3) intervention details and treatment duration; (4) key factors related to the risk of bias; and (5) primary outcome data. If the required data were missing or unclear, the researchers attempted to contact the original authors or retrieve Supplementary information from the original studies.

2.5 Risk of Bias assessment (ROB2 tool)

The Risk of Bias 2 (ROB2) tool provided by the Cochrane Collaboration was used to assess the risk of bias in the included studies. The following six domains were evaluated: (1) bias in the randomization process; (2) bias due to deviations from intended interventions; (3) bias in outcome measurement; (4) bias due to missing outcome data; (5) bias in the selection of reported results; and (6) overall bias. Each study was categorized as having low, moderate, or high risk of bias based on these criteria.

2.6 Grading of Recommendations, Assessment, Development, and Evaluation

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence for each outcome. The evidence was rated as high, moderate, low, or very low. Factors considered in the GRADE assessment included risk of bias, imprecision, inconsistency, indirectness, and publication bias.

2.7 Statistical methods

Meta-analysis was performed using RevMan 5.4 and Stata 15. To ensure broader applicability of acupuncture in various populations, heterogeneity was tested using the I^2 statistic. An I^2 value of less than 50% indicated low heterogeneity, in which case a fixed-effects model was used. For I^2 values greater than 50%, indicating high heterogeneity, a more conservative random-effects model was applied. If there was significant clinical heterogeneity, sensitivity analyses and subgroup analyses were conducted to assess the stability of the results. Dichotomous outcomes used relative risk (RR) as the effect measure, whereas continuous outcomes used weighted mean difference. If different measurement scales were used, standardized mean difference (SMD) was used, all reported with 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Publication bias was assessed using funnel plots and Egger's test in Stata 15.

3 Results

3.1 Characteristics of the included studies

A total of 1,591 articles were initially identified, of which 449 duplicates were excluded. After screening titles and abstracts, 1,067 studies were further excluded as they were case reports, experimental studies (e.g., animal or cell studies), reviews, or meta-analyses, which did not align with the study interventions. After full-text review, 53 articles were further excluded as they were non-RCTs, lacked full text, or did not meet the inclusion criteria. A total of 1,569 articles were excluded. Finally, 22 studies (7–28) were included, with 20 published in Chinese (7–26) and 2 in English (27, 28). The detailed information on the literature search and selection process is presented in Figure 1, with the PRISMA flow diagram being provided in Supplementary material 2.

A total of 1,867 participants were included in the final statistical analysis, with 948 in the treatment group and 919 in the control group. The age range was 14–72 years, and the ratio of men to women was approximately 1:1.54. The overall mean age was 38.27 ± 3.56 years, with a mean age of 38.15 ± 3.71 years in the treatment group and 38.15 ± 3.71 years in the control group. All studies reported no statistically significant differences in baseline characteristics between the treatment and control groups (all $p > 0.05$), indicating that the groups were comparable. The diagnostic criteria in all studies adhered to the EAACI/GA2LEN/EDF/WAO Guideline for the Diagnosis and Management of Urticaria and the Chinese Guideline for the Diagnosis and Treatment of Urticaria (1).

3.2 Results of literature quality assessment

The included studies were subjected to the risk of bias assessment. Regarding bias in the randomization process, all 22 studies were RCTs. Four studies (7, 11, 17, 23) used random envelope allocation, eight studies (16, 18–21, 26–28) generated random sequences using a random number table, nine studies (9, 10, 12, 14, 15, 22, 24, 25, 29) mentioned randomization without specifying the method used, and one study (8) did not mention the randomization method. In terms of allocation concealment and blinding, due to the nature of the intervention, it was nearly impossible to blind the practitioners. However, five studies (11, 25–28) followed blinding of participants and assessors and concealed the allocation scheme.

Regarding incomplete outcome data, 13 studies (7, 10, 12–17, 19–22, 24) reported no loss to follow-up, with complete data sets, whereas nine studies (8, 9, 11, 18, 23, 25–28) reported a total of 22 dropouts in the experimental group and 44 dropouts in the control group (Figure 2).

3.3 Meta-analysis results

3.3.1 Efficacy rate

Seventeen RCTs (7–17, 19–22, 24, 26) involving a total of 1,344 patients were included in the analysis of efficacy rate. All studies

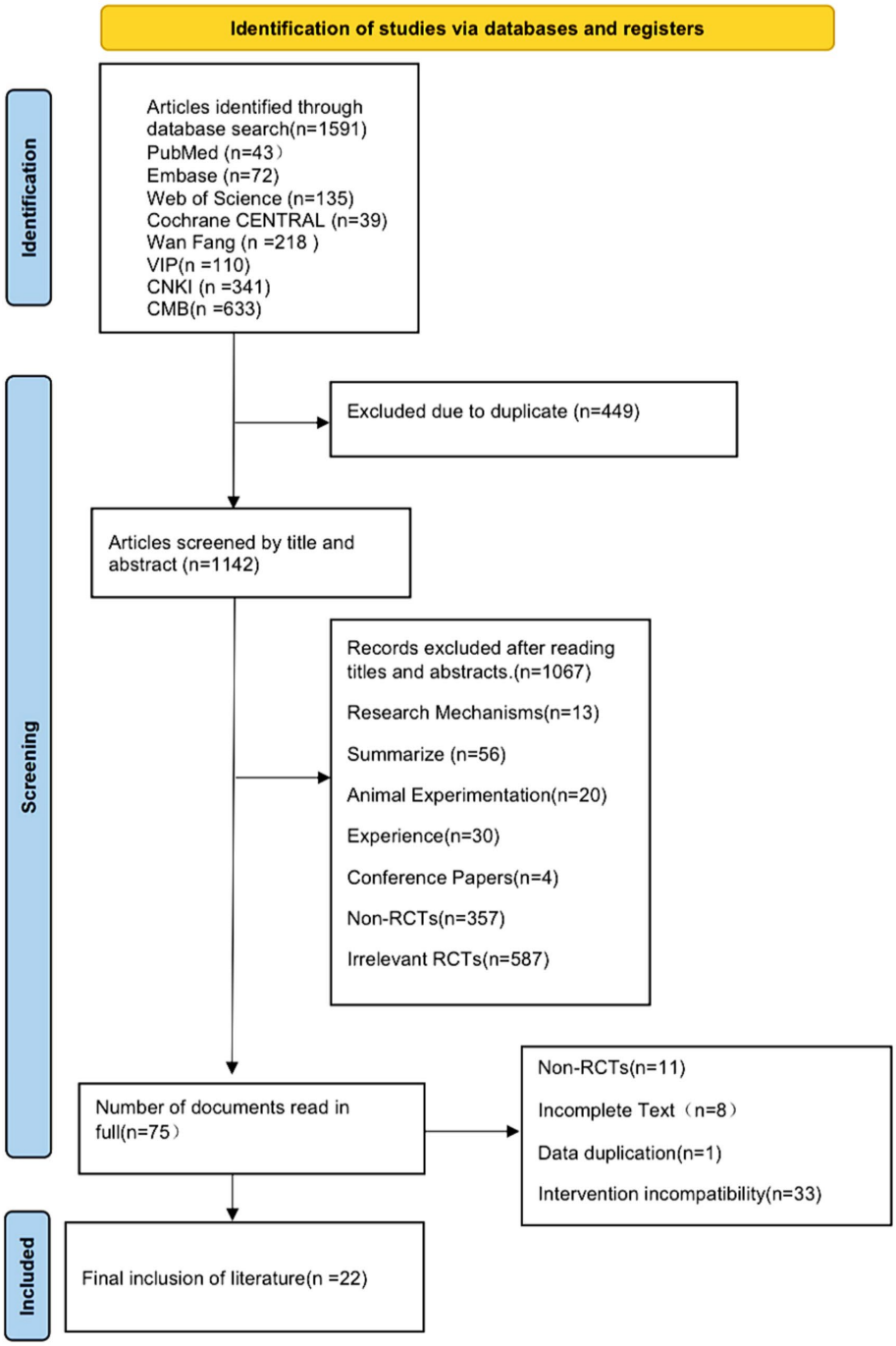

FIGURE 1
Flowchart of literature.

followed the "Guideline for the Diagnosis and Treatment of Urticaria" from the Chinese Society of Dermatology (30). A heterogeneity test was conducted ($chi^2 = 22.57$, $p = 0.13$, and $I^2 = 29\%$), which indicated low heterogeneity. Thus, a fixed-effects model was used for meta-analysis. The results showed a statistically significant difference in the efficacy rate favoring acupuncture over conventional treatment (oral Western medicine) and sham acupuncture groups [RR = 1.20, 95% CI (1.15, 1.26), $p < 0.001$], suggesting that acupuncture was more effective in treating CSU (Figure 3). Publication bias was evaluated using a funnel plot, which appeared roughly symmetrical on both sides (Figure 4). Egger's test was conducted for further quantification ($t = 3.11$, $p = 0.007$), which indicated the presence of some publication bias (for details on Egger's test for efficacy rate data, refer to Supplementary material 3, Egger's test 1.2). Sensitivity analysis (Figure 5) showed that the structure of the included studies remained stable (Table 2).

In the subgroup meta-analysis based on different control interventions, efficacy rate data were categorized into three

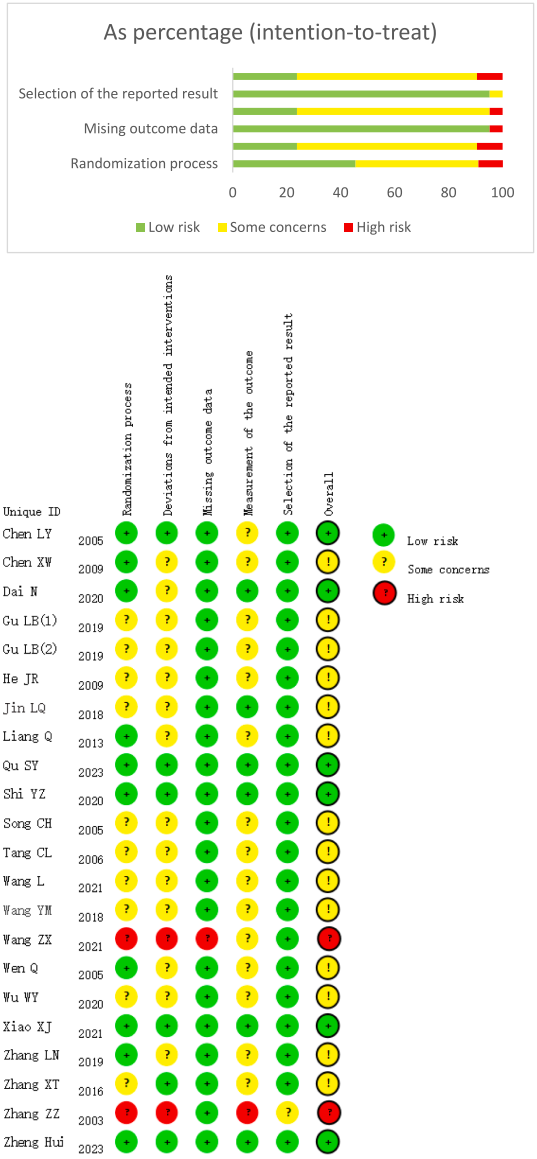

FIGURE 2
(A) Quality of detailed articles. **(B)** Quality of overall articles.

subgroups: acupuncture versus loratadine, acupuncture versus cetirizine, and acupuncture versus cimetidine and chlorpheniramine. Acupuncture vs. loratadine: This subgroup included 14 studies (7, 9–12, 14–22). No heterogeneity was observed in these studies ($chi^2 = 8.49$, $p = 0.78$,$I^2 = 0\%$). The combined results indicated a statistically significant difference in favor of acupuncture [RR = 1.20, 95% CI (1.14, 1.27), $p < 0.001$]. Acupuncture vs. cetirizine: This subgroup included only two studies (8, 13). Heterogeneity was observed ($chi^2 = 4.12$, $p = 0.04$, $I^2 = 76\%$). The combined results also showed a statistically significant difference in favor of acupuncture [RR = 1.20, 95% CI (1.14, 1.27), p < 0.001]. Acupuncture vs. cimetidine and chlorpheniramine: This subgroup had only one study (24), and a qualitative analysis was conducted. The results showed a statistically significant difference [RR = 1.58, 95% CI (1.09, 2.27), $p = 0.01$] (Figure 6). These results indicate that acupuncture is more effective than these conventional treatments across all subgroups although the level of heterogeneity varied between them (Table 3).

A subgroup analysis based on the duration of treatment was also conducted. A total of 15 RCTs were included, with 10 studies (7, 10, 11, 13–17, 22, 24) having a treatment duration of ≤4 weeks and five studies (12, 18–21) with a treatment duration of >4 weeks. In the subgroup with a treatment duration of ≤4 weeks, low heterogeneity was observed ($chi^2 = 17.60$, $p = 0.04$, $I^2 = 49\%$). The combined analysis showed a statistically significant difference favoring acupuncture [RR = 1.20, 95% CI (1.12, 1.27), $p < 0.001$]. In the subgroup with a treatment duration of >4 weeks, no heterogeneity was observed ($chi^2 = 2.54$, $p = 0.64$, $I^2 = 0\%$). The combined analysis also showed a statistically significant difference favoring acupuncture [RR = 1.23, 95% CI (1.13, 1.33), $p < 0.001$] (Figure 7). These results indicate that acupuncture is effective regardless of the treatment duration, with slightly better outcomes observed in the subgroup with a treatment duration of >4 weeks.

3.3.2 Recurrence rate

Five studies (11, 14, 16, 18, 21) involving 247 patients were included in the analysis of recurrence rates (urticaria relapse post-intervention withdrawal). A heterogeneity test was conducted ($chi^2 = 3.49$, $p = 0.48$, $I^2 = 0\%$), which showed low heterogeneity. Therefore, a fixed-effects model was used for meta-analysis. The results showed a statistically significant difference favoring acupuncture in reducing recurrence rates compared with the control group treated with loratadine [RR = 0.33, 95% CI (0.20,0.53), $p < 0.001$], suggesting that acupuncture is associated with a lower recurrence rate for CSU (Figure 8). The funnel plot appeared symmetrical, and Egger's test showed no significant publication bias ($t = -0.21$, $p = 0.845$) (for details on the funnel plot and Egger's test, refer to Supplementary material 3).

3.3.3 Urticaria activity score

A total of nine studies (8, 11, 14, 16, 21, 25–28) involving 728 patients reported urticaria activity score (UAS7) scores. A heterogeneity test was conducted ($chi^2 = 421.34$, $p < 0.001$, $I^2 = 98\%$), which indicated significant heterogeneity. Therefore, a random-effects model was used for meta-analysis. The combined results showed a statistically significant difference favoring acupuncture [mean difference (MD) = −3.30, 95% CI (−5.26, −1.34), $p = 0.001$], indicating that acupuncture resulted in a higher reduction in UAS7 scores than oral loratadine, cetirizine, or sham acupuncture, which indicated the better efficacy of acupuncture in reducing urticaria activity (Figure 9). The funnel plot appeared symmetrical, suggesting no significant publication bias, and Egger's test further confirmed the same (t = −1.28, $p = 0.243$) (for details on the funnel plot and Egger's test, refer to Supplementary material 3, UAS7 Funnel plot 1 and Egger's test 1.2).

Using UAS7 as an indicator, a subgroup analysis was conducted based on different control interventions: acupuncture vs. loratadine, acupuncture vs. cetirizine, and acupuncture vs. sham acupuncture. Acupuncture vs. loratadine: Four studies (11, 14, 16, 21) were included. This subgroup showed significant heterogeneity ($chi^2 = 42.73$, $p < 0.001$, $I^2 = 93\%$). The combined analysis indicated a statistically significant difference favoring acupuncture [MD = −1.63, 95% CI (−3.10, −0.16), $p = 0.03$]. Acupuncture vs. cetirizine: Only one study (8) was included in this subgroup. A qualitative analysis was

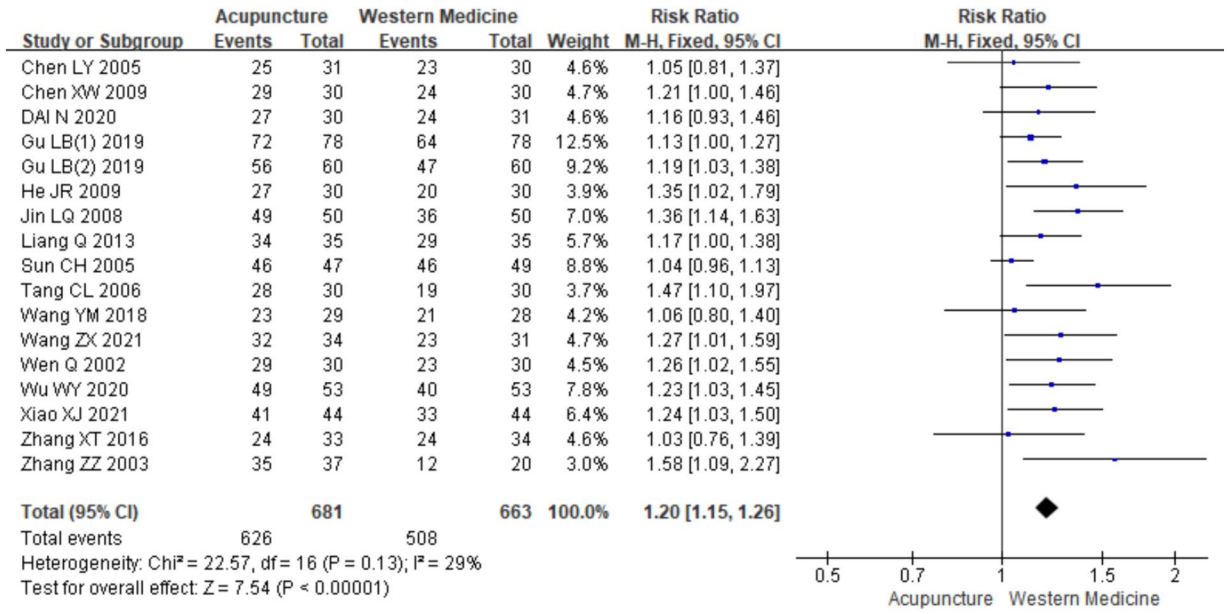

FIGURE 3
Forest plot of efficiency.

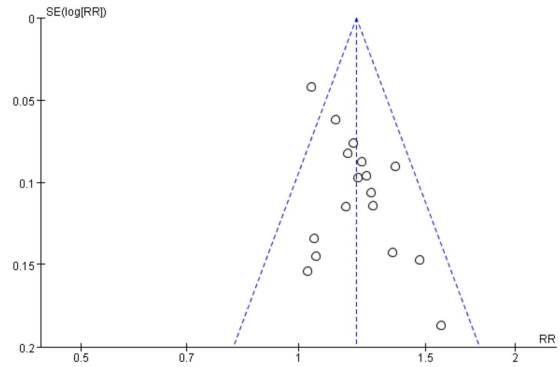

FIGURE 4
Funnel plot of efficiency.

performed, showing a statistically significant difference favoring acupuncture [MD = −0.89, 95% CI (−1.52, −0.26), $p < 0.001$]. Acupuncture vs. sham acupuncture: Four studies (25–28)were included in this subgroup, which also showed significant heterogeneity ($chi^2 = 42.73$, $p < 0.001$, $I^2 = 93\%$). The combined results revealed a statistically significant difference favoring acupuncture [MD = −5.45, 95% CI (−8.44, −2.46), $p < 0.001$] (Figure 10). Despite the positive findings, high heterogeneity persisted after subgroup analysis, indicating that other factors may contribute to the variability in results. Further investigation is needed to identify the sources of this heterogeneity.

3.3.4 Dermatology life quality index

A total of six studies (8, 16, 19, 25, 26, 28) involving 504 patients reported Dermatology Life Quality Index (DLQI) scores. Heterogeneity testing showed significant heterogeneity ($chi^2 = 46.53$, $p < 0.001$, $I^2 = 89\%$). Therefore, a random-effects model was used for meta-analysis. The combined results revealed a statistically significant difference favoring acupuncture, with acupuncture showing lower DLQI scores than loratadine, cetirizine, and sham acupuncture [MD = −3.78, 95% CI(−5.19, −2.36), $p < 0.001$], indicating that acupuncture resulted in a greater improvement in quality of life in patients with CSU (Figure 11). A funnel plot assessment for publication bias showed symmetry on both sides. Further analysis using Egger's test indicated no significant publication bias ($t = 1.12$, $p = 0.293$) (refer to Supplementary material 3 for DLQI funnel plot 1 and Egger's test 1.2).

Based on control group interventions, a subgroup analysis was conducted, categorizing the studies into three groups: acupuncture vs. loratadine, acupuncture vs. cetirizine, and acupuncture vs. sham acupuncture. Acupuncture vs. loratadine: This subgroup included two studies (16, 19). Significant heterogeneity was observed in this subgroup ($chi^2 = 5.36$, $p = 0.02$, $I^2 = 81\%$). The combined analysis showed a statistically significant difference favoring acupuncture, with lower DLQI scores [MD = −4.78, 95% CI (−8.46, −1.11), $p = 0.01$]. Acupuncture vs. cetirizine: Only one study (8) was included in this subgroup. A qualitative analysis was performed, which showed a statistically significant difference favoring acupuncture [MD = −1.69, 95% CI (−2.84, −0.54), $p < 0.001$]. Acupuncture vs. sham acupuncture: This subgroup included three studies (25, 26, 28). Significant heterogeneity was observed ($chi^2 = 14.14$, $p < 0.001$, $I^2 = 86\%$). The combined results revealed a statistically significant difference favoring acupuncture [MD = −3.78, 95% CI (−5.19, −2.36), $p = 0.03$] (Figure 12). These findings suggest that acupuncture significantly improves the quality of life in patients with CSU compared with loratadine, cetirizine, and sham acupuncture though heterogeneity remains high in some subgroups.

3.3.5 Hamilton Depression Scale score

A total of five studies (8, 14, 25, 26, 28) involving 388 patients reported Hamilton Depression Scale (HAMD) scores in patients with

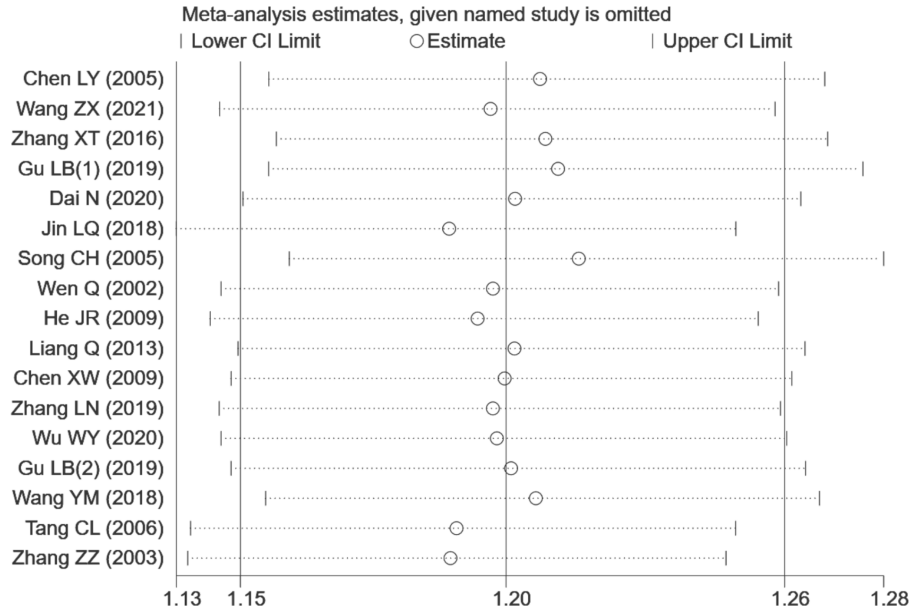

FIGURE 5
Sensitivity analysis of efficiency.

CSU. The combined results showed a statistically significant improvement in HAMD scores in patients treated with acupuncture compared with those treated with loratadine, cetirizine, and sham acupuncture, indicating that acupuncture more effectively reduced depression symptoms in CSU patients (refer to Supplementary material 3 for DLQI funnel plot 1 and Egger's test 1.2 and Supplementary material 4).

3.3.6 Chronic Urticaria Quality of Life Questionnaire

A total of three RCTs (11, 14, 23) involving 388 patients were included. Heterogeneity testing of the three studies showed no heterogeneity ($chi^2 = 0.72$, $p = 0.70$, $I^2 = 0\%$). A fixed-effects model was used for meta-analysis. The combined results of meta-analysis indicated a statistically significant difference favoring acupuncture over loratadine in improving the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) score in patients with CSU [MD = −2.54, 95% CI (−4.49,-0.58), $p = 0.01$] (Figure 13). The funnel plot showed symmetry on both sides, and Egger's test for publication bias indicated no significant bias (t = −0.68, $p = 0.618$). Due to the limited number of studies (only three), funnel plot analysis, Egger's test, and sensitivity analysis were not performed.

3.3.7 Number of urticaria wheals

A total of five RCTs (10–12, 16, 19) involving 483 patients were included in the analysis of wheal numbers. Heterogeneity testing showed significant heterogeneity ($chi^2 = 24.26$, $p < 0.0001$, $I^2 = 84\%$). Therefore, a random-effects model was used for meta-analysis. The combined results indicated a statistically significant difference favoring acupuncture over loratadine in reducing the number of wheals in CSU [SMD = −0.82, 95% CI (−1.29, −0.35), $p < 0.05$] (Figure 14). A funnel plot assessment showed symmetry on both sides, and Egger's test for publication bias indicated no significant bias (t = −0.16, $p = 0.885$) (refer to Supplementary material 3 for the funnel plot and Egger's test results related to the number of wheals, funnel plot 1 and Egger's test 1.2).

3.3.8 Size of urticaria wheals

A total of three RCTs (12, 16, 19) involving 276 patients were included. Heterogeneity testing was conducted, which showed that acupuncture had a greater advantage over cetirizine in reducing wheal size in CSU (refer to Supplementary materials 3, 4).

3.3.9 Itch severity

A total of nine RCTs (10–12, 16, 19, 23, 25, 26, 28) involving 816 patients were included. Heterogeneity testing of these studies showed significant heterogeneity ($chi^2 = 142.96$, $p < 0.001$, $I^2 = 94\%$), so a random-effects model was used for meta-analysis. In assessing itch severity, seven studies (10, 11, 19, 23, 25, 26, 28) used the visual analog scale (VAS), whereas two studies (12, 16) used the numeric rating scale (NRS). Therefore, SMD was used for pooling. The combined results indicated a statistically significant difference favoring acupuncture over loratadine and sham acupuncture in improving itch severity in CSU patients [SMD = −1.35, 95% CI (−2.02, −0.68), $p < 0.001$] (Figure 15). The funnel plot showed symmetry on both sides, and Egger's test for publication bias indicated no significant bias (t = −0.156, $p = 0.163$) (refer to Supplementary material 3 for the funnel plot and Egger's test results related to itch severity, funnel plot 1 and Egger's test 1.2).

In the subgroup analysis based on different control interventions, the studies were categorized into two subgroups: acupuncture vs. loratadine and acupuncture vs. sham acupuncture. Acupuncture vs. loratadine: This subgroup included five studies (7–10, 31). Significant heterogeneity was observed ($chi^2 = 50.48$, $p < 0.001$, $I^2 = 92\%$). The combined results indicated a statistically significant difference favoring acupuncture [SMD = −1.09, 95% CI (−1.79, −0.38),

TABLE 2 Basic characteristics of the included articles.

Author	Years	Total_N	Experimental Group				Control Group				Intervene	Course of treatment	Outcome
			Acupuncture_N	Genders (men/women)	Age	Course	Control_N	Genders (men/women)	Age	Course			
Chen LY (7)	2005	61	31	11/20	33.5 ± 12.6	1.54 ± 1.12	30	13/17	32.9 ± 10.8	1.49 ± 1.16	Acupuncture VS Loratadine	4 weeks	1
Chen XW (17)	2009	60	30	12/18	-	-	30	15/15	-	-	Acupuncture VS Loratadine	4 weeks	1
Dai N (11)	2020	61	30	11/19	38.33 ± 10.41	12.00(6.75,21.00)	31	11/20	38.61 ± 10.43	15.00(7.00,27.00)	Acupuncture VS Loratadine	4 weeks	1.2.3.5.9.11.16
Gu LB(1) (10)	2019	156	78	48/30	37.14 ± 11.37	3.49 ± 1.18	78	50/28	37.28 ± 11.91	3.41 ± 1.09	Acupuncture VS Loratadine	4 weeks	1.3.5.12.13.14
Gu LB(2) (19)	2019	120	60	26/34	40 ± 12	16.35 ± 12.08	60	28/32	41 ± 12	17.01 ± 13.11	Acupuncture VS Loratadine	6 weeks	1.12.13.14
He JR (15)	2009	60	30	13/17	35.9 ± 9.1	6.0 ± 4.2	30	16/14	39.9 ± 10.6	6.8 ± 5.0	Acupuncture VS Loratadine	4 weeks	1
Jin LQ (12)	2018	100	50	28/22	43.43 ± 14.84	6.8 ± 1.9	50	30/20	43.60 ± 14.33	5.1 ± 2.1	Acupuncture VS Loratadine	30 days	1.3.5.6.
Liang Q (16)	2013	70	35	17/18	-	-	35	15/20	-	-	Acupuncture VS Loratadine	8 weeks	1.2.3.4.5.6.7.11
Qu SY (23)	2023	60	32	11/21	45.01 ± 11.76	40.50(12.00, 120.00)	28	11/17	43.57 + 11.66	48.00(20.00 , 99.50)	Acupuncture VS Sham Acupuncture	4 weeks	5.9.11
Shi YZ (28)	2023	80	41	14/27	38.2 ± 12.5	38.4 ± 60.0	39	11/28	39.7 ± 13.0	39.5 ± 44.9	Acupuncture VS Sham Acupuncture	2 weeks	5.7.8.11
Song CH (13)	2005	96	47	19/28	35.5 ± 12.6	-	49	14/35	37.8 ± 13.4	-	Acupuncture VS Cimetidine	4 weeks	1.3.4.5.
Tang CL (22)	2006	60	30	-	-	-	30	-	-	-	Acupuncture VS Loratadine	2 weeks	1
Wang L (25)	2021	49	24	6/18	31.83 ± 8.26	3.04 ± 3.22	25	7/18	32.36 ± 10.78	3.28 ± 3.86	Acupuncture VS Sham Acupuncture	4 weeks	5.7.8.11
Wang YM (21)	2018	57	29	5/24	43.5 ± 10.66	12.18 ± 8.87	28	6/22	43.61 ± 12.59	5.21 ± 0.67	Acupuncture VS Loratadine	6 weeks	1.2.11
Wang ZX (8)	2021	65	34	-	-	-	31	-	-	-	Acupuncture VS Cimetidine	-	1.7.8.11

(Continued)

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TABLE 2 (Continued)

Author	Years	Total_N	Experimental Group				Control Group				Intervene	Course of treatment	Outcome
			Acupuncture_N	Genders (men/women)	Age	Course	Control_N	Genders (men/women)	Age	Course			
Wen Q (14)	2002	60	30	12/18	38.5 ± 2.007	29.10 ± 2.307	30	15/15	39.10 ± 1.830	32.70 ± 3.048	Acupuncture VS Loratadine	2 weeks	1.2.8.9.11
Wu WY (19)	2020	106	53	25/28	42 ± 5	17 ± 5	53	27/26	42 ± 6	18 ± 6	Acupuncture VS Loratadine	8 weeks	1.3.4.5.6.7. 12.13.14
Xiao XJ (26)	2021	134	67	15/52	33(28,48)	24(6,61)	67	18/49	32(27,47)	28(8,62)	Acupuncture VS Sham Acupuncture	4 weeks	5.7.8.11
Zhang LN (18)	2019	88	44	-	40.76 ± 8.86	22.54 ± 6.57	44	-	41.79 ± 7.49	23.21 ± 7.70	Acupuncture VS Loratadine	6 weeks	1.2.12.13.14.16
Zhang XT (9)	2016	67	33	4/29	35.42 ± 9.53	14.12 ± 1.41	34	10/24	31.82 ± 8.97	14.06 ± 1.39	Acupuncture VS Loratadine	-	1.14.15
Zhang ZZ (24)	2003	57	37	15/22	-	-	20	13/7	-	-	Acupuncture VS Cimetidine and Chlorphenamine Maleate	10 days	1
Zheng Hui (27)	2023	200	103	25/85	38.4(36.0 ± 40.9)	-	97	31/79	39.2(36.7–41.7)	-	Acupuncture VS Sham Acupuncture	4 weeks	5.7.8.11

Outcome: 1. Total effective rate. 2. Recurrence rate. 3. Number of wheals. 4. Wheal diameter [size]. 5. Itching severity. 6. Duration of attacks. 7. Dermatology Life Quality Index [DLQI]. 8. Hamilton Depression Rating Scale [HAMD]. 9. Chronic Urticaria Quality of Life. Questionnaire [CU-Q2oL] 10.Itching Visual Analogue Scale [VAS] 11.Urticaria Activity Score [UAS] 12.Serum IgE 13.IFN-γ [Interferon-gamma] 14.IL-4 levels 15.European MILOR score 16.Traditional Chinese Medicine syndrome score.

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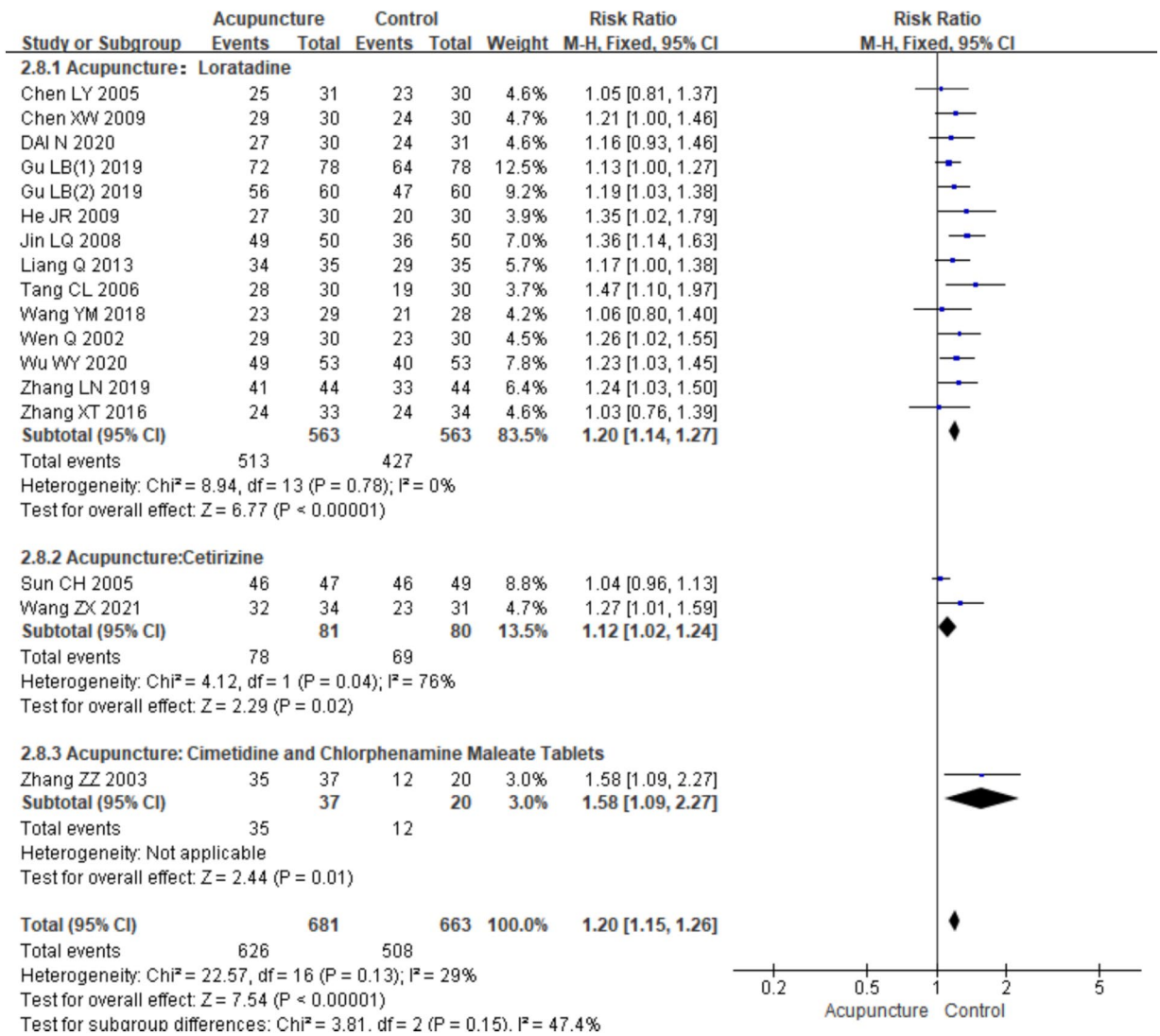

FIGURE 6
Forest plot of subgroup analyses of the efficacy of different intervention methods.

$p = 0.002$], demonstrating that acupuncture was more effective than loratadine in reducing urticaria wheals. Acupuncture vs. sham acupuncture: This subgroup included four studies (2, 3, 6, 11). Similarly, significant heterogeneity was observed ($chi^2 = 92.34$, $p < 0.001$, $I^2 = 97\%$). The combined results also showed a statistically significant difference favoring acupuncture [SMD = −1.81,95% CI (−3.30, −0.32), $p = 0.02$], indicating that acupuncture was more effective than sham acupuncture in reducing wheal size (Figure 16). Despite the subgroup analysis, significant heterogeneity persisted in both subgroups. This suggests that other factors may contribute to the heterogeneity, which warrants further investigation.

