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ORIGINAL ARTICLE

Risk of uveitis in patients with psoriasis in Korea: A nationwide population-based cohort study

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Abstract

Background: Evidence for the association between psoriasis and uveitis according to the severity of psoriasis including psoriatic arthritis (PsA) and type of uveitis is lacking, and there are no data on the frequency or timing of recurrence of uveitis in patients with psoriasis.

Objectives: We aimed to evaluate the risk of first occurrence and recurrence of uveitis in patients with psoriasis in the Korean population. We further evaluated the risk of uveitis according to the severity of psoriasis, comorbidity of PsA and location of uveitis.

Methods: In a nationwide retrospective cohort study, we compared 317,940 adult patients who had psoriasis with 635,880 matched controls. Incidence rates (IRs) and estimated IR ratios of the first occurrence and recurrence of uveitis were calculated using survival analysis and Poisson regression, respectively.

Results: The rate of uveitis incidence and uveitis recurrence in patients with psoriasis was 1.18 and 2.31 per 1000 person-years, respectively. Compared to the controls, the IR ratios of development and recurrence of uveitis in patients with psoriasis were 1.14 (95% CI 1.08, 1.2) and 1.16 (95% CI 1.12, 1.21), respectively. The recurrence rate of uveitis was highest within 3 years after the onset of psoriasis. The corresponding IR ratios for uveitis recurrence in patients with mild psoriasis, severe psoriasis and PsA were 1.11 (1.06, 1.16), 1.24 (1.16, 1.33) and 1.49 (1.31, 1.7), respectively. Patients with psoriasis had an increased risk of recurrence of anterior uveitis, and patients with both psoriasis and PsA had an increased risk of recurrence of both anterior-uveitis and panuveitis.

Conclusions: Patients with psoriasis had a higher risk of both development and recurrence of uveitis, especially with severe psoriasis and PsA. The timing of uveitis recurrence was related to the onset of psoriasis, and patients who had psoriasis with PsA had an increased risk of vision-threatening panuveitis.

INTRODUCTION

Uveitis is characterized by intraocular inflammation occurring in the uveal tract and adjacent ocular structures.[1–3] As a sight-threatening eye disease, uveitis is suggested to be the cause of 5%–20% of all blindness.[4–6] One of the various etiologies of uveitis is autoimmunity, and approximately 1/4–1/3 of patients with uveitis can be associated with having extraocular or systemic manifestations such as psoriasis.[7,8]

The association between uveitis and psoriasis was supported by two cohort studies. A study on the Danish population showed an increased incidence rate of uveitis in patients with mild psoriasis and psoriatic arthritis (PsA) but not in patients with severe psoriasis.[9] Similarly, a study

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in Taiwan revealed that the risk of uveitis increased in patients with severe psoriasis and PsA but not in patients with mild psoriasis without PsA.[10] However, the results of previous studies are not consistent with the finding about the increased risk of uveitis in patients with psoriasis according to the severity of psoriasis and concurrent PsA. Therefore, additional investigation is needed on the incidence of uveitis among patients of diverse races who have psoriasis to establish a more definitive relationship between uveitis and psoriasis. Moreover, to the best of our knowledge, no longitudinal data are available on the frequency and timing of uveitis recurrence, especially in patients with lifelong psoriasis, with no data on the location of uveitis involvement related to psoriasis.

In this study, we aimed to evaluate the risk of development and recurrence of uveitis, including the frequency and timing of recurrence, in patients with psoriasis in a nationwide cohort of the Korean population. We further evaluated the risk of uveitis according to the severity of psoriasis, comorbidity of PsA and location of uveitis.

MATERIALS AND METHODS

Study design and data source

We conducted a retrospective cohort study by examining the population-based data from the Korean Health Insurance Review and Assessment Service (HIRA) from 1 January 2010 to 31 March 2021. Almost every Korean (97%) is enrolled in a mandatory universal single-payer national healthcare system, and the HIRA contains comprehensive information about healthcare services such as treatments, pharmaceuticals, procedures and diagnoses for almost 50 million beneficiaries.[11,12] Diagnostic codes from the International Classification of Diseases, Tenth Revision (ICD-10) is described in Table S1. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

Study population

We identified patients aged 20 years or older who had a diagnosis code for psoriasis at least twice in 1 year from 1 January 2011 to 31 March 2021.[13] Controls, who had never been to medical institutions for psoriasis, were defined as patients aged 20 years or older who had at least one diagnosis code for urticaria from the 2011 longitudinal HIRA database. Patients in whom psoriasis or uveitis was diagnosed in the year before the cohort entry were excluded to avoid any bias introduced by prevalent cases. We also excluded patients with a history of systemic comorbidities that might have caused uveitis (Figure 1).[7,8,14–17] Additionally, we excluded patients with no follow-up data.

