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Risk factors for adverse events or use of high-potency corticosteroids in non-infectious uveitis: a Japan claims database study (J-CAT2)

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ABSTRACT

The J-CAT2 study (#JRCT1030240195) aimed to evaluate treatment and patient factors associated with risk of complications/adverse events (AEs) or high corticosteroid exposure in patients with non-infectious uveitis (NIU) using advanced quantitative and visual analytical approaches. The study included data from a nationwide insurance claims database in Japan. Patients with NIU treatment-related claims (2016–2023) were included ($n=98,842$). A nested case-control design was used to evaluate patient factors associated with complications/AEs or high corticosteroid exposure. Multivariable logistic regression and decision-tree analyses were performed. Sub-Tenon's corticosteroid injections were associated with dose-dependent increased odds of glaucoma treatment and cataract surgery (OR [95% CI]: 1 sub-Tenon's injection, 3.27 [2.60–4.11] and 3.19 [2.39–4.27], respectively; ≥ 2 sub-Tenon's injections, 5.54 [4.03–7.60] and 4.86 [3.44–6.85], respectively). Macular edema was the most likely factor associated with ≥ 2 sub-Tenon injections. Vogt-Koyanagi-Harada disease and sarcoidosis were the most likely factors associated with medium-to-high-dose corticosteroids and long-term oral corticosteroids. The J-CAT2 study used a novel, quantitative and visual framework to understand associations between dose, frequency, and duration of corticosteroid treatment and complications/AE risk in NIU. These findings suggest that optimization of corticosteroid administration protocols and exploration of alternative therapeutic strategies/targeted treatment approaches are necessary to mitigate complication risks.

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1. Introduction

Non-infectious uveitis (NIU) is typically treated with corticosteroid eye drops; however, treatments such as local ocular injections, systemic corticosteroid therapies, immunosuppressants, and biologics may be used when eye drops do not sufficiently control inflammation [1–3]. Findings from the Japanese Medical Database Study to Clarify Actual Treatment Patterns in Patients with Non-Infectious Uveitis (J-CAT) study, using data from a nationwide insurance claims database, indicate that approximately 20% of patients with NIU receive treatments other than corticosteroid eye drops [4]; these patients are considered to have moderate-to-severe NIU. The most common treatments other than eye drops were found to be oral, locally injected, and intravenous corticosteroids [4].

Although corticosteroids can be effective for treating NIU, they have an associated risk of complications/adverse events (AEs). Current evidence suggests that topical and systemic corticosteroids can increase the risk of ocular complications/AEs, including glaucoma, in patients with NIU and in the general population [5–8]. Oral corticosteroids can increase the risk of glaucoma, cataracts, and infections in a dose- and treatment duration-dependent manner in patients with NIU [7]. Findings

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from a retrospective cohort study of patients from 5 tertiary centers also demonstrated that the risk of glaucoma was increased with local ocular corticosteroid injection number; however, the specific route of corticosteroid administration was not evaluated [9]. Findings from the J-CAT1 study showed that patients who received sub-Tenon's corticosteroid injections had a high incidence of various complications/AEs, including glaucoma and cataract [4].

Current evidence on the risk of ocular complications/AEs in patients with NIU and the factors underlying high corticosteroid exposure in this population has limitations. One major gap is the lack of data from large, real-world populations. In addition, the risks associated with different injection approaches for administering ophthalmic corticosteroids have not been fully evaluated. The dose dependency of complications/AEs associated with ocular corticosteroid injections is also unclear and has not previously been evaluated for sub-Tenon's injections, a common treatment for moderate-to-severe NIU in Japan [4]. Further, as intravitreal implants and suprachoroidal injections are not currently approved for treating NIU in Japan, there are a lack of real-world data from a setting where these treatments are not routinely used. In addition, the dose-dependent effects for all methods of administering corticosteroids on the risk of ocular complications/AEs have not been reported for a single analysis population. Other limitations include that factors associated with frequent local ocular corticosteroid injections have not been reported and that previous studies have not fully considered patient factors, such as macular edema, epiretinal membrane formation, and other comorbidities, when evaluating long-term and/or high-dose corticosteroid use. Having a more complete understanding of the complications/AEs associated with NIU treatment and the factors underlying high corticosteroid exposure may help optimize treatment approaches for patients with NIU.

The aim of the J-CAT2 study was to perform a comprehensive evaluation of treatment and patient factors associated with the risk of complications/AEs or high corticosteroid exposure in patients with NIU in Japan using data from a large, national insurance claims database. By applying multivariable logistic regression and decision-tree analysis to a large national claims database, this study was performed to provide a novel, quantitative and visual framework for identifying risk factors and stratifying patients based on corticosteroid dose and frequency, and therefore support the optimization of treatment strategies and reduce the burden of corticosteroid-related complications in NIU.

2. Materials and methods

2.1. Study design and data source

As previously described for the J-CAT1 study [4], the J-CAT2 study (#JRCT1030240195) included data from a nationwide insurance claims database in Japan, which is managed by JMDC Inc. (Tokyo, Japan). Note that individuals aged ≥ 75 years were not included in this study because they were included in a separate insurance system database. In addition, dependent children are followed only until they become independent. As anonymized data were used, the J-CAT study was exempt from ethics review board review/approval and informed consent was not required.

2.2. Study population

2.2.1. Inclusion criteria

As previously detailed [4], patients were included in the analysis if they had an NIU-related claim with any International Classification of Diseases, Tenth Revision (ICD-10) code that may cause NIU between January 1, 2005, and October 31, 2023; an NIU-related disease name; and an initial ophthalmological examination record within the same month of diagnosis between October 1, 2016, and October 31, 2023 (index date, also referred to as the first encounter) to confirm NIU diagnosis.

2.2.2. Exclusion criteria

Patients who developed infectious uveitis after the index date or did not have NIU ICD-10 codes after the index date were excluded from the analyses. In addition, patients with onset of glaucoma or cataract before the initiation of NIU treatment were excluded.

2.3. Study design

A nested case-control design, previously employed for other databases analyses [10], was used to evaluate patient factors associated with complications/AEs or high corticosteroid exposure. Cases were defined as patients with complications/AEs associated with NIU treatment or high corticosteroid exposure, whereas controls were patients without an event on the day of the event in the case group. Case-control matching was performed using disease-risk score (DRS) matching, with a difference of < 0.05 in a ratio of 1:k ($k \leq 4$) by risk set sampling. DRS matching is often used in nested case-control studies and can help increase statistical efficiency [11]. A caliper of < 0.05 was considered to be an appropriate matching condition based on findings from a previous simulation study [12].

DRS was calculated based on the following baseline covariates: age, sex, history of treatment for systemic diseases related to NIU, liver disorder, renal impairment, demyelinating disease, bisphosphonates, thyroid disease, anti-hypertensive drugs, diabetes drugs, hyperlipidemic drugs, anti-histamines, female hormone preparations, anti-depressants/anti-psychotics, anti-cholinergic drugs, benzodiazepines, immunosuppressants (for indications other than NIU treatment), inhaled corticosteroids, interstitial pneumonia/chronic obstructive pulmonary disease/bronchial asthma, and initial NIU treatment (Supplementary Figure s1 and 2). The start of glaucoma treatment, glaucoma surgery, cataract surgery, and vitreous surgery were used as baseline covariates in the calculation of DRS in analyses where these were not the complication/AE outcome of interest. The baseline period for assessing the presence/absence of variables used in the DRS was defined as the 6-month period before the first date of NIU treatment.

Patients were followed from the index date until death, withdrawal from the database, or event date, whichever occurred first. For the control group, the matched case event data were used.

2.4. Outcome measurement and statistical analyses

2.4.1. Factors associated with complications/AEs of NIU treatment

complication/AE outcomes considered to be associated with NIU treatment were as described in the J-CAT1 study [4] and included the start of glaucoma treatment prescriptions, glaucoma surgery, cataract surgery, and infections (ocular and systemic). Infections (based on ICD-10 codes, as previously described [13–15]) that were the same as those observed during the baseline period were not considered to be events.

Factors evaluated were those identified to be characteristic of NIU in the J-CAT1 study [4], specifically NIU type (sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada disease, Posner-Schlossman syndrome, and acute anterior uveitis), long-term use of corticosteroid eye drops, systemic corticosteroids, ocular corticosteroid injections (including as sub-Tenon's, subconjunctival, and intravitreal injection), other treatments (immunosuppressants, tumor necrosis factor- α inhibitors, other ocular corticosteroid injections [including retrobulbar and intracameral injection], colchicine, and phosphodiesterase-4 inhibitors), dose and frequency of treatment for ocular corticosteroid injections and systemic corticosteroids, and duration of corticosteroid treatment other than corticosteroid eye drops. Given that topical corticosteroids are frequently used concomitantly with other treatments, the presence or absence of concomitant use was evaluated at Day 0. For subsequent treatments, our analytical approach estimated odds ratios (ORs) while controlling for conditions to allow for equitable comparisons.