3.3.10 Duration of urticaria flare-ups

A total of three RCTs (12, 16, 19) involving 276 patients were included in the analysis of flare-up duration. Heterogeneity testing indicated significant heterogeneity ($chi^2 = 14.47$, $p < 0.001$, $I^2 = 86\%$), and thus, a random-effects model was applied for meta-analysis. The combined results showed a statistically significant difference favoring acupuncture over loratadine in reducing the duration of CSU flare-ups [MD = −0.98, 95% CI (−1.61, −0.35), $p = 0.002$] (Figure 17). Due to the limited number of included studies (only three), a funnel plot and Egger's test for publication bias were not performed.

3.3.11 Serum IgE levels

A total of four RCTs (10, 18–20) involving 470 patients were included in the analysis of serum IgE levels. Heterogeneity testing showed no significant heterogeneity ($chi^2 = 1.05$, $p = 0.79$, $I^2 = 0\%$), indicating consistency across the studies. A fixed-effects model was therefore used for meta-analysis. The combined results showed a statistically significant reduction in serum IgE levels favoring acupuncture over loratadine [MD = −13.72, 95% CI (−16.12, −11.33), $p < 0.001$], indicating that acupuncture was more effective in reducing serum IgE levels in patients with CSU (Figure 18). Due to the limited number of included studies (only four), a funnel plot and Egger's test for publication bias were not conducted.

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TABLE 3 Acupoint frequency.

Author	Year	Acupoints	Frequency Descriptions
Chen LY (7)	2005	Primary Acupoints:RN12(Zhongwan), RN10(Xiawan), RN6(Qihai), BL26(Guanyuan), Supplementary Acupoints: ST24(Sanyinjiao), ST26(Wailing), SP15(Daheng)	5 times per week
Chen XW (17)	2009	LI11(Quchi), SP10(Xuehai), ST36(Zusanli) and SP06(Sanyinjiao); Wind-Heat Affecting the Exterior:Add DU14(Dazhui); Wind-Cold Constraining the Exterior: Add BL13(Feishu); Stomach and Intestines Excess Heat: Add LI4(Hegu), ST44(Neiting); Blood Deficiency with Wind-Dryness: Add (Geshu), BL20(Pishu).	2 times per week
Dai N (11)	2020	Root-Cutting Therapy Acupoints.	2 times per week
Gu LB(1) (10)	2019	LI15(Jianyu), LI5(Yangxi)	
Gu LB(2) (19)	2019	LI11(Quchi), LI15(Jianyu), LI10(Shousanli)	5 times per week
He JR (15)	2009	Encircling Needling; Rash on the Upper Body: Add LI11(Quchi), LI4(Hegu) Rash on the Lower Body: Add SP10(Xuehai), ST36(Zusanli), SP06(Sanyinjiao); Rash on the Whole Body: Add GB20(Fengchi), DU14(Dazhui).	5 times per week
Jin LQ (12)	2018	Four Needles around the Navel Combined with Abdominal Acupoints. To Guide Qi Back to Its Origin. Abdominal Four Gates, ST25(Tianshu), SP15(Daheng).	Once daily for the first 3 days, then once every 2 days
Liang Q (16)	2013	LI11(Quchi), SJ5(Waiguan), LI4(Hegu), ST36(Zusanli), SP10(Xuehai), SP06(Sanyinjiao), LR3(Taichong); Wind-Heat Affecting the Exterior: Add GB20(Fengchi), DU16(Fengfu); Wind-Cold Constraining the Exterior: Add DU14(Dazhui), BL12(Fengmen); Blood Deficiency with Wind-Dryness: Add BL17(Geshu), LR5(Ligou).	2 times per week
Qu SY (23)	2023	both sides:HT7(Shenmen), PC6(Neiguan), LI4(Hegu), LI11(Quchi), ST36(Zusanli), SP06(Sanyinjiao).	3 times per week
Shi YZ (28)	2023	DU24(Shenting), DU20(Baihui), LI11(Quchi), RN12(Zhongwan), ST25(Tianshu), SP10(Xuehai), ST36(Zusanli), SP06(Sanyinjiao).	5 times per week
Song CH (13)	2005	LI11(Quchi).	6 times per week
Tang CL (22)	2006	Primary Acupoints: BL13(Feishu), LI4(Hegu), SP10(Xuehai), ST36(Zusanli), BL20(Pishu), BL18(Ganshu). Wind-Cold Syndrome: Add DU14(Dazhui), LI11(Quchi), GB20(Fengchi), LU7(Lieque); Wind-Heat Syndrome: Add DU14(Dazhui), LI11(Quchi), LU6(Kongzui), BL11(Dashu); Stomach and Intestines Excess Heat Syndrome: Add ST34(Liangqiu), ST44(Neiting); Qi and Blood Deficiency Syndrome: Add DU14(Dazhui), LI11(Quchi), BL26(Guanyuan), RN6(Qihai), RN3(Zhongji); Disharmony of the Chong and Ren Channels: DU14(Dazhui), LI11(Quchi), ST32(Futu), SP06(Sanyinjiao).	Once daily
Wang L (25)	2021	LI11(Quchi), SP10(Xuehai), SP06(Sanyinjiao), ST36(Zusanli), ST25(Tianshu), RN12(Zhongwan), HT7(Shenmen).	5 times per week for the first 2 weeks, 3 times per week for the 3rd and 4th weeks
Wang YM (21)	2018	HT8(Shaofu), HT7(Shenmen), HT5(Tongli), PC7(Daling), LI11(Quchi), LI4(Hegu), SP10(Xuehai), ST36(Zusanli), SP06(Sanyinjiao).	Once every 2 days, 3 times per week
Wang ZX (8)	2021	GB20(Fengchi), Auricular Points (Heart, Lung, Shenmen), HT7(Shenmen), RN12(Zhongwan), ST25(Tianshu), BL26(Guanyuan), LI11(Quchi), SP10(Xuehai), ST36(Zusanli), SP06(Sanyinjiao)	Once every 2 days, 3 times per week
Wen Q (14)	2002	Primary Acupoints: Qihai, Guanyuan, both sides of RN6(Qihai)(Guanyuan)(Guanyuan), BL26(Guanyuan)(Sanyinjiao). Supplementary Acupoints: Wind-Heat Affecting the Exterior: Add DU14(Dazhui), using the dispersing method. Wind-Cold Constraining the Exterior: Add BL12(Fengmen), using the dispersing method. Stomach and Intestines Damp-Heat: Add ST44(Neiting), using the dispersing method. Qi and Blood Deficiency: Add BL20(Pishu), BL23(Shenshu), using the tonifying method.	6 times per week
Wu WY (19)	2020	GB20(Fengchi), BL12(Fengmen), DU16(Fengfu), SI12(Bingfeng), SJ17(Yifeng), GB31(Fengshi).	5 times per week
Xiao XJ (26)	2021	RN12(Zhongwan), both sides of LI11(Quchi), HT7(Shenmen), ST25(Tianshu), SP10(Xuehai), ST36(Zusanli), SP06(Sanyinjiao)	5 times per week for the first 2 weeks, 3 times per week for the 3rd and 4th weeks

(Continued)

TABLE 3 (Continued)

Author	Year	Acupoints	Frequency Descriptions
Zhang LN (18)	2019	GB20(Fengchi), BL12(Fengmen), DU16(Fengfu), SI12(Bingfeng), SJ17(Yifeng), GB31(Fengshi)	5 times per week
Zhang XT (9)	2016	Wood Acupoints <Dong's Extraordinary Points>	Once every 3 days
Zhang ZZ (24)	2003	LI15(Jianyu), LI11(Quchi), SP10(Xuehai), SP06(Sanyinjiao), ST36(Zusanli)	Once daily
Zheng Hui (27)	2023	LI11(Quchi), SP10(Xuehai), ST36(Zusanli), ST25(Tianshu), SP06(Sanyinjiao), HT7(Shenmen), RN12(Zhongwan).	10 times in the first 2 weeks, 6 times in the next 2 weeks

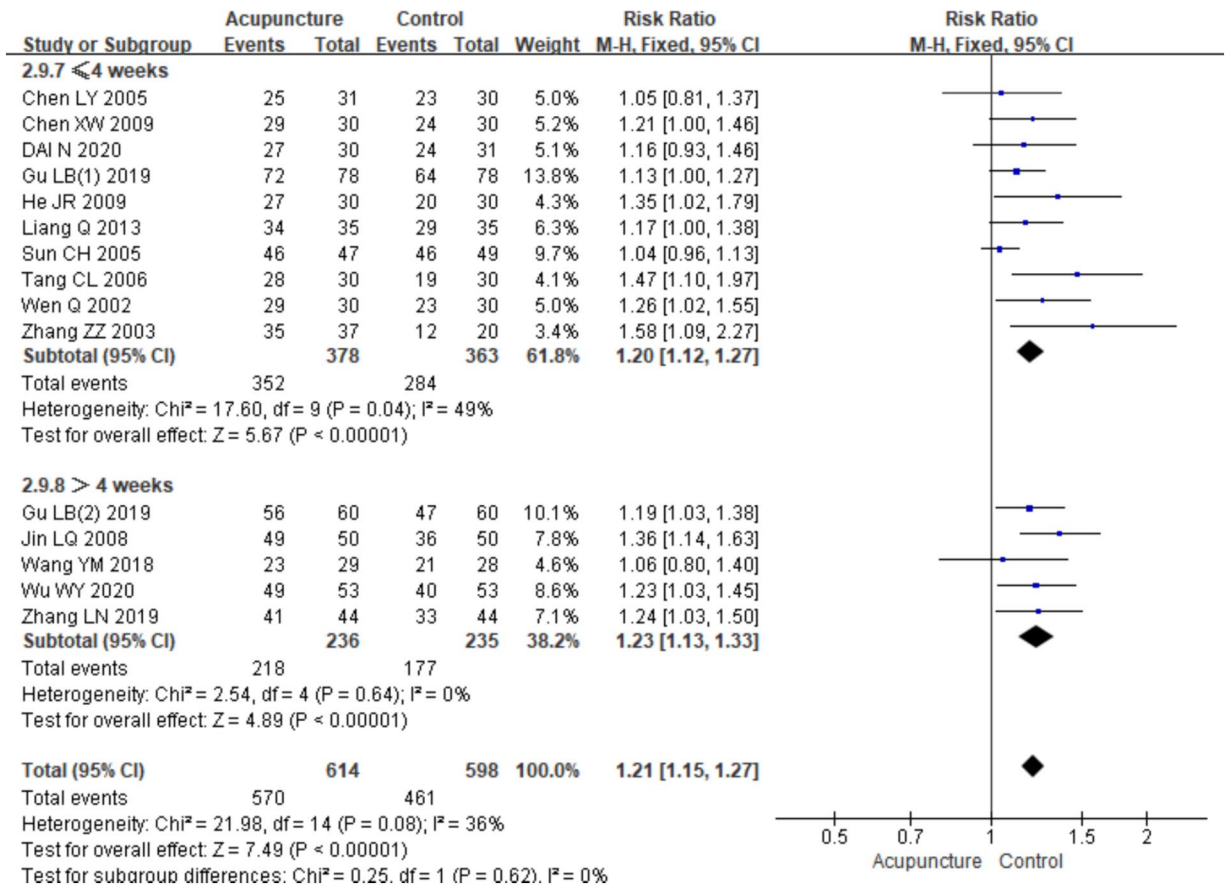

FIGURE 7
Forest plots of subgroup analyses of efficacy across treatment cycles.

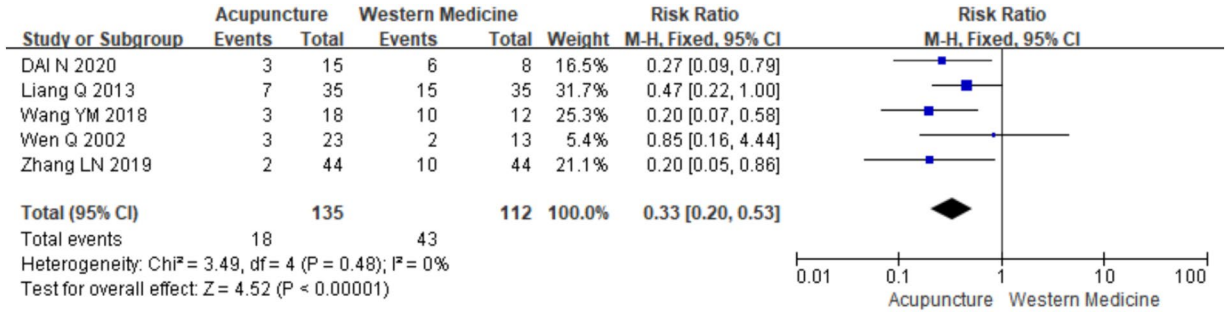

FIGURE 8
Forest plot of recurrence rates.

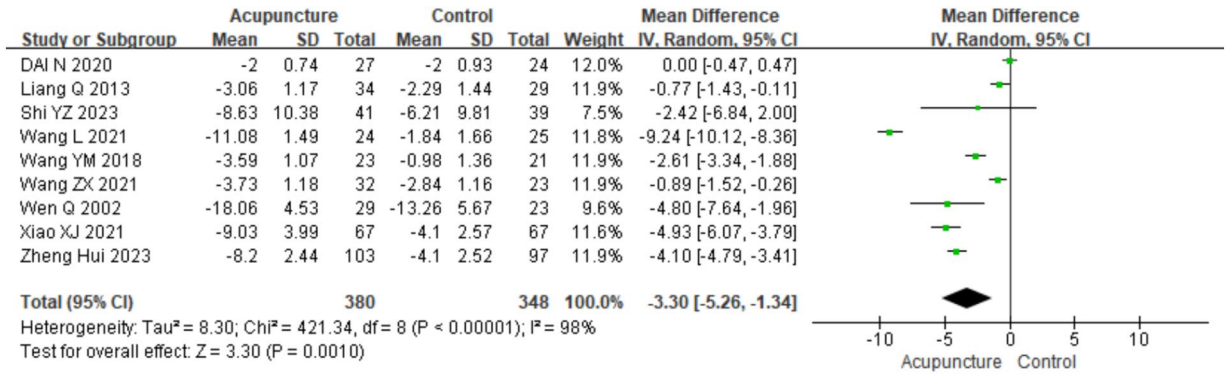

FIGURE 9
Forest plot of UAS7.

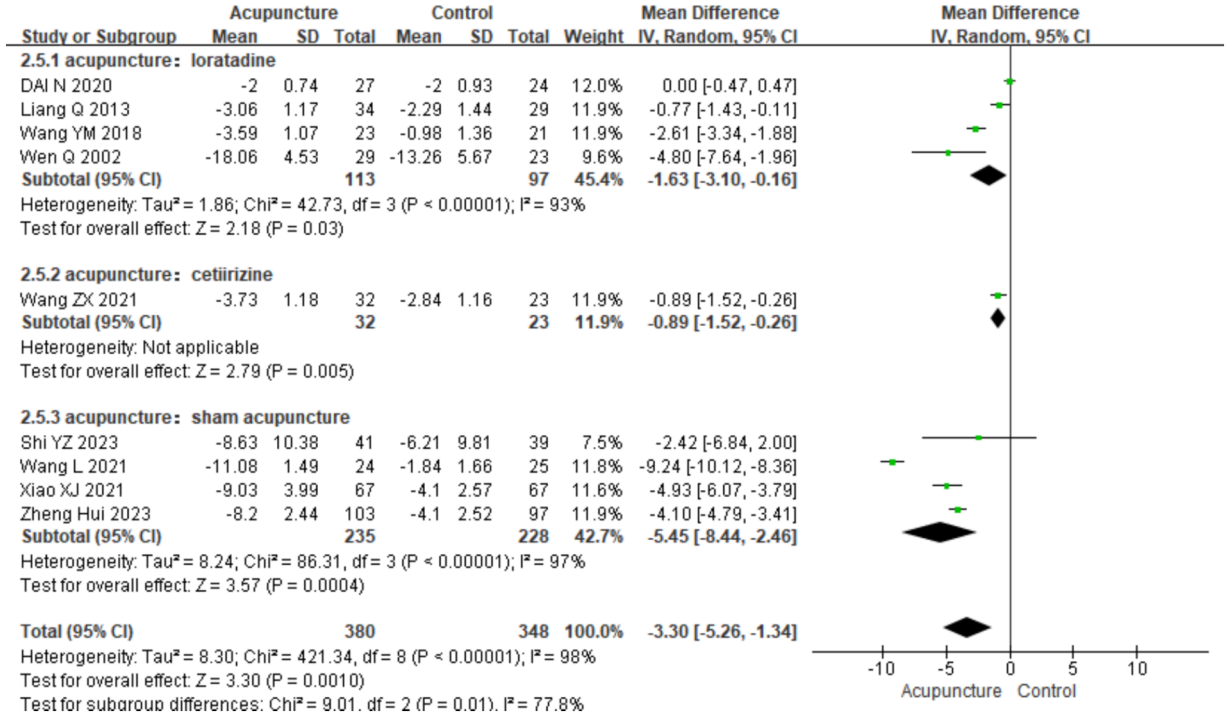

FIGURE 10
Forest plot of subgroup analyses of UAS7 of different intervention methods.

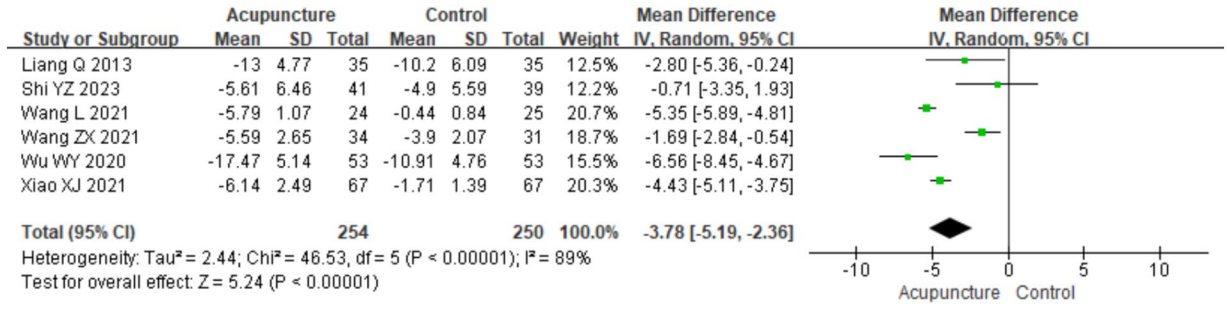

FIGURE 11
Forest plot of DLQI.

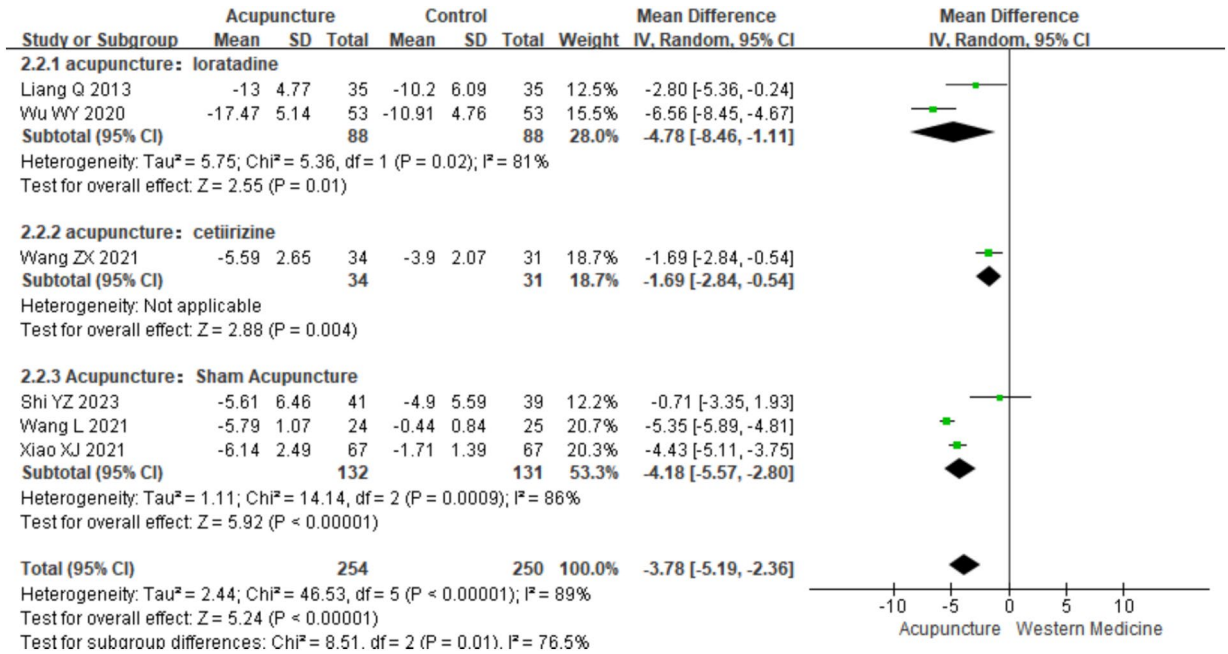

FIGURE 12
Forest plot of subgroup analyses of DLOI of different intervention methods.

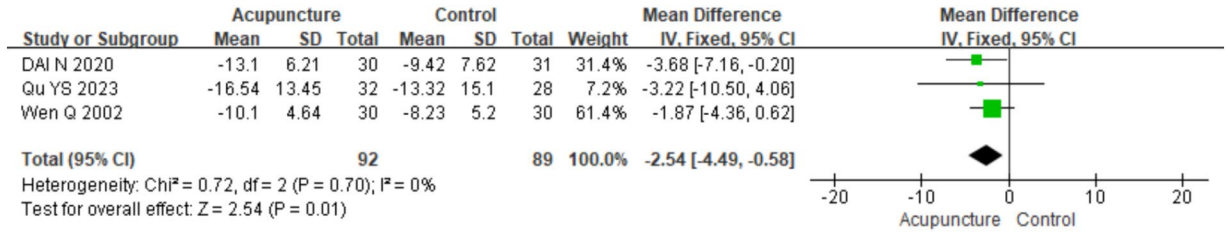

FIGURE 13
Forest plot of CU-Q2oL.

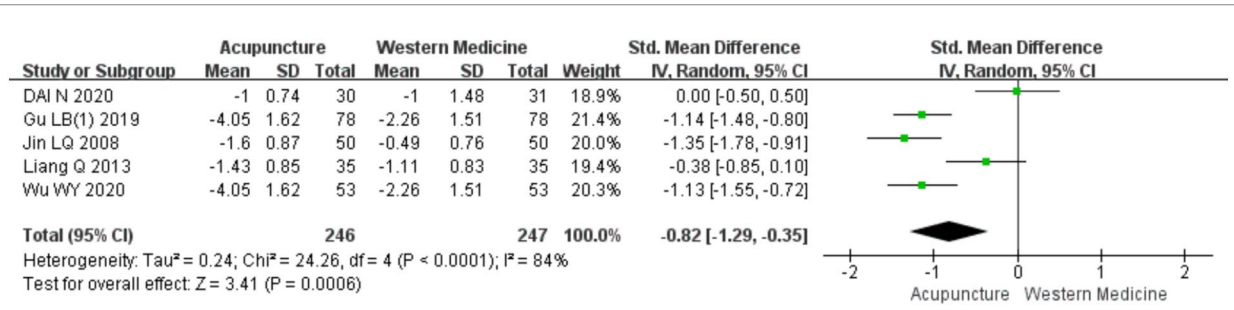

FIGURE 14
Forest plot of the number of urticaria lesions.

3.3.12 IFN-γ levels

A total of four RCTs (10, 18–20) involving 470 patients were included in the analysis of IFN-γ levels. Heterogeneity testing revealed significant heterogeneity ($chi^2 = 57.79$, $p < 0.001$, $I^2 = 95\%$), so a random-effects model was used for meta-analysis. The combined results showed a statistically significant increase in IFN-γ levels favoring acupuncture over loratadine [MD = 5.12, 95% CI (3.84, 6.40), $p < 0.001$] (Figure 19), indicating that acupuncture was more effective in increasing IFN-γ levels in patients with CSU. Due to the limited number of included studies (only four), a funnel plot and Egger's test for publication bias were not conducted.

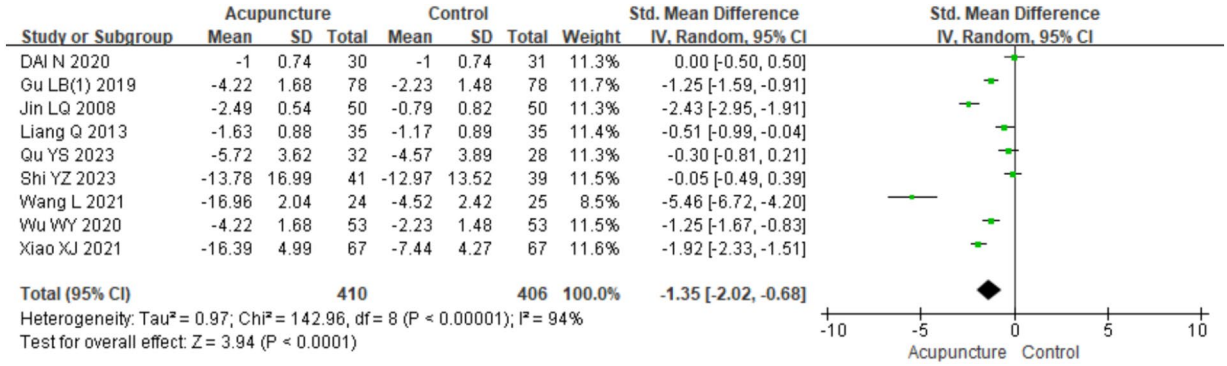

FIGURE 15
Forest plot of degree of itchiness.

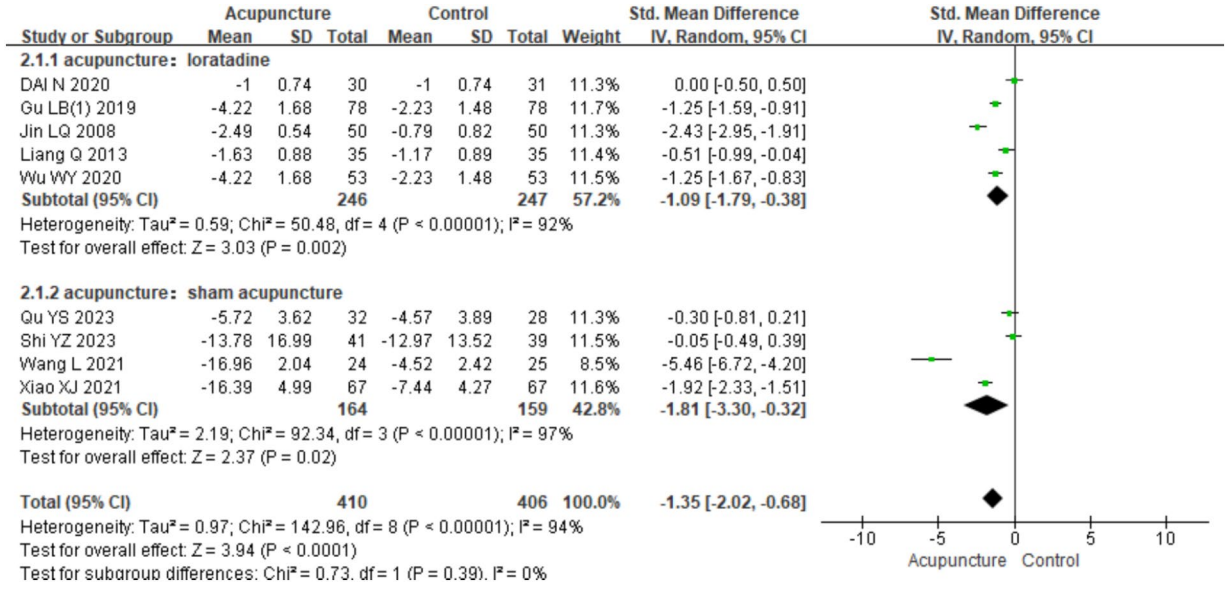

FIGURE 16
Forest plot of subgroup analyses of degree of itchiness of different intervention methods.

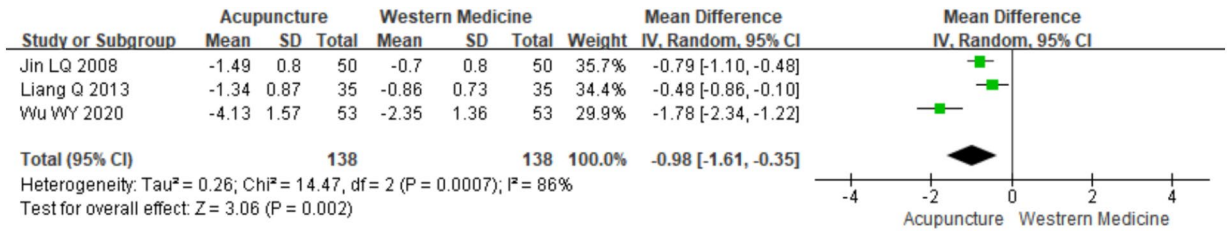

FIGURE 17
Forest plot of seizure duration.

3.3.13 IL-4 levels

A total of four RCTs (10, 18–20) involving 470 patients were included in the analysis of IL-4 levels. Heterogeneity testing showed low heterogeneity ($chi^2 = 4.19$, $p = 0.24$, $I^2 = 28\%$). A fixed-effects model was therefore used for meta-analysis. The combined results indicated a statistically significant reduction in IL-4 levels favoring acupuncture over loratadine [MD = −5.06, 95% CI (−5.95, −4.17), $p < 0.001$], indicating that acupuncture was more effective in reducing IL-4 levels in patients with CSU (Figure 20). Due to the limited number of studies (only four), a

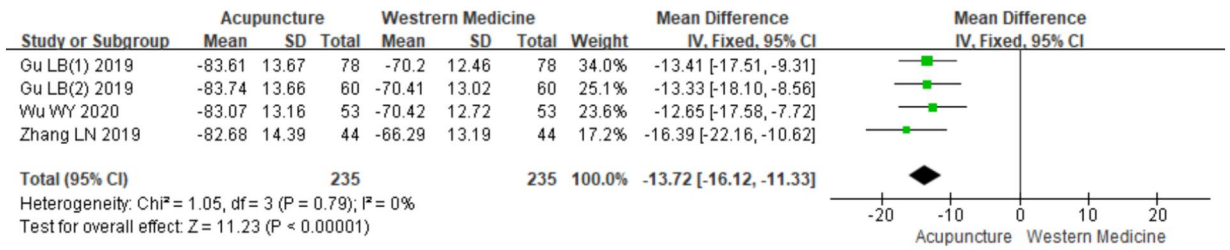

FIGURE 18
Forest plot of IgE levels.

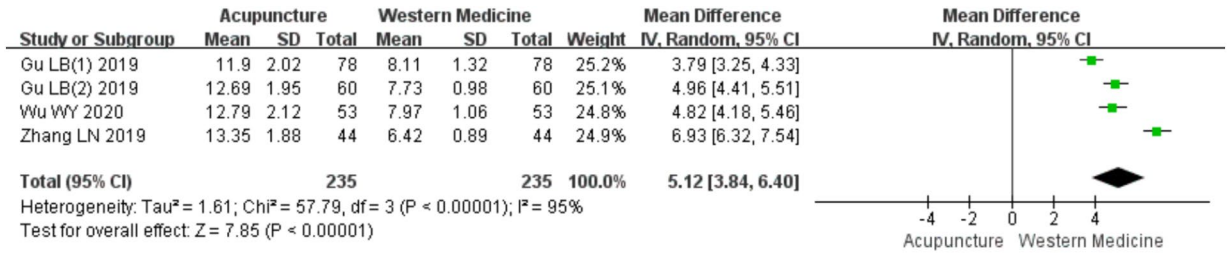

FIGURE 19
Forest plot of IFN-γ levels.

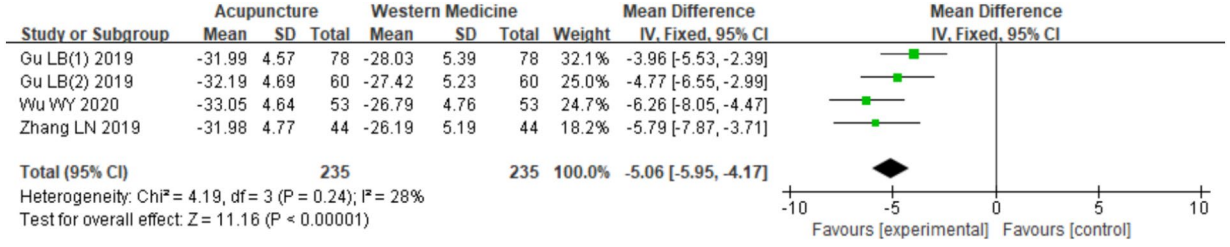

FIGURE 20
Forest plot of IL-4 levels.

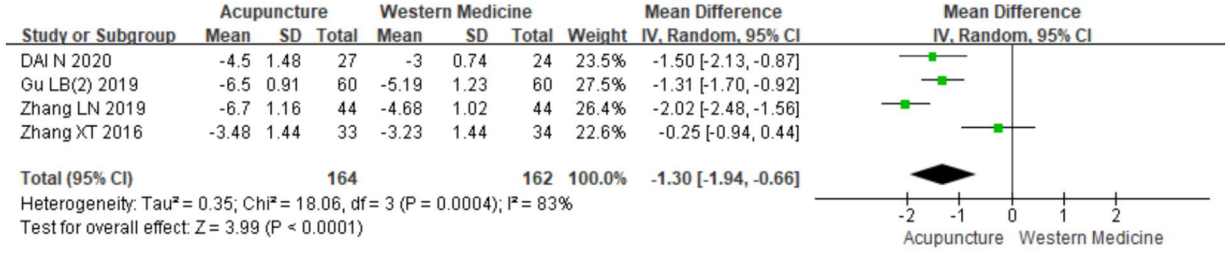

FIGURE 21
Forest plot of TCM score.

funnel plot and Egger's test for publication bias were not conducted.

3.3.14 TCM syndrome score

A total of four RCTs (9, 11, 18, 20) involving 326 patients were included in the analysis of TCM syndrome scores. Heterogeneity testing revealed significant heterogeneity ($chi^2 = 18.06$, $p < 0.001$, $I^2 = 83\%$), so a random-effects model was applied for meta-analysis. Since all four studies used the "Guidelines for Clinical Research of New Chinese Medicine" (14) for assessment, MD was used in the meta-analysis. The results showed a statistically significant difference favoring acupuncture over loratadine in improving TCM syndrome

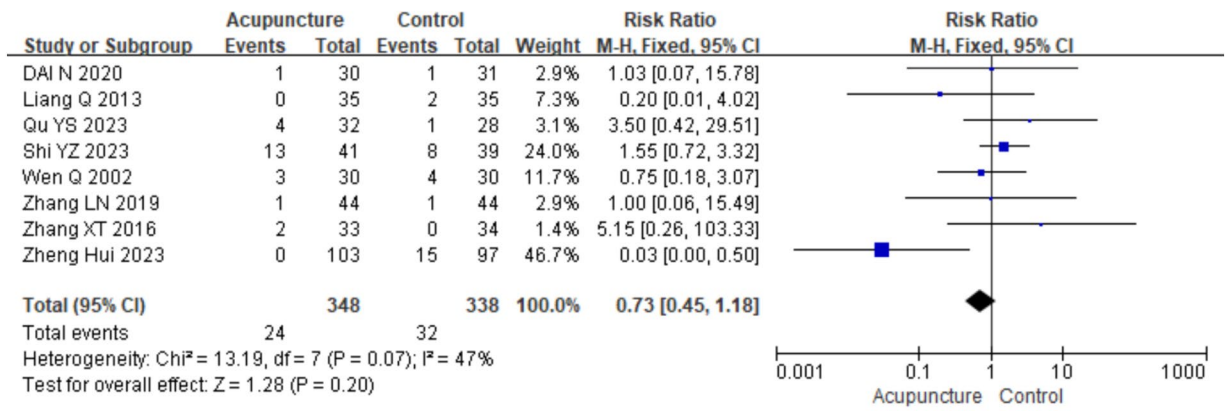

FIGURE 22
Forest plot of security indicators.

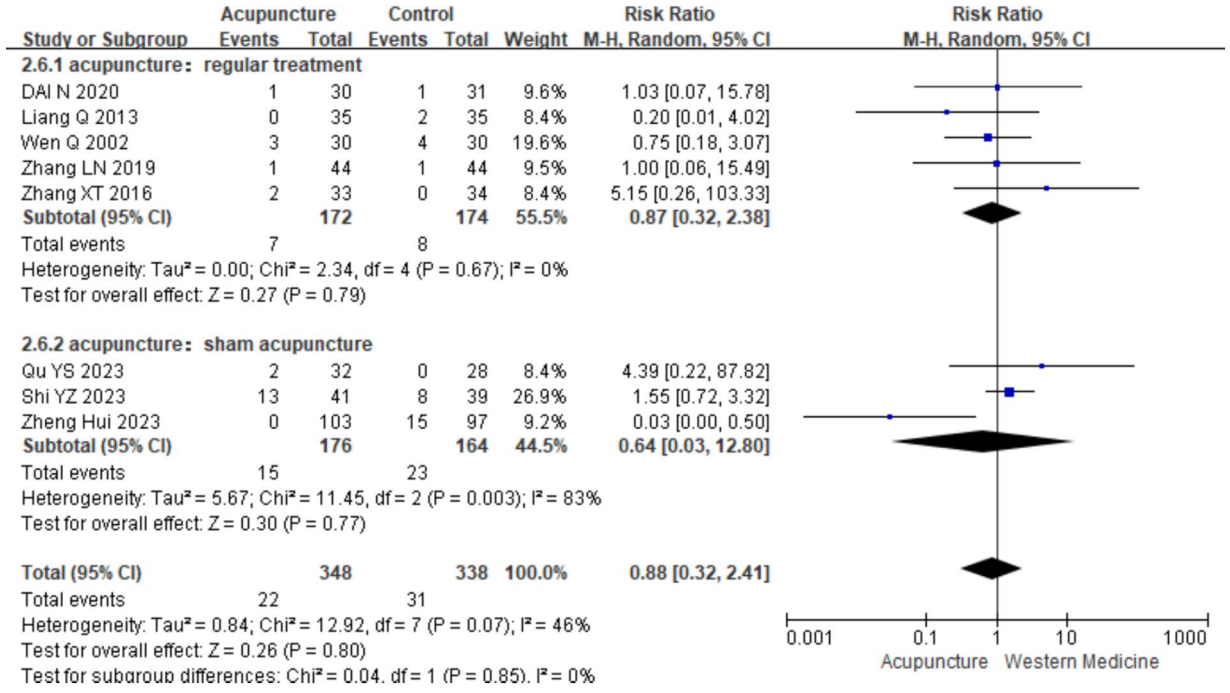

FIGURE 23
Forest plot of subgroup analyses of security indicators of different intervention methods.

scores [MD = −1.30, 95% CI (−1.94, −0.66), $p < 0.001$] (Figure 21), indicating that acupuncture was more effective in improving TCM syndrome scores in patients with CSU. Due to the limited number of studies (only four), a funnel plot and Egger's test for publication bias were not conducted.

