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ORIGINAL RESEARCH

Incidence and Predictors of Ocular Complications in Pediatric-Onset Uveitis: Data from the AIDA Network Uveitis Registry

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ABSTRACT

***Introduction*:** This study aims to describe complications of pediatric-onset uveitis and their predictors among baseline and treatment-related factors.

***Methods*:** This registry-based observational study included patients with noninfectious uveitis with disease onset < 18 years.

***Results*:** A total of 309 patients were enrolled (535 eyes). Uveitis was anterior in 290 eyes (54.2%), panuveitis in 121 (22.6%), intermediate in 88 (16.4%), and posterior in 24 (4.5%). Over a median follow-up of 49.0 months (interquartile range [IQR] 101.0), 137 children (44.3%) developed ≥ 1 complication (14.4 per 100 patient-years).

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Idiopathic uveitis ($p<0.001$), longer topical glucocorticoid (GC) monotherapy ($p<0.001$) and longer delay of immunosuppressive therapy (IST) ($p=0.03$) were associated with a higher frequency of complications. In multivariate analysis, anterior uveitis was protective against complications (odds ratio [OR] 0.10, 95% confidence interval [CI] −4.1 to −1.6, $p<0.001$), whereas a chronic course of uveitis significantly increased the risk (OR 6.13, 95% CI 1.0–2.6, $p<0.001$). Older age at onset was protective against cataract (OR 0.91, 95% CI −0.2 to −0.02, $p=0.020$) and band keratopathy (OR 0.8, 95% CI −0.4 to −0.1, $p=0.003$).

Final best-corrected visual acuity (BCVA) (Snellen decimals) was inversely correlated with the duration of topical GC monotherapy ($\rho=-0.23$; $p=0.001$). In multivariate analysis, panuveitis was linked to a 0.142 decimal reduction (95% CI −0.219 to −0.066, $p<0.001$), and cataract to a 0.295 reduction (95% CI −0.372 to −0.217, $p<0.001$) in the final BCVA.

Conclusions: Children with chronic, idiopathic, early-onset, and non-anterior uveitis are at greatest risk for complications. Structured screening for these children, along with early initiation of systemic IST, is essential to prevent visual impairment.

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Keywords: Pediatric-onset uveitis; Complications; Incidence; Predictors; Visual outcomes

Key Summary Points

Why carry out this study?

Ocular complications are known to affect a considerable portion of children with noninfectious uveitis as a result of poorly controlled inflammation and treatment-related side effects.

In this registry-based study, we aimed to provide a comprehensive description of ocular complications of noninfectious uveitis in children and to identify groups at a higher risk based on baseline characteristics and different treatment strategies.

What was learned from the study?

The incidence of complications in pediatric-onset uveitis was calculated as 14.4 per 100 patient-years.

Factors associated with a higher risk of complications were idiopathic uveitis, chronic course, younger age at onset, longer topical glucocorticoid monotherapy, and longer delay of immunosuppressive therapy.

The presence of panuveitis, cataract, and a longer duration of topical glucocorticoid monotherapy negatively affected the final visual acuity.

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INTRODUCTION

Pediatric noninfectious uveitis (NIU) encompasses a heterogeneous group of intraocular inflammatory disorders with variable clinical presentations and underlying etiologies. While relatively rare, it remains a leading cause of ocular morbidity in children. The most common forms include idiopathic uveitis and uveitis associated with a systemic autoimmune condition, particularly juvenile idiopathic arthritis (JIA). Less frequent associations include Behçet's disease, sarcoidosis, tubulointerstitial nephritis and uveitis (TINU) syndrome, and Vogt–Koyanagi–Harada syndrome. The insidious onset and frequently asymptomatic nature of NIU in children often delay diagnosis, increasing the risk of irreversible ocular damage.

Ocular complications are known to affect a considerable portion of children with NIU as a result of poorly controlled inflammation and treatment-related side effects [1]. Complications such as cataract, band keratopathy, macular edema, and glaucoma have a remarkable impact on visual acuity, may lead to permanent structural changes, and often require more aggressive treatment strategies, including ocular surgery, potentially exposing children to an increased risk of adverse events [2]. Therefore, effective prevention and early identification of ocular complications could be the key to improved visual and general outcomes in children with NIU. In this context, the choice and timing of systemic immunosuppressive therapy and steroid-sparing strategies play a crucial role. Recent studies suggest the early adoption of biologic agents to prevent ocular complications in children with known baseline risk factors, but evidence is still quite limited [3, 4].

In this study, we aimed to provide a comprehensive description of ocular complications of NIU in children and to identify groups at a higher risk based on baseline characteristics and different treatment strategies. Furthermore, as an ancillary aim, we analyzed the incidence of complications over the decades based on an extended data collection in the AIDA Network uveitis registry to identify any changes over time due to improvements in treatment strategies and diagnostic capability.

METHODS

This is a registry-based observational study. Pseudonymized data were retrieved from the AIDA Network uveitis registry and the AIDA Network Behçet's disease registry in January 2025 [5, 6]. All patients affected by NIU with an onset before the age of 18 were included in the study (Fig. 1).

Data had been collected in the registries both retrospectively and prospectively. Patient-level and eye-level data were separated into two distinct datasets to ensure focused analyses.

