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Psoriasis increases the risk of Sjögren's syndrome: evidence from a propensity score-matched cohort study and transcriptomic analysis

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Abstract

Background Despite the well-documented immune dysregulation in both psoriasis and Sjögren's syndrome (SS), the specific link between these two autoimmune diseases has not been extensively explored. The present study aims to investigate the impact of psoriasis on the risk of SS.

Methods A retrospective cohort study using TriNetX data compared SS development in patients with psoriasis and controls using propensity score matching, Kaplan–Meier curves, and Cox models. Transcriptome data were analyzed to identify shared differentially expressed genes and pathways between the two diseases.

Results A total of 293,905 patients with psoriasis and an equal number of individuals without psoriasis were included. After propensity score matching, the baseline characteristics of both groups were balanced. During the follow-up period, 3339 patients with psoriasis and 1937 individuals without psoriasis developed SS. The Kaplan–Meier curves indicated a significantly higher risk of developing SS in the psoriasis group compared to the non-psoriasis group. Upon adjustment for multiple confounding factors, the risk of developing SS in the psoriasis group was 50% higher in the psoriasis group than the non-psoriasis group (hazard ratio [HR] 1.50, 95% confidence interval [CI] 1.42–1.58). Subgroup analyses confirmed the elevated risk of SS associated with psoriasis. Patients with psoriatic arthritis (PsA) and those treated with biological agents had an even higher risk of developing SS. Transcriptomic analysis revealed potential shared pathogenesis of psoriasis and SS involving cellular proliferation, immune cell recruitment, cytokine secretion, and the interferon response to viral infections.

Conclusions Psoriasis might increase the risk of developing SS, which is augmented by PsA. The overlapping immunological mechanisms may underlie the co-occurrence of psoriasis and SS.

Keywords Psoriasis, Sjögren's syndrome, Propensity score matching, Risk factors

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Background

Psoriasis is a chronic autoimmune skin condition characterized by the rapid buildup of skin cells, leading to red or discolored, scaly, and pruritic patches on the skin [1]. The global prevalence of psoriasis has been estimated to be 2–3% [2]. The etiology of psoriasis is complex, involving genetic predispositions, environmental triggers, and immune system dysregulation. Proinflammatory cytokines such as tumor necrosis factor (TNF), interleukins, and interferon (IFN) are overexpressed in psoriatic patients, underlining an immunologic-genetic relationship in its pathogenesis [3]. Psoriasis significantly impacts the quality of life of patients, mainly when skin lesions are extensive or in sensitive areas, leading to psychological distress and an increased risk of depression [4]. It is also associated with several comorbidities, including psoriatic arthritis (PsA) [5, 6], type 2 diabetes [7], metabolic syndrome [8], and cardiovascular diseases [9], imposing substantial burdens on individuals and society.

Sjögren's syndrome (SS) is an autoimmune disease that primarily affects the salivary and lacrimal glands, leading to dry eye and mouth syndromes [10]. Its pathological features include local lymphocytic infiltration, epithelial damage in the target glands, and heightened reactivity of B cells producing autoantibodies [11]. Despite the well-documented immune dysregulation in both psoriasis and SS, the specific link between these two autoimmune diseases has not been extensively explored. Previous studies have reported some connective tissue diseases (CTD) observed in psoriasis, such as rheumatoid arthritis (RA) [12] and systemic lupus erythematosus (SLE) [13, 14], systemic sclerosis (SSc) [15], and fibromyalgia [16]. However, the association between SS with psoriasis may not have been considered significant enough to warrant detailed investigation.

The distinct clinical features and pathophysiological mechanisms of SS have likely contributed to the perception that psoriasis and SS are separate entities. While psoriasis is characterized by T cell activation and the IL-23/Th17 axis [17], SS is primarily driven by B cell hyperactivity, with the production of anti-SSA/SSB autoantibodies [18]. Furthermore, SS's primary involvement of exocrine glands, as opposed to psoriasis's effects on the skin, has led to a further separation of these conditions in research. Although there are several case reports on the association of psoriasis and SS [19], there is a lack of large-scale cohort studies specifically designed to investigate the comorbidity between psoriasis and SS. Therefore, further investigation involving larger populations is warranted to determine whether psoriasis is a risk factor for the development of SS.

Our study utilized the TriNetX database, a global collaborative health research network offering real-time electronic medical record data [20]. We applied propensity score matching (PSM) [20–22] to match patients with psoriasis to those without, aiming to compare the risk of subsequent SS diagnosis between patients with and without psoriasis. Furthermore, we utilized transcriptomic data to explore the potential molecular mechanisms shared between psoriasis and SS. Our findings may offer new insights for clinical practice and provide more personalized treatment and prevention recommendations for patients with psoriasis.

