The Risk of Sympathetic Ophthalmia Following Vitreoretinal Surgery

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Abstract

Purpose

To investigate the clinical course and the outcomes of sympathetic ophthalmia and correlate these with the nature of the inciting event and the number of vitreoretinal procedures undergone by patients.

Design

A retrospective case review.

Subjects

All patients diagnosed with sympathetic ophthalmia who have been treated or monitored at a single centre over a 15 year period.

Methods

A search of the electronic patient record system at Moorfields Eye Hospital, Londo over a 15 year period (between January 2000 and December 2015) was carried out, using the search terms "sympathetic", "ophthalmia" and "ophthalmitis". 61 patients with available records were identified and data collected from their complete electronic and paper records.

Main Outcome Measures

The main outcome measures looked at were the best-corrected visual acuity (BCVA) at 1 year and at the end of follow up and the number of vitreoretinal surgical procedures preceding the diagnosis. Data was also collected to report on patient age, gender, disease duration, ocular and systemic manifestations, ocular complications, retinal angiography and treatment.

Results

There was a wide age range at presentation (2-84) and the length of follow up ranged 1-75 years. The first ocular event was trauma in 40 patients and surgery in 21. Vitreoretinal (VR) surgery accounted for 13 of the 21 surgical first event triggers (62%). 23/61 patients (38%)

underwent VR surgery (1-7 operations) at some point prior to diagnosis. Surgical details were available for 15 patients, who had a total of 25 VR procedures carried out. Based on the surgical activity of the unit, the risk of developing SO following a single VR procedure is estimated at 0.008%, rising to 6.67% with 7 procedures.

A total of 23 patients (38%) experienced a decrease in acuity at the end of the follow up period, versus 9 patients (15%) experiencing an improvement and 18 (30%) remaining unchanged.

Conclusions

We feel that the most significant finding in this study is the calculated risk of SO development following a single VR procedure, which is significantly lower in our cohort than previously reported in the literature. This is seen to rise exponentially with additional procedures.

Introduction

Sympathetic ophthalmia (SO) is an inflammatory condition characterised by bilateral granulomatous panuveitis that is triggered by a traumatic event to one eye. The eye subjected

to trauma (the inciting eye) is associated with an inflamed contralateral eye (the sympathising eye). The pathogenesis is unclear, but thought to represent an autoimmune reaction to either sequestered uveal or retinal antigen/s[1-3], released by the trauma and exposed to the systemic immune system, resulting in a potentially blinding condition. A prospective population based study estimated its incidence at 0.03 per 100,000 per year [4].

Large retrospective SO case series have demonstrated that open globe injury is the inciting trauma in the majority of cases [5, 6]. More recently, however, surgery has been implicated as the prevailing cause, with an incidence of 0.08% following vitreoretinal (VR) surgery [4]. In this study, we investigate the relationship between SO and VR surgery, comparing this to SO secondary to other surgical trauma and open globe injuries.

Methods

This was a retrospective case review that adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Moorfields Eye Hospital, London (reference CA16/MR/03). Seventy-two patients with a diagnosis of SO were identified following a search of the electronic patient record system at Moorfields Eye Hospital, London. Patients presented over a 15 year period (between January 2000 and December 2015). The search terms used were, “sympathetic”, “ophthalmia” and “ophthalmitis”.

SO was diagnosed when the patient reported a history of ocular trauma or intraocular surgery and presented with bilateral inflammation (after excluding other uveitic causes) or a histopathological diagnosis of SO in the enucleated eye. A notes review excluded 11 patients due to unavailability of the records and resulted in a data set of 61 patients. This data set included a number of patients with more than 50 years of follow up; clinical documentation was limited in these cases.

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The 15 year time period of data collection refers to 15 years' worth of records undergoing electronic search for key terms to yield the patient cohort. This time period was used as electronic records were easily obtainable for this period, but more sparse prior to that. Any patient seen in the Hospital during that period would have had an electronic footprint and would have been included in the cohort, be they a de novo diagnosis of SO or a patient under long-term historical follow up.

The data gathered included age, gender, disease duration, ocular and systemic manifestations, ocular complications, best-corrected visual acuity (BCVA), fundus fluorescein angiography (FFA) and indocyanine green angiography (ICG) results and treatment at presentation and further follow-up visits. History of ocular trauma or intraocular surgery and the interval between the inciting event and development of ocular inflammation was also collected. Intraocular inflammation was defined as active using all or combination of the following signs: aqueous cells, flare, keratitic precipitates, Koeppe and Busacca nodules, vitreous cells and choroiditis.

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Commented [L5R4]: I am pretty certain that ICG is likely to have been used to look into choroidal disease. At least since ICG became available.

Snellen visual acuities were converted to their logarithm of the minimum angle of resolution (LogMAR) unit equivalents.[7] Statistical analysis was performed using the SPSS version 26 (SPSS Inc., Chicago, IL) statistical package. Continuous and categorical variables between groups were compared with Mann-Whitney U test and Chi-squared testing respectively. Correlations were assessed using the PMPCC, with significance being declared in cases where $p < 0.05$.

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Results

Patient characteristics

The age range at initial injury was 2-84 (mean 28, median 18) years. The age range at diagnosis was 4-85 years (mean 38, median 39). The age distribution is presented in Figure

1. The sympathising eye was the right eye in 31 patients and the left eye in 30. The range of year of diagnosis was 1938-2015 (1 unknown). The range of follow up length was 1-75 years (mean 23 years) in 56 patients (92%) and less than a year in 5 patients.

Presenting features

The clinical features at presentation were variable for many (or the earlier records were sparse in detail). Where symptom information was recorded, the majority of patients had presented with blurring of vision, floaters and/or photophobia. Throughout their clinical courses, 21 patients (34%) were noted to have Dalen-Fuchs' nodules and 28 patients (46%) were recorded as having a panuveitis, although these instances were not necessarily recorded at the initial presentation. Dalen-Fuch's nodules in particular were first recorded in the range of 59 days-44 years and 7 months from diagnosis (mean 15 years and 2 months, median 2 years and 4 months), although accurate dates of the first instance of noting the nodules were only available in 7 out of 21 patients with this sign. There was one instance of choroidal neovascular membrane formation noted post-diagnosis, which was consequently treated with intravitreal anti-VEGF injections. There were few extraocular signs and symptoms reported at the time of diagnosis; these included 1 case of a preceding cough, 1 concurrent shortness of breath, and 1 preceding case of recurrent nosebleeds.

Causes of inciting trauma

The first event in the trigger (inciting) eye was trauma in 40 patients and surgery in 21. Trauma as the first event was recorded in 11/19 females (58%) and 29/42 males (69%). 57 out of the total of 61 patients had a surgical procedure as the last event before SO diagnosis. A summary of the surgical procedures is presented in the Supplemental Table.

There was an observed trend over time of the increasing significance of surgery as the first trigger. The change in the proportions of traumatic versus surgical first triggers is presented in Figure 2. The summary of the frequency of multiple procedures is given in Table 1. Surgery

Commented [L7]: Do we have the break down by year? It would indicate what you said in the introduction that in the past was mostly trauma, but now is surgery

Commented [ON8]: Brilliant

on ocular adnexa was excluded from the procedure count. Intra-ocular laser procedures were included (Yag capsulotomy, retinal laser, Yag iridotomy, cyclodiode).

Vitreoretinal surgery as a cause

Vitreoretinal surgery, including (all gauge) pars plana vitrectomy (PPV), cryotherapy and scleral buckling (CB) accounted for 13 of the 21 surgical first event triggers (62%). Of these 13, 10 patients had had multiple VR procedures. 15 out of 57 (26%) last events prior to the diagnosis of SO were vitreoretinal. 23/61 patients (38%) underwent VR surgery (1-7 operations) at some point prior to diagnosis. Surgical details were available for 15/23 patients undergoing VR surgery for those patients who underwent their surgery at Moorfields Eye Hospital.

A summary of the vitreoretinal surgical procedures performed on the SO cohort of patients at Moorfields is presented in Table 1. An analysis of operation notes was undertaken and an account of the procedural steps performed at each procedure is presented in table 2.

A total of 25 vitreoretinal procedures were carried out on 15 patients over their clinical course. 6 involved the use of scleral buckling, 21 involved pars plana vitrectomy (one of the cases was combined). There were 6 retinectomies recorded, 5 instances of using gas tamponade and 12 instances of using silicone oil tamponade.