We reduced potential selection bias between the psoriasis and nonpsoriasis control groups with urticaria via 1–2 matching by age group, sex, and presence of diabetes, hypertension and hyperlipidemia. Baseline comorbidities used for matching were defined as the presence of at least one relevant ICD-10 code between January 1 and 31 December 2010.

We divided patients with psoriasis into three groups according to the severity of their condition and concurrent presence or absence of PsA: mild psoriasis without PsA, severe psoriasis without PsA and psoriasis with PsA. The severity of psoriasis was classified based on the treatment patterns. Those who received the systemic antipsoriatic therapy, including oral retinoids, methotrexate, cyclosporine and biologics were defined as patients with severe psoriasis. Those who did not receive any systemic therapy were regarded as patients with mild psoriasis. Patients who had psoriasis with PsA were defined as those who had a diagnosis code for PsA at least once.

Outcome measures

The outcome of interest was the development and recurrence of uveitis not related to infections. Uveitis development was defined as the first visit to a medical institution with a main diagnosis of uveitis. Moreover, because uveitis can occur more than once, we calculated the frequency of all recurrent episodes of uveitis from the index date to the last date of follow-up and defined a recurrence of uveitis when the minimum interval between each diagnostic code of uveitis was >30 days. Patients were followed up until death or the end of the study period. Additionally, we classified uveitis into panuveitis, posterior uveitis and anterior uveitis and evaluated the relative risk of uveitis according to the location of occurrence in patients with psoriasis.

Statistical analysis

We compared the baseline characteristics between patients with psoriasis and control patients with urticaria, using chi-square tests for categorical variables and independent *t*-tests or Mann–Whitney *U*-tests for continuous variables. We calculated the incidence by dividing the number of people with incident uveitis by the person-years of each group. When counting only the first occurrence of uveitis (development of uveitis), we used the Kaplan–Meier method for survival analysis and the Cox proportional hazard model to compare the risk of incident uveitis between groups. When calculating the total number of episodes of recurrent uveitis, we used the Poisson regression model to obtain the rate ratios with 95% confidence intervals (CI) and compare uveitis recurrence rates between groups.

