Asia-Pacific Journal of Ophthalmology 14 (2025) 100199

Contents lists available at ScienceDirect

Asia-Pacific Journal of Ophthalmology

journal homepage: www.sciencedirect.com/journal/asia-pacific-journal-of-ophthalmology

# Programme for ocular inflammation & infection translational research (PROTON) registry: Cross-sectional analysis of baseline patient characteristics

William Rojas-Carabali [a,b,c,d], Kevin Chan [b], Carlos Cifuentes-Gonzalez [a,c,d], Manisha Agarwal [e], Alok Sen [f], Jyotirmay Biswas [g], Ranju Kharel (Sitaula) [h], Rina La Distia Nora [i], Anna Utami [j], Anadi Khatri [k], Padmamalini Mahendradas [l], Ariel Schlaen [m], Chitaranjan Mishra [n], Yan Guex-Crosier [o], Edmund Tsui [p], Apoorva Ayachit [q], Sapna Gangaputra [r], John H. Kempen [s,t,u,v,w], Vishali Gupta [x], Alejandra de-la-Torre [d], Bernett Lee [b,y,z,aa,ab], Rupesh Agrawal [a,b,c,ac,ad,ae,*], On behalf of OASIS 1 and OASIS 2 study groups

[a] *Tan Tock Seng Hospital, National Healthcare Group, Singapore*
[b] *Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*
[c] *Programme for Ocular Inflammation & Infection Translational Research, National Healthcare Group, Singapore*
[d] *Neuroscience Research Group (NEUROS), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia*
[e] *Dr Shroff's Charity Eye Hospital, India*
[f] *SNC Eye Hospital, Ranchi, India*
[g] *Sankara Nethralaya, Chennai, India*
[h] *Department of Ophthalmology, B. P. Koirala Lions Centre for Ophthalmic Studies, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal*
[i] *Cipto Mangunkusumo Kirana Eye Hospital, Jakarta, Indonesia*
[j] *Jakarta Eye Centre, Jakarta, Indonesia*
[k] *Birat Eye Hospital, Biratnagar, Nepal*
[l] *Narayana Netralaya, Bangalore, India*
[m] *Hospital de Clinicas Jose de San Martín Universidad de Buenos Aires/Hospital Universitario Austral, Buenos Aires, Argentina*
[n] *Trilochan Netralaya, Odisha, India*
[o] *Jules-Gonin Eye Hospital, University of Lausanne, Lausanne, Switzerland*
[p] *UCLA Stein Eye Institute, Los Angeles, California, USA*
[q] *M M Joshi Eye Institute, Karnataka, India*
[r] *Vanderbilt Medical Center, Vanderbilt University, USA*
[s] *Department of Ophthalmology and Schepens Eye Research Institute, Massachusetts Eye and Ear/ Harvard Medical School, Boston, USA*
[t] *Sight for Souls, Bellevue, Washington, USA*
[u] *Department of Ophthalmology, Addis Ababa University, Addis Ababa, Ethiopia*
[v] *MyungSung Christian Medical Center (MCM) Eye Unit, MCM Comprehensive Specialized Hospital, Addis Ababa, Ethiopia*
[w] *MyungSung Medical School, Addis Ababa, Ethiopia*
[x] *Advanced Eye Centre, Post Graduate Institute of Medical Education & Research, Chandigarh, India*
[y] *Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Singapore*
[z] *Centre for Biomedical Informatics, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*
[aa] *Infectious Disease Labs (ID Labs), Agency for Science, Technology and Research (A*STAR), Singapore*
[ab] *Khoo Teck Puat Hospital, National Healthcare Group, Singapore, Singapore*
[ac] *Moorfields Eye Hospital, NHS Foundation Trust, London, United Kingdom*
[ad] *Singapore Eye Research Institute, The Academia, Singapore, Singapore*
[ae] *Duke NUS, Singapore*

* Correspondence to: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 308433, Singapore.
*E-mail address:* Rupesh_agrawal@ttsh.com.sg (R. Agrawal).

https://doi.org/10.1016/j.apjo.2025.100199
Received 7 January 2025; Received in revised form 20 April 2025; Accepted 21 April 2025
Available online 25 April 2025

ARTICLE INFO

*Keywords:*
Uveitis
Visual Impairment
Clinical Registry
Aetiology
Multicentric

ABSTRACT

*Purpose:* The Programme for Ocular Inflammation & Infection Translational Research (PROTON) registry collects real-world data on infectious and non-infectious ocular inflammatory diseases (OID) to enhance understanding of disease progression and treatment outcomes. This report presents the baseline characteristics of patients enrolled in two international multicentric studies, OASIS 1 and OASIS 2, over the first two years.
*Design:* A cross-sectional observational study.
*Methods:* PROTON is an observational ambispective cohort registry comprising OASIS 1, a retrospective study (2000–2021), and OASIS 2, a prospective study (2021 onwards). Data is collected at multiple intervals over a 10-year period, focusing on various OID. Participants include patients diagnosed with anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, scleritis, retinal vasculitis, and neuroretinitis. Baseline characteristics, ocular examinations, and treatment outcomes are recorded.
*Results:* A total of 2640 patients (3642 eyes) have been recruited across 17 centers worldwide. Infectious was the most common etiology (31.6 %), followed by idiopathic (28.1 %), undetermined (21.7 %), and non-infectious (16.0 %). Most patients (54.8 %) were male, with anterior uveitis being the most common anatomical location (37.5 %). Visual impairment was present in 53.2 % of cases, with 18.8 % experiencing moderate (0.5–1.0 LogMAR) and 22.6 % severe impairment (>1.0 LogMAR). Tuberculosis (64.0 %) and toxoplasmosis (13.5 %) were the leading infectious causes, while HLA-B27-associated uveitis accounted for 19.4 % of non-infectious cases.
*Conclusions:* The PROTON registry provides valuable insights into the global spectrum of OID, with a substantial representation of infectious causes. This real-world evidence highlights the key prevalence of visual impairment and underscores the importance of research on this topic. As the registry evolves, it will help refine clinical management strategies and improve patient outcomes globally.

## 1. Introduction

Ocular inflammatory diseases (OID) encompass a complex spectrum of disorders affecting all eye tissues, posing significant challenges to diagnostic precision and therapeutic strategies. These conditions, including uveitis, scleritis, and optic neuritis, among others,[1] can stem from various infectious and non-infectious aetiologies, with a prevalence estimated at around 38 – 714 per 100,000 individuals globally.[2,3] The burden of OID is substantial, with many patients at risk for irreversible visual impairment or blindness, particularly among the working-age population. Globally, OID is a leading cause of preventable blindness, contributing significantly to the rates of vision loss, impacting quality of life and work productivity.[2]

The study of OID is of paramount importance due to the potential for these diseases to cause permanent visual impairment. Understanding the risk factors and disease trajectories is crucial for developing effective management strategies.[2,4] A myriad of treatment options, ranging from corticosteroids to biologic agents, are available, yet selecting the appropriate therapy can be complicated by the wide variety of underlying causes and patient-specific factors.[2,5] Identifying risk factors and treatment responses in different populations is vital for understanding and improving therapeutic outcomes and minimizing the long-term impact of the disease.