This study had a mixed analytical approach. The primary objective was addressed using a case–control design, aiming to assess demographic, clinical, and treatment-related factors associated with the presence of ocular complications at the end of follow-up. For these analyses, cases were defined as patients/eyes with ocular complications, and controls were patients/eyes without ocular complications. The specific endpoints were defined as follows: (1) frequency and type of ocular complications occurring in the population studied; (2) presence or absence of ocular complications (at least one) at the end of follow-up, analyzed in relation to baseline and treatment-related factors; (3) presence or absence of the most common individual complications, analyzed in relation to relevant baseline characteristics and treatment parameters.

The analysis of visual acuity at final follow-up was conducted as a cross-sectional analysis, evaluating (4) associations of the final best-corrected visual acuity (BCVA) with baseline characteristics, treatment strategies, and ocular complications.

In addition to the primary case–control analyses, secondary longitudinal analyses were conducted on the same registry cohort to describe the incidence of complications over time and evaluate trends across different diagnostic periods. These exploratory analyses, adopting a cohort design approach, included the following endpoints: (5) incidence of complications in the

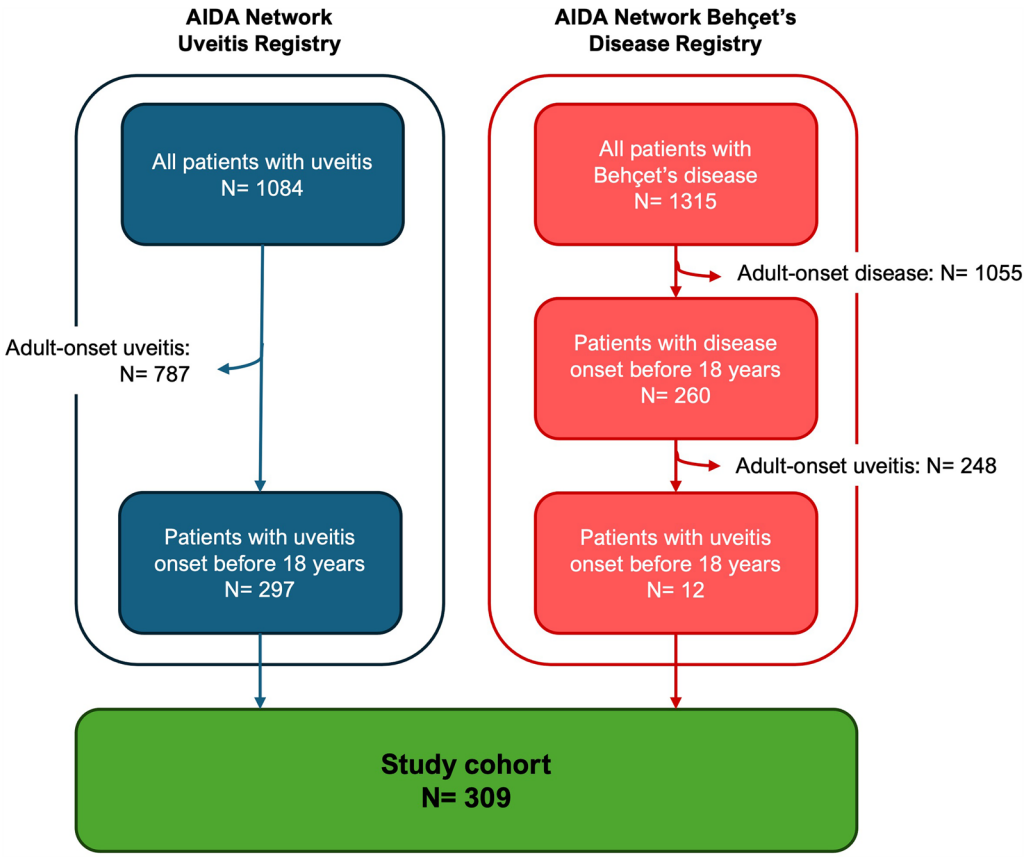

Fig. 1 Flow-chart illustrating the selection process of the cohort from the AIDA Network Uveitis Registry and Behçet's Disease Registry

entire study population; (6) incidence of complications in subgroups of patients diagnosed in different periods.

The anatomical classification of uveitis was attributed by the ophthalmologist according to the Standardization of Uveitis Nomenclature (SUN) criteria [7]. The diagnosis of cataract was attributed as per the Lens Opacities Classification System III (LOCS III) [8]. The diagnoses of uveitis, posterior synechiae, and band keratopathy were made on a clinical basis through slit-lamp examination and/or optical coherence tomography (OCT) by an expert ophthalmologist. Macular edema was identified by fundus examination, OCT, and/or fluorescein angiography; in this regard, the OCT parameters were evaluated by the operator against the reference values of the specific population and instrument employed. Glaucoma was defined according to the Childhood Glaucoma Research Network Classification [9]. Visual acuity, expressed as BCVA decimals, was measured using age-appropriate Snellen charts. When classifying patients based on age-at-onset groups, those with uveitis onset before or at 8 years of age were considered as early-onset, while those with uveitis onset after 8 years of age were considered as late-onset, for consistency with the previous literature [10]. In accordance with registry definitions, uveitis was classified as limited if the duration was less than 3 months, and persistent if it exceeded 3 months. The disease course was categorized as acute in cases of abrupt onset and limited duration; recurrent when characterized by repeated episodes separated by intervals of inactivity greater than 3 months off therapy; and chronic when inflammation persisted with

relapses occurring within 3 months of treatment discontinuation.

