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REVIEW ARTICLE

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Skin disorders are prominent features in primary immunodeficiency diseases: A systematic overview of current data

Jill de Wit[1] | Romke J. K. Brada[1] | Joyce van Veldhuizen[1] | Virgil A. S. H. Dalm[2] | Suzanne G. M. A. Pasmans[1]

[1]Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

[2]Department of Internal Medicine, Division of Clinical Immunology and Department of Immunology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

Correspondence
Jill de Wit, Department of Dermatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.
Email: j.dewit.1@erasmusmc.nl
and
Suzanne G. M. A. Pasmans, Department of Pediatric Dermatology, Sophia Children's Hospital, Erasmus MC University Medical Center, Rotterdam, the Netherlands.
Email: s.pasmans@erasmusmc.nl

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Abstract

Primary immunodeficiency diseases (PIDs) are characterized by an increased risk of infections, autoimmunity, autoinflammation, malignancy, and allergic disorders. Skin disorders are also common clinical features in PIDs and may be among the presenting manifestations. Recognition of specific PID-associated skin conditions in combination with other clinical features as described in the currently used warning signs could raise suspicion of an underlying PID. We aimed to provide a systematically obtained overview of skin disorders and their prevalence in PIDs. Secondary, the prevalence of *Staphylococcus* (*S.*) *aureus*–associated skin disorders and atopy was reviewed, as these are the most prominent skin features in PIDs. A systematic search was performed in EMBASE, MEDLINE, Web of Science, Cochrane, and Google Scholar (up to May 9, 2018). All original observational and experimental human studies that address the presence of skin disorders in PIDs were selected. We rated study quality using the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies. Sixty-seven articles (5030 patients) were included. Study quality ranged from 18.2% to 88.5%. A broad spectrum of skin disorders was reported in 30 PIDs, mostly in single studies with a low number of included patients. An overview of associated PIDs per skin disorder was generated. Data on *S. aureus*-associated skin disorders and atopy in PIDs were limited. In conclusion, skin disorders are prominent features in PIDs. Through clustering of PIDs per skin disorder, we provide a support tool to use in clinical practice that should raise awareness of PIDs based on presenting skin manifestations.

KEYWORDS
atopy, primary immunodeficiency disease, skin manifestation, *Staphylococcus aureus*

1 | INTRODUCTION

Primary immunodeficiency diseases (PIDs) represent a heterogeneous group of inherited disorders caused by mutations in genes encoding functional proteins of the immune cells. Based on registries and epidemiologic surveys, it has been suggested that six million people are living with a PID worldwide, whereas only 27.000-60.000 patients have been identified to date.[1] PIDs are usually characterized by recurrent and/or severe infections as well as an increased risk of autoimmunity, autoinflammation, malignancy, and allergic disorders.[2-4] Moreover, both infectious and noninfectious skin disorders are common in PIDs and may be among the presenting clinical manifestations.[5-8] *Staphylococcus* (*S.*) *aureus*–induced skin infections are the most common infectious

Brada and van Veldhuizen equally contributed to this work.

skin disorders reported in PIDs, including leukocyte adhesion defects (LAD), chronic granulomatous disease (CGD), severe congenital neutropenia, and hyper-IgE syndrome (HIES).[9-11] On the other hand, dermatitis is one of the most prominent noninfectious skin manifestations in PIDs and may be part of the atopic syndrome.[12] Patients with an atopic constitution show next to atopic dermatitis (AD) tendency toward development of food allergies, asthma, and rhinoconjunctivitis.[13]

Based on previous narrative reviews without a systematic approach, *S. aureus* skin infections, dermatitis, and other skin disorders as well as atopy seem to be all fairly common in patients with a PID, but are also frequently described in the general population.[12] Therefore, it is of importance to realize that presence of specific skin symptoms alone does not necessarily point toward a PID. However, recognition of specific skin conditions in combination with other clinical features suggestive of an immunodeficiency should raise awareness to an underlying PID and may facilitate earlier diagnosis of PIDs.[14]

The aim of this review was to provide a systematically obtained overview of skin disorders and their prevalence in patients with PIDs. Focusing on two prevalent skin disorders in PIDs, the relation between PIDs and *S. aureus*-related skin disorders and atopy will be reviewed in more detail.

2 | METHODS

2.1 | Studies

This review with a systematic approach was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, where applicable.[15] All original observational and experimental human studies were included. We selected both articles reporting skin disorders in patients with PIDs and articles presenting a differential diagnosis of a specific skin disorder that includes a PID. No restrictions were made with respect to publication date and language. We excluded case reports (<5 patients), conference abstracts, letters, and editorials as the quality of these types of articles can be highly variable. Also articles describing acquired immunodeficiencies, articles reporting skin disorders in PIDs that developed after or during treatment/intervention, and articles in which the description of skin disorders in PIDs was not part of the results section were excluded. Data on skin disorders were only extracted if at least five patients per PID were reported.

2.2 | Study participants

Patients of all ages with a PID according to Picard et al[16] from both hospital setting and general population were included.

2.3 | Study outcomes

The primary outcome is the presence of skin disorders in PIDs. Secondary outcomes include the prevalence of skin disorders in PIDs, *S. aureus*-associated skin disorders in PIDs, and PIDs associated with an atopic constitution (ie, atopic dermatitis, food allergy, asthma, rhinoconjunctivitis).

2.4 | Search strategy

The electronic search was conducted in EMBASE, MEDLINE, Web of Science, Cochrane, and Google Scholar up to May 9, 2018 (Table S1). The search was composed of terms of the categories primary immunodeficiency, skin disorder, *S. aureus*, and atopy supplemented by specific PIDs and skin disorders based on recent literature.[12,17-19]

2.5 | Study selection and data extraction

All studies identified in the systematic search were screened for relevance by title and abstract. Duplicates and studies that did not meet our inclusion criteria were excluded (Appendix S1). Remaining articles were assessed for eligibility by full-text review. Furthermore, a cross-reference check was performed to identify other eligible studies based on the reference lists of all included articles and relevant review articles. Translation of non-English studies was conducted officially. Study selection and data extraction were performed independently by two researchers (JdW and JvV, JdW and RB or JvV and RB). Disagreements were resolved and consensus was reached. If one population was described in different articles, we included the study with the most detailed description of the results. The methodological quality of the individual articles was rated using the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies (Appendix S1).[20]

2.6 | Analysis of data

The prevalence of skin disorders in PIDs was extracted from the included studies. If required, the prevalence was calculated with the available raw data. Because the reported number of patients with a PID was mainly low, the proportion of patients with a PID and skin disorders was descriptively presented. Proportions of skin disorders in PIDs were compared to the prevalence of skin disorders in the general population.[21-26] Data from the general population were based on a birth cohort in Finland (n = 1932, age 45-47 years) and a Dermatology outpatient clinic in Turkey (n = 11 040, age 1-99 years).[21,22] In addition, a nationwide study of Furue et al[23] reported the prevalence of cutaneous disorders in 67 448 Japanese patients of all ages. In the study of Verhoeven et al,[24] the skin disease prevalence per 1000 patient-years in family practices in the Netherlands was converted to a point prevalence in the general population (n = 501, age 18-97 years). Finally, two studies from the United States of America and the United Kingdom performed in 1978 and 1976 showed the prevalence of skin disorders in community studies in, respectively, 20 749 (age 1-74 years) and 614 (age 15-74 years) patients.[25,26]

3 | RESULTS

3.1 | Study characteristics

The literature search identified 15 871 studies. Removal of duplicates resulted in 12 834 studies. Screening on title and abstract yielded 86 full-text articles of which 36 articles remained after full-text screening. Finally, after cross-reference check, a total of 67 articles (5030 patients) were included for further analysis (Figure 1). Skin disorders in patients with PIDs were described in 67 articles, and three articles reported PIDs as part of the differential diagnosis of a specific skin disorder. Fifty-seven studies showed a mean percentage of males of 62.2%. Both children and adults were included with a mean age of 15.8 years, reported in 26 articles. The IHE Quality Appraisal Checklist for Case Series Studies ranged from 18.2% to 88.5% (Table S1).

