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ORIGINAL ARTICLE

Vitreoretinal complications and surgical outcomes in patients with X-linked retinoschisis

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Abstract

Purpose: X-linked retinoschisis (XLRS) is an inherited vitreoretinal disorder characterized by macular retinoschisis. In a subgroup of patients, peripheral retinoschisis can occur, potentially leading to complications such as vitreous haemorrhage (VH) and retinal detachment (RD). Limited data exist on the optimal management of these complications. This retrospective cohort study evaluates clinical characteristics and outcomes of VH and RD in XLRS patients.

Methods: We included 49 patients diagnosed with XLRS who developed VH and/or RD. Collected data included demographics, best-corrected visual acuity (BCVA), retinal findings, treatment strategies and anatomical and functional outcomes.

Results: The median follow-up was 19.0 years (IQR 11.4–35.6) with 12 visits (IQR 6–19). Median age at first VH was 15.3 years (IQR 5.5–16.3) and 7.5 years (IQR 2.4–15.9) for RD. Peripheral retinoschisis was present in 94% of VH eyes and 80% of RD eyes. Of 39 patients with VH, 10 (26%) had bilateral VH; only 1 (3%) presented with concurrent bilateral VH. VH resolved without intervention in 42 of 49 eyes (86%), although recurrence occurred in 22 eyes (45%). RD was observed in 25 eyes of 21 patients, with rhegmatogenous RD in 16 eyes (64%), tractional in 7 (28%) and exudative in 3 (12%), with one eye showing mixed features. Surgery was performed in 21 eyes (84%), achieving retinal reattachment in 43% after primary surgery and in 90% after multiple procedures. In 15 eyes operated on after 2005, final reattachment was achieved in 93%. BCVA improved postoperatively in 10 of 21 eyes (48%), was stable in 5 (24%) and declined in 2 (10%); 4 (19%) lacked follow-up BCVA.

Conclusion: VH in XLRS is often self-limiting with favourable functional and anatomical outcomes, but recurrence is common. RD typically requires surgical repair, often multiple procedures, with guarded visual prognosis despite anatomical reattachment. Regular follow-up, particularly in young XLRS patients with peripheral retinoschisis, is essential for early detection and management of these potential complications.

1 | INTRODUCTION

X-linked (juvenile) retinoschisis (XLRS) is a relatively common early-onset vitreoretinal dystrophy that affects young males, with a prevalence of 1 in 5000–30 000 (Hahn et al., 2022; Molday et al., 2012). This inherited retinal degenerative disease results from various pathogenic variants in the *RS1* gene, encoding retinoschisin, a cell-surface protein secreted by photoreceptors and bipolar cells (Sauer et al., 1997). This protein is crucial for cell-to-cell adhesion, signal transduction and maintaining the retina's anatomical structure (Wu

et al., 2005). Consequently, the insufficiency or absence of retinoschisin leads to disruption of retinal integrity, causing the formation of striking cystoid fluid collections, which is the hallmark of XLRS. Peripheral retinoschisis, seen as a sharply defined detachment of the inner retina, is seen in up to 50% of the patients, often in the inferotemporal quadrant (Hahn et al., 2022). XLRS typically presents in early childhood with bilaterally reduced best-corrected visual acuity (BCVA), which generally ranges from 20/60 to 20/120 but can vary from near normal to severe vision loss. BCVA remains relatively stable in early life but gradually declines after the fourth or fifth decade due to progressive outer retinal atrophy (Hahn et al., 2022). However, XLRS patients can experience an acute severe decline in BCVA due to complications such as vitreous haemorrhages (VH) and retinal detachments (RD), leading to a poorer prognosis (Hahn et al., 2022). These complications can manifest early, with reports of RD occurring in infancy in severe cases (George et al., 1996; Lee et al., 2009; Savoie & Ferrone, 2017). While gene therapy is currently tested in human trials, no curative treatment is available for XLRS patients to date (Cukras et al., 2018; Pennesi et al., 2022). The cystoid fluid collections can be managed with oral and topical carbonic anhydrase inhibitors, where oral acetazolamide demonstrates greater potency, albeit with limited visual gain and unknown long-term benefit (Hensman et al., 2024). Current management also includes regular fundus examinations and surgical interventions for vitreoretinal complications associated with XLRS. Little is known about the clinical outcomes of patients experiencing VH and RD. In this retrospective study, we report on the clinical characteristics and outcomes of VH and RD in a relatively large cohort of XLRS patients.

2 | METHODS

We reviewed the medical records of 78 consecutive XLRS patients who experienced VH and/or RD between 1955 and 2024. Data from Dutch patients were retrieved from medical records in the Delleman Archive, a database dedicated to hereditary eye diseases at Amsterdam University Medical Centre, and from multiple centres participating in the RD5000 consortium, a nationwide registry for inherited retinal dystrophies in the Netherlands (van Huet et al., 2014). Additionally, patients were included from the Ophthalmic Genetics Unit at the Department of Ophthalmology and the Centre for Medical Genetics in Ghent, Belgium. Eligible patients had either a confirmed pathogenic *RS1* variant or were first-degree relatives of individuals with a known pathogenic variant. Patients without genetic confirmation were included if they exhibited X-linked inheritance, reduced visual acuity and characteristic retinoschisis features on fundoscopic examination and/or spectral-domain optical coherence tomography. We excluded cases with any loss of visual function attributed to factors other than the natural progression of XLRS, such as perforating ocular trauma, which might have affected the outcome measures. Inclusion in this study required clinical data of visits before and after a VH or RD. Rhegmatogenous RD was differentiated from (bullous) peripheral retinoschisis by detachment of the outer retina with one or more full-thickness retinal breaks in the outer retina, confirmed either preoperatively by fundoscopy, ultrasonography (USG), optical coherence tomography (OCT) or peroperatively. The patients underwent routine ophthalmological examinations and imaging at the clinical visits. Key clinical characteristics collected included demographic information, age at the time of complication, BCVA, findings from retinal examinations, results from other ocular investigations, frequency of VHs and RDs, history of preceding trauma, details of any ocular intervention and anatomical outcomes at the final visit. BCVA was assessed using Teller Acuity Cards, the LH visual acuity chart or Snellen charts, depending on the patient's age and the time period of evaluation, while fix-and-follow assessments were performed for infants. Postoperative BCVA was measured 1 to 5 months after the final surgery needed to achieve retinal attachment in eyes requiring multiple procedures. In eyes with VH, the final BCVA was documented at the first visit following resolution of the VH. The grade of visual impairment was classified according to the World Health Organization: mild vision impairment (VA, <20/40 and ≥ 20/60), moderate vision impairment (VA, <20/60 and ≥ 20/200), severe vision impairment (VA, <20/200 and ≥ 20/400) and blindness (VA, <20/400). This retrospective study received approval from the Medical Ethics Committee of both Erasmus Medical Centre and Ghent University Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives. For Belgian patients, informed consent was waived by Ghent University Hospital due to the use of anonymized data.

3 | RESULTS

We included 49 of 78 patients after reviewing their ocular medical history. All but 4 patients were included in the original study population described by Hahn et al., which reported only the occurrence of VH and RD without further details (Hahn et al., 2022). In that study, 45 of 340 patients (13%) experienced VH and 29 of 340 (9%) experienced RD. From these patients, 10 patients with VH and 9 patients with RD were excluded due to a lack of recent data before or after the complication, and 1 patient was excluded due to perforating trauma to the eye leading to RD. From the included patients, 39 of 49 experienced VH and 21 of 49 experienced RD (see Figure 1). The median follow-up time of these 49 patients was 19.0 years (IQR 11.4–35.6), with a median of 12.0 visits (IQR 6.0–19.0). Patients were seen for the first time by the ophthalmologist at a median age of 3.5 years (IQR 1.2–7.6).