This study protocol (NCT05200715) adheres to the principles outlined in the Declaration of Helsinki. Permission was obtained to access and use data from the database/registry utilized in this study. To be eligible for the AIDA Network registries, parents or legal guardians of pediatric patients must provide written consent after receiving appropriate information. Patients' personal information was separated by their clinical data by using pseudonyms. The protocol of the AIDA Network registries was approved by the Ethics Committee of Siena University Hospital (Ref. 14951), and by the Ethics Committees of the participating investigator centers (Table S1).

Statistical analyses were performed using the JASP open-source statistics package (version 0.19.3.0). Descriptive statistics summarized the data. The Shapiro–Wilk test was applied to assess the normality of data distributions. Univariate analyses were conducted to identify candidate factors for inclusion in subsequent multivariate regression models. Specifically, associations between categorical variables were examined using contingency tables with the chi-square test, while differences in continuous variables between independent groups were evaluated using the Mann–Whitney *U* test or Kruskal–Wallis test if > 2 groups. Variables showing a p value < 0.05 in univariate analysis, along with clinically relevant variables (including sex, age at onset, and duration of follow-up), were included in a multivariate logistic regression model to determine the combined effect of multiple predictor variables. This approach allowed for the estimation of adjusted odds ratios (OR) and 95% confidence intervals (CI). Correlations among continuous non-normally distributed or ordinal variables were assessed using Spearman's correlation analysis. Linear regression analysis was performed to identify predictors or the final BCVA. As for longitudinal analyses, the incidence of complications was calculated relative to the effective exposure period, i.e., the follow-up duration since the onset of uveitis. Complications were counted once per patient even if they were recurrent or bilateral. To analyze potential changes in the complication rate over time, patients were arbitrarily categorized into three groups, according to the date of uveitis diagnosis: before the year 2011, from 2011 to 2015, from 2016 to 2020, and from 2021 onwards. Poisson regression with a likelihood ratio test was employed to compare the incidence of complications across groups. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Description of the Population

We enrolled 309 patients with pediatric-onset NIU (535 affected eyes). The demographic and clinical characteristics of the population are detailed in Table 1, while the therapeutic data are provided in supplementary material (Table S2).

Uveitis Complications and Their Predictors

For a median of 49.0 (IQR 101.0) [1.0–677.0] months, 137 children (44.3%) and 216 eyes (40.4%) developed at least one ocular complication. Cataract occurred in 92 eyes (17.2%), posterior synechiae in 80 (15.0%), macular edema in 47 (8.8%), band keratopathy in 27 (5.0%), and glaucoma in 23 (4.3%). Type and frequency of all ocular complications occurring in the population are provided in Table 2 while type and frequency of complications stratified by age-at-onset groups and uveitis anatomical classes are shown in Fig. 2A and B, respectively.

Ocular surgery was performed in patients with uveitis onset ≤ 8 years in 33 cases (12.5%) and > 8 years in 18 cases (7.2%) ($p = 0.045$), while information about age at onset was missing in two cases.

Univariate analyses were conducted to identify potential factors associated with at least one complication and specific complications selected among the most frequent in the population, including cataract, posterior synechiae, macular edema, band keratopathy, and glaucoma/ocular hypertension (results available in supplementary material Tables S3-S8). The results of multivariate regression analyses are reported in Table 3.

Table 1 Demographic and clinical characteristics of the study population

Demographic and clinical variables	**Patients (%)**
Biologic sex	Female 185 (59.9) Male 123 (39.8) Missing 1 (0.3)
Ethnic origin	White 230 (74.4) Hispanic 34 (11.0) Arab 29 (9.4) Asian 1 (0.3) Black 1 (0.3) Missing 14 (4.5)
Laterality of uveitis	Bilateral 226 (73.1) Unilateral 83 (26.9)
Uveitis associated with a systemic disease	147 (48.5)
Uveitis etiology, patients (%)	Idiopathic 148 (47.9) JIA 112 (36.2) HLA-B27—disease spectrum 13 (4.2) Behçet's disease 12 (3.9) Sarcoidosis and Blau syndrome 7 (2.3) Vogt–Koyanagi–Harada syndrome 4 (1.3) Others 5 (1.6)[a] Missing 8 (2.6)
Oculo-specific variables	**Eyes (%)**
Anatomical classification of uveitis	Anterior 290 (54.2) Panuveitis 121 (22.6) Intermediate 88 (16.4) Posterior 24 (4.5) Missing 12 (2.2)
Onset of uveitis	Insidious 258 (60.0) Sudden 172 (40.0)
Duration of uveitis	Limited 91 (21.1) Persistent 340 (78.9)
Uveitis course	Acute 91 (21.1) Chronic 166 (38.5) Recurrent 174 (40.4)
Pathologic classification of uveitis	Non-granulomatous 349 (86.4) Granulomatous 55 (13.6)
Continuous variables	**Median (IQR) [min–max]**
Current age, years	16.0 (8.0) [1.0–73.0]
Follow-up duration, months	49.0 (101.0) [1.0–677.0]
Age at disease onset, years	7.9 (7.0) [1.1–17.9]
Final BCVA, Snellen decimals	1.00 (0.20) [0.00–2.00]

