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Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

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Purpose: Noninfectious uveitis results in vision loss and ocular complications without adequate treatment. We compared the risk of developing ocular complications between patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) and matched controls.

Design: Retrospective analysis of insurance claims data (OptumHealth, Eden Prairie, MN; January 1, 1998–March 31, 2012).

Participants: Cases 18 to 64 years of age with 2 or more NIIPPU diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification codes) were matched 1:1 by sex, age, region, company, employment status, and index date with controls without uveitis. Patients with an ocular complication during baseline were excluded.

Methods: Continuous eligibility for 6 months or more before the first NIIPPU diagnosis date was required. Risks of ocular complications developing during patients' continuous eligibility in the study period were compared using unadjusted Kaplan-Meier survival analysis to estimate risk of and time to complications and adjusted Cox regression analysis to estimate hazard ratios (HRs).

Main Outcome Measures: Percentages of cases and controls who demonstrate ocular complications and 1-, 5-, and 10-year risks and HRs for each complication.

Results: Mean age of the 1769 cases and matched controls was 47 years and 47% were men; 302 cases had persistent NIIPPU. During the study period, NIIPPU cases had a higher risk of any ocular complication ($P < 0.001$); the 5-year risk of any ocular complication was 66% for patients versus 24% for controls. Specifically, NIIPPU patients had greater 5-year risks of glaucoma (20% vs. 9%), cataract (35% vs. 13%), visual disturbance (29% vs. 9%), blindness or low vision (5% vs. 0.5%), retinal detachment (11% vs. 0.8%), and retinal disorder (28% vs. 2%) compared with controls. Hazard ratios indicated greater risks of ocular complications in cases versus controls during the overall observation period (HR, 5.2 for any ocular complication; HR, 4.8 for visual disturbance; HR, 3.2 for cataract; and HR, 2.7 for glaucoma; all $P < 0.001$). Hazard ratios for persistent cases indicated even greater risks.

Conclusions: Noninfectious intermediate uveitis, posterior uveitis, or panuveitis, particularly persistent disease, is associated with a substantial risk of ocular complications. Optimal treatment initiatives remain imperative to reduce the ocular complication—related burden of NIIPPU. *Ophthalmology 2016;123:655-662 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Uveitis is an umbrella term that refers to infectious or noninfectious inflammation in the uveal tract and adjacent structures of the eye, depending on the anatomic site of maximum inflammation. Prevalence estimates of uveitis vary by country, race, age, and cause of the disease. Overall prevalence estimates in the United States, including both infectious and noninfectious uveitis, range from 58 to 115 cases per 100 000 persons.[1–3] Approximately 10% to 15% of preventable blindness in Western countries is caused by uveitis and associated complications.[4–7] In addition, major vision loss (defined as best-corrected visual acuity ≤20/50)

has been reported in 20% to 70% of patients treated in uveitis referral centers or academic ophthalmology clinics.[5,7,8]

Uveitis is classified by the primary anatomic location of the inflammation according to the Standardization of Uveitis Nomenclature guidelines and also whether it is caused by an infectious agent or is associated with an immune-mediated disease.[9] Anterior uveitis, which refers to inflammation of the iris and ciliary body, is the most common form in Western countries,[10,11] accounting for 91% of cases in community-based clinics and more than 50% in tertiary care

centers.[8,12–15] Although less common than anterior uveitis, noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) typically either is idiopathic and comprises many well-defined uveitic ocular conditions or is associated with systemic underlying autoimmune disorders, both of which present with varying degrees of ocular comorbidities; these complications account for most uveitis-related visual morbidity in these patients.[5,16–18] Therefore, the goal remains to subdue inflammation and to prevent complications associated with persistent inflammation complications, where the mainstay of therapy includes corticosteroids, other immunosuppressive agents, or both.[19,20]