3.2 | Skin disorders and their prevalence in primary immunodeficiency diseases

Thirty individual PIDs and their related skin manifestations were found. We categorized the skin disorders in 15 main groups and in 20 more specific subgroups (Table 1). The skin disorders per PID were mainly reported in single studies. Therefore, meta-analysis was not possible. The presence of skin telangiectasia, café au lait macules, and hypopigmented macules in ataxia-telangiectasia (AT); skin abscesses in HIES; atopic dermatitis in hypogammaglobulinemia; atopic dermatitis, alopecia (areata), vitiligo, and psoriasis in selective IgA deficiency (SIgAD); alopecia, vitiligo, and nail dystrophy in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED); and abscesses and granuloma in CGD were confirmed in at least three articles. All reported skin disorders per PID were used to provide an overview of PIDs per skin disorder group (Figure 2).

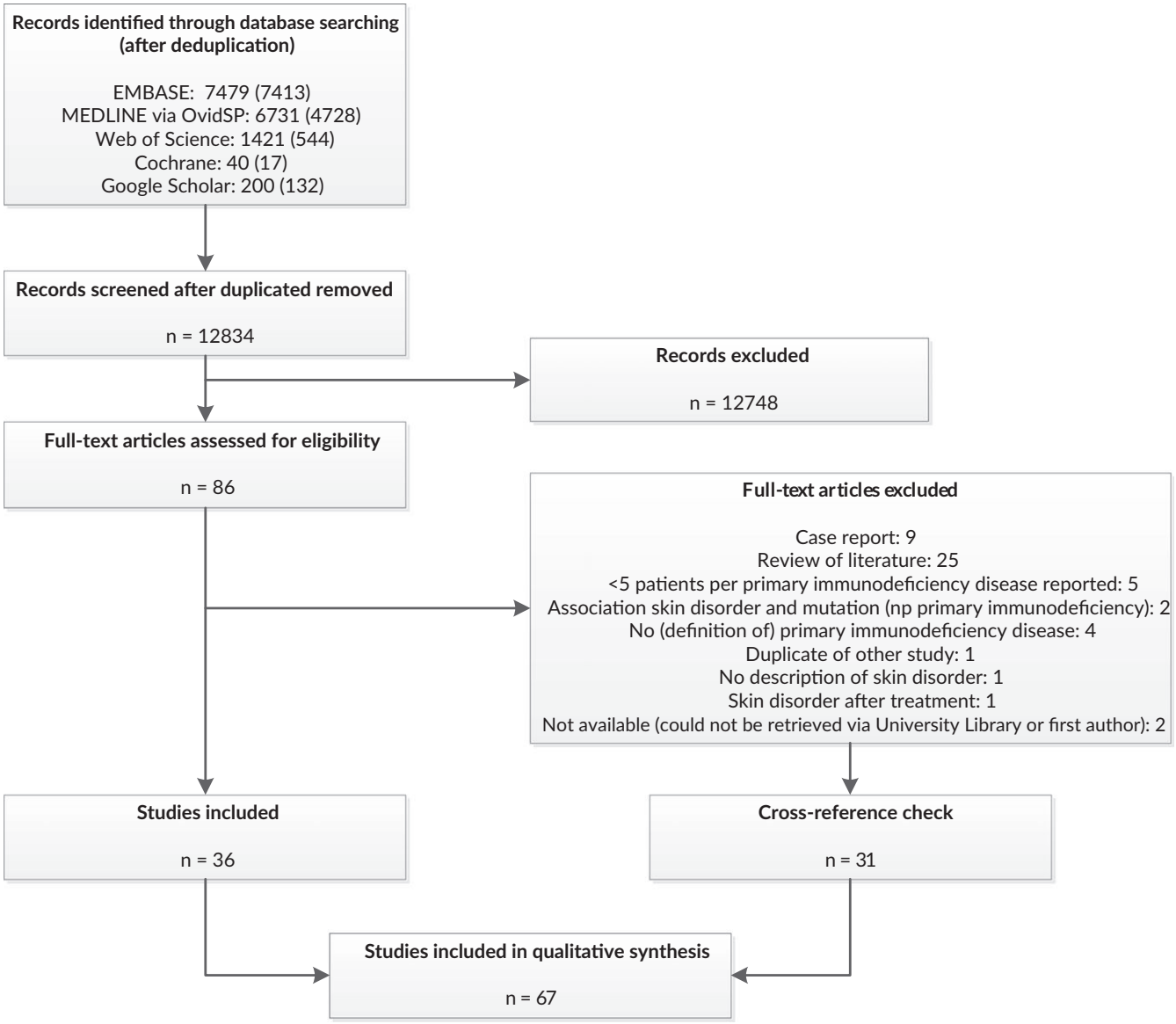

FIGURE 1 Flow chart of search strategy and study selection

TABLE 1 Skin disorders and their prevalence in primary immunodeficiency diseases

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
Immunodeficiencies affecting cellular and humoral immunity					
Severe combined immunodeficiency					
Dermatitis-like lesions		Seborrheic dermatitis	2/9[7]	22.2	2.2-11.7[21-25]
Skin infections	Fungal skin infections	Candidiasis	4/9[7]	44.4	0.6-1.0[22,23]
Omenn syndrome					
Hair abnormalities	Hair loss disorders	Severe alopecia	5/7[52]	71.4	0.4-2.5[21-23]
		Alopecia of eyelashes and eyebrows	3/7[52]	42.9	-
Erythematous skin lesions		Exfoliative erythroderma[a]	7/7[52]	100	0.1[23]
Other skin disorders		Skin induration	6/7[52]	85.7	-
Combined immunodeficiencies with associated or syndromic features					
Ataxia-telangiectasia					
Dermatitis-like lesions		Dermatitis	1/62[6]	1.6	32.4[24]
		Eczema	2/22[53]	9.1	9.0-27.4[21,26]
		Nummular eczema	1/22[53]	4.5	1.9-2.2[21,22]
		Seborrheic rash	2/32[54]	6.3	2.2-11.7[21-25]
Hair abnormalities	Excessive hair growth disorders	Hypertrichosis	7/32[54]	21.9	-
		Hirsutism	2/12[33]	16.7	0.4[22]
	Hair pigmentation disorders	Poliosis	5/12[33]	41.7	-
Skin infections	Fungal skin infections	Oral candidiasis	1/12[33]	8.3	-
		Coccidioidomycosis	1/22[53]	4.5	-
	Viral skin infections	Viral warts	2/32,[54] 8/22[53]	6.3-36.4	3.4-4.5[22,23,26]
		Herpes simplex	2/12[33]	16.7	0.8-1.0[22,23]
	Bacterial skin infections	Chronic impetigo	1/22[53]	4.5	0.8-1.6[22,23]
		Impetigo	1/12[33]	8.3	0.8-1.6[22,23]
Erythematous skin lesions		Pinpoint erythematous macules	2/12[33]	16.7	-
Vascular disorders	Telangiectasia	Skin telangiectasia	6/62,[6] 16/26,[7] 4/12[33]	9.7-61.5	-
