Ophthalmol Ther
https://doi.org/10.1007/s40123-026-01390-5

BRIEF REPORT

Determinants of Non-infectious Scleritis Complications and Their Impact on Visual Outcome: Results from the International AIDA Network Scleritis Registry

Jurgen Sota · Andrea Hinojosa-Azaola · Alejandra de-la-Torre · Henrique Ayres Mayrink Giardini · Silvana Guerriero · Perla Ayumi Kawakami-Campos · Eduardo Martín-Nares · Guillermo Arturo Guaracha-Basañez · Gaafar Ragab · Maria Sole Chimenti · Giuseppe Lopalco · Pravin Hissaria · Marco Cattalini · Piero Ruscitti · Samar Tharwat · Guillermo Ruiz-Irastorza · Juan José García-Madero · Rafael Tierradentro-Alape · Mohamed Tharwat Hegazy · Kerolos Afifi · Giacomo Emmi · Paola Parronchi · Maria Pia Paroli · José Hernández-Rodríguez · Maite Sainz-de-la-Maza · Valeria Caggiano · Jessica Sbalchiero · Serena Bugatti · Carla Gaggiano · Luciana Breda · Rosanna Dammacco · Benedetta Monosi · Marco Capodiferro · Marc Beecher · Alma Nunzia Olivieri · Ezgi Deniz Batu · Seza Ozen · Bruno Frediani · Maissa Thabet · Alberto Balistreri · Vishali Gupta · Alex Fonollosa · Antonio Vitale · Luca Cantarini · Claudia Fabiani · Study Group of Systemic Autoinflammatory Disease of SIR (Italian Society of Rheumatology)

Received: February 17, 2026 / Accepted: April 14, 2026

Luca Cantarini and Claudia Fabiani are co-corresponding authors.

This work is generated within the European Reference Network for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases.

J. Sota · V. Caggiano · J. Sbalchiero · C. Gaggiano · B. Frediani · A. Vitale · L. Cantarini (✉)
Rheumatology Unit, Department of Medical Sciences, Surgery, and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Siena, Italy
e-mail: cantariniluca@hotmail.com

A. Hinojosa-Azaola · E. Martín-Nares · G. A. Guaracha-Basañez
Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

A. de-la-Torre · J. J. García-Madero · R. Tierradentro-Alape
Neuroscience Research Group (NEUROS), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

H. A. M. Giardini
Rheumatology Division, Faculdade de Medicina, Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP), Universidade de São Paulo, São Paulo, Brazil

S. Guerriero · R. Dammacco
DiBrain Department, University of Bari, Bari, Italy

P. A. Kawakami-Campos
Department of Ophthalmology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

G. Ragab · M. T. Hegazy
Rheumatology and Clinical Immunology Unit, Internal Medicine Department, Faculty of Medicine, Cairo University, Giza, Egypt

M. S. Chimenti · B. Monosi
Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

G. Lopalco · M. Capodiferro
Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), Policlinic Hospital, University of Bari, Bari, Italy

P. Hissaria · M. Beecher
Department of Clinical Immunology and Allergy, Royal Adelaide Hospital, Adelaide, Australia

Published online: 09 May 2026

ABSTRACT

Introduction: Scleritis is a rare and severe ocular inflammatory disease that is often associated with potentially sight-threatening ocular complications. The aim of the present study was to characterize ocular complications in non-infectious scleritis and identify predictive variables for their development.

Methods: Data for this registry-based study were extracted from the AutoInflammatory Disease Alliance Network for Scleritis Registry. Univariate analysis was performed to examine potential associations of demographic and clinical variables with the development of ocular complications. Uveitis and peripheral ulcerative keratitis were considered to be extensions of the inflammatory process and not to be true structural complications. Predictive factors of ocular complications were assessed using regression analysis. The impact of ocular complications on visual acuity—measured by best-corrected visual acuity (BCVA)—was also analyzed.

Results: A total of 154 patients (218 eyes) with non-infectious scleritis were enrolled. In 58 of these patients (87 eyes), 102 ocular complications were recorded, with cataract, scleral and corneal thinning, and glaucoma and/or increased ocular pressure being the most frequently recorded complications. Ocular complications were found to be significantly more

P. Hissaria · M. Beecher
Department of Immunopathology, SA Pathology, Adelaide, Australia

M. Cattalini
Pediatric Clinic, University of Brescia and Spedali Civili di Brescia [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Brescia, Italy

P. Ruscitti
Rheumatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

S. Tharwat
Rheumatology and Immunology Unit, Internal Medicine Department, Mansoura University, Mansoura, Egypt

S. Tharwat
Department of Internal Medicine, Faculty of Medicine, Horus University, New Damietta, Egypt

G. Ruiz-Irastorza
Faculty of Medicine and Nursery, University of the Basque Country (UPV-EHU), Leioa, Biscay, Spain

G. Ruiz-Irastorza
Autoimmune Diseases Unit, Biocruces Bizkaia Health Research Institute, Barakaldo, Biscay, Spain

M. T. Hegazy
Rheumatology Unit, Internal Medicine Department, Jahra Hospital, Al Jahra, Kuwait

K. Afifi
Internal Medicine Department, Minia University Hospitals, Minya, Egypt

G. Emmi
Internal Medicine, Immunology and Rheumatology Unit, Department of Medical, Surgical and Health Sciences, Cattinara University Hospital, Trieste, Italy