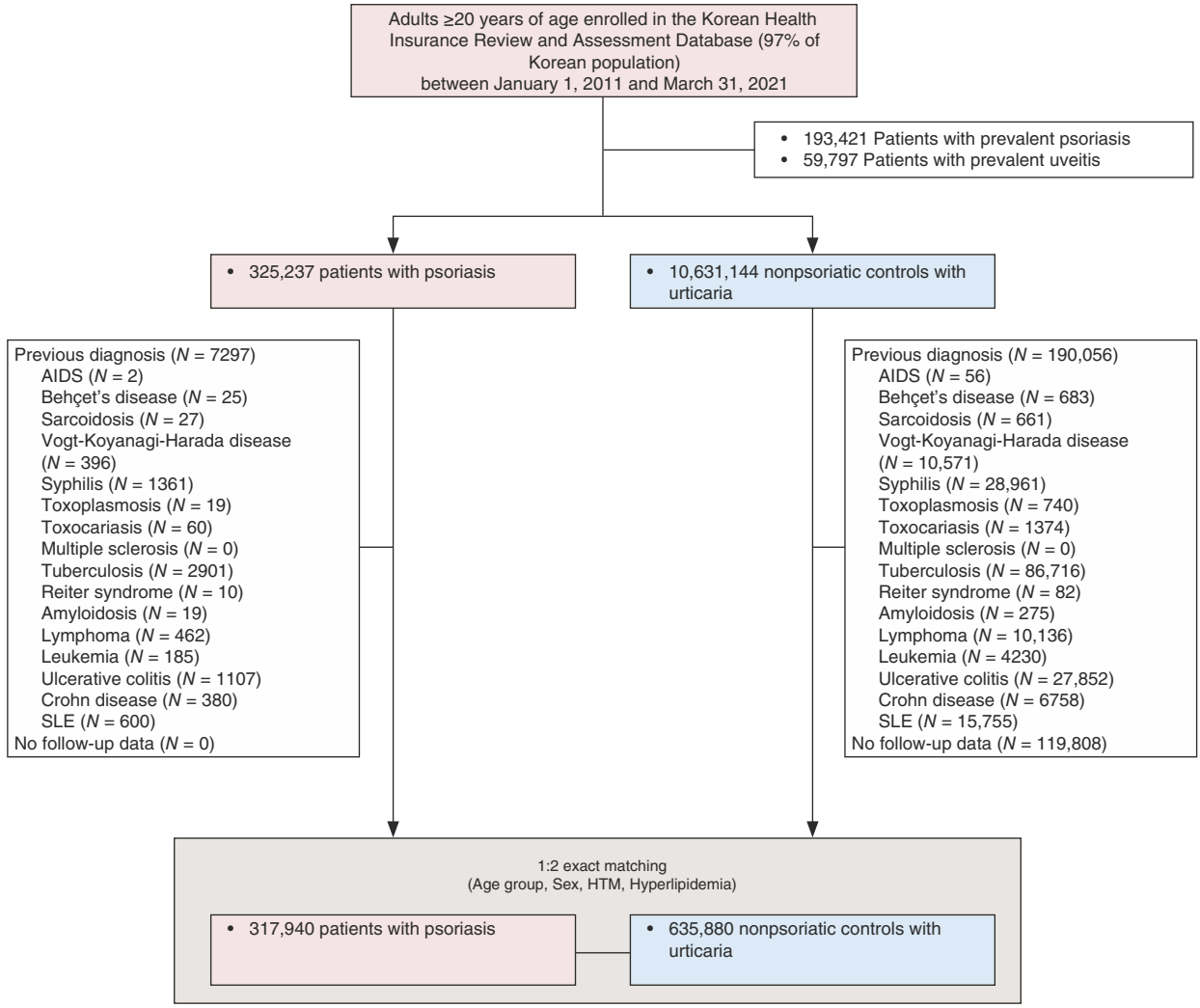

FIGURE 1 Flow chart of selection of the study population.

To evaluate the uveitis recurrence timing in patients with psoriasis compared to controls, we defined the relative recurrence rate of uveitis in patients with psoriasis as the percentage increase (%) of recurrent uveitis in patients with psoriasis compared to controls. This value was calculated by dividing the difference between the incidence of uveitis in patients with psoriasis and the incidence of uveitis in the control group annually before and after the onset of psoriasis by the incidence of uveitis in the control group. Then, the relative recurrence rates of uveitis in patients with psoriasis over time were compared based on the onset of psoriasis.

We performed a sensitivity analysis by more conservatively redefining the minimum interval for recurrent episodes of uveitis as 60 days to confirm the associations between psoriasis and uveitis. Therefore, the second uveitis episode was considered a recurrence only if the main diagnosis code of uveitis developed >60 days after the first visit to any medical institution for uveitis. Data sets were constructed and analysed by using R statistical software (version 3.5.3; R Foundation for Statistical Computing). Statistical significance was set at a 2-sided p-value of <0.05.

RESULTS

Characteristics of the study population

Table 1 shows the demographics and clinical characteristics of the patients with psoriasis and matched controls (mean age, 48.43 ± 16.68 years; 44.4% women in both groups). Because matching was used among selected study participants, the age and sex distribution and the proportion of diabetes, hypertension and hyperlipidemia were comparable across both groups. During the mean follow-up period of 5.19 ± 2.93 years, the mean time to onset of first uveitis was 2.93 ± 2.40 and 3.10 ± 2.41 years, respectively ($p = 0.017$).

TABLE 1 Baseline demographics and characteristics of subjects included in this study.

Characteristics	Psoriasis	Controls	*p* value
Total number	317,940	635,880	
Age, years	48.42 ± 16.70	48.43 ± 16.67	0.717
20–29	50,325 (15.8)	100,650 (15.8)	1.000
30–39	55,883 (17.6)	111,766 (17.6)	
40–49	59,715 (18.8)	119,430 (18.8)	
50–59	66,549 (20.9)	133,098 (20.9)	
60–69	46,176 (14.5)	92,352 (14.5)	
70–79	29,882 (9.4)	59,764 (9.4)	
≥80	9410 (3.0)	18,820 (3.0)	
Sex			1.000
Male	176,709 (55.6)	353,418 (55.6)	
Female	141,231 (44.4)	282,462 (44.4)	
Diabetes	42,718 (13.4)	85,436 (13.4)	1.000
Hypertension	81,111 (25.5)	162,222 (25.5)	1.000
Hyperlipidemia	83,351 (26.2)	166,702 (26.2)	1.000
Mean follow-up, years	5.18 ± 2.93	5.20 ± 2.93	0.069
Time to onset of first episode, years[a]	2.93 ± 2.40	3.10 ± 2.41	0.017*

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

[a]The value was calculated including only patients who developed uveitis.