Multivariate logistic regression models were used to estimate odds ratios and 95% confidence intervals (CIs) (Supplementary Figure 1). Baseline covariates between the case and control groups were considered to be well balanced if the standardized mean difference (SMD) was < 0.2 [16].

Analyses were performed using R version 4.2.1 (<https://cran.r-project.org/bin/windows/base/old/4.2.1>). Conditional logistic regression was performed using the R survival package.

2.4.2. Factors associated with high corticosteroid exposure

The following treatment pattern factors were defined as being indicative of high corticosteroid exposure: two or more or three or more sub-Tenon's injections, use of medium- to high-dose systemic corticosteroids (≥ 10 mg/day of oral corticosteroids for two or more days or a history of prescription

on two or more occasions, corticosteroid infusion, or intravenous injection), and long-term use of corticosteroids (cumulative administration period of oral corticosteroids ≥ 90 days and average dose during this period ≥ 5 mg/day, or a cumulative administration period ≥ 180 days regardless of the dose). The sub-Tenon's injections cut-offs were selected based on results of the primary analysis reported herein and previous findings [9]. The use of medium- to high-dose corticosteroids was selected for evaluation by dose and duration based on previous literature [7] and the primary findings. As oral corticosteroids can be used for a relatively long term with good tolerance at < 7.5 mg/day, long-term administration was defined according to dose [17]. Long-term administration was defined as ≥ 180 days per a previous study [18].

The following factors were evaluated: age, sex, glaucoma treatment, glaucoma surgery, cataract surgery, vitreous surgery, NIU type (sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada disease, Posner-Schlossman syndrome, acute anterior uveitis), and other treatments (immunosuppressants, tumor necrosis factor- α inhibitors, other ocular corticosteroid injections, colchicine, phosphodiesterase-4 inhibitors).

Decision-tree analysis using the chi-square automatic interaction detection (CHAID) algorithm was performed (Supplementary Figure 2). Based on the χ^2 test value calculated by the CHAID algorithm, factors with high correlation were output as a decision-tree model, with up to four branches evaluated in the model. Analyses were performed using the R CHAID package.

3. Results

3.1. Patient characteristics

Overall, 98,842 patients had NIU-related claims between October 2016 and October 2023 and received treatment for NIU. Among these patients, 3,289 had glaucoma treatment prescriptions ($n=13,038$ DRS-matched controls), 461 had glaucoma surgery ($n=1,773$ DRS-matched controls), 1,802 had cataract surgery, ($n=6,984$ DRS-matched controls), and 9,808 had infections ($n=39,047$ DRS-matched controls) (Figure 1). For each complication/AE category, patient characteristics were well matched between cases and DRS-matched controls (Table 1), with all SMDs < 0.2 .

3.2. Factors associated with complications/AEs of NIU treatment

3.2.1. Glaucoma treatment

Type of NIU diagnosis and NIU treatment factors associated with an increased odds (OR [95% CI]) of glaucoma treatment included Posner-Schlossman syndrome (11.23 [7.55–16.73]), long-term use of corticosteroid eye drops (3.75 [3.30–4.25]), local corticosteroid injections (3.36 [2.88–3.91]), and systemic corticosteroids (2.09 [1.84–2.37]) (Figure 2A, Supplementary Table 1).

Local and systemic corticosteroid treatment factors associated with an increased odds of glaucoma treatment included intravitreal corticosteroid injection (5.20 [2.30–11.75]), sub-Tenon's corticosteroid injection (3.93 [3.26–4.75]), other local corticosteroid injections (3.76 [1.91–7.39]), oral corticosteroids (2.09 [1.83–2.38]), and subconjunctival corticosteroid injection (1.80 [1.41–2.31]) (Figure 2B, Supplementary Table 1).

Corticosteroid dose and frequency of treatment factors associated with an increased odds of glaucoma treatment included two or more sub-Tenon's injections (5.54 [4.03–7.60]), one sub-Tenon's injection (3.27 [2.60–4.11]), medium- to high-dose systemic corticosteroids (2.43 [1.96–3.01]), low-dose systemic corticosteroids (2.02 [1.75–2.33]), one subconjunctival injection (1.98 [1.46–2.69]), and two or more subconjunctival injections (1.49 [1.00–2.21]) (Figure 2C, Supplementary Table 1). Short-/medium-term (2.21 [1.93–2.52]) and long-term corticosteroid treatments (1.96 [1.44–2.66]) were associated with an increased odds of glaucoma treatment (Figure 2D, Supplementary Table 1).

3.2.2. Glaucoma surgery

NIU treatment factors associated with an increased odds (OR [95% CI]) of glaucoma surgery included long-term use of corticosteroid eye drops (4.39 [3.28–5.88]), local corticosteroid injections (2.08 [1.45–2.97]), and systemic corticosteroids (1.43 [1.02–2.01]) (Figure 3A, Supplementary Table 1).

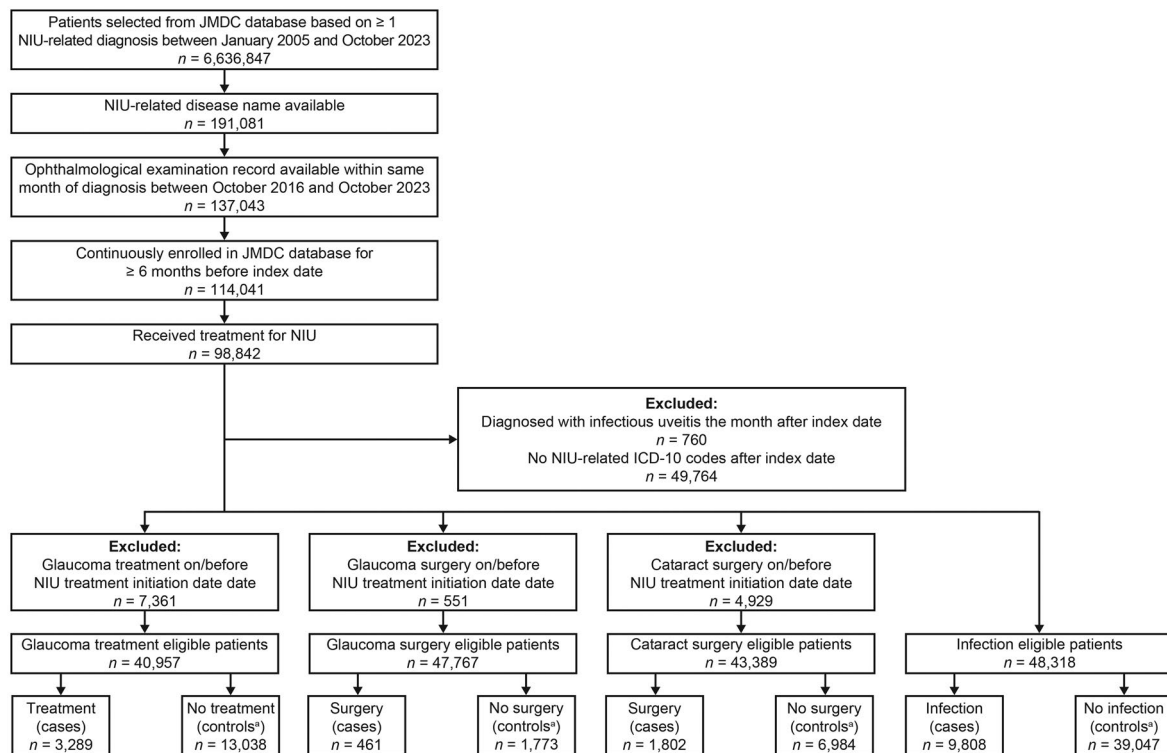


Figure 1. Patient attrition of eligible patients with NIU from the JMDC database. The index date was defined as the date of first encounter. *Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling.

DRS: disease-risk score; ICD-10: International Classification of Diseases, Tenth Revision; NIU: non-infectious uveitis

Local and systemic corticosteroid treatment factors associated with an increased odds of glaucoma surgery included subconjunctival corticosteroid injection (2.46 [1.42–4.26]), oral corticosteroids (1.56 [1.10–2.21]), and other treatment (3.64 [1.22–10.87]) (Figure 3B, Supplementary Table 1). Corticosteroid frequency of treatment factors associated with an increased odds of glaucoma surgery included one subconjunctival injection (2.83 [1.47–5.46]) and one sub-Tenon's injection (1.92 [1.11–3.32]) (Figure 3C, Supplementary Table 1). There were no associations between duration of corticosteroid treatment and glaucoma surgery (Figure 3D, Supplementary Table 1).

3.2.3. Cataract surgery

NIU treatment factors associated with an increased odds (OR [95% CI]) of cataract surgery included local corticosteroid injections (3.07 [2.54–3.71]) and long-term use of corticosteroid eye drops (2.67 [2.32–3.08]) (Figure 4A, Supplementary Table 1). Local and systemic corticosteroid treatment factors associated with an increased odds of cataract surgery included sub-Tenon's corticosteroid injection (3.81 [3.04–4.78]), other local corticosteroid injections (2.17 [1.04–4.53]), and subconjunctival corticosteroid injection (1.63 [1.18–2.25]) (Figure 4B, Supplementary Table 1).