Over the time period of the study, 39391 vitreoretinal procedures were recorded as having been carried out at Moorfields. Given that out of all patients having vitreoretinal procedures at Moorfields 15 SO cases were newly diagnosed in 15 years, the incidence is 1 per year or 0.04% of the total vitreoretinal surgical cohort. A summary of the number of patients having multiple procedures is presented in Table 3

Based on this activity data, the risk of developing SO following a single VR procedure is estimated at 0.008%, rising to 6.67% with 7 procedures. This is shown in Figure 3.

Commented [SW9]: You report an R2 in this figure. I think that you should either mention in the Methods (at the moment it says Pearson Chi square but perhaps you meant Pearson correlation coefficient). An alternative is to take it out (my preference), this relationship does not appear linear so technically shouldn't be using PPMCC unless you have transformed the data.

If this needs to be resubmitted later, maybe consider doing a Poisson or Cox regression modelling SO incidence with input of no of vr procedures (I can do it if helpful).

Commented [ON10]: Excellent

Presenting features including time to SO

The time from the first event to the diagnosis of SO diagnosis had a range of 28-19676 days (mean 2732 days, mode 181, median 780). The time was unknown in 5 cases. The time from the last event to the diagnosis of SO ranged 22-16663 days (mean 3012), with 3 unknown. 23 patients (34%) had only a single ocular event recorded before the diagnosis of SO was made.

There was no statistically significant difference in the time from the first event to diagnosis or the time from last event to diagnosis between the group undergoing VR surgery at some point during their clinical course pre-SO and the non-VR group ($p = 0.14$ and $p = 0.34$ respectively).

There did not appear to be any universal requirement for investigations prior to diagnosis of SO. Diagnosis was made on the basis of the clinical feature of bilateral granulomatous panuveitis and/or histological evidence of SO in the enucleated eye. Evidence of indocyanine green (ICG) angiography having been performed was available in 16 patients (26%). 9 of these were performed within a week of the date of diagnosis and were therefore judged to be part of the diagnostic process, with the remainder being performed as part of flare-up assessment.

Fundus fluorescein angiography (FFA) alone was performed in 1 patient as part of the original work up at diagnosis and in a further 6 patients later on in the course of the disease as part of flare-up assessments.

This variability in investigations performed likely reflects two things: variability in recording and availability of investigations. In the earlier times covered by the study, the availability of immunological investigations would have been limited and much more emphasis would have been placed on clinical findings. With the advent of FFA and ICG, these slowly started to be

used in the diagnostic process, up to the point nowdays, where ICG is considered one of the main diagnostic modalities in suspected SO cases.

Clinical course (final VA, flare ups, treatment)

There were a total of 143 recorded flare ups in the cohort throughout their clinical courses since diagnosis. The majority of recorded flare ups involved only the anterior segment and the majority (98 out of the total number of flare-up episodes -69%) were managed with oral treatment (increased oral steroids and/or non-steroidal agents), the rest being managed with topical steroids only. The decision to manage topically appeared to be supported by ICG evidence in two cases. As well as anterior uveitis, other manifestations of disease activity resulting in increased treatment were intermediate or posterior uveitis, choroiditis, optic nerve involvement, cystoid macular oedema or, in a few selected cases, subjective symptoms of blurring or discomfort. 7 flare-up instances had an adjunctive orbital floor steroid injection (7), +/- intravitreal Triamcinolone (2) or +/- Ozurdex (2). The instances of treatment with Ozurdex occurred in a single patient with a concurrent diagnosis of central retinal vein occlusion (CRVO).

There was no statistically significant difference between the number of flare ups and the number of oral immunosuppressants used in the VR surgery group versus the non-VR group ($p = 0.54$ and $p = 0.81$ respectively).

The visual acuity changes are shown in Table 4 and Table 5. The change in acuity is presented graphically in Figure 4. The visual acuity at presentation tended to be good, with 21 patients (34%) presenting with a visual acuity of 0.3 LogMAR or better. A total of 23 patients (38%) experienced a decrease in acuity at the end of the follow up period, versus 9 patients (15%) experiencing an improvement and 18 (30%) remaining unchanged. There was a

Commented [L11]: Did the ones managed topically had ICGs to show choroid was ok?

Commented [L12]: This is strange. Was it really IU?

Commented [L13]: Intraocular therapy is a strange option for SO. Do we know which cases had them? Was the choroid assessed? We will need to mention this in the discussion

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238 significant lack of visual acuity data among the cohort, however, mostly relating to
239 incomplete early records. The change in visual acuity is shown in Figure 4.
240
241 Amongst the VR cohort, the VA had improved in 7/23 (30%) and reduced in 14/23 (61%) by
242 the end of the follow up period, a worse outcome profile than the average for the whole
243 cohort, although this did not reach statistical significance.
244
245 The mean visual acuity at different time points when split into the single event cases versus
246 the multiple event cases and sub-divided into the VR surgery as the first event versus other
247 surgery and versus trauma as first event groups is given in Table 6. Due to low patient
248 numbers in the 1 event subgroups (2 patients in each case), it was not possible to carry out
249 statistical analysis. A trend towards better visual acuity at the time of diagnosis is noted in the
250 trauma sub-group, however, when compared to both surgical first event sub-groups. This is
251 maintained through to the first year and the final follow up.
252
253 Statistical analysis on the 2 or more events cohort was carried out using the one way
254 ANOVA. Visual acuity differences between the VR, non-VR and trauma as first event sub-
255 groups were not statistically significant at the final follow up (and $p = 0.7086$), though
256 statistical significance was reached at the time of diagnosis and at 1 year of follow up ($p =$
257 0.0103 and $p = 0.00145$ respectively), with better vision in favour of the trauma sub-group.
258
259 Visual acuity reduction could be attributed to a number of factors besides disease progression.
260 The summary of factors contributing to this is presented in Table 7. Only those patients where
261 both the initial visual acuity and final visual acuity data is available are shown. The number
262 and type of co-morbidities is comparable in the group of patients who experienced an overall
263 improvement in VA and the group with reduced VA, although the severity of the comorbidity
264 in each individual case is difficult to judge. For instance, 2/9 patients with improved VA had

no co-morbidities recorded (22%) versus 5/18 patients with reduced VA (28%) and 4/16 patients with unchanged VA (25%).

Treatment

Oral steroids were the first line treatment in 47 patients (6 no oral therapy, 7 unknown), with 26 of these patients concurrently on second line agents at some point during their clinical course. One patient was treated with intravenous Methylprednisolone as a first line agent. The use of agents is summarised in Table 8.

Several patients required concurrent multi-agent therapy either alongside oral steroids or in a steroid-sparing capacity. Combinations of agents used are summarized in Table 9.

The effect of the treatment burden on visual acuity is shown in Figures 4 and 5. There was no strong association with the number of oral treatment agents and the final visual acuity in the cohort, nor with the BCVA change from diagnosis to end of follow up.

Commented [SW15]: Association rather than correlation?

21 patients remained on systemic therapy at the end of the follow up period (10 steroids, 4 non-steroidal agents, 7 combination).

Enucleation and evisceration was performed in 19 patients (31% of cohort). Pre-emptive removal of the globe, typically following severe trauma, formed 37% of all enucleations (7 patients) and enucleation at the onset of symptoms was performed in 12 patients. There was a trend in reducing frequency of globe removal with time (Table 10).

There was a trend towards improvement in the final visual acuity outcomes based on the year of diagnosis, although there was significant spread of acuity results (Figure 5). There was no statistical significance between the visual acuity outcomes at one year post-diagnosis or at the end of follow up and the patients' age, time from first or last event to diagnosis, presenting visual acuity, sympathising eye laterality, number of immunosuppressants required, duration of immunosuppression, enucleation, number of flare ups or VR surgery pre-SO (Table 11).

Statistical significance was reached in between visual acuity outcomes at 1 year and the patient's gender and the nature of the first event. Females were more likely to have a visual improvement at 1 year versus males ($p = 0.031$) and patients suffering trauma as the first event in their clinical course tended to have better visual acuity outcomes at 1 year versus patients with a surgical first event ($p = 0.008$). Both of these differences lost statistical significance by the end of the follow up period.

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No characteristics amongst those studies had any statistically significant effect on the therapeutic load required, with similar proportions of patients amongst the groups requiring oral steroids only versus multiple agents to treat their inflammation (Table 12).