		Telangiectasia on cheeks or nose	4/32,[54] 18/22[53]	12.5-81.8	-
		Telangiectasia on ears	15/32[54]	46.9	-
		Telangiectasia on back/shoulders/neck	5/32[54]	15.6	-
	Vasculitis	Allergic vasculitis	1/22[53]	4.5	-
Pigmentation disorders	Hyperpigmentation disorders	Café au lait macules	27/32,[54] 3/22,[53] 4/12[33]	13.6-84.4	12.4[21]
		Pigmented nevi (>5 mm)	12/32[54]	37.5	-
		Hyperpigmentation	1/62[6]	1.6	-
		Acanthosis nigricans	3/12[33]	25.0	-
	Hypopigmentation disorders	Hypopigmented macules	3/62,[6] 14/32,[54] 2/12[33]	4.8-43.8	-
		Albinism	1/32,[54] 8/22[53]	3.1-36.4	-
		Vitiligo	1/12[33]	8.3	1.2-1.7[21-23]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
	Other pigmentation disorders	Blue nevus	1/22[53]	4.5	1.3[21]
		Freckles	1/22[53]	4.5	-
Neoplastic disorders	Others neoplastic disorders	Basal cell carcinoma	1/22[53]	4.5	0.4-0.5[21,23]
		Juvenile melanoma	1/22[53]	4.5	-
Rash		Facial papulosquamous rash	13/32[54]	40.6	-
Nail disorders	Noninfectious nail disorders	Congenital nail dystrophy	2/12[33]	16.7	-
Granulomatous disorders		Skin granulomas	8/8[55]	100	0.3[23]
Other skin disorders		Lichen simplex chronicus	1/32[54]	3.1	3.0[22]
		Sclerodermoid changes	1/22[53]	4.5	-
		Senile keratosis (actinic keratosis)	1/22[53]	4.5	0.4-0.6[21,23]
		Aged skin	2/22[53]	9.1	-
		Shagreen patch	1/12[33]	8.3	-
		Lipoatrophy	1/12[33]	8.3	-
		Hydroa vacciniforme	1/12[33]	8.3	-
		Dermatofibroma	1/12[33]	8.3	0.2-22.2[21,23]
		Purpura	5/26[7]	19.2	-
Wiskott-aldrich syndrome					
Dermatitis-like lesions		Eczema	5/5[7]	100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Yeast/fungi	18/154[56]	11.7	-
	Viral skin infections	Varicella	25/154[56]	16.2	-
		HSV I/HSV II	24/154[56]	15.6	0.8-1.0[22,23]
		Molluscum contagiosum	13/154[56]	8.4	0.8-0.9[22,23]
		Warts	10/154[56]	6.5	3.4-4.5[22,23,26]
	Bacterial skin infections	Impetigo	19/154[56]	12.3	0.8-1.6[22,23]
		Abscesses	19/154[56]	12.3	1.7[22]
		Cellulitis	19/154[56]	12.3	0.9-1.5[22,23]
Vascular disorders	Vasculitis	Henoch-Schönlein purpura	8/154[56]	5.2	-
		Skin vasculitis	12/55[57]	7.8	-
Hyper-IgE syndrome unspecified					
Dermatitis-like lesions		Atopic dermatitis	5/6,[6] 5/5,[58] 28/43,[34] 5/8[27]	62.5-100	2.2-12.4[21-24]
		Eczema	30/30[59]	100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Candida	4/6,[6] 25/30[59]	66.7-83.3	0.6-1.0[22,23]
	Bacterial skin infections	Skin abscesses	6/6,[6] 36/43,[34] 3/8,[27] 26/30[59]	37.5-100	1.7[22]
	Other skin infections	Skin infection	3/5[58]	60.0	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral aphthous ulcers	1/5[58]	20.0	0.7[22]
		Oral ulceration	8/11[60]	72.7	0.7[22]
Rash		Newborn rash	35/43[34]	81.4	-
		Maculopapular rash	1/6[6]	16.7	-
		Papulopustular eruption	8/8[27]	100	-

