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**Epidemiology of Disease-activity Related Ophthalmological Manifestations in Systemic
Lupus Erythematosus: A Systematic Review**

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Abstract

Objective

Ophthalmic complications in SLE are broad and can occur in up to a third of patients. The British Isles Lupus Assessment Group (BILAG) 2004 Index identifies 13 ocular manifestations of active SLE, as opposed to those related to previous disease activity and/or the consequences of therapy. We conducted a systematic review of published literature to determine the frequency of ophthalmic manifestations of active SLE.

Methods

A systematic literature search of Ovid MEDLINE and EMBASE from their respective inceptions to July 2020 was conducted to identify cohort, case-control and cross-sectional studies.

Results

22 studies meeting eligibility criteria were included. Most studies featured small sample sizes and were judged to have a high risk of methodological bias. The number and quality of studies did not allow us to confidently estimate the incidence of the conditions.

No studies reported epidemiological data for orbital inflammation/myositis/proptosis. The prevalence of each of the other ocular manifestations, with the exception of retinal vaso-occlusive disease, was consistently less than 5%. Retinal vasculitis, uveitis and isolated cotton wool spots tended to be associated with more active SLE disease.

Conclusion

The prevalence of eye disease due to SLE activity is uncommon, but clinicians should be aware that some conditions tend to be associated with more active systemic disease.

Further studies to determine the incidence and risk factors for these ophthalmic manifestations are needed.

Key Words:

Systematic review, SLE, BILAG, ophthalmic, epidemiology, prevalence

Key Messages:

- 1)** Ophthalmic manifestations of active SLE are uncommon.
- 2)** Clinicians should remain vigilant in certain groups of SLE patients due to associated morbidity including permanent visual loss.
- 3)** Further research is needed to elucidate incidence of activity-related eye disease in modern SLE cohorts.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune inflammatory disorder associated with the presence of autoantibodies to nuclear antigens. SLE has an increased prevalence in females and those of African, Caribbean and Hispanic backgrounds.¹

Ocular manifestations of SLE are broad and can affect the front and back of the eye or its adnexa. They can occur due to active SLE disease; secondary to SLE-mediated damage to related tissue; as a consequence of SLE therapy; or due to other comorbidities associated with SLE such as Sjogren's syndrome. Although ocular involvement from all these causes is estimated to occur in up to one-third patients with SLE,² inflammatory ocular disease specifically due to active SLE may be much less common.

It is important to distinguish between ocular disease due to active SLE, and those from other causes. The former, whilst rare, often warrants urgent and intensive topical or systemic immunosuppressive therapy as untreated it may result in rapid irreversible visual impairment.³ Despite the importance of this distinction, there has been confusion among clinicians regarding which specific ocular pathologies represent manifestations of active SLE.

The British Isles Lupus Assessment Group (BILAG) index was developed to help clinicians identify and score features of active SLE across the major body systems, including the ophthalmic system. The most recent iteration, the BILAG-2004, has become a well-validated, comprehensive tool for the assessment of SLE disease activity.⁴⁻⁶ In this index, severe manifestations (A scores) are considered to have a significant risk of visual loss whilst

those scoring B are likely to prompt a change in therapy (following the intention-to-treat principle of the index).

Within the BILAG-2004, there are thirteen specific ocular manifestations of active SLE (Table 1; also see supplementary files in Yee et al.⁷).

The incidence and prevalence of SLE in cohorts of patients with ophthalmic pathologies is relatively well-studied. For example, in a literature review of patients with uveitis, the prevalence of SLE was reported at 0.47%.⁸ Similarly, the prevalence of SLE in patients with scleritis typically ranges between 2% to 4.1%.^{9,10} However, much less is known about the incidence and prevalence of these manifestations in patients with an antecedent diagnosis of SLE.

In summary, ocular manifestations in SLE are numerous. Some of these ocular pathologies are due to active SLE (rather than secondary to SLE-mediated damage to related tissue, consequence of SLE therapy, or other conditions associated with SLE). These SLE disease-activity related ocular pathologies are particularly important to identify as they warrant prompt immunosuppression to prevent potentially rapid and permanent visual loss. The BILAG-2004 provides an evidence-based consensus in listing thirteen specific ocular conditions thought to represent SLE-disease activity. Epidemiological data are needed to determine the frequency of these potentially sight-threatening manifestations to better inform clinical care.

The aim of this systematic review was therefore to determine the incidence and prevalence of the thirteen disease-activity related ophthalmic conditions as listed in the BILAG-2004 index in patients with SLE.

Methods

This systematic review was registered with the International Prospective Register of Systematic Reviews¹¹ (PROSPERO Registration Number CRD42020159610).

Eligibility criteria: We included cohort, cross-sectional and case-control original research studies. We restricted ourselves to full articles in the English language. There was no restriction by type of study setting, geographical location or by publication date.

No minimum number of patients were required for study inclusion, provided that the ophthalmic condition was not identified prior to patient inclusion (for example in case reports or case series).

Population: We included data derived from observational studies of patients with a diagnosis of SLE (including childhood or adolescent-onset SLE) predating eye disease onset.

We excluded studies of participants with other concomitant autoimmune connective tissue diseases or overlap syndromes, and cutaneous, drug-induced or neonatal lupus, as the pathophysiology is fundamentally distinct from SLE.¹²⁻¹⁴

Exposure: Studies were included if patients with SLE fulfilled any of the versions of one of the following classification criteria: American College of Rheumatology (ACR) Criteria,¹⁵ Systemic Lupus International Collaborating Clinics (SLICC) Criteria,¹⁶ International Classification of Diseases (ICD),¹⁷ European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria.¹⁸ Older studies were also included if

they predated these criteria but the diagnosis was made by a rheumatologist and/or included pathological diagnosis such as the presence of LE cells.^{19,20}

Comparators: Where reported, a sample of subjects without SLE (or other autoimmune connective tissue disease) were used for comparison. We included studies without control groups or comparators if they otherwise met our eligibility criteria.