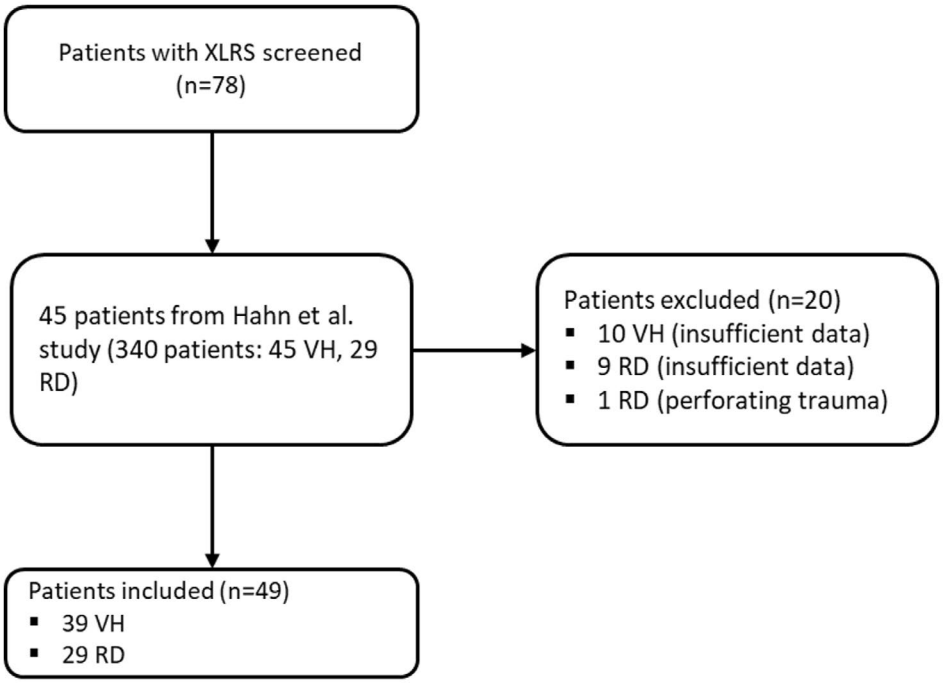

FIGURE 1 Flowchart detailing inclusion and exclusion of X-linked retinoschisis patients with vitreous haemorrhage and/or retinal detachment.

3.1 | Genetic analysis of included patients

A pathogenic *RS1* variant was molecularly confirmed or derived from first-degree family members in 33 of 49 patients (67%). These patients had the following 33 pathogenic variants: 18 missense, 9 deletions, 4 nonsense, 1 splice-site and 1 frameshift. Among these 33 patients, 17 patients (52%) carried predicted mild variants (missense), while 16 patients (48%) had predicted severe variants (deletions, nonsense, splice-site, frameshift or cysteine substitution). The potential severity of the pathogenic variants was predicted based on previously established criteria described by Bowles et al. (2011). The most prevalent variants were the Dutch founder mutation c.214G>A (p.(Glu72Lys)), detected in 15 patients (45%), an exon 3 deletion observed in 3 patients (9%) and the c.120C>A (p.Cys40*) variant found in 3 patients (9%).

3.2 | Characteristics and course of vitreous Haemorrhage in X-linked retinoschisis

Fundoscopic examination revealed findings consistent with VH in at least one eye for all 39 patients. Among them, 10 patients (26%) experienced VH in both eyes at different time points, and only one of these patients (3%) presented with simultaneous bilateral VH (Table 1). Additionally, 9 of 39 patients (23%) had an amblyopic eye, and strabismus was diagnosed in 12 of 49 included eyes (24%) somewhere in the course of the disease. The median age at presentation of the first VH in these 49 eyes was 15.3 years (IQR 5.5–16.3), with the youngest patient being 6 months old and the oldest 67.8 years (see Figure 2). Peripheral retinoschisis was observed on clinical examination in 46 of 49 eyes (94%), with the inferotemporal quadrant being the most commonly affected location (21 of 46 eyes, 46%). Of the 49 eyes, 18 (37%) had a history of antecedent (minor) trauma shortly preceding the onset of VH. Including all episodes of VH, including recurrences, 32 of 88 VH events (36%) were likely associated with a history of (minor) ocular trauma. Two of the 49 eyes (4%) had a concurrent RD associated with the VH. Excluding the fix-and-follow assessments conducted for five younger patients, 15 of 44 eyes (34%) presented with a BCVA worse than 20/200, while 29 of 44 eyes (66%) had a BCVA better than 20/200 at presentation. Recurrence of VH was observed in 22 of 49 eyes (45%), with 6 of 49 eyes (12%) experiencing more than two recurrences. The median time between documented VH episodes in cases of recurrence was 1.2 (0.2–3.1) years. Observation without intervention was chosen for 42 of 49 eyes (86%) for any episode with VH. Seven of 49 eyes (14%) underwent surgical treatment, of which 5 had a pars plana vitrectomy (PPV) and 2 had PPV with silicon oil tamponade procedure. Reasons for intervention were dense persistent VH ($n=1$), suspicion of RD ($n=4$) and VH in the best eye of a (functionally) monocular patient ($n=2$). BCVA improved after VH over time in 42 of 44 eyes (95%). In the remaining 2 eyes (5%), BCVA did not improve, most likely due to the natural course of XLRS, characterized by fluctuating visual acuity measurements sensitive to variability, rather than residual effects of VH.

At the final visit, all 49 eyes with a history of VH had attached retinas and clear media. Of these, 8 eyes (16%) had a BCVA <20/200, including 3 eyes that were legally blind (BCVA <20/400). The causes of low BCVA in these 8 eyes were as follows: amblyopia following VH, possibly due to inadequate treatment or delayed recognition, in 1 eye; amblyopia associated with a VH and untreated RD

TABLE 1 Demographic characteristics and anatomical and functional outcomes in X-linked retinoschisis patients with vitreous haemorrhages.

