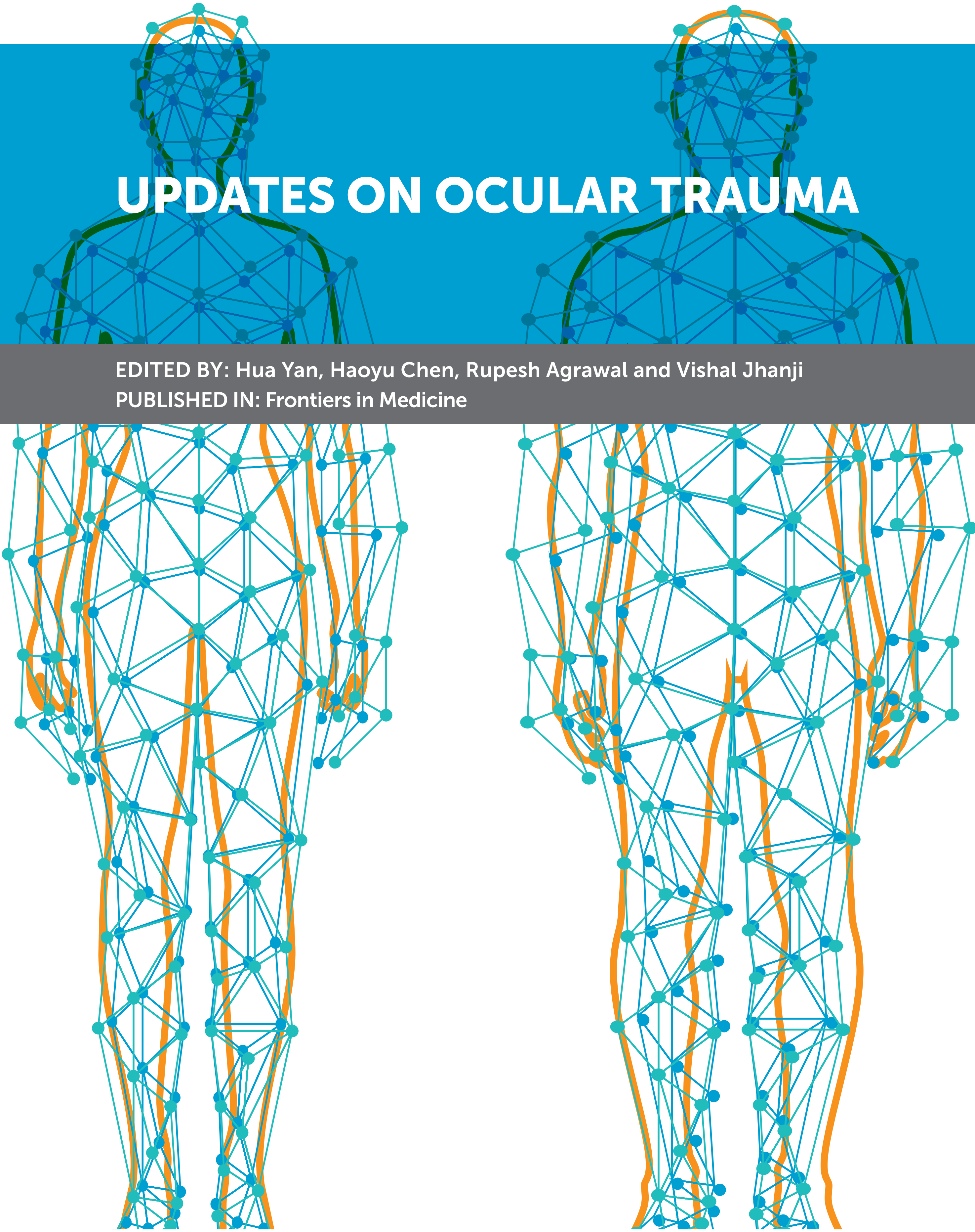

UPDATES ON OCULAR TRAUMA

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UPDATES ON OCULAR TRAUMA

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EDITORIAL
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Editorial: Updates on Ocular Trauma

*Haoyu Chen[1], Vishal Jhanji[2], Rupesh Agrawal[3,4,5,6] and Hua Yan[7]**

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Keywords: ocular trauma, intraocular foreign body, chemical burn, traumatic macular hole, open globe injury, ophthalmic trauma registry

Editorial on the Research Topic

Updates on Ocular Trauma

Ocular trauma is a significant cause of visual impairment worldwide. It is estimated that 19 million people worldwide have uniocular blindness from traumatic injury (1). Severe ocular trauma remains a challenge for physicians and may cause permanent blindness and even the loss of an eyeball. As ocular trauma refers exclusively to globe trauma, the use of the term "ophthalmic trauma" has been recommended to involve globe, adnexal, and orbital trauma. Recently, advances in research and data analytics have promoted our understanding and management of ocular trauma. Molecular biology of human tissues and animal models have revealed inflammation with unique molecular pathways in the pathogenesis of various types of ocular trauma (2). The application of *in vivo* imaging techniques, such as optical coherence tomography (3) and adaptive optics laser scanning ophthalmoscopy, has also helped us better understand the mechanism of damage to ocular tissues by external injuries. The advances of microinvasive vitrectomy, other surgical techniques, and novel surgical materials have improved the outcome of ocular trauma. The International Globe and Adnexal Trauma Epidemiology Study (IGATES) registry has furthered the research in ophthalmic trauma by facilitating global collaboration through a secure web-based platform for capturing both prospective and retrospective data by asking critical questions in patients with an eye injury (4). Novel tools such as the Ophthalmic Trauma Correlation Matrix (OTCM) have been proposed and evaluated for better management of patients with open globe injury (5). The Research Topic, *Updates on Ocular Trauma*, brings readers up-to-date laboratory, imaging, clinical, and epidemiological research on advances in ocular trauma.

An animal model would provide insight into the pathogenesis of ocular trauma and the development of potential treatment. Liu et al. established a new rabbit model of closed globe blast injury using a self-developed gas shock device. The equipment had a high-pressure air compression pump and could deliver different blast pressures of gas to the eyes. They found corneal edema, anterior chamber hyphema, lens opacity, vitreous hemorrhage, commotio retinae, and retinal ganglion cell damage in rabbit eyes with gas shock. Moreover, the severity of injury depended on the pressure. This rabbit model nicely replicates clinical closed globe injury.

Epidemiological studies can identify the prevalence and risk factors of ocular trauma, which would help to develop preventive strategies. Zhang et al. investigated the epidemiology of sports-related eye injuries among athletes. They found that 10.7% of athletes had a history of sports-related eye injury. Handball, water polo, and diving were the top types of sports that injured the eyes. Balls and teammates are both important sources of eye injury. An adnexa wound was the most common type of injury. About 11.9% of the eye injuries resulted in impaired visual acuity. The risk factors for eye injury included $<$18 years old, lower family income, and training $>$ 4 h a day.

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Yu et al. reviewed the prevalence, spectrum, and management strategies of ocular trauma during the COVID-19 pandemic. They found that the prevalence of eye trauma decreased with a trend of delayed treatment during the COVID-19 pandemic. The possible mechanism may be irregular epidemic prevention and control measures, unprotected home activities, and unusual mental states. They discussed several strategies targeting these mechanisms for the prevention of eye injury during the COVID-19 pandemic.

Analysis of clinical spectrum and outcomes would benefit our understanding of ocular injury. Chen et al. analyzed 622 adult patients with light perception or no light perception after open globe injury. They found that 8.5% of the eyes received primary evisceration because of no possible anatomical reconstruction. There were 239 eyes that received vitreoretinal surgery. Over the 6-month follow-up, 21.9% of eyes were eviscerated, 24.0% atrophied, only 21.1% had some visual acuity, and 8.5% had vision better than 0.3. In Chen's other study of pediatric open globe injury, they found the most common injury type was penetration (89%). Scissors, knives, pens, and wood were common causes. Most (76.1%) of the injuries were in zone 1. After management, 32.2% had vision better than 0.3, and 2.7% were eviscerated. Su et al. reported a case with central retinal artery occlusion after a bee sting on the face, accompanied by hypersensitivity, hypercoagulable state, myocardial damage, and hepatic damage.

Surgical interventions are usually needed for severely injured eyes. Wang et al. reported allogeneic cultivated limbal epithelial cell sheet transplantation for severe symblepharon after chemical and thermal burns in 36 cases. Complete lysis was achieved after one surgery in 83.3% of cases and two surgeries in 16.7% without recurrence. Ma et al. compared the paths of giant intraocular foreign body (IOFB) removal in 73 cases. They found that eyes with IOFBs removed from the entrance wound path had a better visual outcome than those with a limbal path. The entrance wound path also allows for larger intraocular foreign body removal compared to the pars plana path. Chen et al. reported two novel suturing techniques to fix traumatic choroidal avulsion in 24 cases. Both techniques, trans-scleral mattress suturing and intraocular suturing, reattached the choroid well and improved both visual acuity and intraocular pressure. Zhou et al. conducted a systematic review and meta-analysis of vitrectomy vs. spontaneous closure of a traumatic macular hole. They found that the pooled macular hole closure rate was 0.37 in the observation group and 0.90 in the surgery group. The pooled rate of visual acuity improvement was 0.39 in the observation group and 0.72 in the surgery group. These articles provide evidence for clinicians to determine interventions for patients with ocular injury.

Studies on predicting outcomes would help us manage patients. Mai et al. reported that eyes with intraocular foreign body injury had generally delayed implicit time and reduced amplitude in all waves of five electroretinogram responses. The maximum change was found in oscillatory potential, which also had the strongest correlation with visual outcome. Their results would help select the appropriate ERG parameter and predict the visual outcome. Mohamed-Noriega et al. reported that the neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were correlated with the visual outcome after surgical repair of open globe injuries in 197 cases. He et al. reported that the incidence of band keratopathy was 28% in a silicone oil tamponade for open globe injury. Silicone oil retention time $\geq$6 months and zone III injury were significant risk factors for band keratopathy.

In general, the articles on this Research Topic and current advancements in the field of ophthalmic trauma have provided updated information on the animal model, incidence, risk factors, clinical spectrum, precise diagnosis, intervention, and prognosis of a patient with an eye injury. There are some potential difficulties in the research of ocular trauma. There is a lack of large sample size high-quality datasets with long-time follow-up. It is not easy to conduct randomized control trials because of highly heterogenous clinical characteristics. Multicenter, even multinational collaboration is needed to collect large sample size, high-quality data and conduct randomized control trials to provide higher-level evidence for clinical decisions (4). The secure web-based global all-encompassing registries like IGATES, can provide real-time pooled data analysis that will not only advance our understanding in the field of ophthalmic trauma but also help us with predictive modeling and novel tools for evidence-based counseling of a trauma victim (4).

AUTHOR CONTRIBUTIONS

HC and HY conceived the idea. RA and VJ critically reviewed the manuscript and revised the article. All authors contributed to the article and approved the submitted version.

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Correlation Between Electroretinogram and Visual Prognosis in Metallic Intraocular Foreign Body Injury

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Purpose: This study aims to investigate the correlation between electroretinogram (ERG) and visual outcome in eyes with metallic intraocular foreign body (IOFB) injury.

Methods: Cases with metallic IOFB injuries with preoperative ERG from January 2008 to May 2020 were reviewed retrospectively. Five ERG responses were recorded, including rod response, maximal response, oscillatory potentials, cone response, and 30-Hz flicker. The results were compared between the affected and the contralateral eyes. All patients received surgery to remove IOFBs. The correlation between amplitudes, implicit times, and grades of ERG with final best-corrected visual acuity (BCVA) was analyzed.

Results: A total of 33 eyes of 33 patients were included. The eyes with IOFB had generally delayed implicit time and reduced amplitude in all waves. The maximum change was found in oscillatory potentials S3 and N1 (0.42 ± 0.42 and 1.95 ± 1.97 of the fellow eyes, respectively, $p < 0.05$). All amplitudes were negatively correlated with the final BCVA (rs: −0.676 to −0.459, all $p < 0.05$). In contrast, all implicit times were positively correlated with final BCVA, although, some of them were not statistically significant (rs: 0.035 to 0.687). Among them, oscillatory potential P3 has the highest correlation coefficient ($rs = 0.687$, $p < 0.001$). All grades of ERG waves were statistically correlated with the final BCVA (rs: −0.596 to −0.664, all $p < 0.001$).

Conclusions: ERG can be used to assess visual outcome in metallic IOFB injury after surgery. Oscillatory potentials provided the most significant responses.

Keywords: intraocular foreign body, electroretingraphy, visual prognosis, eye injuries, penetrating injuries to eye

INTRODUCTION

Intraocular foreign body (IOFB) injury is a specific type of open globe injury, which results in mechanical impact and metallic toxicity to intraocular tissue (1–3). Retained metallic IOFB can cause siderosis bulbi. Anterior segment examination may reveal iron deposits on the cornea and anterior capsule, iris heterochromia, pupillary mydriasis, cataract, and glaucoma. Retina toxicity usually manifests as retinal arteriolar narrowing and sheathing and pigmentary retinal degeneration (4). Our previous study found that photoreceptor damage and inner retinal ischemia are two major findings of metallic toxicity to the retina on OCT.

TABLE 1 | Demographic and clinical information of the included subjects.

Gender	Age	Eye	Injury-ERG (d)	ERG-IOFBR (d)	Wound location	Wound length	Lens	Location of IOFB	Magnetic	Cataract surgery	IOFB removal
Female	41	OD	724	6	Sclera	Unknown	Cataract	Intravitreal	Non-magnetic	Y	PPV
Male	41	OS	33	0	Peripheral cornea	5 mm	Cataract	Peripheral retina	Magnetic	N	External
Male	48	od	3,643	8	Sclera	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	22	OS	3	3	Peripheral cornea	3 mm	Cataract	Intravitreal	Magnetic	Y	PPV
Male	31	OS	2,488	76	Sclera	1 mm	Cataract	Intravitreal	Magnetic	Y	PPV
Male	34	OS	332	34	Peripheral cornea	4 mm	Pseudophakia	Pars plana	Magnetic	N	PPV
Male	37	OS	716	15	Sclera	1.5 mm	Cataract	Pars plana	Magnetic	Y	PPV
Male	40	OS	16	0	Sclera	Unknown	Cataract	Intravitreal	Magnetic	Y	PPV
Male	45	OS	3	1	Peripheral cornea	1 mm	Clear	Intracameral	Magnetic	N	AC
Male	21	OS	17	1	Paracentral cornea	6 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	23	OS	258	33	Paracentral cornea	10 mm	Cataract	Peripheral retina	Non-magnetic	Y	PPV
Male	35	OS	4	1	Peripheral cornea	2 mm	Local cataract	Peripheral retina	Magnetic	Y	PPV
Male	16	OS	2	2	Peripheral cornea	3 mm	Local cataract	Peripheral retina	Magnetic	N	PPV
Male	22	OD	1	0	Sclera	1 mm	Clear	Intravitreal	Magnetic	N	PPV
Male	20	OS	91	0	Sclera	1 mm	Clear	Vascular arcade	Magnetic	N	PPV
Male	41	OS	674	786	Peripheral cornea	2 mm	Local cataract	Peripheral retina	Magnetic	N	PPV
Female	43	OS	54	7	Peripheral cornea	1 mm	Cataract	Intralenticular	Magnetic	Y	AC
Male	31	OD	25	1	Peripheral cornea	2 mm	Local cataract	Intravitreal	Magnetic	N	External
Male	60	OS	3,650	1	Peripheral cornea	2 mm	Mild cataract	Intracameral	Magnetic	N	AC
Male	61	OS	2,190	4	Peripheral cornea	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	46	OS	723	8	Sclera	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Female	42	OD	30	0	Limbus	1 mm	Cataract	Intravitreal	Magnetic	Y	PPV
Male	44	OD	3,651	3	Sclera	Unknown	Cataract	Peripheral retina	Non-magnetic	Y	PPV
Male	58	OS	3,648	4	Peripheral cornea	2 mm	Local cataract	Intracameral	Non-magnetic	N	AC
Male	35	OS	3,637	14	Peripheral cornea	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	30	OS	245	0	Peripheral cornea	1 mm	Cataract	Intravitreal	Magnetic	Y	PPV
Male	28	OD	730	1	Sclera	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	24	OS	60	1	Sclera	Unknown	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	41	OD	2,555	1	Sclera	1 mm	Cataract	Peripheral retina	Magnetic	Y	PPV
Male	56	OD	401	1	Sclera	4 mm	Pseudophakia	Pars plana	Magnetic	N	External
Male	43	OD	1,460	1	Sclera	Unknown	Local cataract	Peripheral retina	Magnetic	Y	PPV
Male	33	OS	31	1	Paracentral	3 mm	Local cataract	Peripheral retina	Magnetic	Y	PPV
Male	26	OS	21	1	Sclera	1 mm	Clear	Intravitreal	Magnetic	N	PPV

d, days; ERG, electroretinography; IOFB, intraocular foreign body; IOFBR, intraocular foreign body removal; PPV, pars plana vitrectomy; AC, anterior chamber.

Retinal electrophysiological examination in metallic IOFB injury has been shown to be associated with delayed implicit time and reduced amplitude in both a wave and b wave, suggesting both inner and outer retinal impairment (5–8). Electroretinogram (ERG) response can also be used to monitor retinal toxicity in IOFB and provide a reference for surgical intervention (9). It was also reported that visual acuity and ERG response improved after the surgical removal of IOFB (6). However, the visual outcome was highly dispersive, and some complications such as retinal detachment and endophthalmitis predicted poor visual outcomes (10). It remains unknown whether the retinal toxicity quantified by the ERG responses can be used to predict the visual outcome of IOFB. Furthermore, which component of the ERG responses is the most significant change also needs further investigation.

The purpose of our study was to quantify and grade the ERG responses after a metallic IOFB injury and analyze the correlation between ERG and visual outcome so as to facilitate visual prognosis after a metallic IOFB injury.

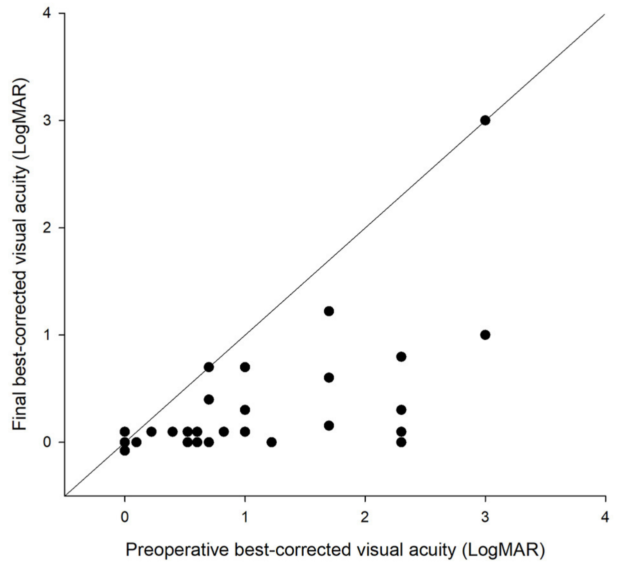

FIGURE 1 | Scatter plot of the preoperative and final best-corrected visual acuity (BCVA) in each intraocular foreign body-injured eye. The dots on the oblique line indicate no change of BCVA after the operation. The dots below the oblique line indicate an improvement of BCVA. The dots above the oblique line indicate a worsening of BCVA after the operation.

METHODS

This retrospective study reviewed all metallic IOFB injury cases between January 2008 and May 2020 in Joint Shantou International Eye Center (JSIEC) of Shantou University and the Chinese University of Hong Kong. This study was approved by the JSIEC Institutional Review Board. Informed consent was waived because of the retrospective nature of this study.

The inclusion criteria were as follows: (1) diagnosis of metallic IOFB injury and (2) ERG was performed after IOFB injury and before its removal. The exclusion criteria were as follows: (1) lack of preoperative ERG data of the injured eye, (2) ERG was conducted using other models rather than Retiport32, (3) presence of retinal detachment or macular hole, and (4) history of retina disease.