3.4 Safety indicators

A total of 10 studies (9, 11, 14, 16, 18, 21, 23, 26–28) evaluated the safety of acupuncture, with all reporting no serious adverse events related to acupuncture. Eight studies (9, 11, 14, 16, 18, 23, 27, 28) involving 686 participants reported mild adverse events, primarily bruising, bleeding, and discomfort related to the "Deqi" sensation, such as distension and numbness. A meta-analysis was conducted on these eight studies. Heterogeneity testing showed low heterogeneity ($chi^2 = 13.19$, $p = 0.07$, $I^2 = 47\%$), so a fixed-effects model was used in the meta-analysis. The results showed no statistically significant difference in the occurrences of adverse events between the acupuncture group and control group [RR = 0.73, 95% CI (0.45, 1.18), $p = 0.20$], indicating that acupuncture does not increase the risk of adverse events in the treatment for CSU (Figure 22). A funnel plot assessment for publication bias showed symmetry, and Egger's test indicated no significant publication bias (t = −0.156, $p = 0.163$) (refer to Supplementary material 3 for the funnel plot and Egger's test results).

In the subgroup analysis of adverse events based on different control interventions, the studies were categorized into two subgroups: acupuncture vs. loratadine and acupuncture vs. sham acupuncture. Acupuncture vs. loratadine: five studies (9, 11, 14, 16, 18) were included. The combined analysis showed no statistically significant difference in the occurrence of adverse events between acupuncture and loratadine ($p = 0.79$). Acupuncture vs. sham acupuncture: Three studies (23, 27, 28) were included. The combined analysis also showed no statistically significant difference in adverse events between acupuncture and sham acupuncture ($p = 0.77$). This suggests that acupuncture does not increase the risk of adverse events compared with loratadine or sham acupuncture in the treatment for CSU. Regarding publication bias, the funnel plot appeared symmetrical, and Egger's test further indicated no significant publication bias ($t = -0.96$, $p = 0.375$) (Figure 23). However, there was still significant heterogeneity in the acupuncture vs. sham acupuncture subgroup, which may be attributable to other factors (refer to Supplementary material 3 for the funnel plot related to adverse events, Funnel plot 2).

3.5 Sensitivity analysis

A sensitivity analysis was conducted using the stepwise exclusion method for different intervention outcome indicators, including efficacy rate, recurrence rate, UAS7, number of wheals, itch severity, DLQI, and HAMD. The results indicated that excluding any individual study had little effect on the effect size of meta-analysis results. This suggests low sensitivity, indicating that the conclusions are stable and reliable (refer to Supplementary material 3 for the sensitivity analysis table).

3.6 Quality of evidence assessment

The quality of the evidence was assessed considering five downgrading factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Among the 22 studies, four used random envelope allocation, eight used random number tables to generate random sequences, nine only mentioned randomization without specifying the method, and one did not mention randomization. Only five studies mentioned blinding of assessors, which lowered the risk of bias by one level. The funnel plot and statistical tests for the outcome measures showed no publication bias, so no downgrading occurred. Of the 14 outcome measures, only five had $I^2 < 50\%$, whereas the remainder had high heterogeneity, leading to a downgrade of one level for inconsistency. Regarding safety outcomes, ten studies reported on safety, with eight reporting mild adverse events but no serious adverse events, so no downgrade was applied for publication bias. In summary, the quality of evidence for efficacy rate, recurrence rate, CU-Q2oL, duration of flare-ups, serum IgE levels, and IL-4 levels was rated as moderate. The quality of evidence for UAS7, number of wheals, wheal size, itch severity, DLQI, HAMD, IFN-γ levels, and TCM syndrome scores was rated as low. Detailed results are presented in Table 4.

4 Discussion and conclusion

4.1 Mechanisms of acupuncture in the treatment for chronic spontaneous urticaria

Urticaria is a common dermatological condition that tends to recur, causing significant disruptions in patients' daily lives (3). The exact pathogenesis of urticaria remains unclear, but it is generally believed to involve the activation and degranulation of MCs through both immune and non-immune pathways, leading to the release of histamine, prostaglandins, leukotrienes, and cytokines, which contribute to the development of CSU (32). Recent research has delved into the mechanisms by which acupuncture treats CSU and found that acupuncture can modulate humoral immunity and cellular immunity and inhibit MC degranulation through multiple pathways, including the regulation of central nervous system pathways.

4.1.1 Acupuncture modulates humoral immunity and reduces inflammatory mediators

4.1.1.1 Reduction in serum IgE levels

While a subset of CSU patients showed higher serum IgE levels compared with healthy individuals, existing evidence regarding its universal correlation with disease severity remains inconclusive (33). IgE, produced by allergen-specific B cells, binds to high-affinity receptors on MCs and basophils. Upon re-exposure to inflammatory triggers, IgE binds to receptors on sensitized cells, activating MCs and basophils and contributing to CSU pathogenesis (34). Clinical studies (35) indicate that acupuncture reduces serum IgE levels in CSU patients. This reduction may involve the suppression of IgE production (e.g., via downregulating Th2 cytokines such as IL-4/IL-13) and/or enhanced IFN-γ activity, which antagonizes IgE synthesis. Acupuncture simultaneously reduces inflammatory mediator release and stabilizes target cell membranes, synergistically regulating humoral immunity (35).

4.1.1.2 Regulation of cytokine and chemokine levels

In addition to the central role of MCs in CSU pathogenesis, various cytokines such as interleukins and transforming growth factor (TGF) are involved in the immune-inflammatory response (36–38). MC-derived mediators, including histamine, tryptase, serotonin (5-HT), prostaglandins, and leukotrienes, along with platelet activation, synergistically exacerbate allergic reactions. An over-release of these components leads to clinical manifestations such as severe itching, wheals, edema, and erythema. By suppressing the release of histamine and other MC-derived mediators (e.g., proteases and prostaglandins) that directly drive vascular hyperpermeability and sensory nerve activation, acupuncture mitigates localized inflammatory responses, thereby alleviating hallmark urticaria symptoms, including pruritus, wheal formation, and angioedema. Animal studies (39) have shown that by inhibiting the release of histamine, 5-HT, TNF-α, and other inflammatory mediators, acupuncture can significantly reduce inflammation and improve urticaria symptoms. In addition, acupuncture decreases IL-33 and ST2 expression at urticarial lesion sites (40), which further confirms its role in modulating humoral immunity.

TABLE 4 Overall evidence for GRADE quality rating of seven included studies.

Outcomes	Number of studies	Study design	Sample size TC	Effect size	Risk of Bias	Inconsistency	Indirect	Imprecision	Publication Bias	Evidence Grade
Efficacy rate	17	RCT	T 681 C 663	1.19,(1.12,1.25)	−1a					Middle
Recurrence rate	5	RCT	T 135 C 112	0.34,(0.21,0.55)	−1a					Middle
UAS		RCT	T 380 C 348	−0.84,(−1.43,-0.25)	−1a	−1b				Low
DLQI	6	RCT	T 254 C 250	−0.85,(−1.35.-0.35)	−1a	−1b				Low
HAMD	5	RCT	T 196 C 192	−1.72, (−2.77, −0.68)	−1a	−1b				Low
CU-Q2oL	3	RCT	T 92 C 89	−2.54, (−4.49, −0.58)	−1a					Middle
Number of wheals	5	RCT	T 246 C 247	−0.82, (−1.29, −0.35)	−1a	−1b				Low
Size of wheals	3	RCT	T 138 C 138	−0.75, (−1.35, −0.14)	−1a	−1b				Low
Itching severity	9	RCT	T 410 C 406	−1.35, (−2.02, −0.68)	−1a	−1b				Low
Seizure duration	3	RCT	T 138 C 138	−0.94, (−1.28, −0.60)	−1a					Middle
IgE	4	RCT	T 235 C 235	−13.72, (−16.12, −11.33)	−1a					Middle
IFN-γ	4	RCT	T 235 C 236	5.12, (3.84, 6.40)	−1a	−1b				Low
IL-4	4	RCT	T 235 C 237	−5.10, (−6.16, −4.05)	−1a					Middle
TCM syndrome score	4	RCT	T 164 C 162	−1.11, (−1.78, −0.43)	−1a	−1b				Low

T, treatment; C, control; RCT, randomized controlled trial; RR, risk ratio; CI, confidence interval. a The design of the trial has a large bias in randomization, allocation concealment, or blinding. b The credible interval overlaps less, the *P*-value of the heterogeneity test is small, and the I of the combined results is large.

10.3389/fmed.2025.1498795

4.1.2 Acupuncture regulates cellular immunity

4.1.2.1 Increase in CD4+/CD8 + ratio

CD4 + and CD8 + cells are critical T lymphocyte subsets in cellular immunity. Studies (29) have shown that the balance of the CD4+/CD8 + ratio reflects immune homeostasis, and its disruption is a key factor in urticaria. Emerging evidence suggests acupuncture may ameliorate CSU through multitarget immunomodulation. Preliminary studies indicate potential regulatory effects on T-cell homeostasis (e.g., helper T cell (Th)1/Th2 rebalancing and regulatory T cell (Treg) induction), coupled with the suppression of MC degranulation via STAT3-dependent pathways. These coordinated actions are correlated with clinical improvements, as evidenced by low UAS7 scores and decreased serum levels of histamine, IL-6, and other effector molecules in responders (41, 42).

4.1.2.2 Th1/Th2 balance

CD4 + T lymphocytes can differentiate into helper T (Th) cells under environmental stimuli, with Th1 and Th2 being two subgroups. Th1 secretes IL-12 and IFN-γ, mediating cellular immunity, whereas Th2 primarily secretes IL-4, IL-5, and IL-13, mediating humoral immunity and allergic responses (43). IL-10 is primarily produced by Treg, whereas IL-8 is predominantly secreted by neutrophils and epithelial cells during inflammatory responses. A disrupted Th1/Th2 balance can lead to urticaria (43). Acupuncture has been shown to restore this balance by reducing Th2 cytokine secretion and modulating Treg/Th17 homeostasis, alleviating CSU symptoms.

4.1.2.3 Th17/Treg balance

Th17 and Treg maintain immune balance, and an increased Th17/Treg ratio may induce IgE production, triggering urticaria (44, 45). Acupuncture can regulate this balance by increasing the expression of TGF-β and forkhead box P3 (Foxp3), reducing IL-17 expression (46).

4.1.3 Acupuncture inhibits mast cell degranulation via multiple pathways

4.1.3.1 Downregulation of the Lyn-Syk/MAPK/NF-KB signaling pathway

Lyn and Syk tyrosine kinases are key proteins in the activation of MCs through the FcεRI receptor. Inhibition of these proteins can reduce MC activation and allergic reactions (47, 48). Studies also reported that acupuncture at specific points reduces serum p-Lyn and p-Syk concentrations, alleviating edema in "allergen-induced chronic urticaria rat models" (it is worth noting that current animal models rely on pharmacologically induced approaches as spontaneous CSU models are unavailable). Animal studies (39) further demonstrated that acupuncture reduces the expression of phosphorylated Lyn and Syk kinases, which are critical components of FcεRI-mediated MC activation. This suppression is correlated with decreased histamine and 5-HT levels, linking pathway inhibition to clinical symptom relief.

4.1.3.2 Inhibition of Ca^{2+} influx

Ca^{2+} influx plays a crucial role in MC degranulation (49). Acupuncture regulates the PIP2/IP3/Ca^{2+} signaling pathway, inhibiting MC degranulation and inflammation (50).

4.1.3.3 Inhibition of the JAK1/STA1, PI3K/AKT signaling pathway

The PI3K/AKT pathway mediates cytokine and growth factor responses and is involved in MC maturation (51). Acupuncture has been shown to regulate this pathway, inhibiting MC degranulation (52–54).

4.1.3.4 Acupuncture regulates the central nervous system

Inflammatory mediators released by immune cells act on neurons, releasing neuropeptides such as substance P and CGRP, leading to neurogenic inflammation and itching (55, 56). Acupuncture can modulate the nervous system, reducing pruritus and improving urticaria symptoms (57, 58).

4.2 Analysis of study results

This meta-analysis included 22 RCTs involving 1,867 patients. Acupuncture showed a higher efficacy than medication (loratadine, cetirizine, cimetidine, and chlorpheniramine) and sham acupuncture in reducing UAS7 scores, recurrence rates, wheal size and number, itching and symptom duration; improving quality of life scores (DLQI, HAMD, and CU-Q2oL); and regulating serum IgE, IFN-γ and IL-4 levels and TCM syndrome scores. No serious adverse events were reported. Despite these promising results, the included RCTs showed moderate to high risk of bias and heterogeneity, likely due to differences in patient characteristics, disease severity, acupuncture points, and treatment duration. Based on GRADE assessments, the evidence supports a low to moderate recommendation for acupuncture in treating CSU although the results remain positive and effective.

Antihistamine-refractory CSU refers to urticaria that remains unresponsive to standard or double-dose antihistamine treatment for 2–4 weeks, with a disease duration of ≥6 weeks, and is associated with non-histamine pathways or autoimmune mechanisms. Available targeted therapies for this condition include Bruton tyrosine kinase inhibitors (e.g., remibrutinib and rilzabrutinib), anti-KIT (barzolvolimab and briquilimab), anti-IL-4Rα (dupilumab), anti-thymic stromal lymphopoietin (tezepelumab), and MRGPRX2 antagonists, to name a few (59, 60). Although these targeted drugs show significant efficacy, they carry risks such as infection, bleeding, and abnormal liver function and are expensive.

Acupuncture, on the other hand, can modulate the immune system through multiple mechanisms, offering better safety at lower costs, which makes it suitable for patients requiring long-term management or those who are intolerant to medications. Future clinical studies should explore the use of acupuncture in treating patients with antihistamine-refractory CSU.

4.3 Limitations

This study has several limitations. First, the search was limited to Chinese and English literature, which may have resulted in missing relevant studies. Second, the outcome measures varied across studies, with some indicators supported by only a few studies, which reduced the robustness of the evidence. Third, some studies had small sample sizes, lacked proper randomization and blinding, and did not register

clinical protocols, which affected the overall quality. Finally, variations in acupuncture points, frequency (ranging from twice weekly to daily sessions), and treatment duration (from 2 to 12 weeks) across studies contributed to heterogeneity. For instance, some studies focused on traditional acupoints like SP10 (Xuehai) and LI11 (Quchi), whereas others incorporated additional points based on syndrome differentiation. This variability reflects diverse theoretical frameworks and clinical practices, which limits the generalizability of our findings and makes it challenging to establish standardized protocols for CSU. Future studies should aim to standardize acupuncture regimens and conduct subgroup analyses to explore the effects of frequency, duration, and techniques on efficacy and safety.

5 Conclusion

In conclusion, this study provides evidence that acupuncture can be an effective treatment for CSU and can improve various clinical outcomes with high safety. However, due to the limitations and heterogeneity observed, future studies should focus on larger, multicenter trials with low risk of bias, standardized acupuncture protocols, and robust methodology to validate these findings. Researchers should also prioritize objective, reproducible outcome measures for inclusion in future meta-analyses to better clarify the relationship between acupuncture and CSU.

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

WW: Writing – original draft, Writing – review & editing. WY: Project administration, Writing – original draft, Writing – review & editing. SZ: Conceptualization, Writing – review & editing. BL: Investigation, Writing – review & editing. ZC: Formal analysis, Writing – review & editing. WZ: Supervision, Writing – review & editing.

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Conflict of interest

This work has been submitted without any conflicts of interest, and all authors have given their consent for publication.

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Supplementary material

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Case Report: Guselkumab treatment for sintilimab-exacerbated psoriasis in a cancer patient

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Psoriasis is a chronic inflammatory skin disease associated with multisystem comorbidities and impaired mental health. The lesions are typically characterized by sharply demarcated, erythematous plaques covered with silvery scales. Treatment options include topical agents, phototherapy, systemic therapies, and biologic agents. Traditional systemic treatments are generally contraindicated in patients with cancer due to their immunosuppressive effects. Although biologics are widely used in the management of psoriasis, their safety in patients with malignancy remains insufficiently evaluated, as individuals with cancer are typically excluded from clinical trials due to concerns about cancer progression. We report the case of a 61-year-old man whose psoriasis markedly worsened following treatment with sintilimab for pulmonary metastases secondary to colon cancer. The patient was successfully treated with guselkumab, an interleukin (IL)-23 inhibitor, resulting in significant improvement in psoriasis symptoms, while the pulmonary condition remained stable during follow-up after completion of standard cancer therapy. This case highlights the potential utility of IL-23 inhibitors as safe and effective treatment options for patients with concomitant psoriasis and malignancy.

KEYWORDS

immune checkpoint therapy, cutaneous adverse effects, psoriasis, biologics, cancer

1 Introduction

Psoriasis is a chronic, immunke-mediated inflammatory skin disease, typically characterized by well-demarcated erythematous plaques with overlying silvery scales. It may involve multiple organ systems and can significantly affect the patient's quality of life and psychological well-being. Psoriasis is broadly classified into chronic plaque psoriasis and less common variants, including guttate, erythrodermic, and pustular forms. The incidence is approximately equal between men and women (1). Standard treatment options include topical agents, phototherapy, systemic therapies, and biologic agents. While the

exact etiology of psoriasis remains unclear, immune dysregulation plays a major contributing factor, and various environmental and genetic factors may contribute to disease exacerbation.

Immune checkpoint therapy (ICT) has revolutionized cancer treatment by offering novel strategies for tumor control. However, ICT is frequently associated with immune-related adverse events (irAEs), which, although typically manageable, can be severe or even life-threatening in some patients (2). Sintilimab is a humanized IgG4 monoclonal antibody that targets the programmed cell death receptor-1 (PD-1), blocking its interaction with ligands to inhibit T-cell apoptosis and enhance antitumor immune response of T cells (3).

The incidence of cutaneous immune-related adverse events (ciRAEs) in patients receiving ICT has been reported to range from 20% to 40% (4). These skin manifestations commonly include nonspecific maculopapular eruptions, eczema-like or psoriatic lesions, lichenoid dermatitis, xerosis, and pruritus (5). However, to date, no published reports have documented sintilimab-induced exacerbation of preexisting plaque psoriasis. This case report presents a patient with preexisting psoriasis that was aggravated by sintilimab and assesses the therapeutic efficacy of guselkumab, an interleukin (IL)-23 monoclonal antibody, in managing this condition.

2 Case description

A 61-year-old male patient with a 10-year history of psoriasis was admitted to our hospital on 25 January 2024 for treatment of pulmonary metastasis following colon cancer resection. The patient received combination therapy consisting of 150 mg of oxaliplatin (L-OHP) administered intravenously on day 1; 0.7 g each of calcium folinate (CF) and 5-fluorouracil (5-FU) given intravenously on day 1; and a continuous infusion of 4.0 g of 5-FU over 46 h. Additionally, 200 mg of sintilimab was administered intravenously on day 1 as immune checkpoint blockade, and 450 mg of bevacizumab was given intravenously on day 1 for antiangiogenic therapy. This regimen was administered every 3 weeks as one treatment cycle. The patient was diagnosed with mild plaque psoriasis at Shanghai Huashan Hospital in 2014, which had remained in remission with topical corticosteroids. He reported no family history of psoriasis. However, 19 days after starting ICT, the patient developed extensive erythematous and squamous lesions, initially appearing on the medial aspects of his feet and lateral lower legs, then spreading to the trunk and scalp, accompanied by thick, layered scales. These psoriasis-like lesions were confirmed by skin biopsy (S1), consistent with a diagnosis of psoriasis. Based on the severe cutaneous manifestations and their temporal association with the PD-1 inhibitor sintilimab—which is known to activate psoriasis-related immune cells such as Th17 cells—a diagnosis of PD-1 inhibitor-exacerbated psoriasis was established. To prevent further exacerbation, sintilimab was temporarily discontinued for one treatment cycle following the second injection, then reintroduced after that cycle to maintain the effectiveness of cancer therapy.

The patient was referred to our dermatology clinic on 2 March 2024, presenting with a Psoriasis Area and Severity Index (PASI) score of 21.2. The skin lesions were deep red, coalescing into large patches and almost entirely covered with thick, layered scales (Figures 1A–H). Given the significant impact of these symptoms on the patient's quality of life, he provided informed consent for biologic therapy after a thorough explanation of the potential risks and expected benefits.

Given the patient's history of colon cancer and evidence supporting the potential antitumor effect of IL-23 inhibitors (6–8), guselkumab was chosen based on its safety, efficacy, and tolerability profile (9). Treatment began with subcutaneous injections of 100 mg per vial of guselkumab. After 4 weeks, the patient received the second injection on 2 April 2024, resulting in a significant reduction in the number of lesions and a decrease in the PASI score to 7.2 (66% improvement). The lesions faded to a faint red with fine, subtle scales (Figures 2A–H). Guselkumab treatment was continued at 8-week intervals.

At the follow-up on 27 August 2024 (25 weeks after initial treatment), the patient achieved a PASI score of 2, representing a 90% improvement from baseline. The lesions appeared light red, with resolved skin elevation and minimal residual scaling (Figures 3A–H).

Guselkumab therapy was initiated on 2 March 2024, with a second dose administered 4 weeks later, followed by maintenance dosing every 8 weeks. Liver and kidney function were monitored weekly during the first 2 months, then biweekly to monthly from months 3 to 5, and approximately every 1 to 3 months thereafter until March 2025. All test results remained within normal limits throughout the treatment period. Screening for HBV, HCV, and T-spot was negative prior to treatment initiation on 24 February 2024, and a follow-up T-spot test in November 2024 also remained negative. No signs of infection or reactivation of latent infections were observed during the treatment period, supporting the safety of guselkumab in this clinical context. The patient tolerated guselkumab well, with no adverse drug reactions reported. Despite continuing the prior chemotherapy regimen, chest computed tomography revealed a slight reduction in the size of pulmonary nodules after 10 weeks of guselkumab therapy (Figures 4A, B) compared with baseline imaging on 19 February 2024, indicating the safety of guselkumab in patients with concurrent cancer and severe psoriasis. At week 29, the pulmonary nodules remained stable (Figure 4C). These findings suggest a stable clinical response for both psoriasis and pulmonary metastasis. A timeline summarizing the clinical course was created to facilitate understanding of this case (Figure 4D).

3 Discussion

The pathogenesis of psoriasis involves the IL-17/IL-23 axis, which plays a crucial role in disease development. PD-1 inhibitor-induced psoriasis is believed to result from prolonged neutrophil activity, inhibition of macrophage apoptosis, and suppression of regulatory T-cell generation (Treg) and function. Activation and

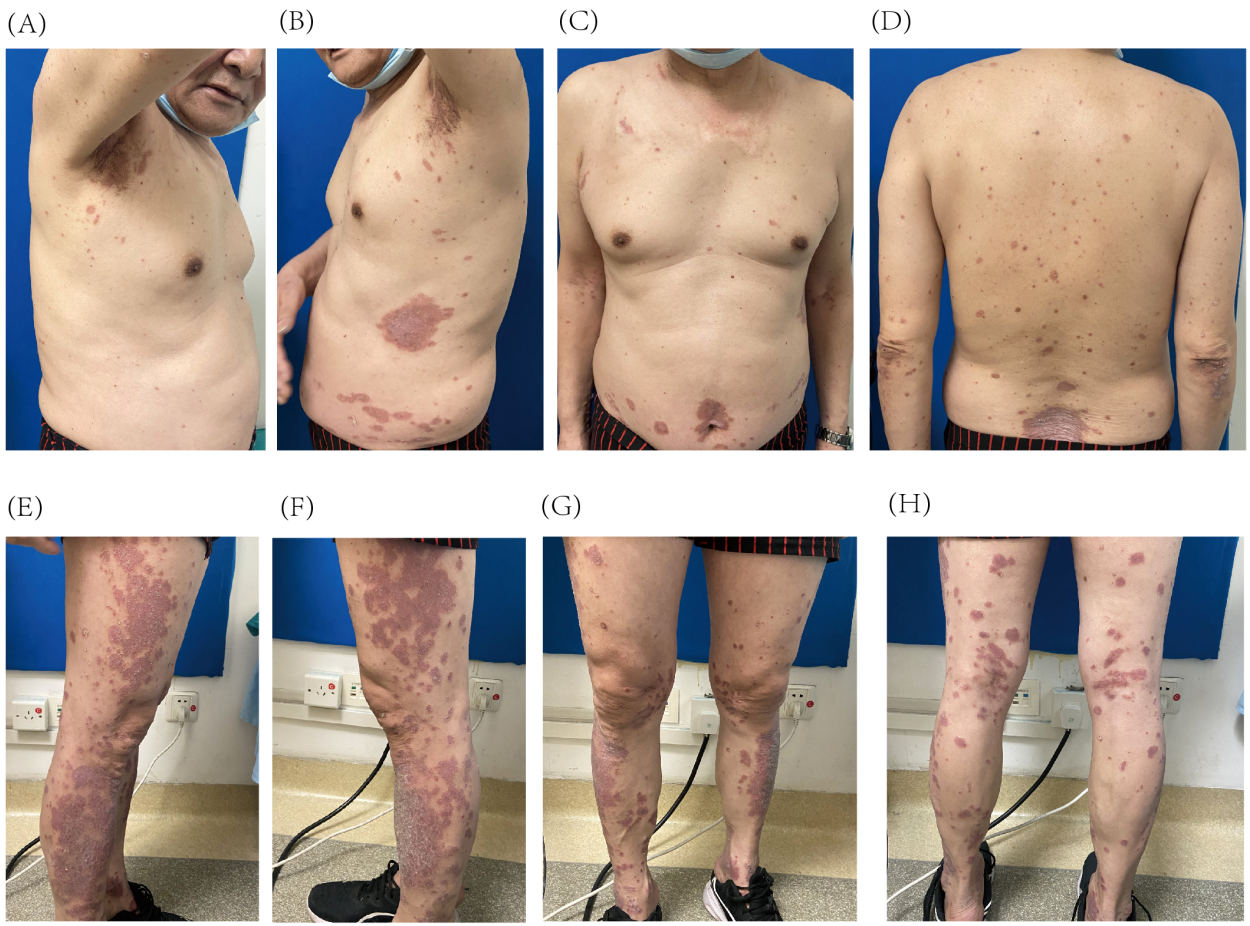

FIGURE 1
Psoriatic lesions on the trunk **(A–D)** and lower extremities **(E–H)** prior to initiation of guselkumab treatment.

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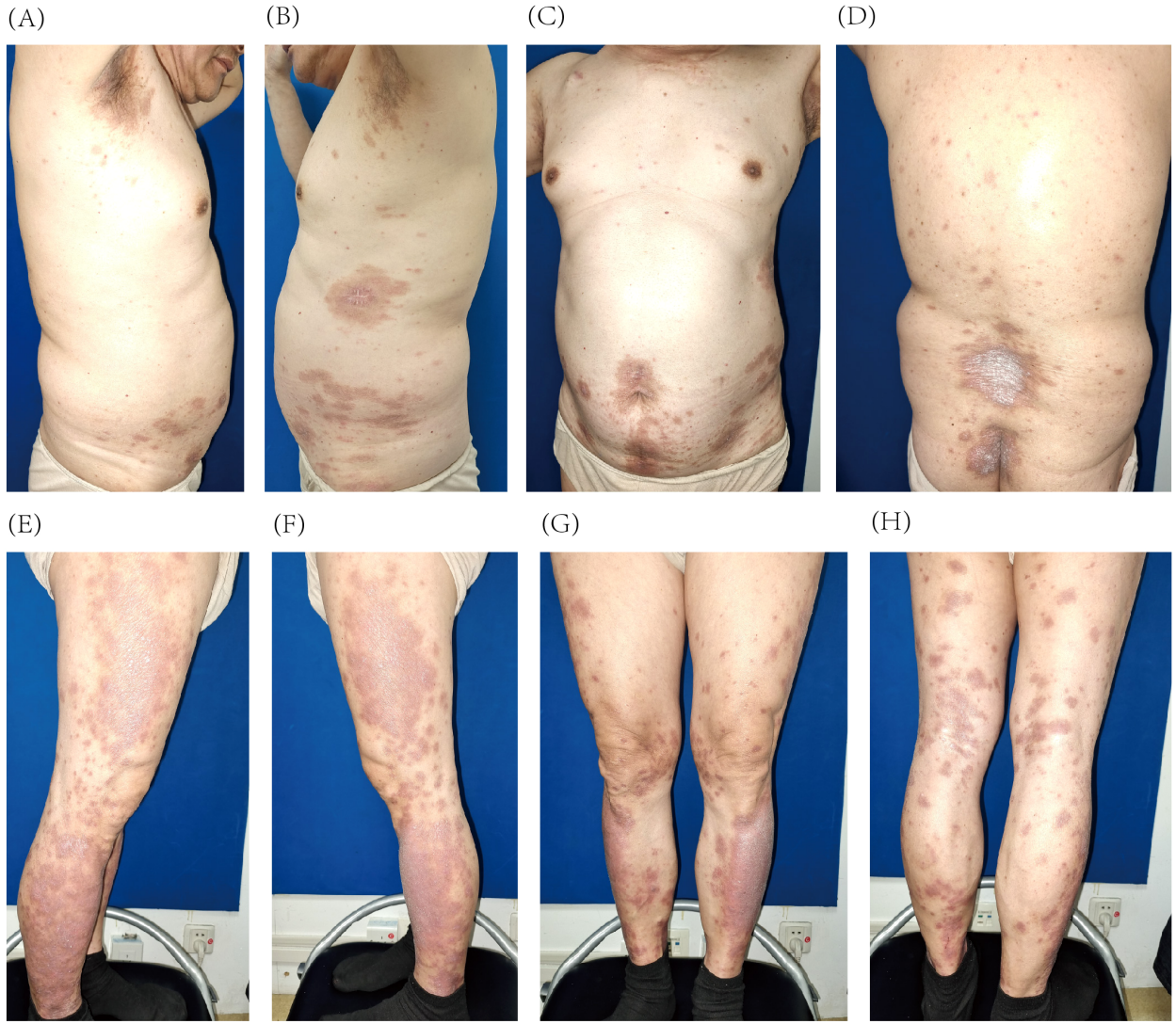

FIGURE 2
Improvement of psoriatic lesions on the trunk **(A–D)** and lower extremities **(E–H)** after 4 weeks of guselkumab treatment.

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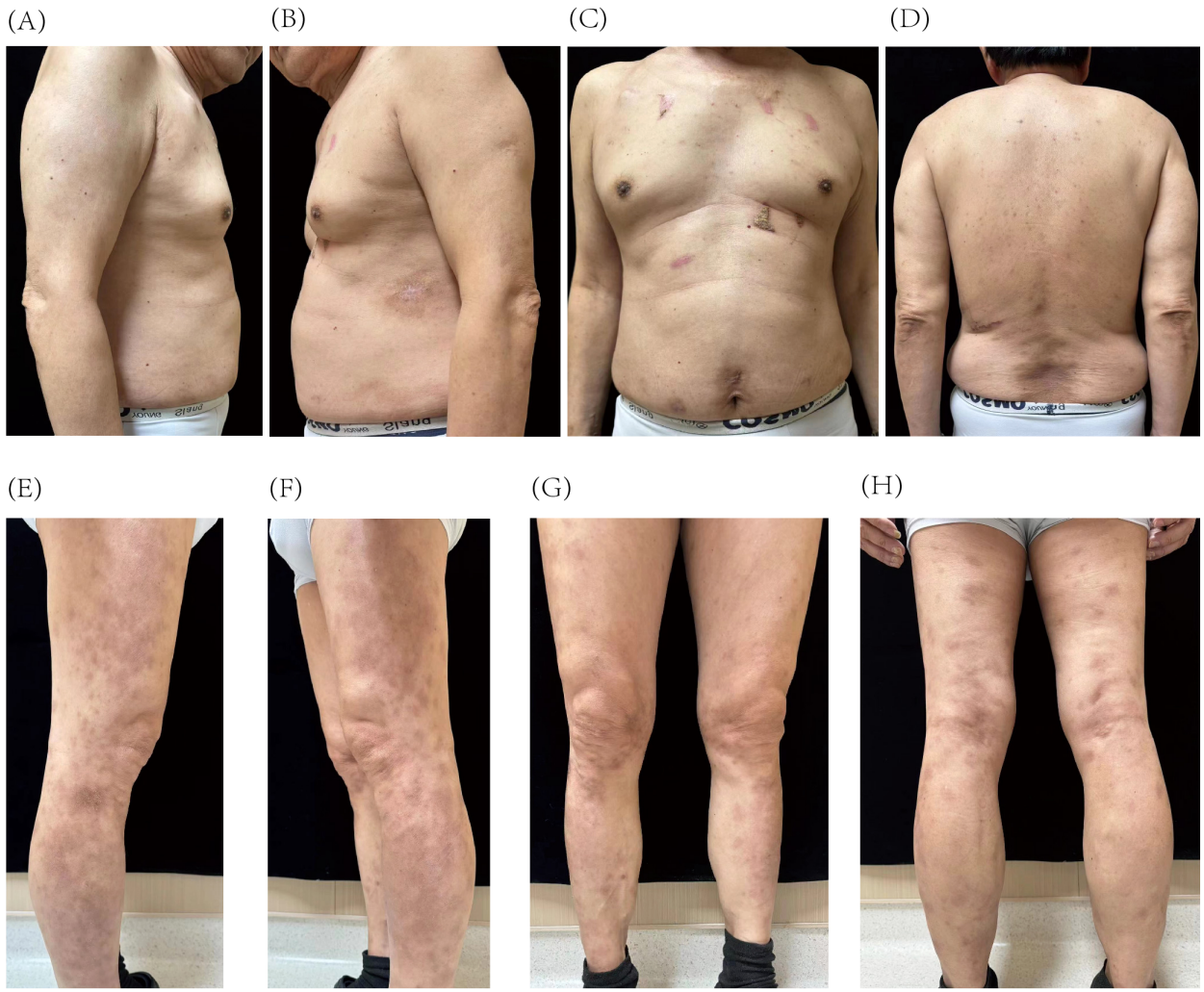

FIGURE 3
Resolution of psoriatic lesions on the trunk **(A–D)** and lower extremities **(E–H)** after 25 weeks of guselkumab treatment.

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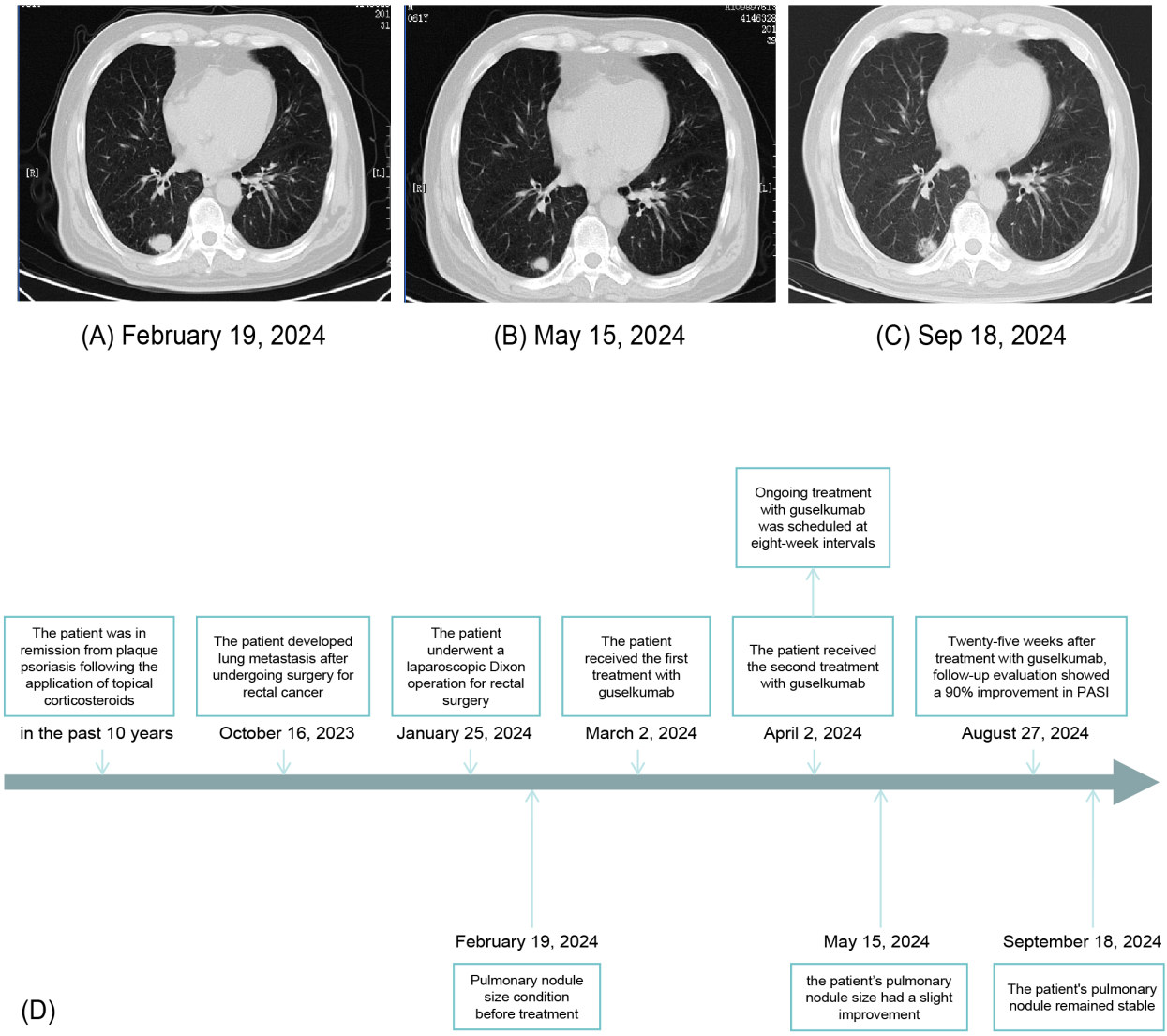

FIGURE 4
Chest computed tomography showing pulmonary nodule size before treatment **(A)**, after 10 weeks of guselkumab treatment **(B)**, and after 29 weeks of guselkumab treatment **(C)**. Timeline of the patient's clinical course and treatment **(D)**.

proliferation of T cells are central to the induction of psoriasis. In patients with a history of psoriasis, tissue-resident memory T cells may significantly contribute to disease recurrence following PD-1 inhibition (10–12).

