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Title: The incidence of sympathetic ophthalmia after trauma: A meta-analysis

Running short title: Sympathetic ophthalmia after trauma

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Highlights:

- Incidence of sympathetic ophthalmia (SO) after open globe injury is unclear.
- The incidence proportion of SO after open globe injury was 0.19%.

The incidence rate of SO after open globe injury is 33 per 100,000 person-years.

ABSTRACT

Purpose

Sympathetic ophthalmia (SO) is a rare, bilateral panuveitis that occurs following open globe injury (OGI), with a variable incidence reported in the literature. Our objective was to determine the incidence proportion and incidence rate of SO following OGI to help guide shared physician-patient decision making.

Design

Systematic review and meta-analysis.

Methods

A systematic literature search was performed using the MEDLINE, EMBASE, and Cochrane databases from inception to November 2020 for population-based studies on OGI and SO in adults and children. Two reviewers independently screened search results. Random-effects meta-analyses were performed to calculate the incidence proportion and incidence rate. The Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool was used to assess the risk of bias. The study was registered on PROSPERO CRD42020198920.

Results

A total of 24 studies were utilized in the meta-analyses. After OGI, the estimated overall incidence proportion of SO was 0.19% (95% CI 0.14%-0.24%) and the incidence rate of SO was 33 per 100,000 person-years, (95% CI 19.61-56.64) with I^2 of 13% and 72%, respectively.

Conclusions

SO after OGI is rare. The estimated incidence proportion and incidence rate are useful when counselling patients regarding management options after OGI. Further studies are needed to examine the influence of age, the extent and location of trauma, timing of repair, and prophylactic eye removal on the incidence of SO.

Key words: Sympathetic ophthalmia; systematic review; meta-analysis; globe injury, ocular trauma; ophthalmology; uveitis

INTRODUCTION

Sympathetic ophthalmia (SO) is a rare, bilateral, granulomatous panuveitis that occurs following accidental or surgical penetrating eye trauma.[1] The injured eye is designated the exciting eye and the contralateral eye that develops uveitis is labelled the sympathizing eye.[2] The exact pathophysiology of SO remains indeterminate, although it is thought to be an autoimmune T cell-mediated reaction against the normally sequestered ocular antigens which become exposed to the systemic immune system through traumatic or surgical disruption of the blood-retinal barrier.[3] Patients with SO typically present with symptoms of blurry vision, pain, epiphora, and photophobia in the sympathizing eye.[4] The classic signs of SO include conjunctival injection and granulomatous uveitis with mutton-fat keratic precipitates and choroidal Dalen-Fuchs nodules. There may also be vitritis, papillitis, retinal vasculitis, and exudative retinal detachment.[5]

The onset of SO can be acute or insidious, and presents days to years after the inciting event. Most cases of SO occur within one year and often have recurrent periods of exacerbation.[6] SO is a serious global public health concern as it can cause bilateral vision loss in patients who otherwise would not have any vision-related morbidity. Moreover, the disease can be extremely challenging to manage for uveitis specialists, with many patients requiring multiple immunosuppressing agents and even eventually becoming steroid dependent. Unfortunately, the disease is often undertreated or refractory to treatment, and subsequent blindness ensues.[7] It was traditionally thought that a severely traumatized eye with poor potential for vision should be prophylactically

removed within 2 weeks of the injury, although this has now become controversial.[8] The prevailing contemporary opinion is to recommend that prophylactic eye removal should not be performed unless globe repair is not possible and there is little potential for vision in the traumatized eye.[9,10] At present, the mainstay treatment is immunosuppressive therapy with systemic and topical corticosteroids for initial treatment of the uveitis, and steroid-sparing agents once the inflammation is controlled.[11,12,3]

Despite its clinical significance, the incidence of SO is not well delineated in the literature in part due to its rarity, which makes SO challenging to study. From individual studies, the incidence proportion of SO after open globe injury varies from zero[13-24] up to 7.6%[25], but these studies are heterogeneous. The determination of a more reliable incidence proportion for SO and an incidence rate following open globe injury (OGI) is important to ascertain so that patients can be accurately informed of their risk, to guide shared patient-physician decision making with regards to management options, and for epidemiologic surveillance. The goal of our study was to determine the global incidence proportion and incidence rate of SO following OGI in the adult and pediatric populations.

METHODS

Search strategy

A systematic literature search for all articles relevant to SO from inception to November 1, 2020, was performed using MEDLINE, EMBASE, Cochrane, and grey literature databases. Specific search strategies were used for each database and were tested by an academic librarian. Restrictions were applied to only include English

language articles. There were no publication status restrictions. Authors of studies in which full-text articles could not be obtained were contacted for additional information. This study was exempt from ethics review and was registered with PROSPERO (ID# CRD42020198920).

Eligibility and exclusion criteria

Search terms used for identifying the articles were keywords and MeSH terms for: “sympathetic ophthalmia,” “open-globe injury,” “penetrating trauma,” “uveitis,” “trauma,” and “globe rupture” (Table 1). Articles were included if they explicitly addressed the presence or absence of SO among their study group. Articles were excluded if they were not published in English; did not have human subjects as their study participants; were a systematic, literature, or scoping review; did not investigate incidence or epidemiological rates of SO; or did not report a total population as their denominator.

