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ORIGINAL ARTICLE

Automated mass screening and association rules analysis for comorbidities of psoriasis: A population-based case–control study

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Abstract

Patients with psoriasis frequently have comorbidities, which are linked to higher mortality rates. An in-depth investigation of comorbidities and their effects on health can help improve the management of patients with psoriasis. We conducted a comprehensive and unbiased investigation of comorbidities in patients with psoriasis and explored the pattern of association between comorbidities. A nationwide population-based study included 384 914 patients with psoriasis and 384 914 matched controls between 2011 and 2021. We used automated mass screening of all diagnostic codes to identify psoriasis-associated comorbidities and applied association rule analysis to explore the patterns of comorbidity associations in patients with psoriasis. Patients with psoriasis had an increased risk of autoimmunity-related diseases such as inflammatory arthritis, Crohn's disease, type 1 diabetes, and acute myocardial infarction. The comorbidities of patients with psoriasis with a history of cardiovascular events demonstrated strong interrelationships with other cardiovascular risk factors including type 2 diabetes mellitus, essential hypertension, and dyslipidemia. We also found comorbidities, such as malignant skin tumors and kidney and liver diseases, which could have adverse effects of anti-psoriasis therapy. In contrast, patients with psoriasis showed a decreased association with upper respiratory tract infection. Our results imply that comorbidities in patients with psoriasis are associated with the systemic inflammation of psoriasis and the detrimental effects of its treatment. Furthermore, we found patterns of associations between the cardiovascular risk factors and psoriasis. Mass screening and association analyses using large-scale databases can be used to investigate impartially the comorbidities of psoriasis and other diseases.

KEYWORDS
association rules analysis, comorbidity, mass screening, psoriasis

1 | INTRODUCTION

Psoriasis is a common, chronic inflammatory disease of the skin.[1] Since the awareness of the increased risk of cardiovascular disease in patients with psoriasis,[2] several studies have investigated the comorbidities in psoriasis patients.[3,4] These comorbidities have also been associated with increased mortality in patients with psoriasis.[5–8] However, previous studies on comorbidities were mostly case–control studies, verifying previously suggested associations.[9]

Chong Won Choi and Sang Woong Youn have contributed to this work equally as co-corresponding authors.

Association rules analysis was developed in marketing research to explore the sets of items that consumers frequently buy together.[10] Since association rules analysis can find the association between the items with the direction of the association, this analysis can be applied to exploring the comorbidities and multimorbidity among multiple diseases in patients.[10] For example, a few studies have recently explored comorbidities and multimorbidity in psychiatric diseases and geriatric subjects.[10–13]

We conducted a population-based, case–control study using automated mass screening methods for all International Classification of Diseases, tenth Revision (ICD-10) diagnostic codes for an unbiased investigation of comorbidities in patients with psoriasis and performed association rules analysis to explore patterns of association among the comorbidities.

2 | METHODS

2.1 | Study design and data source

We conducted a case–control study using population-based data from the Korean Health Insurance Review and Assessment Service (HIRA) between January 2011 and March 2021 (HIRA research data: M20210708364). This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number: X-2105-686-901).

2.2 | Study population

The HIRA database identified patients with psoriasis aged ≥20 years with a principal diagnosis ICD-10 code for psoriasis (L40) at least twice a year between January 2011 and March 2021. Control subjects who had never visited a medical institution for psoriasis were defined as patients aged ≥20 years with at least one diagnosis code for urticaria (L50). The index date was the date of an initial diagnosis of psoriasis or urticaria. We excluded patients with no follow-up data in both case and control groups. We matched cases and controls with a frequency of 1:1 based on age group, sex, and index date. Finally, a total of 384 914 patients with psoriasis and 384 914 controls were included in the study (Figure 1).

2.3 | Definition of comorbid diseases

Comorbid diseases were identified using the ICD-10 codes. Among the ICD-10 codes, we excluded (1) the F code (mental and behavioral disorders), which had restrictions on the use of public data as sensitive information, and (2) the codes that were irrelevant for the comorbidities in patients with psoriasis, such as O (pregnancy, childbirth, and the puerperium); P (certain conditions originating in the perinatal period) code; R (symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified); T (injury, poisoning and certain other consequences of external causes [multiple site]); V-Y (external causes of morbidity and mortality); Z (factors influencing health status and contact with health services); and U (codes for special purposes). Finally, we excluded codes for the control group's disease frequency of <30. A total of 567 comorbidities were included in the analysis.

2.4 | Statistical analysis

Continuous variables are presented as means with standard deviations. The chi square test was used to determine whether there was a significant difference between nominal variables to examine the

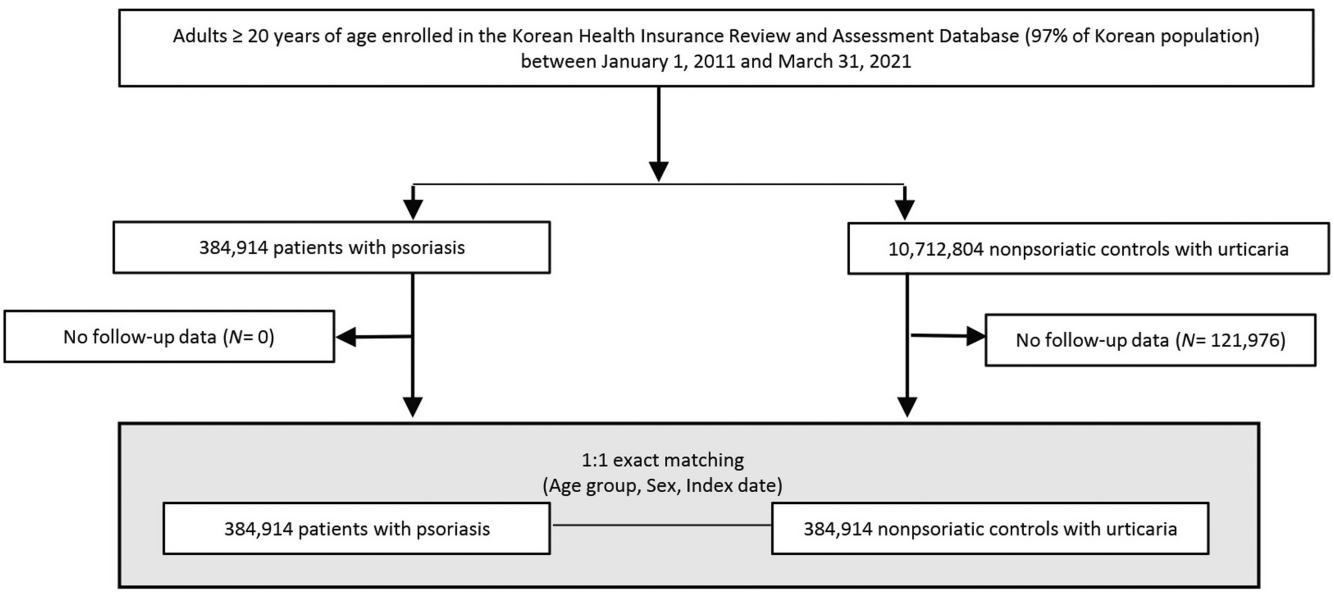

FIGURE 1 Flow chart of selection of the study population.

unadjusted comparisons. We evaluated the occurrence of each comorbid disease in patients with psoriasis and control subjects using logistic regression analysis. SAS version 9.4 (SAS Institute Inc.) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) were used to analyze the data. A detailed description of the methods used for analysis is provided in the Table S1.