This report aims to describe the baseline characteristics of patients recruited under two multicentric, international studies, Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) 1 and OASIS 2, designed to collect real-world evidence on infectious and non-infectious OID. These studies are part of the umbrella Programme for Ocular Inflammation & Infection Translational Research (PROTON). Here, we outline the baseline characteristics and follow-up profiles of the participants over the first two years following the launch of the registry and explore the implications and future directions resulting from these findings.

## 2. Methods

### 2.1. Study design

This cross-sectional report is part of an ambispective cohort, combining data from both OASIS 1 and OASIS 2 studies under PROTON. OASIS 1 is a multicentre, international retrospective study that spans from January 1, 2000, to May 31, 2021. OASIS 2 is a complementary prospective study that started in 2021 onwards. Both studies focus on mapping patterns and treatment outcomes across a spectrum of ocular inflammatory conditions and collect data for up to 10 years following recruitment, with fixed follow-ups at multiple intervals (baseline, 1 week, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 5 years, and 10 years). This approach allows the current analysis to leverage both historical and ongoing real-time data to provide a comprehensive overview of treatment outcomes over time.

This report adheres to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement to ensure clarity and completeness in documenting observational studies.

### 2.2. Setting and participants

The study included data collected from 17 international centers participating in both phases of the OASIS study. All records up to August 25, 2024, from centers that had entered more than ten patients. Eligibility criteria encompassed a diagnosis made by a uveitis specialist of any of the following conditions: Anterior Uveitis, Keratouveitis, Intermediate Uveitis, combined Anterior and Intermediate Uveitis, Posterior Uveitis, Panuveitis, Episcleritis, Anterior and Posterior Scleritis, Retinal Vasculitis, Optic Neuritis, and Neuroretinitis.[1] OASIS 1, OASIS 2, and PROTON initially received approval from the IRB of the National Healthcare Group (Ethics ID: OASIS 1–2020/00301, OASIS 2–2021/00655, PROTON - 2020/00944). For OASIS 1, the requirement for informed consent was waived due to the study's retrospective nature. In contrast, participants in OASIS 2 and PROTON provided signed written informed consents. Additionally, each collaborative center secured approval from its respective local IRB or ethics committee, ensuring that all studies were conducted in accordance with the principles of the Declaration of Helsinki.

### 2.3. Inclusion and exclusion criteria

Participants eligible for inclusion in the study were those who had been diagnosed with one or more of the following ocular inflammatory conditions: anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, keratouveitis, retinal vasculitis, scleritis, or episcleritis, with clinical records available from participating centers. All age groups, including children, were eligible if their medical data could be de-identified and used without risk of re-identification. Patients were

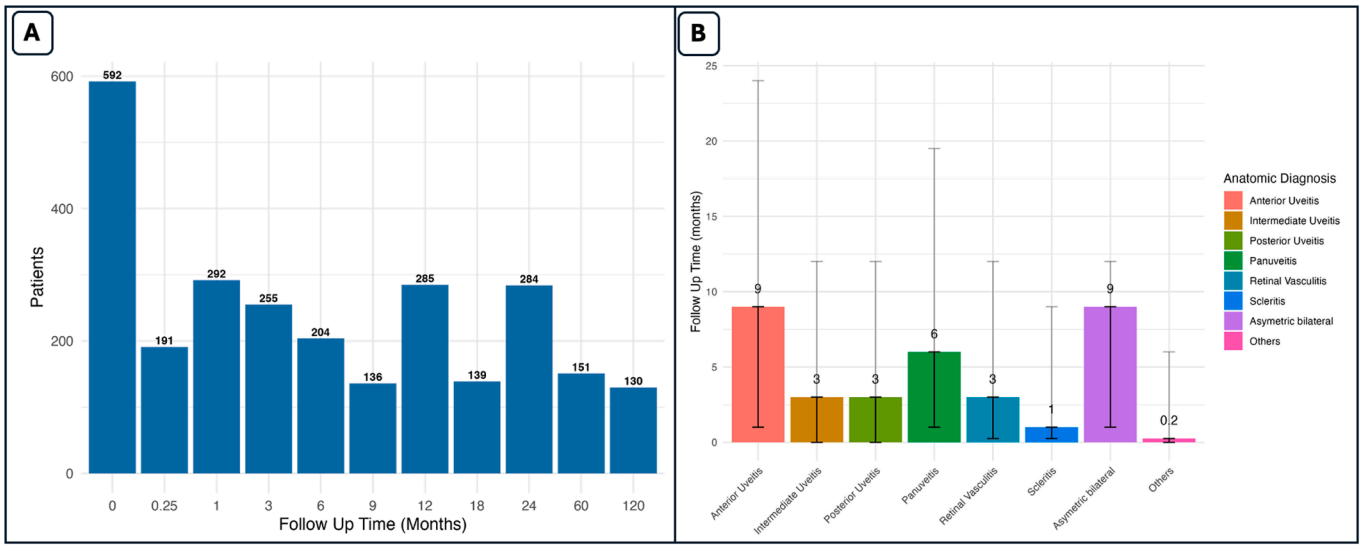


**Fig. 1.** Follow-Up duration in uveitis patients based on time and anatomic diagnosis. A. shows a bar chart displaying the number of patients at various follow-up intervals (in months) over a 10-year span. The bars are labelled with the number of patients at each time point, starting from 0 months (baseline) to 120 months (10 years). The most frequent follow-up occurs at baseline (0 months) with 592 patients, gradually decreasing over time. B. shows the median follow-up time (in months) across different anatomic diagnoses of uveitis. The diagnoses include Anterior Uveitis, Intermediate Uveitis, Posterior Uveitis, Panuveitis, Retinal Vasculitis, Scleritis, Asymmetric Bilateral, and Others. The error bars represent variability around the median follow-up time for each diagnosis.

excluded if they lacked a formal diagnosis of the specified conditions, had incomplete or inaccessible records, or if their data couldn't be anonymized. Additional exclusions included records involving prisoners, individuals whose identities were publicly traceable, or those who were enrolled in interventional clinical trials during the same treatment period that could confound retrospective analysis. Participating centers were encouraged to upload data at their own pace, with chronological entry preferred to ensure consistency and aid in the development of a standardized, time-sequenced analysis.

### 2.4. Data sources and measurement

Data were extracted from a standardized repository detailed elsewhere,[6] incorporating both retrospective data from OASIS 1 and ongoing prospective data from OASIS 2. Variables included demographics, medical and surgical history, tuberculosis-specific data, course of treatment, and comprehensive data from initial and follow-up visits. Clinical presentations, ocular examinations, systemic symptoms, laboratory and ancillary investigations, working diagnoses, and treatment outcomes (both medical and surgical) were comprehensively recorded. Standardization of Uveitis Nomenclature for Reporting Clinical Data was adopted for anterior chamber (AC) cells and flare grading,[7] while the National Eye Institute (NEI) system was used for grading vitreous haze.[8] Idiopathic refers to cases in which no underlying disease is identified despite diagnostic investigations. Visual impairment was classified as Mild (0.3–0.5 LogMAR), Moderate (0.5–1.0 LogMAR) and Severe (>1.0 LogMAR). Cases without an identified cause due to insufficient follow-up or incomplete diagnostic work-up should be labelled as undetermined. All centers, except for Centers 001 and 004, uploaded data to a centralized repository. Centers 001 and 004 managed their data locally, and this data was analysed separately and later merged with the rest for analysis by the Department for Biomedical Informatics at Lee Kong Chian School of Medicine, Singapore.