Discussion

The purpose of this study was to review the incidence and management of SO and to specifically explore the relationship between VR surgery and SO. Several groups have described the demographics and clinical course of SO previously [4, 6, 8-17]. This includes a multicentre case series that has recently been published that includes 30 patients from this study [5]. Our study had a different focus, in that it looked at the longitudinal course of all patients under the care of one centre and also specifically analysed the subset undergoing VR procedures in detail.

Our study cohort is consistent with published data [5, 16, 18]that shows an increased incidence of SO in the male population in addition to a double peak in age of incidence of SO, with a higher incidence in children and the elderly. This likely reflects the higher incidence of trauma in these groups.

In contrast to this, it is notable that Kilmartin et al identified VR surgery as the main risk factor in their prospective epidemiological study [19]. Our longitudinal data supports this, and

highlights a temporal trend for the increasing importance of surgery as the inciting event. This likely reflects improvements in technology and surgical outcomes that have led to an increase in the numbers of ophthalmic surgical procedures being undertaken, as well as a decrease in the overall incidence of ocular trauma.

It is possible that patients who have a predisposition to inflammatory disorders also develop more ocular problems, necessitating more VR interventions, creating a self-perpetuating loop. This could conceivably be postulated, for instance, in cases of proliferative vitreoretinopathy (PVR) causing recurrent retinal detachment. This may play a part in explaining increasing incidence due to surgical triggers, however it is likely not a very significant factor given the large numbers of patients who require multiple VR procedures and develop PVR, without going on to develop SO.

Multiple procedures were common, with the majority of patients with SO having undergone multiple procedures or a combination of trauma and surgery. Only 8 patients (13%) had suffered a single event prior to their SO diagnosis (4 trauma, 4 surgery)." The small patient numbers in the cohort experiencing single ophthalmic insult events prior to their SO diagnosis precluded meaningful statistical analysis of the single event group, although a trend towards better visual outcomes amongst the patients whose single event was trauma (versus surgery) is noted.

In our study, VR surgery was the most frequent surgical inciting event, in common with other previous literature [4, 8-11]: 13 of 21 (62%) cases in the whole cohort were either pars plana vitrectomy or cryotherapy/scleral buckling procedures. Furthermore, VR surgery had been performed prior to the diagnosis of SO in 25 out of 61 cases, representing 41% of the entire cohort. In the 12 cases that had both open globe injury and surgery, it is impossible to determine which ophthalmic insult is the inciting event.

The type of VR intervention may also contribute to the risk of developing SO. Out of 25 VR procedures performed in this cohort, there was a 29% retinectomy rate in PPV and a 57% rate

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of using silicone oil tamponade. Both rates suggest greater surgical complexity than average in VR surgery. In this setting, putative causative factors include insult to the choroid or blood/uveal barrier due to the higher number of procedural steps or an increased length of surgical time to allow a more potent ocular antigen exposure to the immune system; both are thought to increase the risk of SO.

It is interesting to note the diagnostic requirements for first establishing the presence of SO. Although clinical signs have remained the mainstay of raising the possibility of the diagnosis over many decades, the advent of ICG angiography and, more recently, extended depth optical coherence tomography imaging (EDI OCT) are changing the picture in terms of allowing an objective imaging assessment and both more accurate diagnosis and monitoring of treatment response and progression.

There were no statistically significant differences between the sub-groups of patients undergoing at least one VR surgical intervention prior to the SO diagnosis and the non-VR sub-group in terms of time from the first or last event to the diagnosis, nor the perceived clinical severity of the disease as measured by the number of flare ups and the oral immunosuppressant load.

The visual acuity outcomes amongst the subset of patients whose only event was a VR procedure were similar to those who underwent non-VR procedures as the only event and both of these suggested worse outcomes than the trauma single event group. It is not possible to reliably comment on the validity of this association due to the small numbers involved. Furthermore, a subset analysis of the trauma group would be expected to yield a wide range of outcomes based on the type and severity of the trauma event. Amongst the multiple events group, the severity of the visual compromise appeared to be worse in the surgical sub-groups (both VR and non-VR) than for the trauma sub-group, although this did not reach statistical significance at the end of follow up. This is reassuring from the point of view of prognostic indicators for patients developing SO following multiple operations.

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Our cohort clearly identifies the importance of VR surgery as an inciting event in SO. Kilmartin et al quantified the incidence rates of SO in VR surgery in their prospective study and found this to be 1 in 799 vitrectomies (0.13%), 1 in 1357 cryotherapy/scleral buckling procedures (0.07%). This equated to 1 case of SO for every 1152 VR procedures (0.09%). These rates reported were subject to limitations inherent to this surveillance study, in particular either an under-reporting of SO cases or an under-estimate of the number of VR procedures.

Commented [L20]: There is also data on the effect of repeated procedures increasing the risk

In a retrospective analysis of 41365 VR procedures, Tyagi et al found 16 cases of SO following VR surgery alone, corresponding to 1 in 2585 cases (0.04%) [20]. In a similar approach, we analysed 39391 VR procedures were performed over a 15 year period at our institution and found 13 cases of SO resulting from VR surgery only, corresponding to 1 in 3030 cases (0.03%). It is notable that this rate is similar to that reported by Tyagi et al.

To the best of our knowledge, this is the first study that specifically assesses the impact of multiple VR procedures on the incidence rate of SO. This is due to the granularity of the data collection and shows that performing two VR procedures (0.08%) on a patient results in a ten-fold increase in the incidence rate of SO when compared to those patients only having one VR procedure (0.008%). Further increases in the number of procedures results in an exponential increase in risk (Figure 3), with 6.67% of patients having 7 VR procedures developing SO.

Commented [L21]: There is data from Kilmartin on this

Our study also demonstrates the wide variety of treatment regimens used in the management of SO, over the decades, with no conclusions about which of these is associated with improved outcomes.

Retrospective studies such as this paper have inherent limitations. Incomplete data can produce biased or inaccurate estimates. In this study, we excluded 11 potential SO cases due to missing data, corresponding to approximately 15% of the total dataset. Due to the small numbers of cases involved, this omission is likely to result in an under-estimation of

incidence rates and risk. Similarly, our institution is a tertiary referral centre and the case mix, complexity and rates reported here may not be representative of other centres.

Concluding paragraph

We feel that the most significant finding in this study is the calculated risk of SO development following a single VR procedure, which is significantly lower in our cohort than previously reported in the literature[19]. This is seen to rise exponentially with the increasing number of procedures, as evident from the exponential trend line fit. This allows for informed decision making and accurate counselling of patients during the process of consent for surgery and gives an accurate appreciation for the actual risk of each additional VR intervention.

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457

458 **Legends for Figures**

459

460 Figure 1

461 Age at diagnosis, grouped by decades

462 Figure 2

463 First Trigger Event Analysis – Relative Prevalence of Trauma versus Surgery over Time

464 The summary of the frequency of multiple procedures is given in Table 1. Surgery on ocular
465 adnexa was excluded from the procedure count. Intra-ocular laser procedures were included
466 (Yag capsulotomy, retinal laser, Yag iridotomy, cyclodiode). The absolute numbers are
467 shown on the columns.

468 Figure 3

469 Risk of Developing SO with Increasing Number of Vitreoretinal Procedures

VR procedures defined as pars plana vitrectomy for any indication or any scleral buckling or encirclement. Shown with exponential fit trend line.

Figure 4

Visual Acuity Change from Presentation to final follow up.

Visual acuity at presentation is plotted against the change in VA (LogMAR) on the y-axis. A gain in visual acuity is denoted by positive change, a loss in acuity by negative values.

Figure 5

Trend of Visual Acuity Change with Advancing Time

Date diagnosed spans the years 1938-2015.