3 | RESULTS

3.1 | Baseline characteristics of the study population

Between January 2011 and March 2021, we identified 384 914 patients aged >20 years with psoriasis and 384 914 matched controls without psoriasis. The mean age was 48.23 years and 42.5% were women (Table 1).

3.2 | Overall disease association

A meta-analysis (random-effects model) was performed (Table S1) because more frequent hospital visits for patients with psoriasis can lead to a selection bias in which patients with psoriasis make more frequent claims for other mild disorders. A total of 567 odds ratios (ORs) were obtained for 567 comorbidities, and the meta-analysis OR of these individual ORs was 1.1773 (95% confidence interval [CI] 1.1409–1.2150; $I^2 = 98.9\%$). Considering the meta-analysis (OR 1.1773), we also set a threshold of clinical significance of diseases with an OR >1.2 in multivariate logistic regression analysis, as an increased association with psoriasis, and an OR <0.98 as a decreased association with psoriasis. Finally, 94 diseases were found to be both clinically and statistically significant; 79 diseases showed an increased and 15 diseases showed a decreased association (Table 2, Figure 2). In Figure 2, the size of the circles represents the number of controls with an individual disease. Compared to the control group, if the OR for the likelihood that patients with psoriasis have an individual disease was >1.2 or <0.98, it is indicated in red or blue, respectively.

TABLE 1 Clinical characteristics of study population.

Characteristics	Psoriasis	Controls	*p*
Total number	384,914	384,914	
Age, years	48.23 ± 16.37	48.23 ± 16.38	0.962
20–29	57 900 (15.0)	57 900 (15.0)	1.000
30–39	70 616 (18.3)	70 616 (18.3)	
40–49	76 183 (19.8)	76 183 (19.8)	
50–59	80 779 (21.0)	80 779 (21.0)	
60–69	54 179 (14.1)	54 179 (14.1)	
70–79	34 612 (9.0)	34 612 (9.0)	
≥80	10 645 (2.8)	10 645 (2.8)	
Sex			
Male	221 393 (57.5)	221 393 (57.5)	1.000
Female	163 521 (42.5)	163 521 (42.5)	
Insurance type			
Health insurance	308 450 (98.8)	382 354 (99.3)	<0.001*
Medical aid	4464 (1.2)	2560 (0.7)	

Note: Data are presented as mean ± standard deviation or number (%). 1:1 matching: age group, sex, and index date.
*$p < 0.05$.

3.2.1 | Certain infectious and parasitic diseases

We found significant associations between psoriasis and infectious diseases such as sepsis, herpes simplex, superficial fungal infections, and scabies.

3.2.2 | Neoplasms

Malignant skin tumors (C44: OR 2.91, 95% CI 2.31–3.65) and mature natural killer T-cell (T/NK-cell) lymphoma (C84: OR 5.21, 95% CI 4.02–6.74) showed increased association with psoriasis. Moreover, melanocytic nevi (D22: OR 3.13, 95% CI 2.11–4.63) and benign skin tumors (D23: OR 5.04, 95% CI 4.56–5.57) showed increased association with psoriasis.

3.2.3 | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

Psoriasis, purpura, and other hemorrhagic conditions showed a positive correlation (D69: OR 1.71, 95% CI 1.5–1.95).

3.2.4 | Endocrine, nutritional, and metabolic diseases

Type 1 diabetes (E10: OR 1.25, 95% CI 1.18–1.34), Cushing's syndrome (E24: OR 2.61, 95% CI 2.05–3.31), and adrenal disorders (E27: OR 2.05, 95% CI 1.7–2.46) showed significant association with psoriasis. Conversely, dyslipidemia showed a low association with psoriasis (E78: OR 0.96, 95% CI 0.95–0.97). No clinically or statistically significant associations were observed between psoriasis and metabolic disorders including type 2 diabetes (E11) or hypertension (I10) (Table 2).

3.2.5 | Diseases of the nervous system

Cranial nerve disorders (G53: OR 1.23, 95% CI 1.12–1.34) and polyneuropathy (G63: OR 1.25, 95% CI 1.17–1.34) showed an increased association with psoriasis.

TABLE 2 Comorbid diseases in patients with psoriasis.