Data on history, best-corrected visual acuity (BCVA), duration of foreign body, ERG, and follow-up time were collected. Visual acuity was measured using the international standard logarithmic visual acuity chart and converted to minimum resolution angular logarithm (logMAR) unit for statistical analysis. Finger counting was converted to 2.0 logMAR, hand motion was converted to 2.3 logMAR, and light perception was converted to 3.0 logMAR (11).

The pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine, and the other eye was occluded. Standardized full-field ERGs were elicited with Ganzfeld stimuli using the commercial ERG system (Retiport32; Roland Consult, German). Five responses were recorded, including (1) dark-adapted 0.01 ERG (rod response), (2) dark-adapted 3.0 ERG (maximal response), (3) dark-adapted 3.0 oscillatory potentials (oscillatory potentials, OPs), (4) light-adapted 3.0 ERG (cone response), and (5) light-adapted 3.0 flicker ERG (30-Hz flicker) (12). The implicit period and the amplitude were recorded. For non-recordable responses, the amplitude was set as 0, while the implicit time was set as a missing value. The responses were graded into five levels as follows: non-recordable, severely subnormal (5–40% of normal values), moderately subnormal (40–70% of normal values), mildly subnormal (70–90% of normal values), and normal (90–110% of normal values).

The ratios of the parameters of the affected eye to the contralateral eye was calculated. Paired t-test was used to compare the ERG parameters between the injured and fellow eyes. Wilcoxon ranked test was used to compare the preoperative BCVA with the final BCVA. Spearman's correlation was used to analyze the relationship between the ERG implicit period, amplitude, and grade with the final BCVA. Statistical analyses were performed using SPSS Statistics software (version 21.0, SPSS Inc., Chicago, IL). Statistical significance was considered when $p < 0.05$.

RESULTS

A total of 33 eyes of 33 patients were included. There were 30 males and three females (10 right eyes, 23 left eyes). The median IOFB duration time was 291 days. The median follow-up time was 126 days. The location of the wound, length of the wound, lens, location of IOFB, character of IOFB, and type of surgery of each patient are listed in **Table 1**. There was no patient with direct macular injury. There was no significant correlation between the IOFB duration time with preoperative BCVA or final BCVA ($r = 0.241$ and 0.270, respectively; both $p > 0.05$). BCVA improved in 29 eyes, remained unchanged in three eyes, and decreased in one eye after surgery (**Figure 1**). The mean BCVA improved from 1.23 ± 0.92 logMAR preoperatively to 0.36 ± 0.55 logMAR postoperatively ($p < 0.001$).

The implicit times were delayed, and the amplitudes were reduced in all ERG responses (**Table 2**). The ratios of implicit

TABLE 2 | Results of preoperative electroretinogram (ERG) response parameters and their correlation with the final best-corrected visual acuity.

Response	Parameter	*N*	Mean ± SD	Ratio to the fellow eye	Paired *t*-test	Spearman correlation with baseline BCVA		Spearman correlation with final BCVA		Spearman correlation with injury to ERG time	
					P-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value
Rod response	b (ms)	23	103.13 ± 12.86	1.45 ± 0.53	<0.001	0.422	0.045	0.151	0.493	0.244	0.261
	b-wave (µV)	33	138.80 ± 126.00	0.46 ± 0.41	<0.001	−0.438	0.011	−0.607	<0.001	−0.256	0.151
Maximal response	a (ms)	30	24.63 ± 2.30	1.22 ± 0.33	0.001	0.508	0.004	0.565	0.001	0.589	0.001
	b (ms)	30	51.53 ± 7.19	1.12 ± 0.31	0.037	0.394	0.031	0.106	0.576	0.131	0.489
	a-wave (µV)	33	163.30 ± 112.83	0.56 ± 0.36	<0.001	−0.468	0.006	−0.459	0.007	−0.204	0.256
	b-wave (µV)	33	323.15 ± 228.53	0.64 ± 0.65	<0.001	−0.405	0.019	−0.507	0.003	−0.163	0.364
Oscillatory potentials	N1 (ms)	28	16.64 ± 1.91	1.95 ± 1.97	0.014	0.326	0.090	0.446	0.017	0.190	0.334
	P1 (ms)	28	20.82 ± 1.91	1.76 ± 1.78	0.010	0.471	0.011	0.629	<0.001	0.345	0.072
	N2 (ms)	28	23.82 ± 2.75	1.64 ± 1.66	0.008	0.450	0.016	0.445	0.018	0.394	0.038
	P2 (ms)	28	29.07 ± 3.93	1.57 ± 1.58	0.004	0.469	0.012	0.512	0.005	0.410	0.030
	N3 (ms)	27	32.22 ± 4.30	1.54 ± 0.903	0.003	0.487	0.010	0.54	0.004	0.418	0.030
	P3 (ms)	27	35.07 ± 3.81	1.49 ± 0.82	0.002	0.507	0.007	0.687	<0.001	0.526	0.005
	N4 (ms)	25	38.84 ± 4.41	1.48 ± 0.73	0.001	0.422	0.035	0.318	0.121	0.501	0.011
	P4 (ms)	25	41.92 ± 4.38	1.42 ± 0.65	0.002	0.357	0.080	0.288	0.163	0.591	0.002
	OS1 (µV)	33	18.96 ± 14.60	0.48 ± 0.32	<0.001	−0.462	0.007	−0.626	<0.001	−0.358	0.041
	OS2 (µV)	33	53.22 ± 42.07	0.50 ± 0.39	<0.001	−0.490	0.004	−0.611	<0.001	−0.267	0.133
	OS3 (µV)	33	17.82 ± 18.64	0.42 ± 0.42	<0.001	−0.427	0.013	−0.676	<0.001	−0.278	0.117
	OS4 (µV)	33	11.32 ± 13.73	0.66 ± 0.96	0.060	−0.236	0.186	−0.499	0.003	−0.074	0.680
	OS1 + OS2 + OS3 (µV)	33	89.99 ± 70.57	0.47 ± 0.35	<0.001	−0.472	0.006	−0.644	<0.001	−0.302	0.087
Cone response	a (ms)	28	17.04 ± 1.73	1.29 ± 0.53	0.005	0.417	0.027	0.439	0.020	0.456	0.015
	b (ms)	28	33.50 ± 2.94	1.25 ± 0.43	0.003	0.496	0.007	0.523	0.004	0.343	0.074
	a-wave (µV)	33	33.57 ± 22.17	0.59 ± 0.38	<0.001	−0.481	0.005	−0.595	<0.001	−0.275	0.122
	b-wave (µV)	28	96.62 ± 76.29	0.54 ± 0.40	<0.001	−0.473	0.005	−0.602	<0.001	−0.289	0.103
30-Hz flicker	N1 (ms)	29	15.31 ± 2.69	1.36 ± 0.62	0.003	0.532	0.003	0.413	0.026	−0.008	0.967
	P1 (ms)	29	31.79 ± 3.52	1.31 ± 0.43	<0.001	0.462	0.012	0.500	0.006	0.199	0.301
	N1-P1 (µV)	33	70.63 ± 54.27	0.54 ± 0.40	<0.001	−0.371	0.033	−0.539	0.001	−0.191	0.287
	30-Hz amplitude (µV)	33	32.44 ± 22.19	0.56 ± 0.38	<0.001	−0.476	0.005	−0.648	<0.001	−0.275	0.122

ms, implicit period in millisecond; µV, amplitude in microvolt; BCVA, best-corrected visual acuity.

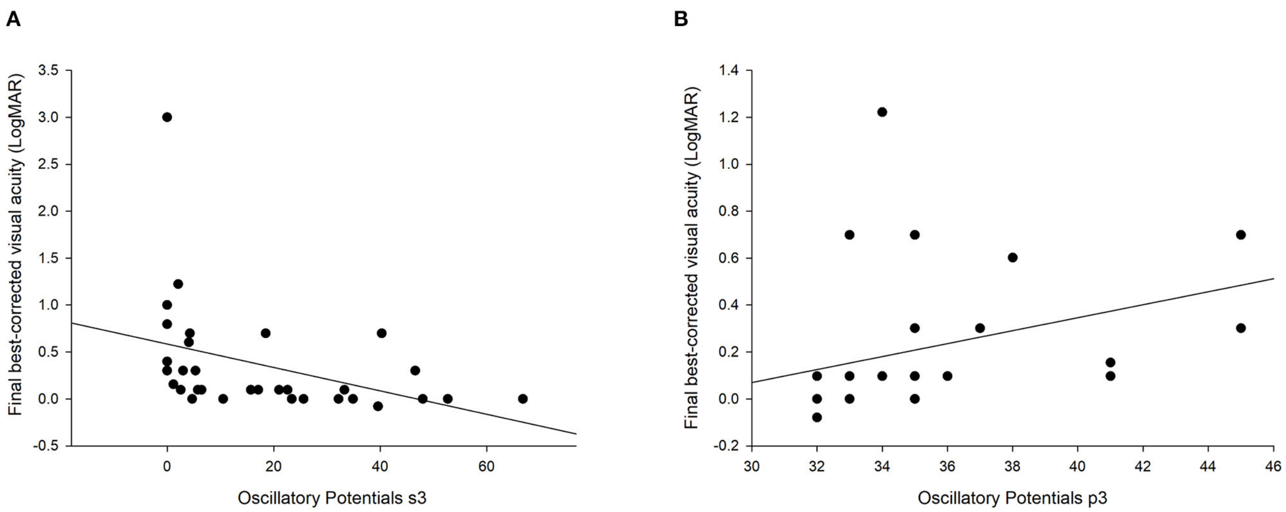

FIGURE 2 | Scatter plots of the oscillatory potentials OS3 **(A)** and P3 **(B)** with the final best-corrected visual acuity. The lines represent the regression lines.

time in the injured eye compared to the contralateral eye ranged from 1.12 to 1.95 (all $p < 0.05$), and the ratios of amplitude ranged from 0.42 to 0.66 (all $p < 0.05$, except the Ops4, whose p-value was 0.060). The maximum ratios were OS3 (0.42 ± 0.42 of the fellow eye) and OP N1 (1.95 ± 1.97 of the fellow eye).

All amplitudes were negatively correlated with the final BCVA (rs: −0.676 to −0.459, all $p < 0.05$, **Table 2**). The maximum correlation was with OS3 (**Figure 2A**). In contrast, the implicit times were positively correlated with the final BCVA, although, some of them were not statistically significant (rs: 0.072 to 0.687, **Table 2**). The maximum correlation was OP P3 (**Figure 2B**). The gradings of all the six ERG waves were statistically correlated with the final BCVA, with the correlation coefficient ranging from −0.596 to −0.664 (all $p < 0.001$, **Figure 3**). The IOFB duration time was positively correlated with the implicit time of Max a wave, OP N2, P2, N3, P3, N4, P4, and cone a wave and negatively correlated with amplitude of OP OS1 (**Table 2**).

There were two eyes with completely non-recordable responses in all waves. In the first case, both the baseline and final BCVA were light perception, while in the second case, the BCVA improved from 1.2 logMAR preoperatively to 0.8 LogMAR at the last follow-up. There was a case with a supernormal ERG response. The time from IOFB injury to ERG examination was 1 day. The iron IOFB located at the peripheral retina and the preoperative ERG showed a slight increase in the amplitudes of all ERG waves in the injured eye (**Figure 4**). There was a corneal scar at the paracentral cornea. The initial and final BCVA was 1.0 and 0.7 logMAR, respectively.

DISCUSSION

In this study, we reviewed the data of 33 eyes with metallic IOFB and found a reduction in the ERG wave amplitudes and delay in implicit periods. The maximum changes were at the OP OS3 and N1. All the amplitudes were negatively correlated with the final BCVA. In contrast, all implicit times were positively correlated with the final BCVA, although, some were not statistically significant. Among them, OP OS3 and P3 had the highest correlation coefficient. The gradings of all the six ERG waves were also statistically correlated with the final BCVA.

Our results showed that metallic IOFB leads to a decrease in amplitudes and implicit periods, which is similar to the literature results (5). There were several components in the five ERG responses. Different components represent the function of different cells. The general reduction in ERG responses suggests that all the retinal cells, including rod and cone photoreceptors, bipolar cells, and vascular function are affected in IOFBs.

A previous study investigated the prognostic value of ERG in severe recent ocular trauma (13). However, there were only seven eyes with IOFBs, and no quantitative data was analyzed. Our results showed that most of the waves differed between the affected and the contralateral eyes and correlated with the final BCVA. OPs were the most significant components. OPs record the activity of inhibitory synaptic circuits within the inner plexiform layer, representing the function of retinal microcirculation (12). It has been reported that b wave and OPs were enhanced, and visual outcomes were good in three eyes with early stage of IOFB injury (14). In another study, the amplitudes of rod and cone ERGs and the OPs were reduced after the injury. After the surgery, the amplitudes of rods and cones were markedly improved, but the OP amplitudes remained unchanged (6). These results suggested that the maintenance of retinal microcirculation after the injury is helpful to the recovery of postoperative vision.

ERG can detect retinal toxicity in metallic IOFBs. It has been reported that retinal dysfunction caused by retinal toxicity of metallic IOFB is reversible in the early stages (6), but the reversal was partial (15). Although, our study did not investigate ERG changes after the surgical removal of IOFB, our results showed that most cases achieve visual improvement. The preoperative

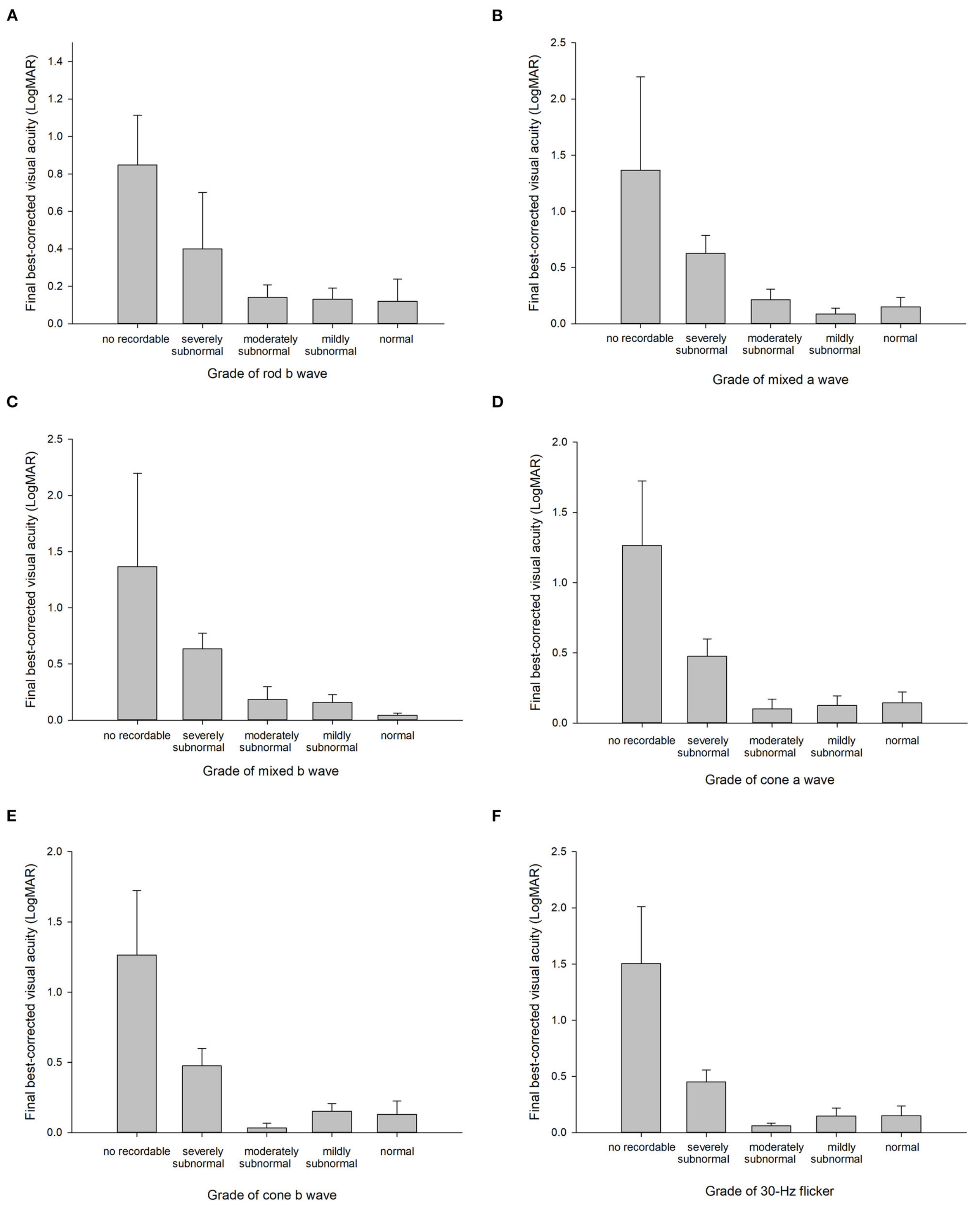

FIGURE 3 | Final best-corrected visual acuity in the different grades of rod b wave **(A)**, mixed a wave **(B)**, mixed b wave **(C)**, cone a wave **(D)**, cone b wave **(E)**, and 30-Hz flicker **(F)**. The error bars represent standard errors.

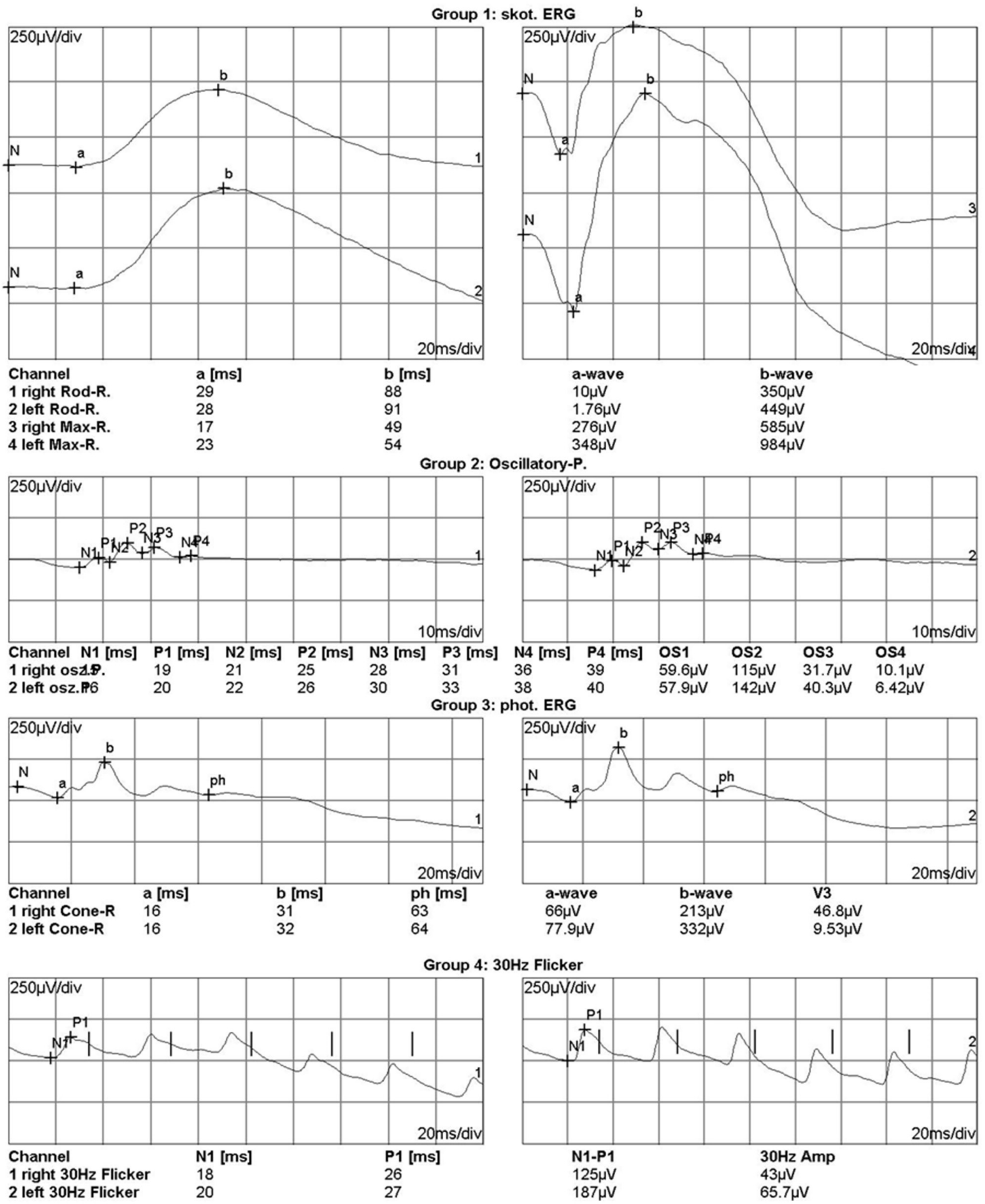

FIGURE 4 | Electroretinogram of a case with enhanced electroretinography responses in the left eye which had intraocular foreign body injury at 1 day before. In the right panels were the responses of the right eye and in the left panels were the responses of the left eye. The iron intraocular foreign body passed through the cornea and finally located in the peripheral retina. The initial best-corrected visual acuity (BCVA) was 0 and 1.0 logMAR for the right and left eye, respectively. The final BCVA was 0 and 0.7 logMAR for the right and left eye, respectively.