Vision-threatening complications in patients with NIIPPU include macular edema, cataract, glaucoma, vitreous debris, and retinopathy, with macular edema remaining the most frequently encountered structural complication of uveitis that results in central visual impairment.[5–8,15,18,21,22] In a retrospective study from 2 uveitis referral centers in the Netherlands, 41% of patients with intermediate uveitis, 28% with posterior uveitis, and 53% with panuveitis had cystoid macular edema, which accounted for 41% of visual impairment and 29% of blindness in these patients.[5] In other studies, macular edema has been estimated to be present in 85% of cases of intermediate uveitis, 35% of cases of panuveitis, and 20% of cases of posterior uveitis, causing up to 30% of permanent uveitis-related vision loss.[7,23,24] Cataract is another significant cause of vision loss in patients with uveitis, present in 18% to 35% of patients.[7,15]

Long-term corticosteroid use (systemic or local) for the treatment of uveitis can lead to glaucoma and cataract, to which significant ocular morbidity can be attributed.[25–27] Overall, the morbidity and burden associated with uveitis and these complications remain a significant cost for health care systems.[28] For the patients, there also remains a negative effect on quality of life.[28–33] To provide additional data informing the burden of disease, we aimed to assess the risk of ocular complications in a privately insured NIIPPU cohort in the United States compared with matched controls without uveitis. In addition, an analysis of persistent NIIPPU cases was conducted.

Methods

Data Source and Patient Sample

Patients were identified using the OptumHealth (Eden Prairie, MN) Reporting and Insights database from January 1998 through March 2012.[34] The OptumHealth database includes medical and drug claims for 16.4 million privately insured individuals in 69 self-insured companies and represents a diversity of industry sectors, such as financial services, manufacturing, telecommunications, energy, and the food and beverage industry. Available data include employees' benefit eligibility and medical and pharmacy service claims. The OptumHealth database is compliant with the American Health Insurance Portability and Accountability Act; ethics approval was not required for this study because the data analyzed were de-identified records from an administrative insurance database.

Patients 18 to 64 years old with a diagnosis of NIIPPU were identified using International Classification of Diseases, Ninth

Revision, Clinical Modification codes for intermediate uveitis, posterior uveitis, or panuveitis (360.12 [panuveitis], 362.12 [exudative retinopathy], 362.18 [retinal vasculitis], 363.0x [focal chorioretinitis and focal retinochoroiditis], 363.10–13 and 363.15 [disseminated chorioretinitis and disseminated retinochoroiditis], 363.2x [other and unspecified forms of chorioretinitis and retinochoroiditis], and 364.24 [Vogt-Koyanagi syndrome]). A diagnosis of uveitis had to be on at least 2 medical claims to confirm the presence of the condition. These codes were modified from those used by Reeves et al[35] to exclude anterior diagnoses and those likely to be infectious. Data for the subgroup of cases with persistent NIIPPU, defined as cases with disease duration of 90 days or more and receiving standard of care such as corticosteroids, immunosuppressant therapy, biologic therapy, or a combination thereof, also were analyzed.[9]

The index date for each case was the first diagnosis of NIIPPU. Cases were required to have continuous eligibility (defined as no more than a 30-day gap between health plan enrollment segments) and no preexisting ocular complications during the baseline period (6-month period before first NIIPPU diagnosis; incident cases were identified during the 6-month baseline period). Potential controls were assigned the index date of their case match. Patients with NIIPPU with no preexisting ocular complications were matched 1:1 by sex, age, region, company, and employment status to controls without a diagnosis of uveitis. The study period spanned from the index date through the duration of continuous eligibility for each patient (Fig 1).

Ocular Outcomes and Risk Factors

Ocular complications were identified by International Classification of Diseases, 9th Revision, Clinical Modification codes and included glaucoma (365.xx); cataract (366.xx); visual disturbances (368.xx, 379.23, and 379.24), including vitreous opacities and vitreous hemorrhage; blindness or low vision (369.xx and 360.41), including blind hypotensive eye (phthisis bulbi); retinal detachment (361.xx); and retinal disorder, including cystoid macular degeneration (cystoid macular edema), retinal ischemia, retinal neovascularization, macular cyst/hole/pseudohole, macular puckering (epiretinal membrane), and retinal (macular) edema (362.53, 362.84, 362.16, 362.54, 362.56, and 362.83, respectively). The primary outcome of interest was time from the index date to the first occurrence of each of the ocular complication events. Time to any ocular complication was calculated as the time from the index date to the day of the first observed claim for any of the ocular complications under investigation. Risk factors and other causes relevant to each ocular complication were identified as potential covariates based on a literature review and were defined using International Classification of Diseases, Ninth Revision, Clinical Modification codes[36–49] (Table 1, available at www.aaojournal.org).