	ICD-10 code	Comorbidity	Psoriasis Events *n*, (%)	Control Events *n*, (%)	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
High association	A41	Other sepsis	180 (0.05)	100 (0.03)	01.8 (1.41, 2.3)	1.8 (1.41, 2.29)
	A53	Other and unspecified syphilis	1481 (0.38)	1168 (0.30)	1.27 (1.18, 1.37)	1.26 (1.17, 1.36)
	B00	Herpes viral (herpes simplex) infections	3132 (0.81)	2332 (0.61)	1.35 (1.28, 1.42)	1.34 (1.27, 1.41)
	B07	Viral warts	1496 (0.39)	342 (0.09)	4.39 (3.9, 4.93)	4.39 (3.9, 4.93)
	B35	Dermatophytosis	27281 (7.09)	9905 (2.57)	2.89 (2.82, 2.96)	2.9 (2.83, 2.96)
	B36	Other superficial mycoses	1021 (0.27)	316 (0.08)	3.24 (2.85, 3.67)	3.24 (2.85, 3.67)
	B86	Scabies	675 (0.18)	492 (0.13)	1.37 (1.22, 1.54)	1.36 (1.21, 1.53)
	C44	Other malignant neoplasm of skin	289 (0.08)	100 (0.03)	2.89 (2.3, 3.63)	2.91 (2.31, 3.65)
	C84	Mature T/NK-cell lymphoma	359 (0.09)	69 (0.02)	5.21 (4.02, 6.74)	5.21 (4.02, 6.74)
	D22	Melanocytic naevi	103 (0.03)	33 (0.01)	3.12 (2.11, 4.62)	3.13 (2.11, 4.63)
	D23	Other benign neoplasms of skin	2305 (0.60)	458 (0.12)	5.06 (4.57, 5.59)	5.04 (4.56, 5.57)
	D69	Purpura and other hemorrhagic conditions	600 (0.16)	349 (0.09)	1.72 (1.51, 1.96)	1.71 (1.5, 1.95)
	E10	Insulin-dependent diabetes mellitus	2123 (0.55)	1679 (0.44)	1.27 (1.19, 1.35)	1.25 (1.18, 1.34)
	E24	Cushing's syndrome	243 (0.06)	93 (0.02)	2.61 (2.06, 3.32)	2.61 (2.05, 3.31)
	E27	Other disorders of adrenal gland	350 (0.09)	170 (0.04)	2.06 (1.71, 2.47)	2.05 (1.7, 2.46)
	G53	Cranial nerve disorders in diseases classified elsewhere	1124 (0.29)	913 (0.24)	1.23 (1.13, 1.34)	1.23 (1.12, 1.34)
	G63	Polyneuropathy in diseases classified elsewhere	2082 (0.54)	1646 (0.43)	1.27 (1.19, 1.35)	1.25 (1.17, 1.34)
	H26	Other cataract	855 (0.22)	686 (0.18)	1.25 (1.13, 1.38)	1.24 (1.12, 1.38)
	H36	Retinal disorders in diseases classified elsewhere	854 (0.22)	668 (0.17)	1.28 (1.16, 1.42)	1.27 (1.15, 1.4)
	I12	Hypertensive renal disease	731 (0.19)	546 (0.14)	1.34 (1.2, 1.5)	1.34 (1.2, 1.49)
	I21	Acute myocardial infarction	3159 (0.82)	2617 (0.68)	1.21 (1.15, 1.27)	1.21 (1.15, 1.27)
	K13	Other diseases of lip and oral mucosa	177 (0.05)	88 (0.02)	2.01 (1.56, 2.6)	1.99 (1.54, 2.57)
	K30	Dyspepsia	1496 (0.39)	1192 (0.31)	1.26 (1.16, 1.36)	1.25 (1.16, 1.35)
	K50	Crohn's disease (regional enteritis)	627 (0.16)	478 (0.12)	1.31 (1.16, 1.48)	1.31 (1.16, 1.47)
	K74	Fibrosis and cirrhosis of liver	1160 (0.30)	758 (0.20)	1.53 (1.4, 1.68)	1.52 (1.38, 1.66)
	L01	Impetigo	1291 (0.34)	639 (0.17)	2.02 (1.84, 2.23)	2.01 (1.83, 2.21)
	L02	Cutaneous abscess, furuncle and carbuncle	5668 (1.47)	3117 (0.81)	1.83 (1.75, 1.91)	1.82 (1.74, 1.9)
	L03	Cellulitis	6185 (1.61)	4250 (1.10)	1.46 (1.41, 1.52)	1.46 (1.4, 1.52)
	L08	Other local infections of skin and subcutaneous tissue	3846 (1.00)	1281 (0.33)	3.02 (2.84, 3.22)	3.01 (2.82, 3.21)
	L13	Other bullous disorders	384 (0.10)	124 (0.03)	3.1 (2.53, 3.79)	3.09 (2.53, 3.79)
	L20	Atopic dermatitis	12307 (3.20)	5115 (1.33)	2.45 (2.37, 2.53)	2.45 (2.37, 2.53)
	L21	Seborrheic dermatitis	26510 (6.89)	5651 (1.47)	4.96 (4.82, 5.11)	4.97 (4.83, 5.12)
	L23	Diaper(napkin) dermatitis	65600 (17.04)	43735 (11.36)	1.6 (1.58, 1.62)	1.6 (1.58, 1.62)
	L24	Allergic contact dermatitis	15911 (4.13)	7161 (1.86)	2.27 (2.21, 2.34)	2.27 (2.21, 2.34)
	L25	Irritant contact dermatitis	8274 (2.15)	5479 (1.42)	1.52 (1.47, 1.57)	1.52 (1.47, 1.57)

TABLE 2 (Continued)