### 2.5. Bias

Efforts to minimize bias included the supervision of data collection by trained uveitis specialists at each participating center. A standardized protocol for data entry was employed, accompanied by regular training sessions and a comprehensive data entry handbook. Data cleaning was managed by a medical doctor with over five years of experience who specialized in data science and research in uveitis.

### 2.6. Statistical

Data was categorized into infectious and non-infectious groups and stratified by uveitis classification at the time of enrolment. Descriptive statistics were calculated for baseline characteristics at both the patient and eye levels, including means (SD) for continuous variables and frequency distributions with percentages for categorical variables. Mean visual acuity, expressed in LogMAR units with standard deviations, was calculated and plotted for each time point. Analyses were conducted using the R System for Statistical Computing, V.4.1.1.

## 3. Results

This report includes data from 3642 eyes of 2640 patients. The study involved at least one center from each continent, excluding Oceania. The distribution of participating countries includes seven centers from India, two each from Nepal and Indonesia, and one each from Colombia, Singapore, Switzerland, the United States, Argentina, and Ethiopia.

Males comprised 54.8 % of the patient population. The most frequently observed characteristics at the patient level included anterior uveitis (37.5 %), unilateral presentation (59.4 %), and patients aged between 17 and 40 years (45.2 %). The average follow-up period was 15.39 months, with a SD of 27.79 months (Fig. 1A). Further details are provided in Table 1.

At an eye level, 46.8 % of the cases had no VI, mild VI (0.3–0.5 LogMAR) was noted in 11.9 % of cases, while moderate (0.5–1.0 LogMAR) and severe VI (>1.0 LogMAR) were observed in 18.8 % and 22.6 % of cases, respectively. The severest forms of visual impairment were particularly prevalent in patients with panuveitis and posterior uveitis (Table 2). Regarding AC cells, 54.7 % of the cases exhibited no AC cells (<1 cell), indicating minimal inflammatory activity at baseline, while 12.3 % showed mild inflammation (0.5 +). Moderate (1 +) to severe (4 +) AC cell presence ranged from 13.8 % to 3.1 %, signifying varying degrees of intraocular inflammation. Vitreous haze evaluation showed that 69.9 % of the patients had no haze. In contrast, 17.8 % of

**Table 1**
Clinical characteristics at baseline.

| | | Anterior Uveitis† | | Asymmetric bilateral | | Intermediate Uveitis | | Others** | | Panuveitis | | Posterior Uveitis* | | Retinal Vasculitis | | Scleritis | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| | | 991 | 37.5 | 16 | 0.6 | 245 | 9.3 | 114 | 4.3 | 335 | 12.7 | 359 | 13.6 | 528 | 20 | 52 | 2.0 | 2640 | 100 |
| Age at presentation | | Mean=46.53, SD=17.30, [2.00 to 89.00] | | Mean=38.44, SD=19.13, [5.00 to 73.00] | | Mean=36.80, SD=15.63, [1.00 to 85.00] | | Mean=41.12, SD=17.18, [1.00 to 82.00] | | Mean=40.07, SD=17.39, [2.00 to 85.00] | | Mean=37.66, SD=16.99, [1.00 to 83.00] | | Mean=35.12, SD=13.96, [5.00 to 86.00] | | Mean=40.79, SD=16.17, [18.00 to 82.00] | | Mean=40.92, SD=17.11, [1.00 to 89.00] | |
| Age group | 0-16 | 42 | 4.2 | 2 | 12.5 | 29 | 11.8 | 6 | 5.3 | 29 | 8.7 | 32 | 8.9 | 30 | 5.7 | | 0 | 170 | 6.4 |
| | 17-40 | 319 | 32.2 | 9 | 56.3 | 119 | 48.6 | 53 | 46.5 | 151 | 45.1 | 172 | 47.9 | 341 | 64.6 | 29 | 55.8 | 1193 | 45.2 |
| | 41-60 | 415 | 41.9 | 3 | 18.8 | 75 | 30.6 | 37 | 32.5 | 106 | 31.6 | 119 | 33.1 | 130 | 24.6 | 15 | 28.8 | 900 | 34.1 |
| | >60 | 215 | 21.7 | 2 | 12.5 | 22 | 9.0 | 18 | 15.8 | 49 | 14.6 | 36 | 10.0 | 27 | 5.1 | 8 | 15.4 | 377 | 14.3 |
| Gender | Female | 505 | 51.0 | 8 | 50.0 | 138 | 56.3 | 53 | 46.5 | 185 | 55.2 | 154 | 42.9 | 116 | 22.0 | 34 | 65.4 | 1193 | 45.2 |
| | Male | 486 | 49.0 | 8 | 50.0 | 107 | 43.7 | 61 | 53.5 | 150 | 44.8 | 205 | 57.1 | 412 | 78.0 | 18 | 34.6 | 1447 | 54.8 |
| Eye compromised | OD | 350 | 35.3 | 2 | 12.5 | 67 | 27.3 | 47 | 41.2 | 75 | 22.4 | 95 | 26.5 | 151 | 28.6 | 22 | 42.3 | 809 | 30.6 |
| | OS | 352 | 35.5 | 3 | 18.8 | 59 | 24.1 | 36 | 31.6 | 65 | 19.4 | 89 | 24.8 | 139 | 26.3 | 15 | 28.8 | 758 | 28.7 |
| | OU | 289 | 29.2 | 11 | 68.8 | 119 | 48.6 | 31 | 27.2 | 195 | 58.2 | 175 | 48.7 | 238 | 45.1 | 15 | 28.8 | 1073 | 40.6 |
| Follow up time (months) | | Mean=18.67, SD=29.65, 0.00 to 120.00 | | Mean=10.89, SD=14.64, 0.00 to 60.00 | | Mean=12.35, SD=28.18, 0.00 to 120.00 | | Mean=5.38, SD=11.30, 0.00 to 60.00 | | Mean=19.98, SD=33.19, 0.00 to 120.00 | | Mean=11.91, SD=24.46, 0.00 to 120.00 | | Mean=13.17, SD=24.52, 0.00 to 120.00 | | Mean=7.45, SD=17.45, 0.00 to 120.00 | | Mean=15.39, SD=27.79, 0.00 to 120.00 | |
| Aetiology | Drug induced | 3 | 0.3 | 0 | 0.0 | 1 | 0.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.2 | 0 | 0.0 | 5 | 0.2 |
| | Idiopathic | 302 | 30.5 | 4 | 25.0 | 87 | 35.5 | 26 | 22.8 | 81 | 24.2 | 54 | 15.0 | 178 | 33.7 | 11 | 21.2 | 743 | 28.1 |
| | Infectious | 159 | 16.0 | 4 | 25.0 | 79 | 32.2 | 46 | 40.4 | 127 | 37.9 | 209 | 58.2 | 188 | 35.6 | 23 | 44.2 | 835 | 31.6 |
| | Masquerade | 2 | 0.2 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 3 | 0.1 |
| | Non-Infectious | 239 | 24.1 | 1 | 6.3 | 19 | 7.8 | 6 | 5.3 | 64 | 19.1 | 44 | 12.3 | 45 | 8.5 | 5 | 9.6 | 423 | 16.0 |
| | Other | 20 | 2.0 | 0 | 0.0 | 6 | 2.4 | 4 | 3.5 | 9 | 2.7 | 11 | 3.1 | 7 | 1.3 | 2 | 3.8 | 59 | 2.2 |
| | Undetermined | 266 | 26.8 | 7 | 43.8 | 53 | 21.6 | 32 | 28.1 | 54 | 16.1 | 40 | 11.1 | 109 | 20.6 | 11 | 21.2 | 572 | 21.7 |