Data selection and extraction

The literature review process was conducted per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) procedures. Two reviewers (BH and ST) independently screened search results using Covidence (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org) for title, abstract and full-text screening. Research items that did not meet inclusion criteria were removed from the study. Discrepancies were resolved by discussion and consultation with a third reviewer (EI).

For each of the included studies, information on the study's total population denominator (ie. all patients with OGI during the time period of the study); country of origin; and demographic characteristics of its SO cases including age, sex, mechanism of traumatic injury, primary surgical interventions, and mean duration of follow-up in years were noted independently by two reviewers (BH and ST).

Information from three abstracts (Savar, 2009; Shah, 2011; and Gilbert, 2014) with overlapping data from the same subjects was combined in our analysis.[26,27] The pediatric information update was added to Shah's study group and only the adult information from Gilbert et al.'s abstract was listed. Since Savar et al.'s study comprised of 92% (660/721) of the adult population from Gilbert et al.'s abstract,[28] the 660 overlapping patients were substituted for the missing details in Gilbert's abstract.

Risk of bias and study quality assessment

Two reviewers (BH and ST) independently assessed the risk of bias in each included study for quality analysis. The Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool was used to assess the risk of bias. Five domains of bias (selection, attrition, detection, performance, and reporting) were assessed for each study and recorded (Table 2). Biases were graded as low, moderate, serious, or indeterminate. The studies' patient population, exposures, outcomes, confounding variables, and analysis methods were assessed to evaluate bias in each study.

Statistical methods for the meta-analysis

The *metarate* function in the R package (R: 4.04 with meta package: 4.17, R Foundation for Statistical Computing, Vienna, Austria, 2013) was used to perform a

meta-analysis of single incidence rates.[29] A generalized linear mixed model (GLMM), specifically, a Poisson regression model was used for the pooling of studies. For study-specific incidence rates, a log transformation of the incidence rates was used, and a continuity correction of 0.5 was applied for any study that had zero events but not in the GLMM.[30]

The *metaprop* function in Stata (Stata 15.1, College Station, Texas) was used to perform a meta-analysis of proportions to determine the incidence proportion.[31] A 0.25 continuity correction as suggested in the literature[32] was used for zero cells. A p-value of less than 0.05 was considered to be statistically significant. The I^2 statistic was used to evaluate statistical heterogeneity among studies,[33] and values of 0–24%, 25–49%, 50–74%, and greater than 75% were denoted as no, low, moderate, and high heterogeneity, respectively.[34]

RESULTS

Systematic review and demographic results

A total of 3,336 articles were retrieved from the literature search, and after removing duplicates (2,236), there were 1,100 unique citations. Screening of the titles and abstracts by two review authors (BH and ST) resulted in the removal of 926 items. The remaining 174 studies underwent a second round of screening of the full text by two authors (BH and ST) which excluded 150 full-text articles. This led to a total of 24 studies that were included in the meta-analysis. A PRISMA flow diagram outlining this process is shown in Figure 1.

From the 24 eligible studies with OGI patients, there was a total of 93 cases of SO from an overall denominator of 37,684 patients, leading to a raw proportion of 0.25% (Table 3). The median population denominator of the studies was 150, with an average of 1,570.

The average age was 40.5 years in the nineteen adult papers and 9.4 years in the five pediatric papers. The median study duration was 9.5 years with an average of 8.4 years. There was no statistically significant difference in the study duration of series that did or did not report SO after OGI (p=0.868).

The twenty-four papers analyzed in our study represented every continent except South America and Antarctica. Eight studies were from North America, six from East Asia, six from other parts of Eurasia, three from Oceania, and one from Africa. There was insufficient detail in the studies to compare the incidence of SO as a function of the location of trauma (i.e., anterior versus posterior), type of trauma (i.e., blunt versus penetrating), or extent of injury (i.e., globe rupture, penetration, perforation, or intraocular foreign body).

Half (n=12) of our SO studies, which comprised of 1,455 cases of OGI, did not report any cases of SO. Eleven of these studies had data on gender of study subjects suffering OGI, in which the weighted proportion of male patients was 76.9%. Ten of these studies had a weighted average age of 34.1 years, with 42.7 years in the eight adult studies and 6.4 years in the two pediatric studies.

With respect to the remaining twelve studies that reported cases of SO, eight of them had data on gender, in which 33 (77%) of the 43 patients were male. Four of these

studies also provided data on age, with a weighted average age of 31.2 years of age across 36 patients, with 42.5 years in the three adult studies and 13.3 years in the one pediatric study. The similarity in age and gender between the OGI series without SO and with SO support the notion that young men may be more prone to OGI but not necessarily to SO once OGI has occurred.

Overall, more than three-quarters of the subjects with SO were male, and the median age was 37 years old, which reflect the typical demographics of the OGI population.[35] Further studies are needed to assess demographic differences in the onset and development of SO.

Meta-analysis of incidence studies

After OGI, the incidence proportion of SO for adults and children as a group was 0.19% (95% CI 0.14%-0.24%) with an I^2 of 13%. The overall incidence rate of SO following OGI as a group was 33 per 100,000 person-years. The R metarate package calculated the overall point estimate using the GLMM method but appeared to use the inverse variance method when we attempted to report subgroups within the forest plot. As such, the adult and pediatric groups were reported separately in the supplementary material.