G. Emmi
Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, VIC, Australia

P. Parronchi
Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

M. P. Paroli
Uveitis Unit, Department of Sense Organs, Eye Clinic, Sapienza University of Rome, Rome, Italy

J. Hernández-Rodríguez · M. Sainz-de-la-Maza
Autoinflammatory Diseases Clinical Unit, Department of Autoimmune Diseases, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Barcelona, Spain

S. Bugatti
Division of Rheumatology, Department of Internal Medicine and Therapeutics (S.B.), Fondazione IRCCS Policlinico San Matteo, Università di Pavia [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Pavia, Italy

L. Breda
Department of Paediatrics, University of Chieti-Pescara, Chieti, Italy

A. N. Olivieri
Department of Woman, Child and of General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

frequent among patients affected by granulomatosis with polyangiitis (GPA) ($p<0.0001$) and concomitant uveitis ($p=0.023$). The mean severity score was significantly higher among eyes experiencing ocular complications ($p<0.0001$). Regression analysis identified three variables capable of predicting the development of ocular complications: a diagnosis of GPA [odds ratio (OR) 7.747, $p<0.0001$]; the presence of concomitant uveitis (OR 3.648, $p=0.019$); and a high severity score (OR 1.138, $p=0.044$). Mean (± standard deviation) BCVA converted to logMAR was found to be significantly higher among eyes without ocular complications (0.12 ± 0.24 vs 0.27 ± 0.49; $p=0.005$).

***Conclusion*:** Scleritis was accompanied by irreversible ocular complications in a considerable proportion of the patients enrolled in this study. Patients with a diagnosis of GPA, concomitant uveitis, and a higher severity score are more likely to develop ocular complications, and thus warrant a tighter follow-up schedule and early treatment in order to minimize the risk of poor visual prognosis.

E. D. Batu · S. Ozen
Pediatric Rheumatology Unit, Department of Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey

M. Thabet
Internal Medicine Department, Farhat Hached University Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia

A. Balistreri
Bioengineering and Biomedical Data Science Lab, Department of Medical Biotechnologies, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Siena, Italy

V. Gupta
Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

A. Fonollosa
Department of Ophthalmology, Biocruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country, Cruces Plaza, 48903 Barakaldo, Bizkaia, Spain

A. Fonollosa
Department of Retina, Instituto Oftalmológico Bilbao, Berástegui 4, 1º Izq, 48001 Bilbao, Spain

Keywords: Scleritis; Granulomatosis with polyangiitis; Uveitis; Severity score; Visual acuity

Key Summary Points

Why carry out this study

Real-life robust evidence on long-term outcomes in patients with non-infectious scleritis is scarce.

This study aimed at characterizing ocular complications and detecting predictive factors for the development of these complications throughout the disease course.

What was learned from the study

Data from the International Autoinflammatory Diseases Alliance (AIDA) Network revealed that patients with scleritis diagnosed with granulomatosis with polyangiitis and those who present with concomitant uveitis are more likely to develop ocular complications.

The scleritis severity score is an often overlooked but reliable tool capable of predicting the development of ocular complications in patients with scleritis.

Our findings allow more accurate patient profiling and identify a subgroup of patients with scleritis that should undergo tight follow-up control and proper management to preserve long-term visual function.

INTRODUCTION

Scleritis is an inflammation of the sclera that encompasses a broad spectrum of conditions, ranging from mild scleral inflammation to severe and

C. Fabiani (✉)
Unit of Ophthalmology, Department of Medicine, Surgery, and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Siena, Italy
e-mail: claudia.fabiani@aidanetwork.com

aggressive variants of the inflammation associated with a high risk of irreversible anatomical damage and poor functional outcome [1, 2]. A significant proportion of cases are characterized by compromised visual function and a potential threat to the anatomical integrity of the ocular globe. Visual loss is present in almost 30% of patients [3, 4]. Previous studies have reported a heterogeneous spectrum of complications, including, scleral thinning and perforation, cystoid macular edema, glaucoma, and exudative retinal detachment, among others [4, 5]. Damage to nearby structures, such as the cornea, including peripheral ulcerative keratitis (PUK), the uvea, and the retina may also occur and further worsen visual impairment [6]. An additional crucial aspect to be considered is the association of scleritis with systemic immune-mediated diseases as this association could influence disease severity, histopathology, and long-term outcomes [4, 7]. Taken together, these considerations warrant the need to identify a specific subgroup of patients with non-infectious scleritis who are more likely to develop long-term complications ultimately leading to a poor visual outcome. Prompt detection of such patients would provide clinicians the opportunity to early administer systemic immunosuppressive treatments in a top–down manner aimed at controlling ocular inflammation and preventing or minimizing visual impairment. In this context, our previous experiences have highlighted the efficacy of biotechnological agents, including both tumor necrosis factor (TNF) inhibitors and non-TNF inhibitors, in the management of non-infectious scleritis [8, 9].