Outcomes: We extracted the incidence (including incidence rates and ratios, incidence proportions and odds ratios) and prevalence data for the ophthalmic pathologies listed in BILAG-2004 index (Table1). Other eye pathologies due to co-morbidities, therapies or lupus damage (e.g. keratoconjunctivitis sicca and hydroxychloroquine-induced lupus retinopathy) rather than active SLE disease were excluded.

Based on an initial scoping review, it was deemed not possible to differentiate between mild and severe ophthalmic pathologies as listed in the BILAG-2004 index and so these were combined. Where reported, subject-level data and definition of outcome were examined in studies concerning isolated cotton-wool spots to ensure patients with other pre-existing retinal pathologies were not included. Studies in which there was insufficient information to make this distinction were excluded.

Study search and data extraction

We searched Ovid MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R); from inception [1946] to present) and Ovid EMBASE (from inception [1974] to present); with the final search conducted on 15th July 2020. There were no search restrictions applied through Ovid's interface. Terms from Ovid's expert search

filters for observational studies²¹ were incorporated into our search strategy to help focus the number of retrieved results within our screening capacity. The detailed search strategy is listed in Supplementary Table S1. The search strategies were peer-reviewed by a healthcare librarian with expertise in literature searches who was not otherwise associated with the project.

Two researchers, NJ and JW, independently screened the titles and abstracts identified from the search strategy, whilst blinded to the decisions of the other. The full article was sought for all studies that potentially met the eligibility criteria or could not be confidently excluded. Discrepancies in the final list of studies included were resolved by discussion. JR arbitrated any non-resolved discrepancies. To maximise the chance of literature saturation, we scanned for additional relevant articles in the reference lists of retrieved studies. Our data extraction pro-forma (see Supplementary Table S2) was adapted from recommendations from COSMOS-E guidance²² and the published literature²³. The items in the proforma were stipulated in our protocol prior to data collection.

One researcher (NJ) extracted data from eligible studies, with one other researcher (JW) checking for errors. Discrepancies were resolved by discussion. Two researchers (NJ and JW) independently assessed the methodology of eligible studies. After forming a global subjective impression of risk of bias, studies were rated as 'high', 'moderate' or 'low' risk by each researcher, whilst blinded to the decisions of the other. The Joanna Briggs Institute checklists²⁴ were used to help inform our assessments. Sources of funding and declarations of conflicts of interest were also considered as part of the overall risk assessment.

Thereafter, inter-rater discrepancies were resolved by discussion with JR arbitrating any unresolved disagreements.

Significant heterogeneity amongst studies precluded a meta-analysis, therefore a narrative synthesis has been used to summarise and explain findings.

Results

After excluding 4 studies where the full article was unavailable in English,²⁵⁻²⁸ we identified 22 eligible studies (5 prospective cohort, 5 retrospective and 12 cross-sectional)²⁹⁻⁵⁰ (Figure 1). Most studies (13/22) were judged to carry a high risk of bias. Individual studies are summarised in the Supplementary Table S2. All studies were either cohort or cross-sectional; no case-control studies were retrieved.

The number of SLE patients in these studies ranged between 8 and 29,690. The number of different eye manifestations reported in each study varied between 1 and 6 (Figure 2). The most commonly reported anterior segment eye pathologies were episcleritis and anterior uveitis (Figure 3). Retinal vaso-occlusive disease and isolated cotton wool spots were the most commonly reported posterior eye pathologies (Figure 4).

Of the 22 studies, 18 were included in our quantitative summary (Table 2). The other 4 studies reported outcomes that were not directly comparable with other studies in their group; Aletaha et al.⁴⁹ and Dubois et al.³⁷ did not differentiate between anterior and posterior uveitis, Yen et al.⁵⁰ reported the incidence of retinal vein occlusion rather than retinal vaso-occlusive disease, and Frith et al.³⁸ considered only recurrent episcleritis. These studies have nonetheless been included in our narrative summary below.

Incidence

There is a paucity of data regarding the incidence of inflammatory eye disease in patients with SLE, with no data for 5 of the 11 outcomes. The incidences of the remaining six outcomes (Table 2) - anterior uveitis, retinal vasculitis, retinal vaso-occlusive disease, isolated cotton wool spots, optic neuropathy and anterior ischaemic optic neuropathy -

were informed by one of two studies,^{30,34} both of which were conducted in the 1980s with limited demographic information regarding their cohort.

There were additionally two large cohort studies retrieved that investigated the incidence of uveitis (anterior and posterior combined)⁴⁹ and retinal venous occlusion⁵⁰ which did not directly align with the 13 manifestations of interest. Although the BILAG-2004 considers anterior and posterior uveitis separately, and the retinal vaso-occlusive disease item does not distinguish between arterial and venous pathologies, these 2 large studies were felt to provide important data.

Aletaha et al.⁴⁹ conducted a retrospective cohort study in the USA of 29,690 adult SLE patients and >19 million controls (matched for age, sex and insurance plans) which reported an incidence rate (IR) for uveitis of 3.7 per 1000 person-years (PY) and Incidence Rate Ratio (IRR) of 9.3. When 2 claims against the ICD-9 criteria (rather than 1) were used to define the outcome, the IR was 1.2 per 1000 PY, with an IRR of 4.0. The IR of 0.4 per 1000 PY (0.3 per 1000 PY with the more stringent uveitis diagnostic criteria) in the control group, is within to the range of 0.17-0.52 per 1000 per year reported by other studies in the general population.⁵⁶

Yen et al.⁵⁰ conducted a retrospective cohort study in Taiwan analysing cases of RVO that met the ICD-9 diagnostic criteria. The study featured 6,756 SLE patients (followed for 39,208 person-years) and 40,536 non-SLE controls (24,6945 person-years) matched for age, gender and index date from a national health insurance research database. The incidence of RVO was 5.61 patients per year, with an IRR (95%CI) of 3.46 (2.01 to 5.83).