Corticosteroid frequency of treatment factors associated with an increased odds of cataract surgery included two or more sub-Tenon's injections (4.86 [3.44–6.85]), one sub-Tenon's injection (3.19 [2.39–4.27]), and two or more subconjunctival injections (2.15 [1.33–3.48]) (Figure 4C, Supplementary Table 1). Long-term corticosteroid treatment (2.14 [1.52–3.00]) was associated with an increased odds of cataract surgery (Figure 4D, Supplementary Table 1).

3.2.4. Infection

Type of NIU diagnosis and NIU treatment factors associated with an increased odds (OR [95% CI]) of infection (ocular or systemic) included sarcoidosis (1.20 [1.04–1.39]), systemic corticosteroids (1.56 [1.46–1.67]), long-term use of corticosteroid eye drops (1.14 [1.07–1.21]), and other treatment

Table 1. Summary of patient baseline characteristics and prior treatments by complication/AE associated with NIU category: glaucoma treatment, glaucoma surgery, cataract surgery, and infection.

Characteristic, n (%)	Glaucoma treatment		Glaucoma surgery		Cataract surgery		Infection	
	Yes (cases) (n = 3,289)	No (controls ^a) (n = 13,038)	Yes (cases) (n = 461)	No (controls ^a) (n = 1,773)	Yes (cases) (n = 1,802)	No (controls ^a) (n = 6,984)	Yes (cases) (n = 9,808)	No (controls ^a) (n = 39,047)
Age, years								
0–19	185 (5.6)	957 (7.3)	10 (2.2)	81 (4.6)	20 (1.1)	76 (1.1)	1,102 (11.2)	4,574 (11.7)
20–39	500 (15.2)	2,403 (18.4)	40 (8.7)	212 (12.0)	74 (4.1)	293 (4.2)	2,233 (22.8)	8,665 (22.2)
40–59	1,946 (59.2)	7,228 (55.4)	270 (58.6)	1,005 (56.7)	998 (55.4)	3,885 (55.6)	4,807 (49.0)	19,345 (49.5)
≥ 60	658 (20.0)	2,450 (18.8)	141 (30.6)	475 (26.8)	710 (39.4)	2,730 (39.1)	1,666 (17.0)	6,463 (16.6)
Sex								
Male	1,884 (57.3)	6,650 (51.0)	279 (60.5)	1,024 (57.8)	1,011 (56.1)	3,655 (52.3)	4,475 (45.6)	18,765 (48.1)
Follow-up, months, median (IQR)	101 (21–431)	88 (10–419)	239 (56–712)	239 (41–704)	324 (62–785)	317 (54–783)	406 (146–820)	392 (132–804)
Liver disorder history	93 (2.8)	346 (2.7)	13 (2.8)	39 (2.2)	51 (2.8)	206 (2.9)	255 (2.6)	1,004 (2.6)
Renal impairment history	25 (0.8)	61 (0.5)	3 (0.7)	5 (0.3)	13 (0.7)	56 (0.8)	60 (0.6)	168 (0.4)
Demyelinating disease history	3 (0.1)	10 (0.1)	0	2 (0.1)	4 (0.2)	7 (0.1)	7 (0.1)	29 (0.1)
Prior treatment for systemic disease associated with NIU	207 (6.3)	818 (6.3)	25 (5.4)	107 (6.0)	117 (6.5)	469 (6.7)	851 (8.7)	2,751 (7.0)
Bisphosphonates	59 (1.8)	229 (1.8)	4 (0.9)	21 (1.2)	57 (3.2)	188 (2.7)	209 (2.1)	791 (2.0)
Thyroid disease	47 (1.4)	165 (1.3)	10 (2.2)	20 (1.1)	22 (1.2)	86 (1.2)	164 (1.7)	574 (1.5)
Anti-hypertensives	650 (19.8)	2,153 (16.5)	112 (24.3)	373 (21.0)	521 (28.9)	1,795 (25.7)	1,588 (16.2)	6,130 (15.7)
Anti-diabetics	249 (7.6)	817 (6.3)	52 (11.3)	146 (8.2)	243 (13.5)	701 (10.0)	642 (6.5)	2,376 (6.1)
Anti-hyperlipidemics	446 (13.6)	1,590 (12.2)	89 (19.3)	272 (15.3)	372 (20.6)	1,310 (18.8)	1,248 (12.7)	4,730 (12.1)
Anti-histamines	687 (20.9)	2,926 (22.4)	95 (20.6)	373 (21.0)	369 (20.5)	1,508 (21.6)	3,015 (30.7)	11,086 (28.4)
Female sex hormone preparations	32 (1.0)	149 (1.1)	4 (0.9)	24 (1.4)	25 (1.4)	95 (1.4)	251 (2.6)	764 (2.0)
Anti-depressants/anti-psychotics	172 (5.2)	623 (4.8)	28 (6.1)	93 (5.2)	88 (4.9)	338 (4.8)	547 (5.6)	1,829 (4.7)
Anti-cholinergics	49 (1.5)	209 (1.6)	3 (0.7)	19 (1.1)	25 (1.4)	111 (1.6)	236 (2.4)	719 (1.8)
Benzodiazepines	310 (9.4)	1,105 (8.5)	44 (9.5)	152 (8.6)	166 (9.2)	632 (9.0)	919 (9.4)	3,504 (9.0)
Other immunosuppressants	30 (0.9)	111 (0.9)	4 (0.9)	14 (0.8)	19 (1.1)	66 (0.9)	119 (1.2)	362 (0.9)
Inhaled corticosteroids	131 (4.0)	513 (3.9)	18 (3.9)	61 (3.4)	65 (3.6)	256 (3.7)	521 (5.3)	1,748 (4.5)
Interstitial pneumonia/COPD	155 (4.7)	673 (5.2)	16 (3.5)	63 (3.6)	65 (3.6)	295 (4.2)	689 (7.0)	2,475 (6.3)
Glaucoma treatment	N/A	N/A	306 (66.4)	1,137 (64.1)	523 (29.0)	1,554 (22.3)	1,225 (12.5)	4,791 (12.3)
Glaucoma surgery	N/A	N/A	N/A	N/A	54 (3.0)	110 (1.6)	62 (0.6)	208 (0.5)
Cataract surgery	280 (8.5)	997 (7.6)	38 (8.2)	128 (7.2)	N/A	N/A	538 (5.5)	1,786 (4.6)
Vitrectomy	91 (2.8)	221 (1.7)	19 (4.1)	39 (2.2)	35 (1.9)	43 (0.6)	145 (1.5)	574 (1.5)
Macular edema	210 (6.4)	563 (4.3)	29 (6.3)	69 (3.9)	118 (6.5)	290 (4.2)	290 (3.0)	1,150 (2.9)
Epiretinal membrane	130 (4.0)	423 (3.2)	17 (3.7)	59 (3.3)	122 (6.8)	261 (3.7)	247 (2.5)	919 (2.4)
NIU initial treatment								
Corticosteroid eye drops	3,073 (93.4)	12,406 (95.2)	437 (94.8)	1,696 (95.7)	1,690 (93.8)	6,660 (95.4)	9,395 (95.8)	37,421 (95.8)
Other	216 (6.6)	632 (4.8)	24 (5.2)	77 (4.3)	112 (6.2)	324 (4.6)	413 (4.2)	1,626 (4.2)

^aControl patients were DRS matched to the case patients.

AE: adverse event; COPD: chronic obstructive pulmonary disease; DRS: disease-risk score; IQR: interquartile range; N/A: not applicable; NIU: non-infectious uveitis.

(1.22 [1.07–1.39]) (Figure 5A, Supplementary Table 1). Local and systemic corticosteroid treatment factors associated with an increased odds of infection included infusion/intravenous corticosteroids (1.66 [1.43–1.93]) and oral corticosteroids (1.48 [1.38–1.58]) (Figure 5B, Supplementary Table 1).

Low-dose (1.51 [1.40–1.63]) and medium- to high-dose systemic corticosteroids (1.84 [1.65–2.04]) were associated with an increased odds of infection (Figure 5C, Supplementary Table 1). Short-/medium-term (1.60 [1.49–1.72]) and long-term corticosteroid treatment (1.30 [1.11–1.52]) were associated with an increased odds of infection (Figure 5D, Supplementary Table 1).

