

Effect of Uveitis on the Development of Keratopathy: A Population-Based Cohort Study

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PURPOSE. The purpose of this study was to evaluate the effect of uveitis on the development of various keratopathies via the use of the National Health Insurance Research Database (NHIRD) in Taiwan.

METHODS. Approximately 1 million patients were randomly sampled from the registry of the NHIRD. Patients diagnosed with uveitis by ophthalmologists were enrolled in the study group after exclusion. Each individual in the study group was age and sex matched to four non-uveitis individuals who serve as the control group. In addition to keratopathy, other possible risk factors and medications were included in the multivariate model, and the effects of different subtypes of uveitis for developing keratopathies were also analyzed.

RESULTS. A total of 4773 uveitis patients (2662 male and 2111 female) and 19,092 non-uveitis patients (10,648 male and 8444 female) were enrolled. There were 406 events of keratopathy in the study group, and another 764 events occurred in the control group. A higher incidence rate was found in the study group after adjustment (adjusted hazard ratio [aHR]: 1.772), with a greater cumulative probability ($P < 0.0001$). For the subgroup analysis, anterior uveitis (aHR = 1.765) and panuveitis (aHR = 3.386) increased the risk of developing keratopathies. Moreover, male sex was associated with a higher aHR than female sex for developing keratopathies in the study group.

CONCLUSIONS. The presence of uveitis significantly elevates the risk for developing keratopathy.

Keywords: uveitis, keratopathy, cornea, population-based

Uveitis refers to an inflammatory disorder that occurs in the uvea that can be vision threatening and needs optimal management.¹ The incidence is estimated to be approximately 5 per 10,000 person-years in the United States,² whereas a higher incidence of 10 to 20 per 10,000 person-years was observed in Asian countries, including South Korea and Taiwan.^{3,4} There are several subtypes of uveitis, such as anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis, with anterior uveitis accounting for nearly half to approximately 80% of patients.⁴⁻⁶ Idiopathic, infectious, and noninfectious etiologies have been reported, which all present with the same features of inflammatory reactions.¹

Certain rheumatoid diseases lead to the development of uveitis.⁷ Ankylosing spondylitis is correlated with acute anterior uveitis, in which dense hypopyon occurs more commonly than in other types of acute anterior uveitis.^{8,9} Juvenile idiopathic arthritis is also a potential risk factor for uveitis according to a previous population-based study.¹⁰ Other morbidities that are associated with uveitis include Behçet disease, syphilis, seronegative spondyloarthropathies, and psoriasis.^{9,11} In general, all of the above diseases and uveitis share a similar pathophysiology of inflammation, which implies that uveitis and related inflammatory reactions may also damage the ocular tissue.¹²



Concerning uveitis and associated ocular diseases, glaucoma, and cataracts have been proven to be associated with anterior uveitis.^{9,13} For the corneal lesions, the association of uveitis with band keratopathy and corneal endothelial impairment has been reported previously,^{7,14-16} whereas the relationship between uveitis and other corneal disorders had not been elucidated. Uveitis and dry eye disease (DED) share similar inflammatory pathophysiology, including the cytokine activation of interleukin and TNF,^{17,18} and the existence of DED leads to corneal damage.¹⁹ Additionally, the dysfunctional immune system in autoimmune diseases can induce the development of both uveitis and corneal diseases.¹² Accordingly, a correlation between uveitis and corneal diseases may be possible and needs to be verified.

Herein, we reported the effects of uveitis on the development of different types of keratopathy via the use of the National Health Insurance Research Database (NHIRD) in Taiwan. In addition, the effects of different subtypes of uveitis and other comorbidities were also analyzed.

MATERIALS AND METHODS

Data Source

This retrospective, population-based cohort study was approved by the National Health Insurance Administration and the Institute Review Board of Chung Shan Medical University. Provided by the Taiwan National Health Research Institutes, the NHIRD contains insurance claims data of more than 99% of Taiwan's population. The claims data used in this study were from the 2010 Longitudinal Health Insurance Database (LHID), which contains data on 1 million patients randomly sampled from the registry of the NHIRD for the year 2010. The LHID 2010 data were linked from January 1, 1997, to December 31, 2013, and the *International Classification of Diseases*, ninth edition (ICD-9), was used to identify the diseases. Medications prescribed, demographics, socioeconomic status, and location of patients were also available in the NHIRD.