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
Acne-like lesions		Neonatal acne	6/43[34]	14.0	-
Other skin disorders		Coarse face	3/6,[6] 2/8[27]	25.0-50.0	-
Autosomal dominant hyper-IgE syndrome					
Dermatitis-like lesions		Eczematous dermatitis	20/21[28]	95.2	32.4[24]
		Eczema	47/82,[35] 17/17[29]	57.3-100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Oral candidiasis	4/21[28]	19.0	-
		Genitalia fungal infection	1/17[29]	5.9	-
	Viral skin infections	Varicella zoster virus infection	9/21[28]	42.9	-
		Herpes simplex virus infection	4/21[28]	19.0	0.8-1.0[22,23]
		Herpes infection	5/67[35]	7.5	0.8-1.0[22,23]
		Molluscum contagiosum	1/21,[28] 1/82[35]	1.2-4.8	0.8-0.9[22,23]
	Bacterial skin infections	Cold abscesses	20/21,[28] 9/17[29]	52.9-95.2	1.7[22]
		Skin abscesses	61/82[35]	74.4	1.7[22]
		Cellulitis	15/82[35]	18.3	0.9-1.5[22,23]
		Pustulosis	14/17[29]	82.4	-
		Folliculitis	7/17[29]	41.2	1.1-6.0[21,23]
	Other skin infections	Recurrent skin infections	17/17[29]	100	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral ulcer	1/17[29]	2.4	0.7[22]
Neoplastic disorders	Cutaneous lymphomas	Pilotropic cutaneous T-cell lymphoma	1/21[28]	4.8	-
	Other neoplastic disorders	Squamous cell carcinoma	1/82[35]	1.2	0.3-0.7[23,24]
Rash		Papulopustular rash (<2 months)	14/21[28]	66.7	-
Nail disorders	Infectious nail disorders	Chronic paronychia	8/21[28]	38.1	-
		Onychomycosis	23/82,[35] 4/17[29]	23.5-28.0	9.4[21]
Urticaria		Urticaria	13/82[35]	15.9	0.5-8.3[21-23]
Other skin disorders		Lichenification	1/21[28]	4.8	-
		Coarse facies	10/21[28]	47.6	-
		Dry skin	18/21[28]	85.7	-
		Thrush	17/82,[35] 6/17[29]	20.7-35.3	-
		Angioedema	9/82[35]	11.0	-
Autosomal recessive hyper-IgE syndrome					
Dermatitis-like lesions		Eczema	19/21,[36] 7/10[37]	70.0-90.5	9.0-27.4[21,26]
		Atopic dermatitis	7/10[37]	70.0	2.2-12.4[21-24]
Skin infections	Fungal skin infections	Mucocutaneous candidiasis	9/21[36]	42.9	0.6-1.0[22,23]
		Chronic candidiasis of mucosal sites	10/13[30]	76.9	-
	Viral skin infections	Viral warts	13/21[36]	61.9	3.4-4.5[22,23,26]
		Verruca plana	1/10[37]	10.0	3.4-4.5[22,23,26]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)[†]**
		Herpes simplex virus	12/21,[36] 8/13[30]	57.1-61.5	0.8-1.0[22,23]
		Recurrent herpes	1/10[37]	10.0	0.8-1.0[22,23]
		Molluscum contagiosum	10/21,[36] 4/13[30]	30.8-47.6	0.8-0.9[22,23]
		Severe primary varicella zoster	7/21,[36] 2/13[30]	15.4-33.3	-
		Herpes zoster	5/21[36]	23.8	1.4-2.4[22,23]
	Bacterial skin infections	Bacterial skin infection	17/21[36]	81.0	-
		Skin abscesses	11/13[30]	84.6	1.7[22]
		MRSA wound infected eczema	1/10[37]	10.0	-
	Other skin infections	Recurrent stomatitis	1/10[37]	10.0	-
Neoplastic disorders	Cutaneous lymphomas	Cutaneous T-cell lymphoma	1/21[36]	4.8	-
	Other neoplastic disorders	Squamous cell carcinoma	4/21[36]	19.0	0.3-0.7[23,24]
Rash		Severe eczematoid rash	13/13[30]	100	9.0-27.4[21,26]
		Newborn rash	5/21[36]	23.8	-
Other skin disorders		Immune thrombocytopenic purpura	1/10[37]	10.0	-
Nijmegen breakage syndrome					
Skin infections	Fungal skin infections	Candidiasis	6/21[61]	28.6	0.6-1.0[22,23]
	Viral skin infections	Herpes virus lip infection	2/21[61]	9.5	0.8-1.0[22,23]
	Other skin infections	Angular cheilitis	2/21[61]	9.5	0.1-0.3[22,23]
Vascular disorders	Telangiectasia	Cutaneous telangiectasia	3/32[62]	9.4	-
Pigmentation disorders	Hyperpigmentation disorders	Café au lait spots	18/21[62]	85.7	12.4[21]
	Hypopigmentation disorders	Vitiligo	14/21[62]	66.7	1.2-1.7[21-23]
Granulomatous disorders		Skin granuloma	5/35[63]	14.3	0.3[23]
Other skin disorders		Hyperkeratosis	1/21[61]	4.8	-
		Gingivitis	19/21[61]	90.5	-
DiGeorge syndrome					
Rash		Rash	5/5[64]	100	-
Comèl-Netherton syndrome					
Dermatitis-like lesions		Eczema[b]	8/9[31]	88.9	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Severe alopecia	9/9[52]	100	0.4-2.5[21-23]
		Alopecia of eyelashes and eyebrows	5/9[52]	55.6	-
	Other hair abnormalities	Bamboo hair	9/9[31]	100	-
Skin infections	Bacterial skin infections	Recurrent/persistent *S. aureus* skin infections	9/9[31]	100	-