On meta-analysis of the adult series, the incidence rate of SO was 24.64 per 100,000 person-years (95% CI 19.68-30.85) with an I^2 of 71%, and the incidence proportion was 0.18% (95% CI 0.14-0.24). In children, the incidence rate was 57.45 per 100,000 person-years (95% CI 35.71-92.41) with an I^2 of 64%, and the incidence proportion was 0.39% (95% CI 0.26-0.76). Although the incidence proportions and

incidence rates for SO following OGI were both higher in children than in adults, there were no statistically significant differences between these groups (Table 4). As such, the pediatric and adult studies were reported as a combined meta-analysis (Figure 3).

Risk of bias and study quality assessment

Quality analysis was performed to evaluate the potential for biases in identifying the number of SO cases out of the total population denominator. Studies that only included a subset of the population (i.e., very specific mechanism of injury, delayed presentation, injury to a specific region of the eye, and injury requiring inpatient admission) were deemed to have selection bias. Attrition bias was assigned to studies that lost a significant proportion of their patients to follow-up or referred patients to other care centers. Notably, the majority of studies included in our review were retrospective, which are more prone to attrition bias than prospective studies. Studies that reported patients who underwent prophylactic enucleation or evisceration to prevent SO were deemed to have performance bias. In 71% of articles, at least one patient underwent enucleation or evisceration, which may have mitigated the development of SO. The median rate of eye removal was 5% and the average rate of eye removal was 12% across our twenty-four studies. Detection bias was assigned to studies that did not have a clear definition of SO upon initial diagnosis or who may have had a previous history of ocular trauma. Finally, reporting bias was assigned to studies that assessed a population that was previously reported (i.e., sub-group analysis of pediatric cases). The majority of studies included in our meta-analysis diagnosed SO clinically, with a minority

of studies including histopathologic diagnoses in their case count.[14,36] A summary of the risk of bias from the papers included are shown in Figure 2.

To determine if our results were affected by the perceived bias in the studies, the meta-analysis was repeated using studies with low bias. In determining which studies had an overall low bias, a point system was created whereby one point was assigned for each of the five low bias categories. Ten studies were identified to have overall low bias. Based on repeat meta-analysis of these ten studies (Table 5), the incidence rate for the random effects model was 34.9 (95% CI, 13.98; 86.89) per 100,000 person years with an I^2 of 46%, and the incidence proportion was 0.20% (95% CI 0.05%; 0.3%) with an I^2 of 27%. In both instances, the point estimates of the low bias studies were very similar to the overall analysis with overlapping confidence intervals. In fact, the confidence intervals derived from the complete analysis (n=24) are tighter than the confidence interval of the low bias studies (n=10).

DISCUSSION

The incidence of SO is difficult to determine given its rarity and potential to occur many years after the inciting trauma or surgery. SO is a clinical diagnosis that is supported with ancillary investigations including fluorescein angiography, indocyanine angiography, autofluorescence imaging, ultrasonography, optical coherence tomography (OCT), and OCT-enhanced depth imaging.[37] The disease has no confirmatory serologic test and is not always confirmed via histopathology either.[4] The

differential diagnosis of SO includes Vogt-Koyanagi-Harada syndrome (VKH), sarcoidosis, and syphilitic posterior uveitis.[4]

Kilmartin et al.'s 15-month prospective survey of SO suggested a minimum estimated incidence of 0.03 per 100,000. However, their population denominator was the entire United Kingdom population of whom the vast majority did not have any ocular trauma or surgery, and at least 43% of their cases of SO were from ocular surgery rather than non-surgical trauma. To counsel patients who have suffered OGI, it is essential to examine studies that describe the incidence of SO after OGI. As such, all series that described consecutive patients with OGI were considered for this study. The reported incidence proportion of SO following OGI typically varies from 0.1 to 3% overall,[38] and 0.24%[39] to 1.4%[26] in the pediatric population. Our meta-analysis found the incidence proportion of patients with SO after OGI was 0.19% overall and 0.39% in children. Our meta-analysis found the overall incidence rate of SO after OGI to be 33 per 100,000 person-years, with a trend towards higher incidence in the pediatric population that was not statistically significant.

The management of SO is directed at controlling inflammation with systemic immunosuppression and occasional removal of the inciting eye if it is blind, although the role of prophylactic evisceration or enucleation remains controversial. Enucleation was traditionally recommended over evisceration to prevent SO.[8] Yet, Bellan demonstrated that even with the oft-quoted incidence of 0.28%,[40] 9,999 enucleations would be required to prevent one case of SO.[28] Among studies included in our review, Du Toit et al. found no cases of SO in a series of 491 primary eviscerations over a 10-year

period.[41] However, Kilmartin et al., found that 75% of patients with SO who were treated with systemic immunosuppressive therapy had a visual acuity of 6/12 or better one year after prompt treatment, further questioning the utility of prophylactic eye removal.[42]

There are numerous sources of potential bias in this study including heterogeneous incidence rates, selection bias from different types of OGI (globe rupture, penetration, perforation, or intraocular foreign body), and inclusion of survey studies such as Liddy et al.'s which are not comparable methodologically to retrospective studies. In some studies, the definition of SO was elusive or ill-defined, particularly in cases that manifested long after the injury.[43] The follow-up times in each study were variable although SO can develop up to 66 years after the inciting injury.[44] This length of follow-up is not feasible within the scope of retrospective studies lending to attrition bias. Patients with OGI who undergo primary or early enucleation may be less likely to develop SO,[45] and this performance bias has already been discussed. Not all studies indicated the number of patients who had early prophylactic enucleation.[28,43] Some of the papers described the incentive for enucleation or evisceration as being prophylactic for prevention of SO,[14,21,43] while others described it as a final resort.[13,16,17,23,24,27,36,39,46-48] A minority of studies did not clarify the rationale for eye removal.[15,18,49-51] In general, however, multiple studies suggest that evisceration is increasingly favored over enucleation when indicated after OGI. The prevailing surgical philosophy is that evisceration provides better motility and aesthetic outcomes than enucleation.[52-55]