Methods

Data source

This retrospective cohort study used de-identified electronic health records from TriNetX (https://trinetx.com/), a large collaborative network in the USA comprising data from around 118 million patients [23–25]. Our research adheres to data privacy standards, including the Health Insurance Portability and Accountability Act (HIPAA) in the USA and the General Data Protection Regulation (GDPR) in Europe, and was approved by Chung Shan Medical University Hospital (Institutional Review Board, CSMUH No: CS2-21176).

Study design and population

A retrospective cohort design was employed to investigate the association between psoriasis and subsequent development of SS. Adults aged ≥ 20 years with records from 2004 to 2022 were included in the TriNetX database. Case group selection criteria: Patients diagnosed with psoriasis using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code L40. Inclusion required at least 2 instances of ICD-10 code for psoriasis during the period. Control group selection criteria: Non-psoriasis patients were identified using the ICD-10-CM code Z00. Exclusion criteria: To minimize potential reverse causality, patients with a prior diagnosis of SS (ICD-10-CM code M35.0) before the index date were excluded from both cohorts.

Covariates

To address potential confounding, comprehensive baseline variables were included, encompassing demographic characteristics (age, sex, race, and body mass index [BMI]), socioeconomic status, lifestyle habits (tobacco use, nicotine dependence, alcohol-related disorders), comorbidities (hypertensive diseases, disorders of lipoprotein metabolism and other lipidemias, diabetes mellitus, depressive episode, ischemic heart diseases, diseases of liver, cerebrovascular diseases and other connective tissue diseases [CTD]), medical utilization (ambulatory, emergency and inpatient encounter), and medications (hormones/synthetics/modifiers

and antirheumatics). The specific ICD-10-CM codes for these factors and medication or biological agent codes in TriNetX dataset are detailed in Additional file 1: Table S1-2.

Outcome

The primary outcome was the initial diagnosis of SS identified by ICD-10-CM code M35.0.

Statistical analysis in the cohort study

PSM was conducted based on baseline characteristics, including demographic features, lifestyle factors, and comorbidities, at a 1:1 ratio with a 0.1σ caliper. Baseline characteristics were compared across psoriasis and non-psoriasis groups using *T*-test (continuous) or *Z*-test (categorical). The standardized mean difference (SMD) was used to signify the baseline characteristics of the individuals between the two cohorts after PSM. An SMD < 0.1 is commonly considered a slight difference.

Descriptive statistics were used to compare baseline characteristics pre- and post-matching, with *T*-tests for continuous variables and *Z*-tests for categorical variables. Kaplan–Meier curves were used to estimate the cumulative incidence of SS over time, stratified by the presence or absence of the disease. Event-free survival was compared between strata using the log-rank test.

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the prospective association between baseline psoriasis and incident SS. Three models with increasing adjustments were fitted: Model 1 matched for age, sex, race, socioeconomic status, BMI, and medical utilization; Model 2 additionally matched for comorbidities; Model 3 further matched for medication use. Additionally, to evaluate the robustness of the results, this study utilized TriNetX's APAC (Asia–Pacific) and EMEA (Europe, Middle East, and Africa) networks for analytical validation.

Subgroup analyses were conducted to examine how factors such as age, sex, race, socioeconomic status, BMI, medical utilization, comorbidities, and medication use might modify the association between psoriasis and SS. For each subgroup of individuals with psoriasis, PSM was applied to match an equal number of individuals without psoriasis on a 1:1 ratio, based on these covariates. This approach ensured balanced comparison groups. HRs were then calculated for each subgroup using the matched pairs.

All statistical analyses were conducted on the TriNetX platform, which relies on the built-in statistical software R 4.0.2.

Transcriptome data acquisition and shared differentially expressed gene analysis

Gene expression data for psoriasis and SS were obtained from the Gene Expression Omnibus (GEO) database, including skin biopsies from patients with psoriasis (GSE30999) [26] and parotid gland tissues from patients with SS (GSE40611) [27]. The "limma" package [28] was used for differential gene expression analysis, identifying differentially expressed genes (DEGs) based on log2 fold change and adjusted *P*-value thresholds, with the Benjamini–Hochberg procedure applied to correct multiple testing. Visualization of DEGs was facilitated through a volcano and Venn diagrams. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment were analyzed using the "clusterProfiler" package [29]. The results of the enrichment analyses were visualized by bar charts.

Construction of protein–protein interaction network and hub gene selection

The STRING database was utilized to establish a protein–protein interaction (PPI) network for the shared DEGs [30], with gene modules identified using the Markov Cluster (MCL) algorithm, and further analyzed in Cytoscape [31]. The CytoHubba plug-in was employed to select hub genes, which were then analyzed using the GeneMANIA platform to construct a detailed gene co-expression network.