BCVA best-corrected visual acuity, *HLA* human leukocyte antigen, *IQR* interquartile range, *JIA* juvenile idiopathic arthritis, *max* maximum value, *min* minimum value

[a]Other diagnosis: Fuchs heterochromic iridocyclitis in 1 patient, juvenile scleroderma in 1 patient, tubulointerstitial nephritis and uveitis (TINU) syndrome in 1 patient, other connective tissue diseases in 2

Table 2 Breakdown of complications of uveitis occurring in the population

Complications	Eyes *n* (%)
No complications	319 (59.6)
At least one complication	216 (40.4)
Cataract	92 (17.2)
Posterior synechiae	80 (15.0)
Macular edema	47 (8.8)
Band keratopathy	40 (7.5)
Ocular hypertension	26 (5.0)
Glaucoma	23 (4.3)
Posterior vitreous detachment	17 (3.2)
Peripheral anterior synechiae	12 (2.3)
Epiretinal membranes	10 (1.9)
Chorioretinal scars	7 (1.3)
Retinal pigment epithelial alterations	7 (1.3)
Other complications	≤ 5 (< 1)

Complications occurring in < 1% of eyes are omitted in the table and detailed as follows: hypotony, pupillary seclusion, vitreous hemorrhage, retinal fibrosis, retinal detachment, macular atrophy, phthisis bulbi, choroidal extramacular neovascularization, retinal ischemia affecting four quadrants, trans-vitreal membrane, iris atrophy, iris bombè, neovascularization elsewhere, vitreous opacities, optic disc swelling, clumps of pigment on the anterior lens capsule, macular hole, retinoschisis, retinal telangiectasias, vitreomacular traction, chorioretinal atrophy, focal chorioretinal atrophy, and macular choroidal neovascularization

When analyzing specifically the subgroup of eyes with anterior uveitis, those with limited acute uveitis faced complications in five cases (8.9%), those with persistent recurrent uveitis in 32 (27.1%), and those with persistent chronic uveitis in 41 (54.7%) ($p<0.001$). In this subgroup, the persistent chronic course was a risk factor for complications development with an OR of 12.3 (95% CI 1.5–3.5, $p<0.001$) when compared to the limited acute course.

When analyzing the subgroup of children with JIA-associated uveitis, those who developed arthritis before uveitis had ocular complications in 31 cases (25.8%), while those who had uveitis before or at arthritis onset had complications in 31 cases (41.3%) ($p=0.020$).

Final Visual Acuity

The final BCVA in the cohort was a median of 1.00 (IQR 0.20) [0.00–2.00] Snellen decimals. The visual outcomes of eyes and patients (best eye) are represented in Fig. 3A and B, respectively.

Factors impacting the final BCVA with statistical significance are shown in Fig. 4. A multivariate regression analysis included ethnic origin, uveitis anatomical and pathological classifications, systemic disease association, and presence of cataract, glaucoma, band keratopathy, posterior synechiae, and macular edema as factors. Compared to anterior uveitis, panuveitis was associated with a reduction of 0.142 decimals in the final BCVA (95% CI −0.219 to −0.066, $p<0.001$); cataract was associated with a 0.295 lower final BCVA decimals (95% CI −0.372 to −0.217, $p<0.001$); the other variables were not statistically significant in the model ($p>0.050$).

In addition, the median final BCVA expressed as Snellen decimals was inversely correlated with topical GC treatment duration (Spearman's rho −0.23, $p=0.001$) and directly correlated with conventional disease-modifying antirheumatic drugs (DMARDs) (Spearman's rho 0.25, $p<0.001$) and biological DMARDs treatment duration (Spearman's rho 0.20, $p=0.020$).

Exploratory Analysis of the Incidence of Complications over Time

The overall incidence of ocular complications was 14.4 events/100 PY; the incidences of cataract, posterior synechiae, macular edema, band keratopathy, and glaucoma were 3.1, 2.6, 1.7, 1.2, and 0.7 events/100 PY, respectively.

When stratifying the cohort based on the diagnosis date, 64 children were diagnosed before 2011 (21.3%), 72 from 2011 to 2015 (24.0%), 90 from 2016 to 2020 (30.0%), and 74 from 2021 onwards (24.7%). Patients diagnosed before the year 2011 developed at least one complication in 39 cases (60.9%), those

