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Characteristics and Outcomes of Patients with Scleritis in the IRIS® Registry (Intelligent Research in Sight) Database

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Purpose: To report patient characteristics and factors associated with poor visual acuity and abnormal intraocular pressure (IOP) in patients with scleritis in the American Academy of Ophthalmology's IRIS® Registry (Intelligent Research in Sight).

Design: Retrospective cohort study.

Participants: Patients in the IRIS Registry with at least 3 office visits associated with an International Classification of Diseases scleritis code from 2013 through 2019.

Methods: We evaluated demographic and clinical characteristics in scleritis and scleritis subtype cohorts. We conducted Cox proportional hazards and multiple logistic regression analyses to assess associations with poor best-corrected visual acuity (BCVA), vision loss, and IOP abnormalities.

Main Outcome Measures: Patient characteristics, BCVA of 0.6 logarithm of the minimum angle of resolution (logMAR) or more, BCVA worsened by more than 3 logMAR units 6 months after presentation, IOP of 30 mmHg or more, and IOP of 5 mmHg or less.

Results: In this cohort of 111 314 patients with scleritis, the mean ± standard deviation age was 58.5 ± 16.6 years, 66% were women, and 30% had bilateral scleritis. Patients with scleromalacia perforans were older and more likely to have bilateral disease. Multiple logistic regression analysis identified factors with increased odds for poor presenting BCVA (older age, male sex, Black race, Hispanic ethnicity, smoking, and scleritis subtypes) and at least 3 lines of vision loss 6 months after initial scleritis diagnosis (older age, smoking, and anterior scleritis). Cox proportional hazards regression modeling of BCVA of 0.6 logMAR or more showed older age (adjusted hazard ratio [aHR] per 10-year unit, 1.11), Black race (aHR, 1.19), Hispanic ethnicity (aHR, 1.22), active smoking (aHR, 1.39), former smoking (aHR, 1.26), and certain scleritis subtypes increase the risk of poor visual acuity development ($P < 0.001$ for all). Older age, male sex, Black race, Hispanic ethnicity, smoking, and scleritis subtypes increased the odds of IOP abnormality.

Conclusions: Older age, Black or Hispanic ancestry, smoking, and specific scleritis subtypes are risk factors for worse visual and IOP outcomes in patients with scleritis in the IRIS Registry. Closer follow-up may be appropriate for older, Black, or Hispanic patients with scleritis; smokers should receive smoking cessation assistance. *Ophthalmology Science 2022;2:100178 Published by Elsevier on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Scleritis is a rare ocular inflammatory disease with the potential for vision-threatening complications.[1] Population-based studies report scleritis incidence rates ranging from 1.0 to 5.5 cases per 100 000 persons per year.[2–6] Approximately 30% to 40% of scleritis is thought to occur in association with systemic inflammatory diseases[1,5–8]; worse visual outcomes and lower incidence of remission have been reported in patients with an underlying systemic inflammatory condition.[1,8–10]

Ocular complications of scleritis include keratitis, uveitis, glaucoma, corneal and scleral thinning, exudative retinal detachment, and inflammation of posterior segment structures. In severe cases, corneal and scleral thinning can progress to globe perforation and require surgical intervention. Reported complication rates vary widely between prior studies (29%–85%),[1,3–5,7,8,11] with higher frequencies of complications reported in tertiary referral center cohorts than in population-based cohorts.

The American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) is the first comprehensive eye disease clinical database in the United States. It includes data on more than 60 million patients as of September 2019,[12] making it uniquely suited to provide clinical practice data on a rare disease such as scleritis. In this study, we used the IRIS Registry to evaluate demographic and clinical features of patients with scleritis

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and to conduct association testing to identify risk factors for bilateral disease, poor vision, ocular hypertension, and hypotony in scleritis.

Methods

Data Source

This study used de-identified patient data from the IRIS Registry, which contains electronic health record data from United States ophthalmology practices.[13] De-identified data for the study cohort were stored securely in an Amazon Redshift data warehouse. The data were extracted and analyzed using DBeaver software. Because the data are de-identified, the University of Minnesota Institutional Review Board determined that this study is exempt from institutional review board approval and granted a Health Insurance Portability and Accountability Act authorization waiver. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Scleritis Cohort and Subcohorts

The scleritis cohort consists of all patients in the IRIS Registry with at least 3 office visits, identified by 1 of the following current procedural terminology codes associated with any scleritis International Classification of Diseases (ICD), Ninth Revision (ICD-9) or Tenth Revision (ICD-10) code (Table S1) between January 1, 2013, and December 31, 2019 (Fig 1): 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 92002, 92004, 92012, and 92014. We defined index date as the date of the first scleritis ICD-coded office visit. We identified a second scleritis cohort specified only with ICD-10 codes for sensitivity analyses (Table S1). Subcohort inclusion for anterior scleritis, brawny scleritis, posterior scleritis, sclerokeratitis, and scleromalacia perforans similarly required at least 3 office visits with a subtype-specific ICD diagnosis code. Because so few cases of brawny scleritis were found, brawny scleritis was not evaluated as a scleritis subcohort and was not included in statistical analyses.

Patient-Level Variables

Patient-level data included demographics, smoking status, and associated systemic disease diagnoses identified by ICD-9 and ICD-10 diagnosis codes recorded by ophthalmic practices in the IRIS Registry (Table S2). We designated patients as having bilateral scleritis if they had both right eye- and left eye-specified scleritis diagnosis codes. We designated patients as having unilateral scleritis if they had no scleritis diagnosis codes with an unspecified eye and either right eye-specified scleritis diagnosis codes only or left eye-specified scleritis diagnosis codes only.