Figure 1

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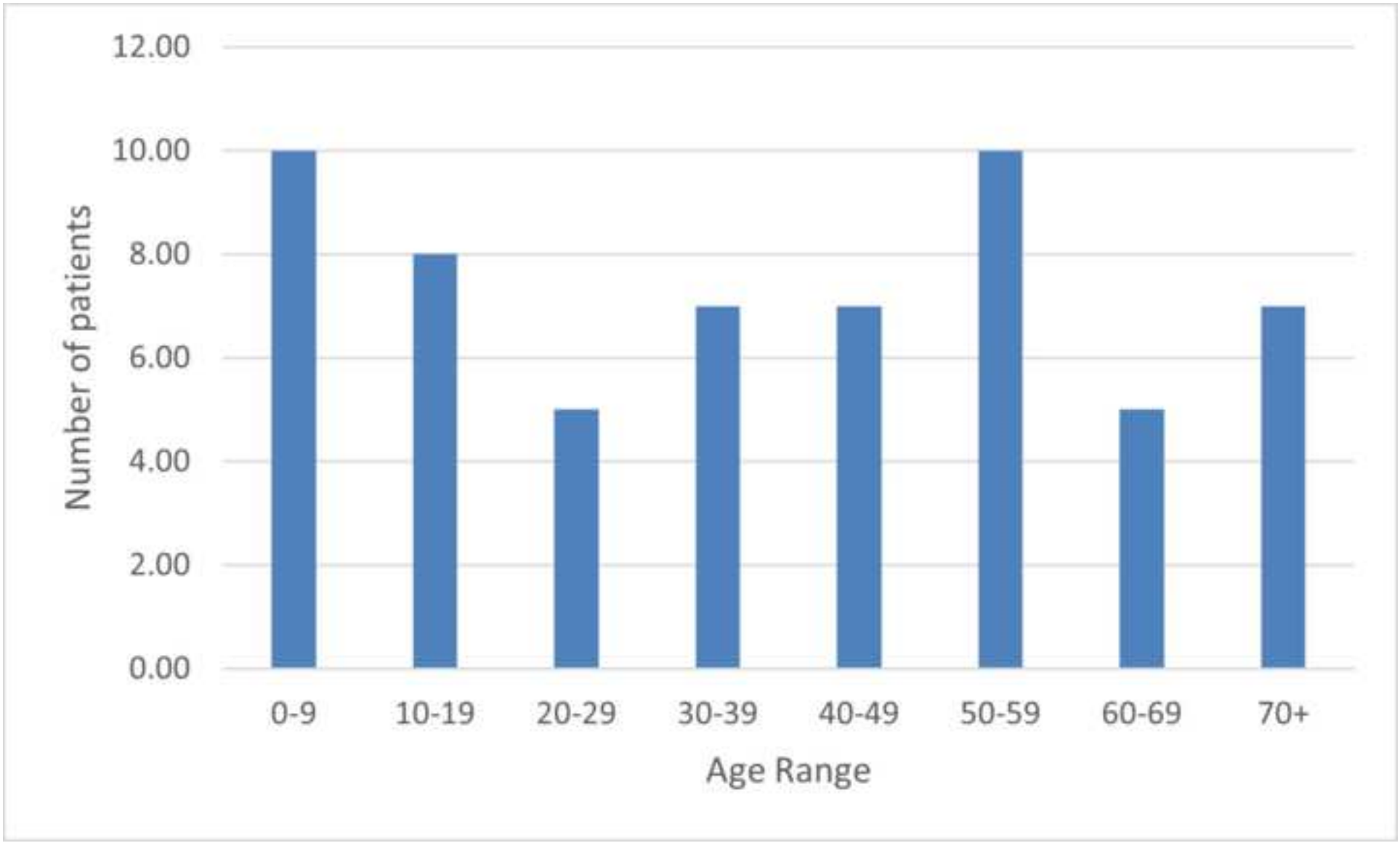

Figure 3

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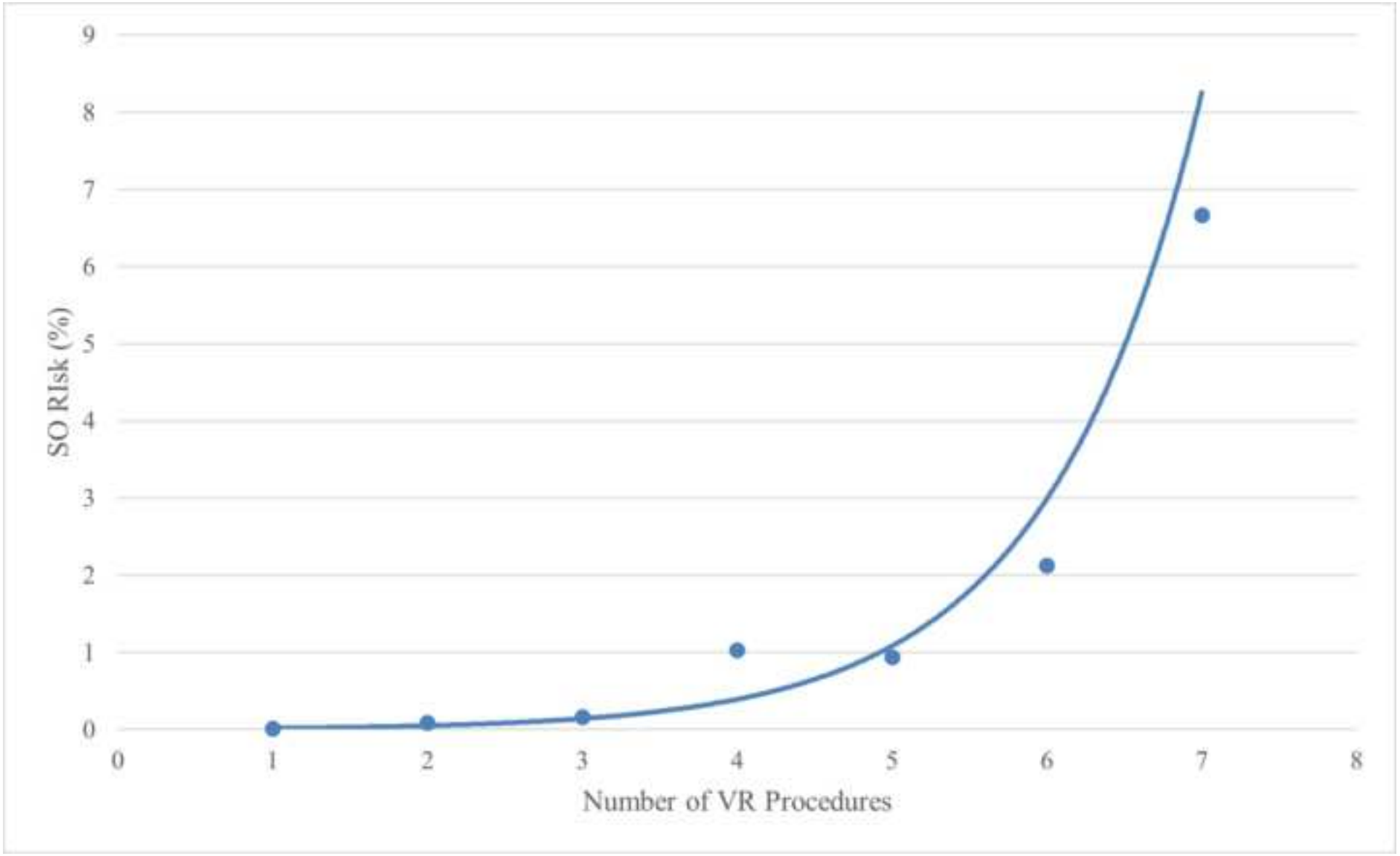