Prevalence

Orbital inflammation/myositis/proptosis

There were no studies meeting our eligibility criteria that reported the prevalence of these conditions orbital inflammation/myositis/proptosis.

Episcleritis and scleritis

The largest study⁴² was a retrospective cross-sectional review of 179 patients from two US veterans' affairs hospitals, where none of the SLE patients had episcleritis or scleritis.

Duration and severity of lupus disease, treatment received, and the autoantibody profiles of the patients were not reported.

The prevalence of episcleritis ranged between 0 to 4.2% across four other studies.^{29, 32, 39, 41}

They featured small sample sizes (range 24-89 participants) and had a high risk of bias as (i) patients were selected from ophthalmology referrals rather than random sampling³² (ii) SLE diagnoses predating the ACR criteria³⁹ or (iii) repeated measures per patient.⁴¹

Frith et al.³⁸ reported that 28% (5/18) of patients with SLE who had ocular symptoms or signs had recurrent episcleritis. The duration of mean (range) duration of disease was 11.6 (0.75-31) years but it is unclear if any of the patients had active systemic disease at the time of recruitment.

One other study⁴³ observed two scleritis cases in patients with an antecedent diagnosis of SLE [prevalence = 2.0% (2/98)], both of whom were ANA positive. Scleritis can be classified as anterior or posterior (the former can be subclassified into diffuse, nodular and

necrotising/non-necrotising forms).⁵¹ Both patients had non-necrotising anterior scleritis, one diffuse and the other nodular subtype. High-resolution ultrasound biomicroscopy, however, revealed that the patient with the initial diagnosis of diffuse (anterior) scleritis subsequently had episcleritis.

Keratitis

The prevalence of keratitis was reported as 0.56% (1/179) and 4.1% (4/98) in two studies of 179⁴² and 98⁴³ patients respectively. In the latter, half (2/4) of affected patients (2% (2/98) of the total SLE sample) had peripheral ulcerative keratitis (PUK), a subtype recognised to occur in association with systemic autoimmune disease and carry a poorer prognosis.⁵² This is similar to the overall prevalence of PUK observed in other autoimmune disorders (1.8% (2/112) in relapsing polychondritis⁵³ and 1.0% (6/589) in rheumatoid arthritis,⁵⁴ and higher than the 0.02% observed in the general population.⁵⁵

Uveitis

Kahwage et al.⁴⁸ found the prevalence of uveitis to be 0.82% (7/852) in their multicentre study of childhood-onset SLE in Brazil. This was the only study that used the Standardization of Uveitis Nomenclature (SUN) anatomical classification of uveitis.⁵⁷ Most patients (4/7 [57%]) had only posterior uveitis, 2/7 (29%) had purely anterior uveitis, and 1/7 (14%) had panuveitis. Conversely in the general population, anterior uveitis is most common accounting for 46% of paediatric uveitis (mostly juvenile idiopathic uveitis).⁵⁸

This study also featured a control group (n=73) randomly chosen from SLE patients without uveitis. There were no significant differences in the age, SLE duration, treatment or autoantibody profile between the uveitis patients and control groups but SLE disease activity (SLEDAI-2K score) was significantly higher (median [range] 19 [15-39] vs. 6 [0-41], p=0.009) in patients with uveitis.⁴⁸

Anterior Uveitis

In Kahwage et al.⁴⁸ the overall prevalence of anterior uveitis was 0.35% (3/852). Anterior uveitis includes both iritis (inflammation of the iris) and iridocyclitis (with further extension to involve the ciliary body).⁵⁷ Drosos et al.³⁴ reported 3 patients with anterior uveitis, 2 of whom were classified as iridocyclitis. The number of anterior uveitis cases were also small in two other studies (1/52³³ and 2/70³⁶); but all were iridocyclitis.

Posterior Uveitis (including pan-, intermediate and posterior uveitis)

In the large study by Kahwage et al.,⁴⁸ the overall prevalence of posterior uveitis was 0.59% [5/852] compared to 0.16% in the general population⁵⁹).

Retinal vasculitis

Retinal vasculitis, without occlusion, warrants prompt immunosuppression and is associated with poor visual prognosis. Typically presenting as painless reduction in visual acuity, a number of features on retinal examination including perivascular sheathing, haemorrhage, and intraretinal and perivascular infiltrates are described.⁶⁰

The prevalence of retinal vasculitis ranged from 0-2.9% across four studies,^{29, 31, 35, 45} none featured general population controls. Moreover, there is a paucity of data for the prevalence of retinal vasculitis in the general population for comparison. The highest prevalence was in Ushiyama et al.³⁵ (2.9%, 2/69). The mean maximum SLEDAI score since SLE diagnosis was 17.5, suggesting that patients had severe disease.

IgG anti-cardiolipin antibodies were detected in both the patients with vasculitis. In the remaining patients without vasculitis that were tested, 41% (24/59) were IgG anti-cardiolipin antibody positive; due to the low numbers of patients with vasculitis (n=2), however, valid statistical analysis for significant difference in the frequency of IgG anti-cardiolipin antibodies between patients with and without vasculitis is not possible. Both patients who developed vasculitis had only recently been diagnosed with SLE, with a mean of 8.5 months between SLE and vasculitis diagnoses.

In a different study conducted in Egypt, no patients (0/40) were observed to have retinal vasculitis.²⁹ However the lupus population here were younger [mean (SD) age = 13(2.8) years] and with milder SLE activity [mean (SD) SLEDAI score = 4.3(3.1)].

Retinal/choroidal vaso-occlusive disease

The prevalence of retinal vaso-occlusive disease ranged from 0-7.31%, across 8 studies.^{29, 31, 33, 36, 43, 44, 45, 47} The largest study⁴⁷ of 5298 Chinese patients with SLE identified a prevalence of 0.23% (12/5298). A control group of 70 SLE patients without any ophthalmological manifestations were randomly selected from the original sample. The frequency of lupus anticoagulant (LA) [33% (4/12) v.s. 12% (8/66)] and IgG anticardiolipin

antibodies, [25% (3/12) v.s. 13% (9/69)] were numerically higher in SLE patients with vaso-occlusive disease than those without, although this was not statistically significant. In the single patient with retinal vaso-occlusive disease in Dammaco et al.,⁴³ anti-cardiolipin and anti-β2GPI antibodies (both IgM and IgG) were positive.