Numerous biological agents targeting the IL-17/IL-23 axis have been developed for psoriasis management. The selection of appropriate biologics is crucial, especially in cancer patients. Guselkemab was preferred over IL-17 inhibitors due to its higher long-term PASI remission rates, better tolerability, and greater stability. Moreover, guselkumab offers longer dosing intervals compared to IL-17 blockers, thereby enhancing patient adherence and convenience (9). IL-17 inhibitors may negatively affect intestinal barrier homeostasis, posing risks for patients with a history of colorectal cancer and potentially leading to inflammatory bowel disease (13). Considering the patient's history of primary rectal cancer, we deemed the use of an IL-17A inhibitor inappropriate. In contrast, treatment with IL-23 inhibitors did not induce any adverse effects. Additionally, the role of IL-17 in cancer remains controversial (14), with some studies suggesting that IL-17 inhibition may compromise the antitumor effects of ICT (15). Conversely, IL-23 inhibitors are supported by data indicating potential antitumor effects (6, 16, 17).

The antitumor properties of IL-12 and the tumor-promoting effects of IL-23 have been well demonstrated in previous studies (18). Therefore, inhibiting IL-12 could potentially compromise the body's antitumor immune response. Additionally, safety data from a pooled analysis of briakinumab indicated that IL-12/23 inhibition in the treatment of psoriasis may be associated with an increased risk of malignancies (19). Based on these findings, we decided against this class of biologics to treat our patients.

Moreover, we opted not to use other IL-23 inhibitors due to differences in drug affinity for IL-23 and economic considerations. Among these agents, risankizumab and guselkumab exhibit approximately fivefold greater binding affinity for IL-23 and more effectively inhibit IL-23 signaling compared to ustekinumab and tildrakizumab. Both risankizumab and guselkumab fully block IL-23 binding to its receptor IL-23Rα, whereas tildrakizumab does not (20). Furthermore, guselkumab is covered by China's national health insurance program, whereas risankizumab is not. As such, guselkumab was selected as the therapeutic option to reduce the patient's financial burden, making it a more accessible and preferred treatment choice for similar patients in China.

Numerous studies have confirmed the involvement of IL-23 in tumor initiation, progression, and metastasis. Although its exact mechanisms remain incompletely understood, IL-23 has been shown to promote inflammation by upregulating matrix metalloprotease 9 (MMP9), enhancing angiogenesis, reducing CD8 T-cell infiltration, increasing Treg cell activity, suppressing natural killer (NK) cell perforin and interferon (IFN)-γ effector functions, and contributing to tumor persistence during the equilibrium phase (7, 8, 16, 18, 21–23).

IL-23 exerts its biological effects through the IL-23 receptor. Wight et al. demonstrated that reducing IL-23 receptor expression decreases the stability of Treg cells, thereby increasing their sensitivity to IL-12 and enhancing IFN-γ production, ultimately improving the efficiency of antitumor immune responses (6). Experimental studies have also shown that inhibition of the p40 subunit of the IL-23 receptor can activate T cells, while inhibition of the p19 subunit promotes NK cell activation (16, 17). Additionally, suppression of IL-23-mediated angiogenesis may contribute to antitumor activity (24). However, the specific effects of IL-23 inhibition depend on several factors, including the patient's genetic profile, tumor type, and the local balance of IL-12 and IL-23. Therefore, IL-23 antibodies should be used with careful consideration of both genetic and disease-specific factors to ensure their rational application in cancer therapy (25).

Guselkumab has demonstrated a favorable long-term safety profile not only in the general psoriasis population but also in patients with a history of malignancy (9, 26). Furthermore, accumulating evidence suggests that IL-23 inhibitors may reduce the risk of various malignancies. Several studies have reported the potential effectiveness of IL-23 inhibitors against melanoma, breast carcinoma, fibrosarcoma, lung metastases, non-small cell lung cancer, non-Hodgkin lymphoma, hepatobiliary cancer, and basal cell carcinoma (7, 16, 21, 27). Nonetheless, further research is needed to elucidate the molecular mechanisms underlying these effects. While guselkumab appears to offer therapeutic benefits for patients with concurrent cancer and inflammatory disease, definitive conclusions regarding its role in oncologic therapy remain unsupported by sufficient evidence. Clinicians should therefore carefully weigh the potential risks and benefits when managing such complex clinical cases. Ongoing investigation is essential to clarify the role of IL-23 inhibitors in cancer treatment and to inform future evidence-based guidelines.

In conclusion, although sintilimab-associated psoriasis is a rare immune-related adverse event in lung cancer treatment, it can profoundly affect a patient's quality of life and mental health. To the best of our knowledge, this is the first reported case of successful management of sintilimab-exacerbated psoriasis using guselkumab, highlighting a potential therapeutic approach for this uncommon but clinically significant complication.

Patient perspective

I agreed to the use of guselkumab for alleviating my lesions after being fully informed by my physician of the potential risk of metastasis, as the severity of my psoriasis had caused me considerable distress. The actual therapeutic response has confirmed that guselkumab was the right choice for managing my condition.

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.

Ethics statement

The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was also obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

JK: Conceptualization, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. MG: Conceptualization, Investigation, Resources, Supervision, Validation, Writing – review & editing. XZ: Conceptualization, Supervision, Writing – review & editing. NL: Writing – review & editing, Resources, Supervision. QM: Supervision, Writing – review & editing, Resources. HD: Resources, Investigation, Writing – review & editing, Conceptualization, Supervision, Funding acquisition.

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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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Targeted therapies induced depigmentation: a review

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Skin depigmentation or vitiligo-like depigmentation (VLD) is one of the most prevalent cutaneous adverse events during targeted therapies for cancers or autoimmune diseases. The depigmentation is usually with high mental burden and affect the disease treatment, some of which are even clinical markers for good prognosis. This study aimed to explore the underlying immunopathologic mechanisms of VLD induced by targeted therapy for cancer and autoimmune disease as well as vaccine, such as immune checkpoint inhibitors (e.g., programmed death 1/programmed death–ligand 1 and cytotoxic T-lymphocyte antigen-4 inhibitors), v-raf murine sarcoma viral oncogene homolog inhibitors, tyrosine kinase inhibitors, and other targeted agents. Additionally, it examined the clinical presentations, prognostic implications, and management strategies for VLD across oncologic and nononcologic contexts, including cases associated with vaccines and biologics. The development of VLD often correlates with improved therapeutic outcomes, but it presents unique challenges in balancing antitumor efficacy with patients' quality of life. This review integrated insights from oncology, dermatology, and immunology, and underscored the need for multidisciplinary approaches to enhance the understanding, prevention, and management of these complex cutaneous adverse events.

KEYWORDS

targeted drugs, depigmentation, melanocytes, vaccine, autoimmunity, adverse drug reactions

1 Introduction

Targeted therapies have transformed the treatment landscape for malignancies and autoimmune diseases by specifically disrupting molecular pathways or modulating immune responses. These advancements have significantly improved therapeutic efficacy and patient survival. However, with the broader adoption of these therapies, the incidence of immune-mediated adverse events, particularly vitiligo-like depigmentation (VLD), has garnered increasing attention. VLD, often observed in patients undergoing treatments such as immune checkpoint inhibitors (ICIs), kinase inhibitors, and biologics, represents a unique intersection of therapeutic benefit and psychosocial challenge. While its occurrence is frequently correlated with enhanced treatment outcomes, the disfiguring nature of VLD

profoundly affects patients' mental health, potentially leading to anxiety, depression, and diminished quality of life. Notably, VLD is not confined to oncologic treatments but is also reported in non-cancer contexts, such as autoimmune disease management and vaccine-induced immune responses. This highlights its broad clinical relevance and the need to understand its underlying mechanisms. This review synthesizes current evidence on therapy-induced VLD, focusing on its immunopathological basis, clinical manifestations, and prognostic implications. By integrating insights from oncology, dermatology, and immunology, it underscores the necessity of multidisciplinary approaches to optimize management strategies that address not only therapeutic goals but also the psychological well-being of patients.

2 Targeted therapies in cancer

2.1 Programmed death protein 1/ligand 1 inhibitor

Programmed death 1 (PD-1) is a critical immune checkpoint molecule that regulates the immune system by downregulating T-cell activity. In the tumor microenvironment, T lymphocytes express high levels of PD-1, whereas its ligand, programmed death 1–ligand 1 (PD-L1), is expressed on the surface of tumor cells. The interaction between PD-1 on activated T cells and PD-L1 on tumor cells allows tumors to evade T-cell immune surveillance, directly suppressing tumor cell apoptosis (1, 2) PD-1 inhibitors block the binding of PD-1 to PD-L1, which relieves tumor-induced suppression of T lymphocytes, and prevents immune evasion by tumor cells, and achieving antitumor effects (3). PD-1/PD-L1 inhibitors help the immune system recognize and enhance the attack on tumor cells. However, melanoma cells and normal melanocytes share common antigens (MART-1/Melan A, gp100, tyrosinase-related protein 1, 2). During the immune destruction of tumor cells, the release of melanocyte antigens leads to the destruction of the immune privilege of normal melanocytes, which may cause normal melanocytes to be attacked by CD8+ cytotoxic T cells (3–10), thereby inducing VLD. Patients with melanoma receiving PD-1/PD-L1 inhibitors have demonstrated an increased incidence of VLD, ranging from 2% to 25%, which is considerably higher than the prevalence of vitiligo in the general population (estimated globally at 0.5% to 1%) (10). Furthermore, studies have indicated that the overall incidence of VLD in patients treated with pembrolizumab and nivolumab was 8.3% and 7.5%, respectively (5). The occurrence of VLD may indicate a better therapeutic response (3, 11, 12), and is associated with increased progression-free survival and overall survival (6, 9, 13–16). Studies have shown that patients experiencing VLD have a twofold and fourfold reduction in the risks of disease progression and mortality, respectively (17, 18). Unlike classic vitiligo, VLD induced by immune checkpoint inhibitors (ICIs) typically occurs in sun-exposed areas and presents as asymmetric, spot-like patches that gradually evolve into larger lesions (4, 10, 13, 19–22). This condition does not accompany the Koebner phenomenon and usually emerges several months after the initiation of treatment and persists even after stopping the therapy (3). Patients generally lack a personal or family history of other autoimmune diseases. Patients with VLD serum levels of CXCL10, CXCR3 expression in skin CD8 T cells, and levels of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are significantly elevated (23, 24). Elevated levels of these markers have also been found in patients with vitiligo, and the IFN-γ-CXCL9/10-CXCR3 axis is believed to play a central role in the progression and maintenance of the disease. This suggests that similar mechanisms of Th1/TC1-driven immune responses may exist in both (10). It has also been suggested that PD-1/PD-L1 function is impaired in patients with vitiligo, leading to loss of peripheral tolerance and ineffective suppression of autoreactive T cells, which in turn attack melanocytes. In the Pmel-1 vitiligo mouse model, PD-L1 fusion protein treatment can restore some pigment loss, increase the number of regulatory T cells in the skin, and reduce melanocyte-reactive T cells, with no significant side effects observed (25).

Systemic immunosuppressive therapy is the first line of treatment for vitiligo. However, this therapy is not recommended for vitiligo induced by ICIs, as it may reduce the therapeutic response to ICIs and has limited efficacy in managing this condition (4, 10). Case reports have documented that narrowband ultraviolet B (NB-UVB) phototherapy improved VLD by 15%-40% (26). Partial spontaneous repigmentation in VLD areas is also observed; however, computed tomography (CT) scans revealed disease progression (27). Repigmentation of VLD may serve as an alternative marker of disease progression or recurrence, particularly in cases responding to PD-1 therapy.

A few recent studies have reported vitiligo-like lesions in patients with other solid tumors, such as renal cell carcinoma (28, 29), non-small-cell lung cancer (NSCLC) (1, 20, 30), esophageal squamous cell carcinoma (31), hepatocellular carcinoma (32), gastric cancer (20), rectal cancer (33), and urothelial carcinoma (34), although these occurrences are relatively rare. For instance, in a case involving a patient with metastatic non-small cell lung cancer (NSCLC), vitiligo-like lesions appeared in sun-exposed areas (face, neck, forearms, and hands) after 15 months of nivolumab treatment. Immunohistochemical analysis revealed substantial CD8+ T-cell infiltration within and around the lesions (35). Antigens released from melanocyte destruction due to intense sun exposure may have caused these vitiligo-like lesions. Alternatively, the patient's NSCLC tumor may have shared antigens with melanocytes. In another case, an elderly patient with stage III b rectal cancer developed vitiligo after treatment with toripalimab. Following radiotherapy (RT), the vitiligo lesions rapidly expanded, accompanied by severe pruritus (33). Upon discontinuation of anti-PD-1 therapy, both the vitiligo lesions and pruritus improved rapidly. Additionally, the patient was treated with topical halometasone cream and a film-forming agent containing salicylic acid, clobetasol propionate, and anthralin, which led to significant repigmentation within 1 month. Both anti-PD-1 therapy and RT possess immune-stimulating capacities, which may exhibit synergistic effects when used in combination.

2.2 Cytotoxic T-lymphocyte-associated antigen-4 inhibitors

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a key regulatory factor in maintaining T-cell homeostasis and tolerance, which blocks the binding of CD28 to CD80 and CD86 (also known as B7–1 and B7-2), thereby reducing T-cell receptor signaling (3, 36, 37). Anti-CTLA-4 antibodies can reactivate and relieve the immunosuppression of $CD4^+$ and $CD8^+$ T cells, enhance the activation and proliferation of effector T cells, and reduce the immunosuppressive effect of regulatory T cells (Tregs) through antibody-dependent cellular cytotoxicity (ADCC), further reducing the presence of Tregs in tumor tissues (3). In the absence of CTLA–4 regulation, $CD4^+$ T cells provide key assisting signals to promote $CD8^+$ T cells to recognize melanocyte differentiation antigens (such as MART-1, TYR, and gp100) and migrate to the epidermis (38, 39). Activated $CD8^+$ T cells release IFN-γ and TNF-α, inducing local chemotaxis mediated by the CXCL10-CXCR3 axis, causing apoptosis and clearance of melanocytes, manifested as vitiligo-like depigmentation (23, 39). Among patients with melanoma treated with anti-CTLA-4 therapy, the incidence of VLD in those receiving anti-CTLA-4 therapy ranges from 2% to 9% (3). Ipilimumab and tremelimumab are fully human monoclonal antibodies of the immunoglobulin G 1 and 2 (IgG1 and IgG2) subclasses, respectively. They block the interaction between the inhibitory molecule CTLA-4 on T cells and the B7 receptors on antigen-presenting cells. Studies have shown that 4%–11% of patients with melanoma treated with ipilimumab experience VLD (36). When combined with PD-1 inhibitors, the overall incidence of VLD rises to approximately 8% (20). Compared with nivolumab monotherapy, combination therapy with nivolumab and ipilimumab results in a shorter onset time for VLD (3.2 vs. 10.3 months). The characteristics of VLD induced by CTLA-4 inhibitors and PD-1/PD-L1 inhibitors are similar, with rare cases of near-total body depigmentation reported (40).

2.3 V-raf murine sarcoma viral oncogene homolog inhibitors

The v-raf murine sarcoma viral oncogene homolog (BRAF) is the most common serine-threonine protein kinase. It plays a key role in regulating intracellular signal transduction from RAS to the MEK pathway. BRAF mutations have been identified in multiple malignancies, with the BRAF V600E mutation being the most common mutation type across several cancers. In China, approximately 23.7% of patients with melanoma harbor BRAF mutations (41). Vemurafenib is the first oral drug approved for treating metastatic melanoma with BRAF V600E mutations and a significant treatment for advanced melanoma. Vitiligo-like lesions are rarely reported with BRAF inhibitors like vemurafenib or dabrafenib. Only isolated case reports, sometimes in combination with MEK inhibitors, have described depigmentation. BRAF inhibitors can enhance the expression of major histocompatibility complex (MHC) class I and class II molecules and, melanocyte differentiation antigen (MDA), while reducing PD-L1 and suppressor cells (Treg/Myeloid-Derived Suppressor Cells), reshaping the tumor microenvironment and promoting $CD8^+$ T cell infiltration and activation. These $CD8^+$ T cells cross-recognize melanocyte antigens (such as MART-1, gp100), combine IFN-γ/TNF-α and CXCL10–CXCR3 chemotaxis, and mediate apoptosis and clearance of normal melanocytes (21, 42). VLD typically appears in symmetric facial regions, forearms, and lower limbs. BRAF inhibitors may induce VLD by altering melanocyte function or triggering an immune response, which is often associated with favorable prognoses (43–45). Evidence suggests that four patients who developed VLD while receiving combined BRAF and MEK inhibitor therapy survived for up to 57 months (21). In another study, a patient who developed VLD following sequential treatment with nivolumab and vemurafenib showed no progression 18 months after the onset of brain metastasis, which is a common occurrence in advanced melanoma with a poor prognosis and median overall survival of approximately 4 months (46).

2.4 Cyclin-dependent kinase 4/6 inhibitors

Cyclin-dependent kinases (CDKs) are critical regulators of cell cycle progression, interacting with cyclin D to promote the hyperphosphorylation of retinoblastoma protein (Rb), thereby advancing the cell cycle from the G1 phase to the S phase. CDK4/6 inhibitors obstruct kinase activity, thereby blocking this G1-to-S phase transition and preventing cancer cell progression. Palbociclib, ribociclib, and abemaciclib are CDK inhibitors approved as targeted therapies for hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer, the largest subtype of this malignancy. Palbociclib was the first CDK4/6 inhibitor approved by the United States Food and Drug Administration (US FDA) in 2015; it targets HR-positive/HER2-negative breast cancer. Ribociclib followed as the second CDK4/6 inhibitor approved in 2017, and abemaciclib was the third FDA-approved CDK4/6 inhibitor, indicated for use with aromatase inhibitors or fulvestrant in treating advanced or metastatic HR-positive/HER2-negative breast cancer (47). A multicenter retrospective study involving 16 patients with stage IV breast cancer reported that VLD was associated with CDK4/6 inhibitor treatment (14 of 16 were treated with ribociclib, and two of 16 with palbociclib) (48). The lesions initially appeared as small hypopigmented spots on sun-exposed areas (face, hands, and chest), gradually expanding bilaterally over the trunk and limbs. All patients reported itching. The patients achieved partial relief after monotherapy or combination treatment using topical calcineurin inhibitors and corticosteroids. Similarly, another multicenter study including 10 patients found that sun-exposed areas, such as arms and face, were the most affected. Although various therapies, such as topicals, lasers, and phototherapy, were attempted, only minimal success was observed, with mild repigmentation noted in one patient treated with ruxolitinib cream (49). Some patients experienced spontaneous depigmentation reduction within months after discontinuing the CDK4/6 inhibitors (50). A pre-inflammatory

phase appears to be another characteristic of CDK4/6 inhibitor-induced VLD. In one study, a 50-year-old woman with metastatic breast cancer developed erythema and periorbital whitening after 1.5 years of ribociclib treatment, which was diagnosed as photosensitive dermatitis and vitiligo (51). Her facial rash resolved completely with twice-daily topical steroids, after which VLD appeared. This was further corroborated in a study of 16 patients, where 11 experienced a pre-vitiligo inflammatory phase characterized by a diffuse papular rash with pruritus (48). The underlying mechanism is likely multifactorial, involving both direct cytotoxic effects on melanocytes and indirect modulation of immune responses.

CDK4/6 inhibitors exert cytostatic effects by inducing G1 cell cycle arrest not only in tumor cells but also in normal proliferative cells, including keratinocytes and melanocytes. Keratinocytes play a vital role in supporting melanocyte survival and function through paracrine factors such as stem cell factor (SCF) and endothelin-1 (ET-1) (52, 53). Inhibition of keratinocyte proliferation may disrupt this supportive niche, rendering melanocytes more vulnerable to stress-induced apoptosis.

Concomitantly, the immunological landscape is significantly altered. CDK4/6 inhibitors have been shown to downregulate regulatory T cell populations and enhance MHC-I expression on both tumor and stromal cells, thereby promoting antigen presentation (54, 55). In the context of melanocyte apoptosis and subsequent release of melanocyte-associated antigens, these immune changes may foster cytotoxic T lymphocyte –mediated responses against melanocytes. Histopathologic findings from VLD cases associated with CDK4/6 inhibitors often reveal loss of melanocytes in the basal layer, $CD8^+$ T cell infiltration, supporting an immune-mediated melanocytotoxic process (56). Collectively, these observations suggest that CDK4/6 inhibitors can lead to melanocyte destruction through mechanisms such as cell cycle disruption, inhibition of keratinocyte-melanocyte crosstalk, and T cell-mediated cytotoxicity. Whether the occurrence of VLD is beneficial to survival is still unclear (48, 49).

2.5 BCR-ABL tyrosine kinase inhibitors

Chronic myeloid leukemia (CML) constitutes 15% of adult leukemias and is characterized by the malignant proliferation of hematopoietic stem cells within the bone marrow (57). The BCR-ABL1 fusion gene encodes the BCR-ABL1 protein, which exhibits potent tyrosine kinase activity, that leads to abnormal signal pathway activation, rapid tumor cell proliferation, and inhibition of apoptosis. Targeted therapy has significantly advanced CML treatment, with BCR-ABL tyrosine kinase inhibitors (TKIs) now the most preferred treatment, which improves the 10-year survival rate from 20% to 80%–90%. TKIs include the first-generation agent imatinib, second-generation agents dasatinib, nilotinib, and bosutinib, and third-generation agents ponatinib and olverembatinib.

Although TKIs have extended the lifespan of patients with CML, they can cause adverse effects. One study reported pigmentary side effects of imatinib, with 40.9% and 3.6% of 118 patients experiencing hypopigmentation and hyperpigmentation (58). In one study, a pediatric patient with Ph-positive acute lymphoblastic leukemia (ALL) relapsed post-hematopoietic stem cell transplantation and received dasatinib. After 4 weeks of treatment, depigmented patches appeared on the neck and dorsum of the hands, and complete depigmentation of hair, eyelashes, and eyebrows was observed (59). In another study, a patient in the chronic phase of CML developed widespread depigmented macules after achieving a deep molecular response with imatinib for 1 year (60). In addition to BCR-ABL, TKIs also target multiple tyrosine kinases, such as the c-Kit proto-oncogene. c-Kit and its ligand stem cell factor (SCF) play important roles in melanogenesis, melanocyte homeostasis, and UV-induced pigmentation. Therefore, inhibition of the c-Kit/SCF signaling pathway is considered to be the cause of pigmentary side effects in patients receiving TKI treatment. A clinical example of this signaling pathway is seen in patients with piebaldism, an autosomal dominant disorder caused by mutations in the KIT oncogene, which results in the loss of melanocytes and the appearance of white spots (61).

2.6 Epidermal growth factor receptor tyrosine kinase inhibitors

Epidermal growth factor receptor (EGFR) is a key stimulator of cancer growth and is closely associated with tumorigenesis, making EGFR-TKIs a critical focus in anticancer drug development. EGFR-TKIs are classified into three generations; the first-generation agents include gefitinib and erlotinib, the second-generation agents include afatinib and dacomitinib, and the third-generation agents include osimertinib, aumolertinib, and furmonertinib. These are widely used to treat colorectal cancer, NSCLC, pancreatic cancer, and other malignancies. Given that the EGFR signaling pathway is essential for maintaining the integrity of the skin barrier, skin toxicity is a prevalent side effect of EGFR inhibitors. Current reports mainly focus on skin inflammation or acne-like rash, and rarely see long-term observations of white spots or skin pigment changes.

Gefitinib is a TKI that targets and inhibits EGFR. It was initially approved for NSCLC treatment. Its use has expanded to other solid tumors, such as breast, colorectal, and head and neck cancers. Gefitinib rarely causes vitiligo. In one reported case, a patient with metastatic squamous cell carcinoma of the parotid gland developed vitiligo 1 month after initiating gefitinib treatment (62). The patient's depigmentation spread, leading to extensive and progressive loss of pigmentation across the arms, upper back, neck, face, left hip, and right chest. The depigmentation persisted even 3 years after stopping the medication. It is currently hypothesized that gefitinib and a similar tyrosine kinase inhibitor, dasatinib, may be caused by mutations in the proto-oncogene c-Kit and blockade of the melanocyte stem cell factor ligand and c-Kit signaling pathways.

2.7 Anaplastic lymphoma kinase - tyrosine kinase inhibitors

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that belongs to the insulin receptor superfamily. It activates multiple intracellular signaling pathways, thereby regulating cell growth, transformation, and anti-apoptotic processes. ALK gene rearrangements, mutations, or amplifications have been identified in various tumors, activating downstream signaling pathways and enhancing cancer cell proliferation, growth, and invasion. ALK TKIs include the first-generation agent crizotinib, the second-generation agents ceritinib, alectinib, and brigatinib, and the third-generation agent lorlatinib. We previously reported a patient with NSCLC who developed new depigmented patches after 1 year of alectinib treatment, achieved rapid and unexpected repigmentation through laser therapy (63). Due to the rarity of such cases, we hypothesize that ALK inhibitors may negatively regulate melanocytes, leading to vitiligo-like depigmentation, but the specific mechanism remains to be further explored.

2.8 B-cell lymphoma-2 inhibitors

Venetoclax, was approved by the FDA in 2016 as the world's first Bcl-2 inhibitor. Venetoclax has a high affinity for the BH3 binding domain of Bcl-2, It inhibits the overexpression of Bcl-2 in acute myeloid leukemia (AML) cells, promoting apoptosis and inhibiting cell proliferation. Venetoclax has been approved as a first-line treatment for chronic lymphocytic leukemia (CLL). The first reported case of venetoclax-induced vitiligo involved a 71-year-old woman treated for AML (64). Vitiligo initially appeared on the back of her hands and spread to her neck and chest. She had to temporarily discontinue venetoclax due to diarrhea and pancytopenia, and during this time, vitiligo completely resolved. However, shortly after resuming the drug, the condition reappeared. Another case involved a 77-year-old man with Rai stage II CLL who developed vitiligo on his limbs after 2 years of treatment (65). Bcl-2 is a key molecule for cell anti-apoptosis. Its inhibition may make melanocytes more sensitive to stress stimuli (such as light and oxidative stress), making them more susceptible to apoptosis or leading to cytotoxic T cell-mediated melanocyte destruction, causing pigmentation reduction.

2.9 Chemokine receptor 4 monoclonal antibody

CCR4 is mainly expressed on regulatory T cells (Tregs) and helper T cells type 2 (Th2). Tregs play a key role in maintaining immune tolerance and preventing autoimmune reactions. Mogamulizumab is an innovative defucosylated monoclonal antibody that targets C-C chemokine receptor 4 and can eliminate Sézary cells through antibody-dependent cell-mediated cytotoxicity (ADCC). In one study, three patients with Sézary syndrome developed vitiligo 6–8 months after starting mogamulizumab treatment, with depigmented patches on the face, hands, scalp, upper limbs, legs, and trunk. Mogamulizumab can also eliminate CCR4-expressing Tregs through ADCC. The depletion of Tregs may lead to a reduction in immunosuppression, resulting in enhanced activity of cytotoxic T cells (CTLs). When Tregs are exhausted, the activity of CTLs may increase, which may lead to an autoimmune attack on melanocytes. Notably, the development of vitiligo was associated with sustained complete remission or significant partial remission of mycosis fungoides (66). These cancer therapies and their association with VLD are summarized in Table 1A.

TABLE 1A VLD associated with cancer therapies.

Drug class	Representative agents	Indications	VLD incidence	Proposed mechanism
PD-1/PD-L1 inhibitors	Pembrolizumab, Nivolumab, etc.	melanoma	Common (2%~25%) (10)	Enhanced immune response destroys melanocytes via shared antigens
		non-melanoma cancers	Very rare (30–34)	
CTLA-4 inhibitors	Ipilimumab	melanoma	Uncommon(2%~9%) (3)	
BRAF Inhibitors	Vemurafenib	melanoma	Very rare (43–45)	
CDK4/6 Inhibitors	Palbociclib, Ribociclib	breast cancer	Rare (48, 49)	Blocks the cell cycle of keratinocytes and melanocytes to reduce melanocyte support
BCR-ABL TKI	Imatinib	chronic myeloid leukemia	Common (40.9%) (58)	Inhibition of the c-Kit/SCF signaling pathway
EGFR TKI	Gefitinib	squamous cell carcinoma	Case reports only (62)	
ALK TKI	Alectinib	Non-small cell lung cancer	Case reports only (63)	Unknown
Bcl-2 Inhibitors	Venetoclax	Acute myeloid leukemia, chronic lymphocytic leukemia	Case reports only (64, 65)	Increased sensitivity to stressors such as light and oxidative stress
CCR4 Antagonists	Mogamulizumab	Sézary syndrome	Case reports only (66)	Depletion of Treg cells

3 Targeted therapies for autoimmune diseases

3.1 Anti-interleukin-17A monoclonal antibodies

Interleukin (IL)-17 inhibitors are biologic therapies approved for moderate-to-severe psoriasis and psoriatic arthritis. Secukinumab is a human IgG1 monoclonal antibody targeting IL-17A, whereas ixekizumab is a humanized IgG4 monoclonal antibody that binds to and inhibits IL-17A, thereby neutralizing both IL-17A homodimers and IL-17A/F heterodimers. IL-17A inhibitors rarely induce VLD. In one study, a patient with severe plaque psoriasis achieved complete skin clearance (PASI 100 response) after 4 weeks of ixekizumab treatment, but depigmented patches and plaques appeared on the face, particularly on the cheeks and chin, by week 12 (67). Vitiligo was confirmed by dermatological examination, including Wood's lamp analysis, confirmed the diagnosis of vitiligo. Another patient with a 32-year history of psoriasis developed extensive new vitiligo in the trunk, limbs, and face after switching from secukinumab (discontinued due to side effects) to ixekizumab for 11 months (68).

The mechanism by which IL-17 inhibitors contribute to vitiligo remains unclear. One theory suggests that IL-17 inhibitors may induce an imbalance in the T helper cell 17 (Th17)/T helper cell 1 (Th1) response, with cytokines secreted by Th1 cells activating natural killer cells and cytotoxic CD8+ T cells targeting melanocytes. In one study, a patient's psoriasis and VLD were both managed successfully after discontinuing IL-17A inhibitors and switching to cyclosporine. Within 3 months of cyclosporine use, 75% repigmentation was achieved (69). This effect could be attributed to cyclosporine's broad T-cell calcineurin-inhibitory activity, which does not disrupt the Th1/Th17 balance, thus controlling both psoriasis and vitiligo.

In a patient treated with secukinumab, previously stable depigmented patches for over 2 years became larger and more pronounced (70). Skin biopsy showed an absence of epidermal melanocytes and gp100 immunoreactivity. Compared with pretreatment psoriatic lesions, posttreatment vitiligo lesions displayed higher staining levels of CD8, IFN-γ, and CXCL10, whereas staining levels of IL-17A and TNF-α were lower. The progression of vitiligo halted following topical tacrolimus therapy. Topical steroids have also shown some efficacy in some patients (71).

In some studies, vitiligo developed after treatment with adalimumab. Discontinuing adalimumab and initiating secukinumab led to gradual improvement in both vitiligo and psoriatic symptoms, with nearly complete repigmentation in depigmented areas after 1 year of treatment (72). Similarly, a 1-year-old patient with generalized pustular psoriasis developed segmental vitiligo following acitretin treatment (73). Despite a 4-month regimen of topical steroids and tacrolimus, vitiligo continued to spread to the face and trunk. After initiation of secukinumab treatment along with topical steroid use, the patient's pustular psoriasis fully resolved, vitiligo progression stopped, and partial repigmentation was observed after three doses.

3.2 Anti-TNF-α monoclonal antibodies

TNF-α is a key mediator of inflammation and is targeted by several anti-TNF agents, including infliximab, adalimumab, and etanercept. To date, approximately one million patients worldwide have received anti-TNF therapy for conditions such as ankylosing spondylitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, and psoriatic arthritis. Also, increased TNF-α levels have been observed in skin samples from patients with vitiligo. TNF-α appears to be a key factor in the pathogenesis of vitiligo, as it inhibits melanocyte proliferation and function.

Paradoxically, cases of new-onset vitiligo or worsening of existing vitiligo have also been reported during anti-TNF therapy. For example, new or expanded vitiligo was found in patients treated with adalimumab (74), infliximab (75), and golimumab (76), with improvements observed upon drug discontinuation or use of adjunctive therapies such as tacrolimus ointment and excimer laser therapy (80, 83, 84). A 10-year cohort study indicated that patients receiving anti-TNF therapy had approximately twice the risk of developing vitiligo compared with those receiving conventional treatment (77). Among anti-TNF drugs, patients treated with etanercept had the highest risk of developing vitiligo, followed by infliximab and adalimumab. In patients younger than 40 years, the risk of developing vitiligo was 3.7 times higher in the anti-TNF group compared with the nonexposed group.

Several theories have been proposed to explain the development of autoimmunity during anti-TNF therapy (74). *In vivo* studies have indicated an increase in nucleosomes, which are major self-antigens released during apoptosis, potentially leading to subsequent autoantibody induction (78). Additionally, cytotoxic T cells are thought to play an essential role in suppressing autoreactive B cells, and TNF blockade may weaken this suppression, possibly allowing autoimmunity to emerge (79). Moreover, TNF inhibition may trigger cytokine shifts and activate autoreactive T cells in the epidermis, destroying melanocyte cells (80).

3.3 Anti-IL-12/23 monoclonal antibodies

Ustekinumab is a monoclonal antibody targeting the shared p40 subunit of IL-12/23, approved for the treating of moderate-to-severe plaque psoriasis, psoriatic arthritis, and inflammatory bowel disease. In one study, a patient with a 4-year history of psoriatic arthritis developed depigmented lesions on the dorsal side of the fingers by week 16 of ustekinumab treatment, which appeared white under Wood's lamp examination (81). Although Ustekinumab inhibits both the IL-12 and IL-23 pathways, its inhibition of the Th17 axis is more significant in real-life settings (82). In the context of Th17 inhibition, the Th1 immune response

may be relatively active due to lack of regulation (83), thereby enhancing the activation of the IFN-γ/CXCL10 axis, promoting $CXCR3^+$ $CD8^+$ T cell recruitment and melanocyte destruction, and inducing or aggravating vitiligo. This hypothesis still needs to be confirmed by more experiments, but it provides a reasonable immunological basis for explaining Ustekinumab-related vitiligo.

3.4 Anti-CD52 monoclonal antibodies

Multiple sclerosis (MS) is a chronic autoimmune T-cell-mediated disease that affects the central nervous system and is primarily seen in young adults. It occurs when the immune system attacks the myelin sheath and, eventually, axons and neurons, causing inflammation and degeneration along the neural axis (84). Alemtuzumab is a humanized monoclonal antibody targeting the glycoprotein CD52, which is expressed on the surface of T and B lymphocytes, natural killer cells, monocytes, and macrophages. Initially approved for treating CLL, alemtuzumab has been used for several years to treat relapsing-remitting multiple sclerosis (RRMS) (85). The first case of nonsegmental vitiligo (NSV) was observed in 2018 in a patient who developed NSV 5 months after the initial cycle of alemtuzumab (86). Another patient with RRMS presented with halo nevi-like depigmentation across the skin, with immunohistochemistry revealing melanocyte loss in the depigmented halo areas and T-cell infiltration in the upper dermis (87). Notably, this patient showed about a sixfold increase in anti-tyrosinase antibodies and about a threefold increase in anti-tyrosinase-related protein-1 antibodies.

