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Risk of acute infections in patients with psoriasis:

A National Health Insurance Service–National Sample Cohort–based study

건선 환자의 급성 감염 발생 위험:

국민건강보험공단 표본 코호트 연구

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Abstract

Risk of acute infections in patients with psoriasis:

A National Health Insurance Service–National Sample Cohort–based study

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Patients with psoriasis have a higher risk of hospitalization for acute infections. However, the impact of psoriasis on milder cases of infection treated in outpatient settings is unknown. We aimed to examine the association of psoriasis with the risk of acute infection including inpatient, outpatient, and emergency room visits and whether the risk of acute infection was associated with systemic antipsoriatic treatment using a large national cohort.

Nationwide retrospective cohort study of 629,527 adults 20 to 70 years of age with no history of psoriasis at baseline were included and followed–up to 10 years (January 1, 2003 to December 31, 2013). The study exposure was psoriasis development, considered to be a time–varying variable. The study endpoint was the development of acute infectious diseases identified from claims from inpatient, outpatient, or emergency room visits over 10 years. We calculated the number of episodes of acute

infectious disease and calculated rate ratios (RRs) with 95% confidence intervals for developing acute infectious diseases using a multivariable Poisson regression model.

Over the follow up, 16,383 (2.6%) developed psoriasis, and the total number of episodes of acute infectious disease was 9,690,990 (15,435 per 10,000 person-years). The majority of episodes were outpatient clinic visits (99.2%). The multivariable-adjusted RR for incident episodes of acute infectious disease comparing patients with to those without psoriasis was 1.89 (95% CI 1.83, 1.94). The corresponding RRs for outpatient and inpatient or emergency room visits were 1.88 (95% CI 1.83, 1.94) and 2.07 (95% CI, 1.74, 2.47), respectively. The overall rates of infection were similar in patients with psoriasis who received systemic treatment compared with those who did not (RR 1.03; 95% CI, 0.95, 1.13).

In conclusion, we showed that patients with psoriasis had a higher risk of acute infections. The increased risk was largely independent of systemic antipsoriatic treatment. Further research is necessary to understand the biological mechanisms underlying the association between psoriasis and infection.

Keywords : cohort study, comorbidity, epidemiology, infection, outpatient, psoriasis

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Introduction

Psoriasis is a common chronic inflammatory disease affecting 1-3% of the general population.[1] Although psoriasis affects primarily the skin, it is considered as a systemic disease characterized by immune system dysfunction and the production of pro-inflammatory cytokines.[2-5] Psoriasis is associated with multiple comorbidities related to systemic inflammation, including cardiovascular disease, obesity, metabolic syndrome, and diabetes,[6-8] and there is substantial interest in identifying the full spectrum of psoriasis-related comorbidities to better understand the clinical burden associated with the disease.

Two prospective studies have identified an increased risk of severe infection requiring hospitalization associated with psoriasis. In a population-based study in the Netherlands, psoriasis patients had double the risk of serious infections requiring hospitalization compared to the general population, particularly respiratory tract, abdominal, and skin infections.[9] In addition, a study in Taiwan, reported a 40% higher risk of hospitalization for pneumonia in patients with compared to those without psoriasis.[10] A higher risk of infection in patients with psoriasis could be related to the underlying immune dysfunction in psoriasis,[10-13] to side effects of

therapy, including conventional systemic immunosuppressants and some biologics,[14–18] or to psoriasis–related comorbidities such as obesity or diabetes mellitus.[6–8]

While hospital admission for infection is an important clinical outcome, most infections do not require hospitalization, and using inpatient data is likely to markedly underestimate the burden of disease associated with psoriasis. In fact, very little is known on the impact of psoriasis on milder cases of infection which may, nonetheless, have major consequences in terms of disease burden and quality of life.

In this study, we aimed to evaluate the overall excess risk of incident acute infections, including inpatient, outpatient, and emergency room visits, in patients with psoriasis compared to the general population using a nationally representative sample. In addition, we evaluated whether the risk of acute infection was associated with systemic immunomodulatory or immunosuppressive antipsoriatic treatment.