Eye-Level Variables

Eye-level data included best-corrected visual acuity (BCVA) recorded as logarithm of the minimum angle of resolution (logMAR), intraocular pressure (IOP), ocular disease diagnoses specified by ICD-9 and ICD-10 codes (Table S2), and ocular procedures specified by Current Procedural Terminology codes. We evaluated these variables only for eyes with specified laterality within the scleritis cohort and subcohorts to ensure that the eye-level analyses included only eyes with an associated diagnosis code for scleritis. We determined BCVA for a given visit by selecting the highest ranked of BCVA > refraction > pinhole > uncorrected visual acuity measurement, after excluding all unknown visual acuity values, near visual acuity measurements, and

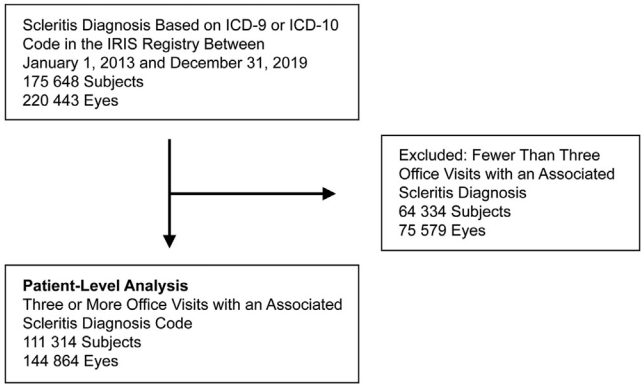

Figure 1. Flow diagram describing the Intelligent Research in Sight (IRIS) Registry selection of the cohort with scleritis. The numbers of unique patients and unique eyes are listed. ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision.

uncorrected visual acuity of more than 0.2 logMAR (Snellen equivalent, worse than 20/32). We selected BCVA of 0.6 logMAR or more as an adverse visual acuity outcome to be consistent with the Snellen 20/80 or worse visual acuity outcome specified in the largest previously reported scleritis cohort.[7]

Data Analysis

Statistical analysis was performed with R software version 4.0.3 (R Foundation for Statistical Computing). Differences in mean age and follow-up duration of scleritis subtypes were evaluated by 1-way analysis of variance with post hoc Tukey's honestly significant difference testing, with P values of less than 0.05 predetermined to meet statistical significance. Density plots were constructed with the ggplot2 package version 3.3.2.[14] Differences in sex, race and ethnicity, smoking, and region between scleritis subtypes and unilateral versus bilateral disease were tested with Pearson's chi-square test. Other and unknown categories were excluded from statistical analyses of demographic characteristics.

We conducted Cox proportional hazards regression and multiple logistic regression analyses to identify variables associated with adverse BCVA and IOP outcomes. Independent variables for these regressions were age, sex, race or ethnicity, smoking status, bilaterality, and scleritis subtype if specified. Index BCVA was included as an independent variable in the Cox proportional hazards regression model and logistic regression model evaluating vision loss at 6 ± 2 months. In patients with bilateral scleritis with both eyes meeting criteria for regression model inclusion, the index BCVA of the patient's poorer-seeing eye was used. We performed Cox proportional hazards regression analysis for poor BCVA using the survival and survminer R packages[15] to evaluate for associations between the independent variables and time to BCVA of 0.6 logMAR or more using data from all patients with scleritis with an index BCVA of less than 0.6 logMAR, at least 1 BCVA value recorded after the index date, and no missing data for the independent variables.

Separate logistic regressions were performed for each of the following dichotomous outcomes: (1) index BCVA of 0.6 logMAR or more, (2) vision loss defined as an increase of more than 0.3 logMAR units between the initial and 6 ± 2-month BCVA in patients with excellent to fair initial visual acuity (index BCVA, < 0.8 logMAR), (3) IOP of 30 mmHg or more at any time, and (4) IOP of 5 mmHg or less at any time. We selected index BCVA of less than 0.8 logMAR for inclusion in the vision loss logistic regression based

Table 1. Demographic Characteristics of Patients with Scleritis in the Intelligent Research in Sight Registry

Characteristic	ICD-9 + ICD-10 Scleritis Cohort (n = 111 314)	ICD-10 Scleritis Cohort (n = 44 315)	Scleritis Subcohorts				Subcohorts Comparison
			Anterior Scleritis (n = 22 467)	*Posterior Scleritis (n = 3423)*	*Sclerokeratitis (n = 1315)*	*Scleromalacia Perforans (n = 2412)*	*P Value**
Age mean ± SD, yrs	58.5 ± 16.6	58.3 ± 16.4	59.2 ± 16.7	55.8 ± 18.2	58.8 ± 18.9	73.3 ± 15.0	< 0.001
Sex							0.01
Female	73 254 (66)	29 052 (66)	14 651 (65)	2265 (66)	812 (62)	1540 (64)	
Male	37 654 (34)	15 085 (34)	7725 (34)	1141 (33)	†	860 (36)	
Unknown	406 (0.4)	178 (0.4)	91 (0.4)	17 (0.5)	†	12 (0.5)	
Race or ethnicity							< 0.001
White	72 819 (65)	26 455 (60)	13 841 (62)	2063 (60)	803 (61)	1602 (66)	
Black	11 706 (11)	5445 (12)	2845 (13)	455 (13)	128 (10)	133 (6)	
Hispanic	8437 (8)	4074 (9)	1801 (8)	329 (10)	121 (9)	321 (13)	
Asian	3495 (3)	1366 (3)	644 (3)	86 (3)	61 (5)	61 (3)	
Other or unknown	14 857 (13)	6975 (16)	3336 (15)	490 (14)	202 (15)	295 (12)	
Smoking status							< 0.001
Active	13 183 (12)	5776 (13)	3053 (14)	598 (17)	168 (13)	246 (10)	
Former	25 323 (23)	9747 (22)	5140 (23)	783 (23)	297 (23)	721 (30)	
Never	69 654 (63)	27 689 (62)	13 665 (61)	1944 (57)	790 (60)	1371 (57)	
Unknown	3154 (3)	1103 (2)	609 (3)	98 (3)	60 (5)	74 (3)	
Region							< 0.001
Midwest	24 414 (22)	8930 (20)	5477 (24)	546 (16)	215 (16)	299 (12)	
Northeast	20 035 (18)	8216 (19)	3814 (17)	755 (22)	302 (23)	432 (18)	
South	41 085 (37)	16 662 (38)	8350 (37)	1381 (40)	504 (38)	713 (30)	
West	18 603 (17)	7890 (18)	3524 (16)	543 (16)	202 (15)	736 (30)	
Unknown	7305 (7)	2665 (6)	1326 (6)	205 (6)	93 (7)	236 (10)	
Follow-up duration (mos)							
Mean ± SD	45 ± 25	39 ± 26	41 ± 26	40 ± 26	42 ± 27	50 ± 23	< 0.001
≥ 6 mos	100 541 (90)	38 538 (87)	19 588 (87)	2974 (87)	1140 (87)	2340 (97)	< 0.001

ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; SD = standard deviation.
Data presented as no. (%), unless otherwise indicated.
*Calculated using 1-way analysis of variance testing for age and follow-up duration and chi-square testing for all other characteristics. Unknown and other categories were excluded from statistical testing.
†Cell count suppressed in accordance with the Centers for Medicare & Medicaid Services Cell Size Suppression Policy.

on United States Social Security Administration disability criteria defining legal blindness as inability to read any letters on the 20/100 line with the better-seeing eye.[16] Logistic regression analyses excluded patients with missing data for the independent variables. The odds ratio (OR), 95% confidence interval (CI), and *P* value were calculated for each independent variable. We evaluated for collinearity using the car package version 3.0-10[17] to calculate the generalized variance-inflation factor[18] for all independent variables in all multivariate logistic regression models and considered a value of less than 3 to be acceptable for model inclusion. Because each regression analysis included 9 or 10 potential predictor variables, we report an adjusted threshold of significance of 0.05 / 9 = 0.0056, rounded down to 0.005, or 0.05 / 10 = 0.005 based on the standard Bonferroni correction.

Results

The study cohort consists of 111 314 unique patients, with 20% of them subclassified as having anterior scleritis, 0.2% as having brawny scleritis, 3% as having posterior scleritis, 1% as having sclerokeratitis, and 2% as having scleromalacia perforans (Table 1). Mean ± standard deviation (SD) age of all patients with scleritis at the time of the initial scleritis-coded IRIS Registry visit was 58.5 ± 16.6 years, with an older age distribution in the scleromalacia perforans subcohort (mean ± SD age, 73.3 ± 15.0 years) and a slightly younger age distribution in the posterior scleritis subcohort (mean ± SD age, 55.8 ± 18.2 years; Fig 2A). Tukey pairwise comparison testing of mean ages between anterior scleritis and other scleritis subtypes showed significant differences in posterior scleritis and scleromalacia perforans (Fig 2B).

The patients with scleritis were predominantly women, with the scleritis cohort and subcohorts being approximately two-thirds women (Table 1). Of all scleritis subtypes, the scleromalacia perforans subcohort showed the highest proportions of White and Hispanic patients, whereas the proportion of Black patients was lower in both scleromalacia perforans and sclerokeratitis cohorts. Most patients with scleritis never smoked (63%). Mean ± SD follow-up duration for the cohort was 45 ± 25 months and 90% had at least 6 months of follow-up after the first

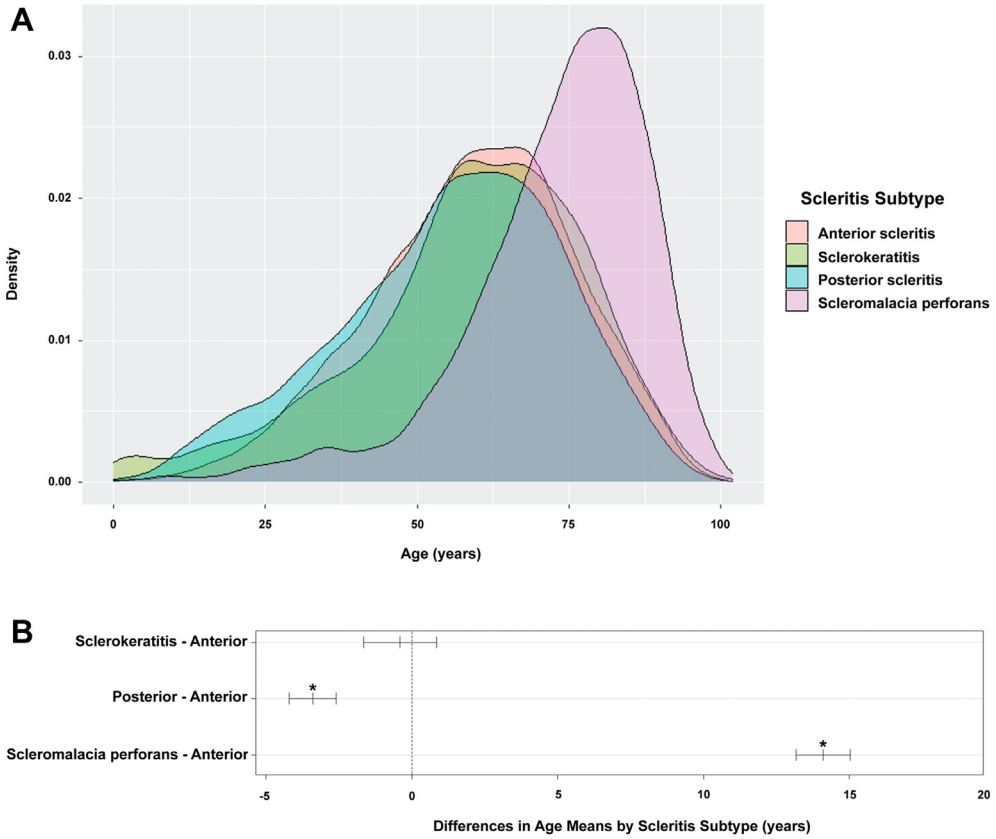

Figure 2. Age distributions in scleritis subtypes in the Intelligent Research in Sight Registry. **A**, Multiple density plot showing age distributions in specified scleritis subtypes. **B**, Differences in age means with 95% family-wise confidence level between anterior scleritis and other specified scleritis subtypes, post hoc Tukey's honestly significant difference test. *Significant at threshold of $P < 0.05$.