ICD-10 code	Comorbidity	Psoriasis Events *n*, (%)	Control Events *n*, (%)	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
L28	Lichen simplex chronicus and prurigo	11426 (2.97)	3668 (0.95)	3.18 (3.06, 3.3)	3.18 (3.06, 3.3)
L29	Pruritus	7548 (1.96)	5811 (1.51)	1.3 (1.26, 1.35)	1.3 (1.26, 1.35)
L30	Other dermatitis	29581 (7.69)	9634 (2.50)	3.24 (3.17, 3.32)	3.24 (3.16, 3.32)
L41	Parapsoriasis	1262 (0.33)	76 (0.02)	16.66 (13.21, 21)	16.63 (13.19, 20.96)
L42	Pityriasis rosea	1697 (0.44)	353 (0.09)	4.82 (4.3, 5.41)	4.84 (4.31, 5.43)
L43	Lichen planus	566 (0.15)	77 (0.02)	7.36 (5.8, 9.34)	7.36 (5.8, 9.34)
L51	Erythema multiforme	531 (0.14)	340 (0.09)	1.56 (1.36, 1.79)	1.56 (1.36, 1.79)
L52	Erythema nodosum	97 (0.03)	42 (0.01)	2.31 (1.61, 3.32)	2.28 (1.59, 3.28)
L53	Other erythematous conditions	884 (0.23)	638 (0.17)	1.39 (1.25, 1.54)	1.39 (1.25, 1.54)
L56	Other acute skin changes due to ultraviolet radiation	326 (0.08)	158 (0.04)	2.06 (1.71, 2.5)	2.06 (1.7, 2.49)
L57	Skin changes due to chronic exposure to nonionizing radiation	285 (0.07)	39 (0.01)	7.31 (5.23, 10.22)	7.32 (5.24, 10.23)
L60	Nail disorders	1208 (0.31)	248 (0.06)	4.88 (4.26, 5.6)	4.89 (4.26, 5.6)
L63	Alopecia areata	1761 (0.46)	506 (0.13)	3.49 (3.16, 3.85)	3.49 (3.16, 3.85)
L64	Androgenic alopecia	232 (0.06)	68 (0.02)	3.41 (2.6, 4.47)	3.41 (2.6, 4.46)
L65	Other nonscarring hair loss	185 (0.05)	48 (0.01)	3.86 (2.81, 5.3)	3.86 (2.81, 5.3)
L66	Cicatricial alopecia (scarring hair loss)	168 (0.04)	59 (0.02)	2.85 (2.12, 3.83)	2.84 (2.11, 3.82)
L70	Acne	524 (0.14)	277 (0.07)	1.89 (1.64, 2.19)	1.89 (1.63, 2.19)
L71	Rosacea	454 (0.12)	213 (0.06)	2.13 (1.81, 2.51)	2.13 (1.81, 2.51)
L72	Follicular cysts of skin and subcutaneous tissue	931 (0.24)	301 (0.08)	3.1 (2.72, 3.53)	3.09 (2.71, 3.52)
L73	Other follicular disorders	2032 (0.53)	803 (0.21)	2.54 (2.34, 2.76)	2.53 (2.33, 2.75)
L74	Eccrine sweat disorders	176 (0.05)	89 (0.02)	1.98 (1.53, 2.55)	1.97 (1.53, 2.55)
L80	Vitiligo	1133 (0.29)	142 (0.04)	8 (6.72, 9.52)	7.98 (6.7, 9.51)
L81	Other disorders of pigmentation	248 (0.06)	79 (0.02)	3.14 (2.44, 4.05)	3.14 (2.44, 4.04)
L82	Seborrheic keratosis	201 (0.05)	48 (0.01)	4.19 (3.06, 5.74)	4.15 (3.03, 5.69)
L84	Corns and callosities	1123 (0.29)	387 (0.10)	2.91 (2.59, 3.26)	2.89 (2.57, 3.24)
L85	Other epidermal thickening	4526 (1.18)	1664 (0.43)	2.74 (2.59, 2.9)	2.74 (2.59, 2.89)
L90	Atrophic disorders of skin	137 (0.04)	45 (0.01)	3.05 (2.17, 4.26)	3.05 (2.18, 4.27)
L91	Hypertrophic disorders of skin	1055 (0.27)	288 (0.07)	3.67 (3.22, 4.18)	3.66 (3.21, 4.17)
L93	Lupus erythematosus	93 (0.02)	36 (0.01)	2.58 (1.76, 3.8)	2.57 (1.75, 3.77)
L98	Other disorders of skin and subcutaneous tissue, NEC	733 (0.19)	149 (0.04)	4.93 (4.13, 5.88)	4.93 (4.13, 5.88)
M06	Other rheumatoid arthritis	1364 (0.35)	1099 (0.29)	1.24 (1.15, 1.34)	1.24 (1.14, 1.34)
M07	Psoriatic and enteropathic arthropathies	4587 (1.19)	712 (0.18)	6.51 (6.01, 7.04)	6.5 (6, 7.03)
M45	Ankylosing spondylitis	744 (0.19)	281 (0.07)	2.65 (2.31, 3.04)	2.64 (2.3, 3.03)
M46	Other inflammatory spondylopathies	270 (0.07)	170 (0.04)	1.59 (1.31, 1.92)	1.59 (1.31, 1.92)
M86	Osteomyelitis	153 (0.04)	82 (0.02)	1.87 (1.43, 2.44)	1.85 (1.41, 2.42)
M87	Osteonecrosis	335 (0.09)	176 (0.05)	1.9 (1.59, 2.29)	1.89 (1.58, 2.27)
N18	Chronic kidney disease	4672 (1.21)	3536 (0.92)	1.33 (1.27, 1.38)	1.32 (1.26, 1.38)

(Continues)

TABLE 2 (Continued)

	ICD-10 code	Comorbidity	Psoriasis Events *n*, (%)	Control Events *n*, (%)	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
	N31	Neuromuscular dysfunction of bladder, NEC	1048 (0.27)	857 (0.22)	1.22 (1.12, 1.34)	1.22 (1.11, 1.33)
	N34	Urethritis and urethral syndrome	952 (0.25)	598 (0.16)	1.59 (1.44, 1.77)	1.59 (1.43, 1.76)
	N40	Hyperplasia of prostate	7758 (2.02)	6498 (1.69)	1.2 (1.16, 1.24)	1.21 (1.17, 1.26)
	N41	Inflammatory diseases of prostate	605 (0.16)	402 (0.10)	1.51 (1.33, 1.71)	1.5 (1.33, 1.71)
	S51	Open wound of forearm	258 (0.07)	148 (0.04)	1.74 (1.42, 2.13)	1.72 (1.41, 2.11)
	S81	Open wound of lower leg	549 (0.14)	308 (0.08)	1.78 (1.55, 2.05)	1.77 (1.54, 2.03)
	S91	Open wound of ankle and foot	414 (0.11)	271 (0.07)	1.53 (1.31, 1.78)	1.52 (1.3, 1.77)
Low association	E78	Disorders of lipoprotein metabolism and other lipidemias	88386 (22.96)	90771 (23.58)	0.97 (0.96, 0.98)	0.96 (0.95, 0.97)
	J01	Acute sinusitis	1240 (0.32)	1528 (0.40)	0.81 (0.75, 0.87)	0.81 (0.75, 0.87)
	J02	Acute pharyngitis	2409 (0.63)	2730 (0.71)	0.88 (0.83, 0.93)	0.88 (0.83, 0.93)
	J03	Acute tonsillitis	3550 (0.92)	4121 (1.07)	0.86 (0.82, 0.9)	0.86 (0.82, 0.9)
	J04	Acute laryngitis and tracheitis	2096 (0.54)	2440 (0.63)	0.86 (0.81, 0.91)	0.85 (0.81, 0.91)
	J06	Acute upper respiratory infections of multiple and unspecified sites	4902 (1.27)	5423 (1.41)	0.9 (0.87, 0.94)	0.9 (0.86, 0.93)
	J20	Acute bronchitis	16278 (4.23)	18410 (4.78)	0.88 (0.86, 0.9)	0.88 (0.86, 0.9)
	J21	Acute bronchiolitis	680 (0.18)	869 (0.23)	0.78 (0.71, 0.86)	0.78 (0.71, 0.86)
	J30	Vasomotor and allergic rhinitis	10737 (2.79)	13602 (3.53)	0.78 (0.76, 0.8)	0.78 (0.76, 0.8)
	J39	Other diseases of upper respiratory tract	321 (0.08)	484 (0.13)	0.66 (0.58, 0.76)	0.66 (0.58, 0.76)
	K21	Gastro-esophageal reflux disease	12159 (3.16)	13096 (3.40)	0.93 (0.9, 0.95)	0.92 (0.9, 0.95)
	M17	Gonarthrosis (arthrosis of knee)	8481 (2.20)	8997 (2.34)	0.94 (0.91, 0.97)	0.93 (0.9, 0.96)
	M54	Dorsalgia	9653 (2.51)	10281 (2.67)	0.94 (0.91, 0.96)	0.93 (0.9, 0.96)
	M75	Shoulder lesions	3918 (1.02)	4344 (1.13)	0.9 (0.86, 0.94)	0.9 (0.86, 0.94)
	M79	Other soft tissue disorders, NEC	5208 (1.35)	5688 (1.48)	0.91 (0.88, 0.95)	0.91 (0.87, 0.94)

Note: Multivariable analysis was adjusted for age, sex and insurance type.