Patient	Laterality	Most recent BCVA before VH	BCVA during VH	BCVA after VH	Final BCVA	Trauma related	Treatment	Peripheral schisis	Age at presentation (years or months in infants)	Age at first VH (years or months in infants)	Recurrence	Fellow eye VH	Follow-up time (years)
1	OS	N/A (child)	HM (3/300)	HM (1/300)	20/400	Yes	Observation	Yes	5	10	No	Yes	51.5
1	OD	20/60	20/67	20/50	20/100	No	Observation	Yes	5	12	No	Yes	51.5
2	OS	Fix and follow	FC (1/60)	FC (1/60)	HM (2/300)	No	Observation	Yes	3	3	No	Yes	51.9
2	OD	Fix and follow	20/100	20/80	20/200	No	Observation	Yes	3	3	Yes, 2	Yes	51.9
3	OD	20/50	20/63	20/50	20/67	Yes	Observation	Yes	2 months	10	No	No	39.3
4	OD	20/40	20/67	20/50	20/50	No	Observation	Yes	4	21	Yes, 1	Yes	37.1
4	OS	20/100	20/125	20/100	20/100	No	Observation	Yes	4	28	No	Yes	37.1
5	OD	20/125	HM (2/60)	20/166	20/100	No	PPV	Yes	2	3	No	No	15.1
6	OD	20/100	20/100	20/67	20/200	Yes	Observation	Yes	2	10	No	Yes	15.5
6	OS	20/200	20/200	20/67	20/125	Yes	Observation	Yes	2	13	No	Yes	15.5
7	OS	20/200	20/200	20/125	20/80	Yes	Observation	Yes	6	9	Yes, 1	Yes	10.1
7	OD	20/200	20/400	20/400	20/320	No	Observation	Yes	6	13	No	Yes	10.1
8	OD	20/80	20/200	20/125	20/200	No	Observation	Yes	30	36	Yes, 1	No	38.6
9	OD	20/125	LP+	20/400	20/400	No	PPV	Yes	6	68	No	No	62.1
10	OS	20/67	20/100	20/67	20/44	Yes	Observation	Yes	4	6	Yes, 3	No	25.2
11	OD	20/100	20/125	20/71	20/63	No	Observation	Yes	11 months	6	Yes, 3	Yes	12.6
11	OS	20/29	20/36	20/32	20/29	No	Observation	Yes	11 months	7	Yes	Yes	12.6
12	OS	N/A (child)	N/A (child)	N/A (child)	20/100	No	Observation	Yes	4 months	2	No	Yes	19.0
12	OD	20/50	20/55	20/50	20/50	No	Observation	Yes	4 months	12	Yes, 2	Yes	19.0
13	OD	20/29	LP+	20/40	20/40	No	Observation, PPV 2nd	Yes	15	19	Yes, 1	No	8.0
14	OD	20/100	20/125	20/100	20/80	No	Observation	Yes	14	15	Yes, 3	No	35.7
15	OS	20/125	20/200	20/125	20/200	No	Observation	Yes	18	56	No	No	44.0
16	OD	20/67	20/100	20/67	20/67	No	Observation	Yes	21	41	No	No	30.2
17	OS	20/40	20/125	20/40	20/40	Yes	Observation	Yes	5	8	No	No	3.5
18	OD	20/80	LP+	20/67	20/400	No	Observation	Yes	3	4	Yes, 4	Yes	18.8
18	OS	20/63	20/67	20/63	20/100	No	Observation	Yes	3	16	No	Yes	18.8
19	OD	20/67	20/67	20/33	20/40	Yes	Observation	Yes	8	33	No	No	35.4
20	OD	20/125	20/200	20/200	20/125	No	PPV	Yes	3	6	No	No	7.1
21	OD	20/125	HM (3/300)	20/125	20/125	No	Observation	Yes	7	12	Yes, 1	No	39.6
22	OD	20/63	20/100	20/63	20/125	Yes	Observation	Yes	4	9	Yes 1	No	15.0
23	OD	20/80 (14 years earlier)	20/125	20/125	20/125	No	Observation	No	11	54	No	No	43.6

TABLE 1 (Continued)

Patient	Laterality	Most recent BCVA before VH	BCVA during VH	BCVA after VH	Final BCVA	Trauma related	Treatment	Peripheral schisis	Age at presentation (years or months in infants)	Age at first VH (years or months in infants)	Recurrence	Fellow eye VH	Follow-up time (years)
24	OS	20/250	HM (2/300)	20/250	20/250	Yes	Observation	Yes	9	17	Yes, 1	No	1.3
25	OD	20/40	20/50	20/40	20/50	Yes	Observation	Yes	13	16	Yes 2	No	11.8
26	OD	20/630	HM (3/300)	20/630	20/400	No	Observation	Yes	1	14	Yes, 1	No	27.9
27	OD	20/125	FC (1/60)	20/80	20/125	Yes	Observation	Yes	7	13	No	No	25.8
28	OS	FC (1/60)	LP+	20/250	20/125	Yes	PPV	Yes	4 months	5	No	No	7.2
29	OD	20/125	20/125	20/125	20/125	No	Observation	Yes	16	63	No	No	50.3
30	OS	N/A (child)	N/A (child)	20/80	20/100	Yes	Observation, PPV 2nd	No	2	2	Yes, 1	No	22.1
31	OS	N/A (child)	20/67	20/50	20/50	Yes	Observation	Yes	1	6	No	No	15.2
32	OS	Fix and follow	Fix and follow	Fix and follow	20/67	No	Observation	Yes	1	1	No	No	17.9
33	OS	20/63	FC (1/60)	20/63	20/80	No	Observation	No	3	5	Yes, 1	No	9.7
34	OS	No fixation	No Fixation	No fixation	LP+	No	Observation	Yes	6 months	6 months	No	Yes	11.0
34	OD	20/40	LP+	20/100	20/125	No	PPV	Yes	6 months	5	No	Yes	11.0
35	OD	20/67	20/100	20/80	20/67	No	Observation	Yes	3	8	Yes, 3	No	12.3
36	OD	N/A (child)	No protest covering eyes	4.8cycli 38 cm	20/100	No	Observation	Yes	6 months	6 months	No	No	11.5
37	OD	20/63	20/125	20/100	20/200	Yes	Observation	Yes	7	12	Yes, 1	Yes	43.0
37	OS	20/100	20/100	20/80	20/125	No	Observation	Yes	7	18	Yes, 2	Yes	43.0
38	OD	20/125	HM (1/300)	20/125	20/200	Yes	Observation	Yes	11 months	10	No	No	11.3
39	OD	20/32	20/80	20/50	20/63	Yes	Observation	Yes	4	5	Yes, 3	No	2.2

Abbreviations: FC, fingers counting; HM, hand movements; LP, light perception; PPV, pars plana vitrectomy; VH, vitreous haemorrhage.

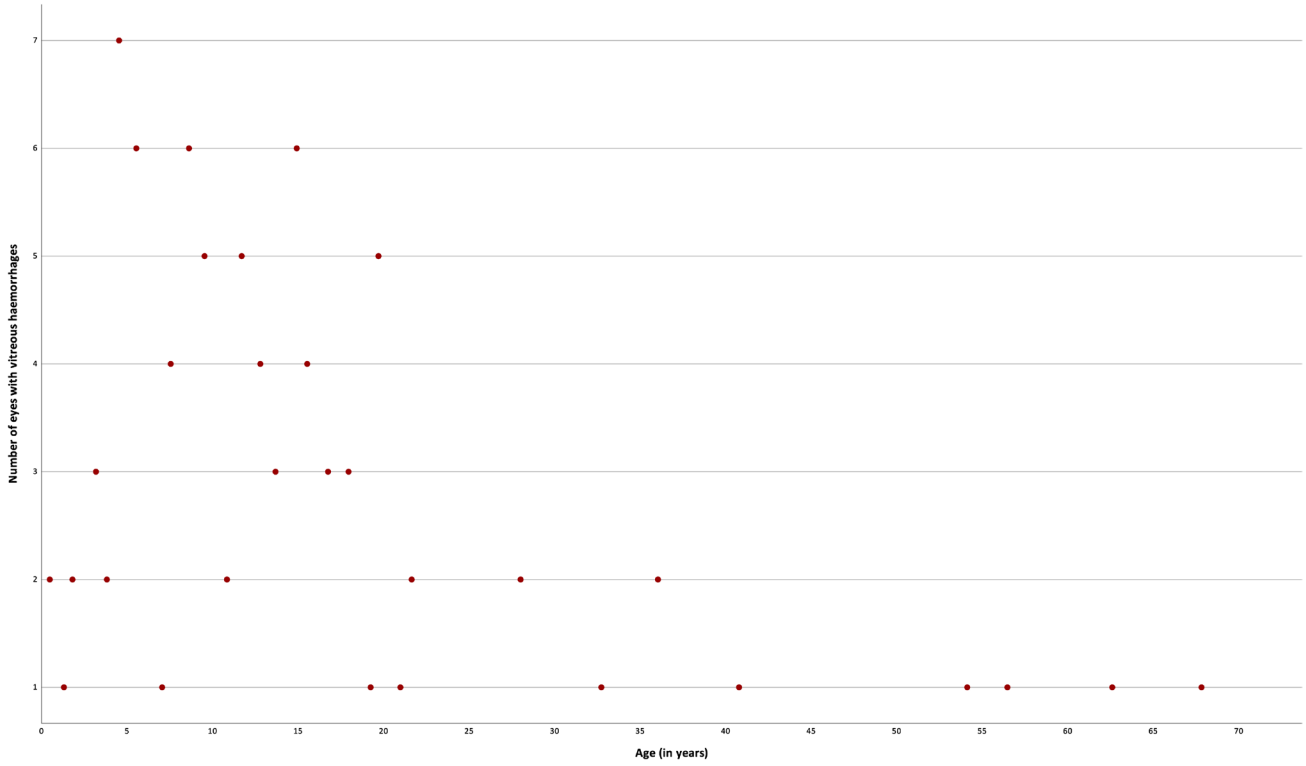

FIGURE 2 Scatter plot of number of eyes with vitreous haemorrhages (including recurrences) in patients with X-linked retinoschisis.

in 1 eye; amblyopia secondary to retinoschisis involving or threatening the macula in 2 eyes; refractive amblyopia in 1 eye; and persistent low BCVA due to the natural course of XLRS in 3 eyes.