Figure 4

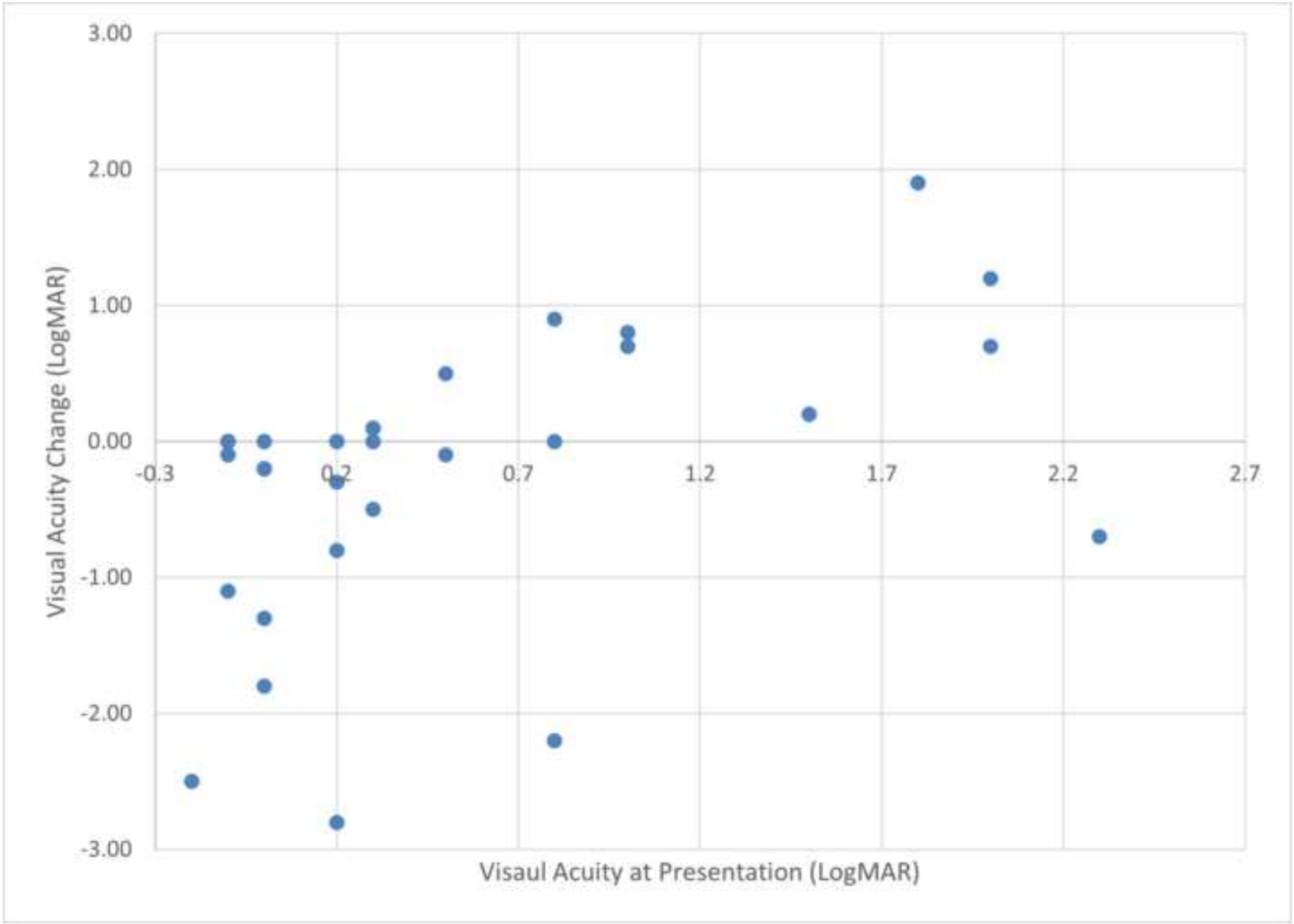

Figure 2 revised

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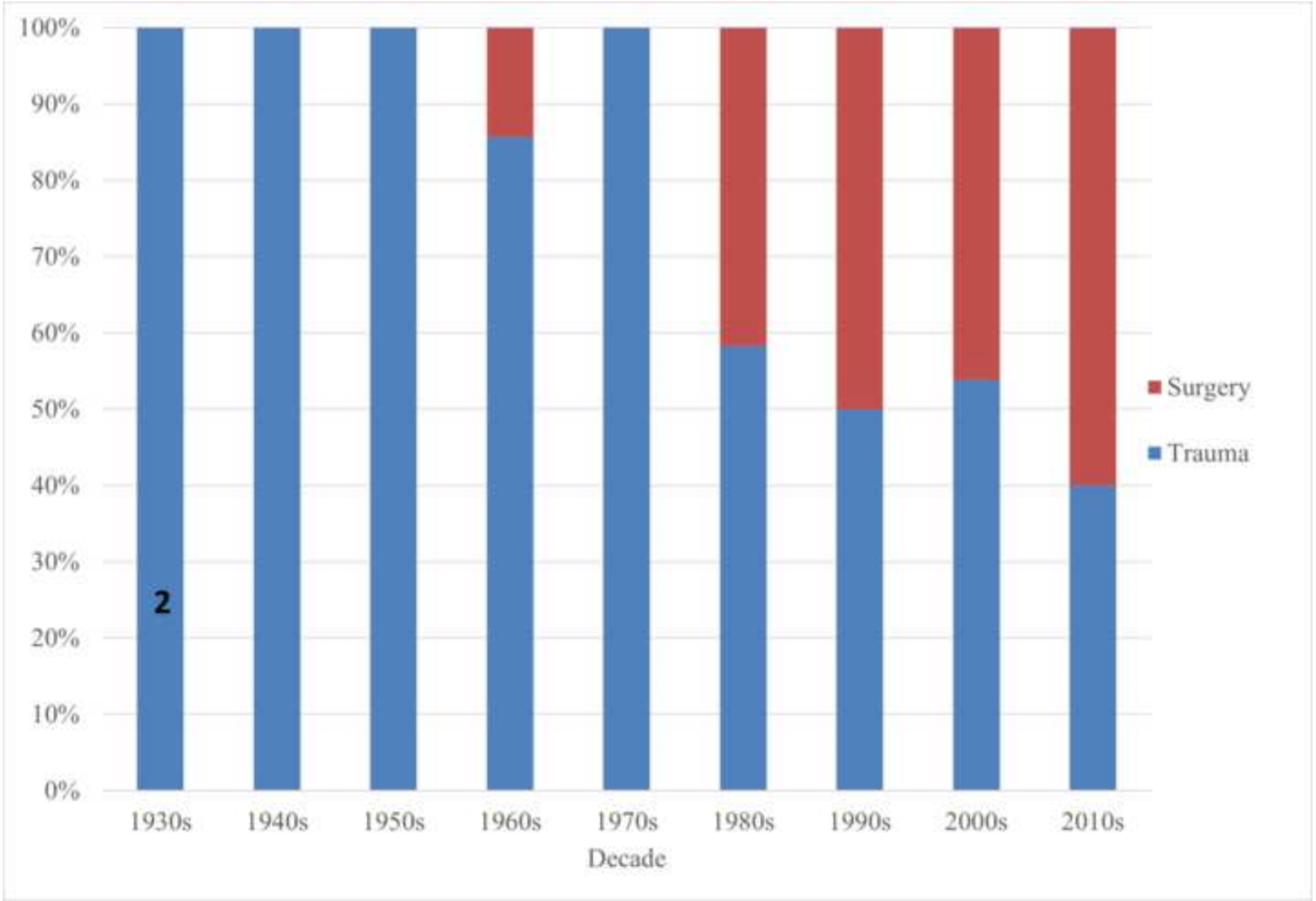

Figure 5 revised

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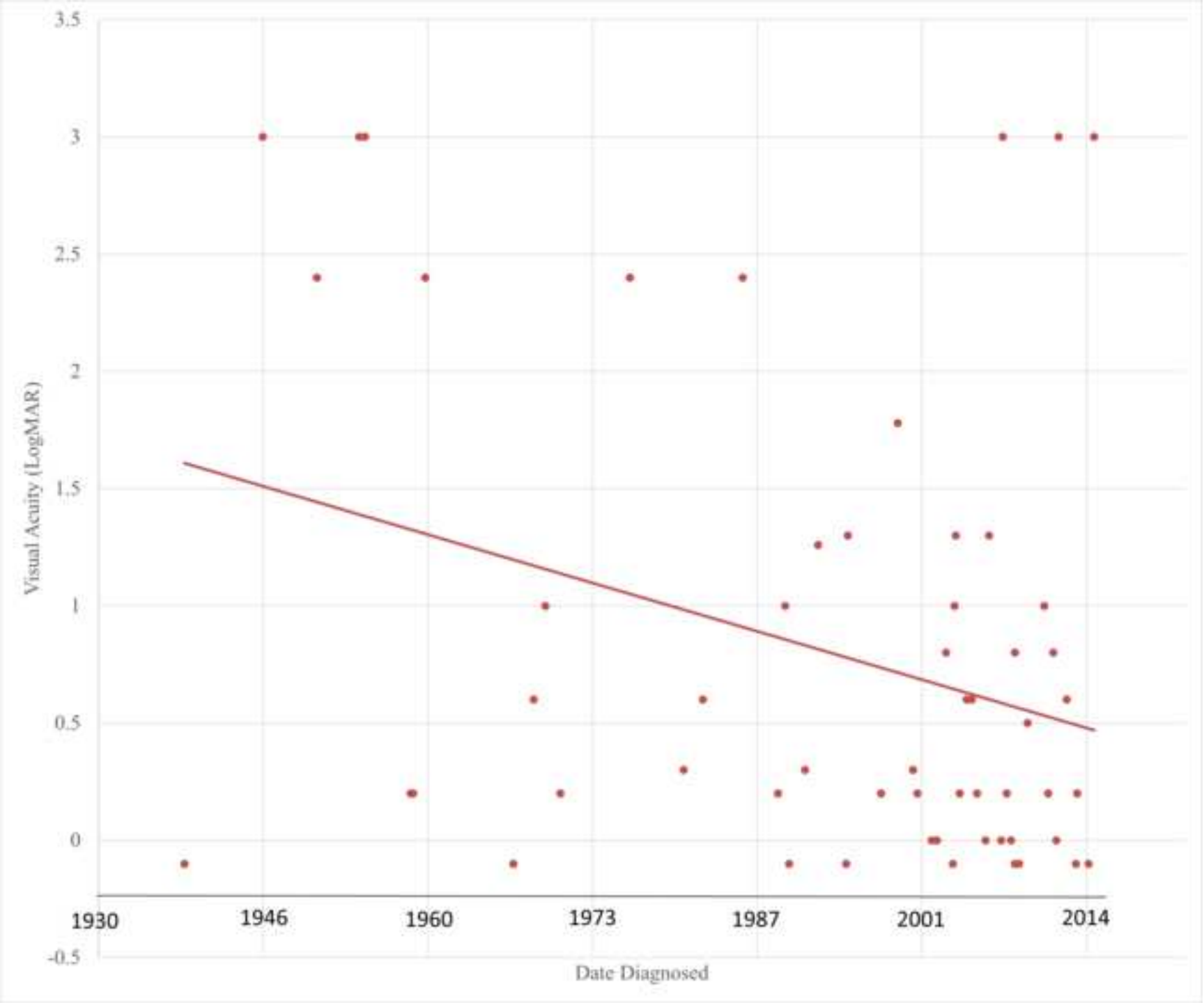

