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Immune-Mediated Inflammatory Diseases Following Pediatric Uveitis Diagnosis

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Abstract

IMPORTANCE Pediatric uveitis is frequently associated with immune-mediated inflammatory diseases (IMIDs); however, population-level estimates of IMID risk and immunosuppressant use are limited, as existing evidence is largely derived from tertiary-center cohorts with substantial referral bias.

OBJECTIVE To estimate the incidence and risk of developing IMIDs among children and adolescents newly diagnosed with noninfectious uveitis without a prior history of IMIDs.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study includes nationwide health insurance claims data from Korea from January 2008 through February 2024. Participants included children and adolescents younger than 20 years who were newly diagnosed with uveitis in Korea between 2011 and 2022. Data were analyzed from February to November 2025.

EXPOSURE Diagnosis of uveitis

MAIN OUTCOMES AND MEASURES Primary outcomes were the estimated 5-year cumulative incidence of a composite of 13 predefined IMIDs and the age- and sex-adjusted standardized incidence ratios (SIRs) compared with the general pediatric population.

RESULTS In this cohort study, 27 656 children and adolescents (mean [SD] age, 12.6 [4.8] years; 16 827 males [58.3%]) with incident noninfectious uveitis and no prior IMID diagnosis or immunosuppressant prescription were identified. The estimated 5-year cumulative incidence of composite IMIDs was 8.52% (95% CI, 8.16%-8.87%). The most frequently newly diagnosed IMID following uveitis was ankylosing spondylitis (2.53%; 95% CI, 2.33%-2.73%); however, the distribution of IMIDs differed across age groups. Compared with the general pediatric population, the overall SIR for IMIDs was 6.78 (95% CI, 6.54-7.02). Disease-specific SIRs were the highest for sarcoidosis (444.48; 95% CI, 357.98-551.89), ankylosing spondylitis (68.9; 95% CI, 64.5-73.7), and Behçet disease (66.3; 95% CI, 57.8-76.0). The use of immunosuppressive therapies varied substantially by level of medical care, with a higher estimated 5-year incidence in secondary and tertiary care settings than in primary care settings (8.42%; 95% CI, 7.67%-9.16% vs 0.67%; 95% CI, 0.55%-0.79%; $P < .001$), along with variation in prescribed agents.

CONCLUSIONS In this cohort study, children and adolescents with uveitis had an approximately 7-fold increased risk of developing IMIDs compared with the general population, with variation in disease patterns and treatment according to demographic and health care factors. These findings highlight the importance of systematic and risk-stratified screening for IMIDs in pediatric patients with uveitis.

Key Points

Question What are the incidence and risk of immune-mediated inflammatory disorders (IMIDs) among pediatric patients with noninfectious uveitis without a previous history of IMIDs?

Findings In this population-based cohort study of 27 656 pediatric patients with uveitis, the cohort had a 5-year cumulative incidence of 8.5% for IMIDs and a significantly higher risk compared with that of the general population.

Meaning These findings suggest that pediatric patients with uveitis should be carefully monitored for diverse IMIDs, with attention to individual patient characteristics and risk profiles.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Uveitis is an intraocular inflammatory disorder involving the iris, ciliary body, vitreous, retina, choroid, and other ocular structures. Pediatric uveitis has a similar or slightly higher association with systemic diseases than adult uveitis. Previous studies report systemic disease in 25% to 57% of pediatric cases compared with 37% to 49% in adults.[1,2] The spectrum of systemic diseases in children differs substantially from that in adults.[3,4] Immune-mediated inflammatory diseases (IMIDs), including juvenile idiopathic arthritis (JIA), Kawasaki disease (KD), and tubulointerstitial nephritis and uveitis syndrome (TINU), are particularly common in the pediatric population.[5,6] Notably, conditions such as spondyloarthritis-associated uveitis and TINU often present initially with ocular symptoms before systemic manifestations appear.[7,8] IMIDs and IMID-associated pediatric uveitis differ from adult disease in several ways. Because pediatric IMIDs often present with aggressive and overlapping symptoms, comprehensive systemic evaluation is essential for timely diagnosis and management.[9,10] Furthermore, pediatric uveitis often follows a chronic and recurrent course, and ophthalmic sequelae, such as cataract, glaucoma, and amblyopia, may have significant long-term impacts on quality of life.[11,12] When systemic disease is identified, early systemic immunosuppressive therapy is recommended, as prompt treatment may reduce ocular complications and the need for surgical intervention.[13,14]

Despite the known association between pediatric uveitis and systemic disease, gaps remain in understanding disease progression. Although previous studies have reported the prevalence of systemic conditions in children with established uveitis, little is known about the subsequent development of IMIDs in those initially presenting with uveitis.[11,15] Moreover, the frequency and patterns of immunosuppressive therapy in these patients have not been well characterized at the population level. This information is clinically valuable for predicting and preventing systemic complications, guiding screening strategies, and informing discussions with patients and families about long-term prognosis. Therefore, we aimed to address these gaps through a comprehensive population-based assessment of the incidence and risk of IMID development in pediatric noninfectious uveitis and the patterns of immunosuppressant use.