3.3 | Characteristics and course of retinal detachments in X-linked retinoschisis

Among the 21 patients with RD, 17 (81%) experienced RD in only one eye, while 4 patients (19%) had bilateral RD (Table 2). Of these, 1 patient (5%) presented with simultaneous RD in both eyes. The median age at presentation with an RD was 7.5 years (IQR 2.4–15.9), with the youngest patient being 8 months and the oldest 55 years (see Figure 3). The aetiology of the RD was rhegmatogenous in 16 of 25 eyes (64%), tractional in 7 of 25 eyes (28%) and exudative in 3 of 25 eyes (12%). One of these 25 eyes (4%) presented with a RD of mixed aetiology, exhibiting both tractional and exudative components. Two of the 3 exudative RD cases were associated with Coats-like vasculopathy. In the 25 eyes with RD, the RD was located inferiorly in 12 eyes (48%), superiorly in 6 eyes (24%), confined to the temporal half in 1 eye (4%) and near-total in 6 eyes (24%). Macular involvement (macula-off RD) was observed in 16 of 25 eyes (64%). Proliferative vitreoretinopathy (PVR) was described in 10 of 25 eyes with RD (40%), with 5 eyes (20%) presenting with PVR at presentation of the RD before surgery, and another 5 eyes (20%) developing PVR after surgery, typically in the setting of recurrent RD. Peripheral retinoschisis was observed in 20 of 25 eyes with RD (80%), absent in 3 eyes (12%) and not documented in 2 eyes (8%). Strabismus was present in 12 of 25 eyes (48%), with 10 eyes (83%) exhibiting strabismus somewhere in the course of the disease prior to the RD. A history of minor ocular trauma shortly preceding the onset of RD was reported in 4 of 25 eyes (16%) among the XLRS patients with RD, including one case where RD developed following an attempted laser retinopexy at the border of peripheral retinoschisis. At the time of RD presentation, the BCVA was ≥20/200 in 6 of 25 eyes (24%), <20/200 in 10 of 25 eyes (40%) and was not documented in the medical records of 9 of 25 eyes (36%).

3.4 | Anatomical outcomes after retinal detachment

Surgical intervention was the primary approach in 21 of 25 eyes (84%). Observation without treatment was indicated for 4 of 25 eyes (16%) due to various reasons. In one case, surgery was not performed in a very young patient of 8 months old due to poor prognosis, which was not further specified. Other reasons for observation included misdiagnosis, poor prognosis secondary to Coats-like vasculopathy and an already blind eye (no light perception) associated with a morning glory disc anomaly. Scleral buckling (SB) alone was performed as the primary surgery in 7 of 21 eyes (33%), whereas 9 of 21 eyes (43%) underwent PPV alone, and 3 of 21 eyes (14%) received a combined procedure of SB and PPV. Electrocoagulation was performed in 1 of 25 eyes (4%) in 1955, and the surgical method was not further specified for 1 of 25 eyes (4%) operated on in 1963. The eye that underwent electrocoagulation achieved retinal reattachment after the first attempt. The eye for which the type of surgery was not specified in the medical files did not achieve retinal attachment. Of the 4 eyes with RD (16%) managed with a watchful waiting

TABLE 2 Demographic characteristics and anatomical and functional outcomes in X-linked retinoschisis patients with retinal detachments.

Patient	Laterality	Most recent BCVA before RD	BCVA during RD	BCVA after surgery	Final BCVA	Type of RD; macula status	PVR	Year of surgery	Primary surgery	Additional surgery	Attached at last visit	Peripheral schisis	Age at detachment (years or months in infants)	Follow-up time (years)
1	OS	20/400	HM (1/300)	FC (1/60)	20/400	RRD; off	Yes	2022	PPV/PFCL	1. PPV/SO 2. PPV SOR 3. PPV/SO	Yes	Yes	55	51.5
5	OS	20/125 (child)	LP−	HM (3/300)	20/400	RRD; off	Yes	2010	PPV/SO	1. PPV/SO 2. SOR	Yes	Yes	3	15.1
6	OD	20/100	20/200	20/200	20/200	RRD; off	No	2018	PPV/SO/ + SB	1. PPV SOR	Yes	Yes	13	15.5
9	OS	20/400	N/A	HM (3/300)	LP−	RRD; off	No	1963	Not specified	None	No	Yes	11	62.1
10	OS	20/40	20/50	20/40	20/44	RRD; on	No	2007	SB	No	Yes	Yes	16	25.2
18	OD	20/400	HM (3/300)	20/400	20/400	TRD/ESD; off	Yes	2018	PPV	No	Yes	Yes	16	18.8
22	OD	20/63	20/125	20/125	20/125	RRD; off	No	2017	SB	1. PPV/SO 2. PPV SOR	Yes	Yes	12	15.0
27	OS	20/200	N/A	*20/160	20/400	RRD; on	No	1998	SB	None	Yes	Yes	7	25.8
28	OD	20/170	FC (2/60)	LP+	LP−	RRD; off	No	2016	SB	1. SB	No	Yes	14 months	7.2
28	OS	20/125	20/400	FC (1/60)	20/125	RRD; off	Yes	2020	PPV/SO/ + SB	1. PPV SO 2. PPV/SO 3. PPV SOR	Yes	Yes	4	7.2
34	OD	20/40	LP+	20/100	20/125	RRD; on	Yes	2015	PPV/SO	1. PPV SO 2. PPV SOR	Yes	Yes	5	11.0
34	OS	No fixation	No fixation	N/A	LP+	RRD; on	No	N/A	None	None	Yes	Yes	8 months	11.0
38	OD	20/100	20/200	20/125	20/200	TRD; off	Yes	2020	PPV+IWR	1. PPV	Yes	Yes	10	11.3
38	OS	20/400	FC (1/60)	20/400	20/400	TRD; off	Yes	2022	PPV+IWR	None	Yes	Yes	12	11.3
40	OD	20/133	FC (1/60)	FC (2/60)	FC (2/60)	RRD; off	No	1986	SB	2. SB	Yes	Not mentioned	47	19.7
41	OS	N/A (child)	N/A (child)	FC (2/60)	LP−	RRD; off	No	1955	EC	None	Yes	Yes	3	18.8
42	OD	20/33	20/40	20/33	20/200	RRD; on	No	2015	PPV	None	Yes	No	51	22.0
43	OD	N/A (child)	N/A (child)	LP+	LP+	ESD; on	Yes	2016	PPV/SO/ + SB	1. PPV/SO 2. PPV/SO 3. PPV/SO	Yes	Yes	2	5.2
44	OS	20/125 (child)	N/A (child)	**20/200	20/125	RRD; off	Yes	2003	SB	1. PPV	Yes	Yes	5	21.1
45	OD	Fix to light	N/A (child)	N/A (child)	20/67	TRD; on	No	2014	PPV	No	Yes	Yes	10 months	9.2
45	OS	Fix to light	N/A (child)	N/A (child)	20/400	TRD; off	Yes	2014	PPV/SO	1. PPV/SO 2. PPV SOR	Yes	Yes	10 months	9.2
46	OD	20/125	20/125	20/125	FC (1/60)	TRD; on	No	1978	SB	None	Yes	Yes	23	33.8
47	OS	N/A (child)	N/A (child)	N/A	LP+	RRD; on	No	N/A	None	None	No	Not mentioned	12 months	19.0
48	OS	LP−	Lp−	N/A	Lp−	TRD; off	No	N/A	None	None	No	No	8	16.2
49	OS	20/200	HM (1/300)	N/A	LP−	ERD Coats; off	No	N/A	None	None	No	No	18	30.3