The chief strength of our study is that it is the first systematic review and meta-analysis to analyze the incidence of SO after OGI, which we report as both an incidence proportion and an incidence rate. We included papers that reported no cases of SO after trauma and used the suggested corrections for zero cell counts from published literature.[29,31] Our population-based studies have a relatively low degree of bias, reasonable sample sizes, and study duration to examine for SO. Future directions include prospective studies to determine the incidence of SO with respect to age, gender, type of injury (globe rupture, penetration, perforation, or intraocular foreign body), location of trauma (anterior versus posterior), and extent of globe injury.

In summary, our meta-analysis of twenty-four population-based studies of SO after OGI with a median study duration of 9.5 years found an incidence proportion of 0.19% and an incidence rate of 33 per 100,000 person-years.

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REFERENCES

1. Gupta SR, Phan IT, Suhler EB. Successful Treatment of Refractory Sympathetic Ophthalmia in a Child With Infliximab. *Arch Ophthalmol.* 2011;129(2):250-252.

2. Galor A, Davis JL, Flynn, HW, Jr, et al. Sympathetic Ophthalmia: Incidence of Ocular Complications and Vision Loss in the Sympathizing Eye. *Am J Ophthalmol.* 2009;148(5):704-710.e2.

3. Cunningham ET, Kilmartin D, Agarwal M, Zierhut M. Sympathetic Ophthalmia. *Ocul Immunol Inflamm.* 2017;25(2):149-151.

4. Arevalo JF, Garcia RA, Al-Dhibi H, Sanchez JG, Suarez-Tata L. Update on sympathetic ophthalmia. *Middle East Afr. J. Ophthalmol.* 2012;19(1):13-21

5. Chu XK, Chan C. Sympathetic ophthalmia: to the twenty-first century and beyond. *J. Ophthalmic Inflamm. Infect.* 2013;3(1):49.

6. Goto H, Rao NA. Sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome. *Int Ophthalmol Clin.* 1990;30(4):279-285.

7. Mahajan VB, Gehrs KM, Goldstein DA, Fischer DH, Lopez JS, Folk JC. Management of sympathetic ophthalmia with the fluocinolone acetonide implant. *Ophthalmology.* 2009;116(3):552-557.e1.

8. Bilyk JR. Enucleation, evisceration, and sympathetic ophthalmia. *Curr Opin Ophthalmol.* 2000;11(5):372-386.

9. Manandhar A. Sympathetic ophthalmia: Enucleation or evisceration? *Nepal J Ophthalmol.* 2011;3(2):181-187.

10. Bilyk JR. Enucleation, evisceration, and sympathetic ophthalmia. *Curr Opin Ophthalmol.* 2000;11(5):372-386.

11. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol.* 2013;9(1):30-30.

12. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. *J Curr Glaucoma Pract.* 2017;11(2):67-72.

13. Adhikary HP, Taylor P, Fitzmaurice DJ. Prognosis of perforating eye injury. *Br J Ophthalmol.* 1976;60(11):737-739.

14. Gürdal C, Erdener U, Irkeç M, Orhan M. Incidence of sympathetic ophthalmia after penetrating eye injury and choice of treatment. *Ocul Immunol Inflamm.* 2002;10(3):223-227.

15. Colyer MH, Weber ED, Weichel ED, et al. Delayed intraocular foreign body removal without endophthalmitis during Operations Iraqi Freedom and Enduring Freedom. *Ophthalmology.* 2007;114(8):1439-1447.

16. Kolomeyer AM, Shah A, Bauza AM, Langer PD, Zarbin MA, Bhagat N. Nail gun-induced open-globe injuries: a 10-year retrospective review. *Retina.* 2014;34(2):254-261.

17. Yu Wai Man C, Steel D. Visual outcome after open globe injury: a comparison of two prognostic models--the Ocular Trauma Score and the Classification and Regression Tree. *Eye (Lond).* 2010;24(1):84-89.

18. Kong GY, Henderson RH, Sandhu SS, Essex RW, Allen PJ, Campbell WG. Wound-related complications and clinical outcomes following open globe injury repair. *Clin Exp Ophthalmol.* 2015;43(6):508-513.

19. Li X, Zarbin MA, Bhagat N. Pediatric open globe injury: A review of the literature. *J Emerg Trauma Shock.* 2015;8(4):216-223.

20. Chien KH, Chang HC, Lu DW. Open globe injury in a tertiary hospital in Northern Taiwan: A 10-year review. J Med Sci. 2016;36(4):131.

21. Fujikawa A, Mohamed YH, Kinoshita H, et al. Visual outcomes and prognostic factors in open-globe injuries. *BMC Ophthalmol.* 2018;18(1):138-4.

22. Sahin Atik S, Ugurlu S, Egrilmez ED. Open Globe Injury: Demographic and Clinical Features. *J Craniofac Surg.* 2018;29(3):628-631.