Here, we report the findings of an international registry-based multicenter study characterizing ocular complications in non-infectious scleritis with a specific focus on identifying predictors of irreversible ocular complications.

METHODS

Study Design, Participants and Data Collection

Medical records of patients diagnosed with non-infectious scleritis, either idiopathic or associated with systemic immune-mediated diseases, were reviewed. Data were extracted in a double fashion, both retrospectively and prospectively, collected up to 2 November 2025, from the international AIDA Network Scleritis Registry. Scleritis Registry is a physician-driven, electronic-based registry implemented for the collection of real-life data on demographics, socioeconomic, clinical, laboratory and therapeutic information [10].

The following data were collected: gender, age at onset, age at diagnosis, associated systemic disease, human leukocyte antigen (HLA)-typing, autoantibodies, best-corrected visual acuity (BCVA) measured on Snellen charts and transformed into logarithm of the minimum angle of resolution (logMAR), scleritis anatomical classification according to Watson and Hayreh [11], number of relapses, concomitant uveitis (diagnosed during or immediately after scleritis diagnosis), treatments given throughout disease course, and ocular complications developed over time from disease onset to the last follow-up visit. When patients had both anterior and posterior scleritis, they were assigned to the group "posterior scleritis". Scleritis severity scoring was established according to the McCluskey and Wakefield [12]. Medical charts with > 20% of values missing were excluded from the study. All patients were regularly followed up on scheduled appointments and in case of necessity (disease flare and/or safety issues).

Ethical Statement

The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments, and received approval from the local Ethics Committee of the University of Siena (Reference No. 14951). All patients or their legal guardians provided written informed consent.

Aims and Endpoints

The primary aim of the study was to identify variables associated with the development of ocular complications in patients with non-infectious

scleritis throughout the ocular disease course. Secondary aims were established as: (1) evaluation of the influence of the severity score in the development of ocular complications; (2) detection of predictive factors of the development of ocular complications; and (3) the consequences of ocular complications on visual function.

The primary endpoint was analyzed using potential statistical differences between patients with and without ocular complications according to the following variables: sex, laterality (monolateral vs bilateral), the presence of autoantibodies, scleritis anatomical classification (anterior vs posterior), concomitant uveitis, the associated immune-mediated systemic disease, and treatment with topical glucocorticosteroids (GCs), oral GCs, conventional disease-modifying anti-rheumatic drugs and biotechnological agents.

Secondary endpoints were examined using (1) the detection of any statistically significant difference between patients with and without ocular complications in the mean scleritis severity score; (2) binary logistic regression with the stepwise backward method to identify predictive factors of the development of ocular complications; and (3) any difference in BCVA.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA). The normality distribution of continuous variables was assessed with the Shapiro–Wilk test. Quantitative variables were reported as the mean and standard deviation (SD) or as the median and interquartile range (IQR), as required, and qualitative variables were reported as absolute frequencies with the corresponding percentages. Cross-tables were analyzed by Pearson's Chi-squared test, and post-hoc analysis through adjusted residuals was used for contingency tables with dimensions $> 2 \times 2$. Differences in median values between groups were tested using the Mann–Whitney U-test. Potential predictors of ocular complications were identified by binary logistic regression computed with the backward stepwise method. Given the dichotomous nature of the dependent variable, patients experiencing multiple complications were coded as having the outcome "complication," regardless of the number of events. The following variables were included in the initial regression model: sex, the presence/absence of GPA, anatomical pattern of scleritis, concomitant uveitis, severity score, and treatment with topical and/or oral GCs. The significance threshold was set at 0.05, and all tests were two-sided.

RESULTS

Of the 162 patients enrolled in the international AIDA Network Scleritis Registry, 154 were enrolled in the present study, for a total of 218 eyes. Eight patients were excluded due to incomplete records. Scleritis was unilateral in 90 cases and bilateral in 64 cases. The female-to-male ratio was 1.83. Mean age at onset and at diagnosis was 44.67 and 45.52 years, respectively. Mean (±SD) disease duration at last follow-up was 71.53 ± 79.48 months [median (IQR) was equal to 48.50 (78.50) months]. More detailed clinical and demographic data are provided in Table 1. Scleritis was classified as idiopathic in 61 cases. In terms of associated systemic immune-mediated diseases, the most frequently encountered diagnosis was granulomatosis with polyangiitis (GPA) (31 patients) followed by rheumatoid arthritis (14 patients) and axial spondyloarthritis (10 patients). The pie chart in Fig. 1 illustrates all the systemic immune-mediated diseases diagnosed in our cohort.

A total of 102 ocular complications were recorded in 58 patients (87 eyes), with cataract being the most frequent complication (31 eyes), followed by scleral thinning (16 eyes), glaucoma (11 eyes), corneal thinning (9 eyes), macular edema (8 eyes), and corneal scars (7 eyes). Figure 2 shows the complications recorded.