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)[†]**
Erythematous skin lesions		Exfoliative erythroderma[c]	9/9[52]	100	0.1[23]
Other skin disorders		Congenital ichthyosis	9/9[31]	100	0.1[22,23]
Predominantly antibody deficiencies					
X-linked agammaglobulinemia					
Dermatitis-like lesions		Dermatitis	4/23[6]	17.4	32.4[24]
Hair abnormalities	Hair loss disorders	Alopecia	1/110[65]	0.9	0.4-2.5[21-23]
Skin infections	Bacterial skin infections	Abscesses	3/23[6]	13.0	1.7[22]
		Furunculosis	2/23[6]	8.7	1.7[22]
		Impetigo	2/23[6]	8.7	0.8-1.6[22,23]
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	0/110[65]	0.0	1.2-1.7[21-23]
Rash		Maculopapular rash	3/23[6]	13.0	-
Psoriasis-like lesions		Psoriasis	0/110[65]	0.0	1.4-8.0[21-26]
Urticaria		Urticaria	2/23[6]	8.7	0.5-8.3[21-23]
Other skin disorders		Pyoderma	1/10[7]	10.0	1.0[22]
		Lichen planus	0/110[65]	0.0	0.3-14.1[21,23,25]
Hypogammaglobulinemia					
Dermatitis-like lesions		Atopic dermatitis	28/28,[66] 0/12,[38] 46/78[39]	0.0-100	2.2-12.4[21-24]
Common variable immunodeficiency					
Dermatitis-like lesions		Dermatitis	6/28[6]	21.4	32.4[24]
		Atopic dermatitis	9/47[67]	19.1	2.2-12.4[21-24]
		Eczema	4/15[68]	26.7	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Alopecia areata	1/28,[6] 1/47[67]	2.1-3.6	0.4-2.5[21-23]
		Alopecia	4/244[65]	1.6	0.4-2.5[21-23]
Skin infections	Fungal skin infections	Candida	4/28[6]	14.3	0.6-1.0[22,23]
		Pseudomembranous candidiasis	4/15[68]	26.7	-
	Viral skin infections	Recurrent herpes labialis	1/15[68]	6.7	0.8-1.0[22,23]
	Bacterial skin infections	Recurrent skin abscesses	2/31[69]	6.5	1.7[22]
	Other skin infections	Skin infections	7/47[67]	14.9	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Recurrent aphthosis	5/47[67]	10.6	0.7[22]
		Oral ulcers	9/15[68]	60.0	0.7[22]
		Oral aphthae	10/31[69]	32.3	0.7[22]
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	8/244,[65] 2/47[67]	3.3-4.3	1.2-1.7[21-23]
Rash		Maculopapular rash	1/28[6]	3.6	-
Psoriasis-like lesions		Psoriasis	2/244,[65] 9/47[67]	0.8-19.1	1.4-8.0[21-26]
Acne-like lesions		Acne	6/47[67]	12.8	0.8-13.1[22-24]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	Subgroups of skin disorders	Skin disorders as reported in included articles	Number of reported cases with skin disorder (proportion)	Prevalence of skin disorder (%)	Prevalence of skin disorder (%)[†]
Urticaria		Urticaria[d]	1/28[6]	3.6	0.5-8.3[21-23]
Other skin disorders		Pyoderma	2/5[7]	40.0	1.0[22]
		Lichen planus	1/244[65]	0.4	0.3-14.1[21,23,25]
Selective IgA deficiency					
Dermatitis-like		Dermatitis	5/17[6]	29.4	32.4[24]
		Eczema	2/39[70]	5.1	9.0-27.4[21,26]
		Atopic dermatitis	13/13,[66] 4/12,[38] 59/102,[67] 12/159,[40] 12/23,[42] 9/123,[41] 1/8,[71] 9/81,[43] 16/347[72]	4.6-100	2.2-12.4[21-24]
		Allergic contact dermatitis	11/347[72]	3.2	1.0-8.5[21-25]
		Seborrheic dermatitis	4/347[72]	1.2	2.2-11.7[21-25]
Hair abnormalities	Hair loss disorders	Alopecia	2/60,[65] 1/102,[67] 1/8[71]	1.0-12.5	0.4-2.5[21-23]
		Alopecia areata	1/8,[73] 1/123,[41] 2/347[72]	0.6-12.5	0.4-2.5[21-23]
		Infection-related alopecia areata	1/8[73]	12.5	0.4-2.5[21-23]
Skin infections	Fungal skin infections	Candida	2/17[6]	11.8	0.6-1.0[22,23]
		Pseudomembranous candidiasis	10/39[70]	25.6	-
	Viral skin infections	Recurrent herpes labialis	10/39,[70] 2/123[41]	1.6-25.6	0.8-1.0[22,23]
		Herpes simplex	4/347[72]	1.2	0.8-1.0[22,23]
		Herpes zoster	1/347[72]	0.3	1.4-2.4[22,23]
		Molluscum contagiosum	2/347[72]	0.9	0.8-0.9[22,23]
	Bacterial skin infections	Folliculitis	1/17[6]	5.9	1.1-6.0[21,23]
		Erysipelas recidivans	1/8[73]	12.5	0.1[23]
		Chronic recurrent furunculosis	1/8[73]	12.5	1.7[22]
		Cellulitis	5/347[72]	1.4	0.9-1.5[22,23]
	Other skin infections	Skin infections	2/102[67]	2.0	4.6-43.5[21,25,26]
		Angular stomatitis	1/39[70]	2.6	-
		Scabies	3/347[72]	0.9	0.2-1.5[22,23]
Ulcers	Oral ulcers	Recurrent aphthosis	5/102[67]	4.9	0.7[22]
		Oral ulcers	24/39[70]	61.5	0.7[22]
		Aphthosis recidivans	1/8[73]	12.5	0.7[22]
Erythematous skin lesions		Erythroderma	1/8[73]	12.5	0.1[23]
		Erythema nodosum	1/123[41]	0.8	0.2-0.3[22,23]
Vascular disorders	Vasculitis	Vasculitis	3/7[7]	42.9	-
		Kawasaki disease	1/8[71]	12.5	-
	Other vascular disorders	Raynaud syndrome	1/8[71]	12.5	-
Pigmentation disorder	Hypopigmentation disorders	Vitiligo	1/7,[7] 3/60,[65] 3/102,[67] 1/8,[73] 7/159,[40] 3/123,[41] 1/81,[43] 2/347[72]	0.6-14.3	1.2-1.7[21-23]
Psoriasis-like disorders		Psoriasis	0/60,[65] 2/102,[67] 7/159,[40] 1/123,[41] 7/347[72]	0.0-4.4	1.4-8.0[21-26]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
Acne-like lesions		Acne	6/102,[67] 69/347[72]	5.9-19.9	0.8-13.1[22-24]
Urticaria		Urticaria	5/23[42]	21.7	0.5-8.3[21-23]
		Atopic urticaria	4/123[41]	3.3	0.5-8.3[21-23]
		Chronic spontaneous urticaria	17/347[72]	4.9	0.5-8.3[21-23]
Other skin disorders		Lichen planus	0/60,[65] 2/159[40]	0.0-1.3	0.3-14.1[21,23,25]
		Immune thrombocytopenic purpura	1/17[6]	5.9	-
		Idiopathic thrombocytopenic purpura	2/123[41]	1.6	-
		Chronic idiopathic thrombocytopenic purpura	1/81[43]	1.2	-
		Epidermolysis bullosa dystrophica	1/8[73]	12.5	-
		Local skin scleroderma	1/123[41]	0.8	-
		Dermatitis herpetiformis	1/123[41]	0.8	0.2-0.3[21,22]
		Ichthyosis and keratoderma of handpalms and footsoles in epileptic patients (Rud syndrome)	1/123[41]	0.8	-
IgM deficiency					
Dermatitis-like lesions		Atopic dermatitis	14/14,[66] 11/53[38]	20.8-100	2.2-12.4[21-24]
IgG deficiency					
Dermatitis-like lesions		Atopic dermatitis	11/11[66]	100	2.2-12.4[21-24]
Diseases of immune dysregulation					
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy					
Dermatitis-like lesions		Recurrent and troublesome napkin dermatitis	5/18[74]	27.8	-
Hair abnormalities	Hair loss disorders	Alopecia	2/15,[71] 6/18,[74] 20/68,[75] 6/35,[76] 6/22[77]	13.3-33.3	0.4-2.5[21-23]
	Hair pigmentation disorders	Poliosis	1/18[74]	5.6	-
Skin infections	Fungal skin infections	Oral candidiasis	41/68[75]	60.3	-
		Dermal candidiasis	6/68,[75] 6/35[76]	8.8-17.1	0.6-1.0[22,23]
		Chronic mucocutaneous candidiasis	18/18,[74] 30/35[76]	85.7-100	0.6-1.0[22,23]
		Mucocutaneous candidiasis	21/22[77]	95.5	0.6-1.0[22,23]
		Lifelong genital moniliasis	1/18[74]	5.6	-