23. Fraco, P.M.W. Causes and effects of eye injuries in children. *Aust. J. Ophthalmol.* 1984;12: 245-251.

24. Choovuthayakorn J, Patikulsila P, Patikulsila D, Watanachai N, Pimolrat W. Characteristics and outcomes of pediatric open globe injury. *Int Ophthalmol.* 2014;34(4):839-844.

25. Acuna OM, Yen KG. Outcome and prognosis of pediatric patients with delayed diagnosis of open-globe injuries. *J Pediatr Ophthalmol Strabismus.* 2009;46(4):202-9.

26. Gilbert A, Heidary G, Andreoli M, Andreoli CM, Shah A. Increased incidence of sympathetic ophthalmia observed in a pediatric open-globe-injury population. *Invest Ophthalmol Vis Sci.* 2014;55(13):4495.

27. Shah AS, Andreoli MT, Andreoli CM, Heidary G. Pediatric open-globe injuries: A large-scale, retrospective review. *JAAPOS.* 2011;15(1):e29.

28. Savar A, Andreoli MT, Kloek CE, Andreoli CM. Enucleation for open globe injury. *Am J Ophthalmol.* 2009;147(4):595-600.e1.

29. Harrer, M., Cuijpers, P., Furukawa, T.A., & Ebert, D.D. (2021*). Doing Meta-Analysis with R: A Hands-On Guide.* Boca Raton, FL and London: Chapmann & Hall/CRC Press. ISBN 978-0-367-61007-4.

30. Schwarzer G. Package 'meta'. General Package for Meta-Analysis Web site. https://cran.r-project.org/web/packages/meta/meta.pdf. Updated 2021. Accessed Feb 5, 2020.

31. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health.* 2014;72(1):39.

32. NCSS, LLC. Meta-analysis of Proportions. NCSS Statistical Software. Available at: https://ncss-wpengine.netdna-ssl.com/wp-

content/themes/ncss/pdf/Procedures/NCSS/Meta-Analysis_of_Proportions.pdf

Accessed Feb 5, 2020.

33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.

34. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.

35. Mir TA, Canner JK, Zafar S, Srikumaran D, Friedman DS, Woreta FA. Characteristics of Open Globe Injuries in the United States From 2006 to 2014. *JAMA Ophthalmol.* 2020;138(3):268-275.

36. Zhang Y, Zhang MN, Jiang CH, Yao Y. Development of sympathetic ophthalmia following globe injury. *Chin Med J (Engl).* 2009;122(24):2961-2966.

37. Mahajan S, Invernizzi A, Agrawal R, Biswas J, Rao NA, Gupta V. Multimodal Imaging in Sympathetic Ophthalmia. *Ocul Immunol Inflamm.* 2017;25(2):152-159.

38. Rua D, Pohlmann D, Pleyer U. Sympathetic Ophthalmia - a Contribution to Immunology, Clinic and Current Imaging. *Klin Monbl Augenheilkd.* 2020;237(9):1060-1069.

39. Kumar K, Mathai A, Murthy SI, et al. Sympathetic ophthalmia in pediatric age group: clinical features and challenges in management in a tertiary center in southern India. *Ocul Immunol Inflamm.* 2014;22(5):367-372.

40. Bellan L. Sympathetic ophthalmia: a case report and review of the need for prophylactic enucleation. *Can J Ophthalmol.* 1999;34(2):95-98.

41. du Toit N, Motala MI, Richards J, Murray ADN, Maitra S. The risk of sympathetic ophthalmia following evisceration for penetrating eye injuries at Groote Schuur Hospital. *Br J Ophthalmol.* 2008;92(1):61-63.

42. Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. *Br J Ophthalmol.* 2000;84(3):259-263.

43. Liddy L, Stuart J. Sympathetic ophthalmia in Canada. *Can J Ophthalmol.* 1972;7(2):157-159.

44. Zaharia MA, Lamarche J, Laurin M. Sympathetic uveitis 66 years after injury. *Can J Ophthalmol.* 1984;19(5):240-243.

45. Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia. A clinicopathologic review of 105 cases (1913--1978). *Ophthalmology.* 1980;87(2):109-121.

46. Sahin Atik S, Ugurlu S, Egrilmez ED. Open Globe Injury: Demographic and Clinical Features. *J Craniofac Surg.* 2018;29(3):628-631.

47. du Toit N, Motala MI, Richards J, Murray ADN, Maitra S. The risk of sympathetic ophthalmia following evisceration for penetrating eye injuries at Groote Schuur Hospital. *Br J Ophthalmol.* 2008;92(1):61-63.

48. Court JH, Lu LM, Wang N, McGhee CNJ. Visual and ocular morbidity in severe open-globe injuries presenting to a regional eye centre in New Zealand. *Clin Exp Ophthalmol.* 2019;47(4):469-477.

49. Mansouri M, Faghihi H, Hajizadeh F, et al. Epidemiology of open-globe injuries in Iran: analysis of 2,340 cases in 5 years (report no. 1). *Retina.* 2009;29(8):1141-1149.

50. Toride A, Toshida H, Matsui A, et al. Visual outcome after emergency surgery for open globe eye injury in Japan. *Clin Ophthalmol.* 2016;10:1731-1736.

51. Mahasneh S, Redmond P, Mancini R. Open Globe Injuries and the Incidence of Sympathetic Ophthalmia at a Large County Hospital. *Invest Ophthalmol Vis Sci.* 2014;55(13):5480.