Methods

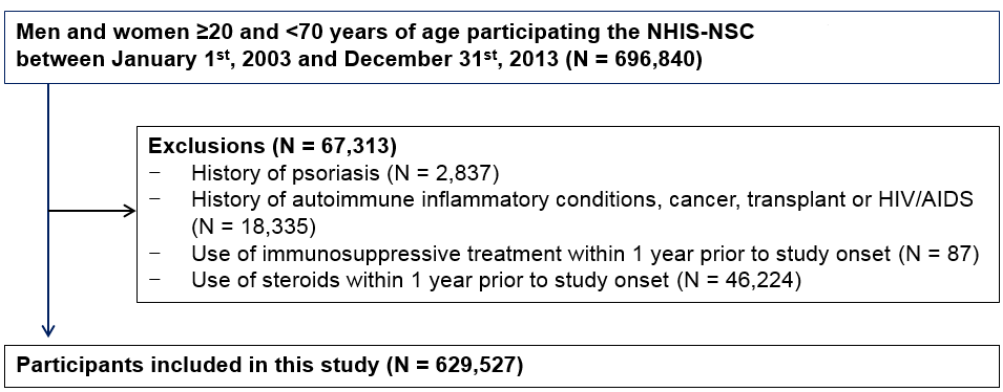
Study population and design

We used data from the National Health Insurance Service – National Sample Cohort (NHIS–NSC), a population–based cohort consisting of a representative sample of 2.2% of Korean citizens enrolled in the NHIS. The NHIS is Korea's mandatory universal single–payer national healthcare system, and it keeps records of all inpatient and outpatient visits, procedures, and prescriptions in South Korea. NHIS–NSC consists of a systematic stratified random sample with proportional allocation within each stratum. The sampling procedures and representativeness of the cohort are described in detail elsewhere.[19]

We used person–level longitudinal NHIS–NSC registration and claims data between January 1, 2002 and December 31, 2013.[19] For this study, we included all men and women 20 to 70 years of age in the NHIS–NSC between January 1, 2003 and December 31, 2013 (N = 696,840). Since we wanted to evaluate new–onset cases of psoriasis (to avoid biases introduced by prevalent cases of disease) and rule out the effects of variables affecting the development of infectious diseases, we excluded participants who had claims for psoriasis (N = 2,837), use of immunosuppressive agents (N = 87)

or steroids (N = 46,224), or immune function-related diseases (N = 18,335) in the 1-year prior to the onset of follow-up (January 1 to December 31, 2002). Immune function-related diseases included autoimmune inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and ankylosing spondylitis, cancer, transplant recipients, and human immunodeficiency virus infection or acquired immunodeficiency syndrome (HIV/AIDS). The final sample size was 629,527 (320,072 men and 309,455 women; Figure 1). The Institutional Review Board of the Samsung Medical Center approved this study (IRB number SMC 2018-02-137) and waived the requirement for informed consent as we used only de-identified data.

Figure 1. Flowchart of study participants



Data collection

We used three databases from the NHIS–NSC including insurance eligibility, medical treatments, and medical care institutions. The insurance eligibility database contains information on age, gender, residential area, type of health insurance, income level, and disability. The medical treatment database contains information from treatment bills, including details of diseases and prescriptions.

NHIS claims for inpatient and outpatient visits, procedures, and prescriptions were coded using the International Classification of Diseases, 10th Revision (ICD-10) and the Korean Drug and Anatomical Therapeutic Chemical Codes.[20,21] NHIS routinely audits the claims, and the data are considered reliable and have been used in numerous peer-reviewed publications.[19,20,22]

Psoriasis was defined as the presence of at least two L40 code in a year. Acute infectious diseases were defined using ICD-10 codes and categorized into six main categories on the basis of existing literature:[7,9,23] respiratory tract infections; gastrointestinal infections; kidney, urinary tract, and bladder infections; skin and soft-tissue infections except psoriasis; reproductive organ infections; and sexually transmitted infections (Table 1).

To assess the risk of acute infections associated with systemic

therapies, treatment codes for cyclosporine, methotrexate, oral retinoids, ultraviolet B phototherapy, photochemotherapy, etanercept, infliximab, adalimumab, and ustekinumab were reviewed and categorized (Table 2).

Comorbidities at baseline were defined as the presence of at least one relevant ICD-10 codes between January 1 to December 31, 2002. Baseline comorbidities included diabetes (E10–E14), hypertension (I10–I13 or I15), hyperlipidemia (E78), chronic obstructive pulmonary disease (COPD; J40–J46) and asthma (J45 or J46).