3.3. Factors associated with high corticosteroid exposure

3.3.1. Sub-Tenon's injection number

Macular edema was found to have the strongest association with two or more sub-Tenon's injections, followed by Vogt-Koyanagi-Harada disease, a history of glaucoma treatment, and sex (Figure 6). Similarly, macular edema was also found to have the strongest association with three or more

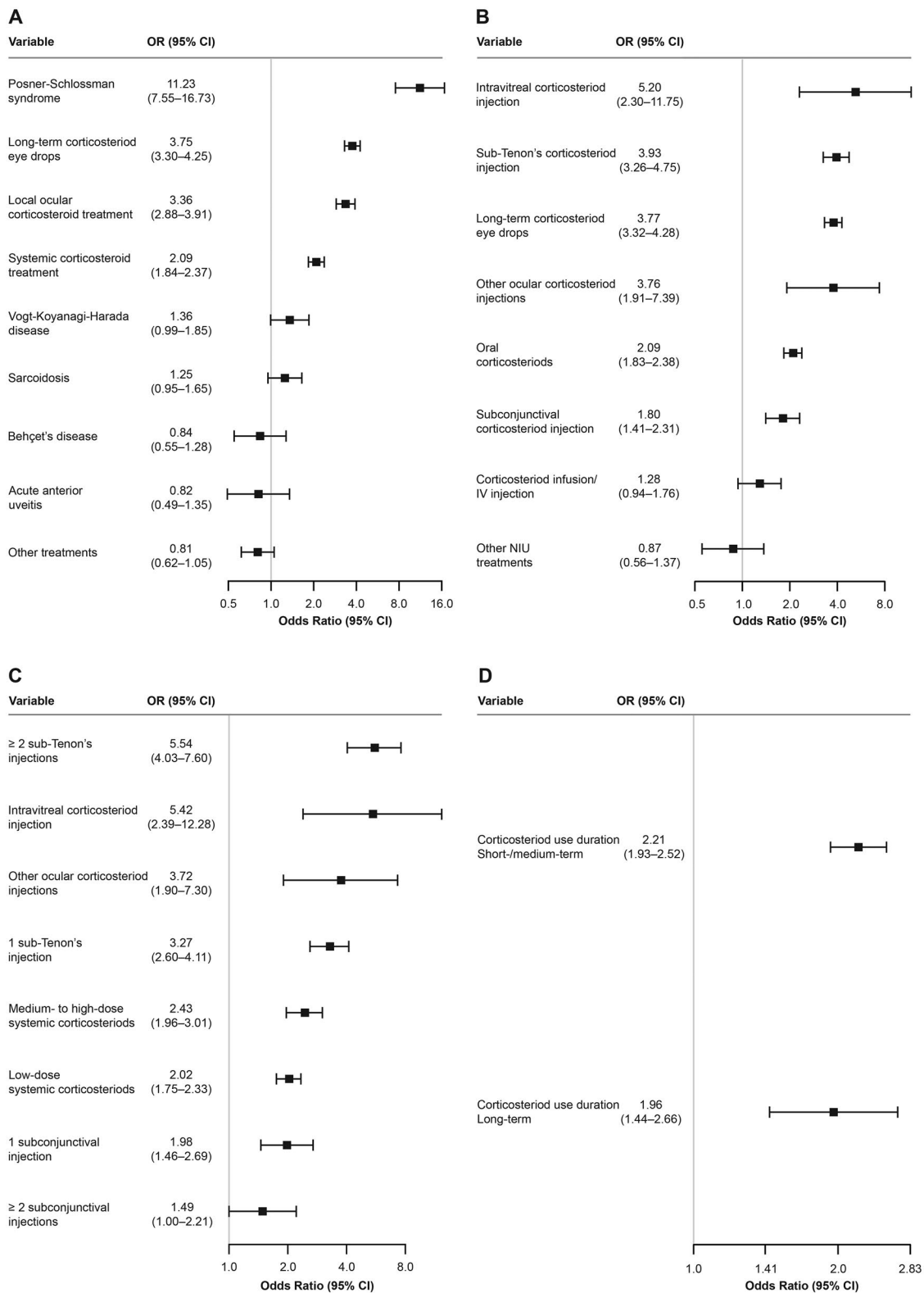


Figure 2. Variables associated with glaucoma treatment. (A) NIU diagnosis and type of treatment (high-level terms for local and systemic corticosteroid treatment). (B) NIU diagnosis and type of treatment (low-level terms for local and systemic corticosteroid treatment). (C) Dose and frequency of corticosteroid treatment. (D) Duration of corticosteroid treatment. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. CI: confidence interval; DRS: disease-risk score; IV: intravenous; NIU: non-infectious uveitis

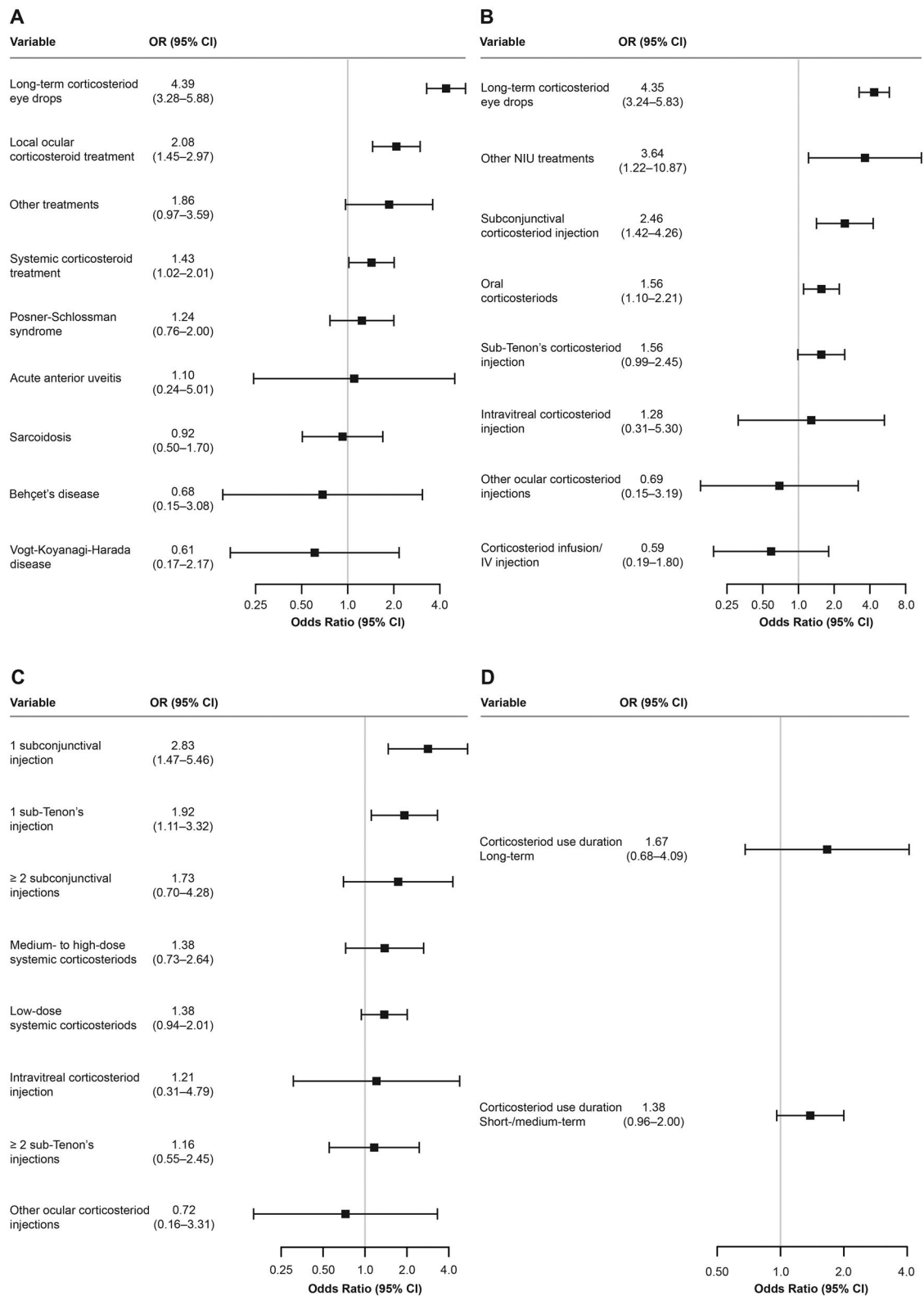


Figure 3. Variables associated with glaucoma surgery. (A) NIU diagnosis and type of treatment (high-level terms for local and systemic corticosteroid treatment). (B) NIU diagnosis and type of treatment (low-level terms for local and systemic corticosteroid treatment). (C) Dose and frequency of corticosteroid treatment. (D) Duration of corticosteroid treatment. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. CI: confidence interval; DRS: disease-risk score; IV: intravenous; NIU: non-infectious uveitis