Ocular complications were found to be significantly more frequent among patients

Table 1 Demographics and clinical characteristics of patients enrolled in the present study

Feature	Description
No. of patients	154
Sex (females/males), *n*	99/54
Ethnicity	White (*n* = 86)
	Hispanic (*n* = 47)
	Arab (*n* = 15)
	Black (*n* = 4)
	Southeast Asia (*n* = 1)
	South Asia (*n* = 1)
Age at onset, years (mean ± SD)	44.67 ± 17.67
Age at diagnosis, years (mean ± SD)	45.52 ± 17.59
Diagnostic delay, years (median [IQR])	0.00 [0.50]
Laterality	Unilateral (*n* = 90)
	Bilateral (*n* = 64)
Anatomic pattern (no. of eyes)	*Anterior scleritis (n = 151)*
	Diffuse (*n* = 96)
	Nodular (*n* = 33)
	Necrotizing (*n* = 7)
	- Necrotizing with inflammation (*n* = 6)
	- Necrotizing without inflammation/scleromalacia perforans (*n* = 1)
	Not reported (*n* = 15)
	Posterior scleritis (n = 37)
	Anatomical classification unavailable for 30 eyes
Concomitant uveitis (no. of patients)	*n* = 28
Concomitant PUK (no. of patients)	*n* = 14
HLA typing	HLA-B*27 positivity (*n* = 3)
	HLA-B*51 positivity (*n* = 6)
	HLA-Cw6 positivity (*n* = 1)
	HLA-DRB1 positivity (*n* = 2)

HLA Human leukocyte antigen, *IQR* interquartile range, *PUK* peripheral ulcerative keratitis, *SD* standard deviation

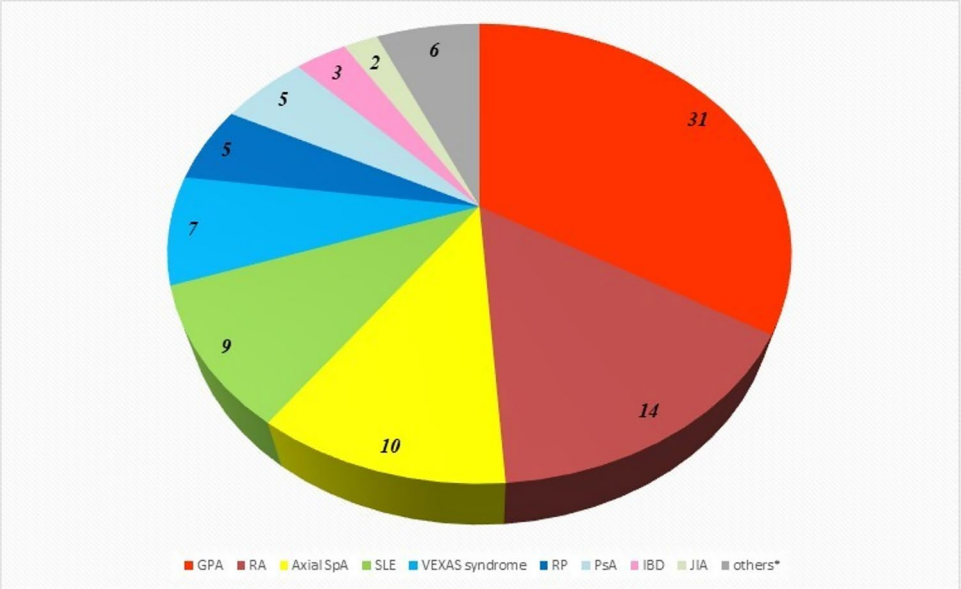

Fig. 1 Systemic immune-mediated systemic diagnosis associated with non-infectious scleritis. Asterisk (*) indicates other diagnoses: IgG4-related disease, Cogan's syndrome, Takayasu arteritis, MPA, GCA, and ADA2 deficiency (one per patient). *ADA2* Adenosine deaminase 2, *GCA* giant cell arteritis, *GPA* granulomatosis with polyangiitis, *IBD* inflammatory bowel diseases, *IgG4* immunoglobulin G4, *JIA* juvenile idiopathic arthritis, *MPA* microscopic polyangiitis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *RP* relapsing polychondritis, *SLE* systemic lupus erythematosus, *SpA* spondyloarthritis, *VEXAS syndrome* E1 enzyme, X-linked, autoinflammatory and somatic

affected by GPA [odds ratio (OR) 5.054, 95% confidence interval (CI) 2.179–11.722, $p<0.0001$] and concomitant uveitis (OR 2.574, 95% CI 1.118–5.927, $p=0.023$), respectively. Specifically, 30% of patients with scleritis without GPA developed ocular complications, compared to 68.8% of patients with scleritis with a diagnosis of GPA. A similar trend was observed in patients with scleritis and concomitant uveitis (57%) compared to those without concomitant uveitis (34%), with 28 patients (36 eyes) with scleritis having concomitant uveitis. The most frequent anatomical pattern of uveitis was anterior (56.7%) while 13.3% and 30% of the eyes had posterior uveitis and panuveitis, respectively. The anatomical pattern of uveitis ("anterior" uveitis group vs "posterior or panuveitis" group) was not significantly associated with the occurrence of ocular complications ($p=0.88$).

The anatomical pattern of scleritis was not significantly associated with the development of ocular complications throughout disease course ($p=0.172$).