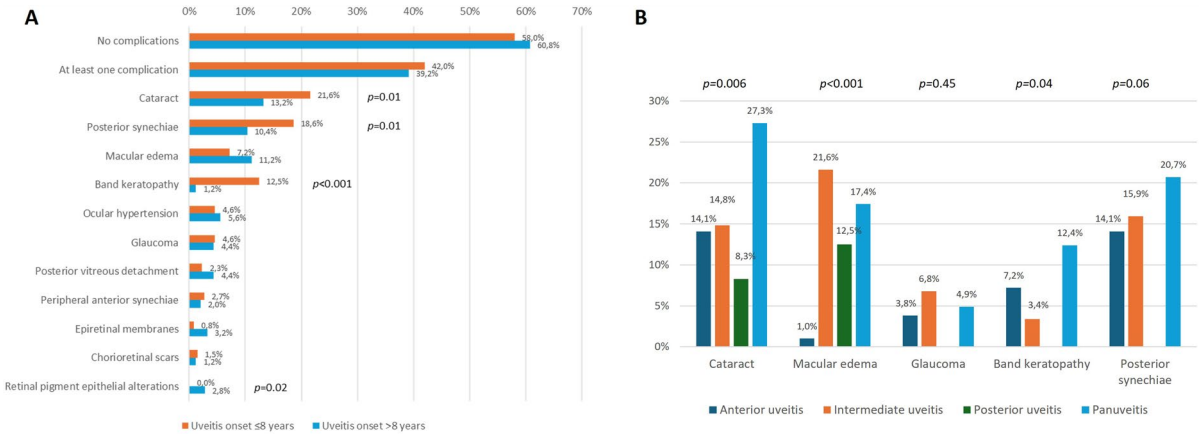

Fig. 2 Frequency of complications observed in 535 eyes stratified by age-at-onset groups (**A**) and across anatomical classes of uveitis (**B**)

diagnosed between 2011 and 2015 in 29 cases (40.3%), those diagnosed between 2016 and 2020 in 39 cases (48.3%), and those diagnosed from 2021 onwards in 27 cases (36.5%) ($p = 0.020$).

The incidence of complications was 6.6 per 100 PY for patients diagnosed before 2011, 18.3 per 100 PY in the period 2011–2015, 31.8 per 100 PY in 2016–2020, and 68.7 per 100 PY from 2021 onwards ($p < 0.001$).

DISCUSSION

This study provides a comprehensive description of ocular complications and their predictors in children with uveitis. During the first four years of follow-up, on average, approximately 40% of the population developed at least one ocular complication, with an estimated incidence rate of 14.4 events per 100 patient-years, underscoring the severe long-term burden of pediatric uveitis. Notably, the complication rate was slightly lower than that reported in previously published cohorts [11–13]. Cataract and posterior synechiae were the most common complications, followed by macular edema, band keratopathy, and ocular hypertension/glaucoma. A chronic course of uveitis was an independent risk factor for the development of complications, whereas an anterior anatomical location was found to be protective compared to other types. However, within the anterior uveitis group, a chronic disease course was associated with a 12-fold higher risk of complications compared to an acute, limited course.

Cataract was associated with panuveitis more than with other types of uveitis. Macular edema was mainly associated with intermediate uveitis and panuveitis, while band keratopathy was associated with panuveitis and anterior uveitis. In addition, panuveitis was associated with a higher risk of low final visual acuity. Our results align with those found in a cohort of 296 Greek children with uveitis followed over 10 years. They reported cystoid macular edema and disc edema as the most frequent complications in intermediate and posterior uveitis, respectively, and posterior uveitis and panuveitis caused more severe final vision loss [14]. In another extensive study based on the Korean National Health Insurance Claim Database, at least one ocular complication occurred in 42% of children with uveitis, which is consistent with the frequency in our population; moreover, they identified non-anterior uveitis as the leading risk factor for glaucoma, retinal detachment, amblyopia, and ophthalmic procedures [1]. Anterior uveitis carried the lowest risk of any complication in comparison with the other types of uveitis in a historical cohort of 148 children with both

Table 3 Results of multivariate analysis performed to identify predictors of complications of uveitis (at least one complication and specific complications)

Factors/covariates	Odds ratio (95% confidence interval [CI])	*p* value
At least one complication		
Anterior uveitis	0.10 (95% CI − 4.1 to − 1.6)	< 0.001
Chronic course of uveitis	6.13 (95% CI 1.0 to 2.6)	< 0.001
Duration of follow-up	1.01 (95% CI 0.003 to 0.009)	< 0.001
Systemic disease association	–	> 0.05
Patient's ethnic origin	–	> 0.05
Sex	–	> 0.05
Age at onset	–	> 0.05
Cataract		
White ethnicity	0.21 (95% CI − 2.3 to − 0.8)	< 0.001
Hispanic ethnicity	0.23 (95% CI − 2.5 to − 0.5)	< 0.001
Older age at uveitis onset	0.91 (95% CI − 0.2 to − 0.02)	0.02
Duration of follow-up	1.00 (95% CI 0.004 to 0.009)	< 0.001
Uveitis anatomical classes	–	> 0.05
Course of uveitis	–	> 0.05
Sex	–	> 0.05
Posterior synechiae		
Chronic course of uveitis	11.8 (95% CI 1.0 to 4.0)	0.001
Non-granulomatous uveitis	0.30 (95% CI − 2.1 to − 0.6)	< 0.001
Patient's ethnic origin	–	> 0.05
Systemic disease association	–	> 0.05
Sex	–	> 0.05
Age at uveitis onset	–	> 0.05
Duration of follow-up	–	> 0.05
Macular edema		
Intermediate uveitis	45.2 (95% CI 1.8 to 5.8)	< 0.001
Panuveitis	54.3 (95% CI 2.1 to 5.9)	< 0.001
Posterior uveitis	45.4 (95% CI 1.3 to 6.4)	0.003
Systemic disease association	–	> 0.05
Associated diseases	–	> 0.05
Sex	–	> 0.05
Age at uveitis onset	–	> 0.05
Duration of follow-up	–	> 0.05