*Indicates a statistical significance with $p < 0.05$.

Compared to controls, patients with psoriasis had an earlier onset of the first episode.

Risk of development and recurrence of uveitis in patients with psoriasis

An increased risk of uveitis in patients with psoriasis was evident for both the development and recurrence of uveitis (Table 2). The incidence rates (IRs) of first and recurrent uveitis in patients with psoriasis were 1.18 and 2.31 per 1000 person-years, respectively. Compared to controls, the rate ratios (RRs) of first and recurrent uveitis in patients with psoriasis were 1.14 (95% CI 1.08, 1.2) and 1.16 (95% CI 1.12, 1.21), respectively. Furthermore, the risk of first and recurrent uveitis was higher in patients with severe psoriasis (RR 1.13; 95% CI 1.02, 1.24 and RR 1.24; 95% CI 1.16, 1.33) and psoriasis with PsA (RR 1.6; 95% CI 1.34, 1.9 and RR 1.49; 95% CI 1.31, 1.7). As shown in Figure 2, the cumulative incidence of first uveitis showed an increasing pattern with time, and all three groups of patients with psoriasis had a higher risk of incident uveitis than the controls. When calculated considering the multiple occurrences of uveitis 5 years before and after the onset of psoriasis, the relative recurrence rate of uveitis was 19.2% higher than that in the control group throughout the 10-year period. Notably, the incidence of recurrent uveitis in patients with psoriasis was the highest (31.4%) within 1 year after the onset of psoriasis and it tended to be higher within the 3 years after the onset of psoriasis than in the other period (mean, 27.9% vs. 15.5%) (Figure 3).

In subgroup analysis according to the location of uveitis, among 3804 episodes of uveitis in patients with psoriasis, 445 episodes of panuveitis (11.7%) and 3359 episodes of anterior uveitis (88.3%) occurred and posterior uveitis did not occur. Patients with psoriasis showed an overall increased risk of the development and recurrence of anterior uveitis (Table 2). Notably, the risk of anterior uveitis occurrence and recurrence increased as the severity of psoriasis and accompanying PsA increased, while that of panuveitis was highly associated only with PsA.

Since the control group in this study was selected as urticaria patients without psoriasis, to exclude the effect of urticaria, patients with psoriasis were classified into two groups, with and without urticaria, and the risk of development and recurrence of uveitis in urticaria patients and psoriasis patients with urticaria was evaluated (Table S2). The RR of uveitis development and recurrence in psoriatic patients with urticaria was 1.31 (95% CI 1.22, 1.41) and 1.33 (95% CI 1.26, 1.4) compared to patients with urticaria, indicating a more pronounced RR than that when the risk of uveitis in total psoriasis patients with or without urticaria was compared to the risk of uveitis in the control group (RR 1.14; 95% CI 1.08, 1.2 and RR 1.16; 95% CI 1.12, 1.21). The Kaplan–Meier curves of cumulative incidence of first uveitis also confirmed an increasing trend for risk of uveitis from controls to severe psoriasis with urticaria to PsA with urticaria (Figure S1).

The sensitivity analysis confirmed that patients with psoriasis had an increased risk of recurrent uveitis, even though the operational definition of recurrent uveitis was more conservative (Table S3). Because the minimum interval for recurrent uveitis was limited to 60 days, the total number of recurrent uveitis episodes in the study population decreased from 10,368 to 9051.

DISCUSSION

Our nationwide cohort study found higher incidence rates and risks of both first and recurrent uveitis in patients with psoriasis compared to matched controls, and this trend became more pronounced with increasing psoriasis severity and with psoriasis with concomitant PsA. We also found that the recurrence of uveitis was most frequent 3 years after the onset of psoriasis. In a subgroup analysis according to the location of uveitis, the risk of anterior uveitis was increased in patients with psoriasis, whereas the risk of panuveitis was increased in patients with both psoriasis and PsA.