In another study, a patient with RRMS receiving alemtuzumab developed acquired hemophilia (AHA) alongside an expansion of stable cervical vitiligo in multiple body areas (84) Following alemtuzumab, B cells recover faster than T cells during the immune reconstitution phase. This T-cell regulation deficiency allows uncontrolled B-cell activity, potentially increasing autoimmunity in certain cell populations (88, 89). This mechanism may explain the induction of melanocyte-specific antibodies in NSV and halo nevus-like depigmentation following alemtuzumab. Ruck and colleagues reported that three cases where patients developed vitiligo approximately 1 year after treatment initiation (90). An increase in activated CD8+ T cells was observed at vitiligo onset in alemtuzumab-treated patients compared with those without vitiligo, suggesting a role for these cells play a role in the pathogenesis of depigmentation. Alemtuzumab selectively depletes circulating T cells, including regulatory T cells, while sparing skin-resident memory T cells. According to a recent study in multiple sclerosis patients, peripheral $CD4^+CD25^+FoxP3^+$ Tregs were profoundly reduced within one week after treatment, with only partial recovery over months (91). In contrast, TRM cells in non-lymphoid tissues such as the skin express lower levels of CD52 and are largely unaffected (92). The transient loss of Treg-mediated immune regulation may allow skin TRM—particularly $CD8^+$ IFN-γ–producing cells—to become activated in a pro-inflammatory microenvironment. This imbalance can promote melanocyte destruction and may underlie the development of VLD observed in patients treated with alemtuzumab. Furthermore, anti-inflammatory cytokines, including IFN-γ, TNF-α, IL-6, and IL-21, are released during alemtuzumab therapy, which may also contribute to VLD development.

3.5 IL -4 receptor antagonist

Dupilumab is a fully human monoclonal antibody (IgG4 type) targeting the IL-4 receptor alpha (IL-4R-α) subunit. It inhibits IL-4/IL-13 signaling pathways, demonstrating high efficacy and tolerability in atopic dermatitis (AD) management. In a patient with AD with a small patch of NSV on the forehead, dupilumab significantly improved AD symptoms, including nodules and itching (93). However, after initiating dupilumab, the vitiligo patch expanded rapidly causing gray hair. Phototherapy and topical corticosteroids proved ineffective. After discontinuing dupilumab, slight repigmentation was observed over the following 17 months, although the size of remained unchanged.

Dupilumab acts by blocking T helper cell 2 (Th2) cytokines, potentially shifting the immune balance toward Th/Tc1 polarization. In vitiligo, CD4+ and CD8+ T cells play crucial roles by producing Th1/Tc1 signature cytokines such as IFN-γ and TNF-α. The inhibition of Th2 cytokines by dupilumab may activate Th/Tc1 cells and CD8+CD49a+ tissue-resident memory T cells in small vitiligo lesions, potentially leading to the expansion of NSV-affected skin patches.

3.6 IL-6 receptor antagonist

Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor. It was approved for treating rheumatoid arthritis and juvenile idiopathic arthritis (JIA). A patient with JIA developed multiple halo nevi after 3 years of tocilizumab treatment, which was unresponsive to UVB therapy (94). Another 33-year-old woman developed halo naevi, vitiligo, and diffuse alopecia areata after tocilizumab treatment. The researchers speculated that IL-6 may cause immune-mediated damage to melanocytes by affecting the balance between Tregs and Th17 cells (95). A summary of these autoimmune disease therapies that can induce VLD is provided in Table 1B.

4 Vaccines

Several studies have reported the onset of vitiligo-like depigmentation (VLD) following Coronavirus Disease 2019 (COVID-19) vaccination. These cases involved individuals of various ages, sexes, and ethnic backgrounds, and were associated with a range of COVID-19 vaccines, including Pfizer-BioNTech, Moderna, AstraZeneca, and Sinovac (96). VLD typically emerged within a few weeks post-vaccination, with an average onset of 2.1 weeks. In certain cases, a strong temporal relationship between vaccination and VLD development was observed (97).

Multiple immunological mechanisms have been proposed to explain this phenomenon. One possibility is molecular mimicry, in

TABLE 1B VLD associated with treatments for autoimmune diseases.

Drug class	Representative agents	Indications	VLD incidence	Proposed mechanism
IL-17 Inhibitors	Secukinumab	psoriasis and psoriatic arthritis	Very rare (67, 68)	Imbalance in the T helper cell 17/ T helper cell 1 response
TNF-α Inhibitors	Etanercept	Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis and psoriatic arthritis	Rare (77)	Increased release of autoantigens, induction of autoantibodies; decreased suppression of autoreactive B cells by cytotoxic T cells
IL-12/23 Inhibitors	Ustekinumab	psoriasis and psoriatic arthritis	Very rare (81)	Imbalance in the T helper cell 17/ T helper cell 1 response
CD52 Monoclonal Antibodies	Alemtuzumab	multiple sclerosis	Very rare (86, 87)	Depletion of regulatory T cells but preservation of skin-resident memory T cells
IL-4R Antagonists	Dupilumab	atopic dermatitis	Case reports only (93)	Blocking T helper 2 cytokines may shift the immune balance toward Th/Tc1 polarization
IL-6R Antagonists	Tocilizumab	rheumatoid arthritis and juvenile idiopathic arthritis	Case reports only (94, 95)	Affects the balance of Tregs and Th17 cells

which structural similarities between viral antigens and self-antigens lead to cross-reactive immune responses. In genetically predisposed individuals, exposure to pathogens or vaccines may activate T or B cells that recognize both viral and host antigens, breaking immune tolerance and redirecting immune responses against melanocytes (98, 99). COVID-19 vaccines specifically introduce the SARS-CoV-2 spike (SP) glycoprotein to elicit immune memory and neutralizing antibodies. Notably, numerous shared heptapeptides have been identified between fragments of the SARS-CoV-2 SP and proteins within the human proteome, suggesting a molecular basis for autoimmune cross-reactivity (100). This peptide overlap may help explain immune-mediated events, including VLD, following both SARS-CoV-2 infection and vaccination.

Tissue-resident memory T cells (TRMs), which play a central role in vitiligo pathogenesis, may be aberrantly activated through molecular mimicry involving the spike protein (96). Beyond mimicry, bystander activation—whereby viral infection induces the release of sequestered self-antigens—has also been implicated (98).

SARS-CoV-2 infection itself may similarly contribute to vitiligo onset. The virus induces a hyperinflammatory state known as the "cytokine storm," characterized by excessive cytokine release and immune cell activation, leading to systemic oxidative stress and tissue damage (101). As oxidative stress is a known contributor to melanocyte destruction in vitiligo, this may serve as a mechanistic link. Moreover, SARS-CoV-2 stimulates dendritic cells to produce high levels of interferons (IFNs), particularly type I and II, which are crucial cytokines in vitiligo pathogenesis (102).

It has also been hypothesized to involve upregulation of CD38 expression on memory spike-specific CD8+ T cells early after vaccination or infection. Elevated CD38 may lead to nicotinamide adenine dinucleotide (NAD^+) depletion, thereby impairing the SIRT1/Nrf2 antioxidative signaling axis. This cascade may result in dysregulated MAPK activity and FAS-mediated apoptosis of melanocytes (103). Genetic and epigenetic variation in the CD38–NAD^+–SIRT1 pathway may influence susceptibility to VLD in some individuals.

Clinically, VLD after COVID-19 vaccination often presents as symmetrically distributed depigmented patches, in contrast to the more localized or asymmetric patterns often seen with immune checkpoint inhibitor (ICI)-induced VLD (104–106). Nonetheless, localized or segmental variants have also been reported (99). Commonly affected areas include the face, neck, hands, feet, arms, and legs (101, 107). some patients, partial repigmentation, especially on the face, has been observed after two months of narrowband UVB (NB-UVB) therapy (108).

A few illustrative cases have been described. For instance, a 66-year-old man with a 10-year history of stable vitiligo on prednisone (15 mg/day) experienced a marked flare following a second dose of the mRNA vaccine (Comirnaty), with new lesions appearing on the limbs, face, perioral area, trunk, axillae, and genital region (107).

Despite these case reports, large-scale epidemiological data have not demonstrated a significant increase in vitiligo risk post-vaccination. A population-based study involving over 3.8 million vaccinated individuals and a matched cohort of unvaccinated controls found no statistically significant elevation in vitiligo incidence among the vaccinated group (109).

In conclusion, while isolated cases suggest a potential link between COVID-19 vaccination and VLD, the overall risk appears low. Further mechanistic and epidemiological studies are warranted to clarify the autoimmune implications of both SARS-CoV-2 infection and vaccination. The key details of VLD cases following vaccination are presented in Table 1C.

5 Discussion

An important question should be discussed, why are melanocytes destroyed in targeted therapy (Figure 1)? In the autoimmune phenomenon caused by targeted therapy and

TABLE 1C VLD following vaccination.

Drug class	Representative agents	Indications	VLD incidence	Proposed mechanism
COVID-19 Vaccines	BNT162b2	COVID-19	Very rare (109)	Molecular mimicry, bystander activation

Frequencies are based on literature reports.
"Common" ≥10%; "Uncommon" 1–10%; "Rare" <1% There are few clinical studies or case series; "Very rare" Mainly case reports, but there are more than two independent literature; "Case reports only" indicates isolated reports.
References are provided where available.
ALK, anaplastic lymphoma kinase; *Bcl-2*, B-cell lymphoma-2; *BRAF*, v-raf murine sarcoma viral oncogene homolog, *CDK*, cyclin-dependent kinases; *CCR4*, chemokine receptor 4; *COVID-19*, coronavirus disease 2019; *CTLA-4*, cytotoxic T-lymphocyte-associated atigen-4; *EGFR*, epidermal growth factor receptor; *IL-4R*, interleukin-4 receptor; *IL-6R*, interleukin-6 receptor; *IL-17*, interleukin-17; *IL-12/23*, interleukin-12/23; *PD-1*, programmed death 1; *PD-L1*, programmed death 1–ligand 1; *Th1/2/17*, T helper cell 1/2/17; *TNFα*, tumor necrosis factor-α.

immune checkpoint inhibitors, melanocytes are more easily misidentified and destroyed by the immune system than keratinocytes, hair stem cells, thyroid follicular cells or pancreatic β cells. The reason is that they have a highly immunogenic antigen spectrum, are located in immune-active tissues, and are susceptible to cytotoxic T cell responses.

First, melanocytes express a series of melanin synthesis-related antigens, such as tyrosinase, gp100, MART-1 (Melan-A), TRP-1, TRP-2, etc. These antigens are not only widely studied as immunotherapy targets in melanoma cells, but also expressed in normal melanocytes. Since ICIs treatment relieves T cell tolerance mediated by PD-1/PD-L1 or CTLA-4, CD8+ T cells that originally remained unresponsive to these "self" antigens are activated, thus triggering cross-attacks on normal melanocytes expressing the same antigens (on-target, off-tumor effect) (110). Compared with other tissues, these antigens of melanocytes are more easily recognized by T cells and induce cytotoxic immunity.

Secondly, melanocytes are located in the basal layer of the epidermis and the upper part of the hair follicle (bulge region), and are an important component of the skin, an immune-active organ. There are a large number of dendritic cells (DCs), Langerhans cells (LCs), and resident memory T cells in the skin. Targeted therapies can modulate the tumor or skin microenvironment and promote innate immune activation. For instance, kinase inhibitors or tumor-directed cytotoxic agents induce immunogenic cell death, leading to the release of damage-associated molecular patterns (DAMPs), such as HMGB1 and ATP, which APCs including dendritic cells and Langerhans cells (111). Upon activation, these APCs upregulate co-stimulatory molecules and secrete Th1-polarizing cytokines such as IL-12, TNF-α, and Type I interferons (IFN-α/β) (112). These factors contribute to a pro-inflammatory and pro-apoptotic immune milieu that enhances local T cell recruitment and activation. In the skin—a highly immune-active organ—TRM and recruited cytotoxic CD8+ T cells may recognize melanocyte-derived antigens presented via MHC-I and

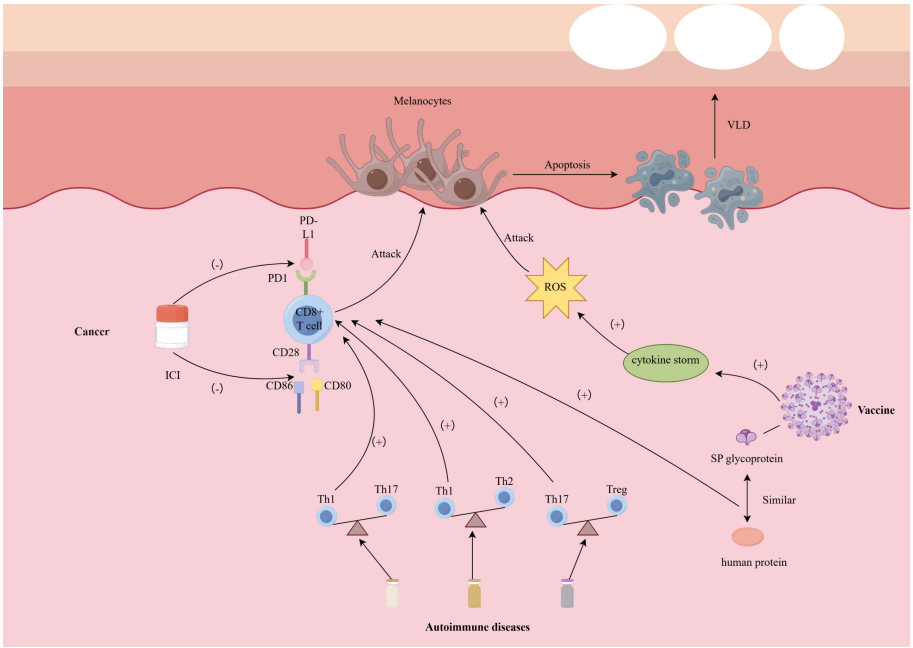

FIGURE 1
Possible mechanism of depigmentation induced by targeted therapies. *CD 28/80/86* cluster of differentiation 28/80/86, *ICI* immune checkpoint inhibitor, *PD-1* programmed death 1, *PD-L1* programmed death 1–ligand 1, *SP* spike, *ROS* reactive oxygen species, *Th1/2/17* T helper cell 1/2/17, *VLD* vitiligo-like depigmentation.

execute direct killing through perforin/granzyme pathways or IFN-γ-mediated apoptosis. The resultant destruction of melanocytes underlies the vitiligo-like depigmentation observed during or after targeted therapies. Although keratinocytes are widely distributed in the epidermis, they do not express these immunodominant antigens and lack sufficient co-stimulatory signals, making them less susceptible to attack by CD8+ T cells; hair follicle stem cells are also in a relatively immunosuppressive "privileged zone" and have low MHC I expression and local TGF-β/IL-10-mediated immune regulation (113).

In addition, different cell types differ in their responsiveness to IFN-γ signals. Studies have shown that melanocytes can significantly upregulate the expression of MHC class I molecules, chemokines such as CXCL9/10 under IFN-γ stimulation, further recruit CXCR3+ T cells to migrate to the skin, and strengthen the positive feedback of immune attack; this mechanism has been repeatedly confirmed in a variety of vitiligo models and ICI-related vitiligo (114). Although thyroid cells and pancreatic β cells may also undergo inflammatory destruction during ICI treatment (such as autoimmune thyroiditis with an incidence of approximately 10% and type 1 diabetes with a lower incidence of approximately 1%), this usually depends on a specific genetic susceptibility background (such as TPO antibody positivity or HLA susceptibility) and does not have broadly consistent target antigen characteristics like melanocytes (115).

VLD is a shared cutaneous phenotype observed across various clinical scenarios; however, its incidence and underlying mechanisms differ markedly among cancer, autoimmune diseases, and vaccine-related conditions. In cancer patients, particularly those receiving immune checkpoint inhibitors, VLD is relatively common (2%–25%) and is closely associated with enhanced antitumor immunity. This association is attributed to the breakdown of immune tolerance and antigenic overlap between melanoma cells and normal melanocytes, which triggers a robust $CD8^+$ T cell response. In contrast, the incidence of VLD is substantially lower during treatment of autoimmune diseases with biologics. Agents such as anti–TNF-α and IL-17 inhibitors may disrupt the Th17/Th1 balance or impair regulatory T cell function, thereby inadvertently enhancing IFN-γ–mediated melanocyte destruction. Notably, both classic vitiligo and drug-induced VLD share key immunologic features, including IFN-γ/CXCL10-mediated chemotaxis and the involvement of tissue-resident memory T cells and melanocyte-specific $CD8^+$ T cells. These shared mechanisms support the notion that VLD reflects an exaggerated Th1-dominant immune milieu.

Since the widespread administration of COVID-19 vaccines, vaccine-associated VLD has been increasingly reported, though it remains rare and largely confined to case reports. Proposed mechanisms include molecular mimicry and transient interferon surges; however, large-scale cohort studies have not demonstrated a statistically significant increase in vitiligo risk post-vaccination.

Compared with previous literature, the present study shares certain common findings but also provides several notable extensions. Consistent with earlier reports, our review identifies ICIs and BCR-ABL tyrosine kinase inhibitors as the most frequently implicated antitumor agents associated with VLD (116). However, we further expand the spectrum of implicated drugs to include not only tumor-targeted agents, but also small-molecule therapies increasingly used for autoimmune diseases, as well as COVID-19 vaccines, which have become globally prevalent in recent years. In addition, we provide a more comprehensive summary of the potential immunologic mechanisms linking these agents to VLD.

Currently, treatment options for VLD—particularly that induced by ICIs and other targeted cancer therapies—are limited, as systemic immunosuppression may compromise antitumor efficacy. While narrowband ultraviolet B (NB-UVB) phototherapy and topical agents have demonstrated variable success, there is no standardized management strategy. Emerging therapeutic approaches for vitiligo are under investigation and target multiple immune pathways, including IFN-γ inhibitors, CXCL10/CXCR3 antagonists, Janus kinase (JAK) inhibitors, PD-1/PD-L1 modulation, and HSP70i DNA-based therapies (117). Topical or oral JAK inhibitors, such as ruxolitinib and tofacitinib, have shown promise in classic vitiligo by suppressing the IFN-γ–STAT1–CXCL10 axis and may hold potential for the treatment of VLD. However, clinical experience remains limited, and concerns persist regarding the impact of systemic JAK inhibition on immune surveillance, especially in cancer patients.

Interestingly, recent clinical trials have demonstrated encouraging results from combining JAK inhibitors with ICIs in certain malignancies, such as non-small cell lung cancer and relapsed Hodgkin lymphoma (118, 119). They are still in the clinical trial stage, and their effects on VLD are still unknown. Carefully designed prospective studies are needed to evaluate whether localized or short-term JAK inhibition can mitigate VLD without compromising oncologic outcomes. A more nuanced understanding of VLD pathogenesis may facilitate the development of targeted interventions and inform interdisciplinary management strategies.

6 Conclusions

VLD significantly affects the quality of life and mental health of patients because of its disfiguring appearance. Systemic immunosuppressive therapies are commonly employed for treating vitiligo, but in the context of VLD induced by targeted therapies, such treatments may reduce antitumor efficacy. Therefore, the management of VLD often relies on phototherapy methods, such as NB-UVB therapy.

Future research should further investigate the specific immunopathological mechanisms underlying VLD, particularly the differences in presentation among patients without melanoma. Additionally, as the variety and application of targeted therapies expand, understanding how to better prevent and manage these cutaneous adverse reactions is crucial for improving treatment outcomes. Future studies should delve deeper into the molecular mechanisms of targeted therapies, collect clinical data, and foster

interdisciplinary collaboration to enhance the understanding of these complex cutaneous adverse events. This approach will help optimize treatment strategies to improve the quality of life of patients.

Author contributions

ZW: Writing – original draft. MW: Writing – original draft. TW: Writing – review & editing. XY: Writing – review & editing. ZY: Writing – review & editing. YS: Writing – review & editing, Supervision.

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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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Comorbidities in primary cicatricial alopecia: a systematic review and meta-analysis

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Background: Primary cicatricial alopecia (PCA) is known to be associated with various comorbidities; however, findings regarding the likelihood of specific comorbidities in PCA patients have been inconsistent.
Objective: This study aimed to assess the prevalence and odds of specific comorbidities in patients with PCA compared to controls, and to explore the distribution of comorbidities across various types of PCA.
Methods: Electronic searches were conducted using PubMed, Embase, and Scopus from the dates of their inception until July 2024. A total of 116 studies with 33,494 PCA patients that reported data allowing for the calculation of odds ratios (OR) or prevalences of certain comorbidities in PCA patients were included.
Results: Systemic lupus erythematosus is more prevalent among patients with lichen planopilaris (LPP) [OR 3.10 (95% confidence interval: 2.24–4.29), prevalence 2%], frontal fibrosing alopecia (FFA) [OR 6.92 (2.73–17.56), prevalence 5%], and central centrifugal cicatricial alopecia (CCCA) [OR 3.13 (1.03–9.49), prevalence 5%]. Hypothyroidism is more prevalent among patients with LPP [OR of 1.73 (1.24–2.42), prevalence 17%] and FFA [OR 1.86 (1.36–2.55), prevalence 19%]. LPP patients are prone to having dermatological diseases such as atopic dermatitis [OR 3.96 (1.14–13.81), prevalence 9%], lichen planus [OR 19.21 (1.47–251.02), prevalence 8%], psoriasis [OR 4.75 (2.04–11.06), prevalence 3%], and rosacea [OR 4.62 (2.96–7.19), prevalence 5%], while FFA patients are prone to having allergic contact dermatitis [OR 3.19 (1.44–7.08), prevalence 41%] and rosacea [OR 2.37 (1.72–3.29), prevalence 16%]. Coronary artery disease is found to be more common in LPP than controls [OR 1.63 (1.43–1.86), prevalence 8%], while dyslipidemia is more common among FFA [OR 1.41 (1.06–1.88), prevalence 20%] and CCCA [OR 4.46 (1.01–19.75), prevalence 54%] than controls, and diabetes mellitus is more prevalent among CCCA than controls [OR 1.67 (1.03–2.69), prevalence 26%]. While skin cancer [OR 2.22 (1.33–3.70), prevalence 2%] and melanoma [OR 4.46 (1.70–11.76), prevalence 1%] were found to be more common in LPP than controls, rheumatoid arthritis [OR 1.65 (1.09–2.51), prevalence 4%] was found to be more common in FFA than controls, and allergic rhinitis [OR 11.77 (1.55–89.24), prevalence 24%] and anxiety [OR 4.69 (1.29–16.98), prevalence 17%] were found to be more common in CCCA than controls.

Conclusions: Patients with PCA are at higher risk of developing a wide range of comorbidities. Physicians should remain vigilant and conduct thorough investigations when clinical clues are present.
Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=564852, identifier CRD42024564852.

KEYWORDS

scarring alopecia, lichen planopilaris, frontal fibrosing alopecia, central centrifugal cicatricial alopecia, hair loss, immune-mediated alopecia, associated diseases, autoimmune diseases

1 Introduction

Cicatricial alopecia, also known as scarring alopecia, results from inflammatory damage to the epithelial stem cells in the follicular bulge region, leading to fibrosis and irreversible hair loss (1). Primary cicatricial alopecia (PCA) occurs when the hair follicle is the primary target of inflammation process, while in secondary cicatricial alopecia, the hair follicle is merely a bystander to the disease process (1). The North American Hair Research Society has proposed classifying PCA into lymphocytic, neutrophilic, mixed, and nonspecific types (2). Lymphocytic PCA encompasses chronic cutaneous lupus erythematosus, classic lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), Graham-Little syndrome, pseudopelade of Brocq (PPB), central centrifugal cicatricial alopecia (CCCA), alopecia mucinosa, and keratosis follicularis spinulosa decalvans (2). Neutrophilic PCA includes folliculitis decalvans (FD) and dissecting cellulitis (DC), while mixed PCA consists of acne keloidalis nuchae (AKN), acne necrotica, and erosive pustular dermatosis (EPD) (2).

Understanding the comorbidities associated with PCA is essential, as they can provide insight into disease etiology and are vital for successful interdisciplinary management. Previous studies on PCA have produced inconsistent findings regarding the prevalence of certain comorbidities and odds of PCA patients having them, likely due to the rarity of PCA and small sample sizes. We aimed to systematically investigate the prevalence of comorbidities and their association with each specific type of PCA, helping guide clinical practice and improve patient care.

2 Materials and methods

2.1 Study design

The protocol for this analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42024564852, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=564852). The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Supplementary Document) (3). Electronic searches were conducted from the database's inception to July 2024 using the PubMed, Embase, and Scopus databases. The search strategy was designed to retrieve all studies on PCA using keywords and a controlled vocabulary. There were no restrictions on the language or publication period in the searches. Only full-text articles were considered, and conference abstracts were excluded due to limited detail and lack of peer review. The search included a combination of terms: 'primary scarring alopecia', 'primary cicatricial alopecia', 'lichen planopilaris', 'frontal fibrosing alopecia', 'Graham Little syndrome', 'fibrosing alopecia in a pattern distribution', 'pseudopelade of Brocq', 'central centrifugal cicatricial alopecia', 'discoid lupus erythematosus', 'alopecia mucinosa', 'keratosis follicularis spinulosa decalvans', 'folliculitis decalvans', 'dissecting cellulitis', 'acne keloidalis', and 'erosive pustular dermatosis.' Supplementary Table 1 provides details about the search strategy. Grey literature and unpublished data were not considered. If multiple studies utilized patient data from the same database with an overlapping inclusion period, data from the more recent publication or from a case-control study is selected. The comorbid data were not quantitatively utilized if they were reported in a composite manner, such as LPP/FFA or PCA.

2.2 Study selection

Two reviewers (TY and KT) independently evaluated each article at both the full-text and title/abstract levels. Full texts of potentially eligible studies were assessed for inclusion. Disagreements regarding the studies' eligibility were resolved via discussion with a third reviewer (PS). Inclusion criteria were: (1) randomized controlled trials, cohort studies, cross-sectional studies, and case-control studies; (2) studies involving patients with confirmed diagnosis of PCA based on clinical and/or histopathological criteria; (3) studies reporting data allowing calculation of odds ratios (OR) or prevalences of specific comorbidities; (4) full-text articles in any language. Exclusion criteria were: (1) conference abstracts; (2) case reports or case series; (3) studies without clear diagnostic criteria for PCA; (4) studies reporting only composite PCA data without subtype specification. Comorbidities were defined based on clinical

diagnosis using ICD codes, physician diagnosis, or validated diagnostic criteria as reported in each study.

2.3 Data extraction

Data were extracted from the included studies using a standardized form. The following data were collected: bibliographic data (authors, year of publication), study characteristics (type of study, single or multicenter, study duration, country), alopecia group characteristics (number, age, gender, ethnicity, body mass index (BMI), comorbidity), and treatment information), control group characteristics (number, age, gender, ethnicity, BMI, comorbidity, whether controls were matched for any relevant factors), and comorbidity data.

Corresponding investigators were contacted via email if there was missing data. Two independent reviewers (TY and KT) extracted data, and any discrepancies were discussed and resolved with input from a third reviewer (PS).

2.4 Quality assessment

TY and KT independently assessed the quality of descriptive and case-control studies using the Newcastle-Ottawa Scale (NOS) (4). The NOS is a scoring tool comprised of seven items with nine scores that assess 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). 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 less than 4. Sensitivity analyses were performed excluding fair-quality studies to assess the robustness of our findings. Meta-analyses were weighted by study quality, with higher-quality studies given greater influence in pooled estimates. Any discrepancies between reviewers regarding the risk of bias in specific studies were resolved through discussion with a third reviewer (PS).

2.5 Statistical analysis

A meta-analysis was performed, using an inverse variance method, to pool the ORs of a specific PCA and a specific comorbidity, as well as the prevalences of various comorbidities associated with a specific PCA. Each PCA disorder was analyzed separately. Quantitative analyses were conducted on comorbidity, either OR or prevalence, that were reported in at least two studies; otherwise, they were only analyzed qualitatively.

Heterogeneity was assessed and considered present if a Cochrane Q test p-value was < 0.1 or Higgins $I^2 \geq 25\%$ (5). The sources of heterogeneity were explored by fitting each covariate (e.g., age, female gender, and BMI) at a time in a meta-regression model. If the τ^2 was decreased by ≥ 50% or statistically significant β was revealed, a subgroup analysis was performed based on that covariate if possible (6).

To evaluate publication bias, Deeks funnel plots of the primary outcomes were generated. The Egger linear regression test was applied when a funnel plot suggested possible asymmetry (7). If Egger's test for a regression intercept gave a p-value < 0.05, a trim and fill method was used to adjust the OR (7). Comprehensive Meta-Analysis software (version 3.3.070, Biostat, Englewood, NJ) was used for all statistical analysis.

3 Results

3.1 Study characteristics

After removing duplicates, 4,797 references were screened by title and abstract. At the full-text stage, 308 full articles met our predefined selection criteria and were sought. We further excluded 192 references for the following reasons: conference abstract or review article (n = 60), not population of interest (i.e., non-alopecia or non-scarring alopecia diagnosis, n = 15), not outcome of interest (i.e., no documented comorbidity prevalence of the patients, n = 115), and duplicate patient data (n = 2) (Figure 1). The review included 116 studies, enrolling a total of 33,494 patients with PCA [8,871 LPP patients (8–31), 6,595 FFA patients (12, 16, 19, 21, 23, 25, 27, 30, 32–83), 3,539 CCCA patients (24, 84–99), 157 PPB patients (20), 24 patients with fibrosing alopecia in a pattern distribution (FAPD) (55), 6,158 FD patients (20, 100–104), 4,752 DC patients (20, 105–108), 3,218 AKN patients (109–120), and 180 EPD patients (121–124)] between 2009 and 2024, were included in the review. Characteristic features of the included studies are provided in Supplementary Tables 2-6.

3.2 Lichen planopilaris

3.2.1 Autoimmune diseases

LPP was found to be significantly associated with systemic lupus erythematosus (SLE) [OR 3.10 (95% confidence interval: 2.24–4.29), prevalence 2%]. Inflammatory bowel diseases [OR 2.49 (0.91–6.77), prevalence 5%], including Crohn's disease [OR 0.75 (0.37–1.49), prevalence 1%] and ulcerative colitis [OR 1.23 (0.32–4.74), prevalence 2%], were not statistically associated with LPP, as were other autoimmune diseases, such as ankylosing spondylitis [OR 1.07 (0.83–1.39), prevalence 1%], celiac disease [OR 1.06 (0.34–3.26), prevalence 2%], multiple sclerosis [OR 1.76 (0.65–4.74), prevalence <1%], rheumatoid arthritis [OR 1.59 (0.90–2.78), prevalence 3%], Sjogren's syndrome [OR 1.24 (0.81–1.89), prevalence 1%], and type 1 diabetes mellitus [OR 0.77 (0.26–2.27), prevalence 1%].

3.2.2 Cardiovascular and metabolic diseases

Coronary artery disease was found to be more common in LPP than controls [OR 1.63 (1.43–1.86), prevalence 8%]. However, we did not find a statistically significant association between LPP and

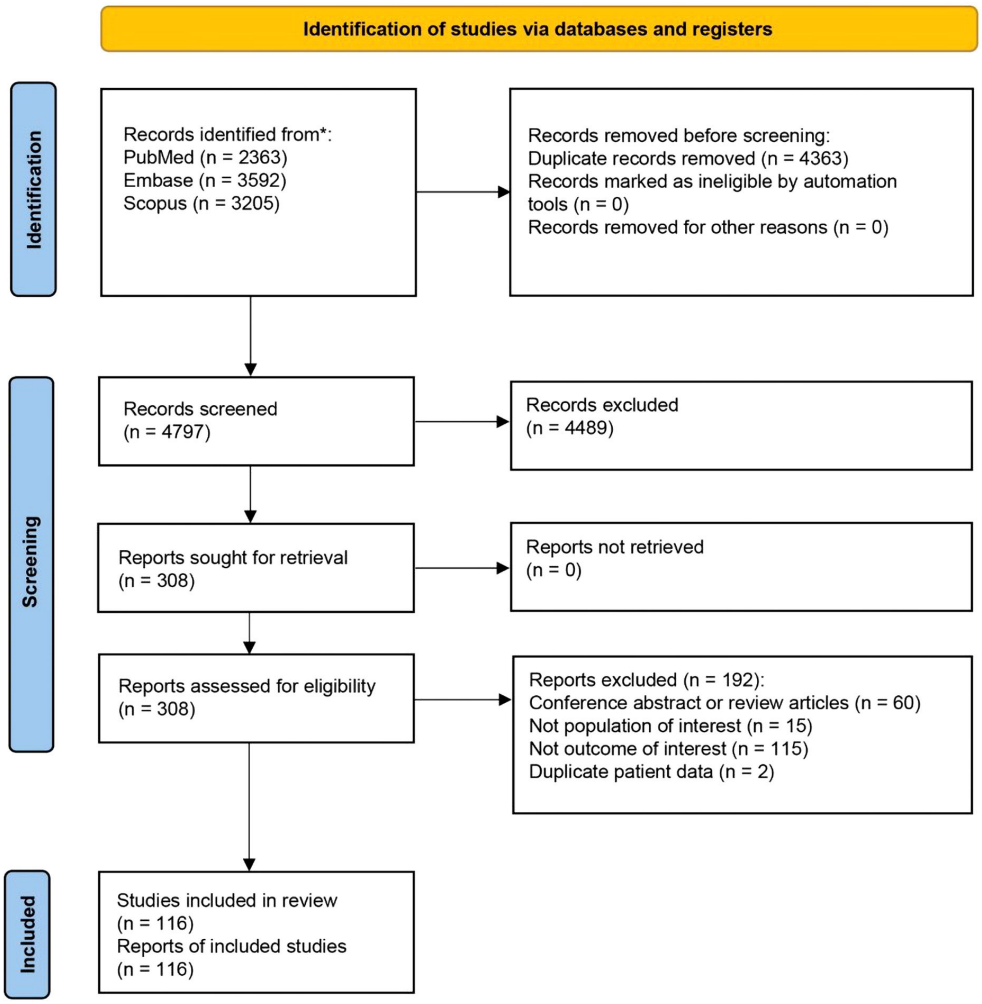

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of search strategy and included studies.

cardiovascular diseases in general [OR 0.74 (0.48–1.16), prevalence 10%] or other cardiovascular comorbidities like congestive heart failure [OR 0.61 (0.15–2.44), prevalence 4%], myocardial infarction [OR 1.27 (0.87–1.86), prevalence 2%], peripheral artery disease [OR 1.03 (0.68–1.58), prevalence 5%], and stroke [0.57 (0.11–2.84), prevalence 3%]. Interestingly, Kim et al. have reported an adjusted hazard ratio (aHR) of 1.93 (1.07–3.49) for coronary heart disease in their cohort of LPP/FFA patients, while aHR of 1.18 (0.69–2.04) and 0.60 (0.23–1.60) were found for cardiovascular disease and stroke, respectively (125).

None of the metabolic diseases, such as diabetes mellitus [OR 0.87 (0.52–1.47), prevalence 10%], dyslipidemia [OR 1.36 (0.64–2.92), prevalence 27%], hypertension [OR 1.21 (0.63–2.33), prevalence 23%], and obesity [OR 1.82 (0.51–6.45), prevalence 20%], were found to be significantly associated with LPP.

3.2.3 Dermatologic diseases

Lichen planus was found to be strongly associated with LPP [OR 19.21 (1.47–251.02), prevalence 8%]. Other dermatological diseases such as atopic dermatitis [OR 3.96 (1.14–13.81), prevalence 9%], psoriasis [OR 4.75 (2.04–11.06), prevalence 3%], and rosacea [OR 4.62 (2.96–7.19), prevalence 5%] were also found to be significantly associated with LPP. Skin cancer [OR 2.22 (1.33–3.70), prevalence 2%] and melanoma [OR 4.46 (1.70–11.76), prevalence 1%] were also found to be more prevalent in LPP than controls. For alopecia areata (AA), however, the association was not statistically significant [OR 2.56 (0.26–25.76), prevalence 3%].

3.2.4 Thyroid disorders

Thyroid diseases, in general, were found to be associated with LPP [OR 2.64 (1.13–6.21), prevalence 24%]. A statistically significant association was found between LPP and hypothyroidism [OR 1.73 (1.24–2.42), prevalence 17%], hyperthyroidism [OR 1.17 (1.00–1.36), prevalence 1%], and thyroiditis [OR 1.21 (1.00–1.46), prevalence 6%]. Although a statistically significant association was found between Hashimoto thyroiditis [OR 4.24 (1.04–17.24), prevalence 7%] and LPP, a publication bias was identified (p=0.014, Egger's test). After to a

trim and fill analysis to account for the publication bias, the association was no longer statistically significant [adjusted OR 1.72 (0.54–5.41)].

3.2.5 Other diseases

Allergic rhinitis [OR 1.05 (0.50–2.19), prevalence 12%], anxiety [OR 1.19 (0.94–1.51), prevalence 22%], asthma [OR 0.91 (0.53–1.56), prevalence 8%], depression [OR 0.85 (0.45–1.61), prevalence 15%], and vitamin D deficiency [OR 0.91 (0.33–2.54), prevalence 19%] were not statistically associated with LPP.

Table 1 provides a summary of the pooled OR for the described comorbidities of LPP patients, along with the associated pooled prevalences. Figure 2, Supplementary Figure 1 depict the pooled OR and prevalence of the comorbidities in patients with LPP, respectively.

3.3 Frontal fibrosing alopecia

3.3.1 Autoimmune diseases

The results showed a strong association between SLE [OR 6.92 (2.73–17.56), prevalence 5%] and FFA. We also discovered a statistical association between FFA and rheumatoid arthritis [OR 1.65 (1.08–2.51), prevalence 4%], but not with multiple sclerosis [OR 0.84 (0.19–3.62), prevalence 4%] or type 1 diabetes mellitus [OR 0.39 (0.07–2.16), prevalence 1%].

3.3.2 Dermatologic diseases

Allergic contact dermatitis [OR 3.19 (1.44–7.08), prevalence 41%] and rosacea [OR 2.37 (1.72–3.28), prevalence 16%] were found to be associated with FFA; however, for psoriasis [OR 2.11 (0.32–13.73), prevalence 4%], the association was not statistically significant.

3.3.3 Metabolic disorders

Dyslipidemia [OR 1.41 (1.05–1.88), prevalence 20%] was found to be associated with FFA, while diabetes mellitus [OR 1.03 (0.72–1.47), prevalence 7%] and hypertension [OR 1.79 (0.85–3.79), prevalence 27%] were not statistically associated with FFA.