Statistical Analysis

Baseline characteristics were compared using univariate analyses. McNemar's tests were used for categorical variables and Wilcoxon signed-rank tests were used for continuous variables. Time to development of ocular complications during the study period was compared using unadjusted Kaplan-Meier survival analysis and log-rank tests. Patients without a claim for an ocular complication during the study period were censored at the last day of follow-up in the study period. The 1-, 5-, and 10-year risks of developing complications were estimated using Kaplan-Meier survival analysis. Adjusted Cox proportional-hazards regression models were used to estimate hazard ratios (HRs) for NIIPPU cases relative to controls, adjusting for age, sex, region, and Charlson comorbidity
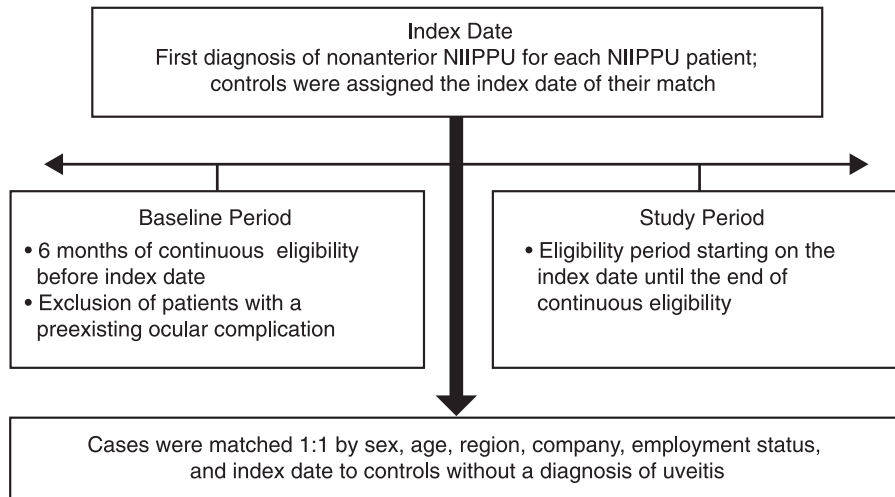
Figure 1. Flowchart showing study design. NIIPPU = noninfectious intermediate uveitis, posterior uveitis, or panuveitis.

index, as well as risk factors and other causes relevant to each ocular complication.

Results

Baseline Data

A total of 1769 NIIPPU cases with no preexisting ocular complications were identified and matched with 1769 controls without uveitis. The mean age of the full NIIPPU sample and their matched controls was approximately 47 years, and just under half were men (Table 2). The mean Charlson comorbidity index score was significantly greater in cases versus controls (0.9 vs. 0.2; $P \leq 0.0001$; Table 3). In the comparison of selected baseline autoimmune comorbidities and risk factors for ocular complication between cases and controls, cases with NIIPPU had a significantly higher rate of autoimmune comorbidities compared with controls (11.5% vs. 2.6%; $P \leq 0.0001$). Individual autoimmune comorbidities that were significantly more prevalent ($P < 0.05$) in the NIIPPU group at baseline were spondyloarthritis (2.0% vs. 0.5%), sarcoidosis (2.4% vs. 0.1%), rheumatoid arthritis (2.1% vs. 0.6%), multiple sclerosis (1.8% vs. 0.3%), systemic vasculitis (1.4% vs. 0.1%), and inflammatory bowel disease (1.2% vs. 0.5%; Table 3). Prevalence of all selected risk factors for ocular complications, except for metabolic syndrome and migraine, was significantly greater for the NIIPPU cohort than for the matched controls (Table 3).