Two representative studies on Danish and Taiwanese populations have shown a correlation between psoriasis and uveitis.[9,10] Compared to prior cohort studies, our data can provide more convincing supporting evidence for the association between psoriasis and uveitis by supplementing ethnic diversity. In addition, our study expands on previous results by showing that the risks of both first and recurrent uveitis

TABLE 2 The rates of uveitis incidence and uveitis recurrence in patients with psoriasis and control patients with urticaria.

Group	*N*	No. of events	Person-years	Incidence rate (per 1000 p-y)	Rate ratios (95% CI)
Development of uveitis (first uveitis)					
Controls	635,880	3436	3,303,396.93	1.04	1 (Ref.)
Total psoriasis	317,940	1952	1,648,020.47	1.18	1.14 (1.08–1.2)
Mild psoriasis	234,358	1374	1,188,304.89	1.16	1.11 (1.04–1.18)
Severe psoriasis	70,375	446	380,162.82	1.17	1.13 (1.02–1.24)
Psoriasis with PsA	13,207	132	79,552.76	1.66	1.6 (1.34–1.9)
Panuveitis					
Controls	635,880	617	3,303,396.93	0.19	1 (Ref.)
Total psoriasis	317,940	330	1,648,020.47	0.2	1.07 (0.94–1.23)
Mild psoriasis	234,358	234	1,188,304.89	0.2	1.05 (0.91–1.23)
Severe psoriasis	70,375	61	380,162.82	0.16	0.86 (0.66–1.12)
Psoriasis with PsA	13,207	35	79,552.76	0.44	2.36 (1.68–3.31)
Anterior uveitis					
Controls	635,880	2819	3,303,396.93	0.85	1 (Ref.)
Total psoriasis	317,940	1622	1,648,020.47	0.98	1.15 (1.08–1.23)
Mild psoriasis	234,358	1140	1,188,304.89	0.96	1.12 (1.05–1.2)
Severe psoriasis	70,375	385	380,162.82	1.01	1.19 (1.07–1.32)
Psoriasis with PsA	13,207	97	79,552.76	1.22	1.43 (1.17–1.75)
Recurrence of uveitis (≥1 episodes)[a]					
Controls	635,880	6564	3,303,396.93	1.99	1 (Ref.)
Total psoriasis	317,940	3804	1,648,020.47	2.31	1.16 (1.12–1.21)
Mild psoriasis	234,358	2629	1,188,304.89	2.21	1.11 (1.06–1.16)
Severe psoriasis	70,375	939	380,162.82	2.47	1.24 (1.16–1.33)
Psoriasis with PsA	13,207	236	79,552.76	2.97	1.49 (1.31–1.7)
Panuveitis					
Controls	635,880	820	3,303,396.93	0.25	1 (Ref.)
Total psoriasis	317,940	445	1,648,020.47	0.27	1.09 (0.97–1.22)
Mild psoriasis	234,358	319	1,188,304.89	0.27	1.08 (0.95–1.23)
Severe psoriasis	70,375	78	380,162.82	0.21	0.83 (0.66–1.04)
Psoriasis with PsA	13,207	48	79,552.76	0.6	2.43 (1.82–3.25)
Anterior uveitis					
Controls	635,880	5744	3,303,396.93	1.74	1 (Ref.)
Total psoriasis	317,940	3359	1,648,020.47	2.04	1.17 (1.12–1.22)
Mild psoriasis	234,358	2310	1,188,304.89	1.94	1.12 (1.07–1.17)
Severe psoriasis	70,375	861	380,162.82	2.26	1.3 (1.21–1.4)
Psoriasis with PsA	13,207	188	79,552.76	2.36	1.36 (1.18–1.57)

Abbreviations: CI, confidence interval; PsA, psoriatic arthritis; p-y, person-years.

[a]The recurrence rate of uveitis was calculated as total episodes of uveitis that occurred during the follow-up period, and the minimum interval between each episode was defined as more than 30 days.

were increased in patients with psoriasis. In particular, the increased risk of recurrent uveitis in patients with psoriasis is a clinically important finding, indicating that proper consultation with ophthalmologists and regular ophthalmological check-ups for the early treatment of uveitis are needed in patients with psoriasis. Relapsing uveitis can exacerbate the disease course, increase the chance of adverse effects from long-term use of drugs and decrease quality of life.[18,19] Therefore, effective management and prevention of uveitis recurrence in chronic and lifelong patients with psoriasis will help maintain their quality of life.