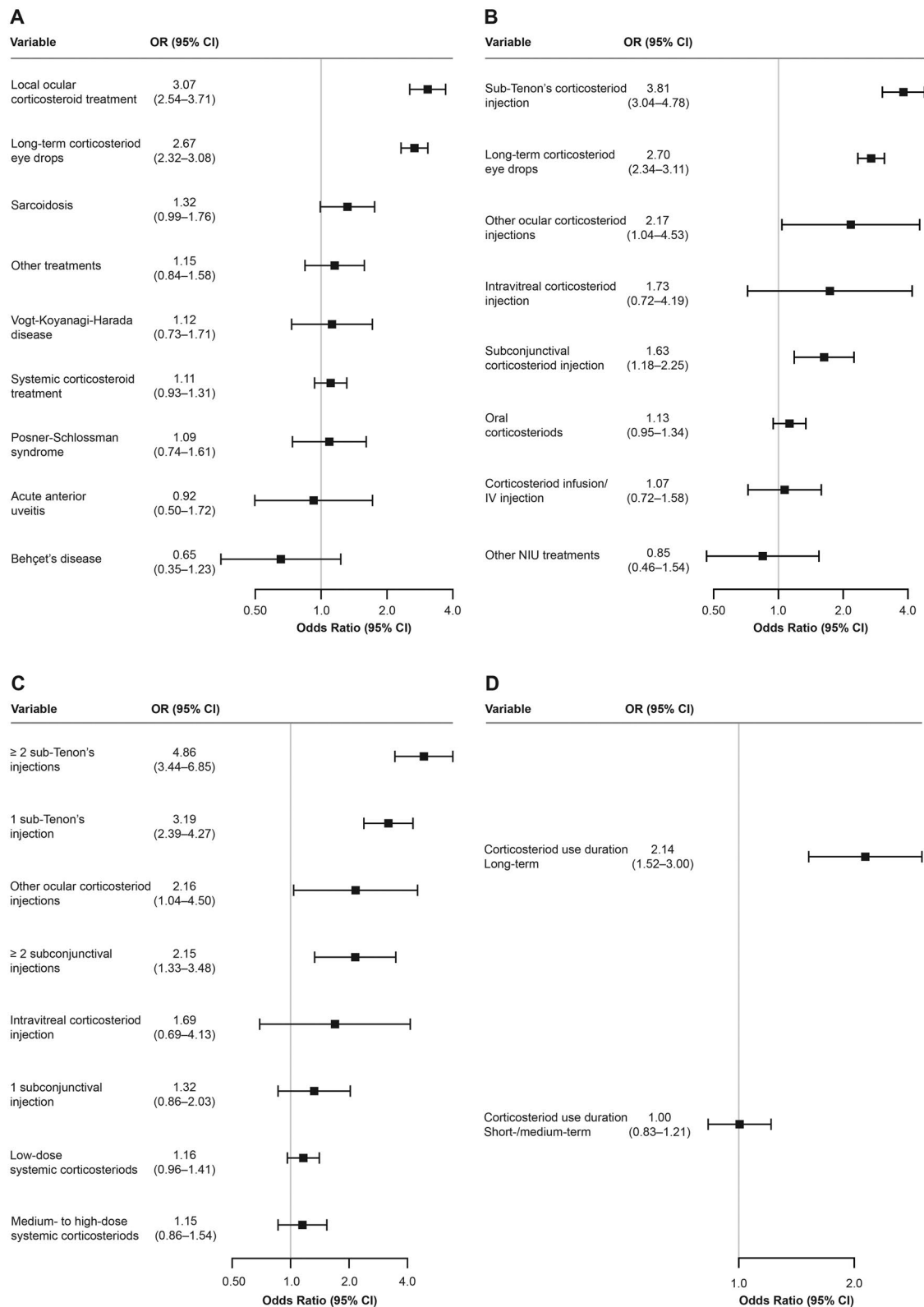


Figure 4. Variables associated with cataract surgery. (A) NIU diagnosis and type of treatment (high-level terms for local and systemic corticosteroid treatment). (B) NIU diagnosis and type of treatment (low-level terms for local and systemic corticosteroid treatment). (C) Dose and frequency of corticosteroid treatment. (D) Duration of corticosteroid treatment. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. CI: confidence interval; DRS: disease-risk score; IV: intravenous; NIU: non-infectious uveitis

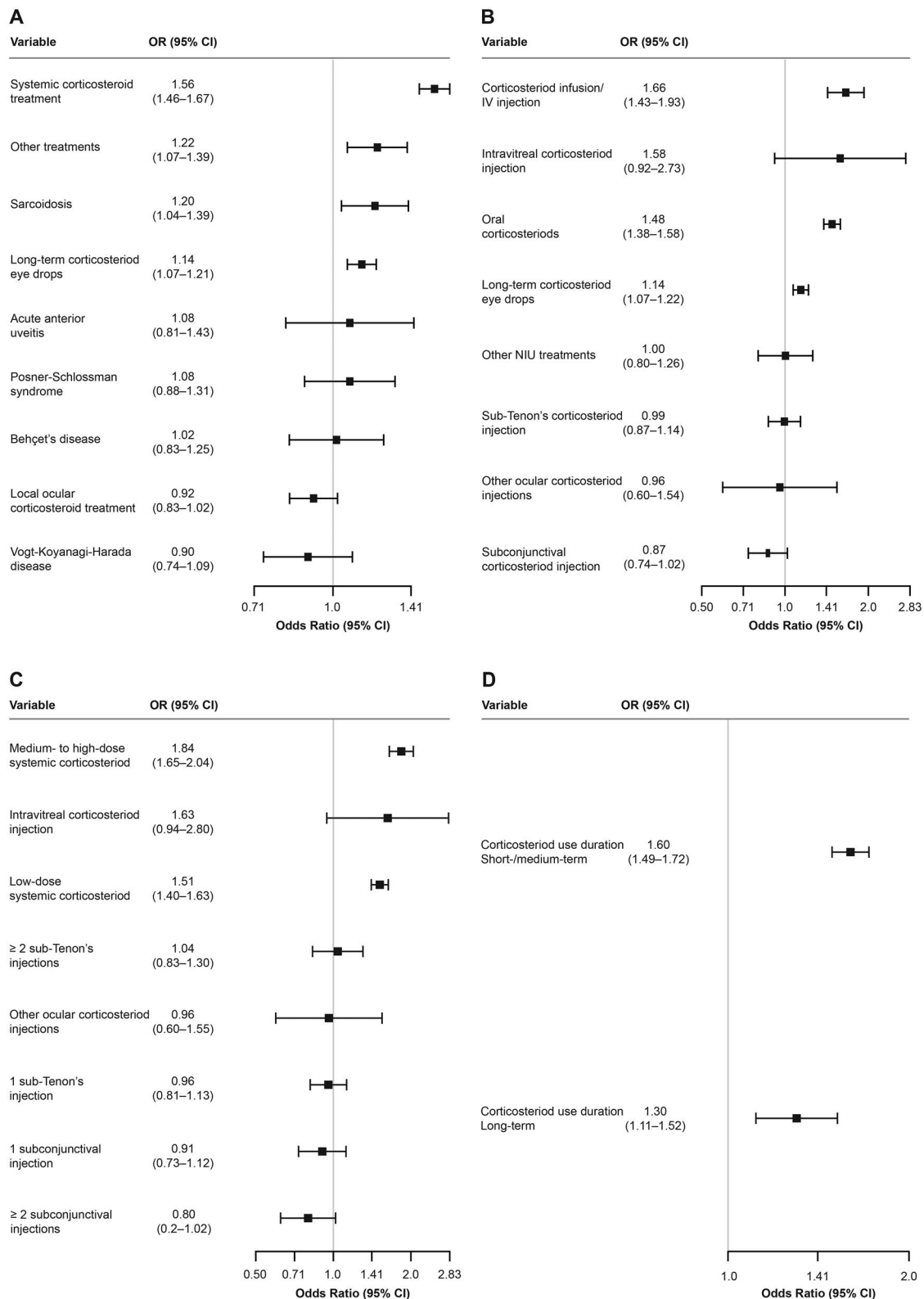


Figure 5. Variables associated with infection. (A) NIU diagnosis and type of treatment (high-level terms for local and systemic corticosteroid treatment). (B) NIU diagnosis and type of treatment (low-level terms for local and systemic corticosteroid treatment). (C) Dose and frequency of corticosteroid treatment. (D) Duration of corticosteroid treatment. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. CI: confidence interval; DRS: disease-risk score; NIU: non-infectious uveitis