†includes cases of keratouveitis, anterior+intermediate uveitis,
*includes cases of optic neuritis and neuroretinitis.
**includes cases of episcleritis, and unknown.

**Table 2**
Ocular characteristics at baseline (analysis per eye).

| | | Anterior Uveitis† | | Asymmetric bilateral | | Intermediate Uveitis | | Panuveitis | | Posterior Uveitis* | | Retinal Vasculitis | | Scleritis | | Others ** | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Visual Acuity | Total | 1248 | | 27 | | 358 | | 518 | | 517 | | 765 | | 67 | | 142 | | 3642 | |
| | No VI (<0.3 LogMAR) | 755 | 60.5 | 16 | 59.3 | 161 | 45.0 | 137 | 26.4 | 215 | 41.6 | 300 | 39.2 | 52 | 77.6 | 67 | 47.2 | 1703 | 46.8 |
| | Mild VI (0.3–0.5 LogMAR) | 162 | 13.0 | 2 | 7.4 | 59 | 16.5 | 66 | 12.7 | 61 | 11.8 | 70 | 9.2 | 7 | 10.4 | 6 | 4.2 | 433 | 11.9 |
| | Moderate VI (0.5–1.0 LogMAR) | 174 | 13.9 | 3 | 11.1 | 89 | 24.9 | 128 | 24.7 | 104 | 20.1 | 173 | 22.6 | 5 | 7.5 | 8 | 5.6 | 684 | 18.8 |
| | Severe VI (>1.0 LogMAR) | 157 | 12.6 | 6 | 22.2 | 49 | 13.7 | 187 | 36.1 | 137 | 26.5 | 222 | 29.0 | 3 | 4.5 | 61 | 43.0 | 822 | 22.6 |
| AC Cells | Total | 1259 | | 26 | | 357 | | 518 | | 513 | | 758 | | 66 | | 141 | | 3638 Missing values (n = 4) | |
| | 0 (<1) | 379 | 30 | 11 | 42.3 | 204 | 57.1 | 186 | 35.9 | 413 | 80.5 | 638 | 84.2 | 55 | 83.3 | 104 | 73.8 | 1990 | 54.7 |
| | 0.5 + (1–5) | 252 | 20 | 6 | 23.1 | 41 | 11.5 | 71 | 13.7 | 37 | 7.2 | 30 | 4.0 | 4 | 6.1 | 5 | 3.5 | 446 | 12.3 |
| | 1 + (6–15) | 240 | 19 | 6 | 23.1 | 53 | 14.8 | 113 | 21.8 | 35 | 6.8 | 54 | 7.1 | 1 | 1.5 | 1 | 0.7 | 503 | 13.8 |
| | 2 + (16–25) | 201 | 16 | 0 | 0.0 | 42 | 11.8 | 76 | 14.7 | 15 | 2.9 | 24 | 3.2 | 5 | 7.6 | 10 | 7.1 | 373 | 10.3 |
| | 3 + (26–50) | 124 | 9.8 | 3 | 11.5 | 12 | 3.4 | 43 | 8.3 | 11 | 2.1 | 10 | 1.3 | 1 | 1.5 | 11 | 7.8 | 215 | 5.9 |
| | 4 + (>50) | 63 | 5 | 0 | 0.0 | 5 | 1.4 | 29 | 5.6 | 2 | 0.4 | 2 | 0.3 | 0 | 0.0 | 10 | 7.1 | 111 | 3.1 |
| Ac Flare | Total | 1220 | | 27 | | 349 | | 498 | | 503 | | 747 | | 66 | | 135 | | 3545 Missing values (n = 97) | |
| | None | 889 | 73 | 23 | 85.2 | 281 | 80.5 | 351 | 70.5 | 451 | 89.7 | 701 | 93.8 | 64 | 97.0 | 106 | 78.5 | 2866 | 80.8 |
| | 1 + (faint) | 212 | 17 | 3 | 11.1 | 49 | 14.0 | 88 | 17.7 | 32 | 6.4 | 34 | 4.6 | 1 | 1.5 | 4 | 3.0 | 423 | 11.9 |
| | 2 + (moderate, iris and lens details clear) | 87 | 7.1 | 0 | 0.0 | 13 | 3.7 | 37 | 7.4 | 14 | 2.8 | 10 | 1.3 | 1 | 1.5 | 10 | 7.4 | 172 | 4.9 |
| | 3 + (marked, iris and lens details hazy) | 21 | 1.7 | 0 | 0.0 | 3 | 0.9 | 14 | 2.8 | 6 | 1.2 | 1 | 0.1 | 0 | 0.0 | 8 | 5.9 | 53 | 1.5 |
| | 4 + (Intense, fibrin or plastic aqueous) | 11 | 0.9 | 1 | 3.7 | 3 | 0.9 | 8 | 1.6 | | 0.0 | 1 | 0.1 | 0 | 0.0 | 7 | 5.2 | 31 | 0.9 |
| Deep vitreous cells | Total | 1253 | | 27 | | 360 | | 507 | | 515 | | 751 | | 66 | | 137 | | 3616 Missing values (n = 26) | |
| | No | 1138 | 91 | 22 | 81.5 | 217 | 60.3 | 320 | 63.1 | 396 | 76.9 | 592 | 78.8 | 65 | 98.5 | 117 | 85.4 | 2867 | 79.3 |
| | Yes | 115 | 9.2 | 5 | 18.5 | 143 | 39.7 | 187 | 36.9 | 119 | 23.1 | 159 | 21.2 | 1 | 1.5 | 20 | 14.6 | 749 | 20.7 |

(*continued on next page*)