Abbreviations: ICD-10, international classification of diseases, tenth revision; OR, odds ratio; CI, confidence level; NEC, not elsewhere classifiable.

3.2.6 | Diseases of the eye and ear

Cataracts (H26: OR 1.24, 95% CI 1.12–1.38) and retinal disorders (H36: OR 1.27, 95% CI 1.15–1.4) showed an increased association with psoriasis.

3.2.7 | Diseases of the circulatory system

Hypertensive renal disease (I12: OR 1.34, 95% CI 1.2–1.49) and acute myocardial infarction (I21: OR 1.21, 95% CI 1.15–1.27) showed association with psoriasis. In contrast, ischemic heart disease (I24) and cerebrovascular diseases, such as cerebral infarction (I63) and cerebral hemorrhage (I60, I61, and I62), did not show a clinically or statistically significant relationship with psoriasis.

3.2.8 | Diseases of the respiratory system

Among the systemic diseases, some respiratory diseases showed a decreased correlation with psoriasis. Acute sinusitis (J01: OR 0.81, 95% CI 0.75–0.87), acute pharyngitis (J02: OR 0.88, 95% CI 0.83–0.93), acute tonsillitis (J03: OR 0.86, 95% CI 0.82–0.9), acute laryngitis and tracheitis (J04: OR 0.85, 95% CI 0.81–0.91), acute upper respiratory infections (J06: OR 0.9, 95% CI 0.86–0.93), acute bronchitis (J20: OR 0.88, 95% CI 0.86–0.9), acute bronchiolitis (J21:

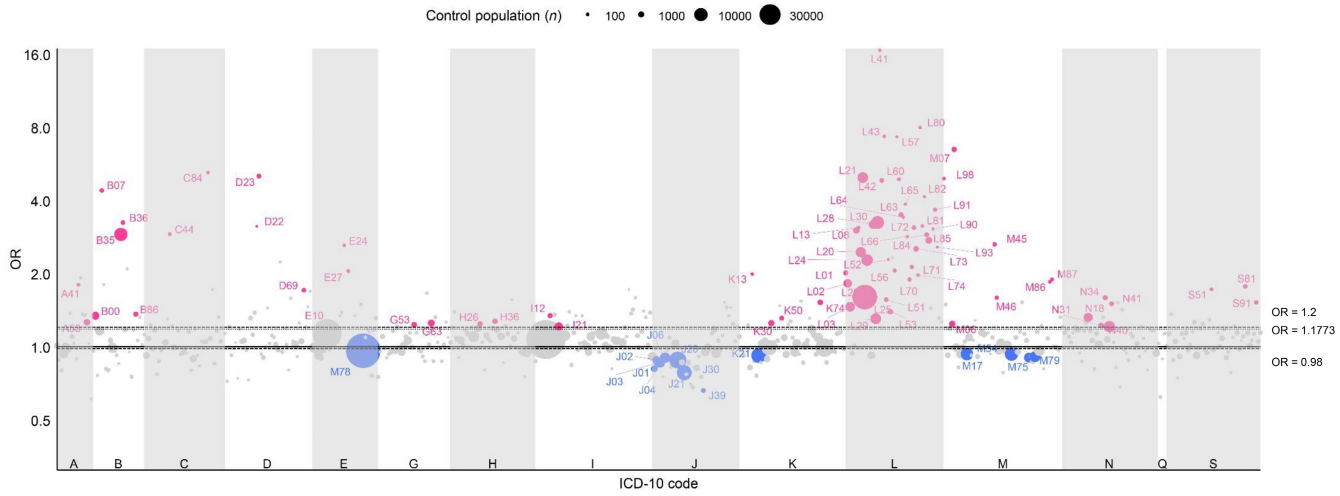

FIGURE 2 Mass screening on comorbidities of psoriasis.

OR 0.78, 95% CI 0.71–0.86), vasomotor and allergic rhinitis (J30: OR 0.78, 95% CI 0.76–0.8), and diseases of the upper respiratory tract (J39: OR 0.66, 95% CI 0.58–0.76) were observed to occur less in patients with psoriasis.

3.2.9 | Diseases of the digestive system

Lip and oral mucosal disorders (K13: OR 1.99, 95% CI 1.54–2.57), Crohn's disease (K50: OR 1.31, 95% CI 1.16–1.47), and liver cirrhosis (K74: OR 1.52, 95% CI 1.38–1.66) were positively associated with psoriasis. Ulcerative colitis (K51) was not associated with psoriasis.

3.2.10 | Diseases of the skin and subcutaneous tissue

Among systemic diseases, skin diseases were most frequently accompanied by psoriasis. Among skin diseases, parapsoriasis (L41: OR 16.63, 95% CI 13.19–20.96) showed the most significant association followed by vitiligo (L80: OR 7.98, 95% CI 6.7–9.51), lichen planus (L43: OR 7.36, 95% CI 5.8–9.34), and skin changes due to chronic exposure to non-ionizing radiation (L57: OR 7.32, 95% CI 5.24–10.23).

3.2.11 | Diseases of the musculoskeletal system and connective tissue

Rheumatoid arthritis (M06: OR 1.24, 95% CI 1.14–1.34) and psoriatic arthritis (M07: OR 6.5, 95% CI 6–7.03) were associated with psoriasis about 1.2 times and 6.5 times higher than in control subjects, respectively. In addition, ankylosing spondylitis (M45: OR 2.64, 95% CI 2.3–3.03), other inflammatory spondylopathies, spondylitis (M46: OR 1.59, 95% CI 1.31–1.92), osteomyelitis (M86: OR 1.85, 95% CI 1.41–2.42), and osteonecrosis (M87: OR 1.89, 95% CI 1.58–2.27) also showed a positive association.

3.2.12 | Diseases of the genitourinary system

Compared with control subjects, patients with psoriasis were associated with chronic kidney disease (N18: OR 1.32, 95% CI 1.26–1.38), neuromuscular dysfunction of the bladder (N31: OR 1.22, 95% CI 1.11–1.33), and urethritis (N34: OR 1.59, 95% CI 1.43–1.76).