Abbreviations: EG, electrocoagulation; ERD, exudative retinal detachment; FC, finger counting; HM, hand movements; IWR, inner wall retinectomy; LP, light perception; N/A, not available; PPV, pars plana vitrectomy; PVR, proliferative vitreoretinopathy; RD, retinal detachment; RRD, rhegmatogenous retinal detachment; SB, scleral buckle; SO, silicone oil; SOR, silicone oil removal; TRD, traction retinal detachment; VH, vitreous haemorrhage.

*BCVA was collected 8 months after surgery. **BCVA was collected 6 months after surgery.

approach, only 1 eye (25%) had an attached retina at the final visit, while the other 3 (75%) had persistent RD. All 4 eyes developed cataract, with 3 (75%) undergoing lensectomy, including the eye with the attached retina.

Of the 7 eyes with SB alone as the choice of primary surgery, 3 (43%) achieved retinal reattachment after a single procedure. The remaining 4 eyes experienced a recurrence of RD. Of these, 2 underwent an additional SB to reattach the retina, while the other 2 underwent PPV. One of these eyes undergoing PPV was complicated by PVR. Silicone oil (SO) was used as a tamponade in the first eye, while SF_6 gas tamponade was used in the eye with PVR. At the final visit, retinal attachment was achieved in 6 of 7 eyes (86%) in the primary SB group. One patient developed a total RD following an attempt to puncture subretinal fluid with a needle. This detachment was left untreated because the patient had already undergone two SB surgeries by the age of 1 year.

In the 9 eyes that underwent PPV as the primary surgical intervention, SO was used as the tamponade agent in 4 eyes (44%), while SF_6 gas tamponade was used in 5 eyes (56%). Inner wall retinectomy was performed in 2 eyes with tractional RD and PVR (Figure 4). Retinal attachment was achieved after a single procedure in 4 of 9 eyes (44%). Recurrent RD occurred in the remaining 5

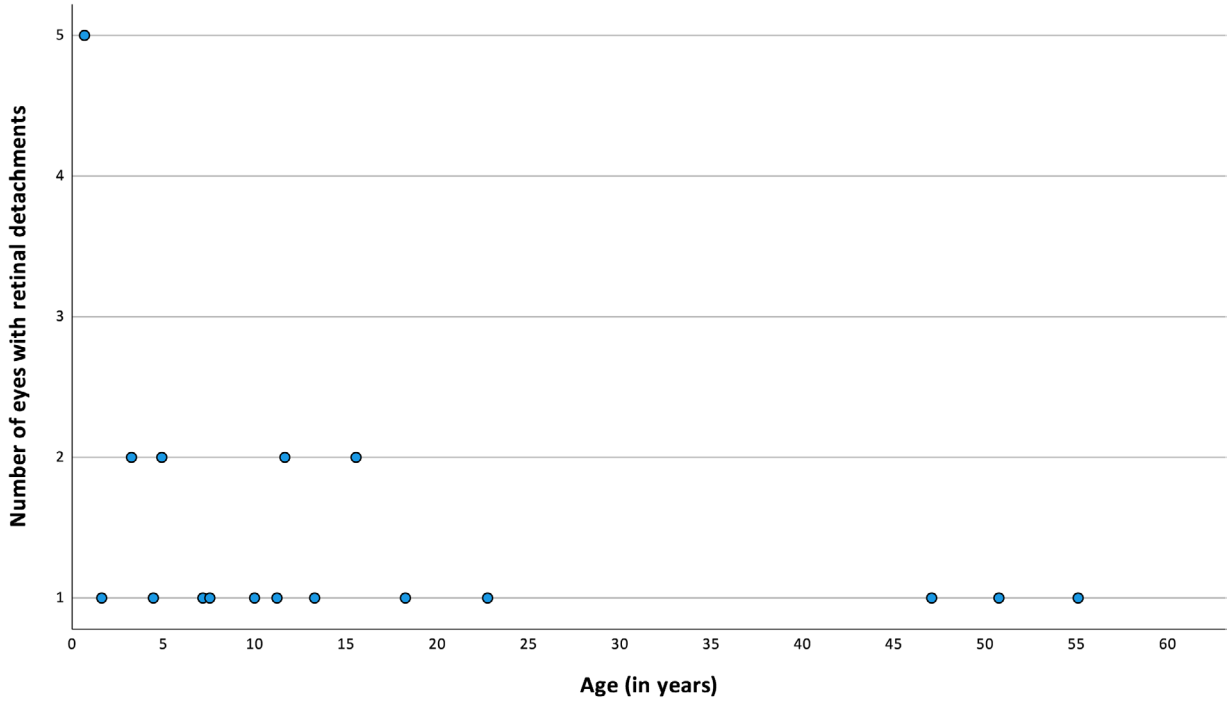

FIGURE 3 Scatter plot of the number of eyes with primary retinal detachments in patients with X-linked retinoschisis.

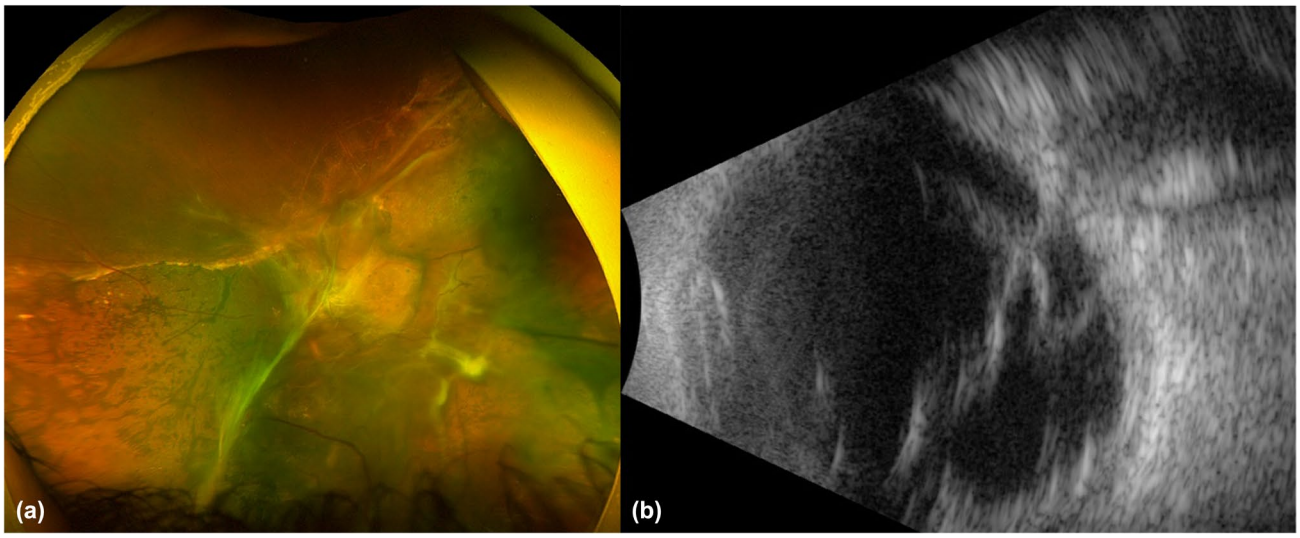

FIGURE 4 Wide-field retinal fundus imaging and ocular ultrasonogram of the left eye of a 12-year-old X-linked retinoschisis patient with tractional retinal detachment and peripheral retinoschisis also extending to the macula with proliferative vitreoretinopathy membranes. (a) Extensive disorganization of retinal landmark structures in the posterior pole, with masking of the optic disc by epiretinal fibrosis, along with extensive multifocal epiretinal and subretinal proliferative vitreoretinopathy and hyperpigmented retinal changes in the inferonasal retina. (b) Extensive complex membranes on ocular ultrasonogram.