Number of Procedures	Number of patients	%
1	8	13
2	30	49
3	7	11
4	6	10
5	2	3
6+	8	13

Number of surgical procedures

Number and percentage of surgical procedures undertaken in the cohort.

Table 2

Click here to access/download;Table;Table 2.docx

Patient	VR Procedure number	Scleral buckle	PPV – all gauge	Cryo/ Laser	Retinectomy	Gas	Oil	ROSO	Phaco / lens	Other	Trauma	Total
1	1	•	•	•			•		•			
	2			•								
	Total	1	1	2			1		1			2
2	1	•		•								
	2		•	•			•					
	3									Scleral buckle removal		
	4									Enucleation		
	Total	1	1	2			1				2	4
3	1	•		•								
	2	•	•	•		•			•			
	3										•	
	4		•	•		•						
	5		•	•			•					
	6									Enucleation		
	Total	2	3	4		2	1		1		1	1	6
4	1	•		•								
	Total	1		1								1
5	1									Squint surgery, scleroplasty		
	2								•			
	3									Yag laser capsulotomy		
	4		•						•			
	5		•	•		•						
	6		•	•			•					
	Total		3	2		1	1		2		3	2
6	1		•	•			•					
	2							•	•			
	Total		1	1			1	1	1			2
7	1		•	•		•						
	2								•			
	3		•	•	•		•					
	4									AC washout		
	5		•	•	•		•		•			
	Total		3	3		2	1	2		2	1		5
8	1		•	•	•		•					
	2		•	•			•		•			
	3									Iridectomy		
	4									Iridectomy		
	Total		2	2		1	1		1		2		4
9	1										•	
	2	•		•						Trans-scleral drain		
	Total	1		1							2	2
10	1										•	
	2								•			
	3		•						•			
	4								•			
	5									AC washout x 2		
	6		•						•			
	Total		2						4		3	7
11	1								•			
	2										•	
	3		•	•	•		•					
	Total		1	1		1	1		1		1	3
12	1		•	•	•		•					
	Total		1	1		1	1					1
13	1										•	
	2									Tap + inject as ?endophthalmitis		
	3								•	•		
	4		•	•	•		•			Avastin		
	Total		1	1		1	1		1		2	4
14	1										•	
	2									Primary repair		
	3		•	•		•						
	Total		1	1		1					1	3
15	1								•	DSAEK		
	2									Penetrating keratoplasty		
	3									Endophthalmitis => tap + inject		
	4		•									
	Total		1						1		3	4

Summary of vitreoretinal procedural steps undertaken in the subset of patients undergoing VR surgery.

Abbreviations: PPV – pars plana vitrectomy, cryo – cryotherapy, ROSO – removal of silicone oil, phaco - phacoemulsification

Number of VR Procedures	Total count at the Unit in same time span	Total SO patients in VR subset	Risk of SO (%)
1	23533	2	0.008
2	4769	4	0.084
3	1267	2	0.158
4	389	4	1.028
5	107	1	0.935
6	47	1	2.128
7	15	1	6.667
8	4	0	0.000
9	1	0	0.000
Total	**39391**	**15**	

All vitreoretinal procedures undertaken at the unit over the study time period, grouped by number of procedures per patient.

VR procedures defined as pars plana vitrectomy for any indication or any scleral buckling or encirclement.

Vision (LogMAR)	Number of patients at presentation (n, %)	Number of patients at 1 year (n, %)	Number of patients at latest follow up (n, %)
NPL	0	0	6 (10)
PL-1.1	5 (10)	3 (5)	8 (13)
1.0-0.4	9 (17)	8 (13)	14 (23)
0.3+	21 (40)	37 (62)	30 (49)
Unknown	17 (33)	12 (20)	3 (5)

Visual acuity at presentation, at 1 year post-diagnosis and at the end of the recorded follow up.

VA Change LogMAR	Number of patients at 1 year (n, %)	Number of patients at latest follow up (n, %)
Improved	10 (16)	9 (15)
Unchanged	20 (33)	18 (30)
Loss 0.1-0.3	6 (10)	7 (13)
Loss 0.3+	3 (5)	9 (17)
Unknown	22 (36)	11 (18)

Changes in visual acuity

Number of patients experiencing changes in visual acuity at 1 year post-diagnosis and at the end of recorded follow up.

	VR surgery as first event	
	1 event	**2+ events**
Mean VA at Diagnosis	0.5	0.97
Mean VA at 1 year	0.4	0.47
Mean VA at End	0.8	0.90
	Non-VR surgery as first event	
	1 event	**2+ events**
Mean VA at Diagnosis	0.89	0.66
Mean VA at 1 year	1.04	0.79
Mean VA at End	0.8	1.12
	Trauma as first event	
	1 event	**2+ events**
Mean VA at Diagnosis	-0.1	0.18
Mean VA at 1 year	0	0.10
Mean VA at End	0.25	0.78

The mean LogMAR visual acuity at different time points when split into the single event cases versus the multiple event cases. Also sub-divided by first event into VR surgery versus other surgery versus trauma.

Table 7

Comorbidities Since Diagnosis	BCVA at Diagnosis	BCVA at 1 year	VA loss at 1 year (LogMAR)	BCVA at End of Follow Up	VA Loss at End of Follow Up (LogMAR)
Cataract (operated)	-0.2	0	-0.20	2.3	-2.50
Cataract (operated)	-0.1	-0.1	0.00	-0.1	0.00
Cataract (operated), glaucoma	0.8	1.3	-0.50	0.8	0.00
FTMH	0.2	1	-0.80	1	-0.80
Glaucoma, Cataract (operated), BK	-0.1	-0.1	0.00	1	-1.10
Subluxed lens	2	unknown		1.3	0.70
Glaucoma	0.3	0	0.30	0.2	0.10
Glaucoma, Cataract (operated)	0.5	0.6	-0.10	0.6	-0.10
	0.2	0.2	0.00	0.2	0.00
	0	-0.1	0.10	0.2	-0.20
Cataract (operated)	0	0	0.00	0.2	-0.20
Glaucoma, Cataract (operated)	0	0	0.00	0	0.00
Cataract (operated)	0	0	0.00	0	0.00
Glaucoma, Cataract (operated), hypotony	0.3	0.3	0.00	0.3	0.00
Glaucoma	-0.1	-0.1	0.00	-0.1	0.00
Glaucoma	-0.1	-0.1	0.00	-0.1	0.00
Glaucoma, hypotony, Cataract (operated), myopic degeneration, CMO	1	0.2	0.80	0.3	0.70
CMO	0	0.2	-0.20	1.8	-1.80
PDR	0.3	0.3	0.00	0.3	0.00
CMO, ERM, GA	0	0.6	-0.60	1.3	-1.30
Cataract (operated)	1	0.2	0.80	0.2	0.80
RD, Cataract (operated)	0.3	0.3	0.00	0.2	0.10
	0.5	-0.1	0.60	0	0.50
BRVO, CRVO, TRD	0.8	0.5	0.30	0.8	0.00
Cataract (operated)	0.3	0.3	0.00	0.8	-0.50
	-0.1	-0.1	0.00	0	-0.10
Cataract (operated), pathologic myopia	2	0.6	1.40	0.8	1.20
RD, glaucoma, Cataract (operated), BK	0	0.2	-0.20	1.3	-1.30
Glaucoma, DSEK for PBK	-0.1	-0.1	0.00	-0.1	0.00
Corneal scar - dendritic ulcer	0.2	0	0.20	0.2	0.00
Cataract (operated)	1.5	1.8	-0.30	1.3	0.20
	0	0.2	-0.20	0.2	-0.20
	0.8	0.8	0.00	3	-2.20
	-0.1	-0.1	0.00	-0.1	0.00
	-0.1	-0.1	0.00	-0.1	0.00
	-0.1	-0.1	0.00	-0.1	0.00
Cataract (operated)	0.2	0.2	0.00	0.5	-0.30
optic neuropathy	0.2	0.2	0.00	3	-2.80
PDR, glaucoma	-0.1	unknown		0	-0.10
	1.8	-0.1	1.90	-0.1	1.90
Glaucoma	0	unknown		0.2	-0.20
	2.3	2.7	-0.40	3	-0.70
Glaucoma	0.8	0	0.80	-0.1	0.90