3.2.13 | Injury, poisoning, and certain other consequences of external causes

A high frequency of open wounds on the forearm (S51: OR 1.72, 95% CI 1.41–2.11), lower leg (S81: OR 1.77, 95% CI 1.54–2.03), and ankle and foot (S91: OR 1.52, 95% CI 1.3–1.77) was observed in patients with psoriasis compared with controls.

3.3 | Discovery of association rules patterns among comorbidities in patients with psoriasis with myocardial infarction

Association rules mining identified 19 rules among the comorbidities of patients with psoriasis and a history of acute myocardial infarction (support > 10%, confidence > 10%, and lift > 1). Table 3 shows the results of the support, confidence, and lift of 19 association rules among six comorbidities (type 2 diabetes mellitus [E11], angina pectoris [I20], essential (primary) hypertension [I10], disorders of lipoprotein metabolism and other lipidemias [E78], chronic ischemic heart disease [I25], and allergic contact dermatitis L23]). As shown in Table 3, the support value ranged from 11 to 26, suggesting that the probability of having both antecedent and consequent comorbidities was >10% in patients with psoriasis and acute myocardial

TABLE 3 Association rules of comorbidities in patients with psoriasis with a history of acute myocardial infarction.

No.	Association rules	Antecedent	Consequence	Support (%)	Confidence (%)	Lift
1	E11, I20 → I10	Type 2 diabetes mellitus and Angina pectoris	Essential (primary) hypertension	11.55	66.61	1.23
2	I10, I20 → E11	Essential (primary) hypertension and Angina pectoris	Type 2 diabetes mellitus	11.55	50.55	1.20
3	E11, I10 → I20	Type 2 diabetes mellitus and Essential (primary) hypertension	Angina pectoris	11.55	44.14	1.19
4	E78 → I10	Disorders of lipoprotein metabolism and other lipidemias	Essential (primary) hypertension	15.35	63.07	1.16
5	I10 → E78	Essential (primary) hypertension	Disorders of lipoprotein metabolism and other lipidemias	15.35	28.28	1.16
6	I25 → I20	Chronic ischemic heart disease	Angina pectoris	13.30	42.94	1.16
7	I20 → I25	Angina pectoris	Chronic ischemic heart disease	13.30	35.87	1.16
8	E11 → I10	Type 2 diabetes mellitus	Essential (primary) hypertension	26.18	62.18	1.15
9	I10 → E11	Essential (primary) hypertension	Type 2 diabetes mellitus	26.18	48.22	1.15
10	I20 → I10	Angina pectoris	Essential (primary) hypertension	22.86	61.66	1.14
11	I10 → I20	Essential (primary) hypertension	Angina pectoris	22.86	42.10	1.14
12	L23 → I10	Allergic contact dermatitis	Essential (primary) hypertension	12.25	61.53	1.13
13	I10 → L23	Essential (primary) hypertension	Allergic contact dermatitis	12.25	22.57	1.13
14	E78 → E11	Disorders of lipoprotein metabolism and other lipidemias	Type 2 diabetes mellitus	11.46	47.07	1.12
15	E11 → E78	Type 2 diabetes mellitus	Disorders of lipoprotein metabolism and other lipidemias	11.46	27.22	1.12
16	I20 → E11	Angina pectoris	Type 2 diabetes mellitus	17.35	46.80	1.11
17	E11 → I20	Type 2 diabetes mellitus	Angina pectoris	17.35	41.20	1.11
18	I25 → E11	Chronic ischemic heart disease	Type 2 diabetes mellitus	13.71	44.27	1.05
19	E11 → I25	Type 2 diabetes mellitus	Chronic ischemic heart disease	13.71	32.56	1.05

Note: Data are presented as mean ± standard deviation or number (%).

infarction. The confidence interval was 22–66. Among them, the confidence of six rules (E11, I20→I10, I10, I20→E11, E78→I10, E11→I10, I20→I10, L23→I10) was >50%, which means that patients diagnosed with antecedent comorbidities among those with psoriasis and myocardial infarction have >50% probability of having consequent comorbidities.

Association rules among the comorbidities were visualized using a network graph (Figure 3). Arrows indicate the path of the comorbidities; the size of the circle represents support, and the circle's color represents lift. The figure shows strong relationships between essential hypertension and type 2 diabetes mellitus and angina pectoris (rules 8 and 11: 62.18% of patients with type 2 diabetes will have essential hypertension, and 42.10% of patients with essential hypertension will have angina pectoris). Furthermore, 44.14% of the patients with type 2 diabetes and essential hypertension had angina pectoris (rule 3). In addition, disorders of lipoprotein metabolism are closely associated with essential hypertension and type 2 diabetes mellitus (15.35% of patients with psoriasis and a history of acute myocardial infarction have both lipoprotein metabolism disorders and essential hypertension (rules 4 and 5), and 11.46% of them will have both lipoprotein metabolism disorders and type 2 diabetes (rules 14 and 15). Finally, chronic ischemic heart disease was closely associated with angina pectoris (rules 6 and 7) and type 2 diabetes mellitus (rules 18 and 19).

4 | DISCUSSION

Comorbidities occur frequently in patients with psoriasis and may be associated with increased mortality in this population. However, most previous studies were case–control studies that verified the previously suggested associations. Therefore, an unbiased investigation of comorbidities across all diseases and their impact on the health of patients with psoriasis was required. In this study, we performed an automated mass screening of all ICD-10 disease codes to explore the comprehensive and unbiased associations of