Table 1. ICD-10 codes used to define acute infectious diseases

Category	Code
Respiratory tract infections	
Nasopharyngitis	J00
Pharyngitis	J02
Tonsillitis	J03
Upper respiratory infections	J06
Bronchitis	J20
Influenza	J09, J10, J11
Pneumonia	J12, J13, J14, J15, J16, J17, J18
Others	A22.1, A36.0, A36.1, A36.2, A54.5, J01, J04, J05, J21, J22, J36, J39.0, J39.1, J85, J86, J90
Gastrointestinal infections	
Gastroenteritis	A04, A08, A09
Appendicitis	K35, K37
Others	A00, A01, A02, A03, A05, A06, A07, A22.2, K61, K63.0, K65, K67
Kidney, urinary tract, and bladder infections	
Pyelonephritis	N12
Cystitis	N30
Urethritis	N34
Others	N10, N15.1, N16.0, N28.83, N28.84, N29.0, N29.1, N39.0
Skin and soft-tissue infections	
Impetigo	L01
Cutaneous abscess, furuncle and carbuncle	L02

Cellulitis and erysipelas	L03, A46
Herpes simplex infections	B00, A60
Herpes zoster	B02
Viral warts	B07, A63.0
Dermatophytosis and candidiasis	B35, B37
Others	A22.0, A26, B01, B03, B04, B05, B06, B08, B09, L00, L04, L05, L08, L73.9
Reproductive organ infections	
Prostatitis	N41.0
Vaginitis	N76.0
Others	N41.2, N41.3, N41.8, N41.9, N43.1, N45, N48.1, N48.2, N49, N70.0, N70.9, N71.0, N71.9, N72, N73.0, N73.2, N73.3, N73.5, N73.6, N73.8, N73.9, N75, N76.2, N76.4, N76.5, N76.6, N76.8
Sexually transmitted infections	
Syphilis	A51, A52, A53
Gonorrhoea	A54
Chlamydia	A55, A56, A74.8, A74.9
Trichomoniasis	A59
Others	A63, A64

Table 2. Drug and procedure codes to define systemic therapies

Category	Code	Route of administration
Drug		
Cyclosporine	139201ACS	Oral
	139202BIJ	Injection
	139203ALQ	Oral
	139204ACS	Oral
	139230BIJ	Injection
	194701ACH	Oral
	194701ACS	Oral
	194701ALQ	Oral
	194702ACH	Oral
	194702ACS	Oral
	194703ACS	Oral
	194730ALQ	Oral
	194731ALQ	Oral
Methotrexate	192101ATB	Oral
	192102BIJ	Injection
	192103BIJ	Injection
	192104BIJ	Injection
	192105BIJ	Injection
	192106BIJ	Injection
	192107ATB	Oral
	192107BIJ	Injection
	192108BIJ	Injection
	192109BIJ	Injection
	192110BIJ	Injection
	192111BIJ	Injection
	192132BIJ	Injection
	192134BIJ	Injection
	192136BIJ	Injection
	192138BIJ	Injection
	192139BIJ	Injection
	192140BIJ	Injection
	192141BIJ	Injection
	192142BIJ	Injection
	192143BIJ	Injection
	192144BIJ	Injection

Oral retinoids	102301ACH	Oral
	102302ACH	Oral
Etanercept	455801BIJ	Injection
	455830BIJ	Injection
	455803BIJ	Injection
	455802BIJ	Injection
	455831BIJ	Injection
Infliximab	383501BIJ	Injection
Adalimumab	488401BIJ	Injection
	488430BIJ	Injection
Ustekinumab	615001BIJ	Injection
	615030BIJ	Injection
	615002BIJ	Injection
Procedure		
Ultraviolet B phototherapy	MM331	
	MM332	
	MM333	
	MM334	
Photochemotherapy	MM341	
	MM342	
	MM343	
	MM344	

The drug code was based on the main active ingredient of the drug.

Statistical analysis

The study endpoint was the development of acute infectious diseases identified from claims from inpatient, outpatient, or emergency room visits from January 1, 2003 through December 31, 2013. When a second claim for the same infectious disease occurred within a month from the first claim, we consider both claims as part of the same infectious disease episode.[7] Participants were followed from January 1, 2003 until the development of an autoimmune inflammatory condition (rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, or ankylosing spondylitis), the development of cancer, the reception of a transplant, the development of HIV/AIDS, death, or the end of the study on December 31, 2013, whichever first.

The study exposure was psoriasis development, considered as a time-varying variable (participants who developed psoriasis contributed unexposed person-time prior to the development of psoriasis and exposed person time from the development of psoriasis until the end of follow-up). We calculated the number of episodes of acute infectious disease each year of follow-up and calculated rate ratios (RRs) with 95% confidence intervals (CIs) for developing acute infectious diseases using a multivariable Poisson

regression model. We adjusted for age (5-year categories), sex, income percentile (≤ 30th, > 30th - ≤ 70th, > 70th percentiles), diabetes (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), COPD (yes or no), and asthma (yes or no).