The persistent NIIPPU sample and their matched controls (n = 302 each) tended to be older (mean age, 48.5 years) than the full NIIPPU sample, and fewer were men (40.7%; Table 2). Mean Charlson comorbidity index score for persistent NIIPPU cases (0.9) was significantly greater than that for the matched controls (0.2; $P \leq 0.0001$; Table 3). Approximately 30% of persistent NIIPPU cases had at least 1 autoimmune comorbidity at baseline compared with 2% for controls ($P \leq 0.0001$); spondyloarthritis, sarcoidosis, systemic vasculitis, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis were significantly more prevalent among persistent cases versus controls (Table 3). Similar to the full NIIPPU cohort, many of the selected risk factors for ocular complications were more common among the persistent NIIPPU cases versus controls, including age-related macular degeneration, diabetes or diabetic

retinopathy, vitreous degeneration or detachment, and cardiovascular disease. Although statistical comparisons between the full NIIPPU case sample and persistent NIIPPU cases were not performed, autoimmune comorbidities and risk factors for ocular complications tended to be more frequent in the persistent sample.

Development of Ocular Complications

Mean follow-up duration in the study period was approximately 5.6 years for cases with NIIPPU and 6.9 years for controls. Overall, 58%

Table 2. Case–Control Matched Patient Characteristics at Baseline*

Characteristics	Incident NIIPPU Group (n = 1769)	Persistent NIIPPU Group (n = 302)
Men	826 (46.7)	123 (40.7)
Age (yrs), mean (SD)	46.7 (11.4)	48.5 (10.1)
Age distribution (yrs)		
18–30	189 (10.7)	20 (6.6)
31–44	502 (28.4)	71 (23.5)
45–54	547 (30.9)	114 (37.7)
55–64	531 (30.0)	97 (32.1)
Region†		
Northeast	460 (26.0)	88 (29.1)
Midwest	338 (19.1)	61 (20.2)
South	620 (35.0)	100 (33.1)
West	197 (11.1)	36 (11.9)
Unknown	154 (8.7)	17 (5.6)

Data are n (%) unless otherwise indicated.
NIIPPU = noninfectious intermediate uveitis, posterior uveitis, or panuveitis; SD = standard deviation.
*The baseline period was defined as the 6 months before the index date. Patients and their matches with an ocular complication (i.e., retinal detachment, retinal disorder, glaucoma, cataract, visual disturbance, and blindness or low vision) during the baseline period were excluded from analysis. Matching yielded identical demographic data for case and control populations; thus, only the case data are displayed.
†The distribution of region is reflective of the regional distribution of claims data available and not the regional distribution of the condition. If the region was unknown, the uveitis patient was matched to a control patient with an unknown region.

Table 3. Autoimmune Comorbidities and Risk Factors for Ocular Complications at Baseline

Comorbidities and Risk Factors	Full Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis Sample		Persistent Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis Sample	
	Cases (n = 1769)	*Controls (n = 1769)*	*Cases (n = 302)*	*Controls (n = 302)*
Charlson comorbidity index score, mean (SD)*	0.9 (2.0)[†]	0.2 (0.8)	0.9 ± 1.8[†]	0.2 ± 0.7
Select autoimmune comorbidities, no. (%)[‡]	203 (11.5)[†]	46 (2.6)	89 (29.5)[†]	7 (2.3)
Spondyloarthritis	36 (2.0)[†]	8 (0.5)	14 (4.6)[§]	1 (0.3)[§]
Sarcoidosis	43 (2.4)[†]	1 (0.1)	22 (7.3)[†]	0 (0)[†]
Behçet's syndrome	1 (0.1)	0 (0)	0 (0)	0 (0)
Multiple sclerosis	32 (1.8)[†]	5 (0.3)	5 (1.7)	1 (0.3)
Systemic vasculitis	24 (1.4)[†]	2 (0.1)	12 (4.0)[§]	2 (0.7)[§]
Inflammatory bowel disease	22 (1.2)[§]	9 (0.5)	8 (2.6)[§]	1 (0.3)[§]
Vitiligo	0 (0)	0 (0)	0 (0)	0 (0)
Systemic lupus erythematosus	11 (0.6)	4 (0.2)	5 (1.7)[§]	0 (0)[§]
Sjögren's syndrome	5 (0.3)	2 (0.1)	2 (0.7)	1 (0.3)
Relapsing polychondritis	4 (0.2)	2 (0.1)	3 (1.0)	1 (0.3)
Rheumatoid arthritis	38 (2.1)[†]	11 (0.6)	21 (7.0)[†]	0[†]
Psoriasis	13 (0.7)	11 (0.6)	5 (1.7)	1 (0.3)
Select risk factors for ocular complications, no. (%)[‖]				
Disorders of refraction and accommodation	53 (3.0)[§]	29 (1.6)	6 (2.0)	6 (2.0)
Age-related macular degeneration	25 (1.4)[†]	2 (0.1)	5 (1.7)	0 (0)[§]
Corneal complications	23 (1.3)[§]	6 (0.3)	5 (1.7)	2 (0.7)
Diabetes, including diabetic retinopathy	190 (10.7)[†]	106 (6.0)	34 (11.3)	20 (6.6)[§]
Vitreous degeneration/detachment	41 (2.3)[†]	1 (0.1)	8 (2.6)	0 (0)[†]
Hypothyroidism	102 (5.8)[§]	56 (3.2)	16 (5.3)	12 (4.0)
Cardiovascular disease	196 (11.1)[†]	120 (6.8)	38 (12.6)	18 (6.0)[§]
Hypertension	301 (17.0)[†]	214 (12.1)	53 (17.5)	39 (12.9)
Metabolic syndrome	3 (0.2)	3 (0.2)	0 (0)	0 (0)
Migraine	34 (1.9)	24 (1.4)	10 (3.3)	4 (1.3)
Retinal vein occlusion	14 (0.8%)[§]	1 (0.1%)	2 (0.7)	1 (0.3%)
Injury to the eye	21 (1.2%)[§]	4 (0.2%)	6 (2.0)	1 (0.3%)