date of scleritis diagnosis documented in the IRIS Registry, with a significantly longer mean follow-up in the scleromalacia perforans subcohort compared with other scleritis subtype cohorts ($P < 0.001$, post hoc Tukey's honestly significant difference). Demographic features of the entire scleritis cohort and patients with scleritis identified by ICD-10 codes (ICD-10 scleritis) were similar.

Patients with scleritis with less than 6 months of follow-up in the IRIS Registry tended to be younger (mean ± SD age, 48.4 ± 16.4 years at index) and were more likely to be men, to have better BCVA at presentation, and to have unilateral scleritis than patients with scleritis with 6 months or more of follow-up (mean ± SD] age, 59.6 ± 16.2 years at index; Table S3). The largest differences between those with and without 6 months of follow-up in the race or ethnicity, smoking status, region, and scleritis subtype categories are the proportions of patients with unknown data.

Factors associated with increased odds of bilateral scleritis were female sex, non-White race and Hispanic ethnicity, and specified scleritis subtypes (Table 2). Sensitivity analysis using only patients with scleritis identified by ICD-10 codes identified the same factors (Table S4). Within the specified scleritis subtypes, bilateral disease was more common in scleromalacia perforans (53%) and posterior scleritis (45%; Table S5). Overall, the demographic patterns in bilateral and unilateral disease in the scleritis subtypes were similar to those in the entire scleritis cohort, with the notable exception of scleromalacia perforans, where White race showed increased odds of bilaterality (OR, 1.89; 95% CI, 1.46−2.46).

Five percent of patients with scleritis had a systemic inflammatory disease diagnosis code recorded in the IRIS Registry (Table 3). Rheumatoid arthritis was the most common systemic inflammatory disease in the scleritis cohort (2%), followed by Sjögren syndrome (1%). Antineutrophil cytoplasmic antibody-associated vasculitis was reported uncommonly in the IRIS Registry population with scleritis (0.2%). We found the same percentages in the cohort with ICD-10 codes for scleritis. Although relapsing polychondritis, Behçet disease, systemic sclerosis, polymyalgia rheumatica, polyarteritis nodosa, Takayasu arteritis, polymyositis, dermatomyositis, hidradenitis suppurativa, undifferentiated connective tissue disease, and gout are reported in the study cohort, each of these diagnoses is reported for fewer than 150 patients with scleritis.

Mean BCVA decreased slightly 6 months after initial presentation (Table 4). Elevated IOP and hypotony were uncommon, occurring in 5% and 2% of eyes, respectively; both were more common in scleritis subtypes than in the overall scleritis cohort. A notable portion of eyes with scleritis were reported to have anterior uveitis based on ICD coding (14% in the scleritis cohort). Posterior

Table 2. Comparison of Bilateral versus Unilateral Scleritis in the Intelligent Research in Sight Registry

Characteristic	Bilateral (n = 20 781)	Unilateral (n = 47 620)	Bilateral Odds Ratio* (95% Confidence Interval)	*P* Value*
Age (yrs), mean ± SD	57.6 ± 16.3	58.8 ± 16.4	1.00 (0.99–1.00)	< 0.001
Sex				< 0.001
Female	14 057 (68)	30 988 (65)	1 (reference)	
Male	6645 (32)	16 462 (35)	0.89 (0.86–0.92)	
Race or ethnicity				< 0.001
White	12 534 (60)	31 244 (66)	1 (reference)	
Black	2638 (13)	4704 (10)	1.40 (1.33–1.47)	
Hispanic	1858 (9)	3583 (8)	1.29 (1.22–1.37)	
Asian	696 (3)	1498 (3)	1.16 (1.06–1.27)	
Smoking status				0.69
Never	12 900 (62)	29 744 (62)	1 (reference)	
Active	2514 (12)	5812 (12)	1.00 (0.95–1.05)	
Former	4863 (23)	11 030 (23)	1.02 (0.98–1.06)	
Scleritis subtype				< 0.001
Anterior	4458 (21)	8582 (18)	1.42 (1.37–1.48)	
Posterior	931 (5)	1134 (2)	2.25 (2.06–2.46)	
Sclerokeratitis	264 (1)	431 (0.9)	1.68 (1.44–1.96)	
Scleromalacia perforans	721 (3)	639 (1)	3.10 (2.78–3.45)	
Unspecified	13 451 (65)	36 898 (77)	1 (reference)	

SD = standard deviation.
Data presented as no. (%), unless otherwise indicated.
*Calculated using logistic regression for age and chi-square tests for all other characteristics.

segment manifestations (optic disc edema, cystoid macular edema, and serous retinal detachment) were more common in posterior scleritis than in other subtypes. Descemetocele, scleral ectasia, or scleral staphyloma were reported in only 0.3% of eyes; these complications were more common in defined scleritis subtypes, particularly scleromalacia perforans. The reported rate of ocular perforation was 1%, and the rate of globe removal was less than 1 in 1000. We found similar rates of these ocular characteristics in the cohort with ICD-10 codes for scleritis.