In addition, we performed stratified analyses to evaluate if the association between psoriasis and the risk of acute infectious diseases varied across pre-specified subgroups defined by age (< 40, ≥ 40 years), sex, diabetes (yes, no), hypertension (yes, no), hyperlipidemia (yes, no), COPD (yes, no), asthma (yes, no), and income percentile (≤ 30th, > 30th - ≤ 70th, > 70th). All analyses were performed using STATA version 14 (StataCorp LP, College Station, TX, USA).

Results

Among 629,527 participants, 16,383 (2.6%) developed psoriasis during follow-up (Table 3). Compared to participants who did not develop psoriasis, those who did were older, and more likely to be male and to have more comorbidities at baseline. Among participants with psoriasis, 2,392 (14.6%) received systemic treatment during follow-up. This subgroup was more likely to be male and younger than psoriasis patients who did not receive systemic treatment (Table 4).

Table 3. Characteristics of study participants at the beginning of follow-up (N = 629,527)

Baseline characteristic	Overall (N = 629,527)	Incident psoriasis		*P* value
		Without psoriasis (N = 613,144)	With psoriasis (N = 16,383)	
Sex				<0.001
Male	320,072 (50.8)	311,153 (50.8)	8,919 (54.4)	
Female	309,455 (49.2)	301,991 (49.3)	7,464 (45.6)	
Age (years)				<0.001
20–29	151,139 (24.0)	147,400 (24.0)	3,739 (22.8)	
30–39	169,103 (26.9)	165,010 (26.9)	4,093 (25.0)	
40–49	154,041 (24.5)	150,025 (24.5)	4,016 (24.5)	
50–59	87,645 (13.9)	85,102 (13.9)	2,543 (15.5)	
60–69	67,599 (10.7)	65,607 (10.7)	1,992 (12.2)	
Diabetes	21,121 (3.3)	20,423 (3.3)	698 (4.3)	<0.001
Hypertension	40,968 (6.5)	39,644 (6.5)	1,324 (8.1)	<0.001
Hyperlipidemia	11,197 (1.8)	10,825 (1.8)	372 (2.3)	<0.001
COPD	29,300 (4.7)	28,397 (4.6)	903 (5.5)	<0.001
Asthma	15,646 (2.5)	15,174 (2.5)	472 (2.9)	0.001
Income percentile				<0.001
$\leq 30^{th}$	149,470 (23.7)	155,176 (23.6)	4,080 (22.5)	
$>30^{th} - \leq 70^{th}$	248,600 (39.5)	242,223 (39.5)	6,377 (38.9)	
$>70^{th}$	231,457 (36.8)	225,157 (36.7)	6,300 (38.5)	

COPD, chronic obstructive pulmonary disease

Values in the Table are number (%).

Table 4. Characteristics of study participants by treatment at the beginning of follow-up (N = 16,383)

Baseline characteristic	With psoriasis and without systemic treatment † (N = 13,991)	With psoriasis and with systemic treatment † (N = 2,392)	*P* value
Sex			0.005
Male	7,553 (54.0)	1,366 (57.1)	
Female	6,438 (46.0)	1,026 (42.9)	
Age (years)			<0.001
20–29	3,145 (22.5)	594 (24.8)	
30–39	3,404 (24.3)	689 (28.8)	
40–49	3,433 (24.5)	583 (24.4)	
50–59	2,216 (15.8)	327 (13.7)	
60–69	1,793 (12.8)	199 (8.3)	
Diabetes	606 (4.3)	92 (3.9)	0.28
Hypertension	1,154 (8.3)	170 (7.1)	0.06
Hyperlipidemia	358 (2.3)	51 (1.9)	0.17
COPD	792 (5.7)	111 (4.6)	0.043
Asthma	404 (2.9)	68 (2.8)	0.90
Income			0.07
$\leq 30^{th}$	3,188 (22.8)	518 (21.7)	
$>30^{th} - \leq 70^{th}$	5,395 (38.6)	982 (41.1)	
$>70^{th}$	5,408 (38.7)	892 (37.3)	

COPD, chronic obstructive pulmonary disease

† Systemic treatment included cyclosporine, methotrexate, oral retinoids, ultraviolet B phototherapy, photochemotherapy, etanercept, infliximab, adalimumab, and ustekinumab.