Table 3 continued

Band keratopathy		
Older age at uveitis onset	0.8 (95% CI − 0.4 to − 0.1)	0.003
Uveitis anatomical classes	–	> 0.05
Patient's ethnic origin	–	> 0.05
Course of uveitis	–	> 0.05
Sex	–	> 0.05
Duration of follow-up	–	> 0.05
Glaucoma or ocular hypertension		
Sudden onset of uveitis	0.3 (95% CI − 2.3 to − 0.3)	0.01
Non-granulomatous uveitis	0.21 (95% CI − 2.5 to − 0.6)	0.001
Uveitis anatomical classes	–	> 0.05
Patient's ethnic origin	–	> 0.05
Sex	–	> 0.05
Age at uveitis onset	–	> 0.05
Course of uveitis	–	> 0.05
Systemic disease association	–	> 0.05
Cataract surgery	–	> 0.05
Duration of follow-up	–	> 0.05

infectious and noninfectious uveitis described by Rosenberg et al. in 2004 [15]. Intermediate uveitis, on the other hand, was found to be a significant risk factor for macular edema, similarly to what emerges from our study. Interestingly, in Rosenberg's cohort, only 12 children received biological therapy for uveitis (etanercept), suggesting that therapeutic approaches had minimal influence across anatomical classes [15].

Complications were more frequently detected in isolated uveitis than in systemic disorders. This difference might reflect the successful implementation of targeted uveitis screening protocols in high-risk pediatric populations, as children with JIA exhibited fewer complications than those diagnosed with idiopathic uveitis (comprising chronic anterior uveitis), Blau syndrome, or Vogt–Koyanagi–Harada syndrome. Additionally, systemic therapies administered to treat underlying conditions could further reduce the incidence of ocular complications. This is further supported by the higher rate of complications found in children with uveitis onset preceding arthritis in the subgroup of JIA-associated uveitis. Similar data emerged from a study by Heiligenhaus et al. comparing the frequency of complications in children with idiopathic antinuclear antibodies (ANA)-positive uveitis, uveitis preceding JIA onset and uveitis following JIA onset: they observed a remarkably lower rate of complications, glaucoma, synechiae, and cataract in the group with JIA diagnosis preceding uveitis onset [16]. On the contrary, in a retrospective case series of chronic anterior uveitis (both idiopathic and JIA-associated) published by Holland et al., no clear relationship between JIA diagnosis and vision-threatening complications or visual acuity loss was established [17].

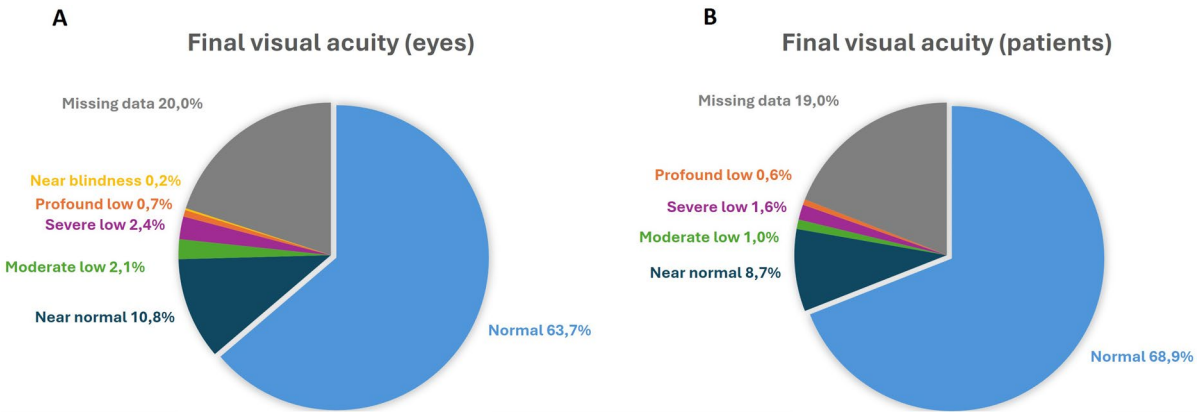

Fig. 3 Final visual acuity in the cohort. Percentages are calculated on the total number of eyes based on the final best-corrected visual acuity (BCVA) expressed as Snellen decimals in (**A**). BCVA of the best eye is displayed in (**B**) with percentages calculated on the total number of patients. The following ranges of BCVA Snellen decimals were considered when stratifying the population into visual acuity groups: normal vision (2.00–0.80), near normal vision (0.70–0.30), moderate low vision (0.25–0.125), severe low vision (0.10–0.05), profound low vision (0.04–0.02), near blindness (0.016–0.01)