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	Subgroups of skin disorders	Skin disorders as reported in included articles	Number of reported cases with skin disorder (proportion)	Prevalence of skin disorder (%)	Prevalence of skin disorder (%)[†]
	Other skin infections	Angular cheilitis	13/18[74]	72.2	0.1-0.3[22,23]
Vascular disorders	Vasculitis	Cutaneous vasculitis	2/68[75]	2.9	-
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	1/15,[71] 2/18,[74] 9/68,[75] 13/35,[76] 6/22[77]	6.7-37.1	1.2-1.7[21-23]
		Halo naevi	1/18[74]	5.6	0.8[21]
Nail disorders	Infectious nail disorders	Ungual candidiasis	33/50[75]	66.0	-
		Candidal paronychia and/or onychomycosis	13/18[74]	72.2	9.4[21]
		Nail candidiasis	12/35[76]	34.3	-
	Noninfectious nail disorders	Nail dystrophy	26/50,[75] 6/35,[76] 4/22[77]	17.1-52.0	-
Urticaria		Urticarial eruption	23/35[76]	8.6	0.5-8.3[21-23]
		Urticarial rash	2/22[77]	9.1	0.5-8.3[21-23]
Other skin disorders		Oral thrush	35/35[76]	100	-
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome					
Dermatitis-like		Atopic dermatitis	7/10[78]	70.0	2.2-12.4[21-24]
		Severe eczema	5/14[44]	35.7	9.0-27.4[21,26]
		Mild eczema	4/14[44]	28.6	9.0-27.4[21,26]
		Eczema	5/5,[79] 2/5[80]	40.0-100	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Alopecia[e]	2/14[44]	14.3	0.4-2.5[21-23]
Skin infections	Fungal skin infections	Chronic mucocutaneous candidiasis	4/5[79]	80.0	0.6-1.0[22,23]
	Viral skin infections	HSV skin infection	1/5[79]	20.0	0.8-1.0[22,23]
		Herpes zoster	1/5[79]	20.0	1.4-2.4[22,23]
	Bacterial skin infections	Staphylococcal superinfection of eczema	1/5[79]	20.0	-
	Other skin infections	Cheilitis	4/10[78]	40.0	0.1-0.3[22,23]
Erythematous skin lesions		Exfoliative erythroderma	2/10[78]	20.0	0.1[23]
Nail disorders	Infectious nail disorders	Onychodystrophy[f]	2/10[78]	20.0	-
		(Peri-)onyxis	1/10[78]	10.0	-
Psoriasis-like lesions		Psoriasiform rash	2/10[78]	20.0	1.4-8.0[21-26]
Other skin disorders		Palmar keratoderma	1/10[78]	10.0	-
		Inflammatory edema (lips and perioral) or Quincke edema	3/10[78]	30.0	-
		Mild xerosis	1/14[44]	7.1	-
		Acrodermatitis enteropathica	1/5[79]	20.0	-
Adenosine deaminase 2 deficiency					
Dermatitis-like lesions		Eczema	5/9[81]	55.6	9.0-27.4[21,26]
Ulcers	Oral ulcers	Oral aphthae	3/9[81]	33.3	0.7[22]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
	Other ulcers	Livedoid vascuclaropathy/ulcers	1/9[81]	11.1	-
Erythematous skin lesions		Erythema nodosum	2/9,[81] 1/8[82]	12.5-22.2	0.2-0.3[22,23]
Vascular disorders	Vasculitis	Cutaneous vasculitis	3/9[81]	33.3	-
		Polyarteritis nodosa	1/9[81]	11.1	-
	Other vascular disorders	Raynaud's phenomenon	1/8[82]	12.5	-
Neoplastic disorder	Other neoplastic disorders	AML chloroma	1/9[81]	11.1	-
Rash		Rash	3/9[81]	33.3	-
Urticaria		Urticaria-like rash	1/8[82]	12.5	0.5-8.3[21-23]
Other skin disorders		Livedo reticularis	3/9,[81] 6/8[82]	33.3-75.0	0.1[23]
		Livedo racemose	1/9[81]	11.1	0.1[23]
		Aspecific skin induration	4/9[81]	44.4	-
Congenital defects of phagocyte number or function					
Leukocyte adhesion defect unspecified					
Skin infections	Bacterial skin infections	Cellulitis	2/6[6]	33.3	0.9-1.5[22,23]
		Folliculitis	2/6[6]	33.3	1.1-6.0[21,23]
Other skin disorders		Periodontitis	2/6[6]	33.3	-
Leukocyte adhesion defect type 1					
Skin infections	Fungal skin infections	Candida infection	8/15[83]	53.3	0.6-1.0[22,23]
	Bacterial skin infections	Skin abscesses	12/15[83]	80.0	1.7[22]
		Cellulitis	4/15[83]	26.7	0.9-1.5[22,23]
Ulcers	Oral ulcers	Oral ulcers	13/15[83]	86.7	0.7[22]
Other skin disorders		Gingivitis	9/15[83]	60.0	-
Chronic granulomatous disease					
Dermatitis-like lesions		Dermatitis	nm/429,[84] nm/39[85]	-	32.4[24]
		Eczema	8/48[45]	16.7	9.0-27.4[21,26]
Skin infections	Bacterial skin infections	Abscesses	23/34,[6] nm/429,[84] nm/39,[85] 1/48,[45] 156/368,[86] 11/49[32]	2.1-67.6	1.7[22]
		Folliculitis	5/34[6]	14.7	1.1-6.0[21,23]
		Impetigo	3/34,[6] 16/95[32]	8.8-16.8	0.8-1.6[22,23]
		Cellulitis	18/368[86]	4.9	0.9-1.5[22,23]
		Furunculosis	nm/429[84]	-	-
		Pustular eruption	10/48[45]	20.8	-
	Other skin infections	Chronic cutaneous infections	1/6[87]	16.7	4.6-43.5[21,25,26]
		Cutaneous/subcutaneous infections	22/48,[45] 43/84[88]	45.8-51.2	4.6-43.5[21,25,26]
		Skin infection	59/130[32]	45.4	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral ulceration	7/9,[60] 2/6[87]	33.3-77.8	0.7[22]
	Other ulcers	Nose ulcers	5/34[6]	14.7	-

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)[†]**
Vascular disorders	Vasculitis	Kawasaki disease	2/48[45]	4.2	-
Nail disorders	Infectious nail disorders	Paronychia	2/34[6]	5.9	-
Granulomatous disorders		Granuloma	2/11,[71] nm/429,[84] 4/48[45]	8.3-18.2	0.3[23]
Acne-like lesions		Acne	nm/429[84]	-	0.8-13.1[22-24]
Urticaria		Urticaria	1/48[45]	2.1	0.5-8.3[21-23]
Other skin disorders		Discoid lupus erythematosus[g]	30/340[86]	8.8	0.1-0.3[21,22]
		Thrush	11/48[45]	22.9	-
Severe congenital neutropenia					
Skin infections	Fungal skin infections	Mucocutaneous candidiasis	5/18[89]	27.8	0.6-1.0[22,23]
	Bacterial skin infections	Cutaneous abscesses	10/18[89]	55.6	1.7[22]
	Other skin infections	Cutaneous infections	7/18[89]	38.9	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral ulcers	13/18[89]	72.2	0.7[22]
Papillon-Lefèvre syndrome					
Nail disorders	Noninfectious nail disorders	Nail changes (mainly slight thickening of nails)	13/47[90]	27.7	3.3-3.4[24,26]
Psoriasis-like lesions		Extensive psoriasiform plaques	3/47[90]	6.4	1.4-8.0[21-26]
Other skin disorders		Punctate hyperkeratosis on palms and soles	8/47[90]	17.0	-
		Well-demarcated hyperkeratosis of knees and elbows	23/47[90]	48.9	-
		Ichthyosis	2/47[90]	4.3	0.1[22,23]
GATA2 deficiency					
Neoplastic disorders	Other neoplastic disorders	Cutaneous melanoma	1/71[91]	1.4	0.1-1.2[21,23]
Defects in intrinsic and innate immunity					
Chronic mucocutaneous candidiasis					
Skin infections	Other skin infections	Perleche (angular cheilitis)	3/7[6]	42.9	0.1-0.3[22,23]
Other skin disorders		Thrush[h]	7/7[6]	100	-
Autoinflammatory disorders					
PLCG2 associated antibody deficiency and immune dysregulation					
Ulcers	Other ulcers	Neonatal-onset ulcerative lesions (cold-sensitive regions)	8/36[46]	22.2	2.0[23]
Erythematous skin lesions		Recurrent red papules and patches	1/36[46]	2.8	-
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	1/36[46]	2.8	1.2-1.7[21-23]
Granulomatous disorders		Granulomatous inflammation	4/36[46]	11.1	0.3[23]

(Continues)

TABLE 1 (Continued)