The pathogenesis of uveitis involves the participation of ocular dendritic cells and interferon-γ (IFN-γ)-producing T helper (Th) 1 cells, which are related to the induction of uveitis. Through activation of STAT3 signalling pathways, interleukin-17 (IL-17)-producing Th17 cells play a pivotal

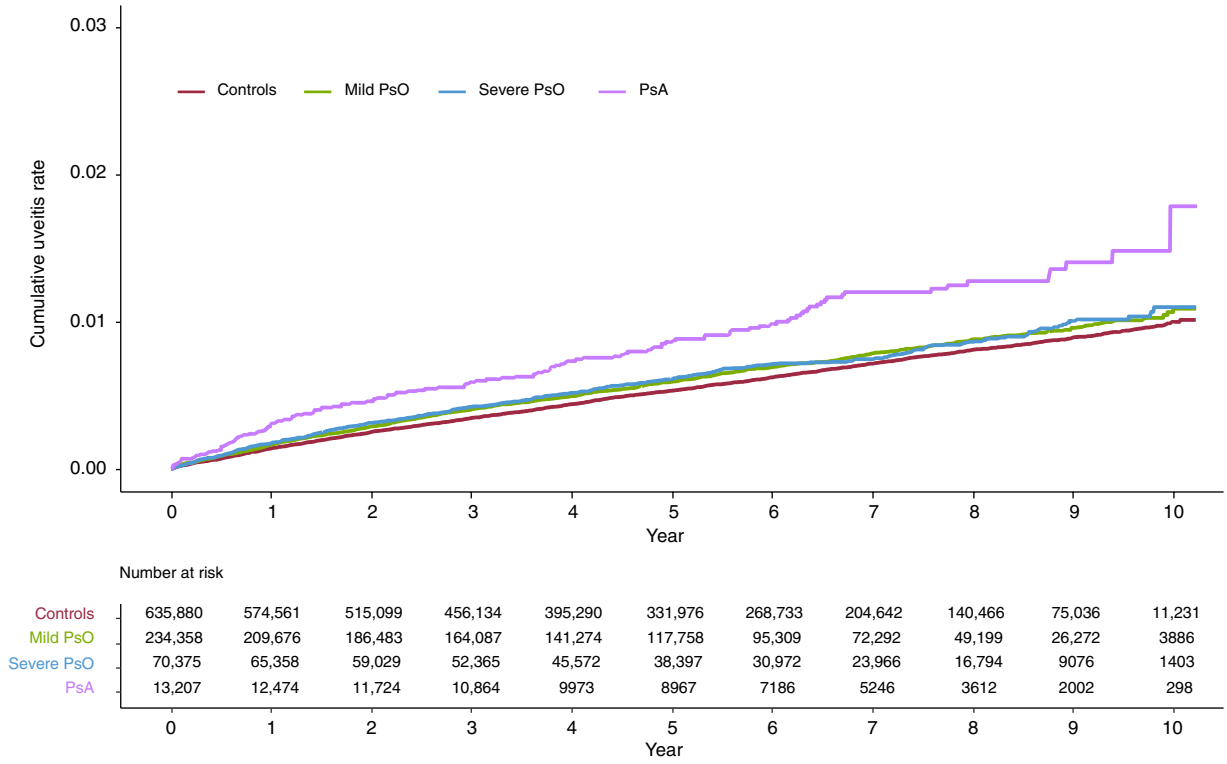

FIGURE 2 Cumulative incidence curves for first uveitis. Compared to the controls, the incidence rate ratios of development of uveitis in patients with mild psoriasis (PsO), severe PsO and psoriasis arthritis (PsA) were 1.11 (95% CI 1.04, 1.18), 1.13 (95% CI 1.02, 1.24) and 1.6 (95% CI, 1.34, 1.9), respectively.