eyes, all due to PVR. Retinal reattachment was achieved in 4 of these 5 eyes (80%) after a second PPV: 3 with SO tamponade and 1 with SF^6 gas tamponade. One eye (20%) experienced a third RD following SO removal, requiring an additional PPV surgery for reattachment. The combined SB and PPV procedure was successful after a single surgery in 1 of 3 eyes (33%). The remaining 2 eyes required multiple PPV surgeries to manage recurrent RD due to PVR. At the final visit, all 12 eyes (100%) that underwent PPV or combined SB and PPV as the primary surgery had achieved retinal attachment.

Overall, retinal reattachment was achieved after the primary surgery in 8 of 21 eyes with RD (38%) and in 19 of 21 eyes (90%) following multiple surgeries. The median number of surgeries required, including SO removal, was 2.0 (1.0–3.0). Of the 8 eyes that underwent PPV with SO as the tamponade agent as the primary surgery or subsequent surgery, SO was removed in 6 eyes (75%), while it was left in situ in 2 eyes (25%) due to at least 2 recurrences of RD. The median number of required surgical interventions was significantly higher with 3.0 (1.8–4.0) in the eyes with PVR ($n=10$) compared to 1.0 (1.0–2.0) in eyes without PVR ($n=11$; $p=0.016$). The choice of primary surgical technique evolved over time, with a trend toward increasing use of PPV in more recent years (see Figure 5). Among the subset of eyes operated on after 2005, 9 of 15 (60%) underwent PPV, 3 of 15 (20%) underwent an SB procedure, and 3 of 15 (20%) underwent a combined procedure of PPV and SB. In this subset of patients who underwent an operation for RD after 2005, retinal attachment after primary surgery was achieved in 5 of 15 eyes (33%) and in 14 of 15 (93%) after multiple surgeries. At the final visit, the lens status was phakic in 12 of 21 eyes (57%), pseudophakic in 5 of 21 eyes (24%) and aphakic in 3 of 21 eyes (14%). All pseudophakic and aphakic eyes had a history of PPV.

3.5 | Visual outcomes after retinal detachment surgery

BCVA measurements at presentation with RD were available for 14 of 21 eyes (67%), not recorded in 5 eyes (24%) due to the young age of the patients and unavailable for review in 2 eyes (10%). The BCVA was ≥20/200 in 6 of 14 eyes (43%) and <20/200 in 8 of 14 eyes (57%), of which 7 were legally blind (<20/400). Of the 8 eyes with a BCVA <20/200, 7 of 8 eyes (88%) had macula-off RD. Including data before RD for the cases without BCVA data during RD, the BCVA improved following surgery in 10 of 21 eyes (48%), stabilized in 5 of 21 eyes (24%), worsened in 2 eyes (10%) and follow-up data were not available for 4 eyes (19%). The 2 eyes with worsened BCVA after surgery both had detached retinas. At the final visit, 9 of 21 eyes (43%) had a BCVA ≥20/200, 12 of 21 eyes (57%) had BCVA <20/200, of which 5 were legally blind (BCVA <20/400). Nine of the 12 eyes (75%) with a BCVA <20/200 had macula-off RD prior to surgery.

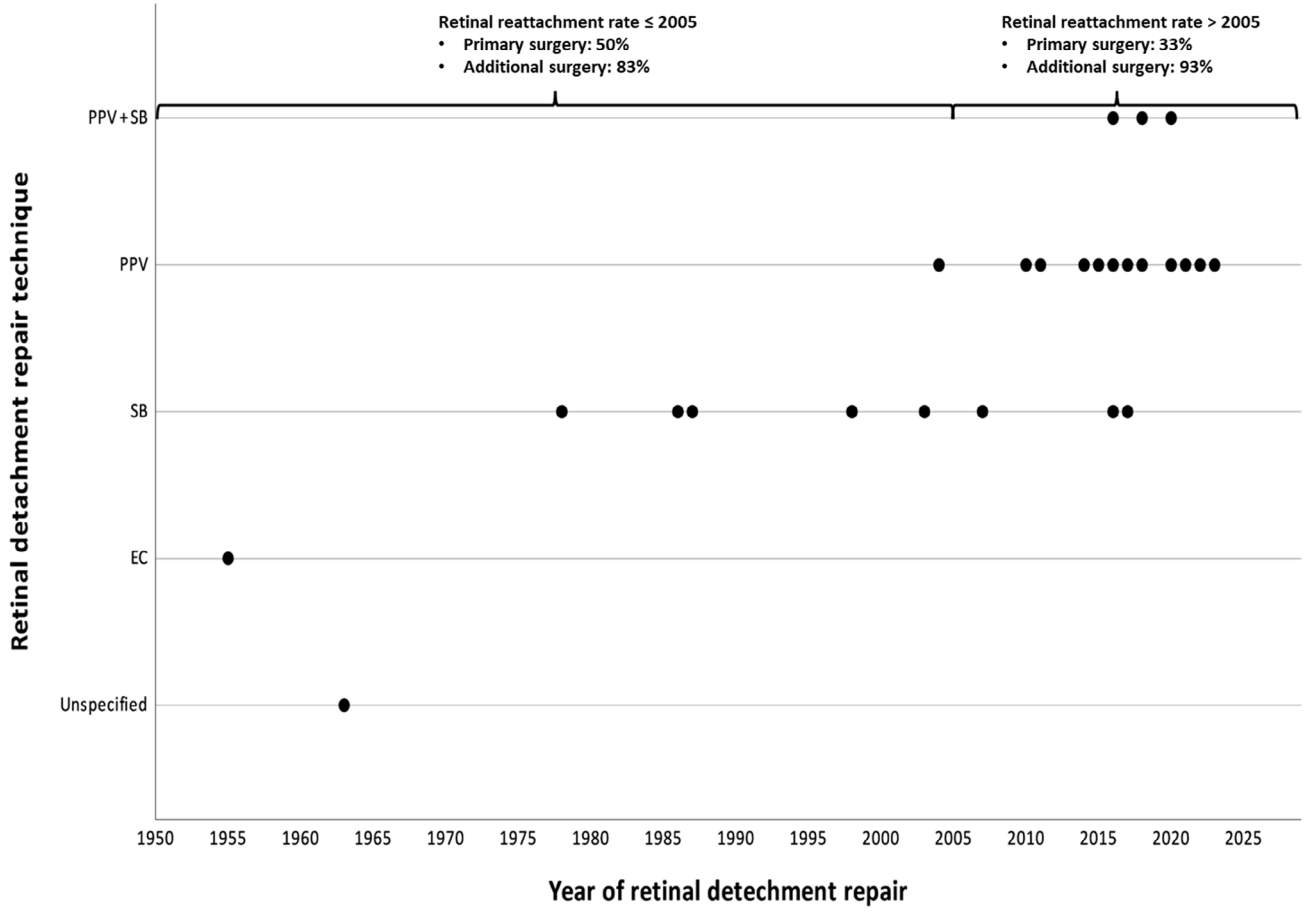

FIGURE 5 Scatterplot of retinal detachment repair technique trends by year in X-linked retinoschisis patients.