Results

Baseline characteristics before and after propensity score matching

We identified 302,019 patients aged ≥ 20 years with two or more visits diagnosed with psoriasis from 2004 to 2022 and compared them to a control group of 11,953,795 individuals without psoriasis. Following the exclusion of cases of SS diagnosed before the index date and performing PSM, both the psoriasis and non-psoriasis cohorts ultimately consisted of 293,905 patients each, as shown in Fig. 1. The mean follow-up time was 4.61 years, with a total follow-up of 1,580,527 person-years in the non-psoriasis group, and 5.61 years, with a total follow-up of 1,832,753 person-years in the psoriasis group. Table 1 details the demographic characteristics, socioeconomic status, lifestyle habits, comorbidities, and medication usage for both groups before and after PSM.

Before PSM, patients in the psoriasis cohort were older at the index than the non-psoriasis cohort, with mean ages of 51.44 ± 15.33 years *vs* 47.60 ± 17.03 years. The psoriasis group had a higher percentage of Whites and a lower percentage of Blacks, African Americans, and Asians than the control group. It also exhibited higher

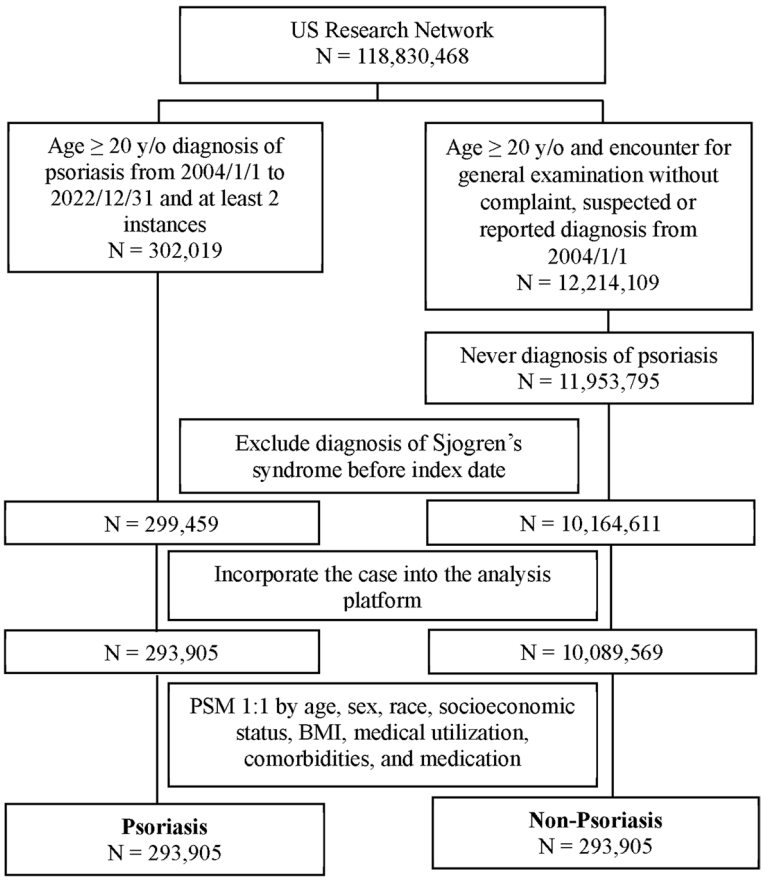

Fig. 1 Flow chart of exclusion criteria in the final cohort from the TriNetX network. BMI: body mass index. PSM: Propensity score matching

BMI, tobacco use, and nicotine dependence rates. After PSM, the two cohorts were closely aligned regarding these factors, with the SMDs below 0.1 (Table 1).

Risk of SS in patients with psoriasis compared to non-psoriasis patients

The risks of developing SS were evaluated in the propensity score-matched psoriasis and control cohorts. Among 293,905 patients with psoriasis during the follow-up period, 3339 developed SS. In the matched non-psoriasis cohort of 293,905 individuals, after matching for various factors in Models 1–3, the number of patients who developed SS were 1659, 1825, and 1937, corresponding to HR of 1.76 (95% CI 1.66–1.87), 1.60 (95% CI 1.51–1.69), and 1.50 (95% CI 1.42–1.58), respectively (Table 2). The Kaplan–Meier curve also revealed a higher risk of incident SS in the psoriasis cohort compared to the control cohort (Fig. 2). Subgroup analyses also confirmed the elevated risk of SS associated with psoriasis. They showed that the risk may vary slightly according to age, sex, race, lifestyle habits, and comorbidities (Fig. 3, Additional file 1: Table S3).

Risk of developing SS in patients with PsA and in patients with psoriasis on biological drugs

We additionally investigated the impact of PsA and the use of biological agents on the risk of developing SS. Patients with PsA were found to have a significantly higher risk of developing SS than those with cutaneous psoriasis alone (HR 2.27, 95% CI 2.06–2.49, Table 2). Furthermore, treatment with biological agents seemed to be associated with an increased risk of SS in patients with psoriasis (HR 1.66, 95% CI 1.44–1.91, Table 2).