ERG results were correlated with visual outcomes. It suggests that retinal damage may be at least partially irreversible in IOFB patients, especially in patients with non-recordable or severely subnormal responses. Our results provide a reference for predicting the visual prognosis in IOFB.

In the two patients with non-recordable ERG in all responses, the final BCVA was light perception in one patient but 0.8 logMAR in the other. It was also reported in the literature that non-recordable ERG might not indicate a poor visual outcome (16). Therefore, surgical removal is still recommended for these patients.

The median time of IOFB retainment was 291 days in this case series. It suggests that this group of patients has delayed presentation to ophthalmologists. There are several reasons of delay in visiting a physician. In some patients, the wound was small and the initial visual acuity was good. Some patients lack medical insurance and have a financial problem, and there was selection bias in that only patients whose wound was closed and IOFB was retained received ERG examination.

We also had a patient with enhanced ERG responses. Similar results were also reported in a case report (17). The enhanced responses occur in the early stage, which may be due to metal ions increasing the intraocular fluid's electrical conductivity and thus changing the resting potential of retinal cells (8). Our case had a history of IOFB injury at 1 day before the ERG examination. The patient's final BCVA (logMAR 0.7) may be due to the corneal scar rather than the retinal toxicity.

Our study has the advantage of a relatively large sample size which allows us to analyze the correlation between ERG components and visual prognosis, and we investigated all the components in five ERG responses and identified the most significant components. Our finding would help physicians to select the appropriate ERG parameter and predict the visual outcome of IOFB patients.

We recognize some limitations in the current study. Firstly, it is a retrospective study, and there may be a selection bias. Secondly, the visual outcome in IOFB patients may be affected by several factors, such as corneal scar. Thirdly, we did not conduct an ERG examination after IOFB removal and did not have longitudinal data.

In conclusion, in our study, ERG response was correlated with visual outcomes after a metallic IOFB injury. Oscillatory potentials were the most important quantitative parameters.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Joint Shantou International Eye Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XM contributed to data collection and first draft. FL contributed to data analysis. YG contributed to data collection. JC and HL contributed to ERG examination. HC contributed to study design and manuscript revision. All authors contributed to the article and approved the submitted version.

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Risk Factors for Band Keratopathy in Aphakic Eyes With Silicone Oil Tamponade for Open-Globe Injuries: A Multicenter Case-Control Study

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Band keratopathy (BK) is a common complication in aphakic eyes with silicone oil tamponade for open-globe injury (OGI), characterized by the grayish-white opacities in the cornea, resulting in a significantly decreased vision when extending to the visual axis. To identify the risk factors for BK in aphakic eyes following vitreoretinal surgical treatment with silicone oil tamponade for OGIs, we performed a multicenter case-control study. The incidence of BK was 28% (28/100 eyes). The multivariate binary logistic regression revealed the silicone oil retention time (SORT) ≥6 months and zone III injury were significant risk factors for BK. From the hierarchical interaction, SORT ≥6 months had a significant risk for BK in eyes with rupture, aniridia, and zone III injury, while zone III injury had a significant risk for BK in eyes with rupture, incomplete/complete iris, and SORT ≥6 months. By using restricted cubic splines with three knots at the 25th, 50th, and 75th centiles to model the association of SORT with BK, we also found a marked increase in the risk for BK at ≥10 months and a slow increase after 6 months, but almost stable within 4–6 months.

Keywords: band keratopathy, open-globe injuries, silicone oil tamponade, aphakic eye, zone of injury, silicone oil retention time

INTRODUCTION

Open globe injury (OGI) is a common cause of unilateral visual impairment and blindness worldwide (1, 2). Severe and complicated ocular trauma can break the iris-lens barrier and affect both the anterior and posterior segments, leading to an enormous variety of anterior segment injuries of the eye, including open corneal trauma, complete or incomplete iris defect, traumatic cataract, ciliary body detachment, and cyclodialysis (3, 4). With the advancement of surgical techniques, vitrectomy combined with anterior segment surgical procedures has become an effective method in treating severe and complicated cases. Retinal detachment (RD) is a vision-threatening complication of OGI (5). For patients with complicated RD in OGI, silicone oil tamponade is necessary, even in the long term in some patients. However, it is well-known that silicone oil tamponade has some complications such as band keratopathy (BK), which is characterized by the deposition of grayish-white opacities in the superficial layers of the cornea, resulting in a significantly decreased vision when the opacities extend to the visual axis. Patients with BK may also suffer from eye irritation and pain (6).

Morphis et al. (7) reported that BK (8%) and corneal decompensation (12%) occurred in eyes with silicone oil tamponade for more than 12 months. Goezinne et al. (8) also concluded that intact natural or artificial lens-iris diaphragms protect corneal endothelial cells from damage by long-term silicone oil tamponade. The lack of the natural barrier, BK, and corneal endothelial decompensation occur more frequently in eyes with traumatic aphakia and aniridia. Secondary intraocular pressure (IOP) changes and silicone oil entering the anterior chamber should also be considered. Shah et al. (9) found that the incidences of postoperative corneal decompensation, BK, ocular hypertension, and hypotony were 4.7, 6.4, 9.4, and 21.9%, respectively, after silicone oil removal. Yüksel et al. (10) placed silicone oil barrier sutures in aphakic eyes with iris defects; hypotony and BK still occurred in 31% of eyes. However, few published reports have detailed the risks of BK in traumatic eyes after vitreoretinal surgical treatment combined with silicone oil tamponade for OGIs with aphakia.

In this study, we analyzed the risks of BK in traumatic eyes following vitreoretinal surgical treatment with silicone oil tamponade for OGIs with aphakia using a multicenter case-control study.

METHODS

Patients

The medical records of all patients with OGI undergoing vitreoretinal surgical treatment with silicone oil tamponade at the Department of Ophthalmology of 10 hospitals from all over China between 2014 and 2020 were screened. The inclusion criteria were OGI eyes with aphakia or posterior capsule rupture treated with pars plana vitrectomy combined with silicone oil tamponade. On the other hand, the exclusion criteria included a history of previous intraocular surgery, keratopathy, postoperative endophthalmitis, incomplete clinical data, and follow-up time of <3 months. Under slit-lamp microscopy, eyes with BK were observed with obvious band-shaped grayish to whitish opacities in the superficial layers of the cornea, most frequently in the interpalpebral zone (**Figure 1**). The patients were divided into two groups according to the outcome of BK: BK and non-BK groups. This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Tianjin Medical University General Hospital Ethics Committee. The requirement for informed consent was waived because of the retrospective nature of the study.

Data Collection

This was a multicenter, case-control study. The demographic information of the patients such as sex and age, and clinical characteristics, including diagnosis, zone of injury, iris status, best-corrected visual acuity (BCVA), IOP, and silicone oil retention time (SORT), were collected from medical records. The BCVAs were measured using Snellen charts with standardized procedures by certified masked research officers, and IOP was measured using non-contact IOP measurements (CT80, Topcon, Japan). According to the Birmingham Eye Trauma Terminology (4), the zone of injury was coded as an ordinal variable: Zone I, cornea only; Zone II, 5 mm posterior to the limbus; and Zone III, ≥5 mm posterior to the limbus. All ophthalmic evaluations were reassessed by senior ophthalmologists before, during, and after the surgery. All the surgeons involved were experienced and performed a standard three-port vitrectomy combined with silicone oil tamponade.

Statistical Analysis

The analysis was performed using Statistical Product and Service Solutions (SPSS) version 25.0 for Windows (IBM Corp, Armonk, NY, USA). Univariate analysis using the chi-square test or Fisher's exact test was performed to determine the significance of categorical variables. An independent *t*-test was used to compare continuous variables. Variables that were significant in

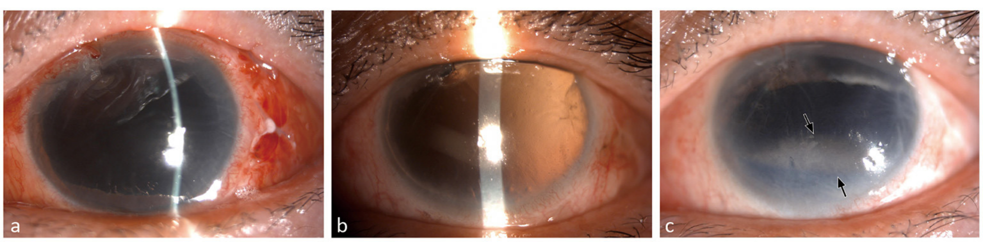

FIGURE 1 | Band keratopathy in a patient. This was a 58-year-old female patient who got eye injured in zone III and diagnosed as rupture with aphakia and aniridia. After the secondary vitrectomy management, the visual acuity was light perception and the intraocular pressure was 10 mmHg. The postoperative corneal transparent was observed at 1 month **(a)** and 3 months **(b)**. Band keratopathy occurred after silicone oil tamponade for 8 months (**c**, black arrow).

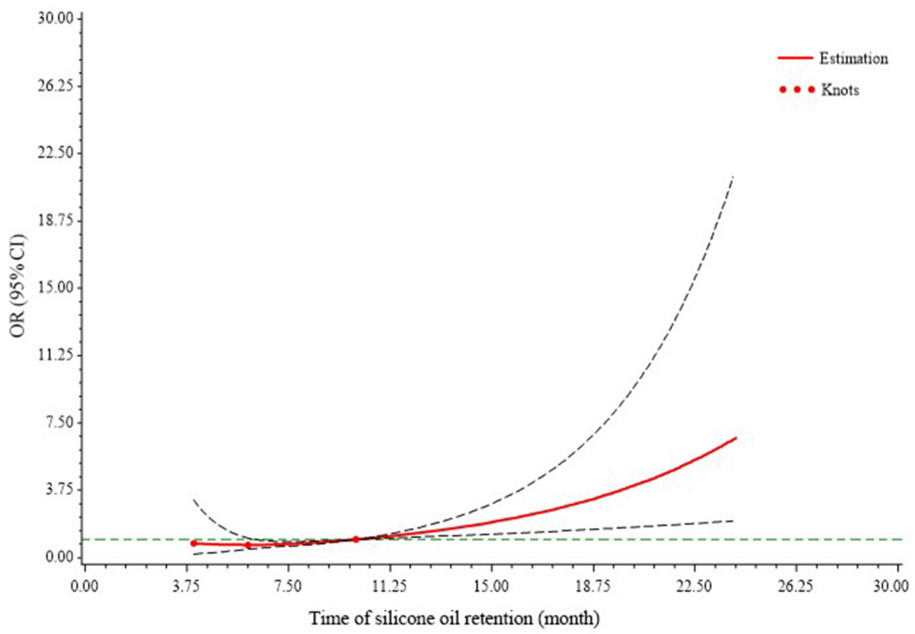

FIGURE 2 | Association between band keratopathy and silicone oil retention time. Restricted cubic splines with three knots at the 25th, 50th, and 75th centiles were used to model the association between band keratopathy and silicone oil retention time. This model was adjusted for intraocular pressure, sex, diagnosis, zone of injury, and iris status. The 95% confidence intervals are indicated by the black dashed lines. The risk of band keratopathy increases with time and remains almost stable within 6 months, increases slowly at 6–10 months, and increases sharply after 10 months postoperatively. CI, confidence interval; OR, odds ratio.

the univariate analysis or clinically meaningful indicators were examined using binary logistic regression analysis to predict independent factors. Hierarchical interaction analysis was used to determine the association between BK and risk factors. All statistical tests were two-tailed, and statistical significance was defined as $P < 0.05$.

For more detailed analyses of the time-response trends, restricted cubic splines (RCS) with three knots at the 25th, 50th, and 75th centiles were used to flexibly model the association of silicone oil retention time with the outcome of BK; the model was adjusted for IOP, sex, diagnosis, zone of injury, and iris status). This was conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) (11).

RESULTS

A total of 100 patients (100 eyes), who met all the inclusion criteria and did not meet the exclusion criteria, were enrolled in the study. During the follow-up period, 28 eyes (28%) developed BK. The demographic and clinical characteristics of the study population are shown in **Table 1**. There were no significant differences in sex and age between the BK and non-BK groups. The SORT was significantly longer in the BK group (13.96 ± 10.71 months) than in the non-BK group (7.86 ± 6.81 months, $P = 0.001$). In the BK group, zone III injured eyes accounted for 75.0%, which was higher than that in the non-BK group (38.9%, $P = 0.01$). Additionally, the BK eyes were more likely to be with rupture (85.7%) and aniridia (42.9%), although these results were not statistically significant.

Table 2 provides the adjusted odd ratios (ORs) and 95% confidence intervals (CIs) for BK using a multivariable logistic regression analysis. After adjusting for age and other selected variables, the results showed that age (OR = 1.04; 95% CI: 1.00–1.08, $P = 0.08$) was close to a borderline, and SORT (OR = 1.32; 95% CI: 1.06–1.21, $P = 0.001$) and zone of injury (OR = 6.88; 95% CI: 1.94–24.44, $P = 0.001$) remained as independent risk factors for BK.

The binary logistic regression model was repeated for BK between strata defined by SORT (**Table 3**) and the zone of injury (**Table 4**). Specifically, the risk of BK associated with silicone oil retention over 6 months was limited to the eyes diagnosed with rupture (OR = 5.08; 95% CI: 1.42–18.16, $P = 0.01$), aniridia (OR = 9.84; 95% CI: 1.26–76.74, $P = 0.01$), and zone III injury (OR = 7.74; 95% CI: 1.76–34.10, $P = 0.03$). Moreover, the impact of zone III injury was more marked in the eyes diagnosed with rupture (OR = 6.84; 95% CI: 1.69–27.69 $P = 0.01$), incomplete/complete iris (OR = 13.80; 95% CI: 2.76–69.08, $P = 0.001$), and silicone oil retention over 6 months (OR = 7.71; 95% CI: 1.73–34.73, $P = 0.01$).

To evaluate the risk of BK with silicone oil retention time, we developed an RCS logistic regression model to fit all the data, which was adjusted for IOP, sex, diagnosis, zone of injury, and iris status (**Figure 2**). The 25th, 50th, and 75th centiles were 4, 6, and 10 months, respectively. There was an approximately linear correlation between SORT and the risk of BK, and a marked increase in risk for BK was observed ≥10 months, but minimal elevation in risk within 6 months. Within 6–10 months postoperatively, the risk of BK increases slowly with time.

DISCUSSION

The present study focused on BK in the eyes following vitreoretinal surgical treatment with silicone oil tamponade for OGI with aphakia and aimed to identify the risk factors for BK. We collected and analyzed the clinical data of 100 eyes from 10 hospitals across China. We found that silicone oil retention time over 6 months and zone III of OGI were independent risk factors for BK, with the risk of BK increasing sharply with time after 10 months postoperatively.

BK is a common corneal degenerative disease characterized by calcium deposition in the superficial layers of the cornea, including the epithelial basement membrane, basal epithelium, and Bowman's membrane (6). Although the pathophysiology of BK is multifactorial, many studies have reported that silicone oil plays an important role in the development of BK (7, 12, 13). With the advancement of vitreoretinal surgical techniques, silicone oil has been widely used as a vitreous substitute in various diseases and situations because of its chemical stability and special physical properties (14–17), especially in complex trauma cases (18). The present study found that silicone oil tamponade over 6 months was an independent risk factor for BK. Silicone oil is usually removed 3–6 months postoperatively. However, severe traumatic eyes with extensive retinal detachment may require sustained or refilled silicone oil to reattach the retina. Along with long-term silicone tamponade, the chance for oil to contact the corneal endothelium is increasing. Studies have shown that it can be related to the tissue toxic reaction of some components in silicone oil, and another hypothesis is that pH changes are caused by decreased flow across the corneal tissue (19). Berker et al. (20) observed anterior dislocation of silicone oil (9.5%) in patients with proliferative vitreoretinopathy. Szaflik et al. (21) also described confocal microscopy observations of the eyes with silicone oil in the anterior chamber and revealed alterations in the upper part of the cornea, which is the part most exposed to the silicone oil, with "multidot" lesions and lesions with thickening cell borders. Furthermore, Dooley et al. (22) reported that corneal pathology (13.8%) and anterior segment emulsification (8.3%) occurred in eyes with long-term heavy silicone oil tamponade. In contrast, incidences of postoperative corneal decompensation

TABLE 1 | Demographic and clinical characteristics of the study population.

Characteristics	Non-BK (*n* = 72)	BK (*n* = 28)	*P*-value
Sex (*n*, %)			0.46
Male	61 (84.7%)	22 (78.6%)	
Female	11 (15.3%)	6 (21.4%)	
Age (year)	44.78 ± 14.69	48.29 ± 15.78	0.29
Diagnosis (*n*, %)			
Rupture	43 (59.7%)	24 (85.7%)	0.92
Laceration	29 (40.3%)	4 (14.3%)	
Zone of injury (*n*, %)			
Zone I/II	44 (61.1%)	7 (25.0%)	0.01*
Zone III	28 (38.9%)	21 (75.0%)	
Iris status (*n*, %)			
Aniridia	16 (22.2%)	12 (42.9%)	0.11
Partial iris	28 (38.9%)	9 (32.1%)	
Complete iris	28 (38.9%)	7 (25%)	
Best-corrected visual acuity (*n*, %)			
No light perception	8 (28.6%)	1 (3.6%)	0.33
Light perception	52 (72.2%)	24 (85.7%)	
Hand motion or better	12 (16.7%)	3 (10.7%)	
Silicone oil retention time (month)	7.86 ± 6.81	13.96± 10.71	0.001*
Intraocular pressure (mmHg)	13.53 ± 6.99	12.12 ± 4.62	0.33

*Values were presented as mean ± standard deviation or number (percentage). *P<0.05. BK, band keratopathy.*

TABLE 2 | Odds ratios for the association between risk factors and band keratopathy.

Characteristics	BK/Non-BK	OR	95%CI	*P*-value
Age (year)	48.29 ± 15.78/44.78 ± 14.69	1.04	1.00–1.08	0.08
Zone of injury (*n*)				
Zone I/II	7/44	1.00		
Zone III	21/28	6.88	1.94–24.44	0.001*
Diagnosis (*n*)				
Rupture	24/43	1.00		
Laceration	4/29	0.35	0.08–1.62	0.18
Iris status (*n*)				
Aniridia	12/16	1.00		
Incomplete iris	9/28	0.50	0.14–1.78	0.28
Complete iris	7/28	1.04	0.25–4.32	0.96
Silicone oil retention time (month)	13.96 ± 10.71/7.86±6.81	1.32	1.06–1.21	0.001*
Intraocular pressure (mmHg)	12.12 ± 4.62/13.53 ± 6.99	0.93	0.85–1.03	0.17

*Variables were mutually adjusted for each other in the multivariable logistic regression models. *P < 0.05. BK, band keratopathy; OR, odds ratio; CI, confidence intervals.*

TABLE 3 | Association between the time of silicone oil retention and band keratopathy stratified by diagnosis, injury zone, and iris status.