Of the 77 325 patients with scleritis with BCVA recorded in at least 1 specified eye, 13 140 (17%) had BCVA of 0.6 logMAR or more, corresponding to Snellen visual acuity of 20/80 or worse, in at least 1 specified eye. In 4686 patients, this poor visual acuity outcome occurred at the index date. Multiple logistic regression analysis of patients with index BCVA of 0.6 logMAR or more showed that older age, male sex, Black race, Hispanic ethnicity, smoking, and all scleritis subtypes evaluated (anterior scleritis, posterior scleritis, sclerokeratitis, and scleromalacia perforans) increase the

Table 3. Systemic Inflammatory Disease Diagnoses in Patients with Scleritis in the Intelligent Research in Sight Registry

Systemic Disease*	Cohort with ICD-9 + ICD-10 Scleritis Codes (n = 111 314)	Cohort with ICD-10 Scleritis Codes (n = 44 315)
Any systemic inflammatory disease	5010 (5)	2090 (5)
Rheumatoid arthritis	1672 (2)	693 (2)
Sjögren syndrome	1141 (1)	384 (1)
Systemic lupus erythematosus	530 (0.5)	173 (0.4)
Vogt-Koyanagi-Harada disease	394 (0.4)	348 (0.8)
Giant cell arteritis	324 (0.3)	128 (0.3)
Sarcoidosis	289 (0.3)	103 (0.2)
Inflammatory spondylarthropathy	256 (0.2)	100 (0.2)
Multiple sclerosis	228 (0.2)	72 (0.2)
Inflammatory bowel disease	191 (0.2)	72 (0.2)
ANCA-associated vasculitis	190 (0.2)	102 (0.2)
Juvenile idiopathic arthritis	180 (0.2)	111 (0.2)

ANCA = antineutrophil cytoplasmic antibody; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision.
Data are presented as no. (%).
*Table does not list systemic inflammatory diseases diagnosed in fewer than 150 patients in the cohort with ICD-9 + ICD-10 scleritis codes. Patients with scleritis may have more than 1 systemic inflammatory disease diagnosis.

Table 4. Ocular Characteristics of Specified Scleritis Eyes in the Intelligent Research in Sight Registry

Ocular Characteristic	ICD-9 + ICD-10 Scleritis Codes (n = 101 951)	ICD-10 Scleritis Codes (n = 53 579)	Anterior Scleritis (n = 22 054)	Posterior Scleritis (n = 3689)	Sclerokeratitis (n = 1204)	Scleromalacia Perforans (n = 2429)
BCVA at index (logMAR)	0.19 ± 0.38	0.21 ± 0.41	0.20 ± 0.37	0.34 ± 0.57	0.39 ± 0.66	0.37 ± 0.59
BCVA 6 mos after index (logMAR)	0.23 ± 0.45	0.25 ± 0.50	0.23 ± 0.46	0.32 ± 0.58	0.43 ± 0.73	0.51 ± 0.77
IOP ≤ 5 mmHg	1822 (2)	1296 (2)	462 (2)	185 (5)	66 (5)	148 (6)
IOP ≥ 30 mmHg	5454 (5)	3644 (7)	1515 (7)	326 (9)	97 (8)	231 (10)
Anterior uveitis	14 705 (14)	9367 (17)	4593 (21)	1015 (28)	188 (16)	207 (9)
Optic disc edema	500 (0.5)	290 (0.5)	88 (0.4)	106 (3)	*	*
Cystoid macular edema	5303 (5)	3469 (6)	1509 (7)	722 (20)	85 (7)	204 (8)
Serous retinal detachment	955 (1)	766 (1)	252 (1)	399 (11)	*	24 (1)
Descemetocele, scleral ectasia, or staphyloma	335 (0.3)	259 (0.5)	102 (0.5)	36 (1)	11 (0.9)	68 (3)
Ocular perforation or laceration	1039 (1)	874 (2)	421 (2)	221 (6)	39 (3)	40 (2)
Globe removal	67 (0.07)	52 (0.1)	16 (0.07)	*	*	*

BCVA = best-corrected visual acuity; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision.
Data presented as no. (%) or mean±standard deviation, unless otherwise indicated.
*Cell count suppressed in accordance with the Centers for Medicare & Medicaid Services Cell Size Suppression Policy.

odds of poor presenting visual acuity (Table 5). Sensitivity analysis utilizing the cohort with ICD-10 scleritis codes identified the same factors as significant except that anterior scleritis was no longer significant at the $P < 0.005$ level.

We analyzed risk factors for substantial vision loss as defined by worsened BCVA in at least 1 eye of more than 0.3 logMAR units (indicating loss of at least 3 lines of vision) between the index date and 6 ± 2 months. Of the 29 502 patients with scleritis with BCVA of less than 0.8 logMAR (Snellen equivalent, better than 20/125) recorded at index and a BCVA measurement recorded 6 ± 2 months after index, 1425 patients (5%) demonstrated substantial vision loss. Multiple logistic regression analysis of this outcome showed that older age, smoking, and anterior scleritis all increased odds of 6-month vision loss after adjusting for bilateral disease and initial BCVA (Table 5). In the cohort with ICD-10 scleritis codes, older age and active smoking increased the odds of 6-month vision loss after adjusting for bilateral disease and initial BCVA.

To evaluate vision loss more broadly, we used survival analysis. Time to reach the outcome of BCVA of 0.6 logMAR or more ranged from 0 to 83 months after index. Cox proportional hazards regression modeling of this outcome showed that older age, Black race, Hispanic ethnicity, smoking, anterior scleritis, posterior scleritis, and sclerokeratitis all increase the risk of poor visual acuity development after adjusting for bilaterality and index BCVA (Table 6). Sensitivity analysis utilizing the cohort with ICD-10 scleritis codes identified the same significant risk factors except that anterior scleritis was no longer significant at the $P < 0.005$ level.