The total number of episodes of acute infectious disease during follow-up was 9,690,990 (15,435 per 10,000 person-years). The two most common categories were respiratory tract infections (6,387,867 episodes; 65.9%) and skin and soft-tissue infections (1,658,346 episodes; 17.1%). The overwhelming majority of episodes of acute infectious disease were outpatient clinic visits (99.2%). The crude incidence rates of episodes of acute infectious disease in patients without and with psoriasis were 15,339 and 22,382 per 10,000 person-years, respectively (Table 5). The multivariable-adjusted RR for incident episodes of acute infectious disease comparing patients with to those without psoriasis was 1.89 (95% CI 1.83, 1.94). The corresponding RRs for outpatient and inpatient or emergency room visits were 1.88 (95% CI 1.83, 1.94) and 2.07 (95% CI, 1.74, 2.47), respectively.

The increased risk of acute infections was evident across all types of infections in both outpatient and inpatient or emergency room visits. The association was particularly strong for skin and soft-tissue infections (multivariable-adjusted RR 3.67; 95% CI 3.49, 3.86), and sexually transmitted infections (RR 1.95; 95% CI 1.58, 2.40) in overall clinic visits, and for respiratory tract infections (RR 2.58; 95% CI 1.91, 3.47) in inpatient or emergency room visits. The rates of infection, however, were similar in

psoriasis patients who were receiving systemic treatment compared to those who did not (overall RR 1.03; 95% CI 0.95, 1.13), except for an increased risk of skin and soft-tissue infections among patients receiving systemic treatment (RR 1.56; 95% CI 1.35, 1.81) (Table 6).

Finally, when we evaluated the association between psoriasis and episodes of acute infectious disease in pre-specified subgroups (Figure 2), the association was present in all subgroups, but it was stronger in men compared to women, in patients > 40 years of age compared to younger patients, in patients without hypertension, without hyperlipidemia, without COPD, or without asthma, and in patients in the lowest category of income groups.

Table 5. Rate ratios (95% CIs) for incident infections associated with psoriasis (N = 629,527)

Type of infection	Incidence rate (per 10,000 person-years)		Adjusted rate ratios (95% CI)*
	Without psoriasis (N = 613,144)	With psoriasis (N = 16,383)	
Overall visits			
All infections	15,339	22,382	1.89 (1.83, 1.94)
All infections except skin and soft tissue	12,742	16,872	1.58 (1.53, 1.63)
Respiratory tract	10,129	13,400	1.54 (1.49, 1.59)
Gastrointestinal	647	951	1.69 (1.57, 1.83)
Kidney, urinary tract, and bladder	709	928	1.64 (1.47, 1.82)
Skin and soft-tissue	2,601	5,510	3.67 (3.49, 3.86)
Reproductive organ	1,151	1,446	1.61 (1.48, 1.76)
Sexually transmitted	122	147	1.95 (1.58, 2.40)
Outpatient clinic visits			
All infections	15,230	22,196	1.88 (1.83, 1.94)
All infections except skin and soft tissue	12,646	16,708	1.57 (1.52, 1.62)
Respiratory tract	10,088	13,315	1.54 (1.49, 1.59)
Gastrointestinal	615	905	1.70 (1.57, 1.84)
Kidney, urinary tract, and bladder	695	906	1.63 (1.47, 1.82)
Skin and soft-tissue	2,589	5,487	3.68 (3.50, 3.87)

Reproductive organ	1,142	1,437	1.62 (1.48, 1.76)
Sexually transmitted	121	146	1.95 (1.58, 2.40)
Inpatient or emergency room visits			
All infections	109	186	2.07 (1.74, 2.47)
All infections except skin and soft tissue	97	163	2.06 (1.71, 2.48)
Respiratory tract	41	85	2.58 (1.91, 3.47)
Gastrointestinal	32	45	1.57 (1.26, 1.97)
Kidney, urinary tract, and bladder	14	22	1.80 (1.26, 2.57)
Skin and soft-tissue	12	22	2.16 (1.43, 3.25)
Reproductive organ	8	10	1.36 (0.86, 2.16)
Sexually transmitted	1	1	1.64 (0.25, 10.58)

CI, confidence interval

* Adjusted for age (5-year categories), sex, income percentile (≤30th, >30th – ≤70th, >70th percentiles), diabetes (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), chronic obstructive pulmonary disease (yes or no), and asthma (yes or no)