	BK/Non-BK (*n*)	OR (95% CI)			*P* interaction
		3–6 months	>6 months	*P*-value	
Diagnosis					
Rupture	24/43	1.00	5.08 (1.42–18.16)	0.01*	
Laceration	4/29	1.00	5.06 (0.33–77.54)	0.25	0.92
Zone of injury					
Zone I/II	7/48	1.00	4.15 (0.41–41.80)	0.23	
Zone III	21/28	1.00	7.74 (1.76–34.10)	0.01*	0.40
Iris status					
Aniridia	12/16	1.00	9.84 (1.26–76.74)	0.03*	
Incomplete/complete iris	16/56	1.00	3.01 (0.76–11.97)	0.12	0.20

*$P < 0.05$. BK, band keratopathy; OR, odds ratio; CI, confidence intervals.

TABLE 4 | Association between the zone of injury and band keratopathy stratified by diagnosis, time of silicone oil retention, and iris status.

	BK/Non-BK (n)	OR (95% CI)			*P* interaction
		Zone I/II	Zone III	*P*-value	
Diagnosis					
Rupture	24/43	1.00	6.84 (1.69–27.69)	0.01*	
Laceration	4/29	1.00	2.55 (0.15–44.89)	0.52	0.76
Time of silicone oil retention					
3–6 months	9/31	1.00	3.70 (0.53–26.10)	0.19	
>6 months	19/30	1.00	7.71 (1.73–34.73)	0.01*	0.40
Iris status					
Aniridia	12/16	1.00	2.06 (0.26–16.55)	0.50	
Incomplete/complete iris	16/56	1.00	13.80 (2.76–69.08)	0.001*	0.40

*$P < 0.05$. BK, band keratopathy; OR, odds ratio; CI, confidence intervals.

(4.7%) and band-shaped keratopathy (6.4%) were lower after silicone oil was removed (9).

In this study, the other independent risk factor for BK was zone III of the OGI, which suggests that the globe opening location would extend more posteriorly than the pars plana (4). OGIs with zone III injury are particularly serious because they are more likely to be associated with RD and worse final visual acuity (23, 24). Knyazer et al. (25) described that eyelid injury, cornea lamellar lacerations or abrasions, iris deformity, and many other signs were associated with a poor prognosis of the eyes with zone III injury. Here, we found a higher rate of BK (21/49 eyes, 48.9%) in OGI with zone III injury. A possible explanation is that zone III of the OGI aggravated the inflammatory response in the anterior segment, leading to sustained damage to the corneal tissues. In uveitis, inadequate control of eye inflammation can result in permanent and severe ocular complications, in which BK is common (26). Similarly, in severe OGIs, excessive, or persistent inflammation may exacerbate corneal damage. Additionally, structural damage to the ciliary body decreases the generation of the aqueous humor; thus, insufficient oxygen and other important nutrients were provided to the cornea, which affects the progression of corneal repair and recovery. Better ciliary body function might promote aqueous humor secretion and nourish the cornea while reducing the occurrence of BK.

From the results of the hierarchical interaction analysis in our study, silicone oil retention over 6 months had a significant risk for BK in eyes with aniridia, while zone III injury had a significant risk for BK in eyes with incomplete/complete iris. Iris status seemed to play a different role in the risk of BK. Evidently, the chance for silicone oil to enter the anterior chamber to contact the corneal endothelium would greatly increase without the barrier of the iris. To prevent BK, Gentile and Eliott (27) first introduced the technique "Silicone Oil Retention Sutures," an effective means to prevent oil-corneal touch in eyes with aphakic and aniridia. In contrast, the remaining iris (either incomplete or complete) possibly play the role of main source of inflammatory mediators. Aketa et al. (28) also reported that the levels of aqueous protein and cytokines in eyes with iris damage were significantly higher than in eyes without iris damage.

The major innovation of this study was the creative application of the RCS model in showing the increasing risk of BK with silicone oil retention time. These results have instructive clinical significance and suggest that 10 months is a key time-point. For patients with severe ocular trauma following vitrectomy combined with silicone oil tamponade, a thorough examination and appropriate intervention is needed for BK during follow-up after 10 months postoperatively.

There were some limitations to this study. We focused on the risk factors for BK after vitrectomy and silicone oil tamponade. However, the effects of ocular trauma on the cornea were not compared and analyzed, which may cause a bias in the risk of BK in OGIs. Moreover, we did not analyze the location, shape, and occurrence time of BK due to the lack of sufficient details from each department. The high variability of the presentations of ocular trauma injuries was a limitation of the study, while the large number of patients and the standard surgical procedure made the conclusions more robust.

In summary, the results of our study are reliable and provide important insights into the risk factors for BK in eyes following vitreoretinal surgical treatment with silicone oil tamponade for OGIs with aphakia because of the limited number of previously published reports in this field. The risks of BK and simulated SORT can also be used for clinical guidance.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tianjin Medical University General Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KH, ML, and HY designed this study. KH, ML, BC, HC, TW, NW, ZX, JL, YW, ZW, HZ, and ZS collected and measured data. KH, YZ, and HY analyzed and interpreted the data set. KH and ML wrote this article. HC and HY revised the manuscript. All authors reviewed and approved the final manuscript.

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Allogeneic Cultivated Limbal Epithelial Sheet Transplantation in Reconstruction of Conjunctival Sac After Chemical and Thermal Burns

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The study aims to evaluate the effect of allogeneic cultivated limbal epithelial cell sheet transplantation (CLET) in reconstructing conjunctival sac for severe symblepharon after chemical and thermal burns. A retrospective, non-comparative case series. Thirty-six eyes (36 patients) underwent CLET for severe symblepharon and conjunctival sac stenosis or atresia. Symblepharon was separated, and pseudopterygium was preserved to replace the palpebral conjunctiva. Allogeneic cultivated limbal epithelial cell sheet using human amniotic membrane as a carrier was transplanted into the recipient's eye to reconstruct the conjunctival sac. The effect of conjunctival sac reconstruction, eye and eyelid movement, ocular surface restitution, and symblepharon recurrence were analyzed after surgery. Symblepharon was completely relieved in 30 of the 36 eyes (83.3%) by a single surgical procedure, with fornix reconstruction, as well as free movement of eye globe and eyelids. Strip-like symblepharon remained in 6 eyes (16.7%) and was completely relieved after the second CLET. Twenty patients without visual function received prostheses 3 months after surgery and the other sixteen patients underwent different corneal transplantation for visual acuity improvement. During the follow-up period, no one had symblepharon recurrence. The transplantation of cultivated allogeneic limbal epithelial sheets offers an effective and safe alternative in the treatment of symblepharon and reconstruction of conjunctival sac in eyes with severe ocular burns, which lays the foundation for subsequent treatments.

Keywords: chemical and thermal burns, transplantation, symblepharon, allogeneic limbal epithelial cell, reconstructing conjunctival sac

INTRODUCTION

Severe chemical and thermal burns can injure the ocular surface. If the limbal and central epithelia are both absent, the neighboring conjunctival epithelial cells will invade the corneal surface, therefore, the surface will be covered with abnormal conjunctiva, called pseudopterygium. In severe cases, symblepharon and conjunctival sac stenosis or atresia may be present. This process is accompanied by chronic inflammation, persistent epithelial defects, stromal scarring, and neovascularization. The key to relieving symblepharon is providing an effective conjunctival substitute. In previous studies, amniotic membrane (AM) (1, 2), autologous nasal mucosa (3), oral mucous membrane (4), as well as cultivated oral mucous membrane (5) with or without a carrier, and autologous cultivated limbal epithelial cells with (6) or without (7) a carrier were used to reconstruct ocular surface. However, most of these methods cannot be used to treat or are ineffective to severe symblepharon in severe burns (8, 9), but limbal stem cell deficiency (LSCD) can. It is known that limited autologous limbal epithelial cells fail to provide enough limbal tissue, and for many patients with severe burns, the contralateral eye is usually involved and could not supply limbal epithelial cells. Oral mucous membrane with abnormal mucus secretion also restricts the use of these methods. Moreover, it is invasive in obtaining autologous tissue. Allogeneic cultivated limbal epithelial transplantation (CLET) for LSCD has been reported, with donor cells obtained non-invasively (10, 11), but its effect on severe symblepharon is unknown. In this study, we aimed to report clinical results of allogeneic CLET in relieving symblepharon and reconstructing conjunctival sac after chemical and thermal burns.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the institutional review board of Shandong Eye Institute. From May 2013 to February 2019, a consecutive series of 36 eyes (36 patients) underwent allogeneic CLET using human AM for severe symblepharon and palpebral fissure deformity from ocular chemical or thermal burns, and each patient completed a follow-up of at least 16 months at Shandong Eye Institute. Among the total, 20 patients (20 eyes) have lost visual function completely (no light perception) before operation and no F-VEP had an analyzable wave pattern preoperatively. Informed consent was obtained from the patients involved in this study. The mean age of the patients was 34.6 ± 15.1 years (range, 7–61 years). The duration between injury and surgery was at least 6 months. The injuries included thermal burns by hot metal in 21 eyes, alkaline burns in 8 eyes, and acidic burns in 7 eyes (**Table 1**).

The eligible eyes in the study met the following inclusion criteria: (1) All eyes had an extensive symblepharon of at least 2 quarters with conjunctival sac contraction, and the pseudopterygium encroaches onto the cornea, with limitation of eye movement and palpebral fissure deformity; (2) intraocular pressure < 22 mmHg without symptoms; (3) no obvious changes of vitreous body and retina, as detected by B-scan ultrasound; (4) allogeneic CLET was performed at more than 6 months after burns.

Cultivation of Limbal Epithelium

Human immunodeficiency viruses 1 and 2 syphilis, hepatitis B and C, and were negative in all donors. Limbal tissue was cut from fresh donor eyeballs, separated into pieces, and inoculated on denuded AM on the transwell insert as an explant culture. Then the surgeon transferred the transwell inserts into a cell culture plate pre-seeded with mitomycin C-inactivated NIH 3T3 feeder cells, after which the incubation was performed until confluence and stratification for up to 5 days, and the medium was changed every 48 h. The cell sheets, which were approximately 2 cm × 2 cm with 3 to 5 layers of stratification on the AM and basal column-shaped cells and superficial flattened scale-like cells, were used for transplantation (12, 13).

Surgical Techniques

The surgery was guided by optical coherence tomography (OCT). Firstly, the pseudopterygium was peeled off from the cornea and sclera. The symblepharon was separated completely until the eye globe could be moved freely by the surgeon during the procedure. Secondly, the surgeon separated the fibrous tissues of the pseudopterygium with blunt dissection until exposing the sclera. We receded the remaining pseudopterygium as the replacement of palpebral conjunctiva (14) and sutured it inside the surface of the eyelid with 10–0 nylon sutures. The human AM with the cultivated allogeneic limbal epithelial sheet was placed on the corneal stroma, sclera, fornix, and palpebral conjunctiva with the epithelial side oriented upward and sutured with interrupted 10-0 nylon sutures. At the end of the surgery, the surgeon placed a therapeutic soft contact lens on the surface of the treated eyes.

Postoperative Treatment

Intravenous methylprednisolone (2 mg/kg) was administered every day for 3 days. Oral prednisolone (1 mg/kg) was given daily at the beginning of the medication treatment and then tapered over about 3 months. Autologous serum eye drops, with 0.02 mg of dexamethasone and 0.1 mg of tobramycin per milliliter of serum in them, were used every 2 h for the first week, and 0.02% fluorometholone eye drops were administered 4 times daily for the next 2 weeks. After the corneal epithelial was cured, 1% cyclosporine A eye drops were administered 4 times daily. Tobramycin ophthalmic ointment was given every night. This therapy was adjusted according to the patients' clinical status after 3 weeks. The patients were observed every day during the first week after the transplantation, weekly during the next 1 month, monthly in the next 3 months, and 3 months thereafter.

Intravenous methylprednisolone (2 mg/kg) was administered every day for 7 days in the cases that immune rejection occurred. Oral prednisolone (1 mg/kg) was given daily at

TABLE 1 | Basic information of the involved patients.

No.	Gender	Age (years)	Burn	Preoperative visual acuity	Visual acuity after first CLET	Injured eye(s)/treated eye	Grading (4)	Width	Degree of symblepharon recurrence	Therapeutic outcomes
1	male	9	alkaline	NLP	NLP	right/right	2	c	no recurrence	prosthesis
2	male	23	acidic	NLP	NLP	both/right	3	b	no recurrence	prosthesis
3	male	31	acidic	NLP	NLP	left/left	3	c	no recurrence	prosthesis
4	male	39	thermal	HM/BE	FC/10 cm	left/left	3	c	no recurrence	improved appearance and visual acuity
5	male	57	thermal	0.08	0.08	right/right	2	b	no recurrence	improved appearance and visual acuity
6	male	16	thermal	0.1	0.2	right/right	3	c	no recurrence	improved appearance and visual acuity
7	male	55	alkaline	LP	HM/BE	left/left	4	c	2b	improved appearance and visual acuity
8	male	22	thermal	NLP	NLP	right/right	4	c	3a	prosthesis, mild blepharoplasty insufficiency, no recurrence again
9	male	45	thermal	NLP	NLP	left/left	4	b	no recurrence	prosthesis
10	male	41	alkaline	NLP	NLP	both/left	4	b	no recurrence	prosthesis
11	male	27	thermal	NLP	NLP	left/left	2	c	no recurrence	prosthesis
12	male	53	thermal	FC/BE	0.05	right/right	4	b	1a	improved appearance and visual acuity, no recurrence again
13	male	17	thermal	NLP	NLP	left/left	3	b	no recurrence	prosthesis, mild blepharoplasty insufficiency
14	male	54	thermal	NLP	NLP	left/left	3	c	no recurrence	prosthesis
15	male	15	thermal	0.05	0.08	right/right	3	b	no recurrence	improved appearance
16	male	42	acidic	NLP	NLP	left/left	2	c	no recurrence	prosthesis
17	male	40	alkaline	NLP	NLP	right/right	2	c	no recurrence	prosthesis
18	male	45	thermal	0.15	0.12	right/right	4	b	2a	improved appearance, no recurrence again
19	male	55	acidic	NLP	NLP	right/right	3	c	no recurrence	prosthesis
20	male	61	alkaline	NLP	NLP	right/right	4	c	2a	prosthesis, no recurrence again
21	female	48	alkaline	NLP	NLP	both/left	3	b	no recurrence	prosthesis
22	male	31	thermal	NLP	NLP	both/left	3	c	no recurrence	prosthesis
23	male	42	thermal	FC/10 cm	FC/20 cm	both/left	3	b	no recurrence	improved appearance

(Continued)

TABLE 1 | Continued

No.	Gender	Age (years)	Burn	Preoperative visual acuity	Visual acuity after first CLET	Injured eye(s)/treated eye	Grading (4)	Width	Degree of symblepharon recurrence	Therapeutic outcomes
24	male	43	thermal	HM/50 cm	FC/20 cm	right/right	3	b	no recurrence	improved appearance and visual acuity
25	male	19	thermal	0.04	0.04	right/right	4	b	no recurrence	improved appearance
26	male	32	alkaline	FC/BE	FC/30 cm	left/left	2	c	no recurrence	improved appearance
27	male	7	thermal	NLP	NLP	left/left	3	b	no recurrence	prosthesis
28	female	46	thermal	NLP	NLP	left/left	3	b	no recurrence	prosthesis
29	female	21	acidic	NLP	NLP	right/right	3	c	no recurrence	prosthesis
30	male	20	alkaline	NLP	NLP	right/right	3	a	no recurrence	prosthesis
31	female	53	thermal	NLP	NLP	left/left	3	c	no recurrence	prosthesis, mild blepharoplasty insufficiency
32	female	20	thermal	0.08	0.1	right/right	4	b	no recurrence	improved appearance
33	male	11	thermal	0.02	0.3	right/right	3	c	no recurrence	improved appearance and visual acuity
34	male	26	acidic	0.05	0.2	both/right	2	c	no recurrence	improved appearance and visual acuity
35	male	16	thermal	0.02	0.5	left/left	4	b	2a	improved appearance and visual acuity
36	male	49	acidic	0.05	0.2	both/right	2	c	no recurrence	improved appearance and visual acuity

the beginning and tapered for 2 months. Tobramycin and dexamethasone eyedrops were given every 2 h for the first 3 days and tapered to 4 times daily for the next 3 weeks. Then, 0.02% fluorometholone eye drops were administered 4 times every day. At the same time, 1% cyclosporine eye drops were applied 4 times daily. Tobramycin and dexamethasone ophthalmic ointment was given every night for 1 month and twice weekly during taper.

Three months after surgery, a suitable ocular prosthesis was implanted in 20 patients who lost visual function, and ofloxacin 0.3% ophthalmic solution was administered 4 times daily for 2 weeks. And at the same time, cyclosporine A 1% eye drops were given twice daily for a long period of time in all patients.

Outcome Measures

After a detailed explanation, the patient's history, symptoms, onset time, frequency of immune rejection, preoperative and postoperative photographs were collected. Slit-lamp microscopy was performed. Symblepharon recurrence, immune rejection, eye globe movement, prosthesis suitability, and eyelid activity were evaluated.

RESULTS

Symblepharon was completely released in 30 eyes (83.3%) 3 months after a single surgical procedure (**Figure 1**). Strip-like symblepharon, <3 mm wide (**Figure 2A**), remained in 6 eyes (16.7%). Further symblepharon separate on combined with second allogeneic CLET was performed (**Figure 2B**), and a suitable prosthesis was implanted in the 20 patients who lost visual function (**Figure 2C**). Over a follow-up period of 18 months (mean, 17.4 ± 3.9 months), no symblepharon recurred in all 36 patients. Three patients (8.3%) with mild palpebral fissure dysraphism suffered immune rejection within 6 months after surgery, restored a stable ocular surface after 7 days of antirejection therapy.

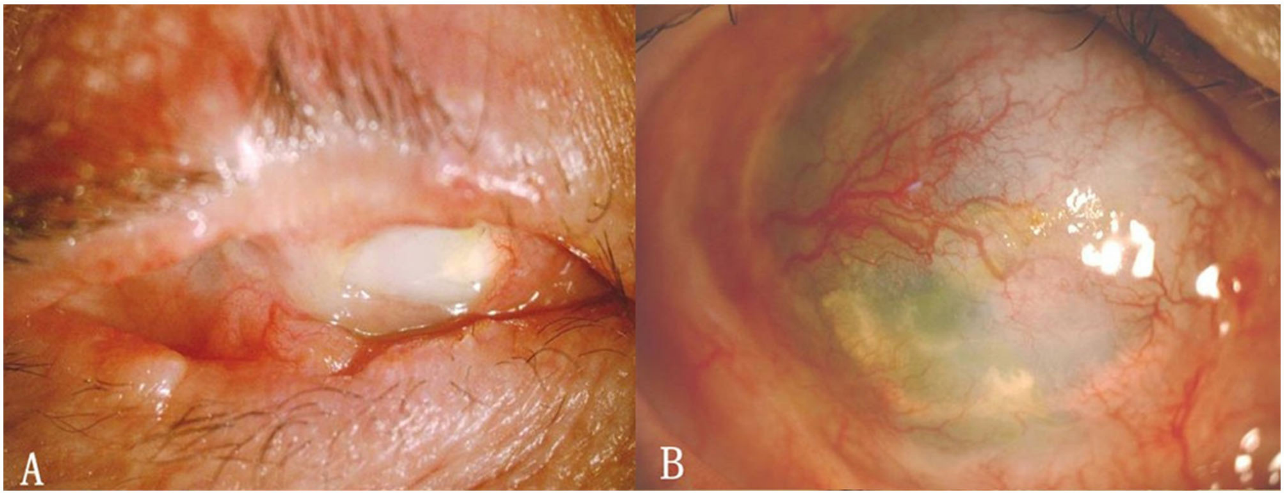

FIGURE 1 | (A) Extensive symblepharon with conjunctival sac atresia. **(B)** Symblepharon was completely released 9 months after allogeneic CLET (A and B are from the same patient).