Patient Selection

Patients were regarded as having uveitis if their medical records indicated a history of uveitis (ICD-9 code: 360.12, 363.0x, 363.1x, 363.2x, 364.0x, 364.1x, 364.2x, and 364.3) from 2001 to 2011, and the index date was set as the date 1 year after the uveitis diagnosis, which thus ranged from 2002 to 2012. To avoid misdiagnosis of uveitis, only patients who received a diagnosis of uveitis from ophthalmologists (department code: 10) were enrolled. In addition, the following exclusion criteria were applied to better elucidate the association between uveitis and keratopathy: (1) having been diagnosed with legal blindness (ICD-9 code: 369.4); (2) having received any type of eyeball removal surgery (ICD-9 codes: 16.5x); (3) having received an ocular tumor diagnosis (ICD-9 codes: 190.0-190.9); (4) having received a diagnosis of major ocular trauma (ICD-9-CM codes 870.x, 871.x, 921.x 940.x) before the index date; (5) having received a diagnosis of any type of keratopathy (see next section for the diagnostic code) before the index date; and (6) missing demographic data. In addition, each individual in the study group was age and sex matched to four non-uveitis individuals who serve as the control group, and the index dates of those in the control group corresponded with matched uveitis patients. Those uveitis patients who could not be matched with four non-uveitis patients were excluded.

Main Outcome Measurement

There is no single ICD-9 diagnostic code for keratopathies to be defined as the primary outcome of the current study. Therefore, the diagnosis of keratopathies in the current study consisted of different disease subgroups: (1) corneal ulcer (ICD-9 codes: 370.0x), (2) superficial and stromal keratitis (ICD-9 codes: 370.2x, 370.8, 370.9), (3) keratoconjunctivitis (ICD-9 codes: 370.3x, 370.4x), (4) interstitial and deep keratitis (ICD-9 codes: 370.5x), (5) corneal neovascularization (ICD-9 codes: 370.6x), (6) corneal opacity (ICD-9 codes: 371.0x), and (7) corneal edema (ICD-9 codes: 371.21-371.23). In practice, ICD-9 codes for "unspecific corneal disorder (ICD-9 codes: 371.9)" and "unspecific corneal edema (ICD-9 codes: 371.20)" are overused for minor corneal lesions; thus, these codes were eliminated to prevent overestimation of the number of clinically significant keratopathy episodes. Moreover, band keratopathy (ICD-9 codes: 371.43) was also excluded because uveitis is a known risk factor for band keratopathy.²⁰ Similar to the uveitis population, only patients who received the above diagnostic code by an ophthalmologist would be regarded as achieving the outcome.

Demographic Variables and Comorbidities

We also considered the effects of demographic conditions (i.e., age, sex, urbanization, and income level) and the following systemic comorbidities in the analysis model to standardize the general health status, erase the potential risk factor for keratopathy, and reduce the effects of some complications from uveitis-related treatment: hypertension (ICD-9 codes: 401-405), diabetes mellitus (DM) (ICD-9 codes: 250.x), hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.4, and 272.9), rheumatic arthritis (ICD-9 codes: 714.x, V82.1), Sjögren's syndrome (ICD-9 codes: 710.2), Wegener's granulomatosis (ICD-9 codes: 446.4), systemic lupus erythematosus (ICD-9 codes: 710.0), polyarteritis nodosa (ICD-9 codes: 446.0), and relapsing polychondritis (ICD-9 codes: 733.99). In addition, immunosuppressants such as corticosteroids and disease-modifying antirheumatic drugs (DMARDs), which are used to treat uveitis, were also involved in the multivariate analysis, including prednisolone (insurance code: H02AB04, H02AB06, S01BA04, S01CA02), betamethasone (insurance code: S01BA06, S01CA05), methylprednisolone (insurance code: H02AB04), triamcinolone (insurance code: H02AB08), dexamethasone (insurance code: H02AB02, S01BA01, S01CA01), cyclosporine (insurance code: L04AD01), sulfasalazine (insurance code: A07EC01), azathioprine (insurance code: L04AX01), methotrexate (insurance code: L04AX03), cyclophosphamide (insurance code: L01AA01), tacrolimus (insurance code: L04AD02), and leflunomide (insurance code: L04AA13). For the ocular morbidities, glaucoma (ICD-9 codes 365.x), cataract (ICD-9 codes 366.10-366.19, 366.8, 366.9), and DED (ICD-9 codes 370.33, 370.34, 372.53, 375.15) were enrolled in the analysis model. We longitudinally traced the data from the index date until the date of keratopathy diagnosis, withdrawal from the National Health Insurance program, or December 31, 2013.