**Table 2** (*continued*)

| | | Anterior Uveitis† | | Asymmetric bilateral | | Intermediate Uveitis | | Panuveitis | | Posterior Uveitis* | | Retinal Vasculitis | | Scleritis | | Others ** | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Retrolental cells | Total | 1257 | | 27 | | 360 | | 506 | | 517 | | 757 | | 66 | | 141 | | 3631 Missing values (n = 11) | |
| | No | 1147 | 91 | 23 | 85.2 | 250 | 69.4 | 420 | 83.0 | 464 | 89.7 | 631 | 83.4 | 66 | 100.0 | 129 | 91.5 | 3130 | 86.2 |
| | Yes | 110 | 8.8 | 4 | 14.8 | 110 | 30.6 | 86 | 17.0 | 53 | 10.3 | 126 | 16.6 | 0 | 0.0 | 12 | 8.5 | 501 | 13.8 |
| Vitreous Haze | Total | 1239 | | 26 | | 345 | | 496 | | 502 | | 752 | | 62 | | 140 | | 3562 Missing values (n = 80) | |
| | 0 (Nil) | 1044 | 84 | 22 | 84.6 | 149 | 43.2 | 259 | 52.2 | 337 | 67.1 | 518 | 68.9 | 59 | 95.2 | 101 | 72.1 | 2489 | 69.9 |
| | 1 (Post pole clearly visible) | 109 | 8.8 | 0 | 0.0 | 78 | 22.6 | 71 | 14.3 | 79 | 15.7 | 98 | 13.0 | 1 | 1.6 | 5 | 3.6 | 441 | 12.4 |
| | 2 (Post pole details slightly hazy) | 33 | 2.7 | 4 | 15.4 | 91 | 26.4 | 84 | 16.9 | 58 | 11.6 | 85 | 11.3 | 2 | 3.2 | 2 | 1.4 | 359 | 10.1 |
| | 3 (Post pole details very hazy) | 15 | 1.2 | 0 | 0.0 | 19 | 5.5 | 45 | 9.1 | 16 | 3.2 | 24 | 3.2 | 0 | 0.0 | 5 | 3.6 | 124 | 3.5 |
| | 4 (Post pole details barely visible) | 16 | 1.3 | 0 | 0.0 | 7 | 2.0 | 17 | 3.4 | 5 | 1.0 | 9 | 1.2 | 0 | 0.0 | 2 | 1.4 | 56 | 1.6 |
| | 5 (Fundus details not visible) | 22 | 1.8 | 0 | 0.0 | 1 | 0.3 | 20 | 4.0 | 7 | 1.4 | 18 | 2.4 | 0 | 0.0 | 25 | 17.9 | 93 | 2.6 |
| Previous episodes of ocular inflammation | Total | 1238 | | 27 | | 345 | | 431 | | 465 | | 743 | | 65 | | 132 | | 3446 Missing values (n = 196) | |
| | No | 849 | 69 | 11 | 40.7 | 241 | 69.9 | 249 | 57.8 | 347 | 74.6 | 601 | 80.9 | 53 | 81.5 | 122 | 92.4 | 2473 | 71.8 |
| | Yes | 389 | 31 | 16 | 59.3 | 104 | 30.1 | 182 | 42.2 | 118 | 25.4 | 142 | 19.1 | 12 | 18.5 | 10 | 7.6 | 973 | 28.2 |

†includes cases of keratouveitis, anterior+intermediate uveitis.
Both eyes were included in bilateral cases.
* includes cases of optic neuritis and neuroretinitis.
** includes cases of episcleritis, and unknown.

**Table 3**
Infectious aetiologies by anatomical localisation.

| | Anterior Uveitis | Asymmetric bilateral | Intermediate Uveitis | Panuveitis | Posterior Uveitis | Retinal Vasculitis | Scleritis | Others | Total n | % |
|---|---|---|---|---|---|---|---|---|---|---|
| Tuberculosis | 75 | 2 | 75 | 87 | 94 | 169 | 22 | 10 | 534 | 64.0 |
| Toxoplasmosis | 2 | - | 1 | 20 | 84 | 5 | - | 1 | 113 | 13.5 |
| Endogenous Endophthalmitis | 1 | - | 1 | 4 | - | - | - | 32 | 38 | 4.6 |
| CMV | 21 | - | - | 2 | 12 | 1 | - | 1 | 37 | 4.4 |
| HSV | 27 | - | - | 1 | 1 | - | - | - | 29 | 3.5 |
| VZV | 15 | - | - | 3 | - | 3 | 1 | 1 | 23 | 2.7 |
| Syphilis | 3 | - | - | 5 | 3 | 3 | - | - | 14 | 1.7 |
| Other | 1 | 1 | 1 | - | 4 | 3 | - | 1 | 11 | 1.2 |
| Viral Unspecific | 7 | - | - | - | 1 | - | - | - | 8 | 1.0 |
| Co-infection | - | 1 | - | 2 | 1 | - | - | - | 4 | 0.5 |
| Endophthalmitis (Fungal) | 1 | - | - | 2 | - | - | - | - | 3 | 0.4 |
| HIV-related | - | - | - | - | 1 | 2 | - | - | 3 | 0.4 |
| Epstein Barr virus | 1 | - | - | 1 | - | - | - | - | 2 | 0.2 |
| FUS | 2 | - | - | - | - | - | - | - | 2 | 0.2 |
| Rickettsia | - | - | - | - | 2 | - | - | - | 2 | 0.2 |
| Toxoplasmosis (Suspected) | 1 | - | - | - | 1 | - | - | - | 2 | 0.2 |
| ARN | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Bartonella (Suspected) | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Brucellosis | 1 | - | - | - | - | - | - | - | 1 | 0.1 |
| Dengue | - | - | - | - | - | 1 | - | - | 1 | 0.1 |
| Lepra | 1 | - | - | - | - | - | - | - | 1 | 0.1 |
| Post-fever retinitis | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Rubella | - | - | - | - | - | 1 | - | - | 1 | 0.1 |
| Syphilis (Suspected) | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Typhoid | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Typhoid (Suspected) | - | - | - | - | 1 | - | - | - | 1 | 0.1 |
| Total | 159 | 4 | 78 | 127 | 209 | 188 | 23 | 46 | 835 | 100 |

ARC, Acute Retinal Necrosis; CMV, Cytomegalovirus; HSV, Herpes Simplex Virus; HZV, Herpes Zoster Virus; HIV, Human Immunodeficiency Virus; FUS, Fuchs Uveitis Syndrome; VZV, Varicella Zoster Virus.

the cases had a vitreous haze equal or greater than 2 + . Further details are provided in Table 2.

Infectious was the most common etiology (31.6 %), followed by idiopathic (28.1 %), undetermined at time of reporting (21.7 %), and non-infectious (16 %). Tuberculosis was the most prominent infectious cause, affecting 64.0 % of infectious cases, primarily in retinal vasculitis and panuveitis, followed by toxoplasmosis in 13.5 % of cases, often associated with posterior uveitis. Other infectious contributors include endogenous endophthalmitis and cytomegalovirus, each accounting for just over 4 % of cases, further details are provided in Table 3. Within the immune-mediated conditions, HLA-B27-associated uveitis and Ankylosing Spondylitis were the most common at 19.4 % and 10.4 %, respectively. Vogt-Koyanagi-Harada disease and sarcoidosis also feature prominently, generating panuveitis and intermediate uveitis, respectively. Further details are provided in Table 4. Geographical differences were observed in the distribution of etiological categories across the included countries, with countries like Indonesia and Nepal contributing mainly infectious cases, while others, such as Singapore and Colombia, predominantly reported idiopathic cases (see Table 5).