Risk of SS in patients with psoriasis compared to those without psoriasis in different TriNetX network database

The risk of developing SS in patients with psoriasis was further evaluated across different geographic regions. The APAC (Asia–Pacific) network showed a higher incidence of SS compared to the EMEA (Europe, Middle East, and Africa) network in both the psoriasis cohort (2.15% *vs* 0.23%) and the non-psoriasis cohort (0.52% *vs* 0.06%). Notably, in the APAC network, psoriasis was linked to a higher risk of SS compared to the non-psoriasis cohort (HR 2.51, 95% CI 1.83–3.41), and

Table 1 Demographic characteristics of patients with psoriasis and non-psoriasis individuals

	Before PSM matching				After PSM matching			
	Psoriasis *N* = 293,905	**Non-psoriasis *N* = 10,089,569**	***p***	**SMD**	**Psoriasis *N* = 293,905**	**Non-psoriasis *N* = 293,905**	***p***	**SMD**
Age, Mean ± SD	51.44 ± 15.33	47.60 ± 17.03	< 0.001	0.237	51.44 ± 15.33	51.45 ± 15.33	0.873	< 0.001
Sex (%)								
Female	154,802 (52.67)	5,420,180 (53.72)	< 0.001	0.021	154,802 (52.67)	154,834 (52.68)	0.933	< 0.001
Male	124,661 (42.42)	4,088,503 (40.52)	< 0.001	0.038	124,661 (42.42)	122,836 (41.79)	< 0.001	0.013
Unknown gender	14,442 (4.91)	580,886 (5.76)	< 0.001	0.038	14,442 (4.91)	16,235 (5.52)	< 0.001	0.027
Race (%)								
White	223,044 (75.89)	6,342,879 (62.87)	< 0.001	0.285	223,044 (75.89)	223,066 (75.90)	0.947	< 0.001
Black or African American	14,406 (4.90)	1,286,954 (12.76)	< 0.001	0.280	14,406 (4.90)	14,386 (4.90)	0.904	< 0.001
Asian	8861 (3.02)	404,728 (4.01)	< 0.001	0.054	8861 (3.02)	9052 (3.08)	0.147	0.004
Other/ unknown race	47,594 (16.19)	2,055,008 (20.37)	< 0.001	0.054	47,594 (16.19)	47,401 (16.13)	0.147	0.004
BMI (%)								
< 18.5	2052 (0.70)	92,154 (0.91)	< 0.001	0.024	2052 (0.70)	3027 (1.03)	< 0.001	0.036
18.5–24.9	23,573 (8.02)	992,430 (9.84)	< 0.001	0.064	23,573 (8.02)	32,437 (11.04)	< 0.001	0.103
25–29.9	34,943 (11.89)	1,222,169 (12.11)	< 0.001	0.007	34,943 (11.89)	42,383 (14.42)	< 0.001	0.075
≥ 30	53,895 (18.34)	1,469,180 (14.56)	< 0.001	0.102	53,895 (18.34)	50,842 (17.30)	< 0.001	0.027
Mean ± SD	31.16 ± 7.79	29.55 ± 7.23	< 0.001	0.214	31.16 ± 7.79	29.68 ± 7.19	< 0.001	0.197
Persons with potential health hazards related to socioeconomic and psychosocial circumstances (%)	1465 (0.50)	68,139 (0.68)	< 0.001	0.023	1465 (0.50)	1461 (0.50)	0.941	< 0.001
Tobacco use (%)	3019 (1.03)	100,539 (1.00)	0.098	0.003	3019 (1.03)	3698 (1.26)	< 0.001	0.022
Personal history of nicotine dependence (%)	8998 (3.06)	259,049 (2.57)	< 0.001	0.030	8998 (3.06)	9759 (3.32)	< 0.001	0.015
Medical utilization (%)								
Ambulatory	178,828 (60.85)	5,434,826 (53.87)	< 0.001	0.141	178,828 (60.85)	178,853 (60.85)	0.947	< 0.001
Emergency	26,089 (8.88)	820,941 (8.14)	< 0.001	0.027	26,089 (8.88)	26,155 (8.90)	0.762	0.001
Inpatient Encounter	17,075 (5.81)	557,968 (5.53)	< 0.001	0.012	17,075 (5.81)	19,672 (6.69)	< 0.001	0.037
Comorbidities (%)								
Nicotine dependence	12,610 (4.29)	332,724 (3.30)	< 0.001	0.052	12,610 (4.29)	11,841 (4.03)	< 0.001	0.013
Alcohol related disorders	3608 (1.23)	91,069 (0.90)	< 0.001	0.032	3608 (1.23)	3097 (1.05)	< 0.001	0.016
Hypertensive diseases	55,293 (18.81)	1,686,276 (16.71)	< 0.001	0.055	55,293 (18.81)	55,293 (18.81)	1.000	< 0.001
Disorders of lipoprotein metabolism and other lipidemias	46,482 (15.82)	1,389,264 (13.77)	< 0.001	0.058	46,482 (15.82)	49,502 (16.84)	< 0.001	0.028
Diabetes mellitus	26,074 (8.87)	720,216 (7.14)	< 0.001	0.064	26,074 (8.87)	26,048 (8.86)	0.905	< 0.001
Depressive episode	16,394 (5.58)	466,098 (4.62)	< 0.001	0.044	16,394 (5.58)	16,514 (5.62)	0.496	0.002
Ischemic heart diseases	12,807 (4.36)	369,715 (3.66)	< 0.001	0.035	12,807 (4.36)	12,844 (4.37)	0.813	0.001
Diseases of liver	8139 (2.77)	169,911 (1.68)	< 0.001	0.074	8139 (2.77)	6573 (2.24)	< 0.001	0.034
Cerebrovascular diseases	5167 (1.76)	170,743 (1.69)	0.006	0.005	5167 (1.76)	5798 (1.97)	< 0.001	0.016
Rheumatoid arthritis with rheumatoid factor	1164 (0.40)	14,519 (0.14)	< 0.001	0.049	1164 (0.40)	1401 (0.48)	< 0.001	0.012