Methods

Data Source

We analyzed medical claims from January 1, 2008, to February 29, 2024, using the Health Insurance Review and Assessment (HIRA) database in South Korea. The country's single National Health Insurance system covers more than 97% of the population, and all claims are submitted to HIRA for review and stored in a centralized database. The database includes inpatient and outpatient health care utilization coded using the Korean Standard Classification of Diseases, Eighth Revision (*KCD-8*), adapted from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, and contains information on diagnoses, procedures, prescriptions, visit dates, and demographics. We accessed claims for ocular and nonocular conditions as well as sociodemographic information. Detailed definitions and codes are provided in eTable 1 in Supplement 1. For standardized incidence ratio (SIR) analyses, data on 13 predefined IMIDs were extracted from the nationwide dataset, including JIA, ankylosing spondylitis (AS), tubulointerstitial nephritis (TIN), Behçet disease, KD, sarcoidosis, systemic lupus erythematosus, multiple sclerosis, psoriasis, psoriatic arthritis, antiphospholipid syndrome, inflammatory bowel disease, and reactive arthritis. The HIRA Deliberative Committee approved conditional use of the database for this study (approval number, M20241012001). Data application was submitted to HIRA in October 2024 and approved in January 2025; data construction was completed in February 2025. Data analysis was conducted from February to November 2025. The study adhered to the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting

guideline. The Institutional Review Board of Yonsei University Severance Hospital approved the study and waived informed consent because deidentified administrative data were used.

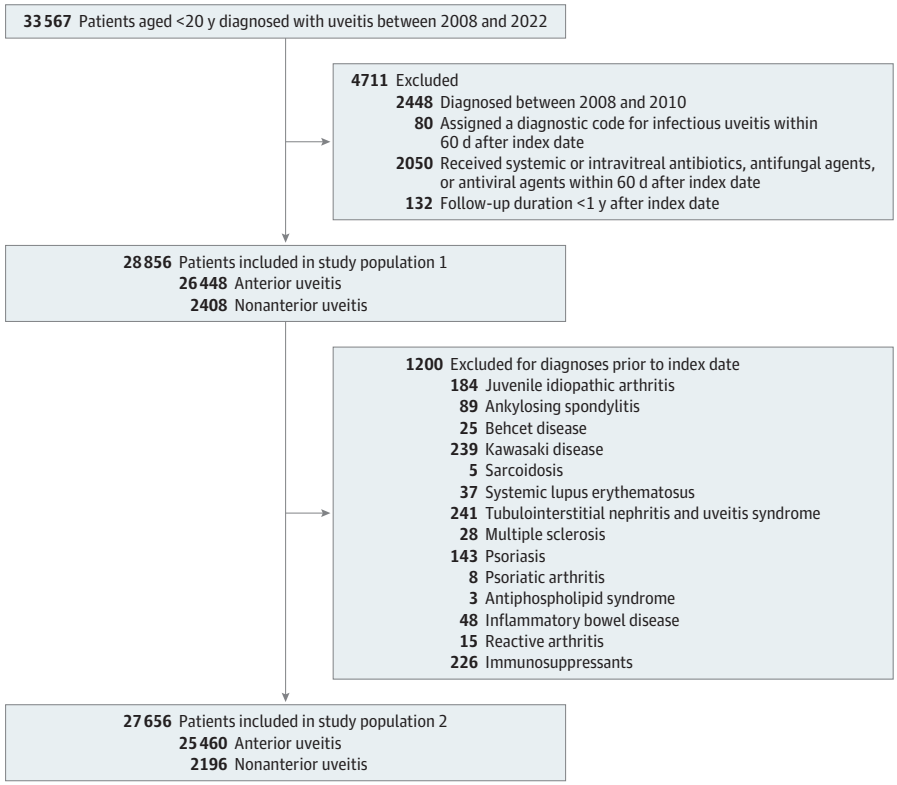
Study Population

The study population was selected as shown in **Figure 1**. To exclude prevalent cases, a 3-year washout period was applied, and patients with uveitis codes from 2008 through 2010 were excluded. Individuals diagnosed between 2011 and 2022 with at least 1 year of follow-up were included. Additional exclusions were infectious uveitis, receipt of systemic or intravitreal antimicrobial therapy, follow-up of less than 1 year after the index date, and missing demographic information. Uveitis was defined as at least 3 outpatient visits or one inpatient admission, with *KCD-8* uveitis codes, along with a prescription for ocular or systemic corticosteroids within 60 days of the earliest claim. The index date was defined as the earliest uveitis-related claim, and cases were classified by year of incident diagnosis. All 3 outpatient visits were required to occur within 1 year of the index date. Other diseases were defined using the same visit criteria with the relevant *KCD-8* codes. Follow-up was censored at the first IMID diagnosis. IMID outcomes were ascertained from the date of the first uveitis-related claim, regardless of whether the third qualifying visit had occurred, provided that both diagnoses met the required criteria. Patients with a prior IMID diagnosis or immunosuppressant prescription before the index date were excluded.