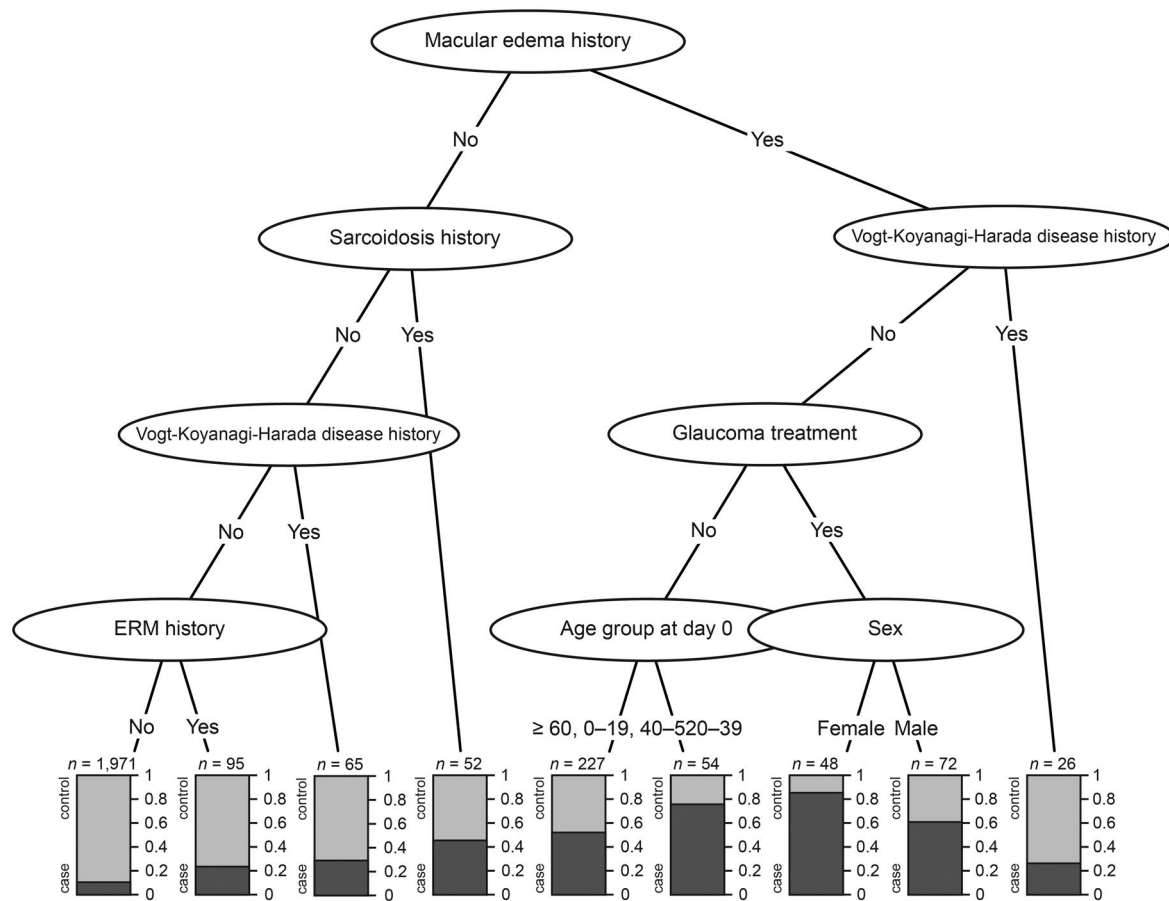


Figure 6. CHAID decision-tree analysis of factors associated with high corticosteroid exposure: ≥ 2 sub-Tenon injections. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. Bars represent the proportion of control and case patients.

CHAID: chi-square automatic interaction detection; DRS: disease-risk score; ERM: epiretinal membrane

sub-Tenon's injections, followed by Vogt-Koyanagi-Harada disease, sarcoidosis, and epiretinal membrane (Figure 7).

3.3.2. Corticosteroid dose

Vogt-Koyanagi-Harada disease was found to have the strongest association with medium- to high-dose systemic corticosteroids, followed by Behçet's disease, sarcoidosis, macular edema, epiretinal membrane, and a history of vitreous surgery (Figure 8).

3.3.3. Duration of oral corticosteroid treatment

Vogt-Koyanagi-Harada disease was found to have the strongest association with long-term oral corticosteroid use, followed by sarcoidosis, macular edema, Behçet's disease, and a history of cataract surgery (Figure 9).

4. Discussion

The J-CAT2 study used a national claims database to evaluate treatment and patient factors associated with complications/AEs or high corticosteroid exposure in patients with NIU in Japan. We identified several associations between corticosteroid treatment, including type, frequency, and dose, and complications/AEs or high corticosteroid exposure. These findings indicate that more tolerable, alternative treatments for NIU are needed.

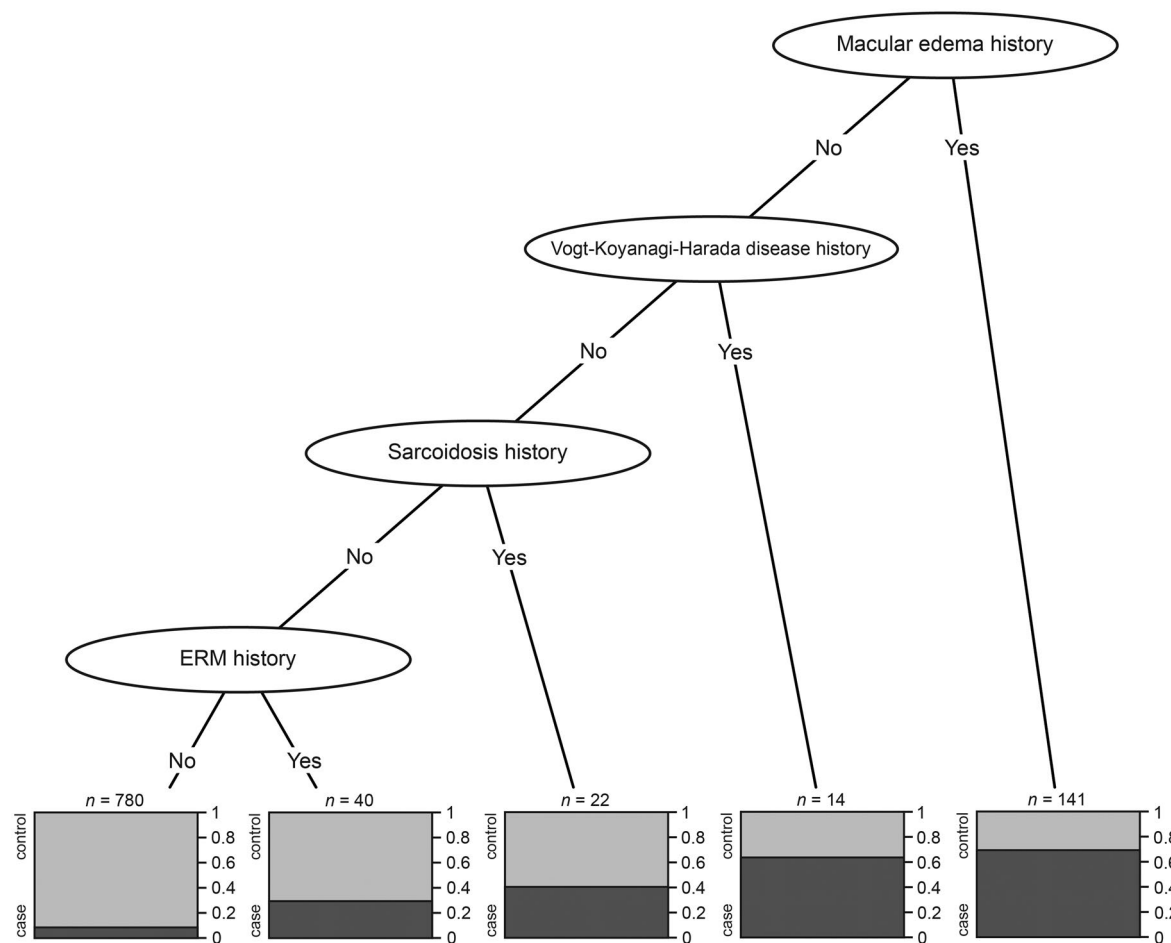


Figure 7. CHAID decision-tree analysis of factors associated with high corticosteroid exposure: ≥ 3 sub-Tenon injections. Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. Bars represent the proportion of control and case patients.

CHAID: chi-square automatic interaction detection; DRS: disease-risk score; ERM: epiretinal membrane

Consistent with previous reports [5–8], we found that corticosteroid treatment for NIU in addition to Posner-Schlossman syndrome, which is characterized by acute intraocular pressure elevation during episodes of ocular inflammation, was associated with the initiation of glaucoma treatment. Notably, the odds of glaucoma treatment increased with the frequency of sub-Tenon's injections. Despite sub-Tenon's injection being a common treatment for NIU [9], the relationship between this treatment approach and glaucoma has not previously been evaluated. We also observed a slight dose-dependent increase in the odds of glaucoma treatment with systemic corticosteroids, which aligns with previous reports [7]. Of note, when the data were separately evaluated by corticosteroid infusion or intravenous administration, there was no significant increase in the odds of glaucoma treatment. A potential explanation for this finding is that patients who received corticosteroid infusion or intravenous administration may have been less susceptible to experiencing increases in intraocular pressure. Such patients could have contributed to an underestimation of glaucoma risk associated with corticosteroids. Interestingly, in a previous study, Huscher et al. reported that the risk of glaucoma in patients with rheumatoid arthritis increased with systemic corticosteroids when the threshold of 7.5 mg/day was exceeded [19].