Primary immunodeficiency disease					General population
Main groups of skin disorders	Subgroups of skin disorders	Skin disorders as reported in included articles	Number of reported cases with skin disorder (proportion)	Prevalence of skin disorder (%)	Prevalence of skin disorder (%)†
Urticaria		Cold urticaria	36/36[46]	100	0.5-8.3[21-23]
Muckle-Wells syndrome					
Ulcers	Oral ulcers	Oral ulcers	7/29[92]	24.1	0.7[22]
Pigmentation disorders	Hyperpigmentation disorders	Hyperpigmented, sclerotic and hypertrichotic plaques	6/6[93]	100	-
Rash		Skin rash	15/15[92]	100	-
Urticaria		Attacks of recurrent urticaria	2/6[93]	33.3	0.5-8.3[21-23]
		Urticaria	8/8[94]	100	0.5-8.3[21-23]
		Cold-induced urticaria	14/29[92]	48.3	0.5-8.3[21-23]
Other skin disorders		Weals caused by cold	16/16[95]	100	-
Neonatal-onset multisystem inflammatory disease					
Urticaria		Urticaria	8/8[94]	100	0.5-8.3[21-23]
Complement deficiencies					
C2 deficiency					
Urticaria		Chronic urticaria	2/47[96]	4.3	0.5-8.3[21-23]
Other skin disorders		Subacute cutaneous lupus erythematosus	2/47[96]	4.3	0.3[22]
		Dermatitis herpetiformis	1/47[96]	2.1	0.2-0.3[21,22]

Abbreviation: nm, not mentioned.

†Data on the prevalence of skin disorders in the general population were based on a birth cohort in Finland (n = 1932, age 45-47 years) and a Dermatology outpatient clinic in Turkey (n = 11 040, age 1-99 years).[21,22] In addition, a nationwide study of Furue et al[23] reported the prevalence of cutaneous disorders in 67 448 Japanese patients of all ages. In the study of Verhoeven et al,[24] the skin disease prevalence per 1000 patient-years in family practices in the Netherlands was converted to a point prevalence in the general population (n = 501, age 18-97 years). Last, two studies from the United States of America and the United Kingdom performed in 1978 and 1976 showed the prevalence of skin disorders in community studies in, respectively, 20 749 (age 1-74 years) and 614 (age 15-74 years) patients.[25,26]

[a-h]See Figure S1.

3.3 | *Staphylococcus aureus*-associated skin disorders in primary immunodeficiency diseases

Skin disorders associated with *S. aureus* in PIDs were reported in six articles (Table S1). In HIES unspecified, 4/7 patients with a papulopustular eruption had a positive *S. aureus* culture.[27] *S. aureus* was also found positive in patients with AD-HIES and a papulopustular rash (2/5), eczematous dermatitis (20/20), cold abscesses (20/20), or wounds (3/4).[28,29] Renner et al[30] described that skin abscesses were frequently due to *S. aureus* infections in AR-HIES. In Comèl-Netherton syndrome, 8/9 described patients showed recurrent or persistent *S. aureus* skin infections once skin lesions had developed.[31] Lastly, *S. aureus* was isolated in 1/4 patients with CGD and suppurative dermatitis.[32]

3.4 | Primary immunodeficiency diseases associated with atopy

The prevalence of at least two atopic symptoms (ie, eczema, food allergy, asthma, and/or rhinoconjunctivitis) in PIDs was described in 17 articles (Table S1). Cohen et al[33] found no atopy in patients with AT. In HIES unspecified, AD-HIES and AR-HIES, all of the atopic symptoms, if reported, were present in about half of the patients.[28,29,34-37] Renner et al[31] described the presence of atopy in most Comèl-Netherton patients. The number of patients with eczema, food allergy, asthma, and rhinoconjunctivitis was presented in two studies with hypogammaglobulinemia patients.[38,39] Eight studies reported the prevalence of atopy in a total of 398 patients with SIgAD, in which 11.6% (46/398) patients had eczema, 3.4% (9/263) had food allergy, 37.1% (43/116) had asthma, and 20.0% (55/275) had rhinoconjunctivitis.[38,40-43] In IgM-deficient patients, eczema, asthma, and rhinoconjunctivitis were prevalent symptoms.[38] Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) patients were mainly positive for eczema.[44] Eight of 48 CGD patients had eczema and one out of 18 had rhinoconjunctivitis.[45] Finally, Aderibigbe et al[46] have shown that one to three out of eight patients with phospholipase C gamma 2 (PLCG2) gene associated antibody deficiency and immune dysregulation (PLAID) had eczema, food allergy, asthma, and/or rhinoconjunctivitis.