Isolated cotton wool spots (ICWS)

The prevalence of ICWS was <0.1% across 4 out of the 5 studies in this group. The largest of these comprised 5298 SLE patients in China with a prevalence of 0.08% (4/5298);⁴⁷ 3 patients had ICWS in both eyes, but the 4th patient had ICWS in only one eye (with cotton-wool spots as well as intraretinal haemorrhages in the other eye). This large retrospective review reported patients (and eyes affected) separately which may influence the accuracy of the results.

Several studies noted a possible association between cotton-wool spots and overall SLE disease severity. In the above study by Gao et al.,⁴⁷ the mean SLEDAI score was 21 in 4 patients with ICWS compared to 10.2 in 70 patients without. Montehermoso et al.⁴⁴ did not use a disease activity index but reported both patients with ICWS (n=2) had active disease compared to 48% of their control population (n=82).

In all studies reporting one or more patients with ICWS, patients with (or retinal lesions related to) diabetes mellitus or systemic hypertension were excluded.

Optic neuritis

The prevalence of optic neuritis in the SLE population ranged from 0 – 2.3% across three studies, compared to 0.12% in the general population.⁶¹ Kampylafka et al.⁴⁶ identified a single patient (1/370; 0.27%) with optic neuritis as part of neuromyelitis optica (NMO), confirmed by positive IgG anti-NMO/Aquaporin-4 antibodies. NMO spectrum disorders (NMOSD) may co-exist with, or precede, other autoimmune connective tissue diseases (CTDs), notably SLE and Sjogren's syndrome.^{62,63} Indeed, 'CTD-NMOSD' overlap syndromes may be a distinct clinical entity and should be considered in SLE patients diagnosed with optic neuritis.⁶⁴

Anterior ischaemic optic neuropathy (AION)

The BILAG-2004 index only considers AION secondary to thromboembolic occlusion of the posterior ciliary arterial system.⁶⁵

In our review, the prevalence of AION ranged from 0-1.22% across two medium risk of bias studies,^{42,44} though it is unclear in either if the cases would have met the BILAG-2004 index definition. Although the latter study had a small sample size (n=82), none of the control group (without autoimmune disease) developed AION. The single patient who developed AION in the SLE group had long-standing SLE (31 years duration), but not active disease at the time of diagnosis; the IgG anti-cardiolipin antibodies were positive.

The aetiologies of AION are generally grouped into arteritic AION (an uncommon cause, almost always associated with temporal arteritis) and non-arteritic ION (the major group, of

which hypoperfusion through the posterior ciliary system is thought to be the leading aetiology in the general population rather than thromboembolic occlusion as in SLE).⁶⁶

Data regarding the prevalence of AION in the general population is sparse, but in one South Korean study the prevalence of non-arteritic AION was 0.1%.⁶⁷ We know of no published literature, however, describing the prevalence of thromboembolic non-arteritic AION in the general population for meaningful comparison.

Discussion

Of those outcomes (incidence of uveitis, prevalence of anterior and posterior uveitis, incidence of retinal vein occlusion) which had both good quality data for both SLE patients and the general population, or control data for comparison, the incidence/prevalence was approximately 3-4 times greater in the SLE population. Overall, the prevalence of ocular manifestations of active SLE is low at less than 5% in all but one study.

The scoring of ophthalmic manifestations in the BILAG 2004 index requires both a diagnosis by an ophthalmologist and that features are attributed to active lupus.^{6,7} Only 14 out of our 22 retrieved studies specifically state the diagnosis was made at an ophthalmology department or that an ophthalmologist was involved. There is a risk of under-reporting in our analysis as 9 studies did not state the specific ocular or neuro-ophthalmic outcomes as defined in BILAG 2004. A further 7 studies localised areas of their interest e.g. corneal/external ocular, vasculopathy, retinopathy, though details regarding specific pathologies of interest *a priori* were absent.

Relatively few studies (around 25%) defined the age of their study population. Three studies^{29,33,48} involved patients with childhood-onset SLE, two of which only included patients <18 years of age.^{29,33} The median age of SLE patients in other studies (where data was provided) suggests predominantly adult, or at least mixed adult-paediatric populations. It is well recognised that childhood-onset SLE differs from adult onset in terms of clinical phenotypes, autoantibodies (notably anti-cardiolipin) and severity.⁶⁸ It remains unclear whether the incidence or prevalence of ocular manifestations also differs between children and adults.

The publication dates of the studies ranged from 1964 to 2019. The ACR criteria (or its revisions) were used in most studies, but some also used the ICD criteria^{42,49,50} or presence of LE cells.^{37,39} These factors may have exacerbated heterogeneity in the SLE populations studied.

We were unable to directly compare the incidence or prevalence of eye manifestations in SLE to the general population, as the majority of studies did not feature a comparable non-SLE control group. The detail of the baseline and demographic data also varied significantly between studies. Notably, data on immunosuppressive regimens and autoantibody profiles of patients were sparse, making it impossible to identify associations between the ocular outcomes and autoantibodies or concomitant therapy.

In terms of geographic populations, studies originating from North America and Europe were well represented in our review. In contrast, Africa was poorly represented, with only two small studies.^{29,40} This is likely to reflect the existing SLE literature as a whole. Similarly, the ethnicity of patients was under-reported in the studies. As there is evidence that SLE complications and their severity are greater in populations of Black African and Caribbean origin,¹ this represents a particular limitation of the available data.

Further research is needed to understand the long-term effects of ocular manifestations on morbidity and quality of life. Visual acuity scores were most often reported in patients with retinal vaso-occlusive disease who invariably presented with a degree of visual loss. A single study,⁴⁴ reporting the best correct visual acuity at presentation and follow-up, demonstrated permanent visual acuity defects in the affected eye of most patients with

retinal vaso-occlusive disease suggesting that this manifestation in particular may be associated with permanent reduction in vision or visual loss.