Outcome Measurements

The primary outcomes were the estimated 5-year cumulative incidence of a composite of 13 predefined IMIDs and the corresponding SIRs among pediatric patients with uveitis without prior IMIDs. Five-year cumulative incidence and SIRs were also calculated for each individual IMID. Subgroup analyses were conducted by sex (male or female), age group (≤9 years or 10-19 years), and uveitis location (anterior vs nonanterior). The secondary outcome was the 5-year cumulative

Figure 1. Flowchart of Study Population Selection



From 33 567 individuals diagnosed with uveitis between January 2008 and December 2022, those meeting the exclusion criteria were removed, yielding study population 1 (N = 28 856). Group 1 (N = 1200) comprised patients diagnosed with any of the 13 predefined immune-mediated inflammatory diseases (IMIDs) or prescribed immunosuppressants prior to the index date. After excluding group 1, study population 2 consisted of 27 656 individuals with uveitis and no history of the predefined IMIDs or prior immunosuppressant use.

incidence of immunosuppressant use after uveitis diagnosis, stratified by level of care and uveitis location. Level of care was defined as having at least 1 visit to a secondary or tertiary care center with a uveitis diagnosis.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and compared using the χ^2 test, while continuous variables were expressed as mean (SD) and compared using the Student *t* test. Cumulative incidence was estimated using the Kaplan-Meier method. To evaluate trends in pediatric uveitis incidence, age- and sex-adjusted incidence rate ratios (IRRs) were calculated for each year from 2011 to 2022 using 2019 as the reference year. IRRs and 95% CIs were estimated using Poisson regression adjusted for the age and sex distribution of the mid-year population. SIRs were calculated as the ratio of observed to expected cases. Expected IMID cases were estimated by multiplying age- and sex-specific incidence rates in the general pediatric population by the corresponding person-years among patients with uveitis. The 95% CIs for SIRs were calculated using a Poisson distribution model (mid-year population data from the Korean Statistical Information Service [KOSIS]) (eTable 2 in Supplement 1). To assess the robustness of our findings, we conducted sensitivity analyses using a less restrictive definition of uveitis and IMIDs (≥2 outpatient visits or ≥1 inpatient admission). Statistical analyses were performed using SAS version 9.4 (SAS Institute), SPSS version 25.0 (IBM), and R version 3.5.3 (R Project for Statistical Computing). Two-sided $P < .05$ was considered statistically significant.

Results

Demographics

Of 33 567 individuals younger than 20 years diagnosed with uveitis between 2008 and 2022, 28 856 remained after applying the exclusion criteria (study population 1). After excluding 1200 patients with prior IMIDs or immunosuppressant use, 27 656 patients comprised the final cohort (study population 2). Most individuals in the database were of Asian ethnicity.

A total of 27 656 pediatric patients with incident noninfectious uveitis (mean [SD] age, 12.6 [4.8] years; 16 132 males [58.3%]; 7253 younger than age 10 years [26.2%]) were identified and included in the final analysis cohort (group 2, also referred to as study population 2) (**Table 1**). These patients were selected from an initial pool of 28 856 individuals (study population 1) diagnosed between 2011 and 2022, after excluding 1200 patients (group 1) with pre-existing immune-mediated inflammatory diseases (IMIDs) or with prior immunosuppressant prescription (Figure 1). The mean (SD) follow-up duration was 5.9 (3.5) years for study population 1, 6.3 (3.3) years for group 1, and 6.0 (3.5) years for group 2 (study population 2). In group 1, the most common IMID was TIN (241 of 1200 [20.1%]), and the least common was antiphospholipid syndrome (3 of 1200 [0.3%]). Immunosuppressants were prescribed to 502 of 1200 patients (41.8%) patients in group 1 and 0 patients in group 2. Anterior uveitis accounted for 988 of 1200 patients (82.3%) in group 1 and 25 460 of 27 656 patients (92.1%) in group 2. Because this study used a nationwide administrative claims database with universal coverage, there were no missing data for the primary variables. Additional demographic characteristics are presented in Table 1 and eTable 3 in Supplement 1.

Incidence of Pediatric Uveitis

The crude incidence rate of pediatric uveitis among individuals younger than 20 years from January 2011 to December 2022 was 24.1 per 100 000 population (**Table 2**). Age- and sex-adjusted IRRs were calculated for each year using 2019 as the reference (Table 2). Uveitis incidence was significantly higher in males than in females throughout 2011 to 2022, except in 2020 (eTable 4 in Supplement 1). Additional subgroup analyses of age- and sex-adjusted IRRs by sex, age, and uveitis location were performed (eTables 5-7 in Supplement 1). IRRs for 2021 and 2022 did not differ significantly from 2019. In 2020, the IRR decreased significantly during the period of strict government-mandated

Table 1. Demographic Characteristics of the Study Population[a]