Anterior uveitis patients had a median follow-up time of 9 months with the interquartile range (IQR) spanning from 3 to 15 months (Fig. 1B). Intermediate and posterior uveitis displayed shorter median follow-up times, both at 3 months, with much narrower IQRs (Fig. 1B). Panuveitis patients had a median follow-up of 6 months, whereas patients with retinal vasculitis had a median follow-up of 9 months, both showing moderate variability in follow-up duration. Patients diagnosed with scleritis showed a significantly longer median follow-up time of 9 months, with an IQR indicating substantial variability, reflecting perhaps the severity or the chronic nature of the condition which necessitates longer monitoring (Fig. 1B). Asymmetric bilateral cases and other unspecified diagnostic categories had notably shorter median follow-up times, with the latter showing minimal variability as indicated by a very narrow IQR. Fig. 1

In cross-sectional analysis of mean visual acuity measured in LogMAR units, data were stratified over several time points, with variability presented as one standard deviation from the mean. Fig. 2A suggests a progressive improvement in overall visual acuity, starting from a baseline mean LogMAR of 0.6 and gently declining to a mean of 0.43 by the 120-month follow-up, suggesting a notable enhancement in visual function over time. Further, visual acuity trends were analyzed across four etiological classifications: idiopathic, infectious, non-infectious, and undetermined. Fig. 2B. Each category exhibited unique trajectories: the idiopathic group showed a slight increase in mean LogMAR from 0.36 to 0.38 over the study period, indicating minimal change in visual acuity. Conversely, the non-infectious group demonstrated marked improvement, reducing from an initial mean LogMAR of 0.49 to 0.29, subsequently stabilizing through to the final observation. The infectious category, starting at a mean of 0.7, exhibited a decrease to 0.56. The undetermined category showed the most significant improvement, plummeting from 0.57 to 0.16 by 120 months.

## 4. Discussion

This first analysis of the PROTON's registry data presents insights into the clinical and follow-up characteristics of our cohort. A significant finding was the observation of a general improvement in visual acuity across 3642 eyes from 2640 patients during the initial 24 months of follow-up, as measured in LogMAR units. Although 28.1 % of cases were idiopathic and 21.7 % were undetermined, this report included a rich diversity of aetiologies involved in uveitis, incorporating more than 60 distinct causes, including 23 of the 25 categories outlined by the Standardization of Uveitis Nomenclature (SUN) Working Group.[9] The

**Table 4**
Non-infectious aetiologies by anatomical localisation.

| | Anterior Uveitis | Asymmetric bilateral | Intermediate Uveitis | Panuveitis | Posterior Uveitis | Retinal Vasculitis | Scleritis | Others | Total | % |
|---|---|---|---|---|---|---|---|---|---|---|
| HLA-B27 associated | 71 | - | 4 | 5 | - | 2 | - | - | 82 | 19.4 |
| Ankylosing Spondylitis | 41 | - | - | 2 | 1 | - | - | - | 44 | 10.4 |
| VKH | 6 | - | 1 | 24 | 9 | - | - | - | 40 | 9.5 |
| Sarcoidosis | 8 | 1 | 7 | 9 | 5 | 6 | - | - | 36 | 8.5 |
| Bechet's Disease | 1 | - | 2 | 10 | 10 | 8 | 1 | 1 | 33 | 7.8 |
| Juvenile idiopathic arthritis | 23 | - | 2 | 3 | - | - | - | - | 28 | 6.6 |
| Rheumatoid arthritis | 9 | - | 1 | 1 | 1 | - | 2 | 2 | 16 | 3.8 |
| Psoriasis | 14 | - | - | 1 | - | - | - | - | 15 | 3.5 |
| Posner Schlossman syndrome | 14 | - | - | - | - | - | - | - | 14 | 3.3 |
| Systemic lupus erythematosus | 2 | - | 1 | 2 | - | 7 | - | 2 | 14 | 3.3 |
| FHS | 12 | - | - | - | - | - | - | - | 12 | 2.8 |
| Eales disease | - | - | - | - | - | 11 | - | - | 11 | 2.6 |
| Autoimmune unspecific | 6 | - | - | 1 | - | 2 | - | - | 9 | 2.1 |
| Multiple sclerosis | 2 | - | 1 | 1 | 2 | 1 | - | - | 7 | 1.7 |
| AZOOR | - | - | - | - | 6 | - | - | - | 6 | 1.4 |
| Autoimmune retinopathy | 3 | - | - | - | 1 | 2 | - | - | 6 | 1.4 |
| Reactive Arthritis | 5 | - | - | - | - | - | - | - | 5 | 1.2 |
| Serpiginous choroidopathy | - | - | - | - | 5 | - | - | - | 5 | 1.2 |
| Sympathetic ophthalmia | 2 | - | - | 2 | 1 | - | - | - | 5 | 1.2 |
| Inflammatory bowel disease | 4 | - | - | - | - | - | - | - | 4 | 0.9 |
| Birdshot Retinochoroidopathy | - | - | - | 1 | 2 | - | - | - | 3 | 0.7 |
| Multifocal choroiditis | - | - | - | - | 2 | 1 | - | - | 3 | 0.7 |
| Relapsing polychondritis | 2 | - | - | - | - | - | 1 | - | 3 | 0.7 |
| Seronegative arthritis | 3 | - | - | - | - | - | - | - | 3 | 0.7 |
| Sjogren syndrome | 2 | - | - | - | - | - | - | - | 2 | 0.5 |
| TINU | 2 | - | - | - | - | - | - | - | 2 | 0.5 |
| AIBSE | - | - | - | - | 1 | - | - | - | 1 | 0.2 |
| ANCA-associated vasculitis | - | - | - | - | - | - | 1 | - | 1 | 0.2 |
| Alport's syndrome | - | - | - | - | - | 1 | - | - | 1 | 0.2 |
| Amyloidosis | - | - | - | - | - | 1 | - | - | 1 | 0.2 |
| Antiphospholipid syndrome | - | - | - | - | - | 1 | - | - | 1 | 0.2 |
| Blau syndrome | - | - | - | 1 | - | - | - | - | 1 | 0.2 |
| Chron Disease | 1 | - | - | - | - | - | - | - | 1 | 0.2 |
| Cryoglobulinaemic vasculitis | 1 | - | - | - | - | - | - | - | 1 | 0.2 |
| Dermatomyositis | - | - | - | - | - | 1 | - | - | 1 | 0.2 |
| Granulomatosis Polyangiitis | - | - | - | - | - | - | - | 1 | 1 | 0.2 |
| Mixed Connective tissue disease | - | - | - | - | - | 1 | - | - | 1 | 0.2 |
| Psoriatic arthritis | 1 | - | - | - | - | - | - | - | 1 | 0.2 |
| Spondyloarthropathy unspecific | 1 | - | - | - | - | - | - | - | 1 | 0.2 |
| Systemic Vasculitis | - | - | - | 1 | - | - | - | - | 1 | 0.2 |
| Ulcerative Colitis | 1 | - | - | - | - | - | - | - | 1 | 0.2 |
| Total | 237 | 1 | 19 | 64 | 46 | 45 | 5 | 6 | 423 | 100 |