In our population, cataracts, posterior synechiae, and band keratopathy were more common in children with pre-puberal onset of uveitis, while macular edema was more common in adolescents. A younger age at uveitis onset was also a predictive factor for cataract and band keratopathy. Consequently, a younger age at onset increases the risk of undergoing ocular surgery in children. According to Lai et al., a greater severity of uveitis course in younger patients may be explained by the immature blood–ocular barrier, as this structure is essential for preserving the immune-privileged environment in the eye [18]. In this regard, Al-Haddad et al. found a higher frequency of posterior synechiae and band keratopathy in children with uveitis onset before or at 8 years, while glaucoma was more prevalent in children with uveitis onset after 8 years of age [10]. Hong et al. observed that children with older age at diagnosis had a higher risk of glaucoma, macular disease, and retinal detachment [1]. Also, a German study focusing on patients with JIA-associated uveitis found that patients who developed macular edema were generally older and had experienced other ocular complications [19]. In this context, it is crucial to recognize that different forms of uveitis, which preferentially affect specific anatomical sites within the eye, may also present at different ages. For instance, conditions such as Blau syndrome, Behçet's disease, and non-anterior idiopathic uveitis typically involve non-anterior segments and tend to manifest during adolescence.

Recent studies suggest that early initiation of immunosuppressive therapies, particularly biologic agents, can reduce the rates of uveitis complications [3, 4]. Our findings are consistent with this notion, as patients who ultimately developed ocular complications had a delay before starting systemic immunosuppressive treatment twice as long as those without complications (median delay of 7 months vs. 4 months), and a remarkably longer treatment with topical GC as monotherapy (median duration of 6 months vs. 3 months). Additionally, prolonged treatment with topical GC as monotherapy had a negative impact on the final visual acuity in our cohort, although the presence of a moderate proportion of missing data (approximately 20%) in the final visual acuity analysis could limit the generalizability of this finding. The detrimental effect of prolonged topical GC therapy in children with uveitis is well known [20, 21]. Thorne et al. demonstrated a dose-dependent increase in the rate of cataract formation in eyes receiving topical GC over a 4-year follow-up, independent of uveitis activity; however, the risk was low if ≤ three

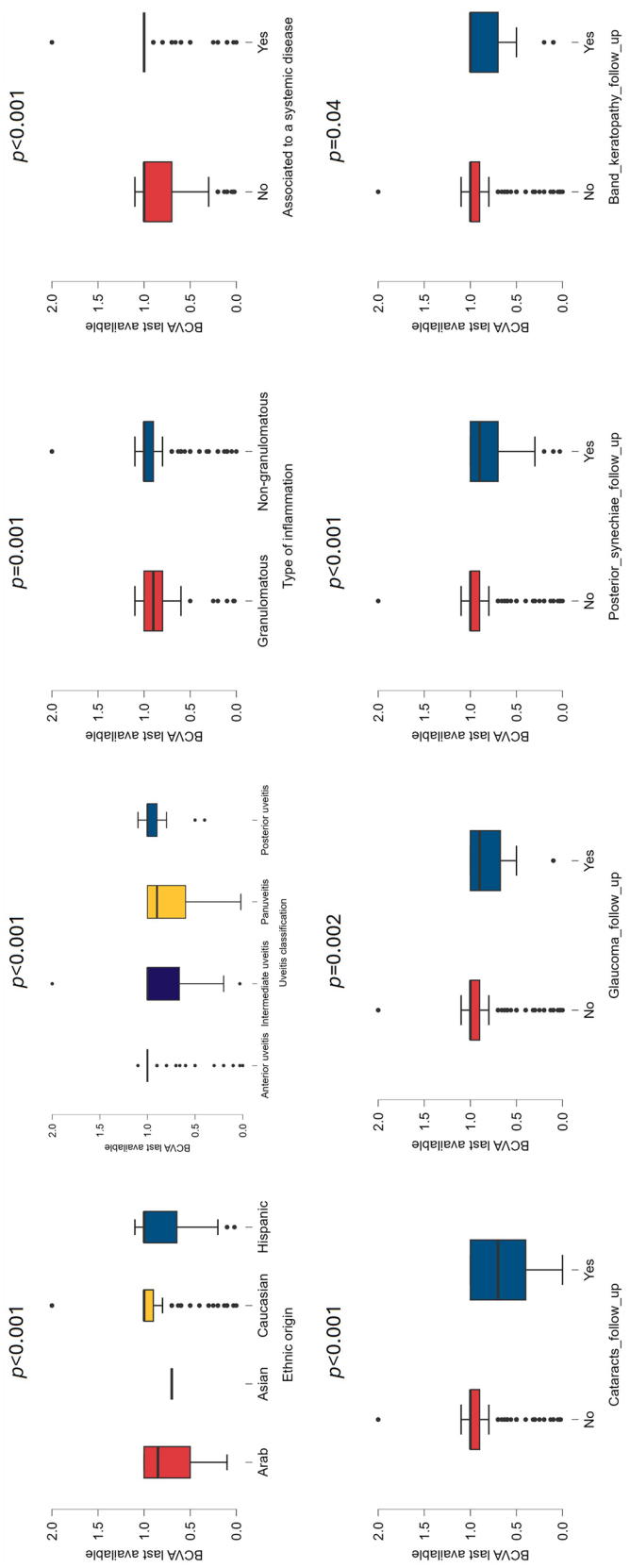

Fig. 4 Factors associated with the final best-corrected visual acuity (BCVA) expressed as Snellen decimals with statistical significance

drops/day were used, and disease activity was effectively suppressed [20]. It is important to note that, in our cohort, patients who received biologic DMARDs for their disease experienced a higher frequency of complications compared to those treated only with conventional DMARDs or no DMARDs at all. This likely reflects a selection bias, as children with more severe ocular involvement were more often prescribed advanced therapies. This also plausibly accounts for the more frequent use of dilators or cycloplegics in children with posterior synechiae, and the earlier initiation of biologic DMARDs in those who developed macular edema. Therefore, interpreting the relationship between treatment strategies and complication risk requires caution: while early, aggressive therapy may indeed capitalize on a window of opportunity to alter disease trajectory, patients deemed at higher risk for poor outcomes are also more likely to receive intensive treatment from the outset, potentially confounding direct comparisons.