Table 1 (continued)

	Before PSM matching				After PSM matching			
	Psoriasis *N* = 293,905	Non-psoriasis *N* = 10,089,569	*p*	SMD	Psoriasis *N* = 293,905	Non-psoriasis *N* = 293,905	*p*	SMD
Other rheumatoid arthritis	7287 (2.48)	53,389 (0.53)	< 0.001	0.161	7287 (2.48)	7249 (2.47)	0.750	0.001
Wegener's granulomatosis	86 (0.03)	1423 (0.01)	< 0.001	0.010	86 (0.03)	68 (0.02)	0.147	0.004
Microscopic polyangiitis	11 (0.00)	200 (0.00)	0.037	0.003	11 (0.00)	10 (0.00)	0.827	0.001
Systemic lupus erythematosus	1127 (0.38)	19,037 (0.19)	< 0.001	0.036	1127 (0.38)	778 (0.27)	< 0.001	0.021
Dermatopolymyositis	191 (0.07)	2862 (0.03)	< 0.001	0.017	191 (0.07)	128 (0.04)	< 0.001	0.009
Systemic sclerosis	189 (0.06)	4019 (0.04)	< 0.001	0.011	189 (0.06)	164 (0.06)	0.183	0.003
Medications (%)								
Hormones/synthetics/modifiers	88,842 (30.23)	2,147,353 (21.28)	< 0.001	0.206	88,842 (30.23)	88,861 (30.24)	0.957	< 0.001
Antirheumatics	45,866 (15.61)	1,043,371 (10.34)	< 0.001	0.157	45,866 (15.61)	37,623 (12.80)	< 0.001	0.080

BMI body mass index, *PSM* propensity score matching, *SMD* standardized mean difference

Table 2 Risk of Sjogren's syndrome in patients with psoriasis compared to non-psoriasis individuals

	N	Follow-up time (person-years)	No. of SS	Cumulative incidence (%)	Incidence rate (cases/1000 person-years)	HR (95% C.I.)
Model 1						
Non-psoriasis	293,905	1,591,701	1659	2.54	1.04	Reference
Psoriasis	293,905	1,832,753	3339	3.32	1.82	1.76 (1.66–1.87)
Model 2						
Non-psoriasis	293,905	1,590,991	1825	2.65	1.15	Reference
Psoriasis	293,905	1,832,753	3339	3.32	1.82	1.60 (1.51–1.69)
Model 3						
Non-psoriasis	293,905	1,580,527	1937	2.88	1.23	Reference
Psoriasis	293,905	1,832,753	3339	3.32	1.82	1.50 (1.42–1.58)
Group						
Psoriasis without PsA	72,242	450,869	623	2.79	1.38	Reference
Psoriatic arthritis	72,242	419,248	1319	4.66	3.15	2.27 (2.06–2.49)
Group						
Psoriasis without biological agents	30,819	185,177	325	2.90	1.76	Reference
Psoriasis with biological agents	30,819	165,402	488	4.79	2.95	1.66 (1.44–1.91)

BMI body mass index, *PsA* psoriatic arthritis, *SS* Sjogren's syndrome, *HR* hazard ratio, *CI* confidence interval

Model 1: Propensity matching by age, sex, race, socioeconomic status, BMI, and medical utilization

Model 2: Propensity matching by age, sex, race, socioeconomic status, BMI, medical utilization, and comorbidities

Model 3: Propensity matching by age, sex, race, socioeconomic status, BMI, medical utilization, comorbidities, and medication

similarly in the EMEA network (HR 3.29, 95% CI 1.39–7.77, Additional file 1: Table S4). Regardless, in both networks, psoriasis was associated with higher risk of subsequent SS diagnosis.