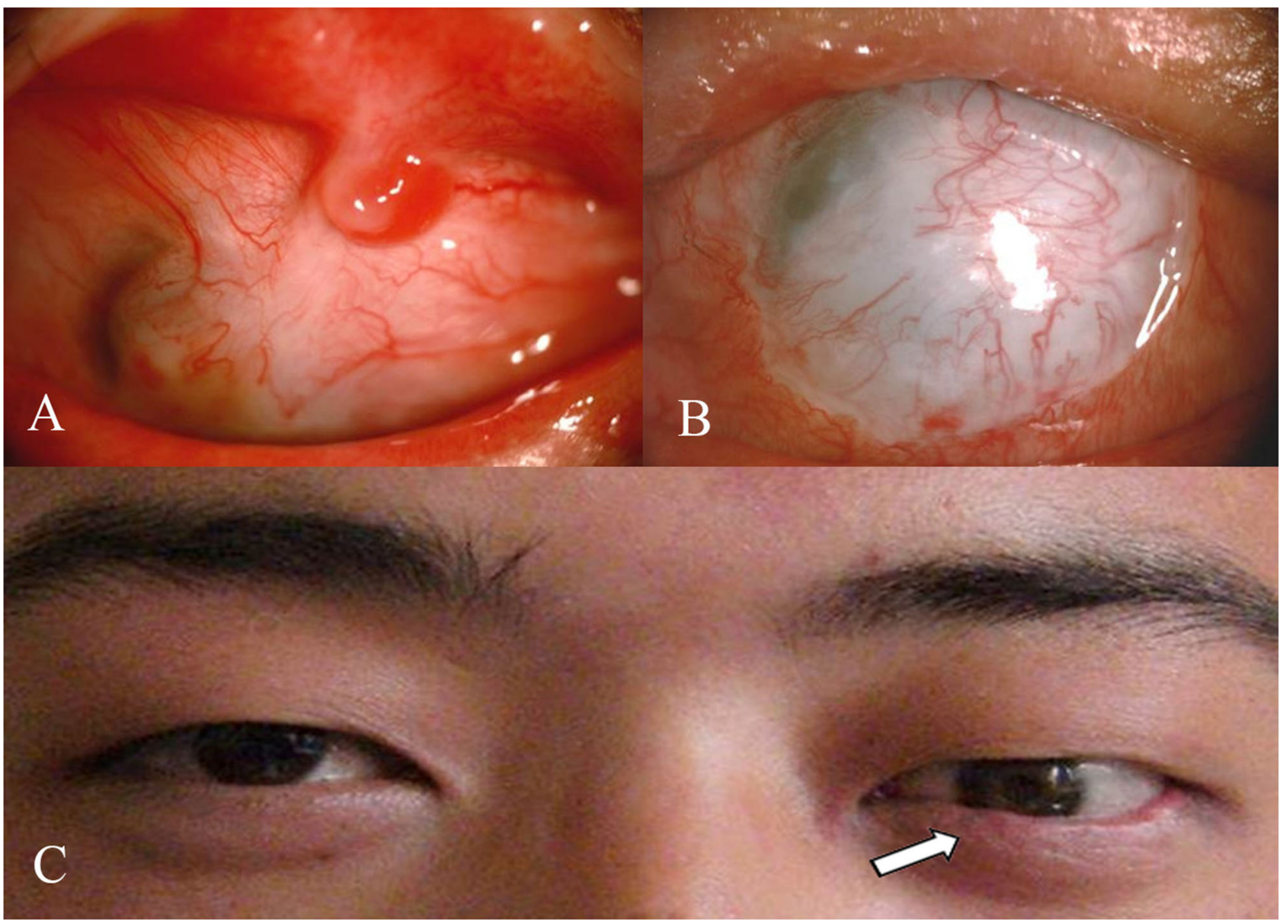

FIGURE 2 | (A) Strip-like symblepharon remained after the first CLET. **(B)** Symblepharon was completely released after the second allogeneic CLET. **(C)** A suitable prosthesis was implanted in the eye that has lost visual function, and the appearance was obviously improved.

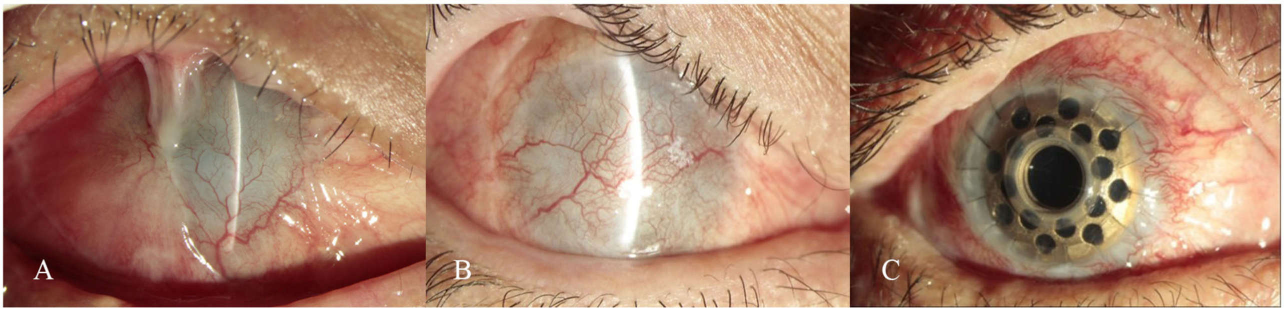

FIGURE 3 | (A) Extensive pseudopterygium covered half of the cornea, with severe symblepharon. **(B)** Symblepharon was completely released at 10 months after allogeneic CLET. **(C)** The best-corrected visual acuity (BCVA) had improved to 0.6 with a stable ocular surface at 6 months after implanting collar-button-shaped Keratoprosthesis.

Reconstruction of Conjunctival Sac

Thirty patients (eyes) could move freely with the smooth ocular surface, the eyelids could blink normally. The incidence rate of Symblepharon after allogeneic CLET was 16.7% (6 eyes of 6 patients) in the first 3 months after surgery. The original injuries included thermal burns in 4 eyes (4 patients) and chemical burns in 2 eyes (2 patients). Six patients (6 eyes) were found strip-like symblepharon of 1–2 mm extent, at 1–3 months after surgery. Follow up 3 months, the wide of symblepharon increased to about 3 mm in one patient, other patients had no distinguishable change, the fornix depth in other parts was not shallow gradually. Further symblepharon separation combined with second allogeneic CLET was performed 2–3 months after symblepharon occurred. Follow up to now, no symblepharon recurrence.

Immune Rejection

3 eyes of 3 patients suffered immune rejection within 6 months after surgery, 1 patient had redness, irritation, photophobia 3 days after stopped taking 1% cyclosporine for 8 days at 4 months after surgery. The clinical manifestation was visual acuity decreased from 0.1 to 0.02, conjunctival congestion, limbal hyperplastic and dilatational vessels, which extended up to the corneal stroma, corneal edema, opacification, epithelial asperity, no rejection line, epithelial defects, keratic precipitates, or anterior chamber reactions. One patient (male, 40 years) with mild palpebral fissure dysraphism suffered immune rejection 1.5 months after surgery, who was burned by alkali severely. He had irritation, Palpebral hypertrophy, ocular surface congestion widely, without secretion and symblepharon recurrence. one patient (male, 55 years) was asymptomatic and diagnosed during the routine follow-up at 2 months after the second surgery, who was also burned by alkali, had severe symblepharon and conjunctival sac atresia. He had the same manifestation as the previous patient. All the 3 patients restored a stable ocular surface after 7 days of antirejection therapy, and the globe and eyelids could move freely without symblepharon recurrence.

Improve Appearance and Visual Function Recovery

Two to three months later, the best-corrected visual acuity (BCVA), intraocular pressure, ocular B-ultrasound and F-VEP were examined. Among the total, 20 patients (20 eyes) have lost visual function completely due to abnormal eye pressure. 3–4 months after surgery, 2 patients with recurrent symblepharon underwent second allogeneic CLET and further symblepharon separation. For follow-up at 3 months, no symblepharon recurred; with a suitable prosthesis, the appearance of these 20 patients was improved.

The other 16 patients (16 eyes) had varying degrees of poor BCVA, and the intraocular pressure was within the normal range, F-VEP had a significant wave pattern, vitreous body with mild opacity in B-ultrasound, denote no obvious abnormality. Over the follow-up period, lacrimal secretion, with or without symblepharon recurrence and immune rejection was observed. More than 6 months after CLET, lamellar keratoplasty (LKP), penetrating keratoplasty (PKP) or transplantation with keratoprosthesis was selected and performed according to the recovery of tears, the degree of limbal stem cells deficiency, and the depth of corneal opacity of each patient to improve the vision. For patients whose Schirmer's test reached 5 mm in follow up, LKP or PKP can be performed; for patients with full-thickness corneal opacity or poor corneal endothelial function, PKP can be performed; if the patient's Schirmer's test reached 2 mm but <5 mm and the patient has a high risk of rejection (severe limbal stem cell deficiencies), transplantation with keratoprosthesis (Guangdong Brilliant Vision Biotechnology Co., Ltd.) can be carried out (**Figure 3**).

DISCUSSION

Severe ocular burns can destroy conjunctiva, limbal stem cells, and cornea, inevitably resulting in severe symblepharon with limitation of eye movement and ocular deformity. Autologous conjunctival transplantation was effective for mild symblepharon, but the application of the method is limited because autologous limbal epithelial cells cannot be removed too much from the fellow eye, or the fellow eye was also involved in burns and can't provide limbal epithelial cells. Moreover, obtaining autologous tissue is invasive and painful. Oral mucous membrane, as well as cultivated oral mucous membrane, can be used to reconstruct ocular surface. Cultivated autologous oral mucous membrane (5) and autologous cultivated limbal epithelial cells (6, 7, 15) were used for conjunctival substitutes in recent years. But oral mucous membrane is different from the conjunctiva, with the defect of opacity, shrink, abnormal mucus secretion and unsatisfactory cosmetic results, epithelial failure, and corneal melting (16, 17). Unfortunately, most of these methods cannot be used for the treatment of severe symblepharon. As we all know, the extensive use of AM has greatly improved the prognosis of acute ocular burns, but AM was a basilar membrane without epithelium. Therefore, it could not substitute for conjunctiva completely and symblepharon recurrences occurred in many cases. A severe symblepharon is often accompanied by eyelid malformation, large-scale conjunctival deficiency, limbal stem cell destruction, and corneal opacification, so a single approach cannot resolve all the problems. Allogeneic CLET has been found to be effective for the treatment of total LSCD. Allogeneic cultivated limbal epithelial cells as a substitute for corneal epithelium can treat corneal neovascu In this study, we first reported that allogeneic CLET is an effective surgical method for symblepharon repair and can maintain a deep fornix.

In our study, the patients with severe symblepharon were treated by CLET to reconstruct the conjunctival sac and improve the activity of the eye globe and eyelids, and a good cosmetic effect was achieved. A few patients suffered strip-shaped symblepharon after the first surgery, which may be related to severe symblepharon, insufficient separation, inadequate allogeneic stem cells, and amniotic membrane contracture. All these patients had severe symblepharon involving more than 3 quadrants before surgery, and the cornea completely adhered to the pseudopterygium. For these patients, it was not difficult to perform a second allogeneic CLET, and favorable results were achieved.

During the surgery, the first step was peeling off the pseudopterygium from the cornea, and then it was used to reconstruct conjunctiva palpebrae. The operation was designed in this way for the following reasons: (1) tissues that are discarded in conventional surgical methods can be used effectively; (2) preservation of pseudopterygium can obviously diminish the conjunctival deficiency area, requiring smaller size of the cultivated graft to reestablish ocular surface; (3) as an autologous tissue, pseudopterygium does not lead to immune rejection.

For the patients who lost visual function, implantation of a suitable prosthesis could achieve satisfactory cosmetic results after allogeneic CLET. For the patients who still have visual function, second corneal transplantation can give them a chance to increase vision (7).

To ensure a successful surgery, we upheld the principles as follows: (1) separate symblepharon completely, expose wound surface sufficiently, and clear up the scar tissue as much as possible; (2) try to preserve the conjunctival surface of pseudopterygium; (3) avoid fluid between the amniotic membrane with cultured epithelial cells and the underlying ocular surface; (4) the graft cell sheet is big enough compared with the wound surface, and if necessary 2 pieces of cell sheets or more are used; (5) a highly permeable contact lens is fixed like a bandage on the eye to improve the survival rate of graft.

Our study had several limitations. First, it was a retrospective study. Further studies with a randomized design, a larger sample size, and a long-term follow-up are needed. Second, a few patients developed immune rejection after surgery, which may be attributed to the inflammation induced by palpebral fissure dysraphism. Fortunately, the rejection was controlled after anti-rejection therapy, with no symblepharon recurrence. This study just introduced a novel method in reconstructing conjunctival sac for severe symblepharon. We did not report further treatment after the following keratoplasty. The therapeutic effect on severe symblepharon was the focus of this study.

In summary, allogeneic CLET can successfully relieve symblepharon and reconstruct conjunctival sac in eyes with severe ocular burns, not only improving the appearance of late-stage patients but also laying a foundation for further improvement of eyesight for some patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Shandong Eye Institute. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TW, WS, and LX contributed to conception and design of the study. TW and FS organized the database. QZ performed the statistical analysis. TW wrote the first draft of the manuscript. FS, QZ, WS, and LX wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Epidemiology of Sports-Related Eye Injuries Among Athletes in Tianjin, China

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Purpose: To investigate the incidence, characteristics, and risk factors of sports-related eye injuries among athletes in Tianjin, China.

Methods: A cross-sectional study was carried out from March 2018 to October 2018. In this study, the athletes from Tianjin University of Sports, Tianjin Vocational College of Sports, and Tianjin provincial sports teams were selected for general investigation. In total, 1,673 athletes were invited and 1,413 participated in the study (response rate of 84.5%).

Results: In total, 1,413 athletes were enrolled; 151 had suffered from sports-related eye injuries, with an incidence of 10.7% (95% *CI*: 9.1–12.0%). Handball (38.5%) was the sport with the highest incidence of eye injuries, followed by water polo (36.4%) and diving (26.7%). Overall, 42.4% of the athletes were injured by ball and 22.5% of injuries came from teammates. The eye injuries usually occurred during training (64.2%) and competitions (14.6%). Adnexa wound (51.7%) was the most common type of injury. About 11.9% of the athletes with eye injuries had the impaired vision; 66.7% failed to see doctors on time. The athletes $<$18 years of age had a higher risk of eye injuries (odds ratio [*OR*] =1.60, 95% *CI*: 1.06–2.40). The athletes with lower family income ($<$1,000 RMB) were at risk population for sports-related eye injuries (*OR* = 3.91, 95% *CI*: 2.24–6.82). Training $>$4 h a day increased the risk of eye injuries (*OR* = 2.21, 95% *CI*: 1.42–3.43).

Conclusion: The incidence of sports-related eye injuries among athletes was 10.7% in Tianjin, China. Handball, water polo, and diving were the most common activities of injury. Age, family income, and training time were the risk factors for sports-related eye injuries.

Keywords: eye injury, athletes, age, family income, training

INTRODUCTION

Sports-related eye injuries were important eye conditions encountered by ophthalmologists since 8.3–17% of eye injuries were sports-related. These eye injuries might lead to blindness because sports accounted for one-third of blindness cases due to ocular trauma (1–4), especially among adolescents (5–8). Therefore, sports-related eye injuries represented a huge burden on the individuals, families, and healthcare systems (9). Sports-related eye injury was of concern considering the emphasis placed on the importance of practicing sports to prevent chronic diseases. Although about 90% of sports-related eye injuries were preventable with adequate protective devices (10). Most people did not have the awareness of the importance of wearing adequate eye protection and the eye injuries should be evaluated on-site with an adequate examination of the eye and adnexa (11, 12). About 42% of people who had ever participated in sports have suffered eye injuries (13), but only 9.4% of those patients were using protective devices during their activities (2).

In the joint policy statement issued by the American Academy of Ophthalmology and the American Academy of Pediatrics in 2004, the eye-injury risk of a sport to the unprotected player was roughly categorized as high risk, moderate risk, low risk, and eye safe (14). However, because of the differences in the types and frequency of sports among countries, sports-related eye injuries had certain geographical and cultural characteristics. The most common causes of eye injuries varied from basketball in America (1), baseball in Korea (2), floorball in Finland (3), and soccer in Israel (15). Nevertheless, no epidemiological data were available from China, which was the most populous country in the world. With the economic development of the Chinese society, more people took part in sports to keep healthy (16), but emergency rooms in China were facing a rise in the numbers of patients with sports-related injuries than before (17, 18). This new state prompted the need to investigate the current situation and risk factors of sports-related eye injuries in China and proposed preventive strategies.

As a high-risk population of sports-related eye injuries, athletes should receive more attention (19). Eye injuries happening to the athletes might be more serious and complex because of the high level of the sports and might have severe repercussions on their entire professional career. To our knowledge, no previous studies specially examined the eye injuries of athletes in China. Therefore, the aim of this study was to investigate the epidemiology and characteristics of sports-related eye injuries among athletes in Tianjin, China, and to explore the risk factors associated with those injuries. The results will benefit the athletes in preventing eye injuries during their activities and will be helpful in convincing the stakeholders of the importance of eye injury in athletic-level sports.

METHODS

Participants

This cross-sectional study was conducted from March 2018 to October 2018. The athletes from Tianjin University of Sport, Tianjin Vocational College of Sports, and Tianjin provincial sports teams were chosen for general investigation. Twenty-five sports were investigated, including soccer, basketball, badminton, baseball, track and field, swimming, weightlifting, volleyball, taekwondo, judo, tennis, table tennis, wrestling, Ryukyu, water polo, diving, synchronized swimming, martial arts, cycling, art gymnastics, handball, field hockey, archery, shooting, and fencing. The athletes with <1 year of training were excluded from the study. The study was performed according to the Declaration of Helsinki and was approved by the ethics committee of Tianjin Medical University General Hospital. All participants signed the informed consent form.

Data Collection

The athletes were asked to complete a questionnaire about socio-demographic characteristics (sex, age, height, weight, myopia, education level, monthly family income, and sleep deficiency), sports-related information (training activities, training age, daily training time, and protective device use), and history of ocular trauma. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2), and was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), and overweight/obesity (≥ 24.0 kg/m^2). Sleep deficiency was defined as <8 h of sleep daily.

The detailed data about the history of ocular trauma were recorded by ophthalmologists. Sports-related eye injuries were defined as ocular trauma that occurred during the training sessions or competitive events over the past year. The athletes with ocular trauma unrelated to sports were excluded from the study. The collected data included laterality, accident location, cause of injury, type of injury, visual acuity after injury, time for medical help, and treatment, which were obtained by consulting the medical records of the sports team and confirming to the participants. The participants received comprehensive ophthalmic examinations, which included best corrected visual acuity (BCVA), refraction, intraocular pressure, slit lamp biomicroscopy examination, and fundus examination.

Statistical Analysis

The incidence of eye injuries was calculated by injuries/total in different sports. The athletes with and without the sports-related eye injuries were compared with respect to socio-demographic characteristics, myopia, training age and time, sleep deficiency, and protective device use, using the chi-square test. Athletes with sports-related eye injuries were classified as the younger group (<18 years) and the older group (≥ 18 years). Laterality, cause, accident location, and type of sports-related eye injuries were compared between the younger and older groups. Using multivariable logistic regression analysis, the odds ratios (*ORs*) and 95% *CIs* of sports-related eye injuries in relation to sex, age, BMI, education level, family income, training age and time, myopia, and protective devices use were determined. The differences were considered statistically significant when $P \leq 0.05$. All the analyses were carried out using SPSS 20.0 (IBM, Armonk, NY, USA).

RESULTS

Characteristics of the Participants

In this study, we intended to investigate all 1,673 athletes registered in Tianjin University of Sport, Tianjin Vocational College of Sports, and Tianjin provincial sports teams. However, since some athletes were not in Tianjin for various reasons during the investigation, only 1,433 athletes were invited to participate in the study, and 1,413 athletes returned the questionnaires and completed the eye examinations, for a total response rate of 84.5%. Among the 1,413 athletes, 914 (64.7%) were male and 499 (35.3%) were female. The mean age of the participants was 19.0 ± 2.8 (range, 7–30) years (**Figure 1**). The average age, height, and weight were 19.3 ± 2.4 years, 179.6 ± 7.7 cm, 72.2 ± 12.7 kg in male and 18.6 ± 3.3 years, 167.4 ± 9.0 cm, 59.6 ± 11.9 kg in female, respectively.