Table 6. Rate ratios (95% CIs) for incident infections comparing psoriasis patients with and without treatment for psoriasis (N = 16,383)

Type of infection	Incidence rate (per 10,000 person-years)		Adjusted rate ratios (95% CI)*
	Without systemic treatment† (N = 13,991)	With systemic treatment† (N = 2,392)	
Overall visits			
All infections	19,574	19,624	1.03 (0.95, 1.13)
All infections except skin and soft tissue	14,888	13,962	0.90 (0.81, 0.98)
Respiratory tract	11,898	10,947	0.86 (0.78, 0.95)
Gastrointestinal	840	797	0.90 (0.73, 1.11)
Kidney, urinary tract, and bladder	818	794	0.99 (0.69, 1.41)
Skin and soft-tissue	4,715	5,662	1.56 (1.35, 1.81)
Reproductive organ	1,266	1,283	1.04 (0.80, 1.36)
Sexually transmitted	127	140	1.22 (0.62, 2.40)
Outpatient clinic visits			
All infections	19,410	19,473	1.21 (0.62, 2.38)
All infections except skin and soft tissue	14,743	13,832	0.89 (0.81, 0.98)
Respiratory tract	11,821	10,887	0.86 (0.78, 0.95)
Gastrointestinal	800	759	0.90 (0.73, 1.11)

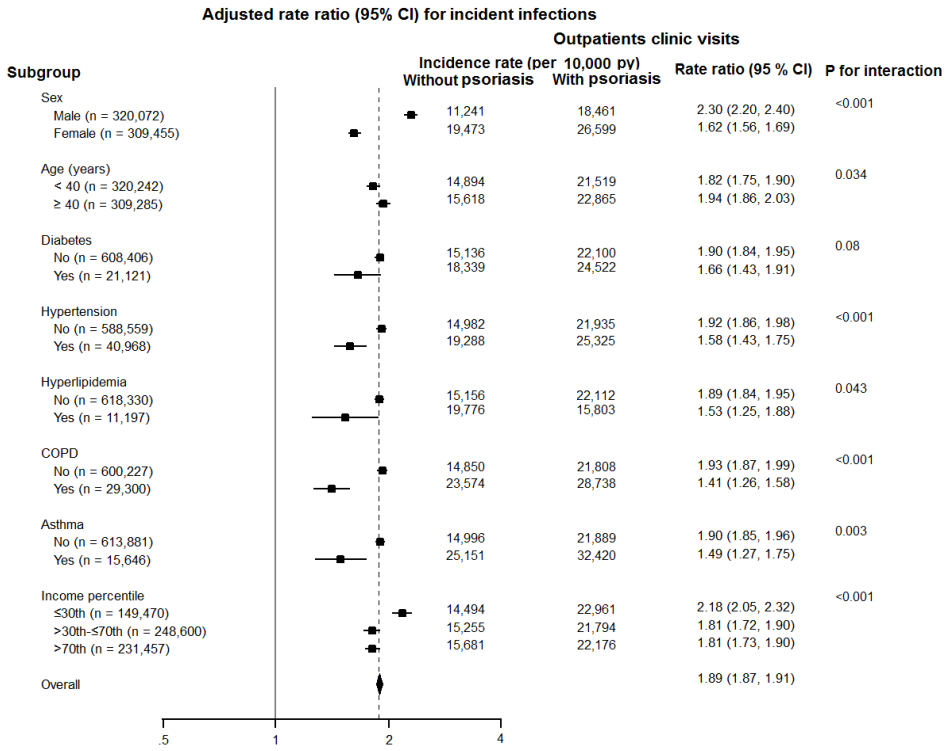
Kidney, urinary tract, and bladder	799	772	0.97 (0.67, 1.41)
Skin and soft−tissue	4,696	5,641	1.56 (1.35, 1.81)
Reproductive organ	1,258	1,273	1.04 (0.79, 1.35)
Sexually transmitted	126	140	1.23 (0.63, 2.41)
Inpatient or emergency room visits			
All infections	164	151	0.97 (0.64, 1.48)
All infections except skin and soft tissue	145	130	0.93 (0.60, 1.44)
Respiratory tract	77	60	0.76 (0.38, 1.53)
Gastrointestinal	41	38	0.85 (0.46, 1.59)
Kidney, urinary tract, and bladder	19	22	1.53 (0.63, 3.73)
Skin and soft−tissue	20	21	1.32 (0.43, 4.01)
Reproductive organ	8	10	N/A
Sexually transmitted	1	0	N/A

CI, confidence interval; N/A, not applicable

* Adjusted for age (5−year categories), sex, income percentile (≤30th, >30th − ≤70th, >70th percentiles), diabetes (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), chronic obstructive pulmonary disease (yes or no), and asthma (yes or no)

† Systemic treatments included cyclosporine, methotrexate, oral retinoids, ultraviolet B phototherapy, photochemotherapy, etanercept, infliximab, adalimumab, and ustekinumab.