Comorbidities as contributing factors to visual acuity change

FTMH – full thickness macular hole, BK – band keratopathy, CMO – cystoid macular oedema, PDR – proliferative diabetic retinopathy, ERM – epiretinal membrane, GA – geographic atrophy, RD – retinal detachment, BRVO – branch retinal vein occlusion, CRVO – central retinal vein occlusion, TRD – tractional retinal detachment, DSEK – Descemet's stripping endothelial keratoplasty, PBK – pseudophakic bullous keratopathy

Drug	Number of unique patients
Mycophenolate mofetil	15
Azathioprine	12
Cyclosporine	9
Tacrolimus	4
Infliximab	4
Methotrexate	2

Summary of patients treated with different immunosuppressants.

Agents	Number of patients
Cyclosporine + Mycophenolate mofetil	4
Azathioprine + Cyclosporine	2
Mycophenolate mofetil + Tacrolimus	2
Mycophenolate mofetil + Cyclosporine + Infliximab	2
Azathioprine + Mycophenolate mofetil	1
Infliximab + Methotrexate	1
Cyclosporine + Azathioprine + Tacrolimus	1
Cyclosporine + Azathioprine + Mycophenolate mofetil + Infliximab	1

Summary of concurrent combinations of immunosuppressants used in the patient cohort

Time Period	Number of Eviscerations	Number of Patients	% of Patients with SO Having Evisceration
1930s	1	1	100
1940s	2	2	100
1950s	5	5	100
1960s	2	4	50
1970s	2	3	67
1980s	2	5	40
1990s	2	8	25
2000-2005	2	13	15
2006-2010	1	10	10
2011-2015	0	10	0

Trend for primary evisceration with advancing time period

Table 11

		VA at 1 year post-diagnosis - sympathising eye (LogMAR)			VA at latest follow up - sympathising eye (LogMAR)		
Characteristic		**Improvement/No Worsening (if ≤0.2)**	**Deterioration/No Change (if ≥0.2)**	***p*-value**	**Improvement/No Worsening (if ≤0.2)**	**Deterioration/No Change (if ≥0.2)**	***p*-value**
Age at diagnosis (years; mean, SD)		41.1 (20.6)	50.5 (22.7)	0.407*	40.5 (20.1)	49.7 (22.3)	0.147*
Gender (n, %)	Male	8	7	**0.031**†	17	13	0.648†
	Female	8	5		7	6	
Time from first event to diagnosis (days; mean SD)		4293.8 (5359.9)	3405.6 (5041.9)	0.960*	4952.5 (5676.8)	2278.7 (3707.6)	0.211*
Time from last event to diagnosis (days; mean, SD)		1624.5 (2669.9)	2456.9 (4488.1)	0.352*	2166.5 (4260.1)	1416 (2023.0)	0.582*
First event	Trauma	19	4	**0.008**†	16	7	0.113†
	Surgery	6	11		8	12	
Presenting VA (LogMAR; mean, SD)		0.04 (0.19)	0.71 (0.73)	0.363*	0.20 (0.41)	1.13 (1.03)	0.407*
Sympathising eye	Right	12	9	0.735†	13	10	0.516†
	Left	13	7		11	11	
Number of immunosuppresants (n, %)	0 (9.8)	4	1	0.742†	4	2	0.97†
	1 (34.4)	8	7		10	7	
	2 (24.6)	5	4		5	4	
	3 (11.5)	3	2		2	3	
	4+ (8.2)	4	1		2	3	
Duration of immunosuppression (years; mean, median) Range 0-56		5.0 (2.5, 3.0)	6.3 (5.0, 5.0)	0.711*	3.5 (2.0, 1.0)	7.2 (5.0, 5.0)	0.363*
Enucleation	Yes	6	4	0.943†	6	5	0.874†
	No	19	12		18	17	
Number of flare ups (mean, median) Range 0-14		3.2	2.6	0.201†	2.8	2.9	0.516†
VR surgery during clinical course	Yes	10	10	0.31†	9	13	0.226†
	No	15	6		15	8	

Table 9. If the patient's vision was recorded as 0.2 LogMAR or better at presentation and did not drop, they were grouped with those improving their vision. If the vision was recorded as worse than 0.2, they were grouped with those whose vision deteriorated. *two-tailed Mann-Whitney U test; †Chi-square test. Significant results marked in bold.

Characteristic		Immunosuppression Load Required: Steroid only	Immunosuppression Load Required: Adjunctive immunosuppresants	*p*-value
Age (years; mean, SD)		43.3 (26.1)	37.8 (20.5)	0.341
Gender (n, %)	Male	13 (41)	19 (59)	0.414
	Female	8 (53)	7 (47)	
Time from first event to diagnosis (days, mean)		3181.1	3286.8	0.940
Time from last event to diagnosis (days, mean)		1948.6	3183.5	0.494
First event (n, %)	Trauma	13 (42)	18 (58)	0.464
	Surgery	9 (53)	8 (47)	
Presenting VA (LogMAR; mean)		0.38	0.42	0.891
VA at 1 year (LogMAR; mean)		0.34	0.29	0.789
Final VA (LogMAR; mean)		0.55	0.93	0.196
Sympathising eye (n, %)	Right	9 (40)	15(60)	0.247
	Left	13 (54)	11 (46)	
Enucleation (n, %)	Yes	7 (50)	7 (50)	0.710
	No	15 (44)	19 (56)	
Number of flare ups (mean, median)		1.59 (1)	3.76 (3)	0.664
VR surgery during clinical course (n, %)	Yes	6 (31)	13 (69)	0.109
	No	16 (55)	13 (45)	

Significance of clinical characteristics in requiring second line immunosuppression