Our longitudinal analysis of ocular complication incidence over recent decades revealed conflicting trends. The proportion of children experiencing at least one ocular complication appeared to have decreased over time, from 56.3% among those diagnosed before 2011 to 36.5% in the most recent cohort. However, the difference in follow-up duration between groups and further external confounders must be considered. Indeed, when incidence was standardized to 100 patient-years, the opposite trend emerged, with the highest complication incidence observed in patients diagnosed after 2020. These findings should be interpreted with due caution and not mistakenly construed as evidence of a decline in quality of care over time. Rather, the increased incidence observed in the cohort diagnosed after 2020 – coinciding with the launch of the AIDA Network Registry – is more plausibly attributable to a reduction in recall bias that may have affected the reporting of complications in earlier diagnostic periods. Additionally, the rising incidence rates of ocular complications may reflect changes in diagnostic practices, as the detection of conditions such as macular edema has significantly improved in recent years with the widespread adoption of optical coherence tomography. In this regard, Lundgren et al. found a tendency towards a reduction in the frequency of complications over time, by comparing two cohorts of patients with JIA-associated uveitis treated respectively in 2002–2011 and 2012–2021 [22]. Similarly, Tappeiner et al. observed a significant decrease in the yearly prevalence of uveitis complications from 2002 to 2013 among patients with JIA-associated uveitis in Germany [23]. However, the incidences of complications accounting for the actual duration of the ocular disease follow-up were not calculated in these studies, thus limiting the possibility of comparison with our results. In Rosenberg's historical cohort, published in 2004, the incidence rates were 16 per 100 patient-years for cataract, 17 per 100 patient-years for posterior synechiae, ten per 100 patient-years for band keratopathy, seven per 100 patient-years for glaucoma or ocular hypertension, and eight per 100 patient-years for macular edema [15]. These estimates are considerably higher than those calculated from the AIDA Network registry in the same period, confirming that the retrospective nature of our data collection may have contributed to an exaggerated disparity between recently diagnosed and historical patients in our study.

This study has limitations inherent to its retrospective, registry-based design, including potential recall bias, incomplete data, and inter-center variability. These were mitigated through the use of standardized registry definitions and diagnostic criteria, as well as expert ophthalmologist review. Differences in follow-up duration may have influenced complication rates; this was addressed by calculating incidence per 100 patient-years and incorporating follow-up duration into multivariate analyses. Nevertheless, non-uniform clinical and imaging schedules could have affected the detection of certain complications across centers. Furthermore, the observational design precludes causal inference, particularly when evaluating treatment strategies. Finally, missing data, especially for final visual acuity, may limit the generalizability of the findings.

CONCLUSIONS

In conclusion, our analysis highlights that children with isolated uveitis, early-onset disease, chronic course, and non-anterior anatomical subtypes—particularly panuveitis—are at the highest risk for developing ocular complications. These patients should therefore receive more frequent and structured screening, along with timely, effective, and steroid-sparing treatment strategies. Uveitis onset before puberty significantly increases the risk of complications such as cataract and band keratopathy, while adolescents are more prone to developing macular edema. Early initiation of systemic immunosuppressive therapy appears crucial in minimizing long-term sequelae. In contrast, prolonged reliance on topical glucocorticoids as monotherapy is associated with a higher incidence of complications and poorer visual outcomes. Although the methodological limitations of retrospective studies must be acknowledged, longitudinal trends suggest that the care of patients with pediatric uveitis has improved over recent decades, particularly in terms of increased awareness, earlier detection, and more targeted treatment of complications, contributing to a reduced proportion of children experiencing vision-threatening outcomes. Nonetheless, the continued implementation of risk-based screening protocols, prompt therapeutic escalation, and strong multidisciplinary coordination will likely further optimize care and reduce the burden of uveitis-related complications in young patients.

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Declarations

Conflict of Interest. Claudia Fabiani is an Editorial Board member of Ophthalmology and Therapy. Claudia Fabiani was not involved in

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Ethical Approval. This study protocol (NCT05200715) adheres to the principles outlined in the Declaration of Helsinki. Permission was obtained to access and use data from the database/registry utilized in this study. To be eligible for the AIDA Network registries, parents or legal guardians of pediatric patients must provide written consent, after receiving appropriate information. Patients' personal information was separated by their clinical data by using pseudonyms. The protocol of the AIDA Network registries was approved by the Ethics Committee of Siena University Hospital (Ref. 14951), and by the Ethics Committees of the participating investigator centers (Table S1).

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