Characteristic	Total[b]	Group 1[c]	Group 2[d]	SMD
Total No.	28 856	1200	27 656	
Age, mean (SD), y	12.6 (4.8)	12.2 (5.4)	12.6 (4.8)	
0-4	2209 (7.7)	132 (11.0)	2077 (7.5)	
5-9	5441 (18.9)	264 (22.0)	5177 (18.7)	0.196
10-14	9157 (31.7)	295 (24.1)	8862 (32.0)	
15-19	12 049 (41.8)	509 (42.4)	11 540 (41.7)	
Sex				
Male	16 827 (58.3)	695 (57.9)	16 132 (58.3)	0.008
Female	12 029 (41.7)	505 (42.1)	11 524 (41.7)	
Comorbidities				
Hypertension	141 (0.5)	33 (2.8)	108 (0.4)	0.191
Type 1 diabetes	136 (0.5)	8 (0.7)	128 (0.5)	0.027
Other diabetes	325 (1.1)	50 (4.2)	275 (1.0)	0.201
Dyslipidemia	640 (2.2)	129 (10.8)	511 (1.9)	0.373
Ischemic stroke	5 (0.02)	0 (0)	5 (0.02)	0.019
Transient ischemic attack	7 (0.02)	2 (0.2)	5 (0.02)	0.049
Hemorrhagic stroke	18 (0.1)	0 (0)	18 (0.1)	0.036
Myocardial infarction	4 (0.01)	1 (0.1)	3 (0.01)	0.033
Chronic kidney disease	17 (0.1)	5 (0.4)	12 (0.04)	0.078
Hyperthyroidism	75 (0.3)	8 (0.7)	67 (0.2)	0.063
Hypothyroidism	131 (0.5)	21 (1.75)	110 (0.4)	0.131
Chronic liver disease	225 (0.8)	48 (4.0)	177 (0.6)	0.225
COPD	63 (0.2)	7 (0.6)	56 (0.2)	0.061
Allergic diseases				
Allergic rhinitis	12 904 (44.7)	674 (56.2)	12 230 (44.2)	0.241
Asthma	583 (2.0)	27 (2.3)	556 (2.0)	0.017
Atopic dermatitis	5486 (19.0)	361 (30.1)	5125 (18.5)	0.272
Immune-mediated inflammatory diseases				
Composite	974 (3.4)	974 (81.2)	0	NA
JIA	184 (0.6)	184 (15.3)	0	NA
Ankylosing spondylitis	89 (0.3)	89 (7.4)	0	NA
Behçet disease	25 (0.1)	25 (2.1)	0	NA
Kawasaki disease	239 (0.8)	239 (19.9)	0	NA
Sarcoidosis	5 (0.02)	5 (0.4)	0	NA
SLE	37 (0.1)	37 (3.1)	0	NA
Tubulointerstitial nephritis	241 (0.8)	241 (20.1)	0	NA
Multiple sclerosis	28 (0.1)	28 (2.3)	0	NA
Psoriasis	143 (0.5)	143 (11.9)	0	NA
Psoriatic arthritis	8 (0.03)	8 (0.7)	0	NA
Antiphospholipid syndrome	3 (0.01)	3 (0.3)	0	NA
Inflammatory bowel disease	48 (0.2)	48 (4.0)	0	NA
Reactive arthritis	15 (0.1)	15 (1.3)	0	NA
Immunosuppressants				
Composite	502 (1.7)	502 (41.8)	0	NA
Methotrexate	246 (0.9)	246 (20.5)	0	NA
Leflunomide	1 (0)	1 (0.1)	0	NA
Hydroxychloroquine	68 (0.2)	68 (5.7)	0	NA

(continued)

Table 1. Demographic Characteristics of the Study Population[a] (continued)

Characteristic	Total[b]	Group 1[c]	Group 2[d]	SMD
Cyclophosphamide	73 (0.3)	73 (6.1)	0	NA
Mycophenolate	52 (0.2)	52 (4.3)	0	NA
Azathioprine	36 (0.1)	36 (0.1)	0	NA
Tacrolimus	13 (0.1)	13 (3.0	0	NA
Cyclosporine	45 (0.2)	45 (3.8)	0	NA
Etanercept	51 (0.2)	51 (4.3)	0	NA
Adalimumab	13 (0.1)	13 (1.1)	0	NA
Infliximab	7 (0.1)	7 (0.6)	0	NA
Colchicine	74 (0.3)	74 (6.2)	0	NA
Mesalazine	29 (0.1)	29 (2.4)	0	NA
Sulfasalazine	160 (0.6)	160 (13.3)	0	NA
Everolimus	1 (0)	1 (0.1)	0	NA
Tofacitinib	1 (0)	1 (0.1)	0	NA
Tocilizumab	4 (0.01)	4 (0.3)	0	NA
Ustekinumab	1 (0)	1 (0.1)	0	NA
Dupilumab	1 (0)	1 (0.1)	0	NA
Uveitis type				
Anterior	26 448 (91.7)	988 (82.3)	25 460 (92.1)	0.294
Nonanterior	2408 (8.3)	212 (17.7)	2196 (7.9)	
Follow-up periods, mean (SD), y	5.9 (3.5)	6.3 (3.3)[e]	6.0 (3.5)	NA
Level of medical care				
Primary	22 275 (77.2)	625 (52.1)	21 650 (78.3)	0.572
Secondary or tertiary	6581 (22.8)	575 (47.9)	6006 (21.7)	

Abbreviations: COPD, chronic obstructive pulmonary disease; JIA, juvenile idiopathic arthritis; NA, not applicable; SLE, systemic lupus erythematosus; SMD, standardized mean differences.