Some ophthalmic manifestations, particularly retinal vasculitis, ICWS and uveitis, were associated with more active SLE disease. In BILAG-2004, ICWS due to systemic hypertension or diabetes mellitus should not be scored; all studies of ICWS in this review excluded patients with retinal lesions attributed to these conditions. Clinicians should carefully consider whether eye involvement is present in patients who present with a systemic flare of disease as if unrecognised and/or untreated some manifestations (such as vaso-occlusive disease) can be sight-threatening. Similarly, retinal vaso-occlusive disease (and possibly AION) may be an important but uncommon manifestation of secondary antiphospholipid syndrome in patients with SLE.

There are other important eye manifestations of active SLE that are not considered in the BILAG-2004 ophthalmic domain, the epidemiology of which are beyond the scope of this study. For example, intracranial hypertension, has been reported in association with severe SLE and lupus nephritis⁶⁹ and may be associated with sight-threatening papilledema.

Conclusion

Overall eye disease was uncommon and incidence data of eye manifestations of active SLE is sparse with few studies conducted in recent years. It is difficult to determine therefore whether changes to the management of SLE, including use of biological drugs, have influenced the outcome. Given the risk of permanent visual loss, clinicians should remain vigilant for eye manifestations especially in patients with active systemic disease or anti-phospholipid antibodies.

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Conflicts of Interest:

Caroline Gordon reports in 2020-2021 personal fees for honoraria from consultancy work from Amgen, Astra-Zeneca, Center for Disease Control, MGP, Sanofi and UCB.

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Figure 1

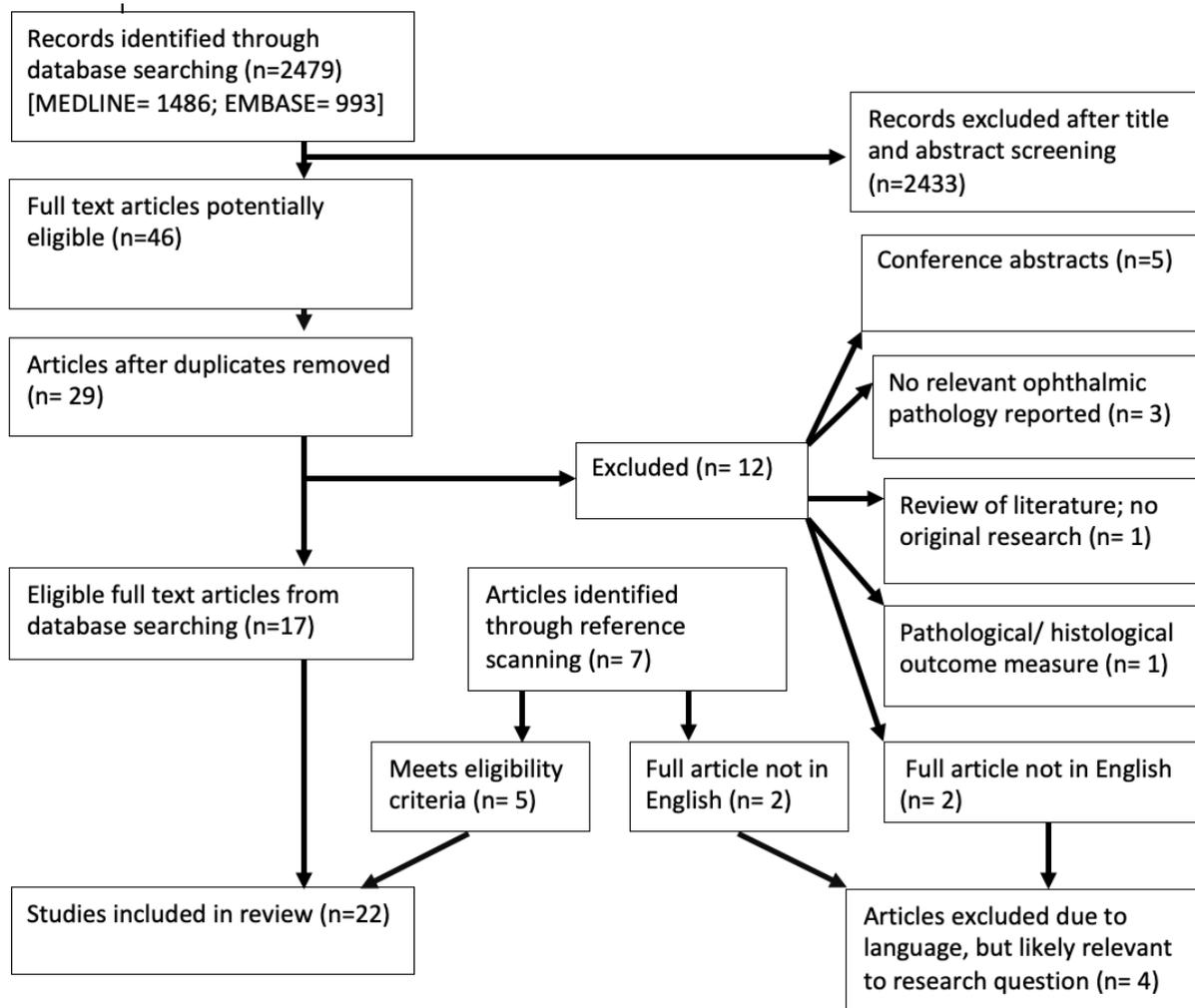


Figure 1: Flow diagram of the review process from identification of database records to final inclusion.