Statistical Analysis

SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for all the analyses. After age and sex matching, the χ^2 test was used to test for differences in the demographic data (age, sex, urbanization, and income level) between the study and control groups. Then, the incidence rate ratio (IRR) with

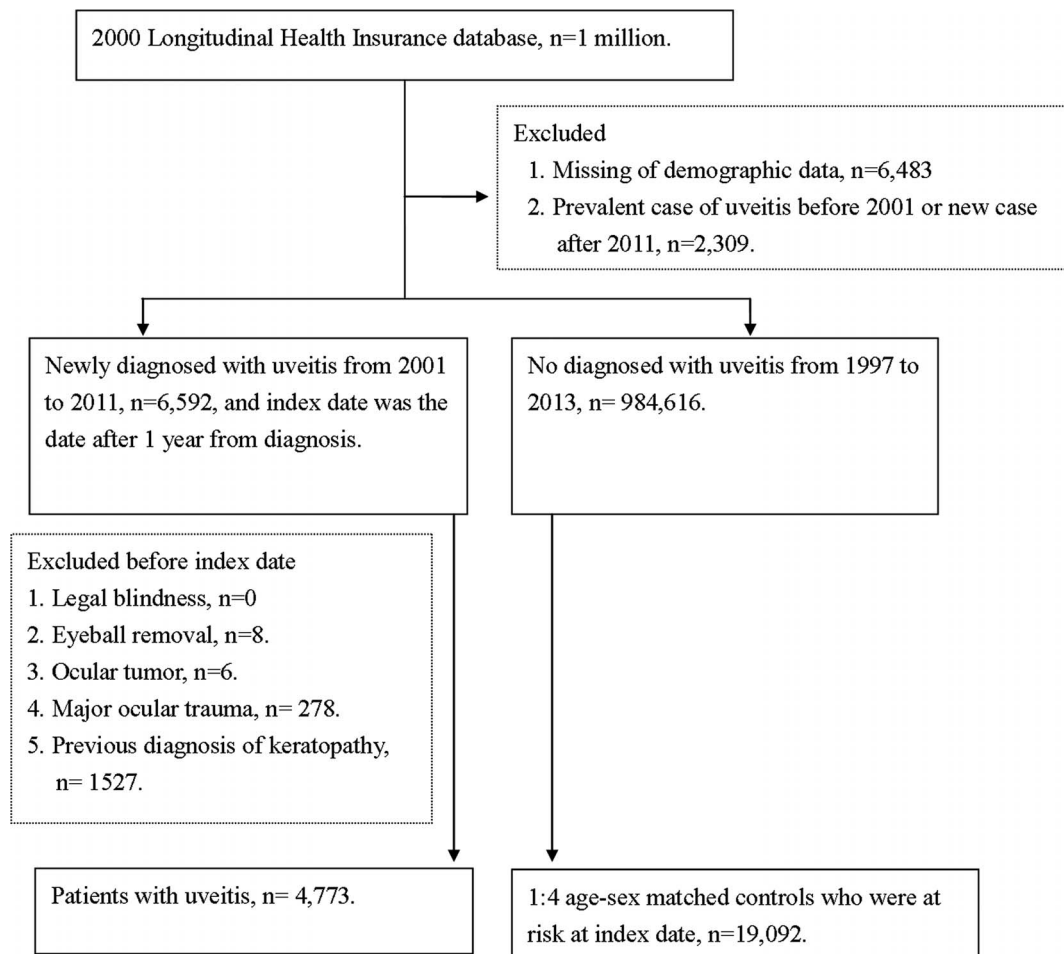


FIGURE 1. Flowchart of patient selection.