[a] None of the patients received the following immunosuppressants: golimumab, sirolimus, fumarate, baricitinib, upadacitinib, abrocitinib, ozanimod, filotinib, deucravacitinib, apremilast, basiliximab, tocilizumab, ustekinumab, belimumab, secukinumab, ixekizumab, guselkumab, risankizumab, tralokinumab, canakinumab, or mizoribine.

[b] Study population 1, which included those of the 33 567 individuals diagnosed with uveitis between January 2008 and December 2022 who met the inclusion criteria.

[c] Group 1: Patients with uveitis who had a diagnosis of any of the 13 predefined immune-mediated inflammatory diseases or had received immunosuppressants before the index date.

[d] Group 2: This was study population 2 and included patients with uveitis who had neither a diagnosis of any of the 13 predefined immune-mediated inflammatory diseases nor a prescription for immunosuppressants before the index date.

[e] For Group 1, follow-up was defined from the index date to the end of the study period, as immune-mediated inflammatory diseases had already been diagnosed before the index date.

Table 2. Comparison of Annual Incidence Rate Ratios of Pediatric Uveitis Between 2011 and 2022 by Age and Sex, Using 2019 as the Reference Year

Year	Mid-year population	Events	Crude incidence rate	Unadjusted IRR (95% CI)[a]	*P* value	Age, sex-adjusted IRR (95% CI)[a]	*P* value
2011	11 450 165.5	2536	22.15	0.90 (0.85-0.96)	<.001	0.87 (0.82-0.92)	<.001
2012	11 217 997.0	2823	25.16	1.03 (0.97-1.08)	.36	1.00 (0.94-1.05)	.86
2013	10 967 676.0	2609	23.79	0.97 (0.92-1.03)	.29	0.95 (0.89-1.00)	.05
2014	10 701 294.0	2610	24.39	0.99 (0.94-1.05)	.86	0.98 (0.92-1.03)	.38
2015	10 434 370.0	2660	25.49	1.04 (0.98-1.10)	.17	1.03 (0.97-1.09)	.35
2016	10 167 570.5	2642	25.98	1.06 (1.00-1.12)	.04	1.06 (1.00-1.12)	.06
2017	9 878 328.5	2341	23.70	0.97 (0.91-1.02)	.25	0.97 (0.91-1.02)	.23
2018	9 572 709.5	2481	25.92	1.06 (1.00-1.12)	.06	1.06 (1.00-1.12)	.06
2019	9 266 584.0	2272	24.52	1 (Reference)		1 (Reference)	NA
2020	8 932 022.5	1786	20.00	0.82 (0.77-0.87)	<.001	0.82 (0.77-0.87)	<.001
2021	8 605 344.0	2118	24.61	1.00 (0.95-1.07)	.90	1.00 (0.94-1.06)	.98
2022	8 343 315.5	1978	23.71	0.97 (0.91-1.03)	.27	0.96 (0.90-1.02)	.14
Sum	119 537 377.0	28 856	24.14	NA	NA	NA	NA

Abbreviation: IRR, incidence rate ratio; NA, not applicable.

[a] IRR indicate annual mean incidence of uveitis during the year per annual mean incidence during 2019.

social distancing because of COVID-19, a trend that persisted in subgroup analysis by age (eTable 6 in Supplement 1).

Incidence of IMIDs in Pediatric Patients With Uveitis

The 5-year cumulative incidence of IMIDs in pediatric uveitis was 8.52% (95% CI, 8.16%-8.87%) overall, 7.45% (95% CI, 7.01%-7.88%) among males, and 10.03% (95% CI, 9.43%-10.63%) among

females (**Figure 2** and eTable 8 in Supplement 1). For children aged 0 to 9 years, the 5-year cumulative incidence was 7.03% (95% CI, 6.40%-7.67%), compared with 9.00% (95% CI, 8.58%-9.42%) among those aged 10 to 19 years. Across the overall population as well as male and female subgroups, the 5-year cumulative incidence was highest for AS (2.53%; 95% CI, 2.33%-2.73%), followed by TIN (1.90%; 95% CI, 1.72%-2.08%), psoriasis (1.59%; 95% CI, 1.43%-1.75%), systemic lupus erythematosus (0.69%; 95% CI, 0.59%-0.79%), Behçet disease (0.68%; 95% CI, 0.57%-0.78%), and JIA (0.66%; 95% CI, 0.56%-0.76%), and was lowest for antiphospholipid syndrome (0.04%; 95% CI, 0.01%-0.06%) (eFigure 1 in Supplement 1). Subgroup analysis by age showed that in the younger subgroup (0 to 9 years), KD had the highest cumulative incidence (2.36%; 95% CI, 2.00%-2.71%), whereas AS had the highest cumulative incidence (3.16%; 95% CI, 2.91%-3.42%) in the older subgroup (10 to 19 years; eFigure 2 and eTable 8 in Supplement 1). KD showed the most pronounced age-related difference: its incidence remained approximately 0.03% in older children throughout the 5-year period. Several other IMIDs, such as AS, Behçet disease, systemic lupus erythematosus, sarcoidosis, and reactive arthritis bowel disease, were more common in the older subgroup. eFigure 2 and eTable 8 in Supplement 1 also showed that KD was diagnosed primarily within the first year after uveitis diagnosis, while JIA, AS, and sarcoidosis also demonstrated similar patterns.