Treatment with topical and/or oral GCs was associated with a significantly lower occurrence of structural ocular complications (OR 0.460, 95% CI 0.237–0.891, $p=0.020$). Also, no significant association was found between the use of advanced therapies with biotechnological agents and the occurrence rate of ocular complications ($p=0.311$). The mean (±SD) [median (IQR)] treatment delay from disease onset to the first biologic used was 33.32 ± 43.14 [13.50 (52.00)] months.

The mean (±SD) severity score among eyes experiencing ocular complications (1.83 ± 2.46)

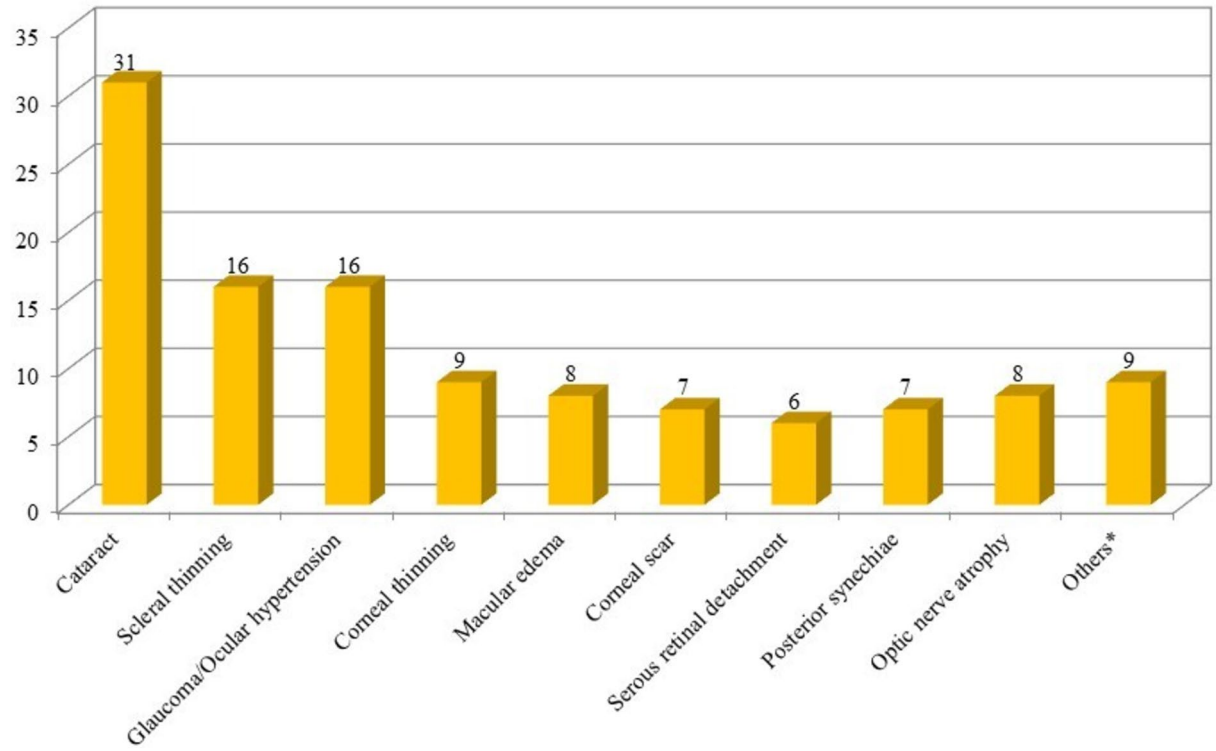

Fig. 2 Ocular complications recorded throughout disease course. Asterisk (*) indicates other complications: phthisis bulbi, blindness, grade IV optic disc edema, superior choroidal folds, retinal vessel congestion, epiretinal membrane, and anterior synechiae

was significantly higher than that among eyes without any recorded complications (0.68 ± 1.58) ($p < 0.0001$).

Regression analysis identified three variables capable of predicting the development of ocular complications: a diagnosis of GPA (OR 7.747, 95% CI 2.891–20.759, $p < 0.0001$), the presence of concomitant uveitis (OR 3.648, 95% CI 1.241–10.722, $p = 0.019$), and severity score (OR 1.138, 95% CI 1.003–1.290, $p = 0.044$). The results of the univariate and multivariate analyses are summarized in Table 2.

Mean (± SD) BCVA converted in logMAR was found to be significantly higher among eyes without ocular complications (0.12 ± 0.24 vs 0.27 ± 0.49; $p = 0.005$).

Table 2 Variables predicting the development of ocular complications in scleritis and their respective significance in univariate and regression analysis

Univariate analysis				
Variable				***p* value**
Sex				0.128
Associated systemic disease				0.183
GPA				< 0.0001*
Autoantibodies				0.074
Laterality				0.132
Concomitant uveitis				0.023*
Anatomic pattern				0.172
Topical and/or oral GCs				0.020*
cDMARDs				0.551
Biotechnological agents				0.311
Regression analysis				
Variable	**OR**	**Lower CI**	**Upper CI**	***p* value**
GPA	7.747	2.891	20.759	< 0.0001
Concomitant uveitis	3.648	1.241	10.722	0.019
Severity score	1.138	1.003	1.290	0.044

cDMARDs Conventional disease modifying anti-rheumatic drugs, *CI* confidence interval, *GCs* glucocorticosteroids, *GPA* granulomatosis with polyangiitis, *OR* odds ratio