Sports-Related Eye Injuries

In total, 151 athletes reported sports-related eye injuries in this study, for the incidence of 10.7% (95% *CI*: 9.1–12.0%). Among 914 male athletes, 100 athletes with sports-related eye injuries were reported, the incidence was 10.9%, and the proportion in female was 10.2% (51 injuries in 499 athletes). Handball (38.5%) was the sport with the highest incidence of eye injuries, followed by water polo (36.4%), and diving (26.7%) (**Figure 2**). The incidence was significantly different among the sports ($P < 0.001$).

The athletes with sports-related eye injuries were younger, had lower education levels, had lower monthly family income, and had longer daily training time than those without sports-related eye injuries (**Table 1**). No significant differences were found in sex, BMI, myopia, training age, sleep deficiency, and protective device use.

In athletes with sports-related eye injuries, 80.1% of the injuries were monocular and 19.9% were binocular. Overall, most injuries were caused by the ball, which accounted for 42.4%, while 22.5% of eye injuries were caused by the teammates. Violent collisions and tumble, each accounted for 10.6% of injuries. In general, 64.2% of the eye injuries occurred during training, and 14.6% happened in the competition. Adnexa wound (51.7%) was the most common type of injury, followed by contusion (29.1%) and corneal abrasion (17.9%) (**Table 2**). The injuries, such as penetrating injuries, globe rupture, perforating injuries, intraocular foreign body injuries, and lamellar laceration were not found in the athletes with eye injuries in the present study and were therefore not listed in **Table 2**.

After stratification for age, younger women and older men more often suffered from eye injuries. The mean age of athletes with eye injuries was 19.2 ± 2.8 years for men and 17.4 ± 4.3 years for women. In the younger group, except for ball and teammate as the most common causes of injuries, the tumble and other causes were reported as the third more frequent reasons for eye injuries. Breach of rules was the third common cause in the older groups (**Table 2**).

Among the athletes engaged in track and field activities, adnexa wounds accounted for 54.2% of injuries. Contusion (41.2%) was the most common type of injury in basketball. About 11.9% of the athletes with eye injuries had impaired vision, and 66.7% failed to see doctors in time. In total, 22 of 151 (14.6%) athletes were operated in a consequence of the eye injury.

Risk Factors for Sports-Related Eye Injury

The risk factors of sports-related eye injuries were listed in **Table 3**. The multivariable logistic regression analysis showed that athletes <18 years of age (*OR*: 1.60, 95% *CI*: 1.06–2.40), athletes with lower monthly family income (<1,000 RMB) (*OR*: 3.91, 95% *CI*: 2.24–6.82), and athletes training >4 h a day (*OR*: 2.21, 95% *CI*: 1.42–3.43) had a higher risk of suffering from eye injuries. On the other hand, sports-related eye injuries were not

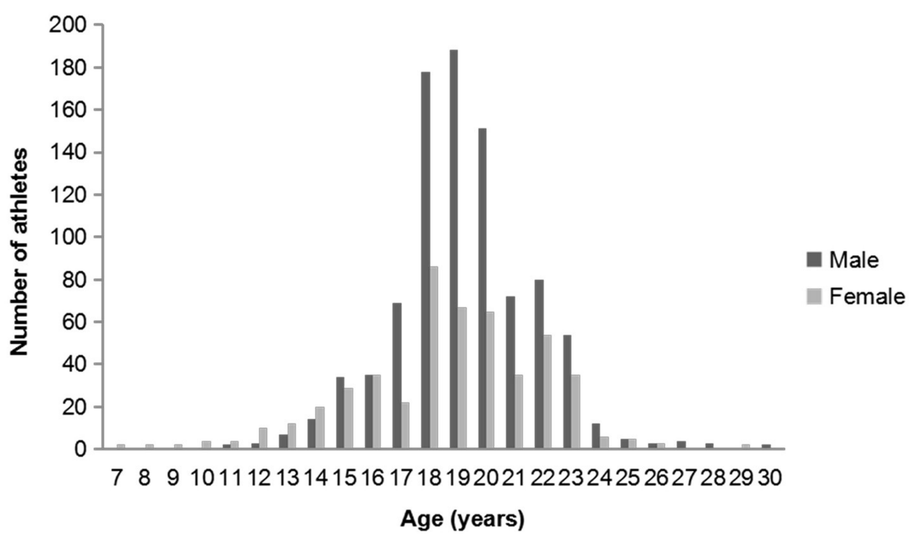

FIGURE 1 | Age distribution of all the athletes by sex.

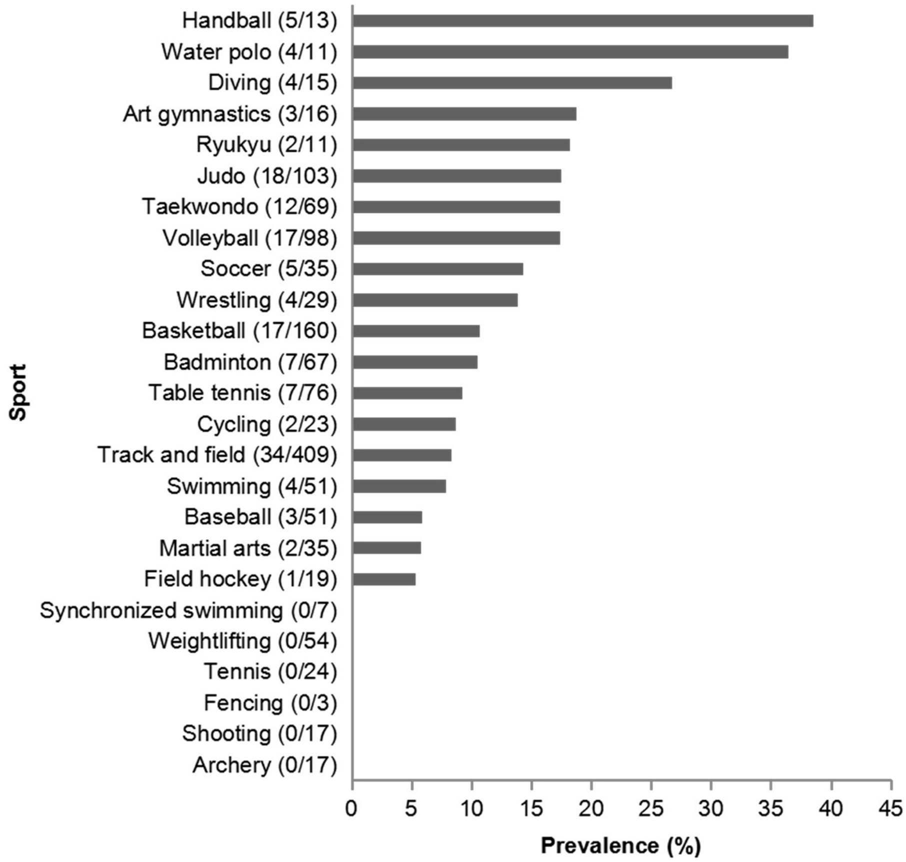

FIGURE 2 | The incidence of eye injuries in different sports. The number in the parentheses was the athletes (injury/total) for each sport.

associated with sex, myopia, education level, BMI, training age, sleep deficiency, and use of protective devices.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the epidemiology, characteristics, and risk factors of sports-related eye injuries among athletes in Tianjin, China. In the present study, the incidence of sports-related eye injuries was 10.7% (95% *CI*: 9.1–12.0%) in athletes, and about 11.9% of them had impaired vision. The eye injuries occurred most frequently when playing handball, playing water polo, and diving. Around 65% of the eye injuries were caused by the ball and teammates. The majority of eye injuries (64.2%) occurred during training. The most common types of eye injuries were adnexa wounds, contusion, and corneal abrasion. Younger age, lower family income (<1,000 RMB), and longer training time (>4 h/day) were associated with a higher risk of sports-related eye injuries in the athletes.

The studies had pointed out that sports-related eye injuries were preventable when using adequate protective devices and adopting appropriate comportment/attitude (20). However, ocular trauma was commonly seen in the emergency rooms and might have serious consequences on the life and professional career of the athletes (12, 21, 22). The patients with sports-related eye injuries visited emergency departments every 13 min in the United States (23). About 11% of the eye injuries led to the long-term functional visual impairment (3) and 28% of the cases of post-traumatic eyeball enucleation were related to sports (24, 25).

In the present study, 151 out of 1,413 athletes reported sports-related eye injuries, resulting in an incidence of 10.7% (95% *CI*: 9.1–12.0%). Around 12% of those with sports-related ocular trauma had impaired vision, but 66.7% of them failed to seek eye healthcare in time. It was reported that only 3.1% of patients with eye injuries have impaired vision in the emergency departments (1), which was lower than in the present study. In addition, the present study was among the rare studies to report the visual impairment of athletes with an eye injury. Our sports teams had complete healthcare record information that recorded the annual physical examination of athletes, including ocular examination. It was not only convenient for us to understand the past ocular conditions of athletes and increase the reliability of the research data but also conducive for coaches to pay close attention to the physical changes of the athletes, which was worthy of extensive learning and reference.

Among the available studies, the sport causing eye injury varied among countries, probably because of the varying popularity of the sports across the world. Moon et al. (2) reported

TABLE 1 | Characteristics of athletes with and without sports-related eye injuries.

Variable	Sports-related eye injury		*P*
	Yes (*n* = 151)	No (*n* = 1,262)	
Age (years), *n* (%)			< 0.001
<18	54 (35.8)	250 (19.8)	
<18	97 (64.2)	1,012 (80.2)	
Sex, *n* (%)			0.675
Female	51 (33.8)	448 (35.5)	
Male	100 (66.2)	814 (64.5)	
Body mass index (kg/m^2), *n* (%)			0.166
<18.5	15 (9.9)	129 (10.2)	
18.5–23.9	95 (62.9)	874 (69.3)	
≥24.0	41 (27.2)	259 (20.5)	
Myopia, *n* (%)	123 (81.5)	1,052 (83.4)	0.555
Education level, *n* (%)			0.001
Primary school and below	3 (2.0)	25 (2.0)	
Junior high school	21 (13.9)	92 (7.3)	
Senior high school	36 (23.8)	195 (15.5)	
University and above	91 (60.3)	950 (75.3)	
Monthly family income[a] (RMB), *n* (%)			< 0.001
<1,000	26 (17.2)	96 (7.6)	
1,000–2,000	22 (14.6)	189 (15.0)	
2,001–5,000	63 (41.7)	490 (38.8)	
>5,000	40 (26.5)	487 (38.6)	
Training age (years), *n* (%)			0.364
<5	54 (35.8)	521 (41.3)	
5–10	80 (53.0)	627 (49.7)	
>10	17 (11.3)	114 (9.0)	
Daily training time (h), *n* (%)			< 0.001
<2	42 (27.8)	505 (40.0)	
2–4	22 (14.6)	330 (26.1)	
>4	87 (57.6)	427 (33.8)	
Sleep deficiency, *n* (%)	64 (42.4)	527 (41.8)	0.883
Use of protective devices, *n* (%)	19 (12.6)	153 (12.1)	0.871

[a] *Family income: average monthly income per person.*

that baseball was the most common sport for eye injuries in Korea, followed by football, hiking, and badminton. In Finland, floorball, soccer, and tennis were the major sports causing eye injuries (3). In the United States, basketball was the main sport leading to eye injury (1). The present study was the first to report epidemiological data about sports-related eye injury in Tianjin, China, and showed that the injuries occurred most commonly as a result of playing handball, followed by water polo and diving. The athletes playing water polo lacked good sight because of the water and goggles and were at higher risk of ball impact and body collision, which resulted in more injuries than during other activities. The incidence of eye injuries in art gymnastics was 18.8%, which was beyond our expectations. We found that eye injuries in art gymnastics mostly came from accidental eyelid poking by ribbons.

Myopia was an important eye problem in China, with an alarming increase in the prevalence of high and very high myopia among teenagers in the last 15 years (26). The prevalence of myopia was 83.2%, which was similar to the previous studies (27, 28). Although myopia was not related to eye injuries, it should draw enough attention because of such a high prevalence and the need to wear some kind of corrective lenses when practicing sports or taking the risk of not seeing the play and the potential threats. It was worthy of our attention that 46.8% of the athletes in this study did not realize their myopia status, which might further increase the potential risks for eye injuries. These results suggested that the athletes should be screened for myopia before starting their careers.

Multiple causes of injury could be found in sports-related eye injuries. Among high school and collegiate athletes, it was reported that most of the eye injuries were caused by contact; in particular, player contact was the leading cause of eye injuries, accounting for 47.3% in high school and 64.5% in college, while the proportion of ball contact was 37.1% in high school and

TABLE 2 | Causes, locations, and types of sports-related eye injuries in athletes, stratified by age and sex.

Variable	Athletes with sports-related eye injury					*P*
	Total (*n* = 151)	<18 years (*n* = 54)	≥18 years (*n* = 97)	Male (*n* = 100)	Female (*n* = 51)	
Laterality, *n* (%)						0.246
Monocular injury	121 (80.1)	46 (85.2)	75 (77.3)	81 (81.0)	40 (78.4)	
Binocular injury	30 (19.9)	8 (14.8)	22 (22.7)	19 (19.0)	11 (21.6)	
Cause of injury, *n* (%)						< 0.001
Ball	64 (42.4)	18 (33.3)	46 (47.4)	43 (43.0)	21 (41.2)	
Teammate	34 (22.5)	12 (22.2)	22 (22.7)	21 (21.0)	13 (25.5)	
Violent collision	16 (10.6)	6 (11.1)	10 (10.3)	14 (14.0)	2 (3.9)	
Tumble	16 (10.6)	8 (14.8)	8 (8.2)	13 (13.0)	3 (5.9)	
Breach of rules	11 (7.3)	0 (0)	11 (11.3)	7 (7.0)	4 (7.8)	
Other causes	10 (6.6)	10 (18.5)	0 (0)	2 (2.0)	8 (15.7)	
Accident location of injury, *n* (%)						0.174
Training ground	97 (64.2)	38 (70.4)	59 (60.8)	59 (59.0)	38 (74.5)	
Competition field	22 (14.6)	4 (7.4)	18 (18.6)	13 (13.0)	9 (17.6)	
Other places	32 (21.2)	12 (22.2)	20 (20.6)	28 (28.0)	4 (7.8)	
Type of injury, *n* (%)						0.189
Adnexa wound	78 (51.7)	34 (63.0)	44 (45.4)	49 (49.0)	29 (56.9)	
Contusion	44 (29.1)	12 (22.2)	32 (33.0)	29 (29.0)	15 (29.4)	
Corneal abrasion	27 (17.9)	7 (13.0)	20 (20.6)	20 (20.0)	7 (13.7)	
Orbital fracture	2 (1.3)	1 (1.9)	1 (1.0)	2 (2.0)	0 (0)	

TABLE 3 | Factors statistically associated with sports-related eye injuries in athletes.

Variable	Multivariable logistic regression	
	Crude OR (95%CI)	Adjusted OR (95%CI)[b]
Age (years)		
≥18	1.00	1.00
<18	2.25 (1.57–3.23)	1.60 (1.06–2.40)
Monthly family income[a] (RMB)		
>5,000	1.00	1.00
2,001–5,000	1.57 (1.03–2.37)	1.51 (0.99–2.30)
1,000–2,000	1.42 (0.82–2.45)	1.73 (0.99–3.03)
<,1000	3.30 (1.92–5.66)	3.91 (2.24–6.82)
Daily training time (h)		
<2	1.00	1.00
2–4	0.80 (0.47–1.37)	0.75 (0.44–1.30)
>4	2.45 (1.66–3.62)	2.21 (1.42–3.43)

[a] *Family income: average monthly income per person.*
[b] *Adjusted for age, sex, body mass index, myopia, education level, monthly family income, training age, daily training time, sleep deficiency, and use of protective devices. Only variables with statistical significance were shown.*

18.3% in college (19). In the present study, ball contact (42.4%) and teammates (22.5%) were also the most common causes of eye injuries. Among the athletes <18 years of age, 33.3% of eye injuries were caused by ball contact and 22.2% were caused by teammates. Among the older athletes, most of the injuries were also caused by ball and teammates, but the frequency of ball contact was higher (47.4%), while that of teammates was similar (22.7%). Using eye protective equipment would effectively reduce the damage caused by the ball. Boden et al. (19) reported that eye injuries caused by ball accounted for 72.7% in the field of hockey, but after forcing the players to wear eye-protective devices, the proportion dropped by 52%.

The types of eye injuries varied with the causes of injuries. Haring et al. (1) found that adnexa wound and contusion were the most common types of injuries after analyzing data from the Nationwide Emergency Department Sample (NEDS) in the United States, which was similar to our results. Boden et al. (19) also reported that contusion accounted for the largest proportion of eye injuries among the athletes in high school and college and that those contusions were closely related to ball and player contact.

According to the multivariable analysis, athletes <18 years of age had a higher risk of eye injury than those >18 years. Younger athletes might lack the awareness for eye protection and related knowledge during training, and might be brasher in the practice of their sport. Elevated risk was also found in athletes with lower family income (<1,000 RMB). With per capita disposable income reaching 28,228 RMB in China in 2018, such a low family income might affect athletes in many aspects, such as sports equipment, nutrition, health condition, and living environment, which might greatly affect athletic performance during training. On the other hand, the health behavior of athletes was affected by socio-economic status leading that lower-income athletes might not pay attention to eye protection. Training time was also a risk factor for eye injuries. Of course, more training increases the likelihood of injury, and athletes training >4 h daily showed a substantially elevated risk of eye injury. Long-time training every day might cause fatigue and tiredness, which could increase the risks of ocular injury. Therefore, it was necessary to improve the awareness of eye protection during activities, especially for younger athletes and those in lower socio-economic status (1). Besides, providing eye protection devices for those who had longer training time might be an effective measure. Specific interventions should be designed and tried in the future.

Many, although not all, sports-related eye injuries were preventable with adequate protective equipment, which had been reported in the previous studies (10, 20). Nevertheless, only 172 of the 1,413 athletes included in the present study were using protective devices during their activities, which accounted for 12.2% only. Since the athletes were mostly engaged in swimming, shooting, fencing, and cycling, regrettably, we could not draw the above conclusion under the overall analysis. In athletes with sports-related eye injuries, 12.6% of them were using protective equipment for their eyes. Such a low use rate reflected the lack of eye protection awareness among the athletes. At this point, it became very important for coaches to supervise and encourage athletes to use eye-protective devices whenever possible. For instance, eye-protective equipment is usually used in fencing, swimming, and cycling, but it should also be used in other sports.

The present study had limitations. Athletes who participated in the investigation were from Tianjin, which might not reflect the incidence of sports-related eye injuries across China. The numbers of athletes in each sport were different, but it reflected the differences in popularity of different sports. Our study might have missed the most severe injuries because those athletes might have stopped practicing their sport, which might underestimate the true incidence of eye injuries among athletes.

In conclusion, sports-related eye injuries commonly occurred in athletes. Improving the awareness of eye protection, paying more attention to underage athletes, providing financial assistance to athletes from poor families, and avoiding athletes from overwork should be helpful in lowering the incidence of sports-related eye injuries. In the future, stakeholders should pay more attention to sports-related eye injuries in China and propose preventive strategies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Tianjin Medical University General Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HY: research design and manuscript preparation. JZ and XZhu: data acquisition, research design, data analysis, and manuscript preparation. ZhiS, JW, and ZhuS: data acquisition, data analysis, and manuscript preparation. JL, TW, YH, RX, HH, XZha, YS, MG, TY, HZ, KH, YLi, YLe, YZ, BC, and YM: data acquisition and manuscript preparation. BH: research design and manuscript preparation. RB: research design and manuscript preparation. All authors approved the final version of this manuscript.