3.6 | Postoperative complications

Elevated intraocular pressure (IOP) was observed in 3 of 21 eyes (14%), all of which had undergone PPV with SO as tamponade. In 2 of these 3 eyes (67%), the elevated IOP was attributed to SO left in situ and was successfully managed with hypotensive topical medications, with 1 eye also requiring a peripheral iridectomy. The third eye exhibited persistent elevated IOP even after SO removal, requiring treatment with an Ahmed glaucoma drainage device to prevent secondary glaucoma.

One eye, which underwent an unspecified surgical procedure and exhibited persistent RD, progressed to phthisis bulbi as a result of hypotony due to long-standing total RD and was eventually enucleated. A total funnel RD appeared in another eye following an unsuccessful attempt to puncture subretinal fluid with a needle. Diplopia developed in one patient who had pre-existing strabismus in the affected eye prior to the RD. Chorioretinal atrophy was observed in 1 eye after electrocoagulation, an older technique that applies high-frequency current to induce coagulation in a circumscribed area of the choroid surrounding the retinal tear that was performed as treatment for RD in 1955. Additionally, outer retinal atrophy was documented in 1 eye that underwent a second PPV with internal limiting membrane peeling for a macular epiretinal membrane. These postoperative complications and their management are summarized in Table S1.

3.7 | Fellow eye complications

Excluding the 8 eyes of 4 patients with bilateral RD, 7 of 17 eyes (41%) with RD experienced VH in the fellow eye, with peripheral retinoschisis observed in 6 of these 7 eyes (86%). Overall, peripheral retinoschisis was identified in 13 of 17 fellow eyes (76%) of patients with RD in the other eye. In 2 of 13 fellow eyes (15%) with peripheral retinoschisis, the retinoschisis gradually progressed to the macula leading to a poor visual outcome of 20/400 in one eye and counting fingers in the other eye. Peripheral full-thickness retinal breaks were seen in 1 fellow eye without peripheral retinoschisis. Of the 7 fellow eyes without complications, 5 (71%) exhibited peripheral retinoschisis.

4 | DISCUSSION

In this study, we analysed the management strategies and clinical outcomes of VH and RD in XLRS patients. While most XLRS patients exhibit a relatively slow, bilaterally progressive disease with stable visual acuity until the 4th decade of life, retrospective cohort studies suggest that 7–21% of patients may experience VH and 6–23% may develop RD during their disease course leading to poor visual outcomes. (da Cruz et al., 2023; Fenner et al., 2023; George et al., 1996; Georgiou et al., 2022; Hahn et al., 2022; Jarvinen et al., 2024; Kellner et al., 1990; Kiraly et al., 2023) Moreover, near 20% of the XLRS patients will experience either VH or RD (Georgiou et al., 2022; Hahn et al., 2022; Kiraly et al., 2023). These complications often arise in the first two decades, but they can occur suddenly at any time during the course of the disease as shown in our study. We observed peripheral retinoschisis in 94% of the eyes with VH and in 80% of the eyes with RD. This is in line with other studies which have shown that XLRS cases with peripheral retinoschisis are more prone to develop these complications (Fahim et al., 2017; Fenner et al., 2023; Jarvinen et al., 2024; Sen et al., 2018). Peripheral retinoschisis is most commonly located in the inferotemporal quadrant, with its height ranging from mild elevation of the inner retinal layers to bullous retinoschisis, in some cases extending over the macula (Hinds et al., 2018; Wakabayashi et al., 2023). The inner retinal layer of these peripheral retinoschisis tends to fragment over time resulting in larger inner retinal breaks.

VH in XLRS often originates from the rupture of fragile retinal vessels traversing the elevated inner retinal layer of peripheral retinoschisis cavities, commonly referred to as 'bridging vessels' (Wakabayashi et al., 2023). These vessels are structurally weak and highly susceptible to rupture, even following minor trauma. Sudden acceleration-deceleration forces induced by minor trauma to the head can generate vitreoretinal traction, leading to vessel rupture and subsequent VH. On fundoscopic examination, preretinal haemorrhages at the site of bridging vessels can be detected as the media clears during follow-up. In some cases, the VH can also occur from retinal neovascularization (Parra & Hartnett, 2022). A minor trauma to the head occurred just before the VH in 36% of all documented episodes in our study, in line with 42% reported by da Cruz et al. (2023). Recurrence of VH was observed in 51% of patients (45% of all included eyes) in this study, with a median interval of 1.2 years between episodes. da Cruz et al. (2023) reported VH recurrence in 7 of 12 eyes (58%) across 6 of 9 patients (67%), with an average recurrence interval of 3.2 years. More than two recurrences were observed in 15% of patients (12% of the included eyes), which may be an underestimation in the current study, as some patients reported experiencing additional episodes of VH during the follow-up period but did not seek medical attention, because these haemorrhages often resolved spontaneously within 1 month without intervention. No established guidelines exist for the management of VH in XLRS due to the lack of large cohort studies comparing different treatment options. Consequently, treatment decisions should be made on a case-by-case basis. In line with our study, the current initial approach for managing VH in XLRS is often observation without treatment, as the VH is quite often self-limiting. We generally do not recommend the use of intravitreal anti-vascular endothelial growth factor injections, as only a few sporadic cases of VH due to neovascularization in XLRS have been described (Parra & Hartnett, 2022). Surgical intervention may be considered in cases of dense VH, persistent VH (especially when there is a risk of development of amblyopia in young children), vision loss in monocular patients, bilateral concurrent VH or when there is a high index of suspicion of simultaneous retinal

TABLE 3 Reported surgical outcomes for retinal detachments in X-linked retinoschisis patients.

Study	Year	Number of patients (eyes) with RD	Surgical techniques	Anatomical success (%)
Regillo et al. 1993	1993	4 (6)	PPV, SB	83.3
Ferrone et al. 1997	1997	7 (9)	PPV	88.9
Rosenfield et al. 1998	1998	9 (12)	PPV, SB	83.3
Wu et al. 2007	2007	12 (12)	PPV, SB	83.3
Sen et al. 2018	2018	28 (34)	PPV, PPV+SB, SB	79.4
Read et al. 2018	2018	9 (9)	PPV, PPV+SB	100
Zhao et al. 2018	2018	*/25 (24)	PPV	100
Sengillo et al. 2023	2023	9 (10)	PPV, PPV+SB, SB	90

Abbreviations: PPV, pars plana vitrectomy; RD, retinal detachment; SB, scleral buckle; VH, vitreous haemorrhage; XLRS, X-linked retinoschisis.
*The exact number of patients is not traceable, as the study also included cases with VH only.

detachment (on fundoscopy and/or ultrasonography) (Regillo et al., 1993; Wakabayashi et al., 2023). A recent review by Strand et al. recommended PPV for nondiabetic VH as the safest and most appropriate approach (Strand et al., 2024). However, in their study, only 25% of cases experienced spontaneous resolution of VH, which was associated with aetiologies such as posterior vitreous detachment without retinal breaks and mild retinal vascular disruptions. In contrast, spontaneous resolution is more common in XLRS, as observed in our study and in the study by George et al. (1996). VH was observed in two infants of 6 months old in our study. Ophthalmologists should also consider XLRS as a cause of VH in infants, after ruling out more common causes of VH in infants, such as retinopathy of prematurity, abusive head trauma (formerly known as shaken baby syndrome), Terson syndrome and hematologic disorders (Spirn et al., 2006). Early recognition of XLRS in these cases is crucial for appropriate management and preventing further complications.