* indicates statistical significance ($p < 0.05$)

DISCUSSION

Scleritis is a rare and severe ocular inflammatory disease that is often associated with potentially sight-threatening ocular complications and, in some instances, even globe perforation [2]. It often accompanies systemic diseases such as GPA, rheumatoid arthritis, and systemic lupus erythematosus [13]. Of the 154 patients with non-infectious scleritis enrolled in the present study, we recorded ocular complications in 58 (37.7%) patients—87/218 (39.9%) eyes. This percentage is lower than that reported in previous similar studies, in which > 75% of the patients with scleritis were found to develop complications [3, 14–16]. This difference could be purely methodological as most previous studies defined concomitant uveitis and PUK as ocular complications whereas we considered these ocular manifestations to be a more extensive inflammatory process involving structures nearby the sclera. In fact, adjacent ocular structures such as the uveal tract and peripheral cornea could be part of the same underlying inflammation process rather than true complications due to a shared immunologic environment. In this context, uveitis and PUK could be part of the same disease spectrum. Anterior uveitis in particular may accompany scleritis, and the extension of scleral inflammation to the anterior uveal tract could worsen the ocular prognosis [5]. The most frequent ocular complication in our cohort was cataract, followed by scleral or corneal thinning and glaucoma/ocular hypertension. These complications—particularly elevated intraocular

pressure, cataract and to a lesser extent scleral/corneal changes—have also been reported to be the most common ocular complications in other studies [15–17]. Ocular hypertension and glaucoma specifically may occur in about one-fifth of patients with scleritis, as described in a large series of patients with scleritis [18]. For completeness, it should be emphasized that both cataract and ocular hypertension may result from chronic GCs use rather than the uncontrolled ocular inflammatory process alone, highlighting the need for the early introduction of steroid-sparing agents. The roughly 2-year delay in initiating a biologic agent in our cohort could explain its non-significant impact on reducing the frequency of irreversible ocular complications.

Applying the Watson and Hayreh classification, we found that anterior diffuse scleritis was more prevalent than posterior scleritis, anterior nodular scleritis, and anterior necrotizing scleritis in our patient population. The anatomical pattern did not impact the occurrence rate of ocular complications, suggesting that anterior scleritis should be equally monitored and receive the same degree of clinical caution as posterior scleritis. Posterior scleritis, however, is associated with a high potential of visual loss, affecting roughly one third of the patients, mainly due to the potential extension of the inflammatory process to nearby structures, such as the choroid, external retina, and optic nerve, leading to macular changes or optic atrophy [4].

In terms of associated immune-mediated diseases, across previous studies, approximately 22–37% of patients with scleritis received a systemic diagnosis [3, 14, 16, 17]. In comparison, a higher proportion of high-burden systemic diseases was detected in our cohort (60%), likely due to referral bias that led to the chronic management of more severe cases. This, in turn, may limit the representation of systemic scleritis in the general population in which milder cases are more prevalent. In previous reports, the autoimmune diseases most commonly associated with scleritis were rheumatoid arthritis, followed by ANCA-associated vasculitis, and relapsing polychondritis [3, 14, 16, 17]. In keeping with these results, we also found that the most common systemic diagnostic entities were GPA and rheumatoid arthritis. According to our findings, patients with scleritis with a diagnosis of GPA are significantly more likely to develop irreversible ocular complications, confirming the findings of earlier studies in which patients with a diagnosis of GPA exhibited a worse ocular prognosis. In the study by Sainz de la Maza et al., GPA was more commonly associated with a necrotizing pattern, visual loss, and PUK [7]. Additionally, ophthalmologists and rheumatologists evaluating patients with scleritis should give an extra consideration to this diagnostic hypothesis, since GPA is less frequently diagnosed before scleritis onset than other systemic diseases such as rheumatoid arthritis [16, 19]. Therefore, testing for PR3-ANCA/MPO-ANCA autoantibodies becomes a crucial part of the serologic work-up, particularly in the subset of patients with positive c-ANCA without evidence of systemic vasculitis, who are more likely to experience difficult-to-treat scleritis [18]. High-impact immune-mediated diseases including GPA and rheumatoid arthritis should be the main focus when screening patients with scleritis for an underlying systemic disease.

We found a significantly higher frequency of ocular complications in patients with scleritis and concomitant uveitis compared to patients with isolated scleritis, likely indicating a more vigorous inflammatory process extending to the uveal tract. This, in turn, may lead to a higher incidence of structural complications, regardless of the anatomical pattern of uveitis.

Our data aligns with the available literature reporting a higher rate of visual morbidity in patients with scleritis and associated uveitis. Liao et al. recently observed a worse visual acuity and a higher risk of posterior segment complications in this subgroup of patients [6]. Other reports have revealed that patients with scleritis-associated uveitis had a significantly higher level of necrotizing scleritis, a greater decrease in vision, PUK, and glaucoma [5]. In this context, regular examination of the uvea is mandatory in patients with scleritis, as the extension of scleral inflammation to the uveal tract warrants a more aggressive treatment approach and a tighter follow-up schedule.