corresponding 95% confidence intervals (CIs) and the crude hazard ratio (HR) were calculated by Poisson regression. In the next step, Cox proportional hazard regression was adopted that enrolled demographic data, prominent ocular diseases, systemic comorbidities, and immunosuppressants mentioned above in the multivariate model to compute adjusted HRs (aHR) of uveitis, which were estimated to reduce the confounding effects from demographic status, systemic comorbidities, ocular disease, and medications for uveitis treatment. Furthermore, the study group was divided into several subgroups according to the subtypes of uveitis, including the anterior uveitis subgroup (ICD-9 codes: 364.0x, 364.1x, 364.2x, 364.3), intermediate uveitis subgroup (ICD-9 codes: 363.21), posterior uveitis subgroup (ICD-9 codes: 363.0x, 363.1x, 363.20, 363.22), and panuveitis subgroup (ICD-9 codes: 360.12). Then, the aHR was calculated in each uveitis subgroup, with the effects of different uveitis subtypes and other indexes enrolled in the multivariate model. We plotted Kaplan-Meier curves to indicate the cumulative incidence proportion of keratopathy between the study and control groups with a maximum interval of 12 years from the index date and used the log rank test to determine the significant difference between the survival curves. Because most patients in the NHIRD are Han Taiwanese, race was not considered as a covariate. The results with $P < 0.05$ were regarded as statistically significant, and $P < 0.0001$ was depicted as $P < 0.0001$.

RESULTS

A total number of 4773 patients diagnosed with uveitis and another 19,092 non-uveitis patients were enrolled. The flowchart of patient selection is shown in Figure 1. There were 4299 patients diagnosed with anterior uveitis, 14 patients diagnosed with intermediate uveitis, 296 patients diagnosed with posterior uveitis, and 423 patients diagnosed with panuveitis. The study group included a higher urbanization level and higher incidence of ocular comorbidities and systemic diseases, except Wegener's granulomatosis, polyarteritis nodosa, and relapsing polychondritis (Table 1). A greater use of immunosuppressant medications, except leflunomide, was observed in the study group (Table 2).

There were 406 events of keratopathy in the study group, and another 764 events occurred in the control group. The IRR was significantly higher in the study group than the control group after adjustment of all the demographics, systemic disorders, ocular comorbidities, and immunosuppressants (aHR: 1.772; CI: 1.530 to 2.053; Table 3). For the subgroup analysis of uveitis, the existence of anterior uveitis (aHR: 1.765; CI: 1.511 to 2.063) and panuveitis (aHR: 3.386; CI: 2.129 to 5.385) significantly increased the risk of developing keratopathies (Table 3). The intermediate uveitis subgroup, however, could not be analyzed due to the rare occurrence. Moreover, the cumulative probability also showed a significantly increased risk of keratopathy in the study group ($P < 0.0001$), and the Kaplan-Meier curve is illustrated in Figure 2.

TABLE 1. Baseline Characteristics Between Study and Matched Control Groups

Baseline Characteristics	Uveitis (n = 4773)	Control (n = 19,092)	P Value
Subgroup of uveitis*			
AAU	4299 (90.07%)	-	
IU	14 (0.29%)	-	
POU	296 (6.20%)	-	
PU	423 (8.86%)	-	
Median of follow-up months	70	75	
Maximum of follow-up months†	144	144	
Age at baseline, mean ± SD	51.49 ± 18.87	51.49 ± 18.87	1.0000
<40	1374 (28.79%)	5496 (28.79%)	
40-59	1663 (34.84%)	6652 (34.84%)	
≥60	1736 (36.37%)	6944 (36.37%)	
Sex			1.0000
Female	2111 (44.23%)	8444 (44.23%)	
Male	2662 (55.77%)	10,648 (55.77%)	
Urbanization			<0.0001‡
Urban	2874 (60.21%)	11,321 (59.30%)	
Suburban	1496 (31.34%)	5704 (29.88%)	
Rural	403 (8.44%)	2067 (10.83%)	
Low income	30 (0.63%)	106 (0.56%)	0.5472
Comorbidities			
Glaucoma	1300 (27.24%)	363 (1.90%)	<0.0001‡
Cataract	1647 (34.51%)	1822 (9.54%)	<0.0001‡
Dry eye	593 (12.42%)	643 (3.37%)	<0.0001‡
Rheumatoid arthritis	114 (2.39%)	239 (1.25%)	<0.0001‡
Sjogren's syndrome	64 (1.34%)	112 (0.59%)	<0.0001‡
Wegener's granulomatosis	1 (0.02%)	1 (0.005%)	0.2888
Systemic lupus erythematosus	20 (0.42%)	31 (0.16%)	0.0006‡
Polyarteritis nodosa	0 (0.00%)	1 (0.010%)	0.6171
Relapsing polychondritis	1 (0.02%)	8 (0.04%)	0.5049
Hypertension	1554 (32.56%)	4909 (25.71%)	<0.0001‡
DM	1024 (21.45%)	2302 (12.06%)	<0.0001‡
Hyperlipidemia	878 (18.40%)	2647 (13.86%)	<0.0001‡