Elevated IOP (≥ 30 mmHg) was more common than low IOP (≤ 5 mmHg; Table 4). These conditions were associated significantly (OR, 13.34; 95% CI, 12.04−14.78; $P < 0.001$, Pearson's chi-square test). Not surprisingly, given the strong association between these 2 outcome variables, similar predictor variables were associated with elevated IOP and low IOP. The odds of both conditions were increased with older age, male sex, Black race, Hispanic ethnicity, smoking, and scleritis subtypes (Table 7). The odds for IOP abnormality were increased with the same factors except for anterior scleritis in the cohort with ICD-10 scleritis codes.

Discussion

This study used the large volume of data available in the IRIS Registry to assess demographic and clinical features of scleritis in a large clinical population and to identify features associated with reduced visual acuity and abnormal IOP. The scleritis cohort comprised 66% women, which concurs with previous work showing a female predominance in scleritis.[1,2,4,7] The mean age of patients with scleritis in this cohort, 58.5 years, is consistent with other population-based[3–5,11] and cohort-based[1,7,8] studies, where scleritis was most common in patients in their forties to sixties. Similarly, our finding of a younger age distribution in posterior scleritis is consistent with the previously reported younger age at presentation in posterior compared with anterior scleritis.[19]

However, a novel finding in our study is the substantially older age distribution in scleromalacia perforans. Prior studies evaluating scleromalacia perforans have reported mean ages of 61.1 and 50.9 years,[7,8] or most cases occurring in the fifth decade of life,[20] but these studies are limited by small sample

Table 5. Multiple Logistic Regression Analyses of Poor Visual Outcomes in Scleritis Patients in the Intelligent Research in Sight Registry

	Best-Corrected Visual Acuity ≥ 0.6 logMAR at Index		Best-Corrected Visual Acuity Loss (> 0.3 logMAR) at 6 Months	
Variable	*Cohort with ICD-9 + ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*	*Cohort with ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*	*Cohort with ICD-9 + ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*	*Cohort with ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*
Age, 10-yr unit	1.37 (1.33–1.40)*	1.34 (1.30–1.38)*	1.12 (1.08–1.17)*	1.16 (1.10–1.23)*
Sex				
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	1.17 (1.10–1.26)*	1.15 (1.06–1.26)*	1.04 (0.92–1.17)	1.01 (0.86–1.18)
Race				
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Black	1.42 (1.29–1.56)*	1.49 (1.32–1.67)*	1.08 (0.91–1.27)	0.99 (0.80–1.23)
Hispanic	1.61 (1.44–1.79)*	1.72 (1.51–1.95)*	1.31 (1.08–1.59)†	1.36 (1.07–1.71)†
Asian	1.03 (0.84–1.25)	1.10 (0.85–1.40)	0.93 (0.65–1.29)	1.30 (0.85–1.90)
Smoking status				
Never	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Active	1.59 (1.45–1.74)*	1.59 (1.42–1.78)*	1.29 (1.09–1.53)*	1.48 (1.20–1.82)*
Former	1.15 (1.07–1.24)*	1.13 (1.02–1.25)†	1.22 (1.06–1.39)*	1.25 (1.05–1.49)†
Bilaterality	1.08 (1.00–1.16)†	1.05 (0.96–1.15)	1.28 (1.13–1.45)*	1.32 (1.13–1.55)*
Index BCVA, 0.1-logMAR unit	N/A	N/A	1.07 (1.05–1.08)*	1.06 (1.04–1.07)*
Anterior scleritis	1.41 (1.31–1.52)*	1.10 (1.00–1.20)†	1.36 (1.20–1.55)*	1.23 (1.05–1.43)†
Posterior scleritis	4.30 (3.80–4.85)*	3.42 (2.99–3.91)*	1.33 (1.03–1.70)†	1.14 (0.85–1.51)
Sclerokeratitis	4.41 (3.60–5.37)*	3.72 (3.00–4.59)*	1.67 (1.06–2.51)†	1.60 (0.99–2.46)†
Scleromalacia perforans	2.58 (2.19–3.03)*	2.24 (1.87–2.68)*	1.28 (0.90–1.77)	1.15 (0.78–1.66)

BCVA = best-corrected visual acuity; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; logMAR = logarithm of the minimum angle of resolution; N/A = not applicable.
Best-corrected visual acuity of ≥ 0.6 logMAR at index regressions included all patients with BCVA recorded at index and no missing data for any of the variables: n = 55 663 for the cohort with International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision scleritis codes and n = 27 811 for the cohort with International Classification of Diseases, Tenth Revision scleritis codes. Best-corrected visual acuity loss at 6-month regressions included all patients with BCVA of < 0.8 logMAR recorded at index, BCVA recorded 6 ± 2 months after index, and no missing data for any of the variables: n = 24 319 for the cohort with International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision scleritis codes and n = 12 803 for the cohort with International Classification of Diseases, Tenth Revision scleritis codes.
*Significant at $P < 0.005$ with Bonferroni correction ($\alpha/10$).
†Significant at $P < 0.05$.

sizes (n < 15). The mean age of 73 years for patients with scleromalacia perforans in this IRIS Registry cohort is notably different. One possible reason for this difference may be that patients with more severe cases of scleromalacia perforans seek treatment at a younger age at academic referral centers than does the more broadly representative IRIS Registry participant base. Another unique finding made possible by the large number of patients with scleromalacia perforans in the present study compared with prior cohorts[7,8,20] is the increased odds of bilateral disease in the scleromalacia perforans subtype (OR, 3.10; 95% CI, 2.78–3.45). Furthermore, the increased odds for bilateral disease in White patients within the scleromalacia perforans cohort suggests that this patient population requires particularly close monitoring.