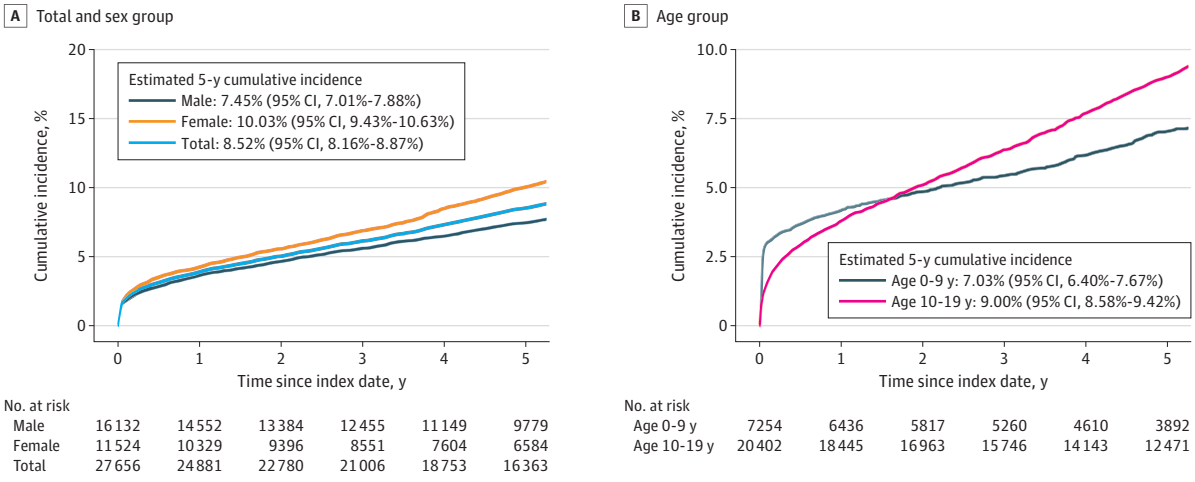
Standardized Incidence Ratios of IMIDs in Patients With Uveitis Compared With the General Population

The risk of developing IMIDs was significantly higher in patients with uveitis than in the age- and sex-adjusted midyear population (SIR, 6.78; 95% CI, 6.54-7.02) (**Table 3**). The risk was higher in females (SIR, 7.81; 95% CI, 7.43-8.21) than in males (SIR, 5.99; 95% CI, 5.69-6.29). The older subgroup (aged 10 to 19 years) had a markedly elevated risk (SIR, 10.02; 95% CI, 9.64-10.42) than did the younger subgroup (aged 0 to 9 years) (SIR, 2.78; 95% CI, 2.56-3.02). Among individual IMIDs, sarcoidosis demonstrated the highest standardized incidence ratio (SIR, 444.48; 95% CI, 357.97-551.89), followed by AS (68.94; 95% CI, 64.45-73.73), Behçet disease (66.29; 95% CI, 57.81-76.02), and SLE (30.69; 95% CI, 27.05-34.82), whereas multiple sclerosis showed the lowest SIR (2.68; 95% CI, 1.71-4.20) (eTable 9 in Supplement 1).

Risk of Immunosuppressant Use After the Diagnosis of Uveitis

After excluding 974 of 28 856 patients (3.40%) who had previously been prescribed immunosuppressants, the risk of immunosuppressant use was analyzed in the remaining 27 882

Figure 2. Five-Year Cumulative Incidence of a Composite of 13 Predefined Immune-Mediated Inflammatory Diseases in Pediatric Patients With Noninfectious Uveitis



A, Cumulative incidence curves by sex (total, male, and female). B, Cumulative incidence curves stratified by age groups (0 to 9 years and 10 to 19 years).