We also found that the odds of glaucoma treatment were higher for a single than two or more subconjunctival injections. Patients who received two or more subconjunctival corticosteroid injections may have been more likely to be corticosteroid non-responders, and therefore less likely to experience increases in intraocular pressure, and hence glaucoma, after treatment. Previous studies have shown an inverse relationship between subconjunctival injections and the initiation of glaucoma treatment [9];

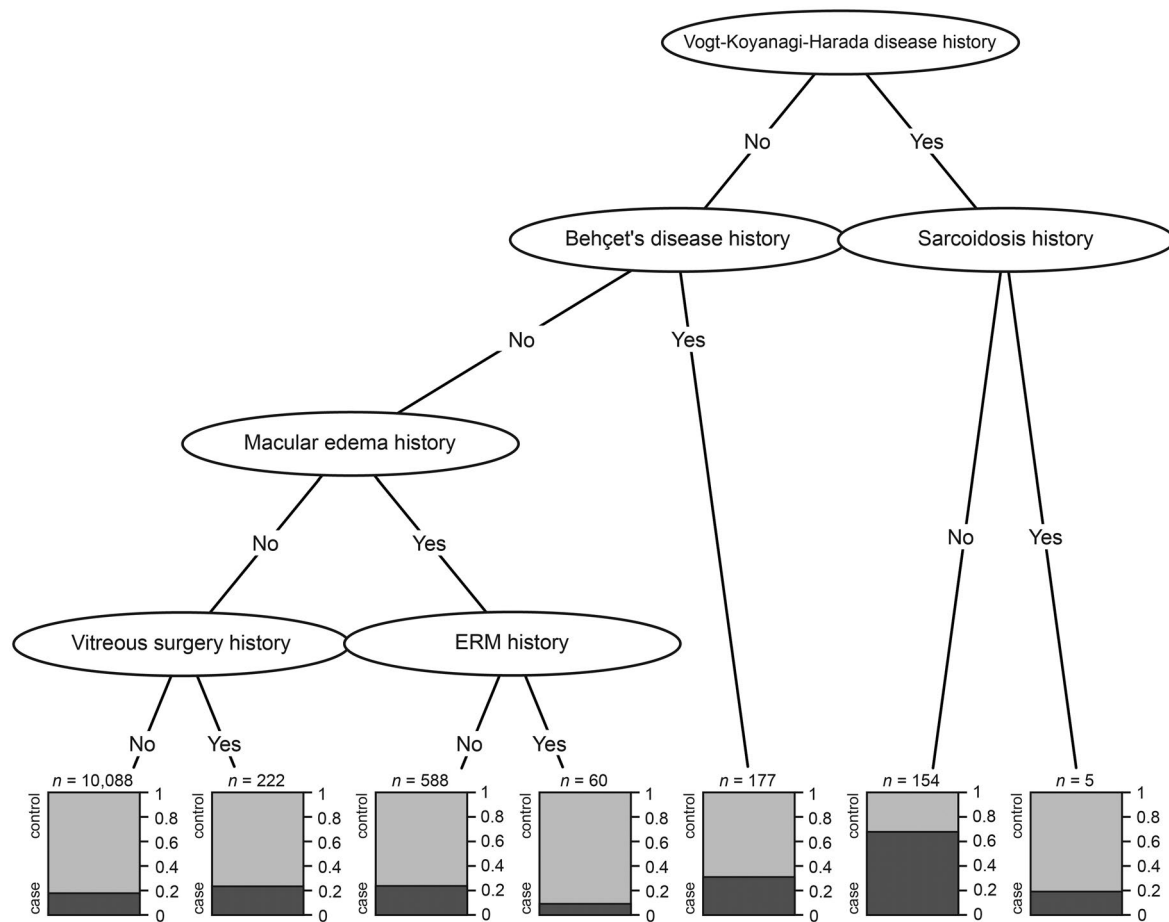


Figure 8. CHAID decision-tree analysis of factors associated with high corticosteroid exposure: medium- to high-dose systemic corticosteroids (≥ 10 mg/day of oral corticosteroids or corticosteroid infusion or intravenous injection). Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. Bars represent the proportion of control and case patients.

CHAID: chi-square automatic interaction detection; DRS: disease-risk score; ERM: epiretinal membrane

therefore, subconjunctival injections may have a protective effect. This may be mediated by more effective control of intraocular inflammation with multiple vs single subconjunctival injections, thereby reducing intraocular pressure and the risk of glaucoma.

Consistent with the glaucoma treatment findings, we found that systemic corticosteroid therapy, subconjunctival injections, and long-term use of eye drops were associated with glaucoma surgery. Further analysis showed no associations between glaucoma surgery and corticosteroid infusion/intravenous administration, sub-Tenon's injection, or intravitreal injection. Furthermore, there were no increases in glaucoma surgery with systemic corticosteroid treatment, sub-Tenon's injection, or subconjunctival injection in terms of either dosage or treatment frequency. A single sub-Tenon's injection was associated with a significantly increased risk of glaucoma surgery. This finding suggests that patients receiving multiple injections are more likely to be non-responders, whereas the single-injection group may have included a higher proportion of patients susceptible to post-treatment increases in intraocular pressure.

Corticosteroid treatment was also found to be associated with cataract surgery. Specifically, associations were found for local corticosteroid injections, long-term use of eye drops, other local corticosteroid injections, subconjunctival injection, and sub-Tenon's injection, including dose-dependent effects for the latter two treatment categories. In contrast, there was no association between cataract surgery and intravenous infusion or intravitreal injection of corticosteroids, and no dose-dependent risk of cataract surgery associated with systemic corticosteroid therapy. Given that the risk of cataract

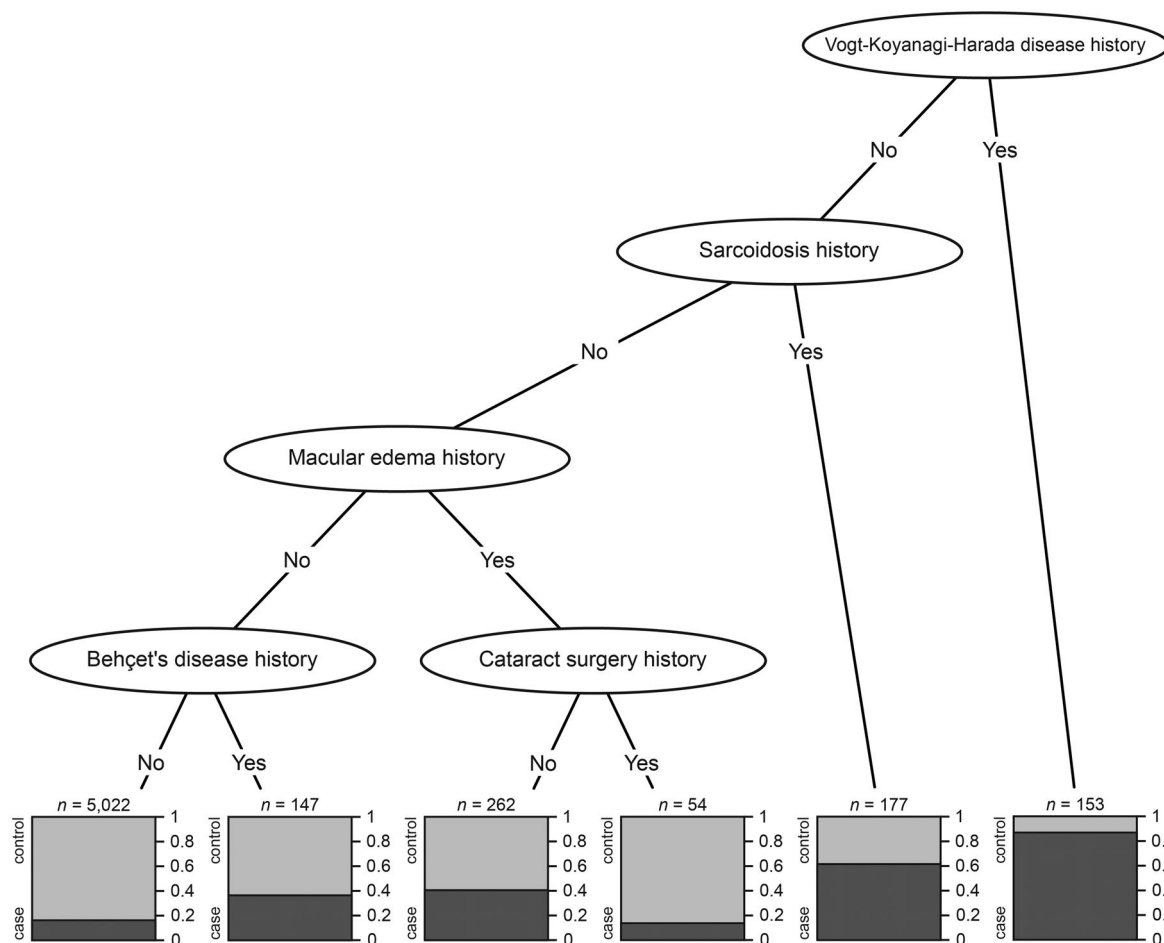


Figure 9. CHAID decision-tree analysis of factors associated with high corticosteroid exposure: long-term use of oral corticosteroids (cumulative administration period of oral corticosteroids ≥ 90 days and average dose during this period ≥ 5 mg/day, or a cumulative administration period ≥ 180 days, regardless of dose). Control patients were DRS matched to the case patients in a ratio of 1:k ($k \leq 4$) by risk set sampling. Bars represent the proportion of control and case patients.