The large size of this IRIS Registry cohort with scleritis also allows robust analysis of patient factors associated with adverse visual acuity and IOP outcomes. Older age, Black race, Hispanic ethnicity, smoking, and specific scleritis subtypes increased the odds for both vision- and IOP-related adverse outcomes in this cohort. Our report identified older age as a risk factor for worse visual outcomes in scleritis in addition to increasing the odds of hypotony and ocular hypertension. Our study also identified race/ethnicity as a factor associated with poor visual and IOP outcomes in scleritis. Studies assessing the relationship between race or ethnicity and scleritis outcomes are limited. Two recent cohort studies examined the remission of anterior scleritis and assessed the impact of race or ethnicity: one did not find an association,[9] whereas the other found that Hispanic patients achieved scleritis resolution faster than White or Black patients and that Black race was associated negatively with steroid-sparing resolution.[21] Whether differences in scleritis outcomes are related to the known disparities in eye care access and use produced by the intersection of race and socioeconomic status[22] or other causes requires additional study. Finally, although IOP abnormalities were relatively uncommon, the correlation between hypotony and ocular hypertension demonstrates the necessity of close IOP monitoring throughout the disease course in scleritis because therapeutic needs may change.

Table 6. Cox Proportional Hazards Regression Analysis of Best-Corrected Visual Acuity of 0.6 logMAR or More among Patients with Scleritis in the Intelligent Research in Sight Registry

Variable	Cohort with ICD-9 + ICD-10 Scleritis Codes		Cohort with ICD-10 Scleritis Codes	
	Adjusted Hazard Ratio (95% Confidence Interval)	P *Value*	*Adjusted Hazard Ratio (95% Confidence Interval)*	P *Value*
Age, 10-yr unit	1.11 (1.08–1.13)	< 0.001	1.09 (1.06–1.13)	< 0.001
Sex				
Female	1 (reference)		1 (reference)	
Male	1.06 (1.00–1.13)	0.04	1.02 (0.94–1.11)	0.65
Race				
White	1 (reference)		1 (reference)	
Black	1.19 (1.10–1.29)	< 0.001	1.23 (1.11–1.37)	< 0.001
Hispanic	1.22 (1.12–1.34)	< 0.001	1.19 (1.05–1.35)	0.005
Asian	1.02 (0.86–1.20)	0.86	1.10 (0.88–1.38)	0.42
Smoking status				
Never	1 (reference)		1 (reference)	
Active	1.39 (1.29–1.51)	< 0.001	1.48 (1.34–1.65)	< 0.001
Former	1.26 (1.18–1.34)	< 0.001	1.24 (1.13–1.36)	< 0.001
Bilaterality	1.45 (1.37–1.54)	< 0.001	1.41 (1.30–1.53)	< 0.001
Index BCVA, 0.1-logMAR unit	1.72 (1.69–1.74)	< 0.001	1.71 (1.67–1.75)	< 0.001
Anterior scleritis	1.17 (1.10–1.25)	< 0.001	1.09 (1.01–1.19)	0.03
Posterior scleritis	1.64 (1.45–1.85)	< 0.001	1.52 (1.32–1.74)	< 0.001
Sclerokeratitis	1.60 (1.27–2.01)	< 0.001	1.57 (1.22–2.02)	< 0.001
Scleromalacia perforans	1.04 (0.89–1.22)	0.62	1.07 (0.89–1.28)	0.50

BCVA = best-corrected visual acuity; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; logMAR = logarithm of the minimum angle of resolution.
All patients with index BCVA of less than 0.6 logMAR, at least 1 BCVA measurement after index date, and no missing data for any of the variables were included in the analysis: n = 51 016 for the cohort with International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision scleritis codes and n = 24 797 for the cohort with International Classification of Diseases, Tenth Revision scleritis codes.

Table 7. Multiple Logistic Regression Analyses of Elevated and Low Intraocular Pressures in Patients with Scleritis in the Intelligent Research in Sight Registry

Variable	Intraocular Pressure ≥ 30 mmHg		Intraocular Pressure ≤ 5 mmHg	
	Cohort with ICD-9+ ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)	*Cohort with ICD-10Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*	*Cohort with ICD-9+ ICD-10 Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*	*Cohort with ICD-10Scleritis Codes Adjusted Odds Ratio (95% Confidence Interval)*
Age, 10-yr unit	1.13 (1.10–1.15)*	1.11 (1.08–1.14)*	1.27 (1.23–1.33)*	1.29 (1.23–1.34)*
Sex				
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	1.50 (1.41–1.60)*	1.50 (1.39–1.63)*	1.44 (1.30–1.59)*	1.38 (1.22–1.57)*
Race				
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Black	1.87 (1.72–2.03)*	1.61 (1.46–1.78)*	1.58 (1.37–1.82)*	1.46 (1.23–1.72)*
Hispanic	1.47 (1.32–1.63)*	1.37 (1.22–1.54)*	1.63 (1.39–1.91)*	1.47 (1.22–1.77)*
Asian	0.98 (0.81–1.18)	0.99 (0.79–1.23)	1.29 (0.96–1.70)	1.26 (0.89–1.74)
Smoking status				
Never	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Active	1.49 (1.36–1.62)*	1.49 (1.34–1.65)*	1.60 (1.39–1.85)*	1.53 (1.29–1.81)*
Former	1.16 (1.08–1.25)*	1.17 (1.06–1.28)*	1.20 (1.06–1.35)*	1.15 (0.99–1.33)
Bilaterality	2.24 (2.10–2.40)*	1.42 (1.31–1.54)*	1.68 (1.50–1.88)*	1.05 (0.92–1.20)
Anterior scleritis	1.55 (1.45–1.66)*	1.12 (1.03–1.21)†	1.61 (1.43–1.81)*	1.16 (1.01–1.32)†
Posterior scleritis	2.07 (1.81–2.36)*	1.49 (1.29–1.72)*	4.11 (3.45–4.88)*	2.95 (2.43–3.55)*
Sclerokeratitis	1.87 (1.48–2.32)*	1.47 (1.14–1.85)*	3.86 (2.91–5.03)*	3.16 (2.35–4.17)*
Scleromalacia perforans	1.82 (1.54–2.13)*	1.34 (1.10–1.62)*	3.46 (2.82–4.22)*	2.39 (1.87–3.03)*

All patients with no missing data for any of the variables were included in the analysis: n = 93 924 in the cohort with International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) scleritis codes and n = 36 465 in the cohort with International Classification of Diseases, Tenth Revision scleritis codes.
*Significant at $P < 0.005$ with Bonferroni correction ($\alpha/9$).
†Significant at $P < 0.05$.