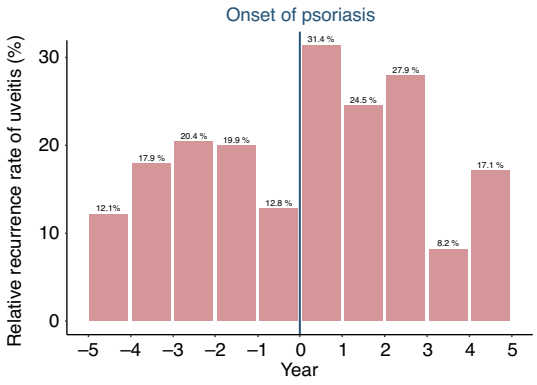

FIGURE 3 Relative recurrence rate of uveitis in patients with psoriasis. The relative recurrence rate of uveitis in patients with psoriasis was the increased percent (%) of recurrent uveitis in patients with psoriasis compared to controls and was calculated as (incidence of uveitis in patients with psoriasis–incidence of uveitis in the control group)/ incidence of uveitis in the control group (%).

role in disease initiation and progression including the breakdown of the blood-retinal barrier.[20–23] Similarly, in the pathogenesis of psoriasis, Th17 cells producing proinflammatory cytokines predominantly participate in the initiation process of psoriasis resulting in hyperproliferation of keratinocytes, and IFN-γ-producing Th1 cells play essential roles in the early stage by stimulating the dendritic cells to produce IL-23, an important cytokine in the differentiation of naïve $CD4^+$ T cells into Th17 cells.[24–26] Notably, our study found that the incidence of recurrent uveitis increased particularly during the 3 years after psoriasis onset. Considering that psoriasis is classified as a systemic inflammatory disease and it shares similar molecular and cellular pathogenesis with uveitis such as the IL-23/Th17/IL-17 axis, the finding that the substantial risk of recurrent uveitis is high when psoriasis is diagnosed is consistent with the biological mechanisms underlying the association between psoriasis and uveitis. Therefore, this high-risk period may be the best time for appropriate multidisciplinary collaboration including the timely diagnosis and management of uveitis, which can prevent serious vision loss.

In addition, numerous studies have suggested that human leukocyte antigen-B27 (HLA-B27) is a molecule likely to elucidate the common pathophysiological link between psoriasis and uveitis.[27,28] Patients with positive HLA-B27 showed correlations with early onset of psoriasis and a high prevalence of uveitis.[29,30] Anterior uveitis is known as the most commonly associated uveitis with psoriasis or HLA-B27-positive PsA.[31,32] Posterior or panuveitis can also develop in patients with psoriasis or PsA, but the exact rate of its psoriasis-related incidence

is unknown. In this study, patients with psoriasis had a higher risk of uveitis, especially those with severe psoriasis and PsA, consistent with the prior studies (Table S4). Furthermore, our results show that the ratio of anterior uveitis to panuveitis in patients with psoriasis is about 8:1. In particular, since the presence of PsA in patients with psoriasis significantly influenced the risk of occurrence and recurrence of panuveitis, proper medical intervention could be more critical to patients who have psoriasis with PsA, considering the poorer visual prognosis of panuveitis compared with anterior uveitis.[33] These further analyses of the location of uveitis related to the visual prognosis as well as the association of relapse of uveitis with psoriasis severity suggest that our data may help provide a practical guideline in the clinical field.

This study has several limitations. Since we could not arbitrarily obtain the matched data of a nonpatient control group from HIRA, nonpsoriasis patients with urticaria were selected as the control.[34,35] To overcome this limitation, the risk of uveitis in psoriatic patients with urticaria compared with that in urticaria patients was analysed, and we confirmed that the control selection did not significantly affect the overall results. Second, the inherent limitation in the diagnostic accuracy of the disease reported by the claim data should also be noted.

In conclusion, the present study found that the risk of developing uveitis in patients with psoriasis increased in cases of both first-occurrence uveitis and recurrent uveitis with increasing psoriasis severity, and the timing of uveitis recurrence was related to the onset of psoriasis. The presence of PsA was associated with the highest incident risk of uveitis, including both anterior uveitis and vision-threatening panuveitis. Therefore, patients with psoriasis should be on the lookout for the occurrence of visual symptoms, and regular follow-ups by an ophthalmologist will be helpful.

AUTHOR CONTRIBUTIONS

Drs Kim and Youn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Kim, Woo and Youn. Acquisition, analysis or interpretation of data: All authors. Drafting of the manuscript: Kim, Choi, Choi and Woo. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kim and Lee. Obtained funding: Youn. Administrative, technical or material support: Lee and Kim. Supervision: Choi, Woo and Youn.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

The requirement for informed consent was waived because all data were deidentified.

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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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