Flow diagram of the review process from identification of database records to final

Figure 2

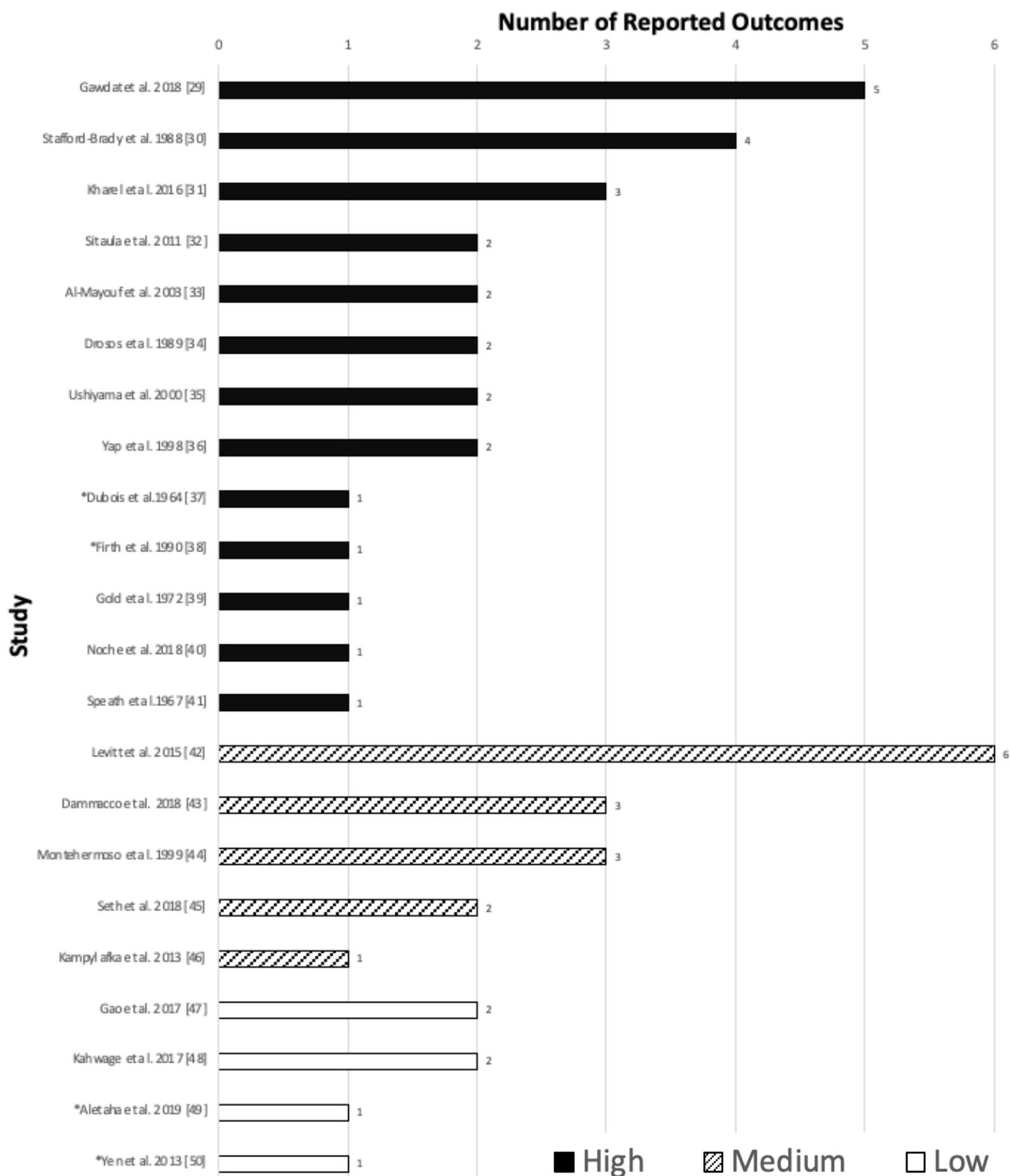


Figure 2: The number of outcomes reported in each of the 22 retrieved studies meeting our eligibility criteria.