3.3.4 Thyroid disorders

Thyroid disease in general [OR 1.66 (1.21–2.28), prevalence 26%] was found to have statistical association with FFA; however, only hypothyroidism [OR 1.86 (1.36–2.55), prevalence 19%] was statistically associated with FFA, not hyperthyroidism [OR 1.11 (0.36–3.41), prevalence 2%].

3.3.5 Other diseases

Breast cancer [OR 1.61 (0.42–6.13), prevalence 5%], allergic rhinitis [OR 0.86 (0.65–1.13), prevalence 4%], and depression [OR 1.22 (0.88–1.69), prevalence 13%] were not statistically associated with FFA.

Table 1 summarizes the pooled OR for the described comorbidities of FFA patients and the associated pooled prevalences. Figure 3, Supplementary Figure 2 present the pooled OR and prevalence of the comorbidities in patients with FFA, respectively.

3.4 Central centrifugal cicatricial alopecia

3.4.1 Autoimmune diseases

SLE [OR 3.13 (1.03–9.49), prevalence 5%] was found to have statistically significant association with CCCA.

3.4.2 Dermatologic diseases

Acne [OR 2.21 (0.31–15.52), prevalence 40%], atopic dermatitis [OR 1.06 (0.05–22.69), prevalence 6%], and seborrheic dermatitis [OR 1.16 (0.74–1.83), prevalence 28%] were not found to be statistically associated with CCCA.

3.4.3 Metabolic disorders

Dyslipidemia [OR 4.46 (1.01–19.75), prevalence 54%] was found to have a strong statistical association with CCCA, while diabetes mellitus [OR 1.67 (1.03–2.69), prevalence 26%] was also statistically associated with CCCA; however, other metabolic diseases such as hypertension [OR 1.62 (0.78–3.34), prevalence 64%], obesity [OR 0.80 (0.28–2.30), prevalence 72%], and hirsutism [OR 2.83 (0.35–22.70), prevalence 9%] were not statistically associated with CCCA.

3.4.4 Other diseases

Allergic rhinitis [OR 11.77 (1.55–89.24), prevalence 24%] and anxiety [OR 4.69 (1.29–16.98), prevalence 17%] were strongly associated with CCCA. Asthma [OR 7.43 (0.85–64.69), prevalence 17%], depression [OR 1.93 (0.65–5.70), prevalence 26%], and leiomyoma [OR 2.23 (0.90–5.52), prevalence 15%] were not associated with CCCA with statistical significance.

Table 1 presents a summary of the pooled OR for the described comorbidities of CCCA patients, as well as the associated pooled prevalences. Figure 4, Supplementary Figure 3 illustrate the pooled OR and prevalence of the comorbidities in patients with CCCA, respectively.

3.5 Other primary cicatricial alopecia disorders

Among 24 FAPD patients, we identified AA [prevalence 12.5%], celiac disease [prevalence 8.3%], rheumatoid arthritis [prevalence 8.3%], frontal fibrosing alopecia [prevalence 8.3%], pernicious anemia [prevalence 4.2%], scalp psoriasis [prevalence 4.2%], and traction alopecia [prevalence 4.2%]. For AKN, common comorbidities include acne [prevalence 29%], acne conglobata [prevalence 14%], FD [prevalence 21%], and pseudofolliculitis barbae [prevalence 26%]. Acne conglobata [prevalence 24%] is also prevalent in DC, and a higher prevalence of hidradenitis suppurativa was found for DC [prevalence 26%], compared to FD [prevalence 4%] and AKN [prevalence 3%]. And for EPD, patients

TABLE 1 Summary of the pooled odds ratio and pooled prevalences of the comorbidities of lichen planopilaris, frontal fibrosing alopecia, and central centrifugal cicatricial alopecia patients.

PCA subtype	Comorbidity	Odds ratio (95% CI)	p-value	No. of studies	PCA	Control	I^2	Egger's test	Prevalence (95% CI)	No. of studies
LPP	Allergic rhinitis	1.05 (0.50–2.19)	0.900	3 (9, 12, 17)	2447	40921	78.31	0.648	0.12 (0.01–0.59)	5 (9, 12, 17, 23, 29)
	Alopecia areata	2.58 (0.26–25.76)	0.419	2 (12, 14)	319	517	60.29	–	0.03 (0.02–0.06)	4 (12, 14, 23, 30)
	Ankylosing spondylitis	1.07 (0.83–1.39)	0.601	2 (14, 17)	2026	40520	0.00	–	0.01 (0–0.13)	2 (14, 17)
	Anxiety	1.19 (0.94–1.51)	0.146	4 (9, 13, 14, 17)	2734	41360	48.69	0.763	0.22 (0.14–0.33)	8 (9, 13, 14, 17, 22, 23, 28, 29)
	Asthma	0.91 (0.53–1.56)	0.723	2 (9, 17)	2360	40598	62.33	–	0.08 (0.02–0.28)	4 (9, 17, 28, 29)
	Atopic dermatitis	3.97 (1.14–13.81)	0.030	3 (9, 13, 17)	2502	41166	90.81	0.976	0.09 (0.03–0.23)	5 (9, 13, 17, 28, 29)
	Cardiovascular disease	0.74 (0.48–1.16)	0.190	3 (12, 14, 15)	527	725	21.51	0.497	0.1 (0.01–0.51)	3 (12, 14, 15)
	Celiac disease	1.06 (0.34–3.26)	0.919	3 (9, 14, 19)	770	1189779	0.00	0.21	0.02 (0.01–0.03)	5 (9, 14, 19, 28, 29)
	Congestive heart failure	0.61 (0.15–2.44)	0.484	2 (14, 17)	2258	40714	87.74	–	0.04 (0.03–0.05)	2 (14, 17)
	Coronary heart disease	1.63 (1.43–1.86)	<0.001	2 (10, 14)	3402	63442194	0.00	–	0.08 (0.07–0.09)	5 (10, 14, 22, 27, 28)
	Crohn's disease	0.75 (0.37–1.49)	0.408	2 (12, 17)	2113	40843	0.00	–	0.01 (0–0.02)	3 (12, 17, 28)
	Depression	0.85 (0.45–1.61)	0.616	4 (9, 12–14)	795	1163	77.81	0.413	0.15 (0.08–0.25)	9 (9, 12–14, 22, 23, 28–30)
	Diabetes mellitus	0.87 (0.52–1.47)	0.606	7 (8–10, 12, 13, 17, 19)	6129	64673077	96.38	0.232	0.1 (0.07–0.13)	13 (8–10, 12, 13, 17, 19, 22, 23, 26, 27, 29, 30)
	Dyslipidemia	1.36 (0.64–2.92)	0.423	9 (8–15, 17)	6552	63484028	99.19	0.271	0.27 (0.21–0.33)	15 (8–15, 17, 22, 23, 27–30)
	Goiter	0.73 (0.36–1.46)	0.371	3 (8, 9, 14)	732	353	0.00	0.121	0.03 (0.02–0.05)	3 (8, 9, 14)
	Hashimoto thyroiditis	4.24 (1.04–17.24)	0.044	3 (8, 9, 19)	704	1189666	0.00	0.014	0.07 (0.04–0.11)	7 (8, 9, 19, 23, 28, 29, 31)
	Hypertension	1.21 (0.63–2.33)	0.566	7 (10–15, 17)	6052	63483869	98.74	0.302	0.23 (0.18–0.3)	14 (10–15, 17, 22, 23, 26–30)
	Hyperthyroidism	1.17 (1.00–1.36)	0.045	7 (8, 9, 12–14, 17, 19)	3191	1231271	0.00	0.875	0.01 (0–0.05)	7 (8, 9, 12–14, 17, 19)
	Hypothyroidism	1.73 (1.24–2.42)	0.001	9 (8, 9, 12–15, 17–19)	3425	1231509	67.03	0.205	0.17 (0.12–0.22)	13 (8, 9, 12–15, 17–19, 21, 26, 28, 29)

(Continued)

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TABLE 1 Continued

PCA subtype	Comorbidity	Odds ratio (95% CI)	p-value	No. of studies	PCA	Control	I^2	Egger's test	Prevalence (95% CI)	No. of studies
	Inflammatory bowel disease	2.49 (0.91–6.77)	0.075	2 (13, 19)	346	1190075	66.36	–	0.05 (0.01–0.19)	2 (13, 19)
	Lichen planus	19.21 (1.47–251.02)	0.024	2 (17, 19)	2230	1230027	96.09	–	0.08 (0.04–0.16)	5 (17, 19, 21, 29, 30)
	Melanoma	4.46 (1.70–11.76)	0.002	2 (13, 17)	2168	41088	0.00	–	0.01 (0–0.05)	4 (13, 17, 28, 29)
	Multiple sclerosis	1.76 (0.65–4.74)	0.262	4 (12, 14, 17, 19)	2549	1230544	13.51	0.043	0 (0–0.01)	4 (12, 14, 17, 19)
	Myocardial infarction	1.27 (0.87–1.86)	0.217	2 (10, 17)	5196	63482520	75.88	–	0.02 (0.02–0.04)	3 (10, 17, 23)
	Obesity	1.82 (0.51–6.45)	0.355	3 (9, 10, 13)	3646	63442646	97.70	0.034	0.2 (0.14–0.27)	7 (9, 10, 13, 22, 26, 28, 29)
	Peripheral artery disease	1.03 (0.68–1.58)	0.873	2 (14, 17)	2258	40714	14.50	–	0.05 (0.01–0.32)	3 (14, 17, 22)
	Psoriasis	4.75 (2.04–11.06)	<0.001	5 (9, 12, 14, 17, 19)	2793	1230996	70.53	0.864	0.03 (0.01–0.08)	8 (9, 12, 14, 17, 19, 23, 28, 29)
	Rheumatoid arthritis	1.59 (0.90–2.78)	0.107	5 (9, 12, 13, 17, 19)	2938	1230867	45.78	0.91	0.03 (0.01–0.08)	7 (9, 12–14, 17, 19, 28)
	Rosacea	4.62 (2.96–7.19)	<0.001	2 (13, 14)	374	762	0.00	–	0.05 (0.02–0.15)	5 (13, 14, 23, 28, 29)
	Sjogren's syndrome	1.24 (0.81–1.89)	0.326	4 (9, 14, 17, 19)	2796	1230299	0.00	0.741	0.01 (0.01–0.03)	6 (9, 14, 17, 19, 28, 29)
	Skin cancer	2.22 (1.33–3.70)	0.002	2 (14, 17)	2258	40714	5.38	–	0.02 (0–0.77)	2 (14, 17)
	Stroke	0.57 (0.11–2.84)	0.489	2 (14, 17)	2258	40714	89.84	–	0.03 (0.01–0.09)	3 (14, 17, 23)
	SLE	3.10 (2.24–4.29)	<0.001	5 (9, 12, 13, 17, 19)	2793	1228996	0.00	0.977	0.02 (0.01–0.04)	7 (9, 12, 13, 17, 19, 23, 28)
	Thyroid disease	2.64 (1.13–6.21)	0.026	4 (8, 15, 16, 18)	428	350	69.24	0.414	0.24 (0.17–0.31)	8 (8, 15, 16, 18, 22, 27, 28, 30)
	Thyroid nodules	0.85 (0.47–1.54)	0.588	2 (9, 14)	566	272	0.00	–	0.02 (0.01–0.07)	5 (8, 9, 14, 28, 29)
	Thyroiditis	1.21 (1.00–1.46)	0.049	2 (14, 17)	2258	40714	0.00	–	0.06 (0.05–0.07)	2 (14, 17)
	Type 1 diabetes mellitus	0.77 (0.26–2.27)	0.639	3 (13, 14, 19)	578	1190269	0.00	0.462	0.01 (0.01–0.03)	5 (13, 14, 19, 28, 31)
	Ulcerative colitis	1.23 (0.32–4.74)	0.763	2 (9, 17)	2360	40598	62.77	–	0.02 (0.01–0.05)	3 (9, 17, 28)
	Vitamin D deficiency	0.91 (0.33–2.54)	0.862	2 (9, 17)	2360	40598	91.84	–	0.19 (0.04–0.55)	5 (9, 17, 24, 26, 28)

(Continued)

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TABLE 1 Continued

PCA subtype	Comorbidity	Odds ratio (95% CI)	p-value	No. of studies	PCA	Control	I^2	Egger's test	Prevalence (95% CI)	No. of studies
	Vitiligo	2.41 (0.94–6.20)	0.069	4 (9, 12, 13, 19)	767	1190476	0.00	0.578	0.01 (0.01–0.03)	9 (9, 12, 13, 19, 23, 26, 28–30)
FFA	Allergic contact dermatitis	3.19 (1.44–7.08)	0.004	2 (36, 42)	44	492	0.00	–	0.41 (0.09–0.83)	2 (36, 42)
	Allergic rhinitis	0.86 (0.65–1.13)	0.278	2 (12, 41)	570	774	0.00	–	0.04 (0–0.41)	3 (12, 23, 41)
	Breast cancer	1.61 (0.42–6.13)	0.483	2 (35, 38)	412	555	71.99	–	0.05 (0.03–0.1)	7 (30, 35, 38, 51, 53, 71, 83)
	Depression	1.22 (0.88–1.69)	0.228	2 (12, 41)	570	774	0.00	–	0.13 (0.06–0.24)	6 (12, 23, 30, 41, 54, 58)
	Dyslipidemia	1.41 (1.05–1.88)	0.020	4 (12, 37, 39, 41)	719	914	11.77	0.375	0.2 (0.15–0.27)	20 (12, 23, 27, 30, 37, 39, 41, 43, 44, 50, 52, 54, 57, 58, 64, 65, 69, 70, 77, 80)
	Diabetes mellitus	1.03 (0.72–1.47)	0.862	5 (12, 19, 37, 39, 41)	893	1190421	0.00	0.253	0.07 (0.05–0.11)	17 (12, 19, 23, 27, 30, 37, 39, 41, 50, 53, 54, 57, 58, 65, 69, 74, 77)
	Hypertension	1.79 (0.85–3.79)	0.128	4 (12, 37, 39, 41)	719	914	83.15	0.233	0.27 (0.21–0.34)	24 (12, 23, 27, 30, 37, 39, 41, 43, 44, 48, 50, 52–54, 57, 58, 64, 65, 69, 70, 74, 77, 79, 80)
	Hyperthyroidism	1.11 (0.36–3.41)	0.855	3 (12, 19, 38)	601	1190177	0.00	0.479	0.02 (0.01–0.04)	7 (12, 19, 38, 57, 70, 77, 79)
	Hypothyroidism	1.86 (1.36–2.55)	<0.001	4 (12, 19, 34, 38)	631	1190207	0.00	0.897	0.19 (0.15–0.24)	24 (12, 19, 21, 34, 38, 44–46, 48, 50, 52–54, 57–60, 68–70, 74, 76, 80, 83)
	Lupus	2.42 (0.86–6.87)	0.096	3 (36, 38, 41)	783	1266	0.00	0.229	0.01 (0–0.04)	3 (36, 38, 41)
	Multiple sclerosis	0.84 (0.19–3.62)	0.811	2 (12, 19)	293	1189830	0.00	–	0.01 (0–0.03)	2 (12, 19)
	Psoriasis	2.11 (0.32–13.73)	0.436	3 (12, 19, 41)	744	1190281	93.01	0.791	0.04 (0.03–0.05)	18 (12, 19, 23, 41, 45, 46, 51, 53, 54, 57, 58, 65, 70, 74, 76, 79, 80, 83)

(Continued)

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TABLE 1 Continued

PCA subtype	Comorbidity	Odds ratio (95% CI)	p-value	No. of studies	PCA	Control	I^2	Egger's test	Prevalence (95% CI)	No. of studies
	Rheumatoid arthritis	1.65 (1.08–2.51)	0.019	4 (12, 19, 38, 41)	1052	1190628	0.00	0.136	0.04 (0.02–0.07)	9 (12, 19, 38, 41, 44, 45, 54, 57, 80)
	Rosacea	2.37 (1.72–3.28)	<0.001	3 (38, 39, 41)	858	838	0.00	0.132	0.16 (0.1–0.23)	20 (23, 38, 39, 41, 48, 49, 54, 57, 59, 60, 64–68, 71–73, 76, 80)
	SLE	6.92 (2.73–17.56)	<0.001	3 (12, 19, 34)	323	1187860	0.00	0.888	0.05 (0.03–0.08)	10 (12, 19, 23, 34, 43, 45, 54, 58, 74, 83)
	Type 1 diabetes mellitus	0.39 (0.07–2.16)	0.279	2 (19, 38)	482	1189854	0.00	–	0.01 (0–0.01)	4 (19, 38, 54, 57)
	Thyroid disease	1.66 (1.21–2.28)	0.002	3 (16, 37, 41)	536	582	0.00	0.474	0.26 (0.2–0.33)	15 (16, 27, 30, 37, 41, 49, 54, 57, 58, 65, 74, 78, 82, 83)
	Vitiligo	4.01 (1.95–8.26)	<0.001	5 (12, 19, 37, 38, 41)	1102	1190728	13.93	0.47	0.03 (0.02–0.04)	17 (12, 19, 23, 30, 37, 38, 41, 45, 46, 49, 54, 57, 58, 65, 74, 80, 83)
CCCA	Acne	2.21 (0.31–15.52)	0.427	2 (87, 88)	105	436	46.28	–	0.4 (0.11–0.78)	3 (87, 88, 98)
	Allergic rhinitis	11.77 (1.55–89.24)	0.017	2 (86, 88)	254	413	56.14	–	0.24 (0.06–0.63)	2 (86, 88)
	Anxiety	4.69 (1.29–16.98)	0.019	3 (85, 86, 88)	407	566	73.46	0.932	0.17 (0.03–0.62)	3 (85, 86, 88)
	Asthma	7.43 (0.85–64.69)	0.069	2 (86, 88)	254	413	59.31	–	0.17 (0.04–0.51)	2 (86, 88)
	Atopic dermatitis	1.06 (0.05–22.69)	0.972	2 (86, 87)	253	425	90.11	–	0.06 (0.04–0.1)	2 (86, 87)
	Depression	1.93 (0.65–5.70)	0.236	2 (85, 86)	354	354	85.55	–	0.26 (0.05–0.71)	2 (85, 86)
	Diabetic mellitus	1.67 (1.03–2.69)	0.036	7 (85–88, 90–92)	1355	41447	87.97	0.586	0.26 (0.19–0.34)	13 (85–88, 90–98)
	Dyslipidemia	4.46 (1.01–19.75)	0.049	3 (85, 86, 88)	407	566	96.01	0.686	0.54 (0.35–0.71)	5 (85, 86, 88, 94, 97)
	Hirsutism	2.83 (0.35–22.70)	0.328	3 (85, 87, 88)	258	589	73.09	0.022	0.09 (0.01–0.51)	3 (85, 87, 88)
	Hypertension	1.62 (0.78–3.34)	0.195	5 (85, 86, 88, 90, 92)	908	1943	92.04	0.438	0.64 (0.55–0.73)	6 (85, 86, 88, 90, 92, 94)
	Leiomyoma	2.23 (0.90–5.52)	0.084	4 (84, 85, 90, 92)	1101	488187	94.36	0.978	0.15 (0.08–0.27)	4 (84, 85, 90, 92)
	Obesity	0.80 (0.28–2.30)	0.676	4 (85, 88, 91, 92)	1028	40926	96.08	0.707	0.72 (0.37–0.92)	4 (85, 88, 91, 92)

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TABLE 1 Continued

PCA subtype	Comorbidity	Odds ratio (95% CI)	p-value	No. of studies	PCA	Control	I^2	Egger's test	Prevalence (95% CI)	No. of studies
	Seborrheic dermatitis	1.16 (0.74–1.83)	0.521	3 (85, 87, 88)	258	589	4.83	0.061	0.28 (0.15–0.45)	5 (85, 87, 88, 96, 98)
	SLE	3.13 (1.03–9.49)	0.044	2 (85, 88)	206	365	0.00	–	0.05 (0.02–0.13)	2 (85, 88)
	Vitiligo	12.14 (0.49–302.35)	0.128	2 (85, 88)	53	212	0.00	–	0.01 (0–0.04)	2 (85, 88)

Summary of the pooled odds ratio and pooled prevalences of the comorbidities of lichen planopilaris, frontal fibrosing alopecia, and central centrifugal cicatricial alopecia patients.
CCCA, central centrifugal cicatricial alopecia; FFA, frontal fibrosing alopecia; LPP, lichen planopilaris; PCA, primary cicatricial alopecia; SLE, systemic lupus erythematosus.

often report actinic keratosis [prevalence 21%], basal cell carcinoma [prevalence 7%], and squamous cell carcinoma [prevalence 13%] as their comorbidities. Supplementary Figures 4-7 show forest plots for the pooled prevalence of the comorbidities in patients with FD, DC, AKN, and EPD, respectively.

3.6 Quality assessment

Supplementary Table 7 provides a summary of the quality assessment scores for comparative and descriptive studies included in the review. The average quality assessment score was 7.78 (range: 4–9), with 101 high-quality and 15 fair-quality studies. No studies were classified as low-quality. The most common quality concerns in fair-quality studies were related to the comparability of cohorts and adequacy of follow-up. Sensitivity analyses excluding the 15 fair-quality studies did not substantially alter our main findings, with all significant associations remaining statistically significant.

3.7 Meta-regression and subgroup analysis

Meta-regression was performed for all analyses that were found to have significant heterogeneity and did not find any potential source of heterogeneity, except for one analysis in which we found that female proportion seems to play a role in the odds of depression in the LPP cohorts (Supplementary Figure 8). However, we chose not to perform a subgroup analysis due to the limited number of studies that included a narrow range of female proportions, specifically from 72.4 to 91.5%.

4 Discussion

This meta-analysis reveals distinct comorbidity patterns across PCA. The high prevalence and diversity of comorbidities suggest these conditions have systemic implications. Specifically, LPP showed strong associations with autoimmune disorders, particularly thyroid disease and lichen planus. FFA demonstrated links to both autoimmune and metabolic comorbidities, whereas CCCA exhibited significant associations with metabolic and hormonal factors. These distinct patterns underscore the complex, multifactorial nature of PCA and suggest they may be manifestations of broader systemic dysregulation rather than isolated scalp disorders. The elevated ORs for specific comorbidities emphasize the importance of a comprehensive approach to managing patients with these conditions, as they are likely at higher risk for multiple systemic conditions.

4.1 Autoimmune diseases

Statistically significantly higher odds of SLE were found among those with lymphocytic PCA, particularly LPP, FFA, and CCCA, compared with controls. Peroxisome proliferator-activated

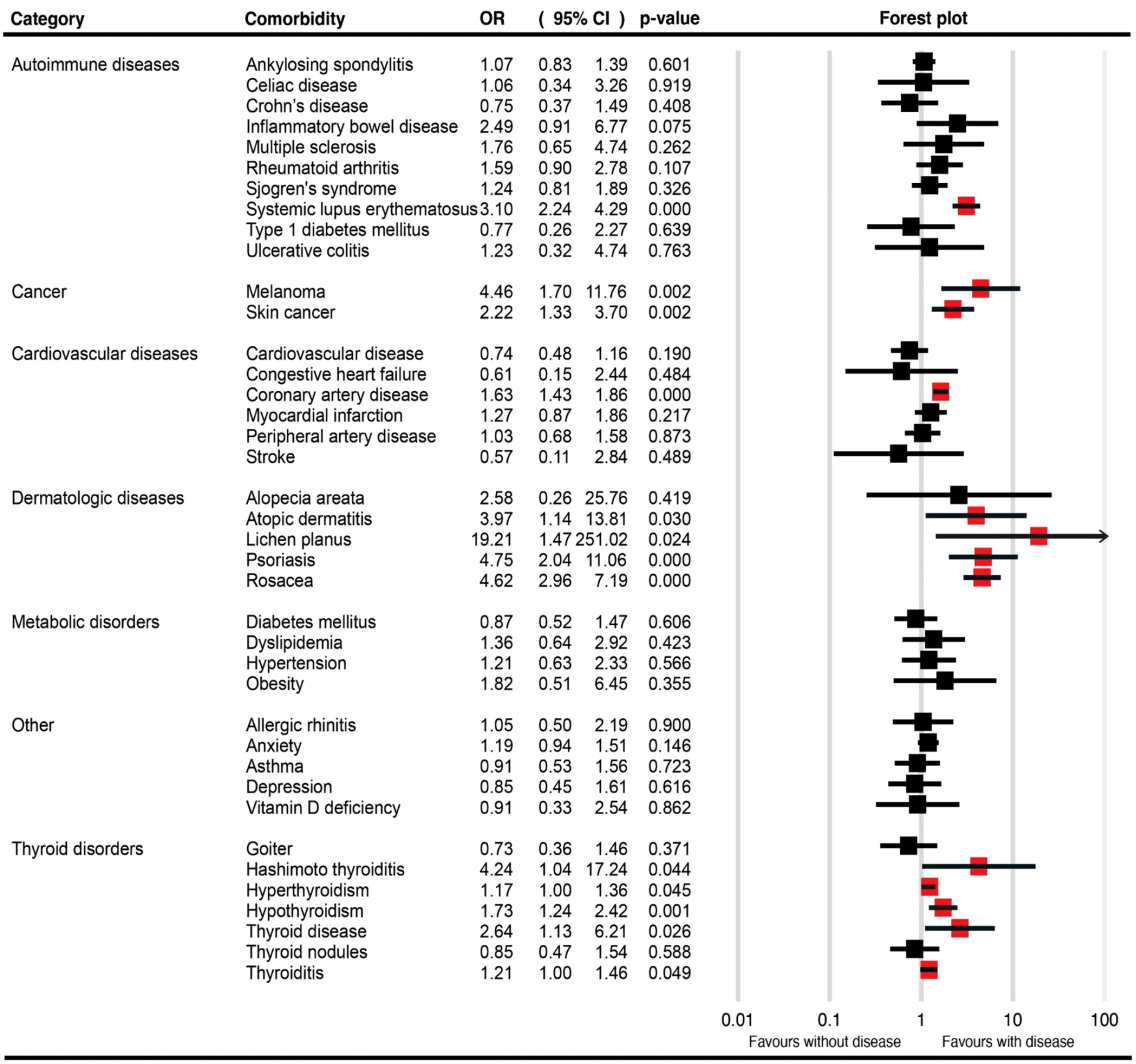

FIGURE 2
Forest plots for the pooled odds ratio of various comorbidities in patients with lichen planopilaris.

receptor-γ (PPAR-γ), a nuclear hormone receptor, is involved in the regulation of inflammation and tissue repair (126). It has been proposed to be the link between LPP and SLE (12), as PPAR-γ has been implicated in the pathogenesis of both PCA and SLE (126, 127). Specifically, PPAR-γ expression is altered in both conditions, potentially contributing to dysregulated immune responses and tissue damages (126, 128–130). PPAR-γ is also involved in the pathogenesis of rheumatoid arthritis (131), which we found to have a significant association with FFA. Therefore, further studies exploring the link between PCA and various autoimmune diseases are needed.

The association between PCA and multiple autoimmune conditions aligns with the concept of Multiple Autoimmune Syndrome (MAS), where at least three autoimmune diseases coexist in the same patient. Tatu and Ionescu described a case of MAS type 3, characterized by the coexistence of autoimmune thyroiditis, vitiligo, and AA (132). Although their report focused on non-scarring alopecia, the principle of shared autoimmune pathophysiology may extend to primary cicatricial alopecias, suggesting that PCA could represent a cutaneous manifestation within a broader autoimmune context.

4.2 Thyroid disorders

Similar to a previous meta-analysis, we also found a statistically significant association between LPP and hypothyroidism (133). In addition, we also found FFA to be associated with hypothyroidism, which can be observed in nearly one fifth of patients with either LPP or FFA. The association between thyroid disorders, especially hypothyroidism, and PCA could be explained by the prevalent immune-mediated hypothyroidism, such as Hashimoto thyroiditis. We believe hypothyroidism should be considered when evaluating LPP or FFA patients, given the well-established link between thyroid diseases and autoimmune skin diseases (134). This association underscores the importance of

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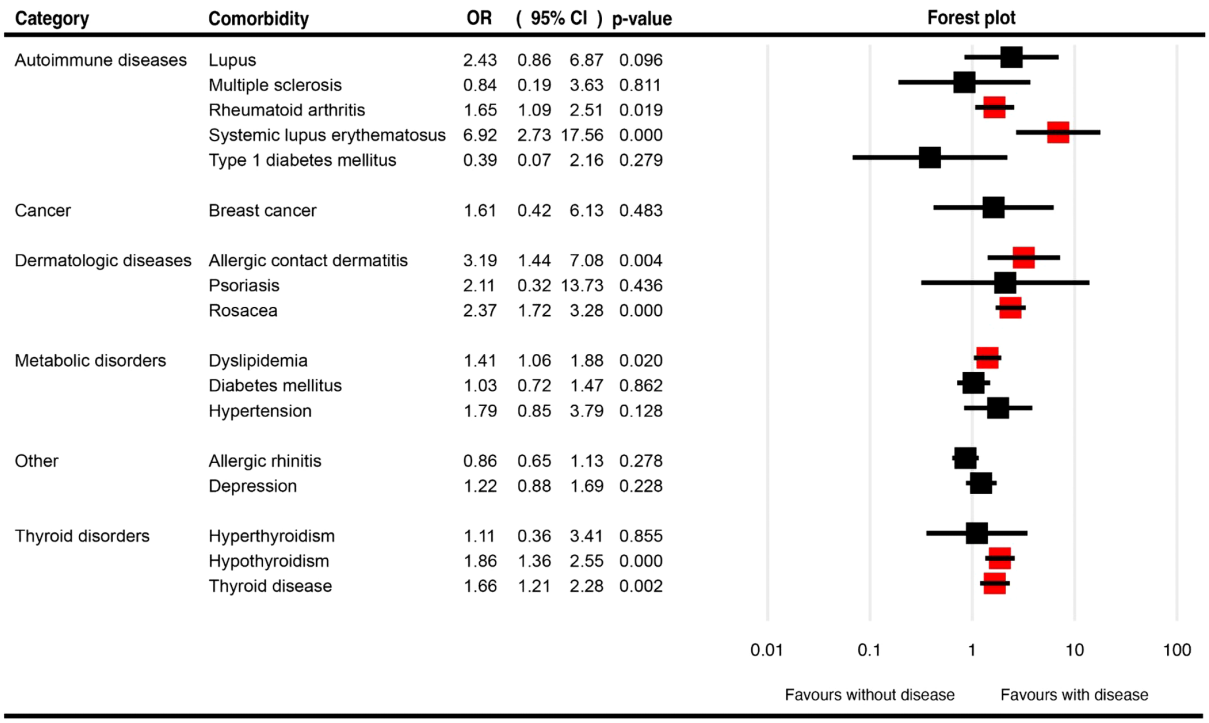

FIGURE 3
Forest plots for the pooled odds ratio of various comorbidities in patients with frontal fibrosing alopecia.

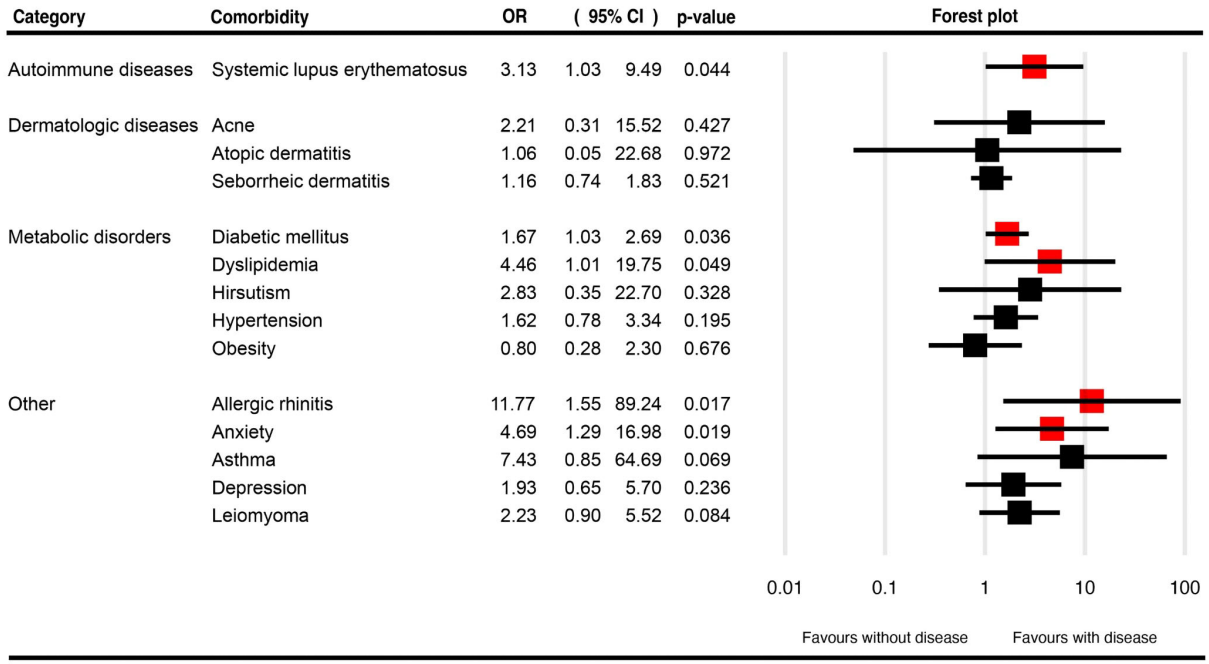

FIGURE 4
Forest plots for the pooled odds ratio of various comorbidities in patients with central centrifugal cicatricial alopecia.

routine thyroid function screening in patients diagnosed with these forms of PCA, especially in cases with clinical suspicion. However, the need for thyroid investigation in asymptomatic patients remains controversial.

4.3 Dermatologic diseases

Compared to previous meta-analysis, we found a similar association and prevalence of rosacea in FFA (135). We also find that rosacea is strongly associated with LPP, although the prevalence is lower than in FFA. Apart from rosacea, LPP is also strongly linked to lichen planus and other immune-mediated skin diseases, including atopic dermatitis and psoriasis.

Although the evidence is limited to two studies, allergic contact dermatitis is also significantly associated with FFA. Given that FFA association with skin care products has been shown previously (136), it may be sensible to inform patients of the risk.

In contrast to other autoimmune skin diseases such as vitiligo and AA (137–140), we found a higher risk of skin cancer and melanoma among LPP patients. Actinic keratosis and non-melanocytic skin cancer are also found to be prevalent among EPD. Given the increased risk of skin cancer and dermatologic diseases, we believe a detailed full-body dermatological examination for patients with PCA is necessary.

4.4 Metabolic disorders

We have confirmed the findings of a previous meta-analysis that dyslipidemia is not statistically associated with LPP (141). Additionally, we also did not identify any association between LPP and other metabolic diseases, including diabetes mellitus, hypertension, and obesity. However, we did find an association between FFA and dyslipidemia, while CCCA is associated with both dyslipidemia and diabetes mellitus. These associations suggest a potential role of metabolic inflammation in their pathogenesis (126). Further studies exploring the association between PCA and metabolic disorders are needed.

4.5 Cardiovascular diseases

Kim et al. have previously found an association between PCA and incident cardiovascular disease, particularly coronary heart disease (125), which is also evident in our LPP findings. Certain interleukins (IL), especially IL-18 (142), are associated with cardiovascular risk, which makes autoimmune patients more prone to coronary diseases. We believe this issue requires further investigation and physicians should be on high alert for coronary events.

4.6 Other diseases

Similar to a previous meta-analysis (143), evidence is limited for vitamin D deficiency and PCA, and evidence so far suggests that vitamin D deficiency is not statistically associated with LPP. In addition, the lack of statistical association between uterine leiomyoma and CCCA is noted in our study, while strong associations between allergic rhinitis, anxiety, and CCCA were found. We suspect that the high prevalence of uterine leiomyoma may not be directly related to the disease. Regular psychosocial assessment and support is crucial for patients with CCCA as well as other PCAs. Further studies exploring the relationship between allergic rhinitis and CCCA are needed.

4.7 Histopathological integration and mechanistic insights

Recent histopathological studies have identified variations in inflammatory patterns across PCA subtypes that may explain their different comorbidity profiles. The predominantly CD8+ T-cell-mediated inflammation in LPP and FFA contrasts with the CD4+ T-cell-predominant mixed inflammatory infiltrate seen in CCCA, potentially explaining their distinct associations with autoimmune and metabolic conditions, respectively (144–146).

The association between PCA and various systemic conditions reflects complex shared pathogenic mechanisms involving inflammatory and immune-mediated pathways. The histopathological hallmark of lymphocytic PCA, destruction of follicular stem cells in the bulge region with perifollicular fibrosis, mirrors inflammatory patterns seen in associated autoimmune conditions. This parallel extends to the molecular level, where PPAR-γ signaling emerges as a crucial link between PCA and systemic disorders.

In LPP and FFA, decreased PPAR-γ expression in hair follicle stem cells triggers proinflammatory cytokine production and subsequent stem cell loss. This mechanism shows striking similarity to PPAR-γ dysfunction in SLE, where impaired PPAR-γ signaling contributes to immune dysregulation and tissue damage (126). The strong association between these conditions likely reflects this shared pathogenic pathway. For CCCA, the significant association with metabolic disorders may similarly reflect common inflammatory mechanisms. PPAR-γ's role in regulating both immune responses and metabolic homeostasis provides a potential molecular explanation for these associations (147). The presence of metabolic inflammation in conditions such as diabetes and dyslipidemia may exacerbate the follicular inflammation characteristic of CCCA.

FAPD has been recently recognized as a subtype of LPP that presents with a pattern mimicking androgenetic alopecia (148). Histologically, FAPD exhibits a lymphocytic scarring process similar to classic LPP, although detailed characterization of the

lymphocyte subtypes in its inflammatory infiltrate remains lacking. While its recognition has expanded our understanding of how scarring alopecia can clinically manifest, data regarding its associated systemic conditions remain limited.