CHAID: chi-square automatic interaction detection; DRS: disease-risk score

in patients exposed to systemic corticosteroids for ≥ 12 months has been reported to increase when the threshold of 5 mg/day is exceeded, the contribution of the duration of administration on risk would appear to be large [19]. This hypothesis is supported by our finding that there was a significant increase in the risk of cataract surgery in the long-term corticosteroid use group.

Sub-Tenon's injection showed higher odds for glaucoma treatment and cataract surgery than subconjunctival injection. The increased risks of glaucoma treatment and cataract surgery with sub-Tenon's corticosteroid injection compared with subconjunctival injection may be a reflection of differences in corticosteroid exposure time/retention associated with these treatment approaches. Specifically, evidence suggests that the effects of sub-Tenon's injection may persist for approximately 2 to 3 months [20], consistent with the duration of action of triamcinolone acetonide (the primary sub-Tenon's injection agent), whereas the effects of subconjunctival injection are shorter [21], consistent with the duration of action of dexamethasone (the primary subconjunctival injection agent). The increased exposure time/retention with sub-Tenon's injection compared with subconjunctival injection may have increased the risk of these complications. In addition, cataracts associated with corticosteroid treatment are known to occur at the back of the lens [22]. The increased risk with sub-Tenon's injection vs. subconjunctival injection is likely a consequence of the posterior to anterior delivery of the sub-Tenon's approach. Although the point estimates showed no significance regarding the association between sub-Tenon's injection and glaucoma surgery, this does not necessarily indicate a null effect given that the CIs showed a trend toward an increased risk.

We found that systemic treatments, including oral and intravenous corticosteroid infusions, and long-term use of eye drops were associated with the risk of infection (ocular or systemic). However, there was no significant association between local corticosteroid injections and the risk of infection, whereas, consistent with a previous report [7], we found that there was only a minor dose-dependent relationship between systemic corticosteroids and the risk of infection. Further study is warranted to evaluate if there are associations between corticosteroid treatment and systemic and local infections in patients with NIU.

Several factors were found to be associated with high levels of corticosteroid exposure. Of note, we found that patients with comorbid macular edema tended to receive frequent sub-Tenon's corticosteroid injections. Patients with Vogt-Koyanagi-Harada disease or sarcoidosis also showed a tendency to receive higher than moderate doses or long-term systemic corticosteroid treatment. The latter is consistent with the findings of a previous study reporting an association between Vogt-Koyanagi-Harada disease and the use of high-dose corticosteroids [23]. Our findings are also consistent with a previous report detailing long-term corticosteroid use in patients with uveitis associated with Vogt-Koyanagi-Harada disease and sarcoidosis [24]. Patients with these characteristics may experience tolerability issues due to high corticosteroid exposure, suggesting the need for new treatment options.

Our study is the first to quantitatively and visually evaluate the treatment and patient factors associated with the risk of complications/AEs or high corticosteroid exposure in patients with NIU using multivariable logistic regression and decision-tree analysis, including the association between sub-Tenon's injection and complications/AEs. Another key strength of our study is the use of a large-scale database and nested case-control design, which provided enhanced statistical power. This facilitated meaningful analysis by the most relevant treatment categories and adjustment for various confounding factors. An additional strength is the use of CHAID for an exploratory evaluation of patient factors leading to high corticosteroid exposure, which allowed for ease of visual interpretation, understanding of non-linear relationships, and prioritization of predictors.

As our study was based on data from a Japan claims database, we acknowledge that some of the findings may not be broadly generalizable to clinical practice elsewhere due to differences in approved treatments for NIU and disease characteristics of patients with NIU [25,26]. For instance, although commonly used in the United States as immunosuppressive agents, methotrexate and mycophenolate mofetil are not used to treat NIU in Japan. Likewise, intravitreal corticosteroid injections, intravitreal corticosteroid implants [27,28], and suprachoroidal injections [29] are not currently approved for NIU in Japan. Unsurprisingly, the number of cases of intravitreal corticosteroid injection in our analysis was low, limiting the meaningfulness of the associated findings. Evidence suggests that the lack of approved indications for alternative agents in Japan is manifested by an overreliance of corticosteroid administration and/or the continuation of corticosteroid therapy, despite concerns over complications [4,30]. Clearly, our findings are most applicable to clinical practice in countries/regions that have similar approved NIU treatments to those in Japan. Nevertheless, a study demonstrating similar increases in intraocular pressure following sub-Tenon's triamcinolone injection, intravitreal triamcinolone, and intravitreal dexamethasone implants [31] does indirectly support more broader applicability. In terms of disease characteristics, it is also worth noting that Vogt-Koyanagi-Harada disease is relatively rare outside of Asia [32]. Lastly, from a generalizability standpoint, the database used for our analyses did not include patients aged ≥ 75 years; hence, the findings are applicable for patients < 75 years, which comprises the majority of the NIU population.

The design of our study has several limitations, including that identification of associations between factors and outcomes using a nested case-control design does not guarantee a causal relationship; more precise, confirmatory analyses are warranted. The observational nature of our study also limits our ability to establish causal relationships. However, as illustrated in our claims database analysis, sample sizes for some treatment categories are small, limiting the feasibility of meaningful prospective studies. Further, although baseline covariates were adjusted using DRS matching, it is difficult to adjust for time-dependent covariates that occur after baseline with this design. Although a prospective cohort design using time-dependent regression model would be a preferred approach, obtaining a sufficiently large sample size would be challenging. Hence, the case-control design may provide sufficient statistical power to evaluate events. In addition, the effects of unmeasured confounding, including visual acuity, cannot be accounted for. Although we endeavored to increase disease specificity using procedural codes and exclusion criteria, as noted previously [4], the validity of NIU diagnoses

based on ICD-10 codes disease cannot be confirmed. Hence, some degree of misclassification/mis-coding, and consequent data inaccuracy, is possible. We also acknowledge that cases of severe inflammation are more likely to result in complications/AEs, regardless of corticosteroid treatment. For instance, anterior chamber flare and elevated aqueous humor cytokines levels have been reported to be associated with AEs [33] and secondary glaucoma [34], respectively, in chronic anterior uveitis. As the claims database does not contain information on clinical parameters, it is possible that some complications/AEs may have occurred independent of corticosteroid exposure. Finally, as claims records were obtained from 2016 to 2023, we cannot rule out the possibility that a reluctance to seek medical care during the COVID-19 pandemic may have had some impact on the results of our analysis. However, we believe that patients with moderate-to-severe disease, as included in our analysis, would have been less likely to refrain from seeking treatment than patients with mild disease and that this, along with the nested case-control design, limited the potential for COVID-19 pandemic-related bias.

5. Conclusion

In conclusion, the novel findings of the J-CAT2 study Japan nationwide claims database analysis indicate that there are dose, frequency, and route specific associations between corticosteroid treatment and complications/AEs in patients with NIU. Further, by employing both multivariable logistic regression and CHAID decision-tree analysis, this study provided a novel, data-driven framework for identifying factors, most notably macular edema, Vogt-Koyanagi-Harada disease, and sarcoidosis, linked with high corticosteroid exposure. Taken together, these findings not only fill critical gaps in the current literature but also suggest that some patients with NIU would benefit from the availability of more tolerable treatments/alternative treatment strategies. Emerging nonsteroid treatment options, particularly those that can target intraocular inflammation in NIU without the adverse effects associated with corticosteroids, may be beneficial for patients.

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Authors' contributions

CRediT: **Sentaro Kusuhara**: Conceptualization, Visualization, Writing – original draft; **Koh-Hei Sonoda**: Conceptualization, Writing – original draft, Writing – review & editing; **Toshikatsu Kaburaki**: Conceptualization, Writing – original draft, Writing – review & editing; **Tachie Fujita**: Conceptualization, Writing – original draft, Writing – review & editing; **Saki Katayama**: Conceptualization, Writing – original draft, Writing – review & editing; **Misako Makishima**: Conceptualization, Writing – original draft, Writing – review & editing; **Takao Nakamura**: Conceptualization, Writing – original draft, Writing – review & editing; **Mariko Nio**: Conceptualization, Writing – original draft, Writing – review & editing; **Takashi Omoto**: Conceptualization, Writing – original draft, Writing – review & editing; **Yukari Matsuo-Tezuka**: Conceptualization, Writing – original draft, Writing – review & editing; **Tomoki Yoshizaki**: Conceptualization, Writing – original draft, Writing – review & editing; **Mio Kitamura**: Conceptualization, Writing – original draft, Writing – review & editing; **Kensuke Sasaki**: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing; **Kairi Ri**: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing; **Keiko Sato**: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing; **Hiroshi Goto**: Conceptualization, Writing – original draft, Writing – review & editing.

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Ethical approval

As anonymized data were used, the J-CAT study was exempt from ethics review board review/approval and informed consent was not required.

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Data availability statement

The data for this study were used under license and are not publicly available due to the privacy policy of JMDC Inc.

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