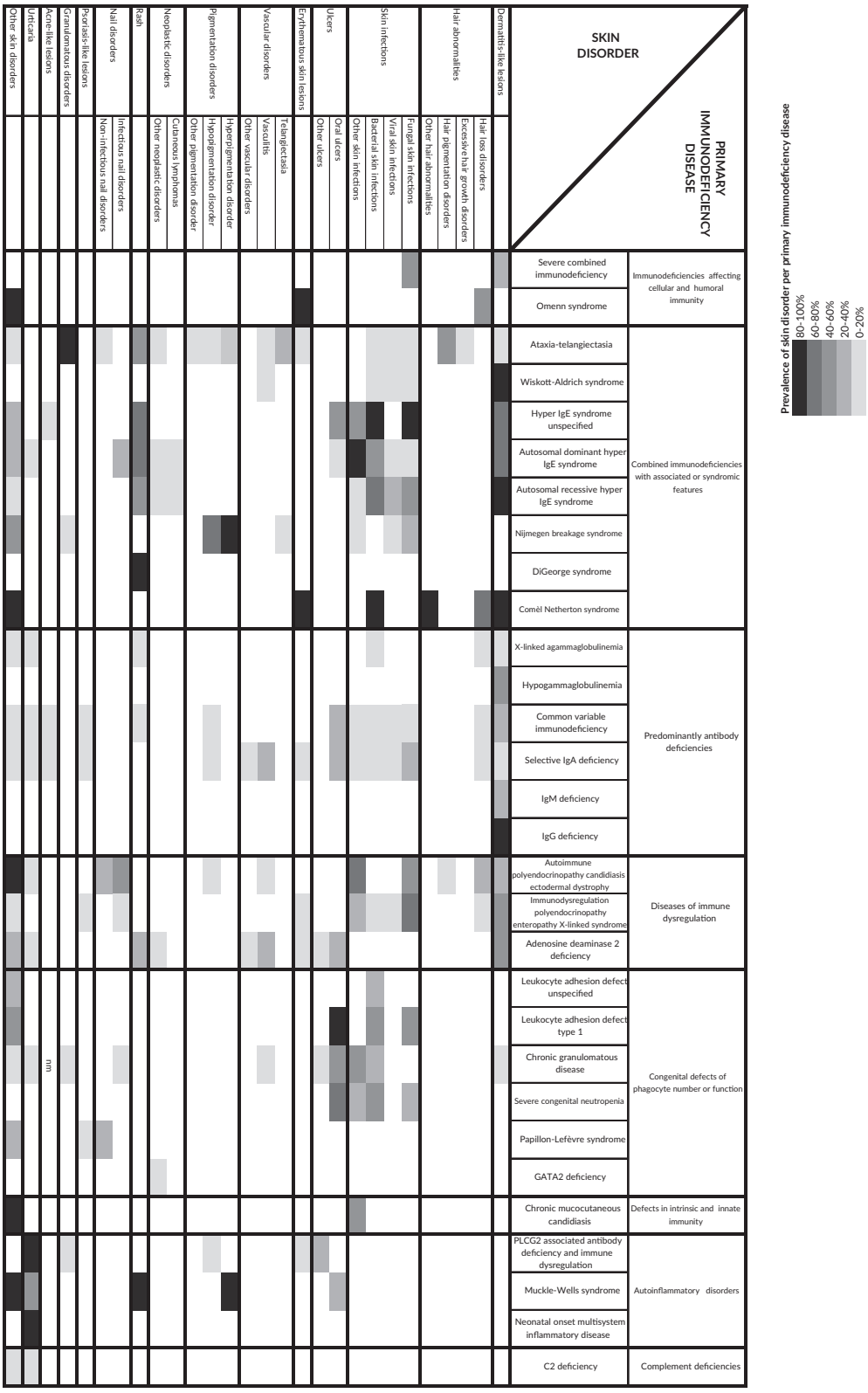

FIGURE 2 Differential diagnosis of primary immunodeficiency diseases per skin disorder. nm, not mentioned†. †The exact prevalence of acne-like lesions in chronic granulomatous disease was not reported in the included article. The prevalence of skin disorders per primary immunodeficiency disease was based on the reported proportion of patients with the skin disorders in the total group of patients with the primary immunodeficiency disease. In case of multiple studies reporting a skin disorder in a primary immunodeficiency disease, the general prevalence was calculated by dividing the total number of affected patients (skin disorder) by the total number of patients with the primary immunodeficiency disease. nm, not mentioned.

4 | DISCUSSION

This review demonstrates that skin disorders are common symptoms in both children and adult patients with PIDs based on data from 67 systematically selected studies. Only a few PIDs related to *S. aureus* -associated skin disorders or atopy were reported in mainly single studies.

This is the first review using a systematic approach without limitations on skin disorders or PIDs. Therefore, we managed to obtain a complete spectrum of skin disorders in PIDs. A recent study of Ettinger et al[47] that focused on PIDs and the respective gene defects included an overview of PIDs per skin disorder in a nonsystematic approach. Although some PIDs are characterized by skin disorders, such as telangiectasia in AT and granuloma in CGD, the novelty of this review is showing an overview of all skin disorders in PIDs including skin disorders of which an association with a PID was not yet known.

Furthermore, we succeeded in composing an overview of PIDs per skin disorder that could serve as a valuable support tool for PID awareness in clinical practice and for registries. In the Netherlands, the diagnostic delay in PIDs (ie, time period between the date of onset of first symptoms and the date of diagnosis) ranges from 0 to 14.5 years and is dominated by the defects in innate immunity (14.5 years), HIES (10.5 years), and hypogammaglobulinemia (10.0 years).[48] Moin et al[6] and Berron-Ruiz et al[7] reported that in, respectively, 31.8% and 78.9% of the PIDs, the cutaneous alterations preceded and were the basis for the clinical immunological diagnosis. Increased attention for these cutaneous manifestations as signal function of PIDs in combination with presence of the current warning signs for the suspicion of PIDs might improve earlier diagnosis of PIDs. These warning signs include (a) four or more new ear infections within 1 year; (b) two or more serious sinus infections within 1 year; (c) two or more months on antibiotics with little effect; (d) two or more pneumonias within 1 year; (e) failure of an infant to gain weight or grow normally; (f) recurrent deep skin or organ abscesses; (g) persistent thrush in mouth or fungal infection on skin; (h) need for intravenous antibiotics to clear infections; (i) two or more deep-seated infections including septicemia; and (j) a family history of PID.[49] In addition, narrowing the number of eligible PIDs through clustering of skin disorders could further reduce the diagnostic delay in PIDs. Using the multistage diagnostic protocol of de Vries[4] or the phenotypic approach for PID classification and diagnosis by Bousfiha et al,[50] the diagnosis of suspected PIDs or PID classes based on clinical symptoms could be confirmed with laboratory tests. For example, a first diagnostic step in case of a supposed antibody deficiency or neutropenia could be blood count and differentiation, IgG, IgA, IgM, and IgE. In case of a possible combined immunodeficiency disease, these tests should be supplemented by lymphocyte subpopulations.

Our review has some limitations. First of all, exclusion of case reports describing fewer than five cases in our analysis might have resulted in loss of information about skin disorders in rare PIDs. However, the quality of case reports is highly variable, potential publication bias plays a role, and thus, exclusion of these case reports might have improved the reliability of this review. Furthermore, through the addition of selected PIDs and skin disorders to our electronic search we could have caused a selection bias. Although we used a cross-reference check, we cannot exclude that we might have missed some articles. Thirdly, demonstrating that specific skin disorders are characteristic for PIDs was not possible. We could only compare the presence of a number of skin disorders in patients with a PID with the prevalence of skin disorders in the general population based on six studies varying in publication year and age of the studied population.[21-26] However, most of these skin disorders were more prevalent in patients with a PID compared with the general population. Lastly, the reliability of the description of skin disorders might be questioned since in only 27 of the 67 included articles the Department of Dermatology was involved. Probably, the described skin disorders were not all diagnosed by a dermatologist, but by an immunologist or pediatrician. Moreover, the majority of studies did not use skin biopsy to confirm the diagnosis of the cutaneous manifestations histopathologically. In severe combined immunodeficiency (SCID) patients, it was shown by Denianke et al[51] that clinically comparable skin lesions could demonstrate different histopathological images, possibly due to an altered immune system. Subsequently, the reported clinical diagnosis of skin disorders reported in articles included in this review might not correlate with the corresponding histopathological diagnosis as well.

Because most PIDs are rare, reliable prevalence of skin disorders in PIDs can only be obtained by reporting skin disorders on an international basis. The international PID database of The European Society for Immunodeficiencies (ESID) registers, among others, data on warning signs of PIDs. These warning signs give only attention to infectious skin disorders. Noninfectious cutaneous symptoms are not included. Based on data of this review, we suggest to start to collect more detailed data on all skin orders in the ESID registry.

Future research is needed to validate these data and support an association between specific cutaneous symptoms and PIDs. Given the low number of articles reporting *S. aureus*-associated skin disorders and atopy in PIDs, more data have to be collected to further improve earlier recognition of PIDs. In addition, data on *S. aureus* associated skin disorders might provide new treatment options for skin disorders, such as targeted therapy directed against *S. aureus*.

5 | CONCLUSION

This review with a systematic approach shows that skin disorders are a prominent feature in PIDs. Earlier diagnosis of PIDs can be facilitated by recognition of specific skin conditions as signal function of PIDs in combination with the current warnings signs for PIDs or by recognizing PID specific clusters of skin conditions. We provide a support tool to use in clinical practice that should raise awareness of PIDs based on the presenting skin manifestations. Limited data are available on *S. aureus* -associated skin disorders and atopy in PIDs.

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CONFLICTS OF INTEREST

JdW, RB, JvV, VD, and SP have no conflict of interest to declare.

ORCID

Jill de Wit https://orcid.org/0000-0001-5080-1453

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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