Identification of shared DEGs and pathways in psoriasis and SS

To explore the molecular link between psoriasis and SS, we analyzed differential gene expression in affected tissues. In psoriasis, we identified 2221 upregulated and

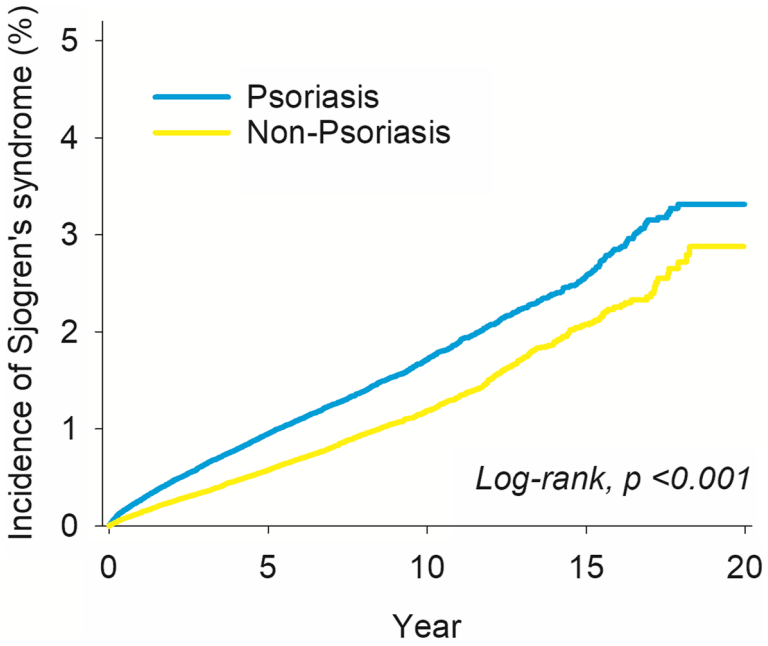

Fig. 2 Kaplan–Meier's analysis of the risk of Sjogren's syndrome among patients with psoriasis was compared with that of the non-psoriasis group

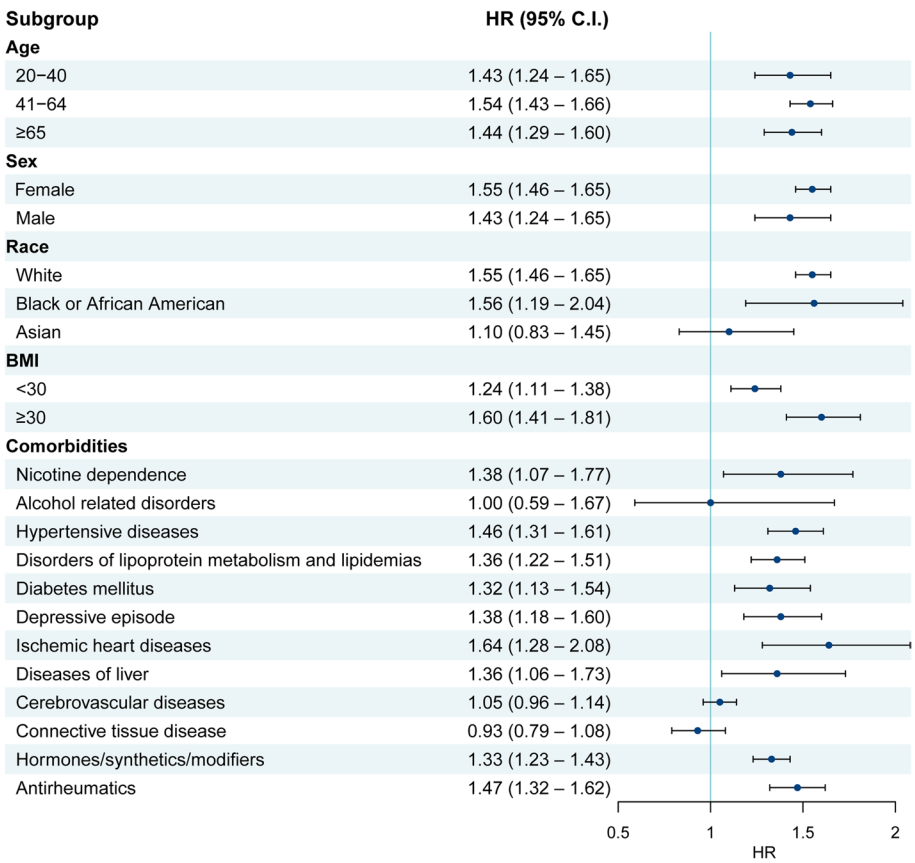

Fig. 3 Forest plot for subgroup analysis of the risk of Sjogren's syndrome exposed to psoriasis compared to the non-psoriasis group. BMI: body mass index

2443 downregulated genes in skin tissue (Additional file 1: Fig. S1A), while SS exhibited 1291 upregulated and 1223 downregulated genes in salivary gland tissue (Additional file 1: Fig. S1B).