SD = standard deviation.

*The 17 conditions included in the Charlson comorbidity index were identified using International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes.[47]

[†]$P \leq 0.0001$ versus controls from McNemar's tests for comparisons of categorical variables and Wilcoxon signed-rank tests for comparisons of continuous variables.

[‡]Comorbidities were defined using International Classification of Diseases, Ninth Revision, Clinical Modification codes.

[§]$P < 0.05$ versus controls from McNemar's tests for comparisons of categorical variables and Wilcoxon signed-rank tests for comparisons of continuous variables.

[‖]Risk factors and other causes relevant to each ocular complication were based on a literature review and defined using International Classification of Diseases, Ninth Revision, Clinical Modification codes (see Table 1, available at www.aaojournal.org).

of cases and 17% of controls had ocular complications during the study period ($P < 0.0001$; Fig 2A). Cataract was the most common ocular complication that developed during the study period (25% vs. 9%), followed by visual disturbances (23% vs. 6%), retinal disorders (23% vs. 1%), glaucoma (15% vs. 6%), retinal detachment (9% vs. 0.6%), and blindness or low vision (4% vs. 0.3%). In the Kaplan-Meier survival analyses and the adjusted Cox proportional-hazards regression models, the risk for developing any ocular complication was significantly greater for NIIPPU cases versus controls, with an overall adjusted HR of 5.2 ($P < 0.001$; Fig 2B). From Kaplan-Meier survival analyses, the estimated 1-year unadjusted risk for any ocular complication was 45% for cases versus 7% for controls, whereas the estimated 10-year risk for any ocular complication increased to 75% and 37%, respectively. The estimated 1-, 5-, and 10-year risks of any ocular complication for persistent NIIPPU cases versus controls were 55% versus 5%, 83% versus 27%, and 88% versus 49%, respectively (Fig 3).