Figure 2. Rate ratios (95% CIs) for overall incident infections (outpatient, inpatient, and emergency visits) associated with psoriasis in selected population subgroups



Adjusted for age (5-year categories), sex, income percentile (≤ 30th, >30th – ≤70th, >70th percentiles), diabetes (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), COPD (yes or no), and asthma (yes or no)

Discussion

In this comprehensive evaluation of the patterns of medical services utilization for acute infections using a nationwide population-based cohort, patients with psoriasis had about twice the risk of having acute infections than patients without psoriasis. While most of the acute infectious episodes were outpatient clinic visits, the relative risks associated with psoriasis were similar for outpatient and inpatient or emergency room visits. In subgroup analyses, the risk of acute infections associated with psoriasis varied by gender, age, income percentile and presence of comorbidities. Among patients with psoriasis, however, the risk of acute infectious episodes was not associated with use of immunomodulatory or immunosuppressive systemic antipsoriatic treatment.

In our study, most of the acute infectious episodes were common mild infections attended in outpatient clinic visits. Prior cohort studies that evaluated the risk of acute infection among patients with psoriasis using representative national data, however, have been restricted to serious infections requiring hospitalization.[9,10,24,25] In a cohort study in the Netherlands, the incidence rate of serious infections requiring hospitalization in

psoriasis patients was twice as high as in the general population.[9] In Taiwan, the rate of pneumonia requiring hospitalization in patients with psoriasis was 40% higher than in subjects without psoriasis.[10] Our study extends these findings and confirms that psoriasis patients are at increased risk of both mild and severe acute infections. Considering that acute infections require urgent care and affect quality of life, patients with psoriasis may require specific prevention and management plans for acute infections.

The most common infections were respiratory tract infections followed by skin and soft-tissue infections and reproductive organ infections. While patients with psoriasis were at increased risk of all types of infections, they were particularly susceptible to skin and soft-tissue infections. Compared to patients without psoriasis, psoriasis patients are more than 3 times more likely to have skin and soft-tissue infections that are bacterial and fungal infections such as impetigo, dermatophytosis, and candidiasis. Although direct comparison is difficult, previous studies in hospitalized patients have also identified a 2–3 times higher risk of cellulitis in inpatients with psoriasis compared to those without psoriasis.[9,24]

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, impaired systemic immunity in psoriasis patients may also increase the risk of infections. Our results also show that psoriasis patients with systemic treatment were more likely to develop skin and soft-tissue infections than those without systemic treatment. Patients with systemic therapy are more likely to have severe psoriasis, which is associated with severe chronic inflammation and a higher risk of immune dysregulation of both innate and adaptive immunity.[4] Moreover, severe psoriasis impairs the barrier function of the skin, the first line of defense against microorganisms.[26]

In our study, patients with psoriasis also had an increased incidence of sexually transmitted infections compared to patients without psoriasis. To the best of our knowledge, this is the first study reporting this association. An increased risk of sexually transmitted diseases in patients with psoriasis may be due to the presence of psoriatic lesions in the genital area that may augment the risk of sexually transmitted diseases, or to differences in sexual activities or behavior in patients with psoriasis. Appropriate education and examination in sexually transmitted diseases may be necessary to psoriasis patients and their sexual partners, especially when patients present with atypical manifestations or with abrupt deterioration. Further research is needed to confirm this association

and to identify effective prevention strategies.

The overall risk of acute infections in our study was not associated with use immunomodulatory or immunosuppressive systemic antipsoriatic treatment. This is consistent with previous studies of serious infections comparing psoriasis patients with systemic treatment to psoriasis patients with topical treatment only.[9,10] Rather than induce immunosuppression, proper immunosuppressive treatment may stabilize the immunologic abnormalities in psoriasis. Additional research is needed to investigate whether the risk of acute infection differs by type of systemic treatment, and especially to assess the long-term effects of recently developed biologics.