Convergence in disease pathology was evident with 320 commonly upregulated genes in both conditions, which are linked to immune response pathways such as JAK-STAT, Toll, NF-κB, and TNF and are involved in processes like viral infection and cytokine signaling (Additional file 1: Fig. S1C,D, Additional file 1: Table S5). Conversely, 170 genes were commonly downregulated, associated with exocrine gland development and metabolic pathways, including AMPK and insulin signaling (Additional file 1: Fig. S1C, E, Additional file 1: Table S6).

PPI network analysis identified three key gene modules via the MCL algorithm. Module 1 was significantly enriched in genes linked to cell proliferation and replication, such as CDC20, MKI67, and CCNA2. Module 2 contained genes involved in immune responses, including cytokines (TNF), chemokines (CXCL9, CXCL10, CXCL13), and T-cell markers (CD3D, CD8A, GZMK), suggesting shared inflammatory mechanisms. Module 3 was particularly enriched in genes associated with the IFN response and antiviral defense, such as IFI44, IFI21, IFIT3, DDX60, AIM2, OAS1, and OAS3, highlighting their role in viral recognition and IFN synthesis (Additional file 1: Fig. S2A-E). The top-hub genes in modules 2 and 3 may serve as central targets in psoriasis and SS pathogenesis (Additional file 1: Fig. S2F-G). Together, these findings indicate that pathways involving cellular proliferation, immune cell recruitment, cytokine release, and the IFN response to viral challenges are likely shared in the etiology of both conditions.

Discussion

In our study, leveraging the expansive TriNetX network data, we discovered a significantly elevated risk of SS in patients with psoriasis after PSM for confounders. We also found that patients with PsA and those treated with biological agents had an even higher risk of developing SS. Moreover, transcriptomic analysis suggests that shared pathological mechanisms between these diseases may include cellular proliferation, immune recruitment, cytokine release, and IFN response to viral infections.

Our research reveals that psoriasis markedly increases the risk of SS, suggesting shared pathogenic mechanisms [32]. Genetic predisposition may influence both conditions, with overlapping loci such as HLA alleles indicating a common autoimmune susceptibility [33, 34].

Our transcriptome analysis shows a significant overlap in immune gene dysregulation between psoriasis and SS, implying a common pathogenic foundation. We found cytokine signaling, T-cell activation, antiviral response genes, and critical autoimmunity-related pathways, including IFN, TNF, JAK-STAT, Toll, and NF-κB, are elevated in both conditions. Activating NF-κB and the JAK-STAT could lead to autoantibody-producing B cells in SS and maintaining the inflammatory state in psoriasis [35]. TNF-α, overexpressed in SS saliva and psoriasis lesions, can suppress AQP5, affecting salivary secretion and boosting autoantibody levels [35–37]. Therapies targeting TNF, including infliximab, adalimumab, and etanercept, have proven effective in treating moderate to severe plaque psoriasis [38]. The activation of Toll and IFN may reflect virus infection in SS and psoriasis, with human immunodeficiency virus (HIV) and hepatitis C virus (HepC) known to exacerbate both conditions [39, 40].

Our findings indicate that the T cell activation pathway and associated markers were upregulated in psoriasis and SS, indicating an augmented T cell-mediated immune response. Psoriasis is marked by heightened activity of Th1 and Th17 cells, which release proinflammatory cytokines, including IFN-γ, TNF-α, IL-17, and IL-23 [35]. Similarly, in SS, increased Th1 and Th17 cells in glandular tissue may drive local inflammation and ectopic lymphoid tissue formation [41]. $CD8^+$ T cells, involved in exocrine gland damage in SS, are also found in psoriatic lesions, suggesting a possible link to arthritis development [42, 43]. Our transcriptome data may potentially explain the increased clinical observation of SS risk in patients with psoriasis.

Our subgroup analyses further confirmed the elevated risk of SS in patients with psoriasis, with significantly higher SS incidence observed in most subgroups within the psoriasis cohort compared to the control cohort. The incidence also varied by age, sex, and ethnicity, potentially reflecting the influence of genetic predispositions, socioeconomic factors, and disparities in healthcare access [44]. However, psoriasis did not increase the risk of SS in the Asian population, individuals with alcohol-related disorders or those in the CTD groups. This lack of association may be due to the relatively small sample sizes within these subgroups, which could have limited the statistical power to detect significant relationships. These findings indicate the need for personalized screening and management strategies for patients with psoriasis.