Using the scoring system for the severity of scleritis, we found a considerably higher score

in patients with scleritis who developed ocular complications. Interestingly, McCluskey and colleagues found a lower response rate to systemic treatment in patients with a higher severity score [12]. Consequently, assessing scleritis severity at an early stage of disease provides a window of opportunity. In this context, an optimized treatment approach could alter the natural course of the disease and preserve long-term visual function. The multivariate analysis confirmed the results of our analysis. Patients with scleritis diagnosed with GPA and those with concomitant uveitis had a 7.7-fold and 3.6-fold increased risk, respectively, of developing ocular complications throughout the disease course. Similarly, for every 5-unit increase in severity score, the odds of recording an ocular complication increases by 1.90-fold. Therefore, patients with these features should alert ophthalmologists as they should be considered to be at high risk of visual impairment. Patients with this profile should then receive early immunosuppressive treatment to minimize the risk of sight-threatening complications. On the contrary, the significant association between treatment with topical and/or oral GCs and the development of ocular complications likely reflects confounding by indication bias as well as the potential risk of GCs-related complications.

The impact on visual function was also significant as patients experiencing ocular complications showed a significantly lower visual acuity.

Study limitations are the registry-based nature of the study, lack of detailed therapeutic data, and referral bias. This registry-based study and the lack of a standardized pre-established protocol account for the differences across the participating centers in terms of diagnostic approach, disease assessment (including McCluskey severity score), and management. Missing data as well as unstandardized treatment algorithms, both consistent shortcomings in retrospective studies, should also be acknowledged. The sample size and the relatively small number of events restrain the number of predictors in the regression model, in accordance with the event-per-variable principle, which might have reduced the power to detect valuable associations. The highly skewed data on follow-up represent a limitation, as patients with longer disease duration are more likely to develop complications, introducing a time-dependant ascertainment bias. This may be better addressed with a time-to-event analysis in a future study with a larger sample size. Finally, most patients who are enrolled and regularly followed in tertiary referral centers represent a more severe patient subset compared to the general ophthalmologic population, as reported in the present cohort. Consequently, applying our findings to milder cases might be imprecise.

CONCLUSION

Non-infectious scleritis is a severe ocular inflammatory disorder that is frequently associated with irreversible ocular complications. Patients with a diagnosis of GPA, those with concomitant uveal inflammation, and those with a high severity score are more at risk of developing ocular complications. Therefore, this phenotype warrants a detailed diagnostic work-up, a tight follow-up schedule, and proper early treatment to prevent or minimize the risk of poor long-term visual prognosis.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Medical Writing/Editorial Assistance. No medical writing or editorial assistance was used during the preparation of this article.

Author Contributions. Jurgen Sota designed the study, performed the statistical analysis, participated in data curation, and wrote the first draft of the manuscript. Luca Cantarini and Claudia Fabiani were responsible for patients' enrollment, established the design of the concept of the study, curated the data, and edited and reviewed the manuscript. Andrea Hinojosa-Azaola, Alejandra de-la-Torre, Henrique Ayres Mayrink Giardini, Silvana Guerriero, Perla Ayumi Kawakami-Campos, Eduardo Martín-Nares, Guillermo Arturo Guaracha-Basañez,

Gaafar Ragab, Maria Sole Chimenti, Giuseppe Lopalco, Pravin Hissaria, Marco Cattalini, Piero Ruscitti, Samar Tharwat, Guillermo Ruiz-Irastorza, Juan José García-Madero, Rafael Tierradentro-Alape, Mohamed Tharwat Hegazy, Kerolos Afifi, Giacomo Emmi, Paola Parronchi, Maria Pia Paroli, José Hernández-Rodríguez, Maite Sainz-de-la-Maza, Valeria Caggiano, Jessica Sbalchiero, Serena Bugatti, Carla Gaggiano, Luciana Breda, Rosanna Dammacco, Benedetta Monosi, Marco Capodiferro, Marc Beecher, Alma Nunzia Olivieri, Ezgi Deniz Batu, Seza Ozen, Bruno Frediani, Maissa Thabet, Alberto Balistreri, Vishali Gupta, Alex Fonollosa, and Antonio Vitale enrolled patients, participated in data curation, and edited and reviewed the manuscript. All authors have given final approval of the manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jurgen Sota, Andrea Hinojosa-Azaola, Alejandra de-la-Torre, Henrique Ayres Mayrink Giardini, Silvana Guerriero, Perla Ayumi Kawakami-Campos, Eduardo Martín-Nares, Guillermo Arturo Guaracha-Basañez, Gaafar Ragab, Maria Sole Chimenti, Giuseppe Lopalco, Pravin Hissaria, Marco Cattalini, Piero Ruscitti, Samar Tharwat, Guillermo Ruiz-Irastorza, Juan José García-Madero, Rafael Tierradentro-Alape, Mohamed Tharwat Hegazy, Kerolos Afifi, Giacomo Emmi, Paola Parronchi, Maria Pia Paroli, José Hernández-Rodríguez, Maite Sainz-de-la-Maza, Valeria Caggiano, Jessica Sbalchiero, Serena Bugatti, Carla Gaggiano, Luciana Breda, Rosanna Dammacco, Benedetta Monosi, Marco Capodiferro, Marc Beecher, Alma Nunzia Olivieri, Ezgi Deniz Batu, Seza Ozen, Bruno Frediani, Maissa Thabet, Alberto Balistreri, Vishali Gupta, Alex Fonollosa, Antonio Vitale, Luca Cantarini have nothing to disclose. Claudia Fabiani is a Section Editor of *Ophthalmology and Therapy*. Claudia Fabiani was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments, and received approval from the local Ethics Committee of the University of Siena (Reference No. 14951). All patients or their legal guardians provided written informed consent.