In subgroup analyses, we found acute infection risk varied by gender, age, income group, and presence of comorbidities. The higher risk of acute infections associated with psoriasis in men could be due to more severe psoriasis in men than in women.[27] Older patients may also have a higher risk due to reduced immune responses to pathogens.[7,28] In addition, the socioeconomic disparities observed in our study have been also observed for the rates of serious infections in inpatients with psoriasis.[24] In our study, the relative risk for infection associated with psoriasis was higher in patients without hypertension, hyperlipidemia, COPD or

asthma compared to patients with those comorbidities. The reasons for these differences are unclear and deserve further research.

Our study has several limitations. First, data on clinical outcomes was based on claims data, and there is the possibility of misclassification of exposure and/or outcome status. Specifically, psoriasis could be misdiagnosed as a skin infection, although NHIS claims data for this clinical outcome is highly specific and has been previously used in population studies.[19,22,29] Second, patients who developed psoriasis may have more frequent contacts with the health care system, which may induce surveillance bias. Finally, the study was conducted in Korea, a country with a single payer national health insurance system. Our findings may not be generalizable to other race/ethnicity groups or to other health care settings.

In conclusion, this nationwide population-based study demonstrated that patients with psoriasis had a higher risk of acute infections, especially skin and soft-tissue infections and sexually transmitted infections. The increased risk was largely independent of systemic antipsoriatic treatment. Patients with psoriasis experience reductions in quality of life comparable to cancer, ischemic heart disease, and diabetes patients.[30] The increased risk of acute infections in patients with psoriasis is likely a major

contributor to reduced quality of life in psoriasis, and it requires the development of education programs and clinical guidelines to prevent and mange acute infections in these patients. In addition, further research is necessary to understand the biological mechanisms underlying the association between psoriasis and infection.

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국 문 초 록

최근 전세계적으로 건선 환자들이 중증 감염으로 인해 입원하는 위험성이 높다는 연구 결과들이 발표되고 있다. 하지만 건선 환자에서 외래를 통해 진단 및 치료가 이루어지는 경증 감염의 발생 위험에 대해서는 알려진 바가 없다. 이번 연구에서는 국민건강보험공단의 표본 코호트 자료를 통해 건선 환자에서 입원, 외래, 응급실 방문을 포함한 전반적인 급성 감염의 발생 위험을 평가하고, 건선 환자의 감염 위험이 전신 면역억제치료와 관련성이 있는지 알아보고자 하였다.

이번 연구는 2003년에서 2013년까지의 국민건강보험공단 표본 코호트 자료에 등록된 20세 이상 70세 미만의 성인 중에서 건선으로 진단된 적이 없는 629,527명을 연구 대상자로 선정하였다. 이번 연구의 독립변수는 건선의 발병으로 시간에 따라 변하는 특성을 갖으며, 결과변수는 2003년 1월부터 2013년 12월까지 입원, 외래, 응급실에서 확인된 급성 감염 질환의 발생으로 정의하였다. 이번 연구는 연구 대상자를 추적 관찰하는 기간 동안 발생한 급성 감염 질환의 빈도를 다변량 포아송 회귀분석을 통해 계산하여 건선 유무에 따른 위험비와 건선의 전신 면역억제치료 여부에 따른 위험비를 산출하였다.

추적 관찰 기간 동안 건선이 발병한 사람은 16,383명(2.6%)이었고, 급성 감염 질환의 전체 발생 건수는 9,690,990건(10,000 인년당 15,435 건)이었다. 대부분의 급성 감염 (99.2%)은 외래를 통해 진단되었다. 건선이 없는 환자 대비 건선 환자의 전체 급성

감염 질환 발생의 다변량 조정 위험비 (95% 신뢰 구간)는 1.89 (1.83, 1.94)였으며, 외래 방문과 입원 또는 응급실 방문을 통해 확인된 급성 감염 질환 발생의 위험비는 각각 1.88 (1.83, 1.94)과 2.07 (1.74, 2.47)이었다. 또한 전신 면역억제치료를 받은 건선 환자의 감염 질환 발생률은 전신 면역억제치료를 받지 않은 건선 환자의 감염 질환 발생률과 비슷하였다 (상대 위험비 1.03; 95% 신뢰 구간, 0.95, 1.13).

결론적으로 이번 연구를 통해 건선 환자는 급성 감염 발생 위험이 높고, 감염 질환의 발생과 건선의 전신 치료는 관련이 없음을 확인하였다. 향후 건선과 감염의 관련성에 대한 생물학적 메커니즘을 이해하기 위해서는 추가적인 연구가 필요하다.

주요어 : 코호트 연구, 동반질환, 역학, 감염, 외래, 건선

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