Table 1

Sex	Age at First Event	Age at Diagnosis	1st Event	Procedures Pre-diagnosis
m	31	31	trauma	Globe repair
m	11	11	trauma	Enucleation
f	9	17	trauma	
f	7	52	trauma	Enucleation
f	7	unknown	trauma	Enucleation
m	16	50	trauma	PPV RD, laser retinopexy, ROSO
m	19	19	trauma	Cataract + vit loss, wound resuturing/iris excision, enucleation
m	13	13	trauma	Enucleation (pre)
f	2	8	trauma	
m	7	7	trauma	Enucleation
m	18	19	trauma	Globe repair x 2
m	20	56	trauma	CB RD x 2
m	7	61	trauma	Enucleation (pre)
f	12	12	trauma	Globe repair, cataract, glauc, RD, enucleation
m	70	70	trauma	Globe repair
m	7	7	trauma	Globe repair
m	8	8	trauma	Enucleation
m	7	7	trauma	Enucleation
f	4	4	trauma	Enucleation
f	16	35	trauma	Enucleation (pre)
f	22	23	trauma	Enucleation (pre)
m	9	12	trauma	Globe repair + IOFB removal
m	13	39	trauma	Enucleation (pre), lid
m	7	8	trauma	
m	23	36	trauma	Lid, cataract
m	5	6	trauma	Enucleation (pre)
m	40	40	trauma	Globe repair
m	33	35	trauma	Globe repair, cataract, trauma, IOL removal, sec IOL
m	37	39	trauma	CB RD
m	18	40	trauma	Cataract , IOL exchange + ant vit, AC washout x 2, PPV + capsulectomy, BVT
f	58	59	trauma	Globe repair
m	5	5	trauma	Globe repair
m	3	18	trauma	Globe repair
m	17	19	trauma	
m	9	26	trauma	Globe repair
m	11	53	trauma	Cataract, CB RD
f	39	47	trauma	PPV RD + cataract
f	4	5	trauma	Enucleation (pre)
m	45	46	trauma	Tap/inject, phaco + IOL, PPV RD
m	46	46	trauma	Globe repair, PPV RD
f	3	52	surgery	Goniotomy x 8, NP trauma, phaco + IOL, Yag caps

m	39	45	surgery	CB RD, PPV RD, SB removal, enucleation
m	16	25	surgery	CB RD, PPV RD + lensecomy + CB, trauma, PPV RD x 2, evisceration
m	unknown	26	surgery	PPV + lensectomy, PTK
m	58	58	surgery	CB RD
f	unknown	50	surgery	Evisceration
f	63	70	surgery	CB RD
m	44	56	surgery	CB RD, cataract x 2
f	4	31	surgery	Squint x 2, scleroplasty x 2, cataract, Yag caps, PPV + ECCE, PPV RD x 2
f	70	79	surgery	PPV RD x 2, ECCE + ROSO
f	78	81	surgery	PPV RD x 3, AC washout, phaco + IOL
m	24	42	surgery	PPV RD x 4, phaco/ROSO, ref laser, PPV RD + CB, phaco + IOL
m	24	26	surgery	PPV RD x 2, PPV RD + cataract x 2, iridectomy x 2, CB RD, cyclodiode x 2
f	84	85	surgery	Plaque brachytherapy
m	78	79	surgery	ECCE, trauma (P), globe repair, PPV RD
m	51	68	surgery	Cataract, CB RD
m	68	70	surgery	Cataract x 2, PPV RD
m	61	64	surgery	Phaco + IOL x 2
m	61	61	surgery	Trab x 2, phaco + IOL
f	61	63	surgery	Phaco/DSAEK, PK, tap/inject, PPV
m	53	58	surgery	Phaco + IOL x 2, PPV RD x 3

Summary of surgical procedure undertaken across the cohort

Legend for abbreviated terms: Enucleation (pre) = enucleation performed prior to diagnosis (vs. concurrent/consequent), trauma (NP) = non-penetrating trauma, trauma (P) = penetrating trauma, cataract = cataract extraction (unspecified modality), phaco + IOL = phacoemulsification + intra-ocular lens implant, PPV RD = pars plana vitrectomy for retinal detachment, CB RD = cryotherapy and scleral buckling for retinal detachment, PTK = phototherapeutic keratectomy, lid = any eyelid surgery, Yag caps = Yag laser capsulectomy, ECCE = extracapsular cataract extraction, ROSO = removal of silicone oil, trab = trabeculectomy, BVT = Baerveldt drainage tube implant, DSAEK = Descemet's stripping automated endothelial keratoplasty, PK = penetrating keratoplasty, Glauc = unspecified glaucoma procedure

Table 1

Sex	Date of Diagnosis	Age at First Event	Age at Diagnosis	1st Event	Procedures Pre-diagnosis
m	1940	8	8	trauma	Enucleation
f	1946	4	4	trauma	Enucleation
f	1951	4	5	trauma	Enucleation (pre)
m	1954	5	6	trauma	Enucleation (pre)
f	1955	7	unknown	trauma	Enucleation
m	1958	7	7	trauma	Enucleation
m	1959	11	11	trauma	Enucleation
m	1960	13	13	trauma	Enucleation (pre)
f	1967	9	17	trauma	
m	1969	19	19	trauma	Cataract + vit loss, wound resuturing/iris excision, enucleation
m	1969	7	8	trauma	
f	1971	12	12	trauma	Globe repair, cataract, glauc, RD, enucleation
m	1977	31	31	trauma	Globe repair
f	1979	7	52	trauma	Enucleation
f	1981	22	23	trauma	Enucleation (pre)
m	1983	18	19	trauma	Globe repair x 2
f	1985	2	8	trauma	
m	1986	7	7	trauma	Globe repair
m	1986	7	7	trauma	Enucleation
m	1989	16	50	trauma	PPV RD, laser retinopexy, ROSO
m	1989	39	45	surgery	CB RD, PPV RD, SB removal, enucleation
m	1990	9	12	trauma	Globe repair + IOFB removal
m	1991	58	58	surgery	CB RD
m	1992	16	25	surgery	CB RD, PPV RD + lensecomy + CB, trauma, PPV RD x 2, evisceration
m	1995	13	39	trauma	Enucleation (pre), lid
m	1995	17	19	trauma	
f	1995	63	70	surgery	CB RD
m	1997	44	56	surgery	CB RD, cataract x 2
m	1999	23	36	trauma	Lid, cataract
m	2000	20	56	trauma	CB RD x 2
f	2000	unknown	50	surgery	Evisceration
m	2002	70	70	trauma	Globe repair
m	2002	33	35	trauma	Globe repair, cataract, trauma, IOL removal, sec IOL
m	2003	18	40	trauma	Cataract , IOL exchange + ant vit, AC washout x 2, PPV + capsulectomy, BVT
f	2003	78	81	surgery	PPV RD x 3, AC washout, phaco + IOL
f	2004	58	59	trauma	Globe repair
m	2004	unknown	26	surgery	PPV + lensectomy, PTK

m	2004	24	26	surgery	PPV RD x 2, PPV RD + cataract x 2, iridectomy x 2, CB RD, cyclodiode x 2
m	2005	7	61	trauma	Enucleation (pre)
m	2005	37	39	trauma	CB RD
m	2006	5	5	trauma	Globe repair
f	2006	84	85	surgery	Plaque brachytherapy
f	2007	16	35	trauma	Enucleation (pre)
m	2008	40	40	trauma	Globe repair
f	2008	70	79	surgery	PPV RD x 2, ECCE + ROSO
m	2008	78	79	surgery	ECCE, trauma (P), globe repair, PPV RD
m	2008	51	68	surgery	Cataract, CB RD
m	2009	3	18	trauma	Globe repair
m	2009	9	26	trauma	Globe repair
m	2010	11	53	trauma	Cataract, CB RD
f	2011	39	47	trauma	PPV RD + cataract
f	2011	4	31	surgery	Squint x 2, scleroplasty x 2, cataract, Yag caps, PPV + ECCE, PPV RD x 2
m	2012	24	42	surgery	PPV RD x 4, phaco/ROSO, ref laser, PPV RD + CB, phaco + IOL
m	2012	68	70	surgery	Cataract x 2, PPV RD
m	2012	61	64	surgery	Phaco + IOL x 2
f	2013	3	52	surgery	Goniotomy x 8, NP trauma, phaco + IOL, Yag caps
m	2014	45	46	trauma	Tap/inject, phaco + IOL, PPV RD
m	2014	46	46	trauma	Globe repair, PPV RD
m	2014	61	61	surgery	Trab x 2, phaco + IOL
f	2015	61	63	surgery	Phaco/DSAEK, PK, tap/inject, PPV
m	2015	53	58	surgery	Phaco + IOL x 2, PPV RD x 3

Summary of surgical procedure undertaken across the cohort

Legend for abbreviated terms: Enucleation (pre) = enucleation performed prior to diagnosis (vs. concurrent/consequent), trauma (NP) = non-penetrating trauma, trauma (P) = penetrating trauma, cataract = cataract extraction (unspecified modality), phaco + IOL = phacoemulsification + intra-ocular lens implant, PPV RD = pars plana vitrectomy for retinal detachment, CB RD = cryotherapy and scleral buckling for retinal detachment, PTK = phototherapeutic keratectomy, lid = any eyelid surgery, Yag caps = Yag laser capsulectomy, ECCE = extracapsular cataract extraction, ROSO = removal of silicone oil, trab = trabeculectomy, BVT = Baerveldt drainage tube implant, DSAEK = Descemet's stripping automated endothelial keratoplasty, PK = penetrating keratoplasty, Glauc = unspecified glaucoma procedure