52. Shah Ruchi D, Singa Ramesh M, Aakalu Vinay K, Pete S. Evisceration and Enucleation: A National Survey of Practice Patterns in the United States. *Ophthalmic Surgery, Lasers and Imaging Retina.* 2012;43(5):425-430..

53. Timothy NH, Freilich DE, Linberg JV. Evisceration versus enucleation from the ocularist's perspective. *Ophthalmic Plast Reconstr Surg.* 2003;19(6):417-20

54. Reed D, Papp A, Brundridge W, et al. Evisceration Versus Enucleation Following Ocular Trauma, a Retrospective Analysis at a Level One Trauma Center. *Mil Med.* 2020;185(3-4):409-412.

55. Koh V, Chiam N, Sundar G. Survey of Common Practices Among Oculofacial Surgeons In The Asia-Pacific Region: Evisceration, Enucleation and Management of Anophthalmic Sockets. *Orbit.* 2014;33(6):477.

LEGENDS FOR FIGURES AND TABLES

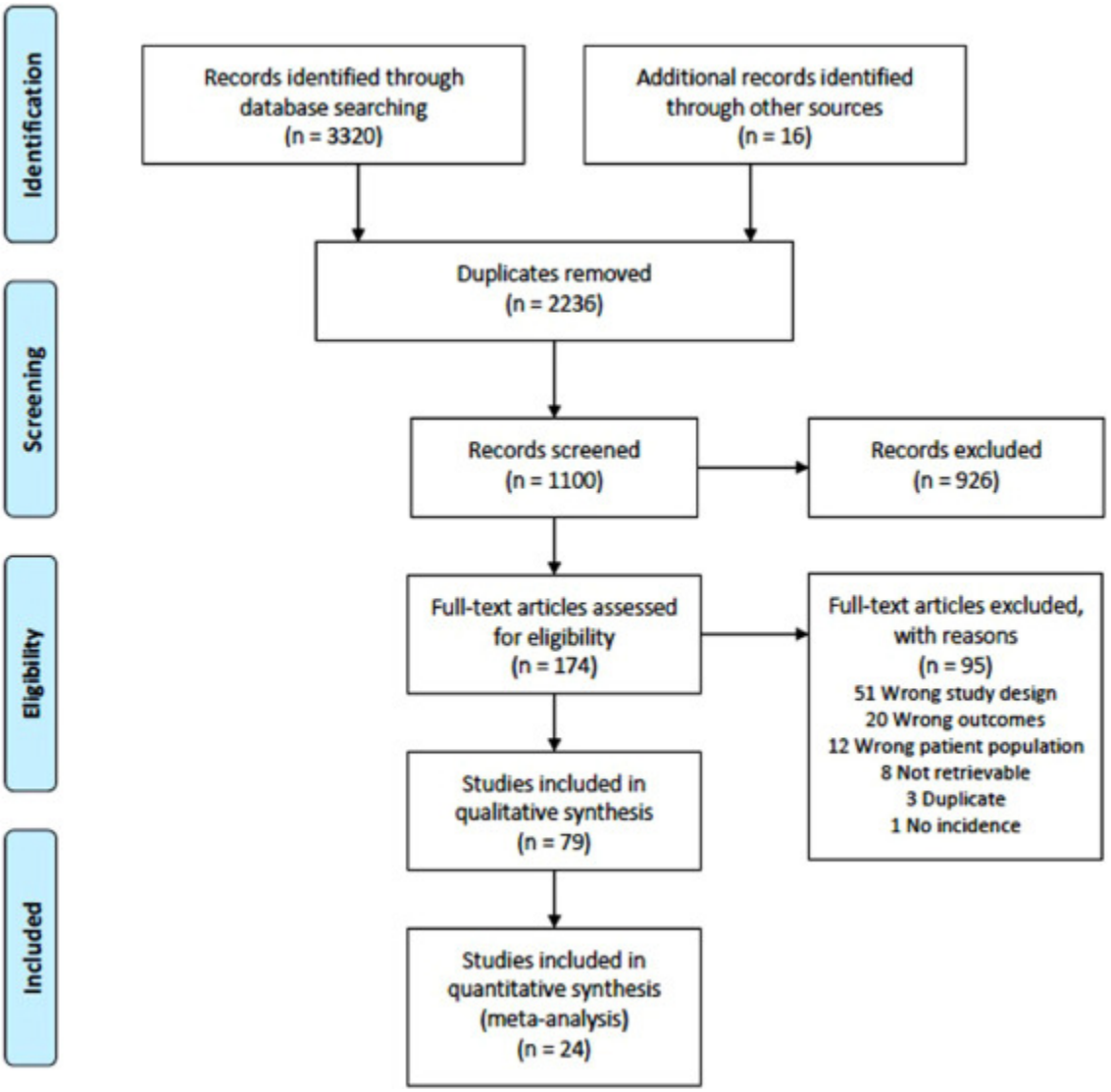

Figure 1. PRISMA flow diagram outlining the systematic literature search process.