AZOOR, Acute Zonal Occult Outer Retinopathy; AIBSE, Acute Idiopathic Blind Spot Enlargement; HLA-B27, Human Leukocyte Antigen B27; TINU, Tubulointerstitial Nephritis and Uveitis; VKH, Vogt-Koyanagi-Harada disease.

comprehensive, real-world data collection framework enhances our understanding of OID patterns, treatments, and evolution, particularly highlighting that up to 29 % of cases initially classified as idiopathic uveitis may be subsequently diagnosed with an underlying condition upon detailed investigation and extended follow-up. [10]

Idiopathic causes usually account for 30 %-60 % of uveitis cases worldwide,[11] but there is a noticeable variation in global patterns, where developed countries report a higher proportion of non-infectious cases, which can comprise up to 71.37 % of the total cases in some cohorts.[12] In contrast, developing countries, such as India or Colombia, have classically exhibited a predominance of infectious causes.[13,14] Although this study is multicentric, the results largely reflect the contribution of the included centers. Notably, most of these centers (seven) were located in India, which explains the significant number of tuberculosis-related cases. Additionally, 21.7 % of cases were classified as undetermined, and another 28.1 % as idiopathic. These findings are consistent with previous reports from other cohorts.[15] However, we acknowledge the ongoing debate surrounding the use of these terms. A longitudinal analysis of our patient cohort will help us better distinguish which cases eventually lead to a specific diagnosis and which should be definitively categorized as idiopathic after sufficient follow-up and thorough investigation.

The mean follow-up time was 15.4 months (SD = 27.8) and 28.2 % of cases had a previous inflammation (Table 1). However, 40.7 % of patients have one month or less follow-up, and it was variable across anatomical locations, with anterior uveitis showing the highest median follow-up of 9 months (Fig. 1). Other studies have evaluated visual acuity outcome over time in non-infectious uveitis with a median follow-up of 6 months (IQR month 1–18).[16] This reassures the value of PROTON registry to explore risk and treatment factors related to visual acuity outcomes, considering their apparent variability evidenced in the present study (Fig. 2).

Several risk factors for reduced visual acuity in non-infectious uveitis patients have been identified. Long delays prior to referral to subspecialty care were associated with worse visual acuity (VA) outcomes, as was poorly controlled inflammation, particularly severe vitreous haze

**Table 5**
Distribution of etiological categories across the included countries.

| | Argentina | | Colombia | | Ethiopia | | India | | Indonesia | | Nepal | | Singapore | | Switzerland | | USA | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Idiopathic | 9 | 22.5 % | **126** | **27.6 %** | **19** | **61.3 %** | **335** | **32.81 %** | 28 | 12.79 % | 28 | 11.43 % | **182** | **30.59 %** | 6 | 31.58 % | **10** | **71.43 %** | 743 |
| Infective | **15** | **37.5 %** | 119 | 26.1 % | 9 | 29.0 % | 328 | 32.13 % | **105** | **47.95 %** | **154** | 62.86 % | 92 | 15.46 % | **12** | **63.16 %** | 1 | 7.14 % | **835** |
| Non-infective | 9 | 22.5 % | 93 | 20.4 % | - | - | 144 | 14.10 % | 19 | 8.68 % | 7 | 2.86 % | 147 | 24.71 % | 1 | 5.26 % | 3 | 21.43 % | 423 |
| Undetermined | 5 | 12.5 % | 113 | 24.8 % | 1 | 3.2 % | 182 | 17.83 % | 52 | 23.74 % | 48 | 19.59 % | 171 | 28.74 % | - | - | - | - | 572 |
| Drug induced | - | - | 3 | 0.7 % | - | - | 2 | 0.20 % | - | - | - | - | - | | - | - | - | - | 5 |
| Masquerade | 1 | 2.5 % | - | - | - | - | - | - | - | - | - | - | 2 | 0.34 % | - | - | - | - | 3 |
| Other | 1 | 2.5 % | 2 | 0.4 % | 2 | 6.5 % | 30 | 2.94 % | 15 | 6.85 % | 8 | 3.27 % | 1 | 0.17 % | - | - | - | - | 59 |
| Total | 40 | | 456 | | 31 | | 1021 | | 219 | | 245 | | 595 | | 19 | | 14 | | 2640 |

(grade 2 + or greater). Structural complications of uveitis, such as macular edema, hypotony, choroidal neovascularization (CNV), and elevated intraocular pressure (IOP), were also linked to poorer visual outcomes. Cataract surgery performed before subspecialty care resulted in significantly worse VA compared to surgery under subspecialty management. Higher age, beginning in the 55–65 range, was associated with reduced VA, as was current smoking, with past or never smoking showing similar outcomes, suggesting smoking cessation may benefit VA. Hispanic race/ethnicity was associated with worse VA, potentially due to more severe posterior segment disease, while Behçet's Disease was linked to a relatively poor prognosis. Prior retinal detachment surgery and pars plana vitrectomy (PPV) were associated with poorer VA, likely reflecting the severity of underlying disease, and glaucoma surgery also had modest VA outcomes, reflecting the severity of uveitis rather than the surgery itself.[4,17] However, there is less evidence about the risk factors for reduced visual acuity in infectious uveitis and a lack of clinical practice guidelines for uveitis.[18,19] Through the PROTON registry, we will be able to evaluate these factors in future studies and further explore non-infectious causes as well.

### 4.1. *Strengths, limitations and perspectives*

PROTON registry's design illustrates a trade-off between broad coverage and the granularity of specific clinical data, such as lesion size and localisation in toxoplasmosis cases. While this breadth allows for extensive epidemiological insights, it occasionally limits detailed individual data analysis, such as in survival analysis, where fixed time points might not capture the nuances of disease progression fully.

PROTON registry covers all aetiologies of OID, including infectious and non-infectious in an ambispective fashion, similar to The Portuguese Ocular Inflammation Registry (UVEITE.PT),[20] and the Fight Uveitis Blindness! Registry.[21] In contrast to Treatment exit options for non-infectious uveitis registry (TOFU), which is one of the largest and most comprehensive prospective registries of non-anterior non-infectious uveitis to date.[22,23] and Autoinflammatory Disease Alliance (AIDA) Network Registry, which focuses on non-infectious uveitis[24] and scleritis,[25] both retrospective and prospectively.