patients from the study population 1. eFigure 3 and eTable 10 in Supplement 1 show that the overall cumulative incidence of immunosuppressant use was 2.39% (95% CI, 2.19%-2.59%), with a higher incidence in females than in males (2.54%; 95% CI, 2.22%-2.85% vs 2.29%; 95% CI, 2.04%-2.54%) and in the older subgroup than in the younger subgroup (2.57%; 95% CI, 2.34%-2.81% vs 1.86%; 95% CI, 1.52%-2.20%). Immunosuppressants were used more frequently in nonanterior uveitis than in anterior uveitis overall and across all sex and age subgroups (eFigure 4 and eTable 10 in Supplement 1). There was a difference in treatment patterns between primary vs secondary and tertiary medical care centers. The cumulative incidence of immunosuppressant use showed that 0.67% (95% CI, 0.55%-0.79%) of patients were prescribed immunosuppressants in primary medical care centers, whereas the incidence was 8.42% (95% CI, 7.67%-9.16%) in secondary and tertiary centers (eFigure 5 and eTable 11 in Supplement 1). In addition, the frequency of specific immunosuppressant prescriptions differed across care levels. In 22 095 primary centers, the most frequently prescribed agents were colchicine (234 [1.06%]), sulfasalazine (134 [0.61%]), and methotrexate (91 [0.41%]) (eTable 12 in Supplement 1). In secondary and tertiary centers, antimetabolites were prescribed significantly more often than in primary centers, including methotrexate (526 of 6259 [8.40%] vs 0.41%), mycophenolate (121 of 6259 [1.93%] vs 16 of 22 095 [0.07%]), and azathioprine (42 of 6259 [2.00%] vs 125 of 22 095 [0.19%]). Immunosuppressant use stratified by the presence of IMID status showed an estimated cumulative incidence of 8.62% (95% CI, 7.65%-9.58%) in patients with IMIDs and 1.37% (95% CI, 1.21%-1.53%) in those without IMIDs (eFigure 6 in Supplement 1).

Sensitivity Analysis

In the sensitivity analysis using a less strict definition of uveitis requiring at least 2 outpatient visits (compared with 3 visits in the main analysis), the overall trends were consistent with those of the main analysis (eTables 13 to 25 and eFigures 7 to 12 in Supplement 1). The 5-year cumulative incidences of IMIDs and immunosuppressant use, as well as SIRs, were all comparable with those in the main analysis, and the rank order of 5-year cumulative incidences across individual IMIDs was largely preserved.

Discussion

This cohort study evaluated the incidence and risk of IMIDs and immunosuppressant use in pediatric patients with noninfectious uveitis using the HIRA database. Overall, 3.4% of patients who had a diagnosis of 1 of the 13 predefined IMIDs before uveitis onset and approximately 8.5% of those included in the study developed IMIDs during 5-year follow-up. Thus, approximately 12% of pediatric uveitis cases were associated with IMIDs. In contrast, a tertiary-center study by Shin et al[1] reported systemic rheumatic diseases in 28.4% of pediatric uveitis cases, likely reflecting referral bias in

Table 3. Incidence Rate and Standardized Incidence Ratio of a Composite of 13 Predefined Immune-Mediated Inflammatory Diseases in Pediatric Patients With Noninfectious Uveitis

Characteristic	Immune-mediated inflammatory disease cases	Sum of person-year	Incidence rate (95% CI)[a]	Expected immune-mediated inflammatory diseases cases	Standardized incidence ratio (95% CI)[b]	*P* value
Total	3057	165 891.9	18.43 (17.79-19.09)	451.22	6.78 (6.54-7.02)	<.001
Sex						
Male	1533	40 410.2	37.94 (36.08-39.88)	256.07	5.99 (5.69-6.29)	<.001
Female	1524	125 481.8	12.15 (11.55-12.77)	195.14	7.81 (7.43-8.21)	<.001
Age group						
0-9	563	98 783.4	5.70 (5.25-6.19)	202.40	2.78 (2.56-3.02)	<.001
10-19	2494	67 108.5	37.16 (35.73-38.65)	248.81	10.02 (9.64-10.42)	<.001

[a] Incidence rates are presented per 1000 person-years.

[b] Standardized incidence ratios are adjusted by age and sex.

tertiary settings. Overall population-level risk is substantially lower when primary through tertiary care settings are included.

Our findings are consistent with epidemiological patterns reported in previous studies of Korean pediatric uveitis. The incidence in our data was 24/100 000 person-years, comparable to 52/100 000 person-years in the study by Rim et al[16] and 20/100 000 person-years in that by Hong et al.[11] Population-based studies from Korea and Taiwan showed higher incidence in males and in older pediatric patients.[11,17] Similarly, in all study years (2011 to 2022), incidence was higher in males and older patients in our data. Although the cumulative incidence was initially higher in patients aged 0 to 9 years, it increased more rapidly over time in those aged 10 to 19 years (Figure 2). The early pattern in younger children was largely driven by KD, which occurred predominantly within the first year after uveitis diagnosis (eTable 8 in Supplement 1). A rapid increase in the cumulative incidence of several IMIDs, including KD, JIA, AS, and sarcoidosis, during the first year after the index date may reflect prompt referral of uveitis patients to pediatric rheumatologists. Although we could not distinguish whether IMIDs diagnosed after uveitis represent prodromal disease, delayed recognition of preexisting subclinical disease, or shared pathophysiology, the sharp early increase in cumulative incidence may partly reflect detection of previously unrecognized disease after systematic rheumatologic evaluation.