Figure 3

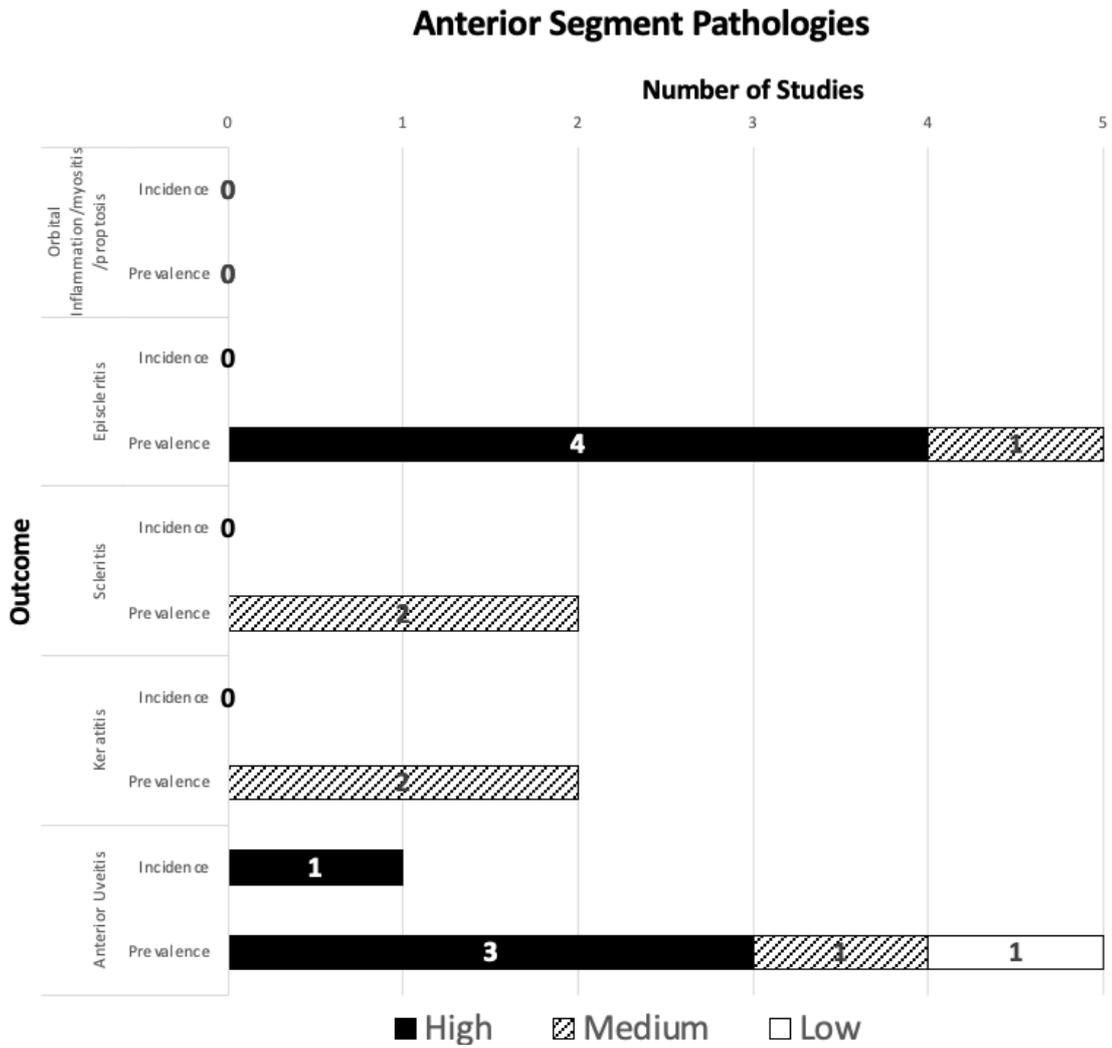


Figure 3: The number of studies per each (anterior eye segment) pathology of

Figure 4

Posterior Segment Pathologies

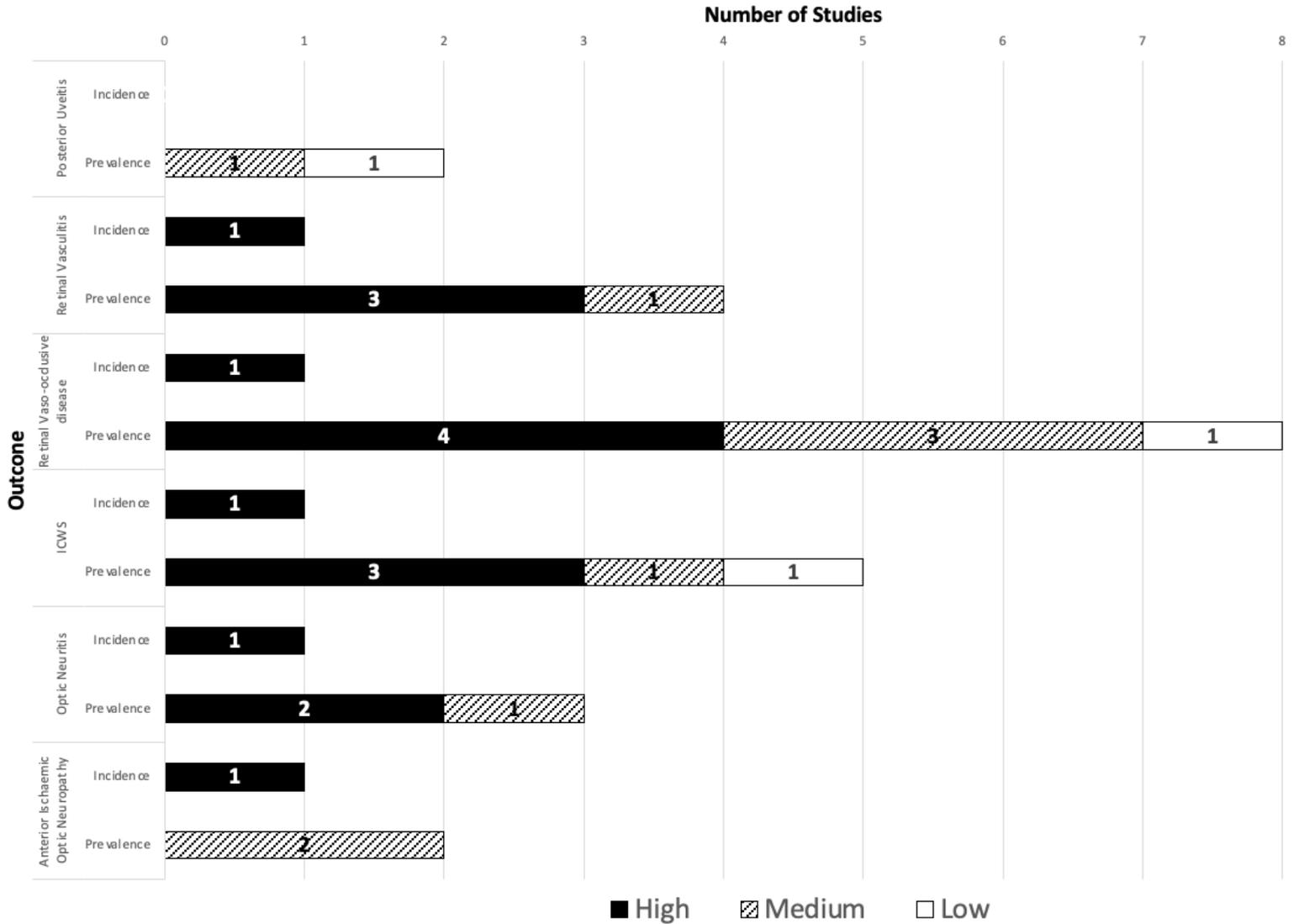


Figure 4: The number of studies per each (anterior eye segment) pathology of interest.

Table 1

Orbital inflammation/myositis/proptosis
Episcleritis
Scleritis - severe
Scleritis – mild
Keratitis - severe
Keratitis - mild
Anterior uveitis
Posterior uveitis/retinal vasculitis - severe
Posterior uveitis/retinal vasculitis - mild
Retinal/choroidal vaso-occlusive disease
Isolated cotton-wool spots (cytoid bodies)
Optic neuritis
Anterior ischaemic optic neuropathy

Table 1 - The thirteen SLE-disease activity related ophthalmic pathologies in the BILAG-2004.