Although RD can occur at any stage of the disease, most patients in this study developed RD before the age of 16, including four cases in infancy. This finding aligns with a study describing 12 XLRS patients with RD by Kellner et al. (1990), in which 7 of 12 patients (58%) experienced RD before the age of 11. Rhegmatogenous RD was the most common type observed in our study, which often occurs secondary to an outer retinal break in an area of peripheral retinoschisis with inner retinal layer holes or full-thickness retinal tears following posterior vitreous detachment. Tractional RD is associated with posterior hyaloid contraction and often develops from the retinoschisis cavity. Ferrone et al. (1997) reported that tractional RD was associated with the posterior border of the peripheral retinoschisis in all 5 XLRS patients in their study. However, as demonstrated in our study and by Garg et al., tractional RD can also occur in the absence of peripheral retinoschisis (Garg et al., 2006). Exudative RD in XLRS may develop secondary to Coats-like vascular abnormalities, with the underlying aetiology believed to involve vascular changes leading to exudation and transudation (Wakabayashi et al., 2023).

Management of RD in XLRS patients is challenging because of the fragile retina due to its underlying pathology and the young age at presentation. Recurrent RD is common in XLRS patients, as outer retinal breaks are often small compared to the larger inner retinal holes, making them more challenging to detect and the common presence of PVR at presentation (Sen et al., 2018). Until the introduction of the modern vitreoretinal instruments and techniques, SB was the standard surgical procedure in XLRS cases with rhegmatogenous RD. Currently, SB can still be the surgical treatment of choice when the outer retinal break is located at the equator or anterior to the equator and can be supported by a buckling element. In children with XLRS-associated rhegmatogenous RD, in whose eyes inducing posterior vitreous detachment can be challenging due to very adherent vitreoretinal interface, and cataract can be prevented, SB is also the preferable technique. In our study, the retinal attachment rate for cases of rhegmatogenous RD managed solely with SB was 80%. In addition, all eyes that underwent PPV or a combined PPV and SB procedure achieved retinal attachment at the final follow-up visit. Our finding of an overall retinal attachment rate of 43% after primary surgery and 90% following additional surgical procedures when necessary, is comparable to reattachment rates described in previous studies (Table 3) (Ferrone et al., 1997; Read et al., 2018; Regillo et al., 1993; Rosenfeld et al., 1998; Sen et al., 2018; Sengillo et al., 2023; Wu et al., 2007; Zhao et al., 2018). The presence of PVR significantly increased the number of surgeries required for attached retina, which also aligns with previous studies on RD outcomes in XLRS reporting PVR as a common cause of recurrent RD (Regillo et al., 1993; Rosenfeld et al., 1998; Sen et al., 2018). The high incidence (40%) of PVR in the eyes included in this study may be attributed to two key factors: delayed presentation in eyes with pre-existing visual impairment in both adults and paediatric patients and the more robust immune response and increased vitreous cellularity observed in the paediatric population, which may be even more pronounced in XLRS cases with dysfunctional and disorganized peripheral retinoschisis (Sen et al., 2018). In our study, an inner wall retinectomy was performed in two eyes of a patient with bullous retinoschisis threatening the macula with PVR (Figure 1). As reported by Iwahashi et al., inner wall retinectomy is a safe and effective technique to create a clear visual axis for patients with bullous peripheral retinoschisis hanging over or threatening the macula (Iwahashi et al., 2023). Removing the inner wall of the retinoschisis has no effect on the visual function, as this corresponds to the scotoma on the visual field in these patients (Ferrone et al., 1997). Inner wall retinectomy is not recommended for patients

without bullous retinoschisis threatening the macula or obstructing the visual axis, as it may increase the risk of postoperative PVR (Iwahashi et al., 2023). Moreover, Sen et al. found no significant difference in anatomical outcomes between eyes treated with inner wall retinectomy and those without (Sen et al., 2018). PPV is the preferred surgical technique for tractional RD, exudative RD, PVR, or cases where SB alone does not sufficiently relieve vitreoretinal traction. The choice of tamponade varies across studies, but SO is frequently used in cases with PVR, monocular patients and young children, where maintaining proper postoperative positioning with gas may be challenging. Outer retinal breaks are best visualized using OCT and ocular USG. However, in cases where OCT or USG imaging is limited due to persistent or dense VH, PPV remains indispensable for directly identifying outer retinal breaks. Intraoperative OCT can be a valuable adjunct in these cases, allowing for real-time assessment and guiding surgical decision-making. Although peripheral retinoschisis is a risk factor for the development of rhegmatogenous RD, we do not recommend prophylactic laser barricade of the peripheral retinoschisis border, as such an intervention may induce VH or even RD, as observed in our study and the study by Kellner et al. (1990). Most eyes in our study had a stable or improved BCVA following RD surgery, as reported by previous studies: Sen et al. reported post-surgical improvement in 59% of cases, Wu et al. in 53%, Rosenfeld et al. in 58%, while Sengillo et al. observed no visual improvement in their treated patients (Rosenfeld et al., 1998; Sen et al., 2018; Sengillo et al., 2023; Wu et al., 2007). A higher rate of favourable BCVA outcomes (74%) was reported by Zhao et al. (2018), but their study also included patients with solely VH in the analyses.

Complications in the fellow eye were common in our study, with two-thirds with RD in one eye also experiencing fellow eye complications. Bilateral RD was observed in 4 out of 21 patients (19%) in this study, which is consistent with the findings of Sen et al. and Sengillo et al., who reported bilateral RD in 6 out of 28 patients (21%) and 2 out of 9 patients (22%), respectively (Sen et al., 2018; Sengillo et al., 2023). Moreover, a third of the XLRS patients in our study developed VH in the fellow eye, and peripheral retinoschisis was observed in 86% of fellow eyes. In two cases, the peripheral retinoschisis progressed to the macula, leading to severe visual impairment.

We found a potential association between minor ocular trauma and the onset of complications, with 18 of 49 eyes (37%) developing VH and 4 of 25 eyes (16%) developing RD following such events. This may indicate that patients with XLRS, at least those who also have peripheral retinoschisis, should consider taking precautions when participating in high-risk sports and other activities involving sudden impact or acceleration–deceleration forces. We did not find a clear genotype–phenotype correlation between the RS1 genotype and development of vitreoretinal complications, which is similar to previous findings (Fenner et al., 2023; Georgiou et al., 2022; Hahn et al., 2022; Riveiro-Alvarez et al., 2009).

Our study was limited by its retrospective design and variability in surgical repair techniques, also due to the broad time range of inclusion that also resulted in the inclusion of procedures of surgical RD repair prior to the era of modern vitreoretinal surgery. Nonetheless, it contributes to the scarce existing data on the management of XLRS complications with a longer follow-up time compared to previous studies.

In conclusion, favourable anatomical and visual outcomes can be expected for patients with VH, as VH in these cases is quite often self-limiting. However, patients with VH should be warned about the risk of recurrence of VH in the same eye and possibly in the fellow eye. In contrast, RD is a vision-threatening complication of XLRS, which requires surgical intervention. Favourable retinal reattachment rates can be achieved through repair surgery, but multiple surgeries are commonly necessary. In these RD cases, the visual prognosis remains poor despite visual improvement following surgery. Given the occurrence of RD in infants and young children, who may be unable to communicate visual changes, and the increased risk associated with peripheral retinoschisis and even minor ocular trauma, we recommend frequent, dilated fundus examinations in XLRS patients with these risk factors to ensure timely detection and intervention.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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