* Because one individual may be diagnosed with more than one type of uveitis, the overall incidence of uveitis excess 100%.

† From January 2002 to December 2013.

‡ Significant difference between the study and control groups.

Concerning age and sex, both male and female sex and all age populations in the study group showed a higher aHR than that in the control group, and male sex revealed a greater risk for developing keratopathy than female sex (Table 4).

TABLE 2. Immunosuppressant Use From Uveitis Diagnosis to Index Date

Immunosuppressant	Uveitis (n = 4773)	Control (n = 19,092)	P Value
Corticosteroid	4480 (93.86%)	7587 (39.74%)	<0.0001*
Prednisolone	3605 (75.53%)	2940 (15.40%)	<0.0001*
Betamethasone	1682 (35.24%)	933 (4.89%)	<0.0001*
Methylprednisolone	280 (5.87%)	666 (3.49%)	<0.0001*
Triamcinolone	925 (19.38%)	2830 (14.82%)	<0.0001*
Dexamethasone	2744 (57.49%)	3638 (19.06%)	<0.0001*
DMARDs	223 (4.67%)	107 (0.56%)	<0.0001*
Cyclosporine	28 (0.59%)	6 (0.03%)	<0.0001*
Sulfasalazine	169 (3.54%)	58 (0.30%)	<0.0001*
Azathioprine	17 (0.36%)	9 (0.05%)	<0.0001*
Methotrexate	44 (0.92%)	37 (0.19%)	<0.0001*
Cyclophosphamide	12 (0.25%)	18 (0.09%)	0.0061*
Tacrolimus	7 (0.15%)	4 (0.02%)	0.0003*
Leflunomide	3 (0.06%)	5 (0.03%)	0.2158

* Significant difference between the study and control groups.

DISCUSSION

Briefly, the results of the current study demonstrated that there was a higher IRR for developing keratopathies in the patients with uveitis than non-uveitis individuals. Furthermore, the aHR for developing keratopathies was still higher in the study group with a higher cumulative probability in a longer disease course. The subgroup analysis also implied that the incidence of keratopathies was higher in anterior uveitis and panuveitis, showing the general risk of keratopathies in the uveitic population.

The previous studies showed that uveitis, especially chronic uveitis, would lead to band keratopathy.^{20,21} Nevertheless, the inflammatory process in uveitis that involves cytokine alteration such as IL-6 and TNF may influence the corneal condition,¹⁷ because the use of cyclosporine that suppresses interleukin activity can relieve some categories of keratopathies.²² Moreover, the corneal endothelial cells were damaged with an altered central corneal thickness in patients with uveitis,^{14-16,23} whereas inflammatory cell infiltration into the corneal stroma was also observed during the onset of anterior uveitis.²⁴ On the other hand, the same inflammatory mediators and immune cells increased with uveitis and keratopathies,^{17,25,26} indicating that a general immune reaction and inflammatory response could cause both uveitis and several types of keratopathies. In clinical studies, systemic disorders featuring immune and inflammation impairment, such as

TABLE 3. Incidence Risk of Keratopathy Among Different Subgroups of Uveitis and Control Groups