For each of the individual complications studied during the entire study period, results from the Kaplan-Meier survival analyses and the adjusted Cox proportional-hazards regression models are depicted in Figure 4 (available at www.aaojournal.org). For cataract (Fig 4A), cases were significantly more likely to demonstrate this complication compared with controls, with an adjusted HR of 3.2. The estimated 1-year unadjusted risk for cataract was 14% for cases versus 3% for controls, the estimated 5-year risk was 35% for cases versus 13% for controls, and the estimated 10-year risk was 48% for cases versus 25% for controls. Additionally, cases were significantly more likely to experience visual disturbance than controls, with an adjusted HR of 4.8 (Fig 4B). The 1-, 5-, and 10-year unadjusted probabilities for developing visual disturbance in cases were 16%, 29%, and 39%, respectively, compared with 2%, 9%, and 14% for controls. Similarly, the risk of glaucoma developing was significantly greater for cases versus controls, with an adjusted HR of 2.7 (Fig 4C). The 1-year unadjusted risk for glaucoma was 10% for cases versus 2% for controls, increasing to 26% for cases and 13% after 10 years. Cases also had significantly greater risks of retinal disorder (Fig 4D), retinal detachment (Fig 4E), and blindness or low vision (Fig 4F) developing compared with controls; however, the event counts for these complications in the control group were too small to estimate stable HRs.
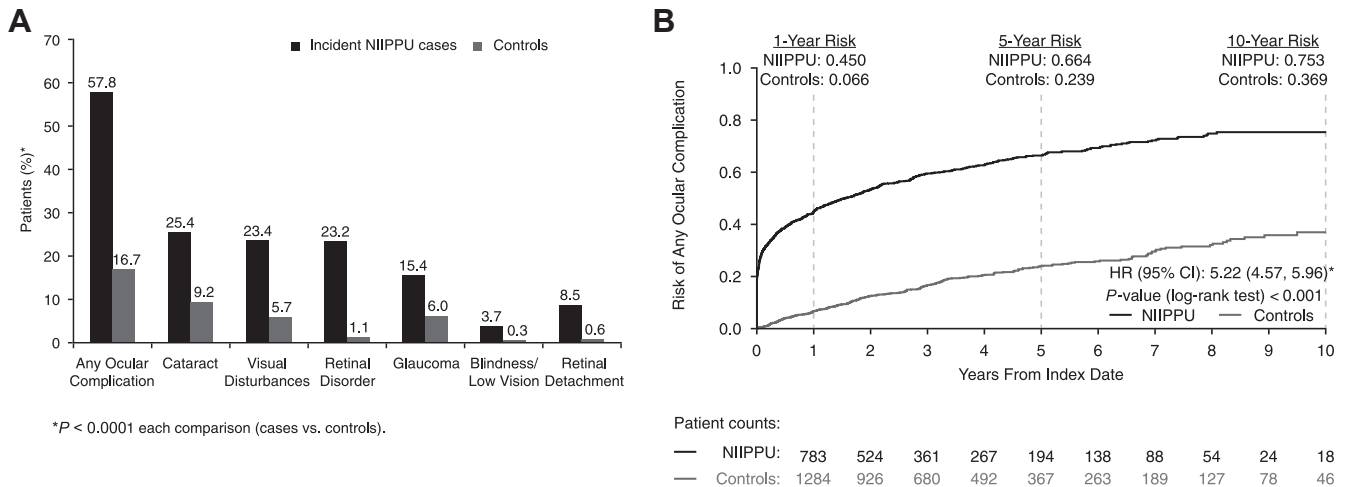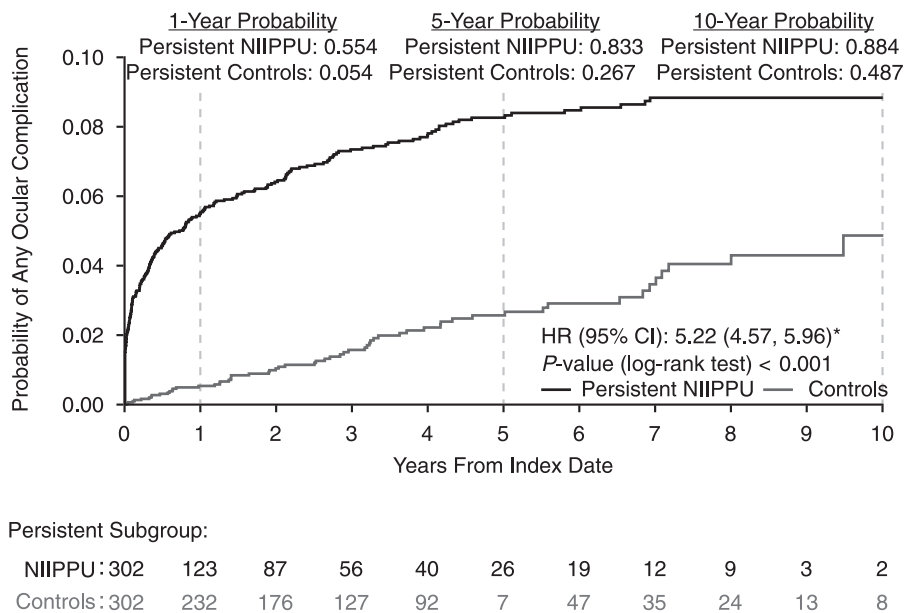
Figure 2. Overview of ocular complications in cases with noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) versus controls. **A,** Bar graph showing the percentages of patients who experienced ocular complications during the study period. **B,** Survival analysis for time to any ocular complication. *Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from adjusted Cox regression analyses.