As there are other registries focus on OID, further work to achieve PROTON's registry interoperability with other registries will enhance our capacity to develop a more comprehensive and nuanced understanding of several aetiologies of OID on a global scale. This will require to advance toward a common data model in ophthalmology, specially focused in uveitis. However, an analysis on how effectively general eye examination data from a widely used electronic health record (EHR) system could be mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) revealed that while there was high intergrader agreement on the mapped OMOP concepts, with significant gaps in concept coverage. Specifically, only 25 % of EHR to OMOP mappings were found to be equivalent. Half of the mappings were deemed wider, missing key details such as laterality, which was absent in 46 % of these cases. Moreover, 21 % of the mappings did not match at all. These findings highlight critical areas for improvement in the OMOP CDM to enhance its applicability in ophthalmology research, particularly by enriching the model with more comprehensive ophthalmic concepts and attributes.[26]

Protecting patient confidentiality is of utmost importance. To address this, we employ secure, one-time anonymized data extraction processes, ensuring our studies meet the highest ethical standards. Data is securely managed via HTTPS-encrypted online forms and stored on the AWS cloud platform, which complies with both PCI DSS Level 1 and HIPAA standards—widely recognized benchmarks for secure data handling in medical research.[6] In addition, we have developed a hybrid architecture that allows centers to input their data either online or offline, accommodating restrictions on cloud data uploads. This strategy, combined with federated analysis techniques, enables statistical analysis while mitigating data-sharing challenges.

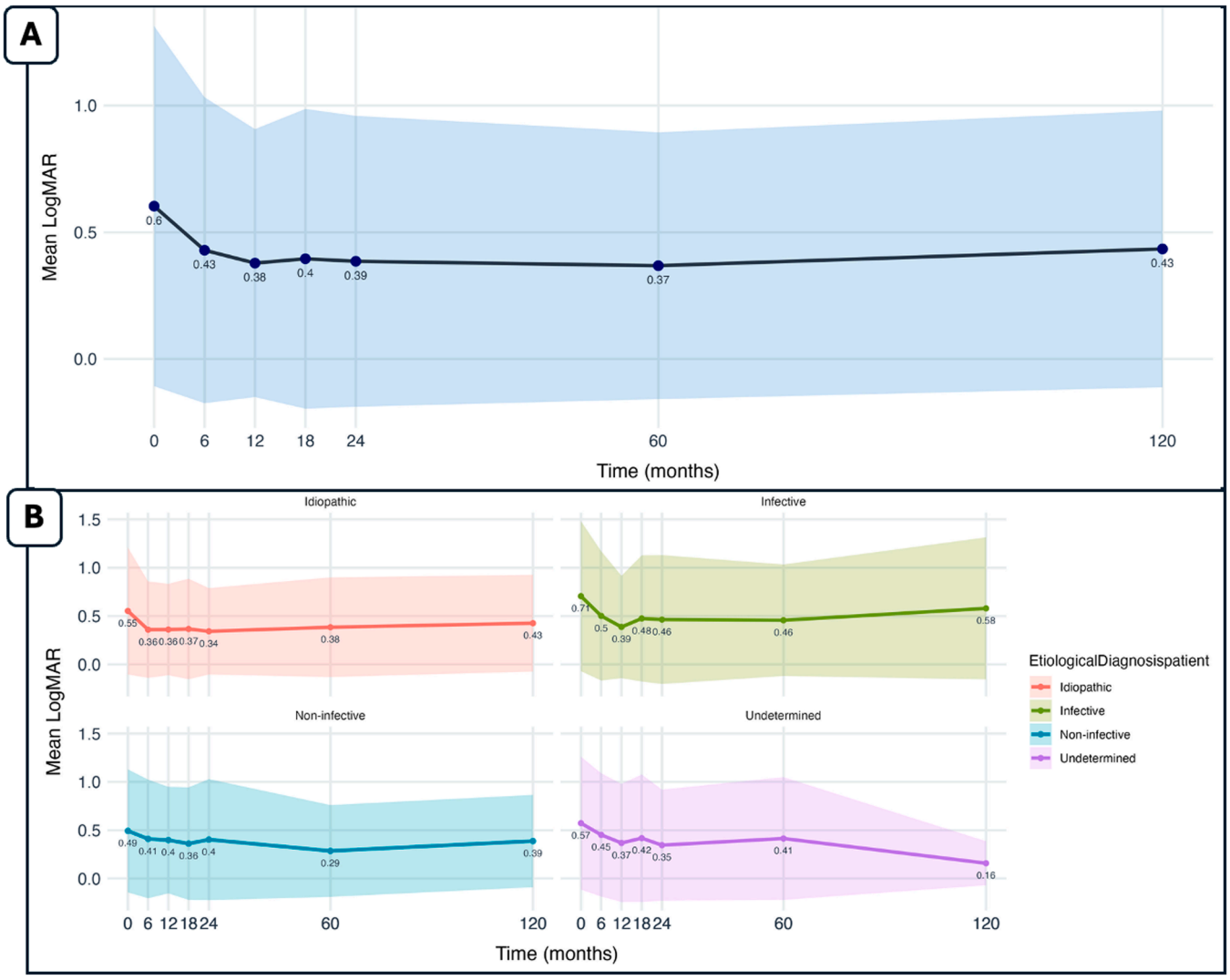


**Fig. 2.** Mean visual acuity in LogMAR over time. A. All patients. Mean visual acuity (measured in LogMAR) at each timepoint for all patients. The blue line represents the mean LogMAR values, and the shaded blue region indicates the standard deviation. Visual acuity generally improves over time, with a decline in LogMAR from baseline to 24 months, stabilizing thereafter. B. Analysis by Etiological Diagnosis. Mean visual acuity (LogMAR) at each timepoint, stratified by etiological diagnosis. The subgroups include Idiopathic (red): Visual acuity improves slightly but stabilizes over time. Infectious (green): Shows notable initial improvement, with a gradual stabilization of visual acuity. Non-infectious (blue): Improvement in visual acuity is observed initially, which then stabilizes. Undetermined (purple): A decline in LogMAR is seen over the first few months, followed by relative stability over time.

## 5. Conclusion

The PROTON registry provides a tremendous opportunity to explore and understand the complexities of OID by gathering real-world evidence from a diverse, multicentric cohort. The data collected through OASIS 1 and OASIS 2 offers valuable insights into both infectious and non-infectious causes of uveitis and the outcomes of various treatment approaches. Notably, the PROTON registry enables a deeper investigation into infectious uveitis, a critical area with limited existing evidence. As the registry continues to expand and evolve, it will be crucial in improving our understanding of disease patterns, guiding treatment strategies, and ultimately enhancing patient outcomes globally.

## Conflict of Interest

Competing interests: RA was supported by grants awarded by the National Medical Research Council (NMRC), Ministry of Health, Republic of Singapore grant number NRMC/CSAINV22jul-0004, NMRC/CSAINV19nov-0007, and NMRC/CIRG21nov-0023. The funders had no role in study design, data collection and analysis, publication decisions, or manuscript preparation.

## Acknowledgments

None.

*Synopsis*

The PROTON registry reveals a global spectrum of ocular inflammatory diseases, predominantly infectious in origin, with significant visual impairment (53.2 %). These findings highlight critical research opportunities to enhance disease management and patient outcomes.

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