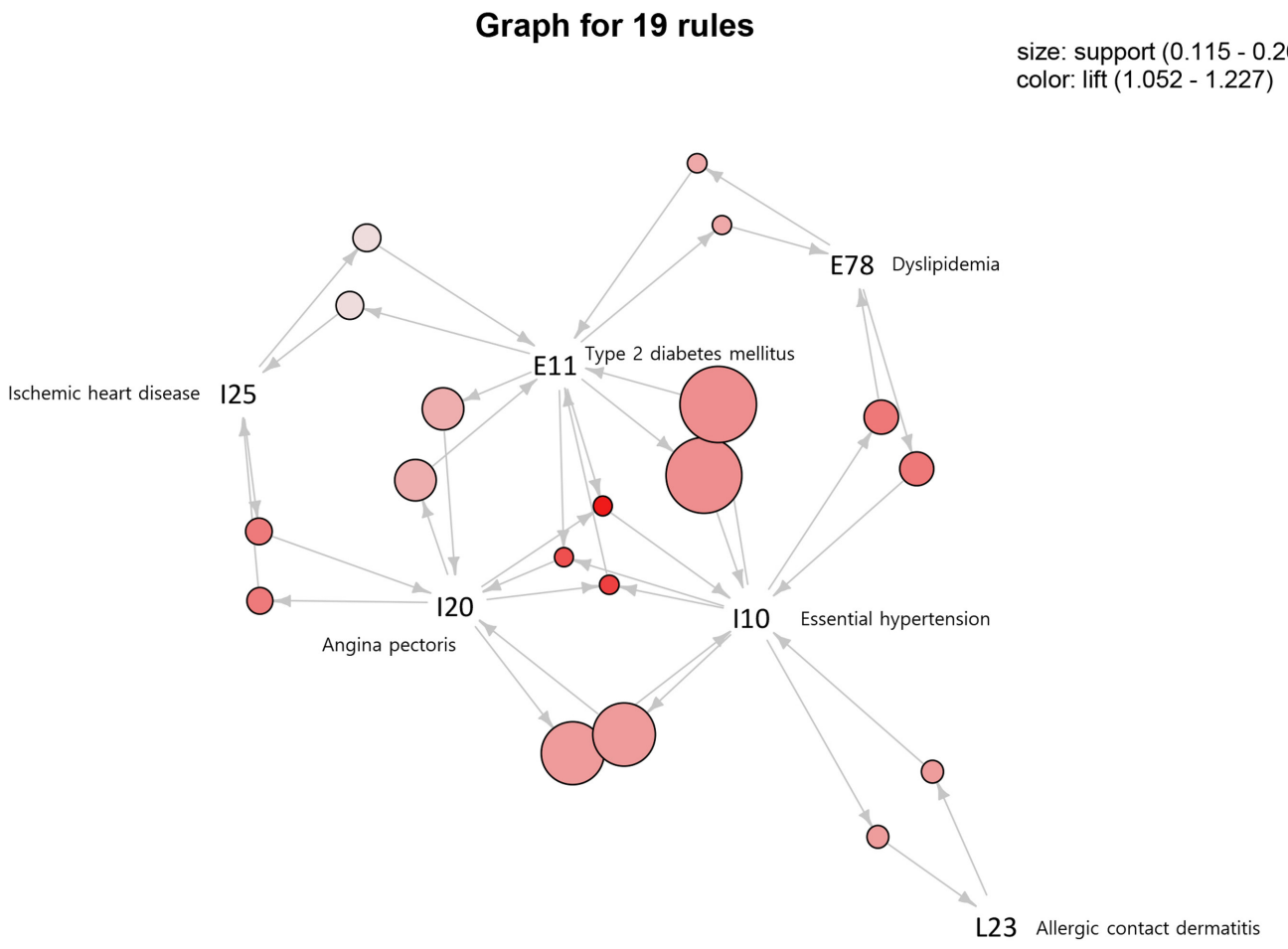

FIGURE 3 Network graph of comorbidities in patients with psoriasis with a history of myocardial infarction.

comorbidities in patients with psoriasis. We also conducted association rules analysis to detect patterns among comorbidities in patients with psoriasis.

Our automated mass screening reaffirmed the previously identified comorbidities in patients with psoriasis. After compensating for possible selection bias due to the frequent hospital visits of patients with psoriasis, we identified 94 disease codes that met clinical and statistical significance criteria out of 567 possible associations. Notably, some of the 79 diseases showing positive associations were identified as comorbidities in previous studies. First, psoriatic arthritis and spondylitis were comorbidities that showed an increased prevalence in patients with psoriasis identified using the automated mass screening. In addition, we observed a positive association between type 1 diabetes mellitus and Crohn's disease in patients with psoriasis. Recent studies have suggested autoimmunity-related comorbidities in patients with psoriasis.[14,15] Considering that autoimmune diseases share disease mechanisms and can be found in clusters in one patient, our results again confirmed that patients with psoriasis are at an increased risk of having multiple autoimmune diseases. The incidence of these autoimmune diseases remains low; however, careful observation by clinicians is required to identify autoimmunity-related comorbidities in patients with psoriasis.

Patients with psoriasis have an increased risk of death compared with healthy subjects.[8] In addition, the excess risk of death in patients with severe psoriasis was the highest for cardiovascular disease.[8] Our analysis also found a positive association between psoriasis and acute myocardial infarction, similar to previous studies.[16,17] Furthermore, our association rule analysis found a strong interrelationship between essential hypertension, type 2 diabetes mellitus, and disorders of lipoprotein metabolism in patients with psoriasis with a history of acute myocardial infarction. Moreover, they are strongly associated with angina pectoris and chronic ischemic heart disease. Our results suggest that psoriasis in patients with myocardial infarction is strongly associated with other cardiovascular risk factors. Despite psoriasis being an independent risk factor for myocardial infarction,[17–19] systemic inflammation by psoriasis can induce insulin resistance, dysfunction of vascular endothelial cells, and atherosclerosis and can lead to psoriasis patients having multiple cardiovascular risk factors.[2,20,21] When subgroup analysis of the OR of acute myocardial infarction was performed by age group (<40 and ≥40 years), patients with psoriasis aged ≥40 years still had a significantly (1.21 times) higher risk of acute myocardial infarction, while the risk of acute myocardial infarction in young psoriasis patients aged 20–39 years was 1.13 times higher

than that of the control group of the same age but not statistically significant (Table S1). This result also supports the hypothesis that the risk of acute myocardial infarction increased with age in patients with psoriasis because systemic inflammation due to psoriasis can accumulate, thereby increasing the cardiovascular risk factors. As the co-existence of multiple risk factors in a single patient has been associated with an increased risk of cardiovascular disease, and psoriasis is related to the development of other risk factors for cardiovascular diseases, patients with psoriasis should be recommended to start risk factor screening at the early age, even without having other risk factors.[18,22]

Psoriasis is a persistent skin disease with no permanent therapy; therefore, continuous long-term psoriasis treatment is required. As a result, adverse effects of long-term continuous therapy may be observed. Our study found positive associations between Cushing's syndrome, osteonecrosis, purpura, and cataracts, which could be associated with the long-term use of systemic or topical steroids for treating psoriasis.[23–25] Despite most treatment guidelines and textbooks not recommending systemic steroids in treating psoriasis, recent studies from multiple countries revealed that systemic steroids are frequently prescribed to patients with psoriasis for their skin lesions.[26–29] Systemic steroids can be a risk factor for Cushing's syndrome, osteonecrosis, and purpura found in patients with psoriasis.