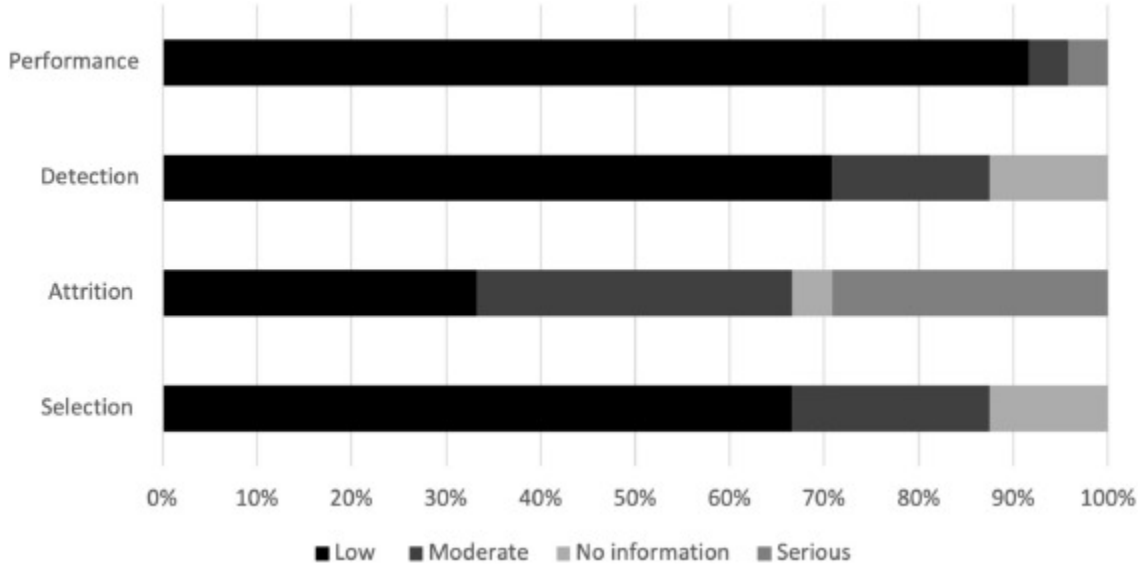

Figure 2. Risk of bias summary.

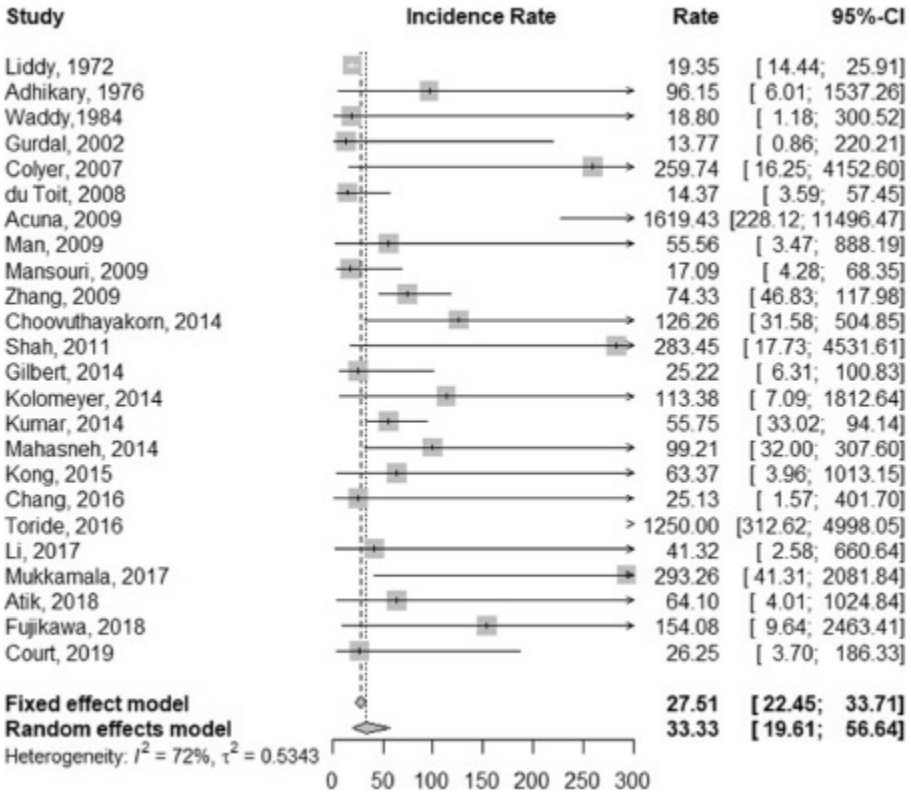

Figure 3. Random-effects meta-analysis of the incidence rate of sympathetic ophthalmia post open globe injury. (There was no statistically significant difference between pediatric versus adult incidence rates (p= 0.163), so they were combined for the meta-analysis).

Table 1. Syntax used in MEDLINE and EMBASE to obtain articles reporting incidence of sympathetic ophthalmia.

MEDLINE	EMBASE	Cochrane	Grey literature
"exp Ophthalmia, Sympathetic/", "(sympathetic and ophthalmia).af."	"('sympathetic ophthalmia'/exp OR 'sympathetic ophthalmia' OR (('sympathetic'/exp OR sympathetic) AND ('ophthalmia'/exp OR ophthalmia))) AND [english]/lim"	"Sympathetic" AND "Ophthalmia"	"Sympathetic ophthalmia"

Table 2. Risk of bias summary for all articles that were included in the study.