Uveitis Subgroup	Follow-Up in Person-Months	Event of Keratopathy	Incidence Rate* (95% CI)	Crude HR (95% CI)	aHR† (95% CI)
Overall					
uveitis (<i>n</i> = 4773)	341,745	406	118.80 (107.79-130.93)	2.215 (1.964-2.498)	1.772 (1.530-2.053)
Control (<i>n</i> = 19,092)	1,430,651	764	53.4 (49.75-57.33)	Reference	Reference
Anterior uveitis subgroup					
Exposure (<i>n</i> = 4299)	306,029	369	120.58 (108.88-133.53)	2.213 (1.950-2.510)	1.765 (1.511-2.063)
Control (<i>n</i> = 17,196)	1,284,795	697	54.25 (50.37-58.43)	Reference	Reference
Posterior uveitis subgroup					
Exposure (<i>n</i> = 296)	22,367	28	125.19 (86.43-181.32)	2.270 (1.431-3.599)	1.541 (0.890-2.669)
Control (<i>n</i> = 1184)	92,850	51	54.93 (41.75-72.27)	Reference	Reference
Panuveitis subgroup					
Exposure (<i>n</i> = 423)	31,526	46	145.92 (109.30-194.79)	3.633 (2.448-5.393)	3.386 (2.129-5.385)
Control (<i>n</i> = 1692)	133,048	53	39.83 (30.43-52.15)	Reference	Reference

* Per 100,000 person-months.

† Adjusted for age, sex, urbanization level, comorbidities, and medical use (including corticosteroids and DMARDs).

rheumatoid arthritis and psoriasis, were associated with the occurrence of uveitis and keratopathies.^{9,11,12,27} Additionally, the concomitant uveitis and keratitis in patients with rheumatoid arthritis had been reported.²⁸ The above evidence suggests a more universal risk of keratopathies in patients with uveitis resulting from the uveitis itself or a diffuse inflammatory reaction, which was proved by the current study.

In the current study, the IRR of keratopathies in patients diagnosed with uveitis is higher than that in the control group with a significantly greater aHR and cumulative probability. Except for the development of band keratopathies in uveitic patients reported previously,²⁰ the current study showed a universal risk of developing keratopathies in the whole uveitis population by excluding the occurrence of band keratopathies. Moreover, the previous studies mainly focused on the correlation between the anterior uveitis and corneal disorders,¹⁴⁻¹⁶ whereas panuveitis yielded a significant effect on the development of keratopathies in the current study. To our knowledge, this is a preliminary experience to reveal that uveitis other than anterior uveitis will increase the occurrence

of keratopathies even after adjustment, and the risk would positively relate to the disease period according to the significant cumulative probability in the study group. The highest aHR was observed for the panuveitis subgroup, which may result from the diffusing inflammation and worst prognosis compared with other uveitis subtypes.^{29,30} Although the aHR in the posterior uveitis subgroup did not show a significant difference, the aHR reached 1.541, which still elevates the risk of developing keratopathies to some degree. On the other hand, there were 406 episodes of keratopathy from 4773 patients in the study group, which has a much higher occurrence rate than the gross Taiwanese population and another Asian population,^{4,31} indicating that a majority of the uveitic patients are at risk of developing keratopathy.

Ocular diseases such as glaucoma, cataracts, and DED showed significantly higher numbers in the study group compared with the control group. Glaucoma was proven to be associated with certain types of uveitis, with a significant difference from preceding articles.^{5,13,32} Moreover, cataracts also occurred more commonly in individuals with chronic