We also investigated the influence of PsA and the use of biological agents on the risk of developing SS. Our findings indicate that PsA, characterized by skin and joint inflammation, significantly increases SS susceptibility due to severe systemic inflammation and immune dysregulation, potentially predisposing patients to additional autoimmune conditions [45]. Biologics targeting specific inflammatory pathways like TNF, IL-17, and IL-23 have revolutionized psoriasis treatment, offering

high response rates and long-term remission [46–48]. Additionally, small-molecule inhibitors, which modulate intracellular immune pathways, provide alternative options for patients who are unresponsive to biologics or experience side effects, offering broader therapeutic choices for moderate-to-severe cases [49]. Contrary to current understanding, our study suggests that the use of biological agents may also elevate the risk of SS. While these treatments are known to raise the risk of malignancy [50], severe infections [51], and cardiovascular events in psoriasis [52], no direct association with SS or other autoimmune diseases has been previously established. We suspect that biological drug use in this study is a marker for more severe psoriasis and PsA. Further research is needed to confirm whether biological agents indeed heighten the risk of SS.

The association between psoriasis and CTDs reflects a broader trend of autoimmune overlap but shows notable variability among diseases. Patients with psoriasis have been found to face higher risks of CTDs, including RA and SLE, with adjusted HRs of 1.63 and 1.86, respectively [13]. These findings suggest some shared immunopathogenic mechanisms, such as Th17-mediated inflammation. Interestingly, even after adjusting for CTDs as covariates in our study, psoriasis was still significantly associated with an elevated risk of SS. Our finding suggests that the impact of psoriasis on SS may involve some mechanisms distinct from other CTDs.

Our study has several strengths, such as the large sample size, using PSM to balance the baseline characteristics, adjusting multiple confounders, and validating the results in different datasets. However, several limitations are present. First, the TriNetX network data are based on electronic health records, which may have inherent biases, such as coding errors, missing data, and misclassification. Additionally, the diagnosis of psoriasis and SS was based on ICD-10-CM codes, which may not reflect the clinical criteria or the disease severity. Second, although we found a significant association between psoriasis and SS, "screening bias" may influence these results. Patients with psoriasis, especially those with PsA, are more likely to undergo screening for other autoimmune diseases if they show symptoms like arthritis. This increased surveillance, including antinuclear antibody(ANA) testing, may lead to a higher diagnosis rate of SS in PsA patients, potentially reflecting more frequent screening rather than a true increase in incidence. Another potential bias is the potential role of vitamin D deficiency in patients with psoriasis. Reduced sun exposure due to covering lesions may lead to lower vitamin D levels, which are known to contribute to immune dysregulation and exacerbate autoimmune diseases like SS [53]. Although we could not assess vitamin D levels, this factor warrants further investigation as a modifiable risk factor in future studies linking psoriasis and SS. Third, due to the lack of data, we could not evaluate the role of other potential risk factors, such as viral infections, hormonal factors, and autoantibodies. Furthermore, we were unable to evaluate the impact of psoriasis progression over time due to the limitations of the TriNetX platform, which lacks data on disease severity or duration. This limitation underscores the need for future longitudinal studies with detailed clinical data to better understand how psoriasis progression may influence SS onset. Fourth, we could not perform a causal inference analysis, as the data were observational and not randomized. Finally, the relatively low incidence rate of SS in psoriasis could potentially limit the immediate clinical actionability of our findings. However, we excluded the patients with SS before the index date to minimize potential bias, so the actual frequency of SS was underestimated in the present study. Therefore, future studies could confirm our findings with robust methods such as prospective cohorts and randomized trials, and explore the molecular links between psoriasis and SS to identify biomarkers and therapeutic targets for SS management in psoriasis patients.

Conclusions

Our study suggests that psoriasis is a risk factor for SS and that the risk may vary slightly according to age, sex, race, lifestyle habits, and comorbidities. PsA may augment the risk of developing SS. The overlapping immunological mechanisms may underlie the co-occurrence of psoriasis and SS.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03856-y.

Additional file 1: Table S1. Variable definition by ICD-10-CM codes in the TriNetX dataset. **Table S2**. Medication or biological agents codes in TriNetX dataset. **Table S3**. Subgroup analysis of risk of Sjogren's syndrome in psoriasis patients compared to non-psoriasis individuanls. **Table S4**. Risk of Sjogren's syndrome in psoriasis patients compared to non-psoriasis patients in different TriNetX network databases. **Table S5**. Genes significantly upregulated in both psoriasis and Sjögren's syndrome. **Table S6**. Genes significantly downregulated in both psoriasis and Sjögren's syndrome. **Fig. S1**. Identification of shared DEGs between psoriasis and Sjogren's syndrome. **Fig. S2**. Visualization of the PPI network by STRING.

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Authors' contributions

S-MD conceived the idea and designed the study. JCW and Y-HW extracted the data. Y-HW, ZK, and YD analyzed the data. ZK and YD wrote the manuscript. RC, QW, MC, and Y-HW discussed the data and helped refine the manuscript. S-MD and JCW critically reviewed the manuscript and are responsible

for the overall content as the guarantors. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The TriNetX platform is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR). The Western Institutional Review Board has granted TriNetX a waiver of informed consent since this platform only aggregated counts and statistical summaries of deidentified information. The present study was approved under the authority of the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH No: CS2-21176).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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