4.8 Clinical significance of risk estimates

The magnitude of associations found in this meta-analysis has important clinical implications. A 3-fold increased risk of SLE in LPP patients translates to an absolute risk of approximately 2%, compared to 0.65% in the general population. While this remains a relatively low absolute risk, it warrants clinical vigilance given SLE's potential severity. More practically significant is the 17-19% prevalence of hypothyroidism in LPP and FFA, a frequency that justifies routine screening.

The 8% prevalence of coronary artery disease in LPP patients (OR 1.63) represents a clinically meaningful increase that should prompt cardiovascular risk assessment and aggressive management of modifiable risk factors. Similarly, the high prevalence of dyslipidemia in CCCA (54%) and diabetes mellitus (26%) necessitates proactive metabolic screening and intervention in this population.

4.9 Clinical implications and screening recommendations

Based on our findings, we recommend a comprehensive screening approach for PCA patients. Initial assessment should include thyroid function tests and thyroid antibody screening for all PCA patients. Autoimmune screening with antinuclear antibody testing should be considered in patients presenting with systemic symptoms. Metabolic screening including lipid profile and fasting glucose is particularly important in FFA and CCCA patients. Annual full-body skin examinations are warranted in LPP patients due to their increased skin cancer risk.

The complexity of comorbidities in PCA necessitates multidisciplinary care coordination. Establishing collaborative relationships with endocrinology for thyroid management, rheumatology for suspected autoimmune conditions, and maintaining regular dermatologic surveillance are essential components of comprehensive care. Mental health support should be integrated into the management plan, given the significant psychological burden associated with PCA. This coordinated approach ensures that the multiple systemic manifestations of PCA are adequately addressed, ultimately improving patient outcomes and quality of life.

4.10 Limitations

This study has some limitations. Firstly, some comorbidities were infrequently reported and thus were not able to be quantitatively analyzed. Additionally, there is an inadequate number of cohort studies that document incident cases of various comorbidities for quantitative analysis. Furthermore, significant statistical heterogeneity was found in some of our analyses, and despite meta-regression analysis, we were unable to identify the source of heterogeneity, except for one analysis. This is partly due to the limited number of available studies. Potential sources of heterogeneity include variations in diagnostic criteria for PCA subtypes, differences in study populations (such as ethnicity, age distribution, geographic location, disease severity, and comorbidity burden), methodological differences across studies, differences in healthcare systems and access to specialist care, and temporal changes in awareness and screening practices for both PCA and associated conditions. These factors highlight the need for cautious interpretation of pooled estimates for these specific associations. While we employed appropriate statistical methods, the adjusted results may still be influenced by unreported negative findings.

5 Conclusions

This meta-analysis significantly contributes to our understanding of PCA by providing a comprehensive overview of associated comorbidities. PCA patients are at an increased risk of developing a variety of comorbidities, such as SLE, hypothyroidism, metabolic diseases, and various dermatologic conditions. The findings emphasize the need for a multidisciplinary approach to patient care and highlight the importance of considering PCA as potentially systemic disorders with localized scalp manifestations. Therefore, clinicians should maintain a high level of vigilance for comorbid conditions in PCA patients and conduct investigations when clinical signs are observed. Future research should focus on elucidating the mechanisms behind these associations through prospective cohort studies, which would help establish causality and determine whether interventions targeting comorbidities improve outcomes in PCA. While limitations such as study heterogeneity and the challenge of establishing causality exist, this analysis provides valuable insights that can guide clinical practice and future investigations in PCA.

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

TY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. KT: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. PS: Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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/fimmu.2025.1516407/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Forest plots for the pooled prevalence of the comorbidities in patients with lichen planopilaris.

SUPPLEMENTARY FIGURE 2
Forest plots for the pooled prevalence of the comorbidities in patients with frontal fibrosing alopecia.

SUPPLEMENTARY FIGURE 3
Forest plots for the pooled prevalence of the comorbidities in patients with central centrifugal cicatricial alopecia.

SUPPLEMENTARY FIGURE 4
Forest plots for the pooled prevalence of the comorbidities in patients with folliculitis decalvans.

SUPPLEMENTARY FIGURE 5
Forest plots for the pooled prevalence of the comorbidities in patients with dissecting cellulitis.

SUPPLEMENTARY FIGURE 6
Forest plots for the pooled prevalence of the comorbidities in patients with acne keloidalis nuchae

SUPPLEMENTARY FIGURE 7
Forest plots for the pooled prevalence of the comorbidities in patients with erosive pustular dermatosis of the scalp

SUPPLEMENTARY FIGURE 8
Bubble plot for the meta-regression analysis of the pooled odds ratio of depression in patients with lichen planopilaris, using the female proportion as a covariate.

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Case Report: Psychogenic purpura in a uremic patient on peritoneal dialysis

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Psychogenic purpura (Gardner-Diamond syndrome) is a rare autoimmune vasculopathy characterized by the spontaneous onset of painful edema and infiltrative cutaneous lesions that rapidly develop into ecchymosis after severe psychological stress events. In this article, we report an 87-year-old female uremic patient who was admitted to the hospital with erythema and subcutaneous ecchymoses on the head and face following an Aedes mosquito sting. She was previously diagnosed with "toxic insect stings and skin bacterial infections" and was given anti-infective treatment by an outside hospital, which was ineffective. Subsequent laboratory tests at our hospital revealed only an increase in fibrinogen and leukocytosis. Tracing the history revealed that the patient's purpura episodes were related to a major life event, the death of her husband. After consultation with the dermatology department, the patient's autoerythrocyte sensitization test was positive, and she was finally diagnosed with "psychogenic purpura". Treatment included glucocorticoids and immunomodulators, supplemented by anti-infective and renal replacement therapy, and the patient's ecchymosis gradually subsided and resolved after one month of follow-up. This case highlights the complexity of diagnosing psychogenic purpura and the significance of medical history in the diagnosis. Only accurate and timely diagnosis can effectively avoid unnecessary treatment.

KEYWORDS

psychogenic purpura, gardner-diamond syndrome, autoerythrocyte sensitization syndrome, uremia, autoimmunity, differential diagnosis

1 Introduction

Psychogenic purpura (PP), also known as Gardner-Diamond syndrome, autoerythrocyte sensitization syndrome, or painful bruising syndrome, is a rare disease. To date, only more than 280 cases have been reported worldwide (1). It was first described by Gardner and Diamond in 1955 in the U.S (2). PP primarily affects young to middle-aged women under the age of 50, accounting for more than 90% of cases (3). Patients usually

have a history of mental disorders or have experienced extreme psychologically distressing events (4, 5). It is characterized by painful edema and infiltrative skin lesions induced by psychological stress, which subsequently develop into ecchymosis within 24 hours and expand into larger ecchymosis within 4 to 5 days. Other typical symptoms include gastrointestinal symptoms, arthralgia, myalgia, dizziness, and in some cases, hematuria and oral bleeding (6–8). The pathogenesis of PP is unclear, with studies suggesting that it may involve auto-sensitization to erythrocyte membrane phosphoglycerol esters, and others suggesting a link to oestrogens or hypovolemia (3).

The diagnosis of PP is challenging, as its clinical manifestations often resemble infections, coagulation disorders, or autoimmune disorders, making it easy to misdiagnose it as dengue, idiopathic thrombocytopenic purpura (ITP), or systemic lupus erythematosus (SLE). Due to the lack of a gold standard for diagnosis, PP is usually a diagnosis of exclusion. A correct diagnosis can only be made after a thorough medical history taking and laboratory examination. In this article, we report a case of PP in an elderly Chinese female uremic patient who got it after the death of her husband and an Aedes mosquito sting, and discuss its clinical features and the difficult diagnostic process.

2 Case presentation

On May 30, 2023, an 87-year-old woman was admitted to the hospital with a 2-day history of redness and swelling of the head and face after an Aedes mosquito sting, as well as multiple painful ecchymoses on the head, face and neck. She had a history of hypertension and chronic renal failure. With regular treatment, the condition was stable. She denied any other chronic diseases, infectious diseases and allergies. After being stung by an Aedes mosquito on the left cheek during outdoor activities 2 days ago, the patient rapidly developed redness, swelling and pain on the left cheek, with a palpable 2×2 cm subcutaneous hard nodule, followed by extensive subcutaneous ecchymoses on the head and neck, which were obvious to palpation (Figure 1A). At that time, she was examined in a foreign hospital, which indicated the following: coagulation function: fibrinogen (FIB) 4.68 g/L, bleeding time (BT), prothrombin time (PT) and partial thromboplastin time (PTT) were normal; renal function: see Figure 2; blood routine: white blood cell count (WBC) 10.20×10^9/L (93.8% neutrophils), hemoglobin (Hb) 107g/L, and the rest of the indicators were roughly normal; inflammatory indicators: serum amyloid A 13.21 mg/L; maxillofacial MR: infectious lesions with abscess formation in the left temporal, maxillofacial, and cervical regions, and chronic inflammation of the sieve sinuses and maxillary sinuses bilaterally. Based on the patient's normal BT, PT, PTT, and PLT results, ITP, factor XIII deficiency, and other coagulation disorders were excluded. She was diagnosed with chronic renal failure (uremic stage), toxic insect stings, and skin bacterial infections, and was referred to our hospital because of the ineffectiveness of antibiotic treatments.

On admission, the patient's vital signs were normal; physical examination revealed redness, swelling, and pain in the left cheek, with a palpable subcutaneous hard nodule of 2×2 cm, and multiple subcutaneous ecchymoses in the head and neck (Figure 1B). Further refinement of laboratory tests showed that coagulation function, blood routine indexes and renal function were not significantly different from before (Figure 2); electrolyte: calcium 2.04 mmol/L, phosphorus 1.53 mmol/L; inflammation indexes: procalcitonin 0.21 ng/ml; stool routine: OB (+). The preliminary diagnosis was "chronic renal failure (uremia stage), renal anemia, renal bone disease, hyperphosphatemia, hypertension grade 3, gastrointestinal hemorrhage, toxic insect stings, skin bacterial infections, dengue", and the treatment was based on symptomatic therapy such as regular peritoneal dialysis, antibiotic treatments, supplementation of protein raw materials, lowering of phosphorus, lowering of blood pressure, and protection of gastrointestinal mucosa. Specific medications are as follows: 2000ml of 1.5% peritoneal dialysis solution three times a day, intravenous piperacillin sodium and tazobactam sodium 3.375g every 8 hours, oral compound α-keto acid 1.89g/day, oral sevelamer carbonate 1.6g/day, oral amlodipine besylate 5mg/day, and intravenous omeprazole sodium 40mg/day.

On May 31, 2023, a dermatology consultation was requested, and the immune-related examinations showed weakly positive antinuclear antibody (ANA), IgG 6.620 g/L, hemosiderosis (ESR)

FIGURE 1
A timeline of the patient's symptom progression. **(A, B)** The patient presented with redness, swelling, and pain on the left cheek, with a palpable 2×2 cm subcutaneous hard nodule. Multiple ecchymoses were noted on the head and neck. **(C)** The patient's left cheek exhibited a darkening of the induration, with ecchymoses spreading to the anterior chest. **(D, E)** The patient's ecchymoses had lightened in color and were gradually fading. **(F)** The patient had recovered.

A

Chart of changing trend of hematological parameters

Timeline	FIB (g/L)	GFR (ml/min/1.73m^2)	PLT (10^11/L)	Scr (10^2umol/L)	WBC (10^9/L)
Day 1	4.68	3.48	3.15	9.03	10.20
Day 3	4.68	3.57	3.18	8.02	12.08
Day 9	5.09	5.10	2.92	5.98	8.25
Day 15	3.6	6.00	2.61	5.57	11.19

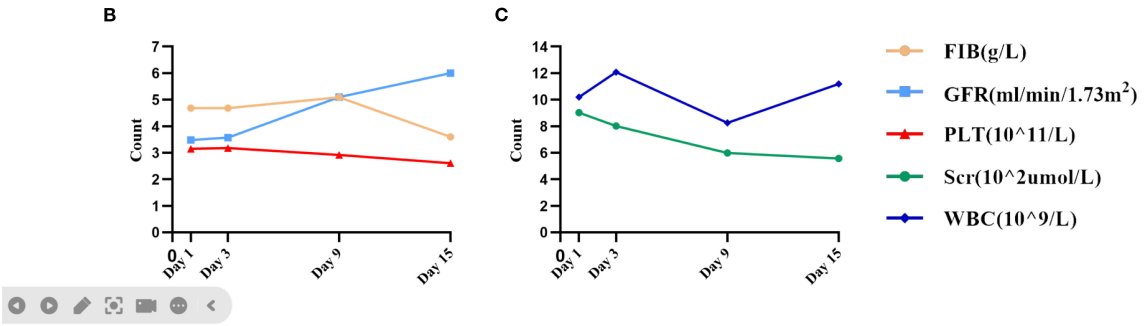

FIGURE 2
Key hematologic parameters from admission to discharge. **(A)** A graph of specific values corresponding to the figure. **(B)** The trends in fibrinogen (FIB), glomerular filtration rate (GFR) and platelet count (PLT). **(C)** The trends in blood creatinine (Scr) and white blood cell (WBC) count.

65.0 mm/h, and C-reactive protein (CRP) 99.500 mg/L. Other indicators such as anti-streptococcal hemolysin "O" (ASO), anti-double-stranded DNA (anti-dsDNA) and rheumatoid factor (RF) were all negative, according to which we excluded the diagnosis of dengue and other immune-related diseases. In the course of the ward rounds, we asked the patient and her family about her medical history in detail again. The family complained that two days before admission, the patient was in grief because of her husband's burial, and she suddenly suffered from chest tightness and breathlessness. Then she was sent to the hospital by ambulance and was in a coma during the emergency transportation due to excessive grief. Based on this important history of psychological stress, combined with the patient's symptoms and laboratory indicators, the dermatology department diagnosed "psychogenic purpura, skin bacterial infections", and the patient's right forearm was sensitized to auto-erythrocytes. The dermatologist recommended anti-inflammatory, immunomodulatory, and antibiotic treatments, including immediate intravenous dexamethasone sodium phosphate 3 mg, oral prednisone acetate 12 mg/day, oral thalidomide 50 mg/day, intravenous vitamin C 2 g/day, oral rutin 120 mg/day, and intravenous antibiotics as before. After 24 hours, the autoerythrocyte sensitization test was positive, with a burning sensation and ecchymosis; meanwhile, the saline control was negative, confirming the diagnosis of PP (Figure 3).

On June 5, 2023, the patient's hard nodule on the left cheek darkened, pressure pain decreased, and ecchymoses spread to the anterior chest (Figure 1C). Continuous monitoring of blood indicators (Figure 2) revealed a lower white blood cell count than before, suggesting the effectiveness of antibiotic treatments. The patient's symptoms improved, so the medication regimen was adjusted: oral prednisone acetate and intravenous vitamin C were discontinued, and oral methylprednisolone 8 mg/day was initiated.

On June 13, 2023, the patient's ecchymoses on the head and neck became lighter in color and gradually dissipated without pressure pain (Figure 1D). Reviewing the blood indices (Figure 2), the patient's white blood cell count was elevated, but only the monocyte count (1.73×10^9/L) was elevated. A repeat thin-layer CT of the maxilla showed that the subcutaneous soft tissue of the left cheek presented as nodular, slightly hyperdense shadows, accompanied by a slight swelling, and the inflammation of the bilateral maxillary sinuses had lessened than before. The patient's symptoms improved without fever and other discomforts, so the raised white blood cells were attributed to the use of immunomodulators, and the immunomodulators were stopped after 2 days.

On June 21, 2023, the patient was discharged from the hospital with significant improvement (Figure 1E), and a review of the diagnostic and treatment timeline is shown in Figure 4. On July 10, 2023, we followed up with the patient's family by telephone, who indicated that the patient's psychogenic purpura had resolved (Figure 1F). Currently, the patient has been followed for 1.5 years with no signs of recurrence.

3 Discussion

PP is a rare bleeding disorder of the skin, usually induced by psychological stress. The onset of the disease is often preceded by physiological stressors, such as minor mechanical injury, stress, surgery, or hard physical labor, as well as prodromal symptoms,

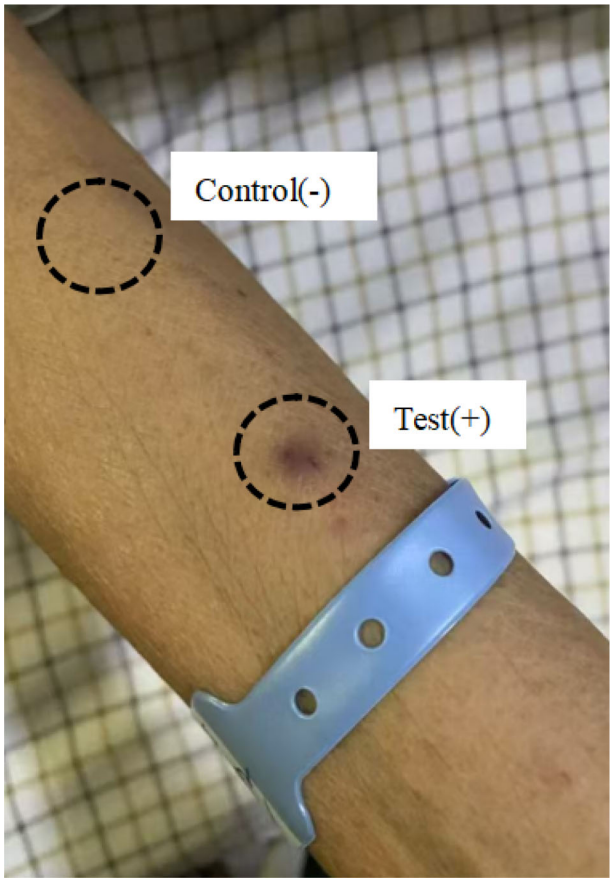

FIGURE 3
An autoerythrocyte sensitization test: positive with an ecchymosis, negative with saline control.

such as pain, burning sensation, and itching. The disease is characterized by painful edema and infiltrative lesions of the skin, which subsequently develop into ecchymosis within 24 hours, and expand into larger ecchymosis within an average of 4 to 5 days. Skin changes may be associated with a variety of systemic diseases, including fever, arthralgia, myalgia, headache, and dizziness. More than half of the PP patients reported different gastrointestinal symptoms, including epigastric pain, gastrointestinal bleeding, nausea, vomiting, and diarrhea. In addition, some studies have documented symptoms of hematuria and oral bleeding (6–8).

The pathogenesis of PP has not been fully elucidated. In 1955, Gardner and Diamond suggested that the disease may involve auto-sensitization of erythrocyte membrane phosphoglycerides (2). In 1968, Ratnoff and Agle first proposed a psychosomatic basis for PP, emphasizing that there is a direct relationship between mental stress and cutaneous manifestations, which gave birth to the name "psychosomatic purpura" (9). Currently, the pathogenesis of PP is considered to be a synergistic interaction between psychoimmunology and mechanical damage to the skin, in which preexisting psychosomatic disorders may affect skin immune function and weaken dermal capillaries. As a result, even minor skin injuries may disturb the capillary walls, ultimately leading to erythrocyte infiltration (10). Based on the pathogenesis of PP, the autoerythrocyte sensitization test is considered a criterion to confirm the diagnosis. The test is performed by injecting self-washed erythrocytes into the flexor surface of the forearm, and the results are usually read after 30 minutes and 24 hours, with the presence of induration and ecchymosis at the injection site deemed positive (11). However, some patients with PP have a negative response to this test, and a previous review showed a positive test rate of 85.7% (12). Therefore, this test can only be used as a reference, and not as a gold standard for diagnosing PP.

The diagnosis of PP presents significant complications. First, its clinical presentation lacks specificity and needs to be differentiated from dermatitis artefacta (DA), ITP, factor XIII deficiency, anaphylactic purpura, vascular hemophilia, Pfeifer-Weber-Christian syndrome, Ehlers-Danlos syndrome, malignant hematological disorders, dengue, vasculitis, and SLE (13). If necessary, the possibility of domestic violence and abuse should also be considered (14). Most of the above diseases have specific laboratory indicators and are not difficult to distinguish clinically. However, since DA and PP often show no obvious abnormalities in laboratory tests, and both are more common in women and accompanied by psychiatric symptoms, differential diagnosis becomes more challenging. At this point, a detailed medical history is crucial. DA patients typically have a history of self-harm, often intentionally damaging their skin through mechanical or chemical means, resulting in diverse skin lesions such as erythema, blisters, erosion, and crusting (15). In contrast, PP patients do not exhibit self-harm behaviors, and their skin lesions are more

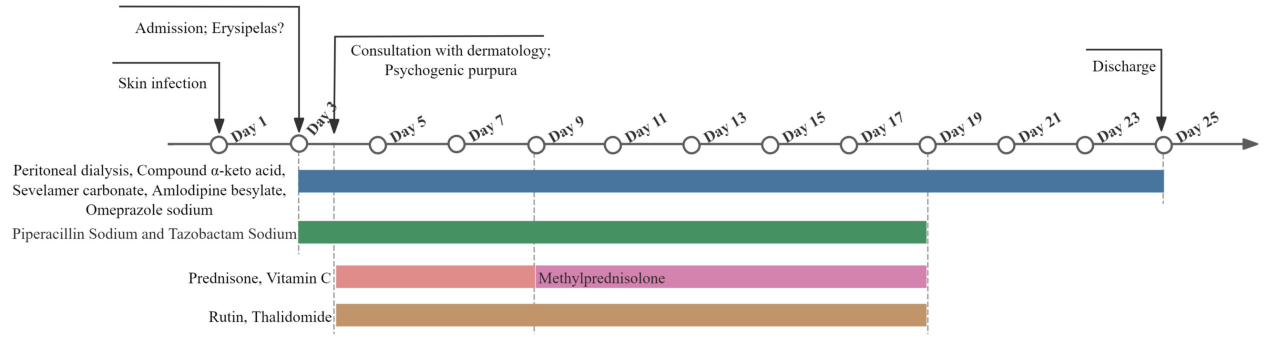

FIGURE 4
A timeline of diagnostic and treatment.

uniform in appearance, typically developing into ecchymoses within 24 hours. Second, laboratory testings are typically unremarkable, with just a few patients showing modestly abnormal laboratory values that support the diagnosis of any hematologic or immunological disorder. Furthermore, the autoerythrocyte sensitization test lacks accuracy, which does not allow for complete confirmation of PP. Based on the above, the diagnosis of PP is often referred to as a "diagnosis by exclusion". In diagnosing PP, the first step is to take a thorough medical history, looking for a history of mental diseases or psychological stressors, and looking for a correlation between psychological events and the onset of symptoms. Secondly, the clinical manifestations should be carefully observed to see if they conform to the typical evolutionary pattern of "physiological stressor → prodromal symptoms → painful edema → ecchymosis", and to exclude diseases with similar manifestations by the accompanying symptoms. Finally, necessary laboratory tests should be performed, including CBC, ESR, PLT, BT, PT, PTT, CRP, direct and indirect Coombs test, ANA, anti-dsDNA, RF and complement level (16). In general, the absence of obvious abnormalities in each index proves that there is no underlying hematological disease or other recognizable pathology.

In this case, the patient had just experienced the extremely painful event of her husband's death, and the onset of symptoms was highly synchronized with the psychological stressor. The clinical manifestations conformed to the typical evolutionary pattern of "physiological stressor → prodromal symptoms → painful edema → ecchymosis", and the accompanying gastrointestinal bleeding was also a common concomitant symptom of PP. The diagnosis of PP was confirmed after thorough laboratory tests to rule out ITP, salpingitis, SLE, and others. Because the patient had concurrent skin infections and no platelet abnormalities, only infection-related diseases were initially considered, and the immune response caused by psychological factors was ignored. This emphasizes the need to have complete awareness of the patient's medical history and consider the correlation between psychological status and disease occurrence when making a diagnosis.

In the treatment of PP, both psychological interventions and symptomatic support are usually administered (17). For psychological intervention, psychological counseling and social support are used, or antidepressants based on selective 5-hydroxytryptamine reuptake inhibitors (SSRIs). For symptomatic support, corticosteroids, antihistamines, and immunosuppressants are commonly used to relieve skin symptoms. The most recent systematic evaluation on PP showed that approximately 26% of patients relapsed after adequate follow-up, but only 8% of patients who received ≥1 psychiatric treatment (psychotherapy or medication) relapsed, resulting in 92% of patients in complete remission (3). Thus, psychological interventions are essential for achieving the best possible results.

In this case, the patient was only experiencing psychological stress due to the death of her husband, rather than a psychiatric disorder. Therefore, instead of prescribing antidepressants, we actively communicated with the family and instructed them to provide the patient with psychological comfort to ensure the patient received adequate social support. For symptomatic treatment, glucocorticoids and immunomodulators were used, among which dexamethasone, prednisone acetate and methylprednisolone could inhibit excessive inflammatory response, thalidomide reduced petechial inflammation by inhibiting inflammatory factors and angiogenesis, and rutin and vitamin C enhanced capillary stability in order to reduce erythrocyte extravasation. For concomitant symptoms, we applied antibiotics in sufficient quantity and course to treat skin infections caused by toxic insect stings, and used pantoprazole sodium for a long period to protect the gastrointestinal mucosa, thereby treating and preventing gastrointestinal bleeding. At the same time, we actively managed the primary disease by intensifying peritoneal dialysis to reduce edema pressure on the subcutaneous microcirculation, promote petechial absorption, and avoid further damage to the vascular endothelial barrier due to the accumulation of uremic toxins, such as indolephenol sulfate, caused by inadequate dialysis (18).

4 Conclusion

This patient is the second case of uremia combined with psychogenic purpura reported worldwide, following the first report in 2021 (19). This suggests that the possibility of psychogenic purpura should be considered when a uremic patient presents with painful ecchymosis. Diagnosis of PP requires complete awareness of the patient's medical history, attention to the chronological association between psychological factors and clinical symptoms, and exhaustive laboratory tests to exclude other

hematological and immunological disorders. Meanwhile, the successful management of this elderly uremic patient with PP confirms the effectiveness of a multidimensional treatment strategy. Through the comprehensive application of psychological intervention, immunomodulation, anti-infection and the treatment of primary disease, not only were the acute phase symptoms effectively controlled, but also the lasting effect of the treatment was verified by the long-term follow-up (ecchymoses completely disappeared after 1 month and did not recur for 1.5 years).

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.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LZ: Investigation, Methodology, Writing – original draft, Writing – review & editing. HZ: Resources, Writing – review & editing. YZ: Methodology, Writing – review & editing. TZ: Data curation, Writing – review & editing. ZZ: Formal analysis, Writing – review & editing. YQ: Methodology, Writing – review & editing. YT: Writing – review & editing. HS: Writing – review & editing. JL: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. BY: Conceptualization, Methodology, Writing – review & editing.

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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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Transcriptomic analysis of skin biopsies in Prurigo nodularis patients: with and without atopic dermatitis

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Background: Nodular dermatitis (PN) is a severely itchy chronic skin disease with symmetrically distributed nodules, often linked to an atopic background in some patients. However, the pathogenesis of PN with atopic dermatitis remains unclear.
Objective: The objective of this study is to compare the transcriptomes from skin biopsies of prurigo patients with and without atopic dermatitis, aiming to identify unique gene expression patterns and gain insights into the molecular mechanisms underlying Atopic dermatitis Prurigo (ADP) and Non-Atopic dermatitis Prurigo (NADP).
Method: We conducted transcriptome analysis to compare gene expression between normal controls and atopic dermatitis patients, identifying DEGs and performing KEGG and GO analyses, along with correlations between disease severity and itch NRS.
Results: We performed transcriptome profiling on 5 patients with ADP, 6 patients with NADP, and 6 healthy controls. Gene expression analysis revealed significant differences in inflammatory cytokines, suggesting that cytokine-mediated pathways play an important role in the pathogenesis of ADP. GO and KEGG analyses revealed cytokine-cytokine receptor interactions, with Th2 cytokines (SERPINB4, IL4R, IL24) upregulated in ADP and structural repair (BMP2) and metabolic genes (LEPR) elevated in NADP. Severity analysis showed positive correlations with SERPINB4, S100A8, IL24, and TGFB1, and negative correlations with BMP2, IL33, and LEPR. Keratinocyte hyperproliferation and inflammatory genes were commonly upregulated in both ADP and NADP.
Conclusion: These results provide insight into the molecular mechanisms of PN, particularly in the context of atopic dermatitis, and highlight that immune dysregulation and impaired skin barrier function are key factors in pathogenesis.

KEYWORDS

Prurigo nodularis (PN), atopic dermatitis (AD), chronic pruritus, differentially expressed genes (DEGs), Th2 inflammation, skin barrier dysfunction

Introduction

Prurigo nodularis (PN) is a chronic inflammatory skin disorder characterized by intensely pruritic and hyperkeratotic nodules, predominantly located on the extensor surfaces of the extremities and trunk (1). This debilitating condition significantly impairs quality of life, often leading to severe psychosocial stress due to persistent itching and the appearance of nodules (2, 3). PN is notoriously therapy-resistant; however, the recent FDA approvals of dupilumab and nemolizumab offer promising treatment options (4, 5).

Despite its prevalence, the pathogenesis of PN remains poorly understood, particularly in relation to atopic dermatitis (AD) and the clinical variations observed across racial and ethnic groups. Recent research suggests that PN is driven by a distinct Th22/IL-22-mediated immune response, characterized by elevated IL-22 levels in both systemic circulation and lesional skin (6). $CD4^+$ and $CD8^+$ T cells play a central role in this pathway, contributing to keratinocyte hyperplasia and disrupted epidermal differentiation, thereby exacerbating pruritus and aligning with PN's histopathological features (6).

Transcriptomic analyses have also revealed racial differences in immune responses among PN patients. For instance, African American individuals exhibit lower IL-31 upregulation compared to Europeans, who display stronger Th2/IL-13 responses (7). This pattern is supported by the efficacy of nemolizumab in alleviating IL-31-driven pruritus and Th2 inflammation in European PN cohorts, highlighting the importance of personalized treatments tailored to racial and genetic backgrounds (1, 8, 9).

AD significantly contributes to PN development, as both conditions share overlapping immune pathways, including Th1, Th2, and Th17 polarization (9, 10). Mechanisms such as immune-mediated inflammation, bacterial colonization, and impaired skin barrier function are common to both diseases. The upregulation of Th2 cytokines, including IL-13 and IL-4R, underscores this shared immunologic profile (9, 11). The therapeutic success of IL-4R-targeting biologics, such as dupilumab, further supports their common pathophysiology (8, 12–14).

Nonetheless, transcriptomic comparisons between atopic dermatitis-associated prurigo (ADP) and classic AD have revealed significant distinctions (9). ADP exhibits more pronounced Th22 polarization, with higher IL-22 levels and increased expression of IL-22 receptors (IL22RA1 and IL22RA2), which are not commonly elevated in AD (9). ADP also displays neural dysregulation, evidenced by increased nerve fiber density and neuroimmune interactions in lesional skin—features that are less prominent in classic AD (4, 9). In addition, ADP is associated with macrophage activation (M1/M2), increased tumor necrosis factor (TNF) production, fibrosis, tissue remodeling, and angiogenesis, further differentiating it from AD (4, 9, 15). Ultimately, PN is a distinct dermatological entity with both unique and overlapping immunological pathways when compared to AD. While previous studies have primarily focused on distinguishing AD from PN, the transcriptomic differences between ADP and non-atopic dermatitis prurigo (NADP) have not been well characterized. Elucidating these molecular mechanisms may guide the development of more personalized therapeutic approaches and improve clinical outcomes for patients with PN.

Materials and methods

Human participants and sample collection

Skin tissue samples were obtained from 17 participants (12 males, 5 females) aged 19 to 75 years, divided into three groups: chronic pruritus without atopic dermatitis (n=6), chronic pruritus with atopic dermatitis (n=5), and normal controls (n=6). *A priori* power analysis ($\alpha = 0.05$, power = 0.80) indicated that at least 17 participants per group are required. Atopic dermatitis and Prurigo nodularis (PN) were diagnosed by dermatologists based on established criteria. Normal skin samples were collected from the calf region, while PN samples were obtained from affected areas via punch biopsies. Exclusion criteria included immunosuppressive drug use, systemic inflammatory conditions, pregnancy, or breastfeeding.

Samples were collected using sterile techniques, flash-frozen in liquid nitrogen, and stored at -80°C. The study was conducted in accordance with the Declaration of Helsinki and approved by the IRB of Kangnam Sacred Heart Hospital (IRB No. 2022-03-038). Written informed consent was obtained from all participants. Clinical characteristics are summarized in Table 1.

Transcriptome analysis of skin tissue samples

A total of 17 skin tissue samples were analyzed using Macrogen's transcriptome sequencing method. RNA was extracted from the skin tissue samples following the manufacturer's protocol. RNA sequencing was performed on an Illumina HiSeq 2500 platform to generate 100bp paired-end reads. Data preprocessing and quality checks included filtering, logarithm transformation, and normalization, with reproducibility assessed through box plots and density plots. Sequencing reads were aligned to the human reference genome (GRCh38) using HISAT2, and differential expression analysis was conducted using DESeq2. Publicly available transcriptomic data of lesional atopic dermatitis and healthy control skin samples were obtained from the Gene Expression Omnibus [GSE5667 (16) and GSE213849 (17)] and previously published. Platform heterogeneity was corrected by removing batch effects with the *ComBat function* of the *sva package*.

Principal component analysis

Principal component analysis (PCA) was performed using the DESeq2 package in R to analyze sample variance and clustering. Count data were normalized with variance stabilizing transformation (vst) to adjust for sequencing depth and variability. Genes with low counts (0–10 in fewer than 8 of 17

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TABLE 1 Clinical characteristics of participants.

Characteristics	Normal	Prurigo Patients (Atopic Dermatitis)	Prurigo Patients (Non-atopic Dermatitis)	*P* value
Tissue	6	5	6	
Gender (Female / Male)	2 / 4	2 / 3	1 / 5	0.853
Age (Mean±SD)	30±25.1	54±17.24	63.83±10.87	0.326
Pruritus NRS	0.00±0.00	7±0.63	7±1.15	1
Chronic nodular prurigo (CNPG)	0.00±0.00	3.2±0.75	3.33±0.47	0.452

Values are shown as counts or mean ± SD. P-values were calculated as follows: Gender (Female / Male), χ^2 test (two-sided); Age, one-way ANOVA across the three groups; Pruritus NRS, Kruskal–Wallis test; CNPG score, Kruskal–Wallis test. Abbreviations: SD, standard deviation; NRS, numeric rating scale; CNPG, chronic nodular prurigo.
CNPG Score: 0: Clear, 1: Almost Clear, 2: Mild, 3: Moderate, 4: Severe
SD: Standard Deviation; Pruritus NRS: Pruritus Numeric Rating Scale

samples) were filtered out. The vst-transformed data were used for PCA, and results were visualized with ggplot2, with samples categorized as Normal, NADP (Non-Atopic Dermatitis Pruritus), or ADP (Atopic Dermatitis Pruritus). A DESeqDataSet was created with count data and metadata, and DESeq2 was used for differential expression analysis. vst-normalized data were used for PCA, visualized with plotPCA, showing percent variance of the first two components. ggplot2 enhanced the plot with ellipses indicating 95% confidence intervals for each group.

Differential gene expression analysis

DEG analysis using DESeq2 identified significant genes (padj < 0.05), selecting the top 250 upregulated and downregulated genes by log2FoldChange. Adjusted P-values were calculated with the Benjamini–Hochberg false-discovery-rate procedure. Volcano plots highlighted the top 25 genes, marking significance and fold-change thresholds, while heatmaps visualized expression patterns, including focused views of the top 25 genes. Comparisons (Normal vs. ADP, Normal vs. NADP, NADP vs. ADP) revealed the top 50 DEGs for each group, illustrating the magnitude and significance of expression changes.

KEGG and GO enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted using the clusterProfiler package. For GO enrichment analysis, significant genes (padj < 0.05) were annotated using the org.Hs.eg.db database, with the analysis encompassing Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) categories. The results were adjusted using the Benjamini-Hochberg (BH) method, and significant pathways were visualized using dot plots to highlight the top 20 enriched GO terms.

For KEGG pathway enrichment analysis, gene symbols were first mapped to ENTREZ IDs using the bitr function. Mapped genes were analyzed for pathway enrichment in Homo sapiens (hsa) using the enrichKEGG function, with results similarly adjusted using the BH method. Significant pathways were visualized using both dot plots and bar plots. Additionally, specific pathways, such as "hsa04060" (Cytokine-cytokine receptor interaction pathway), were visualized using the pathview package, which generates detailed pathway maps with color-coded gene expression data. This pathway is highly relevant to prurigo nodularis pathogenesis, as it includes key inflammatory mediators (e.g., IL-4, IL-13, IL-24) that play central roles in immune dysregulation and pruritus.

Correlation analysis of cytokine-cytokine receptor interaction genes with disease severity and pruritus numerical rating scale in patients

Cytokine-cytokine receptor interaction genes from KEGG analysis were correlated with Severity and Pruritus NRS scores.

The top 250 upregulated and downregulated genes were log2-transformed and aligned with clinical data. Correlation analyses identified the top 10 genes with the strongest positive and negative correlations for Severity and Pruritus NRS. Scatter plots with regression lines visualized these relationships.

Results

Comprehensive genetic and pathway analysis of prurigo nodularis patients with and without atopic dermatitis: insights from GO enrichment and KEGG pathway studies

This study analyzed gene expression in 17 skin transcriptomes, comparing 6 normal individuals and 11 Prurigo Nodularis (PN) patients (5 AD, 6 NAD). Table 1 presents the demographic and clinical characteristics of the normal and patient groups.