Author	**Year**	**Country**	**Selection**	**Attrition**	**Detection**	**Performance**	**Reporting**
Liddy	1972	Canada	Moderate	No information	Moderate	No information	Moderate
Adhikary	1976	England	Low	Low	Low	Low	Low
Waddy	1984	Australia	Moderate	Low	Low	Low	Low
Gurdal	2002	Turkey	Moderate	Low	Low	Serious	Low
Colyer	2007	USA	Serious	Moderate	Moderate	Low	Low
du Toit	2008	South Africa	Moderate	Serious	Low	Serious	Low
Acuna	2009	USA	Moderate	Low	Low	Low	Low
Man	2009	England	Low	Low	Low	Moderate	Low
Mansouri	2009	Iran	Low	Moderate	Low	Low	Low
Zhang	2009	China	Low	No information	Low	Low	Low
Shah	2011	USA	Low	No information	No information	No information	Low

Choovuthayakorn	2014	Thailand	Low	Moderate	Moderate	Low	Low
Gilbert	2014	USA	Low	No information	No information	No information	Serious
Kolomeyer	2014	USA	Serious	Moderate	Low	Low	Low
Kumar	2014	India	Low	Moderate	Low	Low	Low
Mahasneh	2014	USA	Low	No information	No information	No information	Low
Kong	2015	Australia	Low	Moderate	Low	Low	Low
Chang	2016	Taiwan	Low	Low	Moderate	Moderate	Low
Toride	2016	Japan	Low	No information	Low	Low	Low
Li	2017	Hong Kong	Low	Low	Low	Low	Low
Mukkamala	2017	USA	Serious	Low	Low	Low	Low
Atik	2018	Turkey	Low	Moderate	Low	No information	Low
Fujikawa	2018	Japan	Low	No information	Low	Low	Low
Court	2019	New Zealand	Low	Moderate	Low	Low	Low

Table 3. Characteristics of the twenty-four population-based studies used in the meta-analysis with information about sympathetic ophthalmia after open globe injury. (KEY: Study age: adult versus pediatric study; % male: percentage of male patients; Cases: number of cases of sympathetic ophthalmia in the report; Population denominator: number of open globe injuries in the report; Duration: study duration in years; Cases per population per duration: number of cases of SO / number of open globe injuries / duration of study; % eye removal: percentage of patients that underwent either enucleation or evisceration)

Author	Year	Study age	% male	Average age (years)	Cases	Population denominator	Duration (years)	Cases per population per duration	% eye removal
Liddy	1972	Adult			45	23,260	10	0.000193	.
Adhikary	1976	Adult	85		0	130	4	0	9.2
Gurdal	2002	Adult			0	121	30	0	100
Colyer	2007	Adult	96	27	0	70	2.8	0	0
du Toit	2008	Adult			2	1,392	10	0.000144	36
Man	2009	Adult	74	36	0	100	9	0	14
Zhang	2009	Adult	83	36.7	18	4,843	5	0.000743	1.8
Mansouri	2009	Adult	81	22.4	2	2,340	5	0.000171	5.3
Kolomeyer	2014	Adult	100	31.6	0	42	10.5	0	2.4
Gilbert	2014	Adult	79	42	2	721	11	0.000252	.
Mahasneh	2014	Adult	84	40.4	3	432	7	0.000992	.

Kong	2015	Adult	83	44.8	0	263	3	0	5.2
Toride	2016	Adult	70	58.9	2	40	4	0.0125	7.5
Chang	2016	Adult	68	44.5	0	199	10	0	16
Li	2017	Adult	63	54	0	121	10	0	9.9
Mukkamala	2017	Adult	90	36.6	1	31	11	0.002933	0
Fujikawa	2018	Adult	66	57.9	0	59	5.5	0	3.4
Atik	2018	Adult	78	36.9	0	156	5	0	0.6
Court	2019	Adult	79	37	1	381	10	0.000262	0.5
Waddy	1984	Pediatric	73	5.9	0	266	10	0	.
Acuna	2009	Pediatric	62	5.8	1	13	4.75	0.016194	0
Shah	2011	Pediatric	75	12.7	2	144	11	0.001263	13.0
Choovuthayakorn	2014	Pediatric	84	9.3	0	49	3.6	0	16.0
Kumar	2014	Pediatric	71	13.3	14	2,511	10	0.000558	0.2

Table 4. Incidence proportion and incidence rate of sympathetic ophthalmia following open globe injury.

	Overall (95% CI)	Adults only (95% CI)	Pediatric Only (95% CI)	t-test
Number of studies	24	19	5	
Incidence Proportion (%)	0.19 (0.14-0.24) I^2 =13%	0.18 (0.14-0.24)	0.39 (0.26-0.76)	p=0.138
Incidence Rate (per 100,000 person-years)	33.3 (19.6-56.6) I^2=72%	24.6 (19.7-30.9) I^2 = 71%	57.4 (35.7-92.4) I^2 = 64%	p=0.200

Table 5. Risk of bias assigned by points (1 = low, 3 = moderate, 5 = high) for all articles that were included in the study.

Author	Year	TOTAL
Liddy	1972	9
Adhikary	1976	5
Waddy	1984	7
Gurdal	2002	11
Colyer	2007	13
du Toit	2008	15
Acuna	2009	7
Man	2009	7
Mansouri	2009	7
Zhang	2009	4
Shah	2011	2
Choovuthayakorn	2014	9
Gilbert	2014	6
Kolomeyer	2014	11
Kumar	2014	7
Mahasneh	2014	2
Kong	2015	7
Chang	2016	9
Toride	2016	4
Li	2017	5
Mukkamala	2017	9
Atik	2018	6
Fujikawa	2018	4
Court	2019	7