Hazard ratios from adjusted Cox regression analyses for the persistent NIIPPU analysis indicate significantly greater risk (all $P < 0.001$) for any ocular complication (HR, 8.9), visual disturbance (HR, 8.1), cataract (HR, 6.2), or glaucoma (HR, 4.2) in persistent cases versus controls (Table 4). Kaplan-Meier survival curves estimating risk of and time to each individual ocular complication for the persistent NIIPPU population are provided in Figure 5 (available at www.aaojournal.org).

Discussion

The chronic inflammation resulting from untreated or poorly controlled uveitis is a major cause of visual disability,

ocular complications, and potential blindness.[4,5,7,8,15,18,22] Moreover, the potential that patients with uveitis will experience a permanent sight-threatening outcome is underrecognized.[16,50] In this study, we confirmed the association between uveitis and ocular complications such as glaucoma, cataract, visual disturbance, blindness or low vision, retinal detachment, and retinal disorders including macular edema, with a focus on NIIPPU in a large sample of patients being treated in real-world clinical practice. Further, it should be noted that the lack of differences among disorders of refraction and accommodation in our analyses suggests that there is indeed an increased risk of ocular complications associated with uveitis and that these

Figure 3. Survival analysis for time to any ocular complication for persistent noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIPPU) cases versus controls. *Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from adjusted Cox regression analyses.

Table 4. Risk of Developing Ocular Complications in Patients with Persistent Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

Ocular Complication	Hazard Ratio*	95% Confidence Interval	P Value
Any ocular complication	8.9	7.1—11.0	<0.001
Visual disturbance	8.1	5.9—11.2	<0.001
Cataracts	6.2	4.8—8.0	<0.001
Glaucoma	4.2	3.0—5.9	<0.001
Blindness and low vision[†]	—	—	—
Retinal detachments[†]	—	—	—
Retinal disorder[†]	—	—	—

*The hazard ratios represent the risk for persistent noninfectious intermediate uveitis, posterior uveitis, or panuveitis patients relative to controls.
[†]Hazard ratios were not calculated for blindness or low vision, retinal detachments, or retinal disorders because of low event counts.

associations are not just the result of a greater intensity of visits and coding. In addition, we assessed whether there were any morbidity changes in patients with chronic uveitis by estimating the risk of ocular complications in a more severe subset with persistently active NIIPPU, according to the Standardization of Uveitis Nomenclature guidelines.[9] To identify persistent cases, we assumed that prolonged treatment was required for chronic disease or to maintain remission; therefore, persistent cases were required to have chronic disease (defined as duration ≥90 days) and to be receiving treatment for NIIPPU.[9] These data suggest that there is a high unmet need for treatments that reduce the occurrence of ocular complications in these patient populations, particularly considering that other studies have reported unacceptable corticosteroid maintenance doses of up to 40 mg daily in patients with uveitis.[8,16]