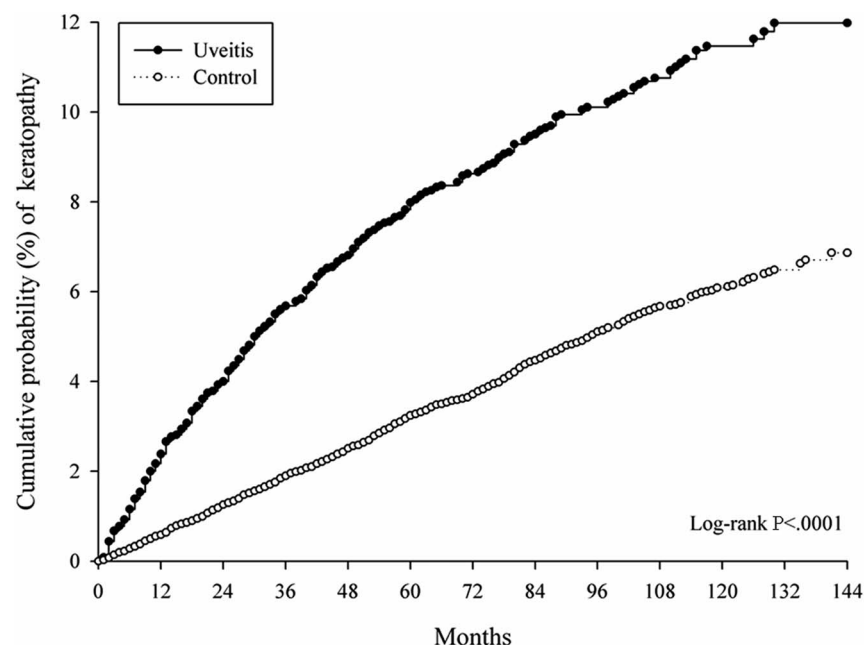


FIGURE 2. Kaplan-Meier curves with a cumulative proportion of keratopathy in matched uveitis and control groups.

TABLE 4. Subgroup Analysis of the Risk of Keratopathy With Uveitis

Subgroup	aHR*	95% CI	P Value
Subgroup: sex			
Female	1.550	1.266–1.899	<0.0001
Male	2.063	1.663–2.559	<0.0001
P for interaction			0.0103†
Subgroup: age, y			
<40	1.872	1.383–2.536	<0.0001
40–59	1.825	1.403–2.374	<0.0001
≥60	1.615	1.288–2.025	<0.0001
P for interaction			0.1921

* Adjusted for age, sex, urbanization level, comorbidities, and medical use (including corticosteroids and DMARDs).

† Significant difference among subgroups.

forms of uveitis.⁵ Because antiglaucoma medication and DED would impair the ocular surface and cornea,^{33–35} the higher disease numbers in the study group may disturb the effect of uveitis on keratopathy. Nevertheless, the aHR for developing keratopathies was higher in the study group after adjustment. On the other hand, higher incidences of hypertension, DM, and hyperlipidemia were also found in the study group, which probably results from the systemic administration of corticosteroid and cyclosporine in the uveitic and rheumatologic patients in the study group,^{36–40} and DM itself is a risk factor for keratopathies.^{41,42} Although the corticosteroid and immunosuppressant would lead to certain types of keratopathy, the effect of uveitis on the development of keratopathies was still significant after adjusting the influence of immunosuppressant and immunosuppressant-induced systemic diseases, which indicates that uveitis is an independent risk factor for keratopathies. In addition, a higher urbanization was observed in the study group, which may result from medical accessibility.⁴³

There are still several limitations in the current study. First, the retrospective and observational nature allow the standardization between groups to become less precise, and the diagnosis of uveitis and other diseases was based on the diagnostic code of the insurance database rather than real medical records; thus, the details such as laterality and severity cannot be assessed. Second, there still exist some differences about the etiology of each uveitis, such as infectious and noninfectious, while the current study categorized uveitis into few subgroups and may lead to bias. Although the index date was set as the day 1 year after the uveitis diagnosis to prevent the inclusion of synchronous corneal lesions in uveitis, certain diseases such as herpes simplex virus and cytomegalovirus infection could present with both corneal lesions and uveitis, but some physicians might have only recorded the uveitis initially, and the persistent corneal lesion was documented by others years later. In this situation, the synchronous corneal defect in uveitis cannot be excluded. Moreover, some medications for uveitis treatment such as dexamethasone intravitreal implant and rituximab were self-paid in Taiwan at that time; thus, we cannot evaluate the effects of these medications on keratopathies directly. Nevertheless, the immunosuppressant-related complications such as hypertension, DM, and hyperlipidemia were analyzed between the two groups, which might decrease the influence of the absence of these medications.

In conclusion, the presence of uveitis will elevate the risk for developing keratopathy compared with non-uveitis individuals, which correlated to the disease interval. Moreover, panuveitis may have a similar or even greater effect on developing keratopathies compared with anterior uveitis. Further, large prospective studies focusing on the effect of

different types of uveitis on the development of each keratopathy are mandatory.

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