Table 2

Anterior Segment Pathologies													
Outcome	Epidemiology	Number of Studies	No. Retrospective /No. Prospective	Risk of Bias	Publication Dates	Geographic Location	SLE group Sample sizes	Adult/Paediatric	Range of average ages	Range - %Female	Range - SLE duration	Range - SLE Severity	Incidence/Prevalence
Orbital inflammation/myositis/proptosis	Incidence							No studies retrieved					
	Prevalence							No studies retrieved					
Episcleritis	Incidence							No studies retrieved					
	Prevalence	5	1/4	High - 4; Medium - 1	1967-2018	Nepal, USA, Egypt	24-179	Adult - 1; not stated -4	13-26.6 (3)	80-96 (4)	22.6 months (1)	SLEDIAI-2K - 4.3 points (1)	0-4.2%
Scleritis	Incidence							No studies retrieved					
	Prevalence	2	2/0	Medium - 2	2015-2018	USA, Italy	98-179	Adult - 1; not stated - 1	33 years (1)	92 (1)	Not stated (2)	SELENA-SLEDIAI 2005 - 9.1 (1)	0-2.0%
Keratitis	Incidence							No studies retrieved					
	Prevalence	2	2/0	Medium - 2	2015-2018	USA, Italy	78-179	Adult - 1; not stated - 1	33 years (1)	92 (1)	Not stated (2)	SELENA-SLEDIAI 2005 - 9.1 (1)	0.56-4.1%
Anterior Uveitis	Incidence	1	1/0	High	1989	Greece	112	Not stated	Not stated	Not stated	Not stated	Not stated	2.7% over 7 years
	Prevalence	5	3/2	High - 3; Medium - 1; Low - 1	1998-2018	Brazil, Cameroon, USA, Singapore, Saudi Arabia	52-852	Adult - 1; Childhood-onset SLE - 1; Paediatric - 1; Not stated - 2	11.3-32.9 (4)	87-94 (4)	Not stated (5)	SLEDIAI-2K - 6 (1); SLEDIAI - 9.5(1)	0-2.9%
Posterior Segment Pathologies													
Outcome	Epidemiology	Number of Studies	No. Retrospective /No. Prospective	Risk of Bias	Publication Dates	Geographic Location	SLE group Sample sizes	Adult/Paediatric	Range of average ages	Range - %Female	Range - SLE duration	Range - SLE Severity	Parameter
Posterior Uveitis	Incidence							No studies retrieved					
	Prevalence	2	2/0	Low - 1; Medium -1	2015-2017	Brazil, USA	179-852	Adult - 1; Childhood-onset SLE (diagnosed before the age of 18years) - 1	12.5 (1)	92 (1)	4 months (1)	SLEDIAI-2K - 6 (1)	0-0.59%
Retinal Vasculitis	Incidence	1	0/1	High - 1	1988	Canada	550	Adult (>=18y/o)	Not stated	Not stated	Not stated	Not stated	0.36% over 15 years
	Prevalence	4	0/4	High -3; Medium - 1	2000-2018	Nepal, Japan, India, Egypt	40-437	Paediatric-onset (5-18 at recruitment) - 1; Not stated - 3	13-41 (4)	80-95 (4)	12 months (1)	SLEDIAI-2K - 4.3 (1)	0-2.9%
Retinal Vaso-occlusive Disease	Incidence	1	0/1	High - 1	1988	Canada	550	Adult (>=18y/o)	Not stated	Not stated	Not stated	Not stated	0.36% over 15 years
	Prevalence	7	2/5	High - 4; Medium - 3; Low - 1	1998-2018	Singapore, China, Spain, Egypt, Saudi Arabia, Italy, Nepal	40-5298	Paediatric-onset (5-18 at recruitment) - 1; Paediatric clinic - 1; Not stated - 6	11-36 (7)	80-95 (7)	12-88 months (2)	SLEDIAI - 9.5-10.2 (2); SLEDIAI-2K 4.3 (1); SELENA-SLEDIAI - 9.1 (1)	0-7.3%
Isolated Cotton-wool Spots	Incidence	1	0/1	High -1	1988	Canada	550	Adult (>=18y/o)	Not stated	Not stated	Not stated	Not stated	3.6% over 15 years
	Prevalence	5	1/5	High - 3, Medium - 1; Low - 1	1999-2018	China, Japan, Nepal, Spain, Egypt	40-5298	between 5-18 years old at recruitment - 1, Not stated - 4	13-40.7 (4)	80-95 (4)	88 months (1)	SLEDIAI-2K - 4.3 (1)	0-2.4%
Optic Neuritis	Incidence	1	1/0	High -1	1989	Greece	112	Not stated	Not stated	Not stated	Not stated	Not stated	0.89% over 7 years
	Prevalence	3	0/3	High - 2; Medium -1	2011-2018	Nepal, Egypt, Greece	40-370	Children <18 at time of recruitment - 1; Not stated - 2	13-32 (3)	80-94 (3)	22-108 months (2)	SLEDIAI-2K - 4.3 points (1); SELENA-SLEDIAI - 3.6 (1)	0-2.3%
Anterior Ischaemic Optic Neuropathy	Incidence	1	0/1	High -1	1988	Canada	550	Adult (>=18 years old).	Not stated	Not stated	Not stated	Not stated	0.36% over 15 years
	Prevalence	2	1/2	Medium - 2	1999-2015	USA, Spain	82-179	Adult - 1; Not specified -1	36 years (1)	94 (1)	88 months (1)	Not stated (2)	0-1.2%

Table 2: Summary of the incidence and prevalence for each of the ophthalmic BILAG outcomes observed across relevant studies.

The publication date, country, sample sizes and outcome statistics were extracted from every study. Other demographic data were variably reported across studies; numbers in () brackets indicate the number of studies reporting the demographic.