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Creation of a New Explosive Injury Equipment to Induce a Rabbit Animal Model of Closed Globe Blast Injury *via* Gas Shock

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To establish a rabbit animal model of closed globe blast injury with an application of self-developed explosive injury equipment, we tend to explore the anatomic and pathological changes of eyes under different gas pressure. The device comprises of high-pressure air source compression pump, air channel, and gas shock. There were 36 healthy bluish blue rabbits exposed to one of five blast pressures (500, 1,000, 1,500, 2,000, and 5,000 Kpa). Slit lamp microscope, B-mode ultrasonography, fundus photography, optical coherence tomography (OCT), and intraocular pressure (IOP) examination were performed at 0-, 1-, 3-, and 7-days post exposure, while gross histopathology was assessed with H&E stain at 7 days. The contralateral eyes and non-blast exposed rabbits were used as controls. Definitive evidence of closed globe blast injury was obtained. Corneal edema and hyphema were observed in the models under all pressures with no full-thickness globe injury, or lens rupture, as the severity was pressure independent. There was no obvious retinal abnormality on B ultrasound or OCT scan, while light vitreous hemorrhage, commotio retinae, and heavy retinal pigmentation presented on one eye, respectively, in the eyes exposed to 5,000 Kpa. Increased retinal thickness with disorganizations on the retinal ganglion cell (RGC) layer and RGC apoptosis in groups under higher pressure (>500 Kpa). IOP of injured eyes were statistically decreased at day 1 and 7 post injury ($p < 0.05$). Conclusively, the rabbit animal model induced by self-developed equipment could mimic the clinical features of closed ocular blast injury successfully that was feasible and easy to operate. This will be a new rabbit animal model for investigating mechanisms and new therapeutic interventions of closed globe blast injury in the future.

Keywords: self-developed explosive injury equipment, rabbit animal model, closed globe blast injury, hyphema, retinal injury, corneal edema

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INTRODUCTION

Mass casualties caused by blasts were common in war, bombing, or terrorism occurred around the world that have been documented in the Iraq War (2003), the Boston Marathon bombing (2013), and Tianjin Blast injury (2015), in which the rates of ocular injury were varied (1–3). Unlike other body parts covered with clothes, the eyes are more susceptible to blast injury due to lack of protection or spectacles wearing that can exacerbate the blast damage, especially in the military explosions where the soldiers wear chest and head protection. As reported, the injuries resulting from explosions are classified into four parts as followed: the primary injury caused by detonation wave itself, fragments propelled by the explosion (glass, dust, and masonry from exploded constructions), displacement of victims due to blast wind induced acceleration of the body, and thermal injury caused by tremendous and temporary heat produced by the explosion (4, 5). Hence, the ocular blast injury is combined and complicated eye damage that includes mechanical, chemical, and thermal damages, which can result in vision loss inordinately and even enucleation. Although there were ∼80% of ocular injuries associated with blast fragmentation in military conflicts, the primary blast was predominantly accounted for the ocular blast injury (6). According to the published literatures, the categories of blast injuries were relatively feasible and well-studied aside from the primary blast, which might be due to the practical limitations of equipment and techniques involved in an experimental study.

As literature reported, a blast ocular injury can cause closed globe injury, open globe injury, and ocular foreign body when the explosive fragments retained. Cockerham's study indicated that the closed globe injury accounted for 43% of blast ocular injury, which was underestimated and neglected in the military survivors of blast injury (7). Blanch et al. illustrated types of closed globe injuries induced by blast in soldiers, such as corneal abrasions, corneal edema, iris, ciliary body contusion, hyphema, angle recession, cataract, commotio retinae, choroidal ruptures, vitreous hemorrhage, retinal hemorrhage, tears, traumatic retinal detachment, and traumatic optic neuropathy (8). Clinically, it is impossible to dissect out an ocular damage resulted from the primary blast wave alone in patients. Hence, it is necessary to establish an animal model of primary blast induce globe injury to reveal the underlying cellular and molecular mechanisms (9).

The literatures demonstrating the animal models that mimic progression of blast induced ocular injury have been published, in which various methods and mechanisms were applied. Rodents, such as mouse and rat were the most common animal species for the animal model development for low costs, multiple options for testing, and ease to obtain knock-out or overexpressed transgenic model for exploration of potential mechanisms (10), but with few samples obtained due to small size of the eyes. Enucleated porcine eyes were also used for their similarity to humans, especially in the anterior segments (11). Additionally, a computational model of a porcine eye was used to simulate the effects of the primary blast that was invented for mechanism exploring (12). However, a rabbit animal model was seldomly used. In those studies, devices for the blast generation were different, such as paintball guns, shock tubes, rifles, and small magnitude explosives at different levels of pressure (9, 13, 14). Although the corneal edema, retinal thickening, and optic neuropathy were observed in the experimental animal models, there are some disadvantages about the above devices and damage to the anterior segments were lacking. For example, the shock tubes occupy a large area, high cost, and are hard to control on the damaged location and degree; the paintball is dangerous to operate and cannot simulate the real explosion (15).

In this study, we invented a new gas shock generation device independently to create closed globe blast injury in rabbits by avoiding confounding injuries to the other parts of the body. We captured the progression and pathological changes of the blast induced globe injury in the rabbit animal model under different levels of gas pressure, which was identical to the veterans who suffered blast ocular injury in the clinic. Hence, our rabbit animal model may be an ideal model for the investigation of the mechanism and potential therapeutic strategy for human eyes.

MATERIALS AND METHODS

Animals

There were 36 healthy blue rabbits of 3–6 months old and weighing 2–2.5 kg (male, purchased from Tianjin Yuda Lab, Tianjin, China) that were fed in Tianjin Medical University General Hospital Animal Room at controlled room temperature 20–27°C and humidity at 40–60%. Light in the animal house did not exceed 300 Iux with a 12 h light/dark cycle maintenance. This study was strictly in accordance with the standards of animal ethics and animal experiment regulations of the Animal Management Ethics Committee of Tianjin Medical University, Tianjin, China.

Explosive Injury Equipment

The device used in this study was self-designed with patent approved (201920642373.7), which was successively connected by a high-pressure air source compression pump, air flow pipeline, and gas injection unit (**Figure 1**). The output section of the pump is sealed with the port of the connecting flange and the airflow pipeline followed by connection to the gas pressure regulators, the valve, and gas pressure measuring device in turns, and the part of the jet gas is composed of an integrated connecting pipe and nozzle. The high-pressure gas compression pump compresses the air in the air storage tank, and the flow of gas in the pipeline was controlled *via* opening or closing valve. The pressure of the gas is adjusted by the pressure regulating part. High-pressure gas flowed through the air storage, pressure regulating part, air flow pipe, and connecting pipe, then, the gas was injected to the eye of the rabbit through the nozzle. By compressing the high-pressure gas to the gas storage tank with the gas pressure adjusted according to the indicator, the high-speed solenoid valve controls the switch of the jet nozzle to spray the high-pressure gas that can simulate the blast eye injury.

Closed Globe Blast Injury

In this study, 36 rabbits were divided into six groups according to the different blast pressures imposed evenly ($n = 6$): blank control, 500 Kpa group, 1,000 Kpa group, 1,500 Kpa group, 2,000 Kpa group, and 5,000 Kpa group. The rabbits were starved for 12 h and anesthetized with chloral hydrate (3.5 ml/Kg) for general, followed by Obrucaine hydrochloride eye drops for topic anesthetization. Left eye of the rabbit was fixed 0.5 cm from the nozzle, followed by adjustment of blast pressure to the predicted value. Then, a high speed-solenoid valve switch was turned on, and the corneal center was exposed to the shock wave, hitherto, the closed globe blast injury was created by the blunt block. The

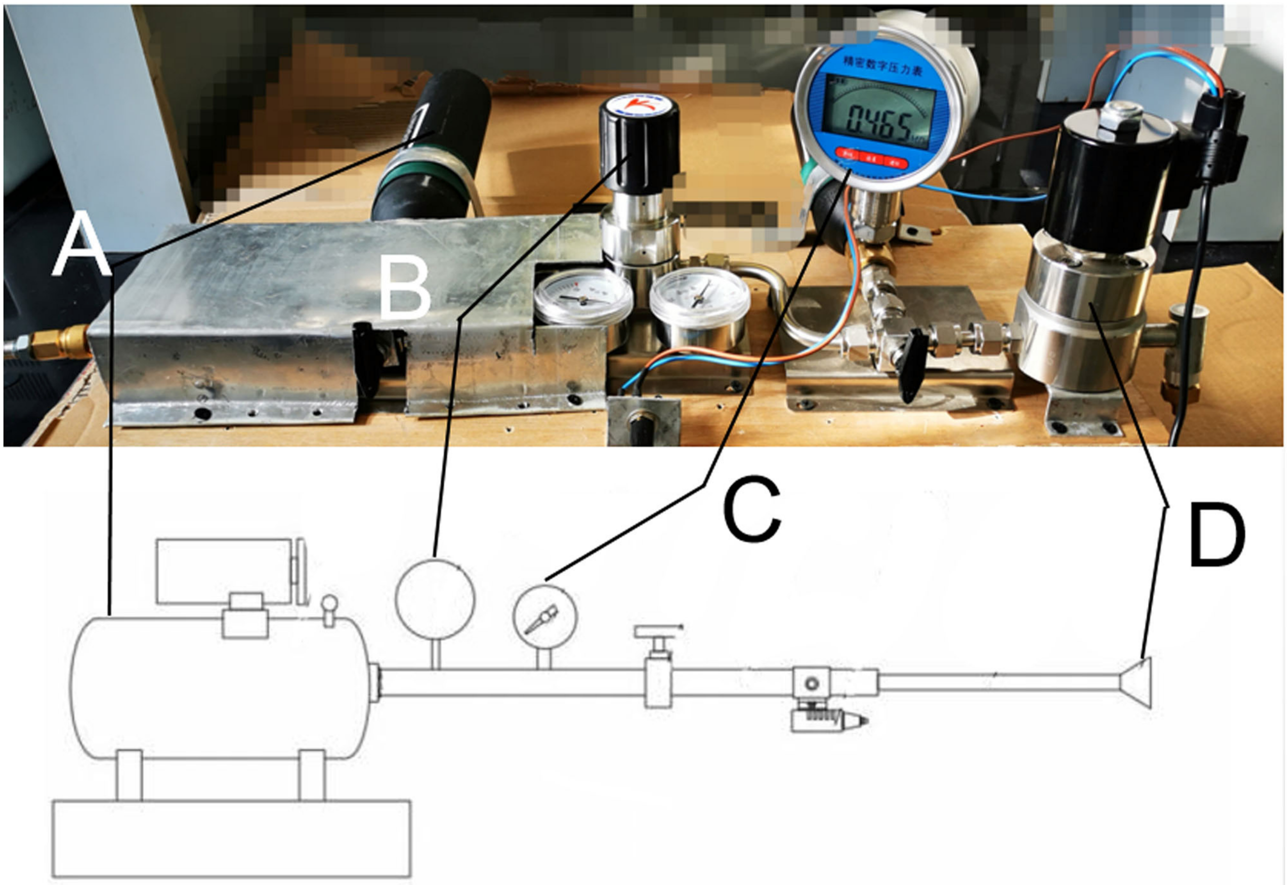

FIGURE 1 | Picture of the real blast device corresponding to the schematic diagram. **(A)** High-pressure air source generating device. **(B)** Pressure regulating valve. **(C)** Piezometer. **(D)** Nozzle.

antibiotic eye drops were used for the injured eyes four times a day for 3 days.

Eye Examination

The eyes of all the rabbits' pre- and post-injury were carefully examined by slit lamp and fundus scope with photographs of anterior and posterior segments collected. The abnormality of the eyes was recorded thoroughly.

Measurement of Intraocular Pressure

Intraocular pressure (IOP) of the rabbit animal model were measured pre-injury and at 0, 1, 3, 7 days post-injury using a tonometer (NIDEK, JAPAN).

Optical Coherence Tomography

Rabbits were anesthetized as above, with sufficient pupil dilation. Then, the head of the rabbits was fixed to the holder of the optical coherence tomography (OCT) scan machine. The retinas were thoroughly imaged using the OCT system from the optic disc to the peripheral retina as much as possible. Representative images were presented in the Results Section.

B Ultrasound Scan

The rabbits were anesthetized as above and wrapped to keep warm. The probes of the ultrasound machine went through the eyes in turns to observe the position of the lens, vitreous status, papilledema, retinal, and choroidal changes. Typical images with positive changes were illustrated in the Results Section.

Eye Histopathology

The entire eye was carefully enucleated with part of the optic nerve left 7 days post-injury. Then, the eye was fixed, dehydrated, and embedded in sequence. Afterward, the slices were cut and dyed with hematoxylin-eosin to observe the tissue pathology in detail.

Statistics

A statistical analysis was performed by SPSS 26.0 (SPSS Inc., Chicago, IL, USA). The values of IOP were described as Mean ± SE. The values of IOP in each group at different pressure were analyzed *via* ANOVA and the least significant difference (LSD) *post-hoc* test for different time points at the same pressure. When the distribution does not conform to the normal distribution, data were described as median

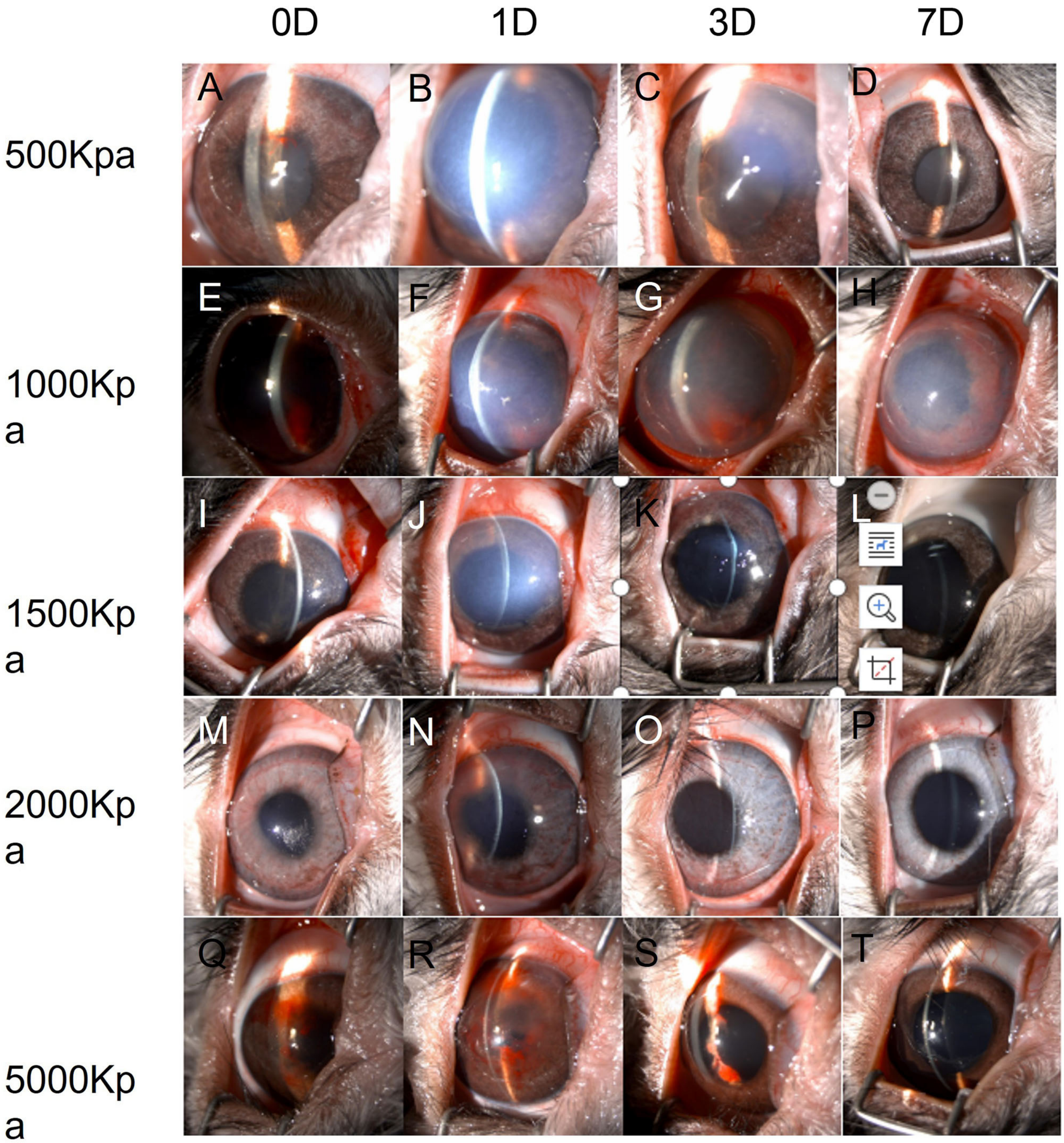

FIGURE 2 | Changes of eyes exposed to different pressure examined by slit lamp chronologically. **(A–D)**: Changes of eyes exposed to 500 Kpa. **(A)** Minor hyphema combined with corneal lesion on day 0. **(B)** Corneal opacity at day 1 **(C)** Corneal edema was ameliorated at day 3. **(D)** Transparent cornea and anterior chamber at day 7. **(E–H)**: Changes of eyes exposed to 1,000 Kpa. **(E)** Moderate hyphema combined with corneal lesion on day 0. **(F)** Corneal opacity at day 1. **(G)** Corneal edema was ameliorated, and blood-fluid level occurred at day 3. **(H)** Slightly residual cornea edema and clear anterior chamber with irregularly dilated pupil at day 7. **(I–L)** Changes of eyes exposed to 1,500 Kpa. I. Minor corneal edema on day 0. **(J)** Moderate corneal opacity at day 1. **(K)** Transparent corneal with dilated pupil at day 3. **(L)** Transparent corneal with dilated pupil at day 7. **(M–P)** Changes of eyes exposed to 2,000 Kpa. **(M)** Minor corneal lesion with scattered hyphema on day 0. **(N)** Moderate corneal lesion with lightly scattered hyphema at day 1. **(O)** Minor corneal edema at day 3. **(P)** Transparent corneal at day 7. **(R–T)** Changes of eyes exposed to 5,000 Kpa. **(Q)** Minor corneal lesion with severe hyphema on day 0. **(R)** Enlarged corneal edema with hyphema attached to the corneal endothelium at day 1. S. Minor corneal edema at day 3 with residual hyphema. **(T)** Transparent corneal with dilated pupil at day 7.

Pathological changes of the anterior segment in 500Kpa group (n=6)				
	0d	1d	3d	7d
Normal	5	4	5	6
Corneal edema	0	2	0	0
Hyphema	1	1	1	0
Iris injury	0	0	0	0
Opacity of lens and rupture of lens	0	0	0	0

Pathological changes of the anterior segment in 1000Kpa group (n=6)				
	0d	1d	3d	7d
Normal	0	0	1	4
Corneal edema	5	6	4	2
Hyphema	2	2	2	1
Iris injury	0	0	0	0
Opacity of lens and rupture of lens	0	0	0	0

Pathological changes of the anterior segment in 1500Kpa group (n=6)				
	0d	1d	3d	7d
Normal	0	0	1	3
Corneal edema	6	6	5	3
Hyphema	3	3	3	2
Iris injury	0	0	0	0
Opacity of lens and rupture of lens	0	0	0	0

Pathological changes of the anterior segment in 2000Kpa group (n=6)				
	0d	1d	3d	7d
Normal	2	3	5	6
Corneal edema	4	3	1	0
Hyphema	0	0	0	0
Iris injury	0	0	0	0
Opacity of lens and rupture of lens	0	0	0	0

Pathological changes of the anterior segment in 5000Kpa group (n=6)				
	0d	1d	3d	7d
Normal	2	2	2	5
Corneal edema	3	3	3	0
Hyphema	1	2	2	1
Iris injury	0	0	0	1
Opacity of lens and rupture of lens	0	0	0	0

FIGURE 3 | Summary of pathological changes of anterior segment in eyes exposed to all pressure.

(interquartile interval), and the rank sum test was used to analyze the differences. *P*-value < 0.05 was considered of statistical significance.