Another key finding in our multivariable regressions is the consistent association between smoking and adverse outcomes in patients with scleritis. Smoking is a reported risk factor for greater disease activity in uveitis,[23] and our results suggest that smoking also may impact the severity and comorbidity of scleritis. Smoking was identified as a risk factor for all adverse vision and IOP outcomes in patients with scleritis after adjusting for other predictor variables. The OR or hazard ratio consistently was higher for active smoking than for former smoking in all vision and IOP analyses. These results suggest that smoking cessation may be beneficial for scleritis outcomes and should be recommended to patients with scleritis.

Study Limitations

Only 5% of patients in the IRIS Registry scleritis cohort had a systemic inflammatory disease diagnosis, lower than prior estimates in tertiary care center scleritis cohorts (33%–39%),[1,7,8] a community-based referral practice (36%),[24] and population-based studies of scleritis (23%–41%),[3,5,11] although similar to the Northern California Epidemiology of Uveitis Study (6%).[4] Because the IRIS Registry extracts ICD-9 and ICD-10 diagnosis codes from ophthalmology practice visits, this low rate of concurrent systemic inflammatory disease may reflect intrinsic underreporting, rather than a true lack of associated systemic conditions in the patient population. Despite this limitation, rheumatoid arthritis was the most common systemic inflammatory disease associated with scleritis, in concordance with prior studies.[1,3,5,7,8,11,20,24,25] The second most common systemic inflammatory disease in our cohort, Sjögren syndrome, was identified in association with scleritis in 2 recent studies,[6,25] but had not been reported in previous tertiary center series.[1,7,8,20] We hypothesize that the known ocular manifestations in Sjögren syndrome may increase the reporting rate of Sjögren syndrome compared with other systemic inflammatory conditions in eye office visit coding. Although this may lead to a proportional overestimation of Sjögren syndrome within this scleritis cohort, our findings still support including Sjögren syndrome in the assessment for etiologic conditions in patients with scleritis.

An additional limitation inherent in the IRIS Registry is that race and ethnicity analyses are limited by electronic health record reporting. Within the scleritis cohort, 87% of patients had specified race or ethnicity, and 13% were categorized as other or unknown; this unknown proportion is higher than in other demographic characteristics evaluated. We evaluated demographic and clinical features, including adverse vision and IOP outcomes, and found these to be similar in the subset of patients with scleritis with unspecified race or ethnicity compared with the scleritis cohort (Table S6). Although we cannot exclude the possibility of systematic bias, the similarities between those with unspecified race or ethnicity and the scleritis cohort are reassuring. Our findings indicate that race and ethnicity may be important for scleritis outcomes, and we urge evaluation of these factors in future scleritis studies.

Finally, like other big data studies of de-identified patient data, this study depends on coding performed by others. Because the IRIS Registry database does not currently include examination elements for the sclera and anterior segment, ICD codes cannot be compared with examination findings for diagnosis verification. A prior study of the predictive value of ICD-9 codes for scleritis or episcleritis identified a positive predictive value of 60%; however, a large proportion of the miscoding was made by non-eye specialists.[26] Two strengths of the present study are use of ophthalmic practice coding using the IRIS Registry and cohort inclusion criteria requiring multiple office visits associated with a scleritis ICD code. Additionally, the present study improves selection for scleritis by using ICD-9 codes more specific than the 379.0 ICD-9 code used in prior studies,[26,27] which codes for episcleritis as well as scleritis. Our study used 379.00, but not 379.0, to limit episcleritis cases. A large portion of this cohort was not subclassified into secondary scleritis subtypes, likely because the general ICD-9 scleritis code 379.00 and ICD-10 scleritis codes H15.00x are billable codes. As clinicians become comfortable with more specific ICD-10 coding, scleritis subtype specification may become more commonplace.

In conclusion, this analysis of scleritis in the IRIS Registry revealed novel findings and confirmed several previously reported demographic features and complications of scleritis. This study highlights that the characteristics of scleromalacia perforans differ substantially from other scleritis subtypes. Although the overall rate of severe ocular complications such as ocular perforation was low, the complication rate is particularly important considering the IRIS Registry practice composition, which is weighted toward community-based practice. Older age, Black race, Hispanic ethnicity, smoking, and certain scleritis subtypes are risk factors for worse vision and IOP outcomes in scleritis. Additional work is needed to delineate how these risk factors impact disease outcomes and optimize therapeutic approaches in these higher-risk populations.

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Author Contributions:

Conception and design: Armbrust, Kopplin

Analysis and interpretation: Armbrust, Kopplin

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Abbreviations and Acronyms:
aHR = adjusted hazard ratio; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **ICD** = International Classification of Diseases; **ICD-9** = International Classification of Diseases, Ninth Revision; **ICD-10** = International Classification of Diseases, Tenth Revision; **IOP** = intraocular pressure; **IRIS** = Intelligent Research in Sight; **logMAR** = logarithm of the minimum angle of resolution; **OR** = odds ratio; **SD** = standard deviation.

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