Our results also show that compared to the control group, patients with psoriasis had a strong association with skin infections, such as impetigo, cellulitis, and dermatophytosis. Although a direct comparison is difficult due to the heterogeneity of the study design and controls, previous epidemiological studies have identified a higher risk of skin infections in patients with psoriasis compared to those without psoriasis.[30–32] Psoriasis patients might be more susceptible to skin and soft tissue infections due to long-term use of topical steroids, which may make lesional psoriasis skin vulnerable to local cutaneous infections. In addition, long-term use of systemic treatments, such as steroids or immunosuppressants, may predispose patients with psoriasis to skin infections. Recent findings have revealed that biologic agents used to treat moderate-to-severe psoriasis, such as tumor necrosis factor-α inhibitors and interleukin-17 inhibitors, increase the risk of localized cutaneous candidiasis, cellulitis, and folliculitis,[33,34] which are also considered to contribute to the skin infections in patients with psoriasis.

Furthermore, our study's positive association of psoriasis with malignant skin tumors or melanocytic nevi can be attributed to long-term phototherapy for treating psoriasis,[35–37] which include pigmentary disorders, photoaging, cataracts, and carcinogenesis. Ultraviolet (UV) radiation is associated with melanocytic activation and hyperplasia and is acknowledged as the primary cause of photocarcinogenesis through UV-induced DNA damage or mutation.[38,39] Therefore, patients using long-term phototherapy should receive regular skin examinations and education from doctors to reduce complications and side effects, which may also increase the diagnosis or detection of melanocytic nevi and other benign skin tumors.

Previous cohort studies reported that patients with psoriasis had an elevated risk of overall malignancy compared with the general population but reported inconsistent results on the association between psoriasis and malignant lymphomas.[40–42] In our study, a strong association was observed between psoriasis and mature T/NK-cell lymphoma. An increased risk of malignancy in patients with psoriasis could be associated with the intrinsic immunologic dysregulation of psoriasis itself, chronic inflammation, or immunomodulatory anti-psoriatic treatments. In particular, several studies have reported that the risk of malignant lymphomas in patients with psoriasis was significantly increased but only in patients who received systemic treatment, especially a TNF-α inhibitor.[40,42] Furthermore, the result showing a positive relationship between psoriasis and mature T/NK-cell lymphoma may indicate the possibility that psoriasis was misdiagnosed as cutaneous T-cell lymphomas, such as early mycosis fungoides. A recent critical review of the relationship between mycosis fungoides and psoriasis suggested that the reported higher risk of mycosis fungoides in psoriasis was derived from an initial misdiagnosis of early mycosis fungoides as psoriasis.[43] Further evidence and exact analysis are needed to overcome limitations such as the rare incidence of lymphoma, the lack of sufficient follow-up for the duration of the use of biologics, and the diagnostic inaccuracy of claim data. However, we believe that dermatologists should deliberate on these potential risks while managing patients with psoriasis until conclusive results are available.

Finally, our study also found positive associations with liver cirrhosis, hypertensive renal disease, and chronic kidney disease in patients with psoriasis. Jing et al. reported an increased risk of chronic kidney disease and end-stage renal disease in psoriasis patients. They suggested that direct damage by over-activated Th17 cell-mediated inflammation in patients with psoriasis and using drugs for psoriasis treatment can cause renal damage in patients with psoriasis.[44] Moreover, an increased risk of liver disease in patients with psoriasis induced by systemic inflammation of psoriasis and the detrimental effect of psoriasis treatment has been proposed.[45]

Our analysis revealed a decreased association between psoriasis and upper respiratory tract infections. In contrast to a previous study reporting increased pneumonia admissions in patients with psoriasis,[46] this negative association between psoriasis and upper respiratory disease has not been previously reported. Given the higher incidence of respiratory infections in patients with atopic dermatitis,[47] we can infer that distinct cytokine changes in patients with psoriasis may be associated with decreased upper respiratory infections. Further studies are needed to clarify these negative associations in different populations and investigate the underlying mechanisms.

This study had some limitations. First, psoriasis and other comorbidities were diagnosed using ICD-10 codes. We did not verify the accuracy of the diagnosis; therefore, there could have been erroneous diagnoses of psoriasis and other comorbidities. For example, parapsoriasis, lichen planus, and early lesions of mycosis fungoides are often clinically confused with psoriasis. The relationship between

psoriasis and the skin diseases analyzed in this study could be due to the initial misdiagnosis of these diseases as psoriasis. Additionally, we cannot exclude the possibility of redundancy of the diagnosis as the nature of health insurance claims data means that a classification of the same pathology is not always correlated with a single diagnosis. For example, myocardial infarction can be included in the category of ischemic heart disease, and the actual level of correlation between these comorbidities and psoriasis may be quite different from our findings. Second, since we obtained data from the HIRA, we could not randomize healthy people as controls, nor could we obtain detailed information regarding the severity and type of psoriasis and other comorbidities. Although urticaria patients in this study comprise a relatively large control group corresponding to one-fifth of the entire Korean population, discrepancies with the actual general population may exist. Moreover, given that comorbidities are more prevalent in patients with severe psoriasis or without treatment, additional subgroup studies in patients according to severity or treatment status will reveal in-depth relationships between psoriasis and comorbidities. Recent studies show that systemic therapies represented by biologics possibly reduce the risk of comorbidities, such as psoriatic arthritis, and improve the narrowing of coronary arteries in psoriasis cases, which suggests that the treatment status of psoriasis can affect the incidence of comorbidities.[48–50] Therefore, when comparing the results of the previous studies, our results that assess treatment trends over 10 years since 2011 when ustekinumab was approved for patients with psoriasis in Korea, should be considered for evolutional change in the systemic treatment for psoriasis. Third, although our study explored the association between psoriasis and other comorbidities, our results did not elucidate a causal relationship between psoriasis and comorbidities. However, this study has several advantages that deserve consideration. First, we conducted an unbiased and comprehensive investigation of the comorbidities covering all possible comorbidities in patients with psoriasis from a large sample representing a country. Second, we performed association rules mining for the comorbidities of patients with psoriasis and a history of cardiovascular events and found a pattern of association between the comorbidities. Through this association rules analysis, we conducted an in-depth investigation of the pattern of association between comorbidities in patients with psoriasis.

With the availability of large-scale databases, innovative data analysis approaches can be used in epidemiological studies. This study conducted mass screening using all ICD-10 codes and association rules mining among the comorbidities of patients with psoriasis. These strategies can be applied to a wide range of diseases and can reveal more information about disease associations.

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CONFLICT OF INTEREST STATEMENT

None declared.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study was exempted from the review by the institutional review board of Seoul National University Bundang Hospital (X-2105-686-901). The requirement for informed consent was waived because we used only de-identified data.

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SUPPORTING INFORMATION

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

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