We also investigated SIRs for developing IMIDs. Patients with uveitis had an overall SIR of 6.78, with higher SIRs in females and older subgroups. To our knowledge, this is the first epidemiological study to systematically analyze SIRs of 13 common pediatric IMIDs in patients with uveitis. We recommend referring noninfectious uveitis patients to pediatric rheumatologists given that the highest incidences and SIRs of IMIDs are for pediatric rheumatic diseases. Across all subgroups, the highest SIR was observed for sarcoidosis. Although sarcoidosis is uncommon in children and typically peaks in the fifth decade of life, one study showed that uveitis developed in almost half of pediatric patients with sarcoidosis.[18,19] The highest SIR observed for sarcoidosis may reflect the predilection of pediatric sarcoidosis to present with ocular involvement. Unlike adult sarcoidosis, which more commonly presents with pulmonary symptoms, pediatric sarcoidosis, particularly in younger children, frequently manifests as a triad of uveitis, skin rash, and arthritis, often without apparent systemic symptoms at onset.[20] Therefore, uveitis may serve as the first and sometimes the only clinical sign prompting further systemic evaluation, ultimately leading to a sarcoidosis diagnosis. While absolute incidence varied considerably owing to baseline disease prevalence, the hierarchy of SIRs did not necessarily correspond to absolute incidence rates. Despite this discrepancy, our findings can guide targeted evaluation during systemic work-up of pediatric uveitis.

Of the 28 856 newly diagnosed patients with uveitis, 502 had been prescribed immunosuppressants before the uveitis diagnosis. Among patients without prior immunosuppressant use, 2.4% were prescribed these medications within 5 years, with higher rates in nonanterior uveitis. This pattern aligns with clinical practice, where intermediate, posterior, and panuveitis often require immunosuppression.[3,21,22] The 3 most prescribed drugs across all care levels were methotrexate, sulfasalazine, and colchicine. Methotrexate is a well-established first-line steroid-sparing therapy in pediatric uveitis and other pediatric IMIDs, such as JIA.[23-25] Notably, colchicine was the most frequently prescribed medication in primary centers (234 [1.1%]) and the third most common in secondary and tertiary centers (134 [2.1%]). Its relatively favorable safety profile may account for its frequent use in primary care.[26,27]

Most pediatric patients with uveitis in our data were treated in 22 095 primary care centers rather than referred to 6259 secondary or tertiary centers. In secondary and tertiary centers, synthetic agents were prescribed roughly 10 times more often than biologics, such as etanercept, adalimumab, infliximab, and golimumab, consistent with findings from a Korean tertiary-center study.[1] Additionally, antimetabolites and biologics were used significantly more often in secondary and tertiary centers, suggesting that patients requiring these medications are more likely to be referred to higher levels of care.

Limitations

This study has several limitations. First, it used a single-country dataset from a relatively homogeneous Asian population, which may limit generalizability to other ethnic groups and health care systems. However, the nationwide coverage of the South Korean National Health Insurance database minimizes selection bias and strengthens internal validity. Second, the HIRA claims database uses the *KCD-8* classification, which lacks detailed subhierarchical coding. Therefore, nonanterior uveitis could not be further classified into intermediate, posterior, or panuveitis. Nevertheless, the distinction between anterior and nonanterior uveitis is commonly used in claims-based studies and reflects differences in clinical management.[11,15] Third, our definition of uveitis required corticosteroid use, which may have excluded mild cases managed without steroids. However, most pediatric uveitis cases are unlikely to be treated without first-line steroid therapy.[16,28,29] While the combination of diagnostic codes and corticosteroid prescription enhances face validity by capturing treated, clinically relevant cases, as previously adopted in large claims-based studies of noninfectious uveitis, we acknowledge the absence of direct validation studies for this specific algorithm in Korean pediatric claims data.[30,31] Fourth, immunosuppressant use may have been influenced by national insurance policies, as some biologic agents were not approved for pediatric uveitis in South Korea during the study period. In addition, the requirement for 3 outpatient visits might have led to an underestimation of the true incidence of uveitis. To ensure the robustness of our findings and mitigate potential selection bias, we performed a sensitivity analysis using a less restrictive definition (at least 2 outpatient visits). This analysis yielded similar trends, although with lower cumulative incidences and SIRs. We speculate that these differences may reflect the less restrictive definition of uveitis in the sensitivity analysis, which may have included some nonuveitis patients. Despite these limitations, this study provides population-based evidence on the epidemiology and management of pediatric uveitis.

Conclusions

In this cohort study of 27 656 pediatric patients with noninfectious uveitis, a nearly 7-fold elevated risk of IMIDs was observed, with substantial heterogeneity by demographic and disease factors. Evidence-based risk estimates were provided that can inform systematic screening and multidisciplinary management. Because pediatric uveitis may be a sentinel manifestation of systemic disease, these results supported targeted surveillance and timely intervention to reduce long-term morbidity.

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SUPPLEMENT 1.

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SUPPLEMENT 2.
Data Sharing Statement