This study reports the high risk of ocular complications in patients with NIIPPU in a large population representative of privately insured, employed United States patients. A prior study evaluated costs and ocular comorbidities in privately insured patients receiving corticosteroids, immunosuppressants, or biologics for uveitis; however, those results are difficult to compare with those of the present study because the prior analysis included patients with anterior uveitis.[28] Compared with anterior disease, which is more common and also can give rise to complications such as cataract, macular edema, and glaucoma,[8,15,16] NIIPPU carries a greater morbidity and poorer prognosis. This excess morbidity is not exclusively the result of the systemic treatment required; it also results because the disease often is associated with underlying autoimmune disorders and has a higher prevalence of irreversible sight-threatening pathologic features.[8,10,14,15,17,18,28] In this study, we found that cases with NIIPPU had significantly greater comorbidity compared with controls. After adjusting for these differences, cases had significantly greater risks of each of the studied ocular complications developing. Thus, even when NIIPPU is associated with systemic disease, the ocular disease alone independently gives rise to complications and necessitates treatment to prevent morbidity. These ocular complications may add significantly to the overall economic

burden of the disease, for direct medical costs related to the treatment of ocular complications would be expected (i.e., more ophthalmologist visits) as well as indirect costs associated with loss of work productivity and early retirement (e.g., loss of functional independence and ability to drive). The economic burden of ocular complications in patients with NIIPPU represents an important topic for future research. More recently, and although it is not possible to compare directly with the present study, reports from tertiary uveitis referral centers in the United Kingdom have demonstrated outcomes in large patient numbers; together, the United Kingdom studies corroborate the burden of disease, not least through demands for health care resources.[8,15] Because the course of disease often is persistent, residual damage occurs despite expert care in combination with the high need for pharmacologic therapy (including corticosteroid dependence and use of second-line immunosuppressant agents).

Strengths of this analysis include that it was based on data from privately insured individuals covered by a large set of companies with locations across the United States in a wide range of industries and occupations. Moreover, the age distribution of the NIIPPU sample is representative of the natural history of the disease, in which the diagnosis typically occurs during the working years, with peak onset in the fifth decade of life.[1,6—8,28] This sample includes claims from both community and tertiary care centers rather than a single center, supporting its generalizability. By design, the control cohort had no history of uveitis or baseline ocular comorbidities; however, the control population reduced ascertainment bias in that underlying comorbidities not related to uveitis, such as hypertension, cardiovascular disease, diabetes, and autoimmune comorbidities, were present.

Limitations of this study include those common to retrospective analyses of health care claims data. For example, it is possible that there were errors in the database or omission of relevant claims, and details of the physicans' clinical judgment were not available to confirm the accuracy of the diagnostic coding. However, these types of limitations are likely to affect the case and control cohorts equally and are unlikely to bias the results or substantially alter interpretation of the findings. Because uveitis is a rare disease, even if a large number of cases were misclassified as controls, the misclassifications would have a relatively small effect on the risk ratios and other outcomes measured because any effect would be diminished by the large number of controls. Although the age range (18—64 years) of the study population largely eliminates age-related macular degeneration from the control group, which may change the relative risk of retinal complications, this limitation is expected to have a minimal effect on the outcomes reported in this study because the age at presentation of uveitis among the working-age population typically is younger than that of age-related macular degeneration. When assessing whether there were any morbid changes among the subgroup of persistent uveitis cases, it is important to keep in mind that the methodology used may have introduced 2 opposing biases related to treatment: the first, in which patients with more severe disease are more likely to be treated and followed up, thereby increasing the estimated risk of

complications; and the second, in which patients with more severe disease are treated effectively, thereby decreasing the estimated risk of complications. In addition, the study sample included only privately insured employees and their dependents; hence, it may not be reflective of other populations such as the general United States population, the uninsured or Medicaid populations, or the elderly. Finally, it should also be noted that the reported associations may be underestimated because patients with major ocular problems may be unable to work, and therefore no longer have private medical insurance as a result of disability. Because this study was retrospective, the findings should be interpreted as an association of what seems to be a greater risk of ocular complications in the NIIPPU cohort rather than a causal association. Nevertheless, longitudinal studies of claims data can be a useful means of assessing the burden of less common diseases such as uveitis, particularly because it is a heterogeneous condition that may be diagnosed by a variety of health care providers.

In conclusion, patients with NIIPPU were 5 times more likely and patients with persistent NIIPPU were 9 times more likely to experience an ocular complication compared with matched controls who did not have uveitis. Cataract, visual disturbance, and retinal disorder, including macular edema, were the most common ocular complications that developed during the study period. These findings highlight the importance of pursuing optimal treatment initiatives to reduce the burden of ocular-related complications in patients with NIIPPU.

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