To evaluate differentially expressed genes (DEGs) between PN patients with and without atopic dermatitis (AD), we performed PCA, which demonstrated clear gene expression differences between normal controls and PN patients, highlighting the influence of AD (Figure 1A). A heatmap of the top 50 significant genes (Figure 1B) and a Volcano plot (Figure 1C) revealed distinct expression profiles among normal controls, PN patients with AD, and those without AD.

GO enrichment analysis indicated associations with epidermal development, keratinocyte differentiation, pruritus, and neurological functions (Figure 1D), while KEGG pathway analysis highlighted cytokine-cytokine receptor interactions involving IL-4, IL-13, IL-25, TSLP, and IL-33 (Figure 1E, Supplementary Table 1). These findings suggest that the top 50 DEGs are closely linked to AD-related pathways and skin inflammation in PN patients.

Comparative gene expression and pathway analysis in atopic dermatitis prurigo

We analyzed the gene expression differences between Non-Atopic Dermatitis Prurigo (NADP) and Atopic Dermatitis Prurigo (ADP) using a Volcano plot (Figure 2A, Supplementary Table 2) and performed GO enrichment and KEGG pathway analysis (Figure 2B, Supplementary Table 3). The functional classification of genes was provided as follows (Supplementary Table 4–6). In the NADP/ADP comparison, the upregulated genes of ADP were related to skin and allergic inflammation, while the downregulated genes were related to AD-related inflammation in other tissues, highlighting the importance of AD-related pathways. GO enrichment and KEGG pathway analysis were also performed for the Normal/ADP, Normal/NADP, and NADP/ADP groups (Figure 2B). Although the NADP/ADP group had too few genes to obtain meaningful results, the Normal/ADP and Normal/NADP groups were related to epidermal development, keratinocyte differentiation, and synaptic organization in neurological processes, which was consistent with the results of the normal/itch comparison. Additionally, integration with public transcriptomic data (GSE213849) revealed that A total of 128 differentially expressed genes overlapped with GSE213849 and GSE5667. Several genes significantly upregulated in classic AD were also elevated in our ADP samples, indicating shared molecular signatures and reinforcing the immunological overlap between AD and ADP (Supplementary Figure 1).

Distinct gene expression patterns highlighting immune dysregulation and skin barrier dysfunction in Prurigo subgroups

These results were analyzed to classify the expression patterns associated with specific genes into various AD-related subgroups (Th1, Th2, Th17, NK cells, Skin barrier, Tissue remodeling, Nerve function, etc.) and identify genes or biomarkers that play important roles in each subgroup. The gene expression analysis in PN patients reveals distinct patterns associated with immune dysregulation and skin barrier dysfunction Figure 3. The ADP subgroup shows Th2 inflammation (IL13, IL4R, TGF-β1), skin barrier disruption (LCE3A, KRT16), and tissue remodeling (MMPs), highlighting potential therapeutic targets for personalized treatments. Further supporting our findings, analysis of public microarray data (GSE5667) revealed that genes associated with skin barrier integrity and inflammation, such as SPRR2G and LCE3D, were upregulated in both AD and our ADP dataset (Supplementary Figure 2).

Correlation analysis of severity and NRS in atopic dermatitis: inflammation and immune regulation insights

We conducted a correlation analysis between prurigo severity and pruritus (as measured by the NRS) and gene expression levels in ADP (Figure 4). Genes such as SERPINB4, S100A8, IL24, and TGFB1 positively correlate with disease severity, suggesting their involvement in inflammation and immune responses in ADP. Conversely, genes like BMP2, IL33, and LEPR show negative correlations. S100 family genes and CCL18 further highlight their role in inflammation, offering potential therapeutic targets for managing ADP. These results suggest that gene expression patterns vary with disease severity and that specific genes are associated with the progression of ADP, depending on whether their expression levels are increased or decreased.

Differential gene expression in atopic and non-atopic Prurigo highlights shared and unique pathways in inflammation and tissue remodeling

Gene expression analysis of ADP and NADP revealed that ADP has higher expression of inflammatory and immune-regulating

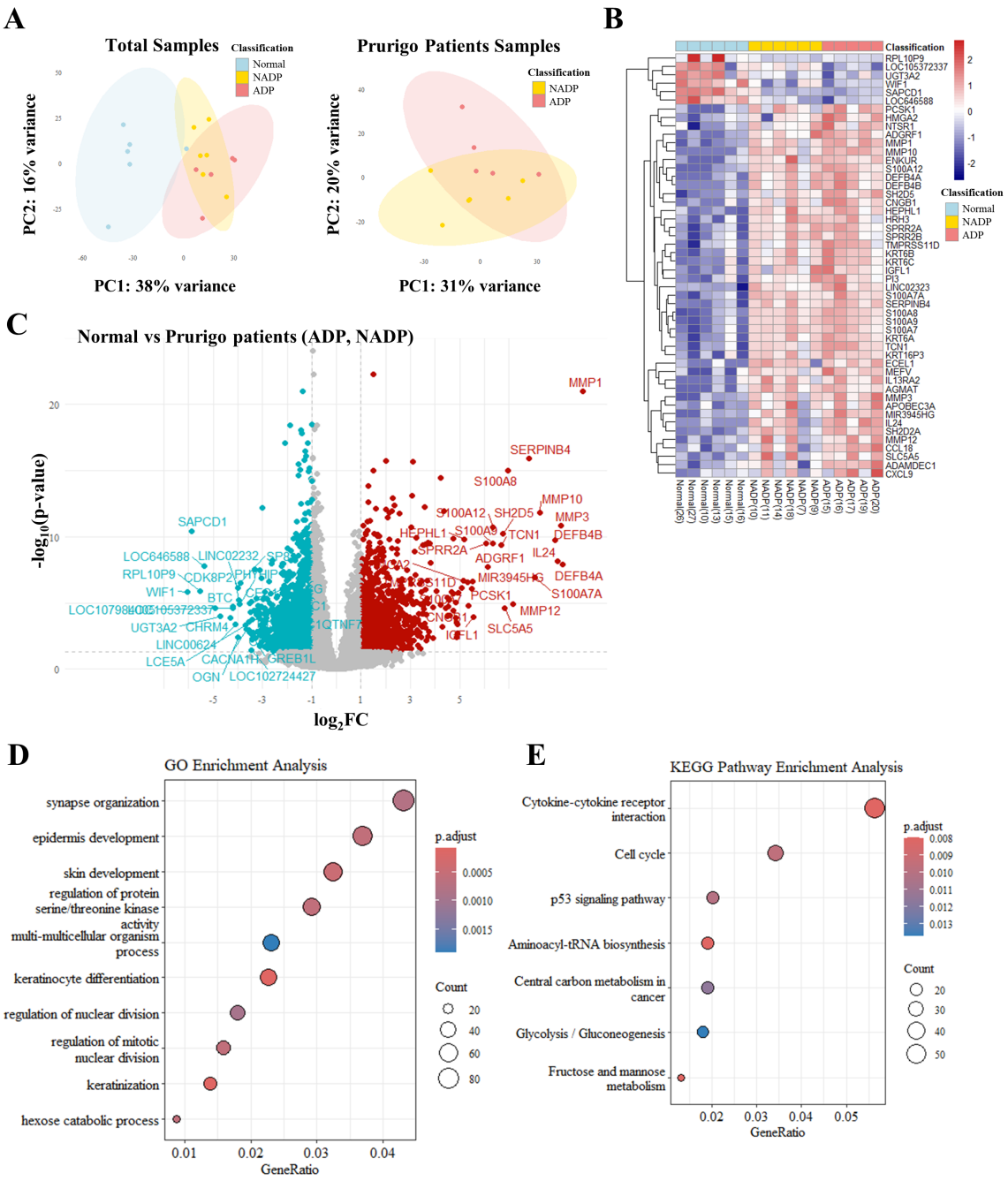

FIGURE 1
Transcriptomic analysis of skin tissues from healthy controls and patients with Prurigo Nodularis. **(A)** Principal component analysis (PCA) of transcriptomic data. The left plot shows PCA results for skin tissues from healthy controls, non-atopic prurigo nodularis (NADP), and atopic prurigo nodularis (ADP). The right plot shows PCA results comparing NADP and ADP tissues. **(B)** Heatmap of differentially expressed genes (DEGs) among normal, NADP, and ADP tissues, showing the top 50 genes with the most significant expression changes. **(C)** Volcano plot representing DEG analysis between healthy and PN patient tissues. Red dots represent genes that are upregulated in prurigo Nodularis tissues (log2FC ≥ 1 and p-value ≤ 0.05), while teal dots represent genes that are downregulated in prurigo Nodularis tissues (log2FC ≤ -1 and p-value ≤ 0.05). **(D)** Gene Ontology (GO) enrichment and **(E)** KEGG pathway enrichment of DEG patterns identified in normal and prurigo Nodularis tissues.

genes (e.g., SERPINB4, S100 family, IL4R, IL24), while NADP shows relatively lower expression of inflammatory markers and distinct expression patterns in structural repair (e.g., BMP2) and metabolic regulation genes (e.g., LEPR). Notably, although BMP2 and LEPR were initially considered elevated in NADP, Figure 5 indicates these genes are in fact downregulated compared to healthy controls. These differences highlight potential pathway divergence and suggest that a Th2-mediated immune response is particularly

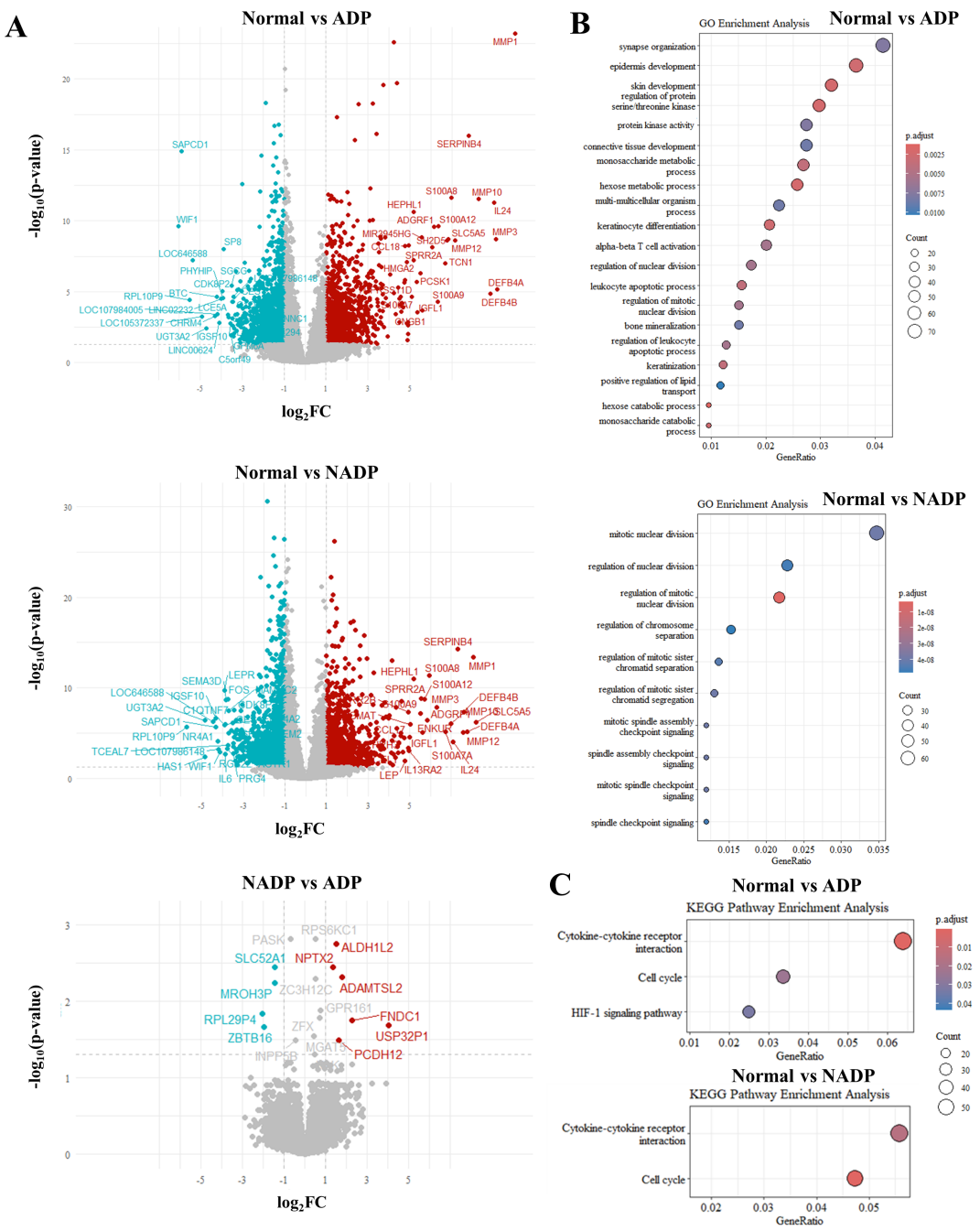

FIGURE 2
Differential gene expression analysis between Normal, NADP, and ADP tissues. **(A)** Volcano plots showing differential expression analysis for three comparisons: Normal vs. ADP (top), Normal vs. NADP (middle), and NADP vs. ADP (bottom). Red dots indicate genes with significant upregulation (log2FC ≥ 1, p-value ≤ 0.05), while teal dots represent genes with significant downregulation (log2FC ≤ -1, p-value ≤ 0.05). **(B)** GO enrichment analysis based on DEGs from Normal vs. ADP (top) and Normal vs. NADP (bottom). **(C)** KEGG pathway enrichment analysis for DEGs identified in Normal vs. ADP (top) and Normal vs. NADP (bottom).

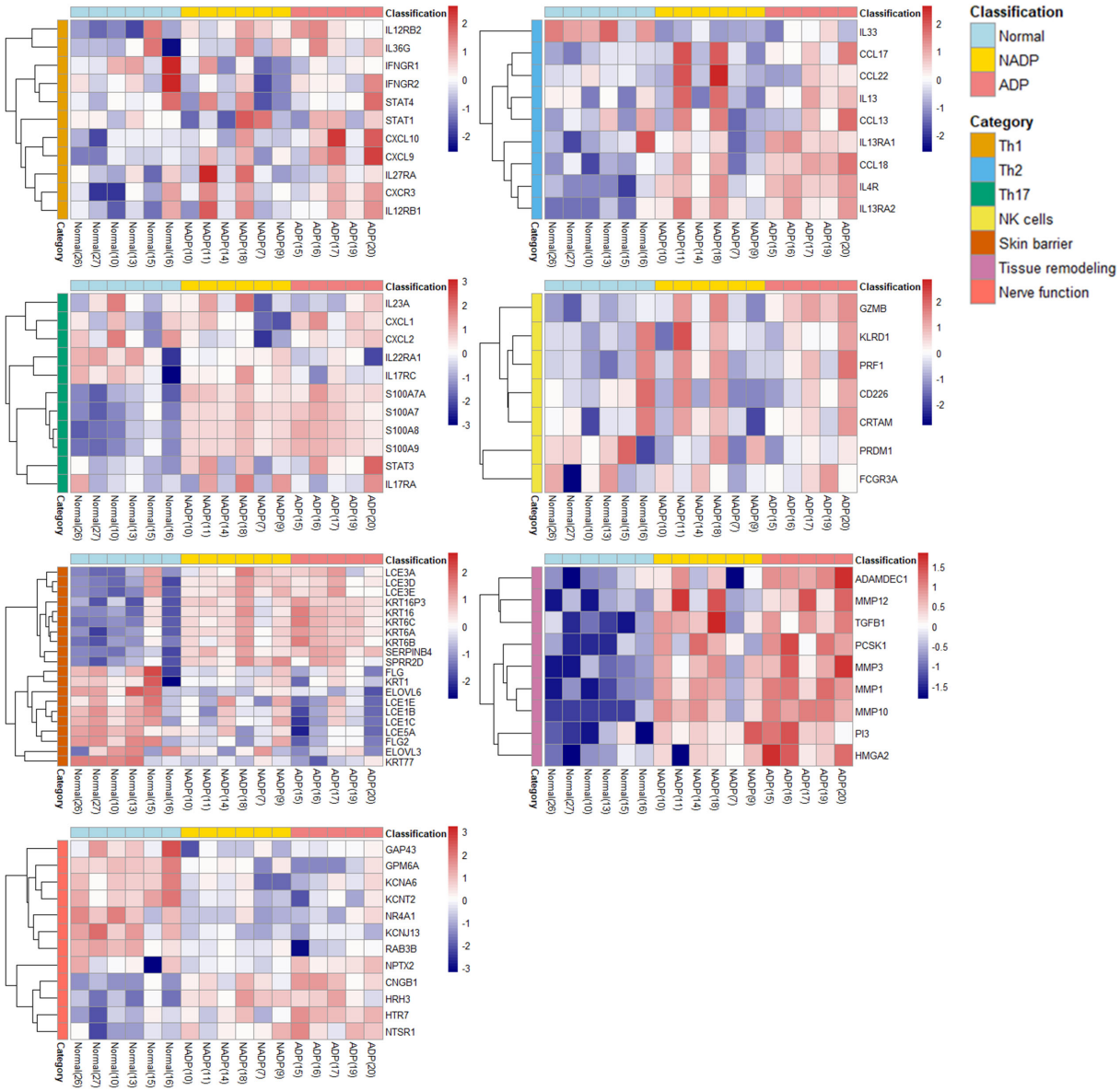

FIGURE 3
Functional categorization and heatmap analysis. The heatmap displays the expression patterns of DEGs classified into functional categories, including Th1, Th2, Th17, NK cells, skin barrier, tissue remodeling, and nerve function. Gene expression levels are compared across Normal, NADP, and ADP tissues. All DEGs included in the heatmap were selected based on an adjusted p-value (padj) < 0.05 from DESeq2 analysis, indicating statistical significance. Functional grouping was based on known gene functions and prior literature.

prominent in ADP, supported by the upregulation of SERPINB4, S100A8, IL4R, and IL24. Targeting Th2 cytokines may therefore offer effective therapeutic strategies (Figure 5). Moreover, genes such as TOP2A and SELL, previously identified as significantly upregulated in PN compared to healthy controls (GSE213849), were also elevated in our ADP samples, suggesting a shared transcriptional landscape between ADP and classical PN (Supplementary Figure 3).

Differential gene expression and pathway analysis in atopic dermatitis: insights into inflammation, keratinocyte hyperproliferation, and immune dysregulation

Our study identified 415 genes uniquely upregulated in ADP, 412 in NADP, and 836 in both groups, while 840 were commonly

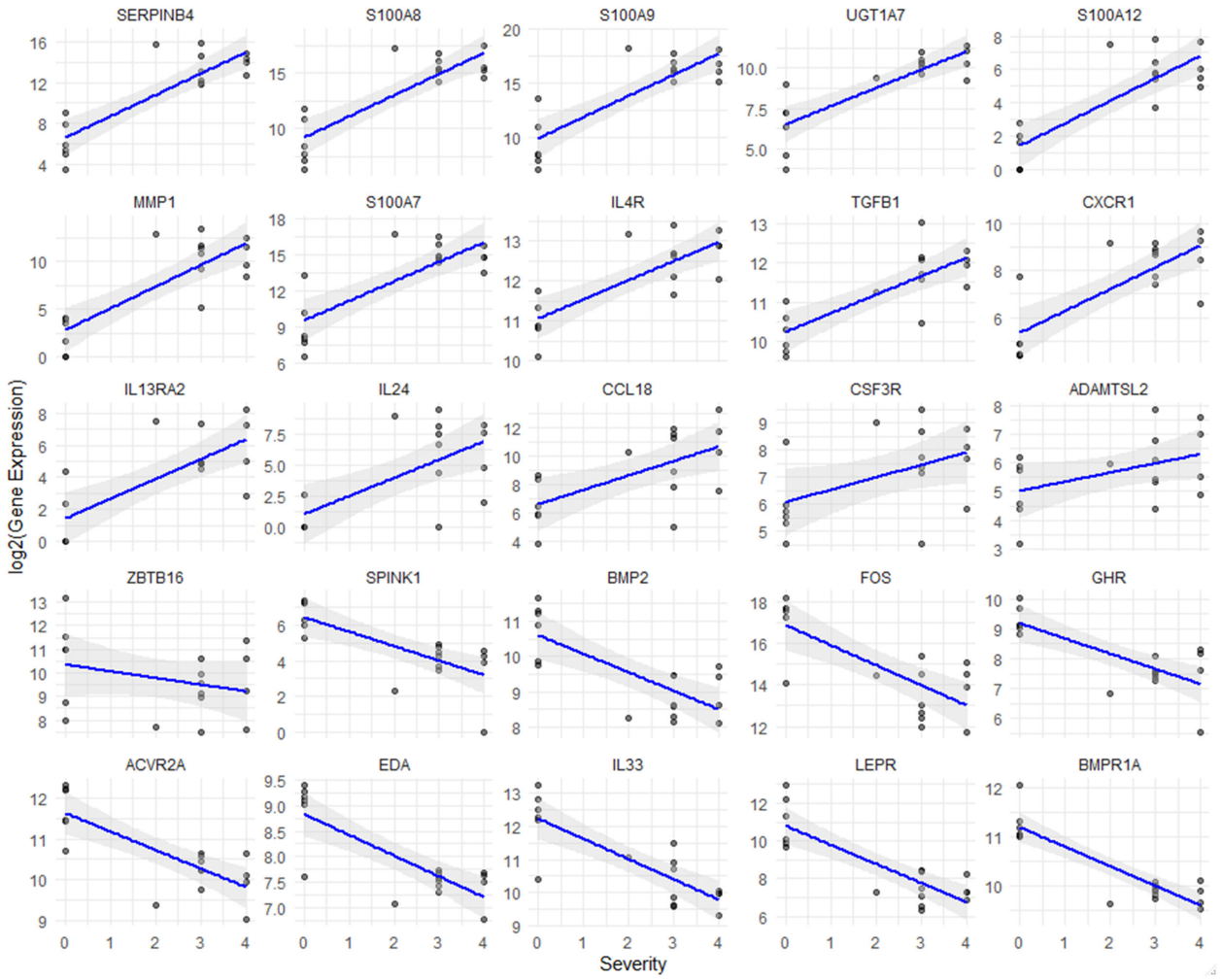

FIGURE 4
Correlation analysis between gene expression and severity of prurigo nodularis. Scatter plots show the relationship between gene expression levels and chronic nodular prurigo severity scores (0-4). The x-axis represents the severity score, while the y-axis indicates log2-normalized FPKM values for each gene. The blue line represents the regression trend, and the shaded grey area indicates the confidence interval. All genes shown in the plots demonstrated statistically significant correlations with severity (Spearman correlation, $p < 0.05$).

downregulated Table 2. Genes linked to keratinocyte hyperproliferation (MMP1, S100A8, S100A9) and inflammation (IL24, CXCL9) were upregulated in both groups Table 2. whereas downregulated genes like WIF1 and CHRM4 highlighted distinct pathways. Upregulated fibrosis and tissue remodeling genes (MMP3, MMP12) suggest potential therapeutic targets to improve AD treatment strategies.

Discussion

This study presents a comprehensive gene expression analysis of PN patients, differentiating between Atopic dermatitis Prurigo (ADP) and Non-Atopic dermatitis Prurigo (NADP) subtypes and comparing them with healthy controls. Our results revealed distinct transcriptomic differences not only between PN patients and healthy controls but also between ADP and NADP subgroups, underscoring the importance of understanding genetic and molecular distinctions within PN for developing targeted therapies.

PCA revealed distinct gene expression profiles between PN patients and normal controls, with differences between ADP and NADP. GO and KEGG analyses identified unique immunological features, including upregulated cytokine-cytokine receptor interactions. In particular, particularly the Th2 pathway involving IL-4, IL-13, IL-33, and TSLP. This is consistent with previous findings that both ADP and AD share Th2 polarization (9). Previous studies demonstrated the efficacy of Th2-targeting therapies, such as dupilumab, in treating PN (8, 12–14), which aligns with findings from Japanese cohorts identifying Th2 as a major driver in PN among Asian populations (18, 19).

Our study examined the Th22/IL-22 pathway, which is known to disrupt the skin barrier and exacerbate pruritus in atopic dermatitis. IL-22 promotes keratinocyte proliferation and impairs barrier function; however, in our dataset, Th22-related gene

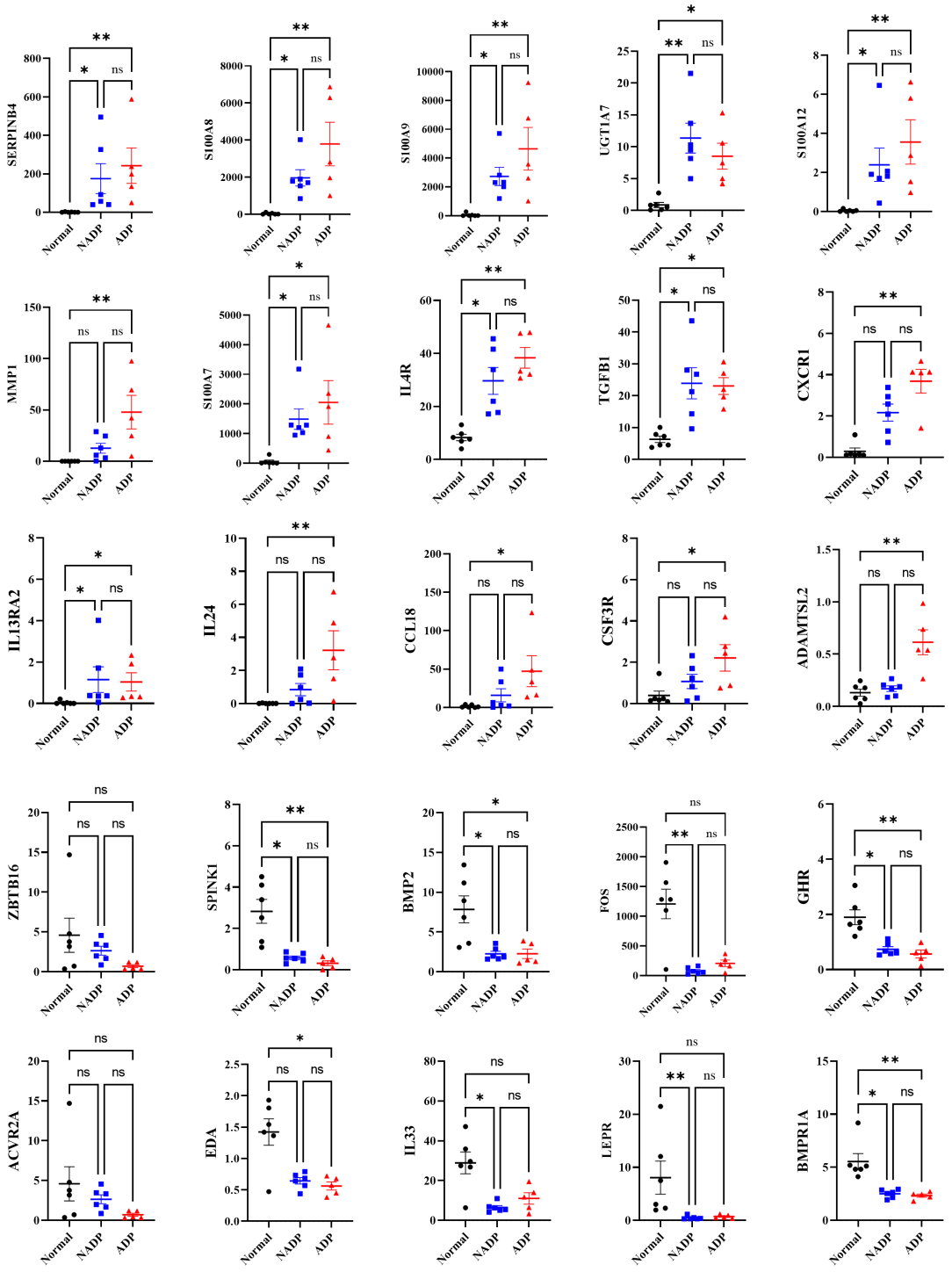

FIGURE 5
Gene expression levels of core genes identified as potential biomarkers in prurigo nodularis. The graphs display the expression levels of core genes identified as potential biomarkers for distinguishing between disease groups in prurigo nodularis. The y-axis represents FPKM values, with black dots indicating the Normal group, blue dots indicating the NADP group, and red dots indicating the ADP group. Error bars represent the mean ± standard deviation. Asterisks denote statistical significance (*$p \leq 0.05$, **$p \leq 0.01$).

expression, including IL-22 and its receptors (IL22RA1, IL22RA2), was not significantly elevated in either the ADP or NADP groups, as also reflected in Figures 3-5. This finding suggests that the Th22 axis is not a dominant immune pathway in our Asian PN cohort, aligning with previous transcriptomic studies in similar populations (6). This contrasts with African-American or European populations, where IL-22 and other Th22 cytokines are often upregulated and play a central role in disease pathology (6). These observations underscore racial and ethnic variations in immune activation pathways, with lower Th22 activity but

TABLE 2 Functional categorization of differentially expressed genes in PN patients.

Functional categorization	Gene
Keratinocyte hyperproliferation	MMP1, SPRR2A, S100A8, S100A9 ↑ WIF1 ↓
Fibrosis and tissue remodeling	MMP1, MMP3, MMP10, MMP12 ↑ LEPR, IGSF10 ↓
Pruritus and neurogenic inflammation	IL24, MMP1, NTSR1, HRH3, HTR7 ↑ CHRM4, KCNJ13 ↓
Chronic inflammation (Th1/Th2/Th17/Th22)	IL24, CXCL9, CXCL10, IL4R, IL13RA2, S100A8, S100A9, SERPINB4 ↑ NR4A1 ↓
Innate immunity	DEFB4A, S100A8, S100A9 ↑

relatively heightened Th2-mediated responses in Asian patients, which may have important implications for tailored therapeutic strategies.

IL-31, a cytokine strongly linked to pruritus and inflammation, is known to stimulate cutaneous nerve fibers and drive neuroimmune activation in prurigo nodularis (PN) patients (20). However, in our current transcriptomic analysis of lesional skin samples, IL-31 expression was not significantly elevated in either the ADP or NADP groups compared to healthy controls. This finding is consistent with previous reports in Asian PN cohorts, where IL-31 expression was either low or absent at the transcriptomic level (6, 20). One possible explanation for this discrepancy lies in racial or ethnic differences in immune signaling, with IL-31-mediated pathways more prominently observed in European populations, while IL-17 or IL-22-related pathways appear to be more dominant in Asian patients (6, 21). Additionally, the tissue specificity of IL-31 expression—more frequently detected in serum or peripheral blood mononuclear cells than in skin tissue—may also contribute to the lack of differential expression in our skin biopsy data (11). These observations underscore the complex and heterogeneous pathogenesis of PN and highlight the need for integrative analyses combining transcriptomic, proteomic, and serum-based cytokine profiling in future studies.

For pathway analysis, GO enrichment and KEGG assessments on normal/ADP, normal/NADP, and NADP/ADP groups revealed prominent pathways. Epidermal development and synaptic organization were highly significant in ADP compared to normal controls, and cytokine-cytokine receptor interaction pathways were relevant for both ADP and NADP. The IL-17 signaling pathway, in particular, was more active in NADP compared to controls, paralleling findings in psoriasis, where IL-17 is known to play a central role (6). These findings highlight the IL-17A-Endothelin-1 axis as a potentially important driver in PN pathogenesis (21).

Comparative analysis of gene expression between ADP and NADP further clarified pathophysiological distinctions, revealing upregulation of genes such as NPTX2, ADAMTSL2, USP32P1, FNDC1, PCDH12, and ALDH1L2 in ADP. NPTX2, associated with chronic pruritus, is highly expressed in sensory neurons (22), while FNDC1 in fibroblasts (23), and PCDH12, a marker for MrgprA3+ neurons linked to itch perception (24) were more pronounced in ADP. The upregulation of genes related to neural function and tissue remodeling in ADP suggests that neuroregulatory dysfunction and fibroproliferative tissue remodeling may be more pronounced in ADP than NADP.

Fibrosis is central to PN pathology, marked by increased keratinocyte proliferation, ECM remodeling, and tissue thickening. Upregulated MMPs (e.g., MMP1, MMP3, MMP12) drive ECM breakdown and fibrotic nodule formation. Similarly, SPRR2A, associated with hyperproliferative (25) and reparative responses (26–28), and decreased IGSF10 expression may exacerbate uncontrolled fibrosis, contributing to the increased dermal thickness typical of nodular prurigo (27).

Among commonly upregulated genes in both ADP and NADP, SERPINB4—induced by IL-22, IL-17, IL-4, and IL-13—correlates with disease severity, highlighting its potential as a biomarker for treatment efficacy. IL-24, another promising therapeutic target, exacerbates pruritus and inflammation, particularly in response to *Staphylococcus aureus* (28). Antimicrobial peptide DEFB4B, critical in skin barrier integrity, shows decreased expression in PN, linking it to susceptibility to infection (29). IGFL1, which supports epithelial proliferation, and SPRR2A (25), crucial for keratinocyte differentiation, emerge as targets for enhancing skin recovery and preventing disease progression in PN and AD (30). Upregulated IL4R, CCL18, and TGFB1 indicate shared Th2-driven inflammation in ADP and NADP, while ADP-specific genes like CSF3R and ADAMTSL2 highlight heightened inflammation, remodeling, and neuroimmune interactions.

Single-cell RNA-sequencing in PN and AD reveals fibroblasts in AD lesions expressing CCL2, CCL19, and CCL11, which drive immune cell recruitment and inflammation via the IKKβ/NF-κB pathway, worsening AD pathology (31). Comparative studies between PN and AD have shown that both conditions exhibit type 2 immune bias, but AD showed extensive immune activation of CD8A+IL9R+IL13+ cytotoxic T cells (32). In contrast, PN is characterized by extracellular matrix remodeling, collagen synthesis, and fibrosis, and has been shown to have CXCL14-IL24 + fibroblasts (33). In addition, a recent study identified a population of COL6A5+COL18A1+ fibroblasts that are present exclusively in AD lesions (34). Our study found significant upregulation of IL-4R, IL-13R, and IL-24 in AD lesions, contributing to Th2 responses. KEGG analysis revealed cytokine-cytokine receptor interactions as

key to PN and AD progression. Genes like S100 family, CCL18, and CSF3R increased with AD severity, linking gene expression to disease progression and identifying therapeutic targets for inflammation and itching. Correlation analysis between the severity of PN with the top 500 significant genes revealed a positive correlation for IL4R, IL13RA2 (Th2), TGFB1 (fibrosis in PN), CXCR1 (chemoattractant), and IL24 (Th2). Similarly, a positive correlation with pruritus NRS was observed for IL4R, CXCR1, TGFB1, IL13RA2. These findings suggest that these cytokines and their receptors could serve as potential therapeutic targets. Additionally, KEGG pathway analysis identified upregulation of ADP-related DEGs such as CLCF1, CXCL9, and CXCL10, suggesting that the CXCL9/CXCL10 axis may play a key role in pruritic neuroinflammation (35). Increased expression of IL24, S100A8, and S100A9 contributes to neuroinflammation, thereby activating sensory neurons that induce itch. MMP1 degrades extracellular matrix components, exposing the nerves to inflammatory mediators, thereby increasing nerve sensitivity. Conversely, decreased expression of CHRM4 and KCNJ13 may impair sensory nerve signaling, thereby increasing nerve excitability and altering itch perception.

Several genes, including BMPR1A, EDA, IL33, and BMP2 were notably downregulated in PN. BMPR1A regulates skin inflammation via key signaling pathways (36, 37). while EDA is associated with cell death, differentiation, and migration processes (38). In this study, IL-33 levels were found to be reduced in PN and negatively correlated with pruritus severity (6, 39, 40). A potential hypothesis is that while IL-33 is a key driver of allergic inflammation (39–43), it also plays an essential role in promoting re-epithelialization (43–45), inducing ILC2 proliferation (46, 47), facilitating wound healing (43–45, 47) and supporting the induction and maintenance of regulatory T cells (Tregs) (48–50). Reduced IL-33 expression may impair wound healing, preventing the resolution of scratch-induced lesions and promoting the transition from acute to chronic inflammation (39–42, 51, 52).

BMP2, which plays a role in cell growth, maturation, and fibrotic proliferation across the dermis and epidermis, was also downregulated (53). Decreased BMP2 and related genes in PN indicate a shift to chronic fibrosis, while downregulated LEPR and GHR in ADP suggest systemic dysfunction. Targeting these and structural repair pathways may offer holistic therapies.

In conclusion, this study elucidates critical molecular and immunological differences between ADP and NADP, providing insights into distinct inflammatory pathways in each subtype. Pathways such as IL-17 in NADP and neuroregulatory dysfunction in ADP highlight the potential for personalized treatments, particularly by targeting cytokines such as IL4R, IL13RA2, and TGFB1, which are associated with disease severity. The influence of racial and ethnic factors further emphasizes the need for individualized therapies based on molecular characteristics, warranting further research to refine treatment strategies for PN's diverse subtypes.

Data availability statement

The RNA-seq datasets generated and analyzed for this study involve human participants and are therefore not publicly available due to ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The study protocol (Protocol Version 2.0, dated September 4, 2025) was approved by the Institutional Review Board of Kangnam Sacred Heart Hospital (IRB No. 2023-04-015) and conducted in accordance with the Declaration of Helsinki. The participants provided their written informed consent to participate in this study.

Author contributions

SL: Investigation, Writing – original draft, Writing – review & editing, Resources. JU: Investigation, Validation, Writing – original draft, Writing – review & editing. HBK: Investigation, Validation, Writing – original draft. H-WY: Data curation, Software, Writing – original draft. IK: Resources, Writing – original draft. BC: Validation, Writing – original draft. CP: Validation, Writing – original draft. HOK: Conceptualization, Formal analysis, Writing – review & editing.

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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/fimmu.2025.1572413/full#supplementary-material

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