REFERENCES

1. Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P. Scleritis: immunopathogenesis and molecular basis for therapy. Prog Retin Eye Res. 2013;35:44–62. https://doi.org/10.1016/j.preteyeres.2013.02.004.

2. Nevares A, Raut R, Libman B, Hajj-Ali R. Noninfectious autoimmune scleritis: recognition, systemic associations, and therapy. Curr Rheumatol Rep. 2020;22(4):11. https://doi.org/10.1007/s11926-020-0885-y.

3. Wieringa WG, Wieringa JE, ten Dam-van Loon NH, Los LI. Visual outcome, treatment results, and prognostic factors in patients with scleritis.

Ophthalmology. 2013;120(2):379–86. https://doi.org/10.1016/j.ophtha.2012.08.005.

4. McCluskey PJ, Watson PG, Lightman S, Haybittle J, Restori M, Branley M. Posterior scleritis: clinical features, systemic associations, and outcome in a large series of patients. Ophthalmology. 1999;106(12):2380–6. https://doi.org/10.1016/S0161-6420(99)90543-2.

5. Sainz de la Maza M, Foster CS, Jabbur NS. Scleritis-associated uveitis. Ophthalmology. 1997;104(1):58–63. https://doi.org/10.1016/s0161-6420(97)30361-3.

6. Liao A, Fajoles-Vasseneix C, Rali A, et al. Visual morbidity and outcomes of scleritis associated with intraocular inflammation compared to isolated scleritis. Ocul Immunol Inflamm. 2024;32(6):947–54. https://doi.org/10.1080/09273948.2022.2164726.

7. Sainz de la Maza M, Foster CS, Jabbur NS. Scleritis associated with systemic vasculitic diseases. Ophthalmology. 1995;102(4):687–92.

8. Fabiani C, Sota J, Sainz-de-la-Maza M, et al. Effectiveness of TNF-α blockade in the treatment of refractory non-infectious scleritis: a multicentre study. Clin Exp Rheumatol. 2020;38(6):1138–44.

9. Fabiani C, Sota J, Sainz-de-la-Maza M, et al. New potential weapons for refractory scleritis in the era of targeted therapy. Mediators Inflamm. 2020;2020:8294560. https://doi.org/10.1155/2020/8294560.

10. Della Casa F, Vitale A, Pereira RM, et al. Development and implementation of the AIDA international registry for patients with non-infectious scleritis. Ophthalmol Ther. 2022;11(2):887–97. https://doi.org/10.1007/s40123-022-00466-2.

11. Watson PG, Hayreh SS. Scleritis and episcleritis. Br J Ophthalmol. 1976;60(3):163–91. https://doi.org/10.1136/bjo.60.3.163.

12. McCluskey P, Wakefield D. Prediction of response to treatment in patients with scleritis using a standardised scoring system. Aust N Z J Ophthalmol. 1991;19(3):211–5. https://doi.org/10.1111/j.1442-9071.1991.tb00663.x.

13. Generali E, Cantarini L, Selmi C. Ocular involvement in systemic autoimmune diseases. Clin Rev Allergy Immunol. 2015;49(3):263–70.

14. Keino H, Watanabe T, Taki W, Nakashima C, Okada AA. Clinical features and visual outcomes of Japanese patients with scleritis. Br J Ophthalmol. 2010;94(11):1459–63. https://doi.org/10.1136/bjo.2009.171744.

15. Tanaka R, Kaburaki T, Ohtomo K, et al. Clinical characteristics and ocular complications of patients with scleritis in Japanese. Jpn J Ophthalmol. 2018;62(4):517–24. https://doi.org/10.1007/s10384-018-0600-y.

16. Raiji VR, Palestine AG, Parver DL. Scleritis and systemic disease association in a community-based referral practice. Am J Ophthalmol. 2009;148(6):946–50. https://doi.org/10.1016/j.ajo.2009.07.021.

17. Sainz de la Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119(1):43–50. https://doi.org/10.1016/j.ophtha.2011.07.013.

18. Heinz C, Bograd N, Koch J, Heiligenhaus A. Ocular hypertension and glaucoma incidence in patients with scleritis. Graefes Arch Clin Exp Ophthalmol. 2013;251(1):139–42. https://doi.org/10.1007/s00417-012-2108-3.

19. Akpek EK, Thorne JE, Qazi FA, Do DV, Jabs DA. Evaluation of patients with scleritis for systemic disease. Ophthalmology. 2004;111(3):501–6. https://doi.org/10.1016/j.ophtha.2003.06.006.