RESULTS

Corneal Edema and Hyphema Occurred After Blast Injury With No Laceration or Globe Rupture

Corneal edema and hyphema were observed in all eyes induced by gas shock at all pressure, although the percentage of that was much higher in groups of higher pressure (≥1,000 Kpa). However, no iris laceration, lens rupture, or lens dislocation were observed in any of the groups.

In 500 Kpa group, four out of six rabbits did not show any obvious anterior segment damage, while the two rabbits (33.3%) showed corneal edema 1 day post-injury with one accompanied with hyphema on the day of injury. All the above signs disappeared on day 7 post-injury (**Figures 2A–D**, **3**).

In 1,000 Kpa group, corneal edema occurred on five injured eyes and hyphema occurred on two injured eyes, none of them were recovered by 1 day post-blast. One of the rabbit models recovered completely on day 3, and three recovered on day 7 of post-blast (66.66%) (**Figures 2E–H**, **3**).

In 1,500 Kpa group, corneal edema occurred on all the injured eyes with three combined with hyphema, which were more severe in appearance compared with the other groups. On day 1 post-injury, the symptoms of one eye were relieved and the rest were accelerated. One of the injured eye recovered from the entire damaged signs on day 3, while the other two eyes were recovered on day 7 (50%) (**Figures 2I–L**, **3**).

In 2000 Kpa group, corneal edema occurred on four injured eyes, whereas no hyphema occurred. On day 7, all the above eyes had transparent cornea, normal iris, and no infiltration or hyphema (one on day 1 and two on day 3) (**Figures 2M–P**, **3**).

In 5,000 Kpa group, corneal edema occurred on three injured eyes and hyphema occurred on one injured eye on the day of blast, one of which was recovered on day 1 and three were relieved to normal on day 7 (80%). Additionally, one eye presented corneal edema and hyphema on day 1, in which hyphema were organized to definite membrane overlapping the lens and posterior synechia of the iris occurred on day 7 (**Figures 2Q–T**, **3**).

In total, there were 22 rabbit models that showed obvious damages of the anterior segment at four time points, with no open injury of cornea, opacity of lens, or rupture of lens were observed. There was no significant correlation between the severity of anterior segment damage and gas pressure. Finally, 16 cases of rabbit models were self-healed without any interventions (**Figure 3**).

Slight Vitreous Hemorrhage and Commotio Retinae Induced by 5,000 Kpa Gas Pressure

There was abnormality shown on the fundus photograph of the control group: transparent vitreous, clear edge of optic disc, normal vessels, and attached retina (**Figure 4**). Except for the blurred fundus due to corneal opacity, no vitreous hemorrhage or opacity, retinal tear, retinal hemorrhage, or retinal detachment occurred in the rabbit models induced by pressure <2,000 Kpa (**Figure 4**). In rabbit animal models induced by gas shock under 5,000 Kpa: one had slight vitreous hemorrhage without retinal detachment on day 7 (**Figure 5**); another one presented fuzzy fundus appeared as orange due to the severe corneal edema on day 3, which tended to brown yellow with substantial pigmentation and no retinal

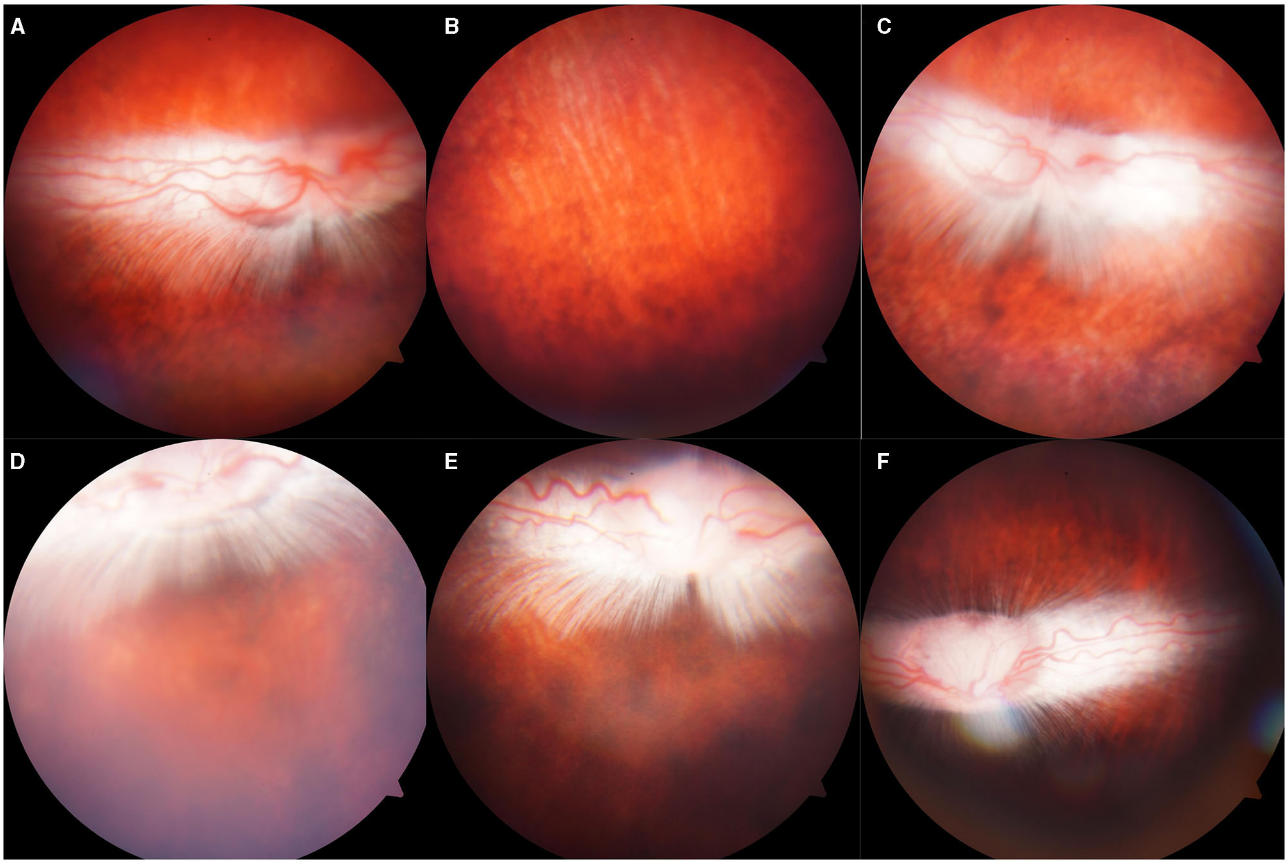

FIGURE 4 | Representative fundus photographs obtained from the eyes of the rabbits. **(A,B)**: Normal group: Retina was well-attached with clear vessels. **(C–F)**: Eyes exposed to 500, 1,000, 1,500, 2,000: Retina was attached, no retinal bleeding or vitreous hemorrhage was detected.

detachment indicating commotio retinae occurred previously (**Figure 5**).

Compared with the pre-blast rabbits of experimental groups and control group, none of the injured eyes showed vitreous strong echo or retinal detachment 7 days post-blast (**Figure 6**). Similarly, all retinas on the injured eyes were attached with distinct structures of each layer stood out on the OCT scans on day 7 (**Figure 7**).

Increased Retinal Thickness and RGC Apoptosis Induced by Gas Shock at Higher Pressure

A histopathological test showed that the retinal layers of the blank control group were intact with normal structure and morphology, and the cells were arranged neatly and compactly. However, in 1,000, 2,000, and 5,000 Kpa group, the retinas of the rabbit animal model were thickened, and the retinal ganglion cell layer (RGCL) were arranged disorderly, and the nucleus of RGC was packed densely. Moreover, the retinal nucleus developed to pyknosis gradually as the increase of gas pressure was exposed to rabbit eyes at day 7 post-blast, and the arrangement of RGCL also tended to be more disordered accompanied by a patch of tear in the IS/OS layer. The retinal structure and cells in rabbits exposed to 500 Kpa gas shock were neatly arranged compared with other gas pressure groups, which was similar to that of the blank control group (**Figure 8**).

Blast Injury Caused Inflammatory Cells Infiltration in Cornea and Stroma Damage

In all the established rabbit models, there was no significant change in the corneal epithelial cell layer and endothelial cell layer on day 7 after blast exposure. However, in the rabbit with residual corneal edema, the stroma layer was thickened obviously, where the inflammatory cells infiltrated close to the external elastic layer (**Figure 9A**). Corneal histology of rabbit eye with corneal edema immediately after blast exposure and receded at day 7 showed that the thickness of corneal stroma layer was basically normal (**Figure 9B**). Under the observation of higher magnification, the tissue of stroma layer was loose, whereas the structure of the epithelial cell layer and endothelial cell layer was still intact (**Figure 9C**).

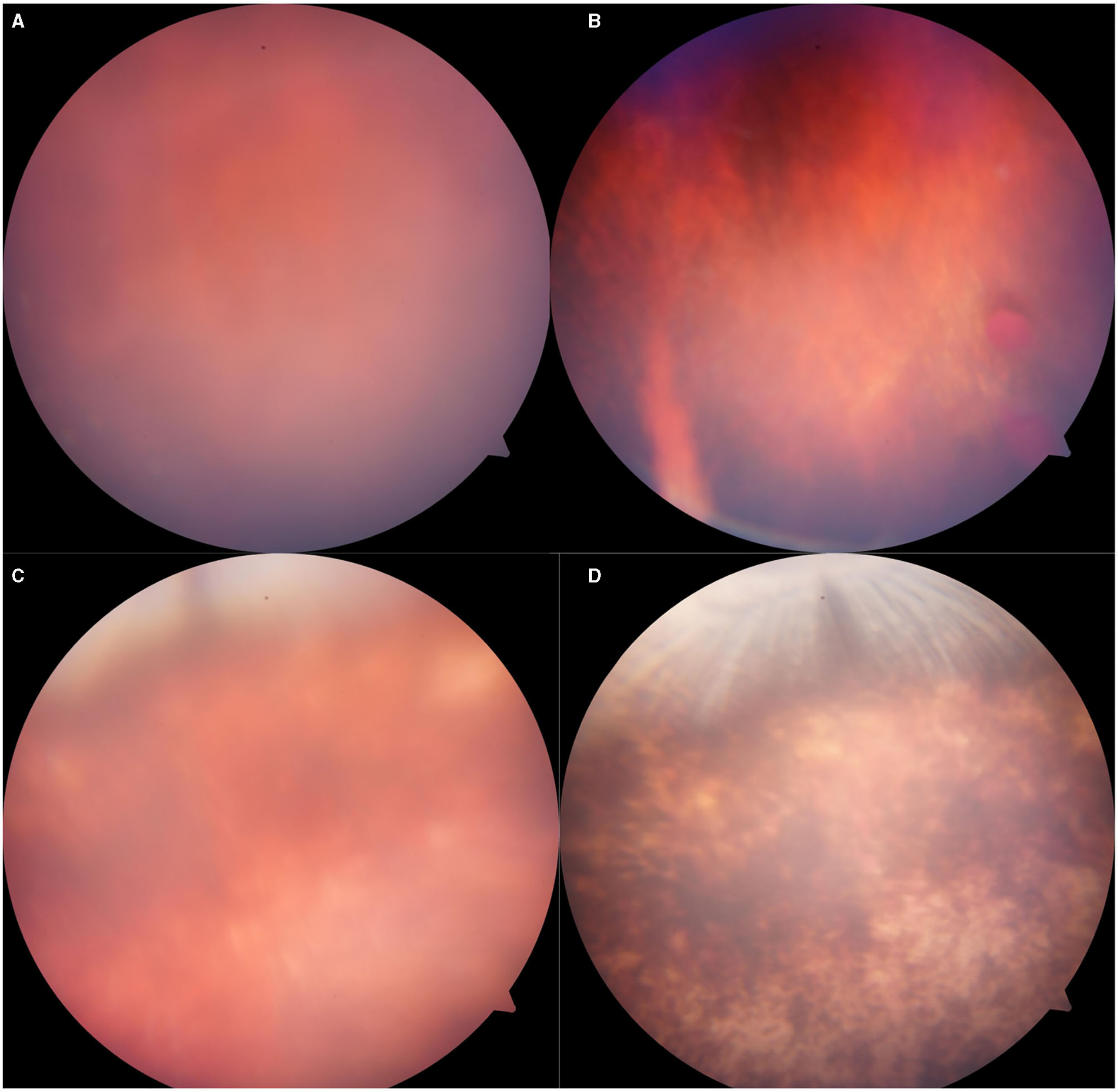

FIGURE 5 | Representative fundus photographs obtained from the eyes of rabbits exposed to 5,000 Kpa. **(A)** Fuzzy fundus at day 3. **(B)** Minor vitreous hemorrhage. **(C)** Blurred fundus with suspected commotio retinae at day 3. **(D)** A majority of retinal pigmentation.

IOP Decrease Was Independent of Blast Pressure and Injury Duration

The IOP of the rabbits' eyes received gas shock under 500, 1,000, 2,000, and 5,000 Kpa were decreased significantly on day 1 and 7 post-blast ($P < 0.05$). The IOP of other groups detected at the specific time point were not statistically significant despite a minor increase or decrease within 5 mmHg. Longitudinally, there was no clear correlation between the change of IOP and the injured time (**Table 1**). In addition, changes of IOP gas pressure-independent statistically with $P > 0.05$ (**Figures 10**, **11**).

DISCUSSION

In this study, we successfully established the reproducible rabbit animal model of closed globe blast injury induced by self-developed instruments under an optimized condition similar to eye damage reported in the survivors of the war or civilian explosion, especially for the anterior segment (7, 16). Although there were no clinical signs for the retinal changes, definite retinal thickening and apoptosis were detected. On behalf of the development of a stable animal model, the gas shock produced

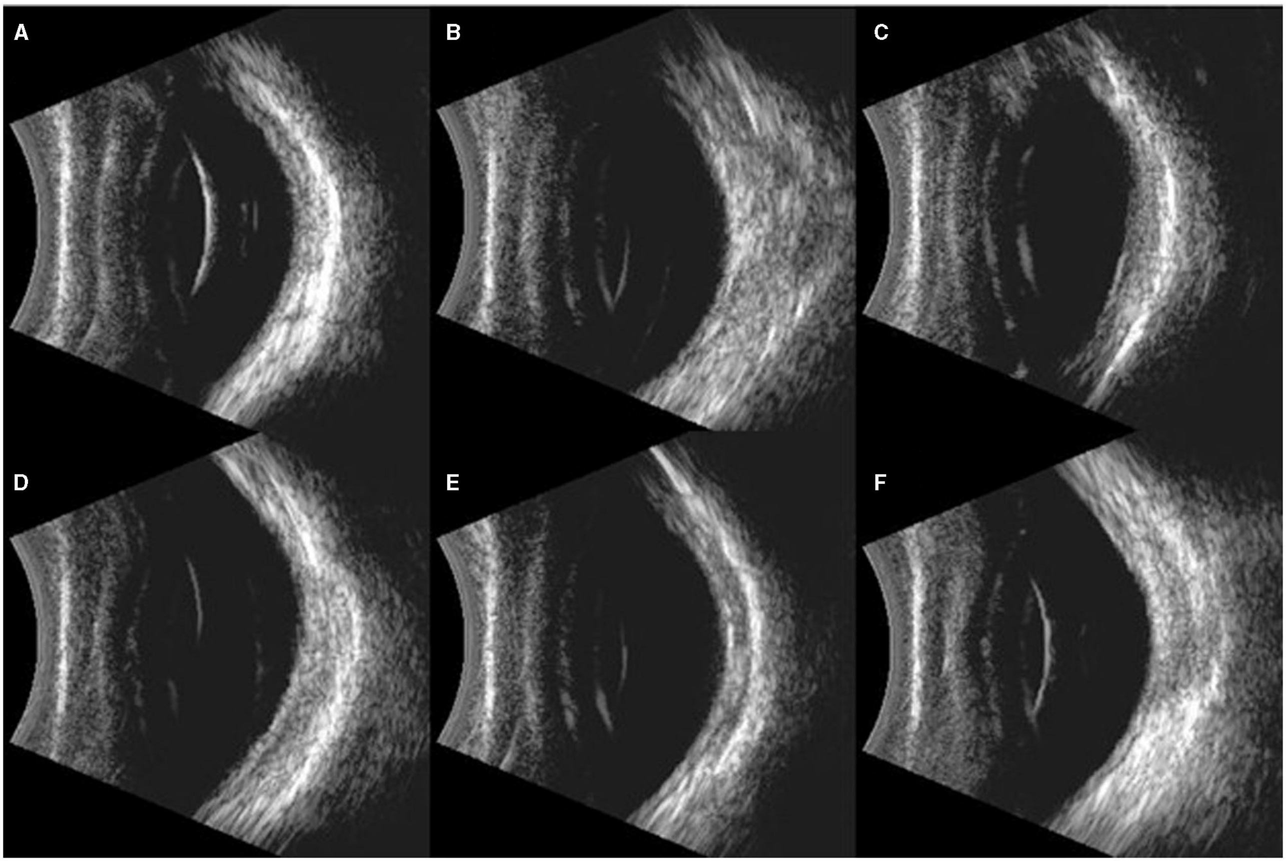

FIGURE 6 | Typical images of B ultrasound scan on the eyes of rabbits. **(A)**: Blank control group: Retina was well-attached with clear vitreous. **(B–F)**: Eyes exposed to 500, 1,000, 1,500, 2,000, and 5,000 Kpa: Retina was well attached, and no vitreous lumpy echo was detected.

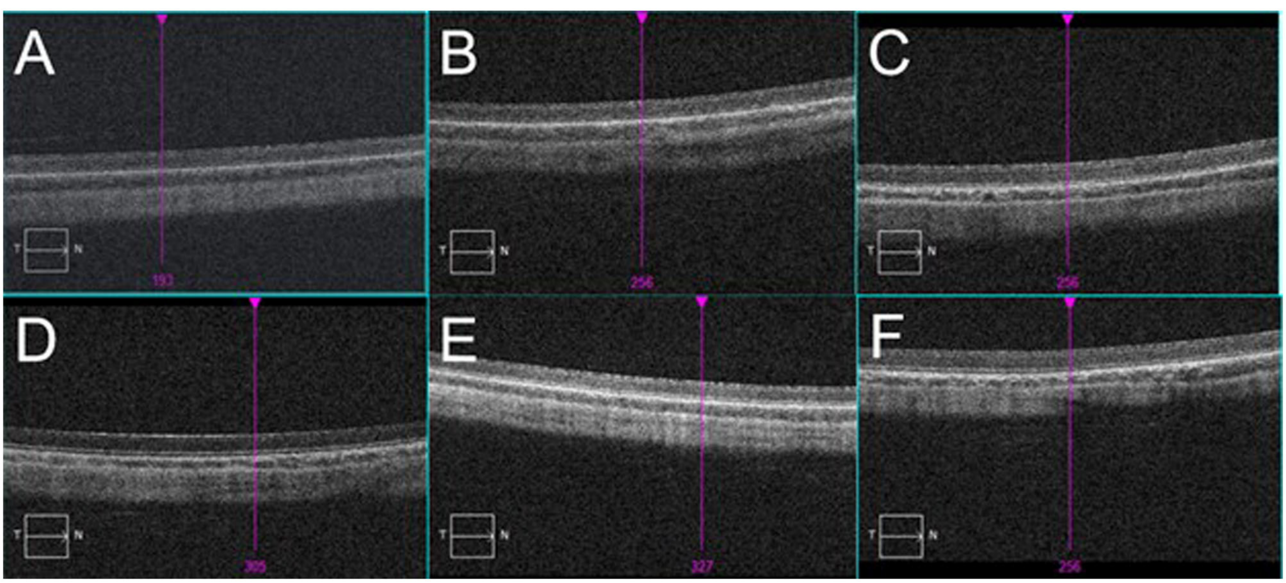

FIGURE 7 | Typical images of OCT scan on the eyes of rabbits. **(A)**: Blank control group: retina was well-attached, and layers of retina were in order. **(B–F)**: Eyes exposed to 500, 1,000, 1,500, 2,000, and 5,000 Kpa: No abnormality was observed.

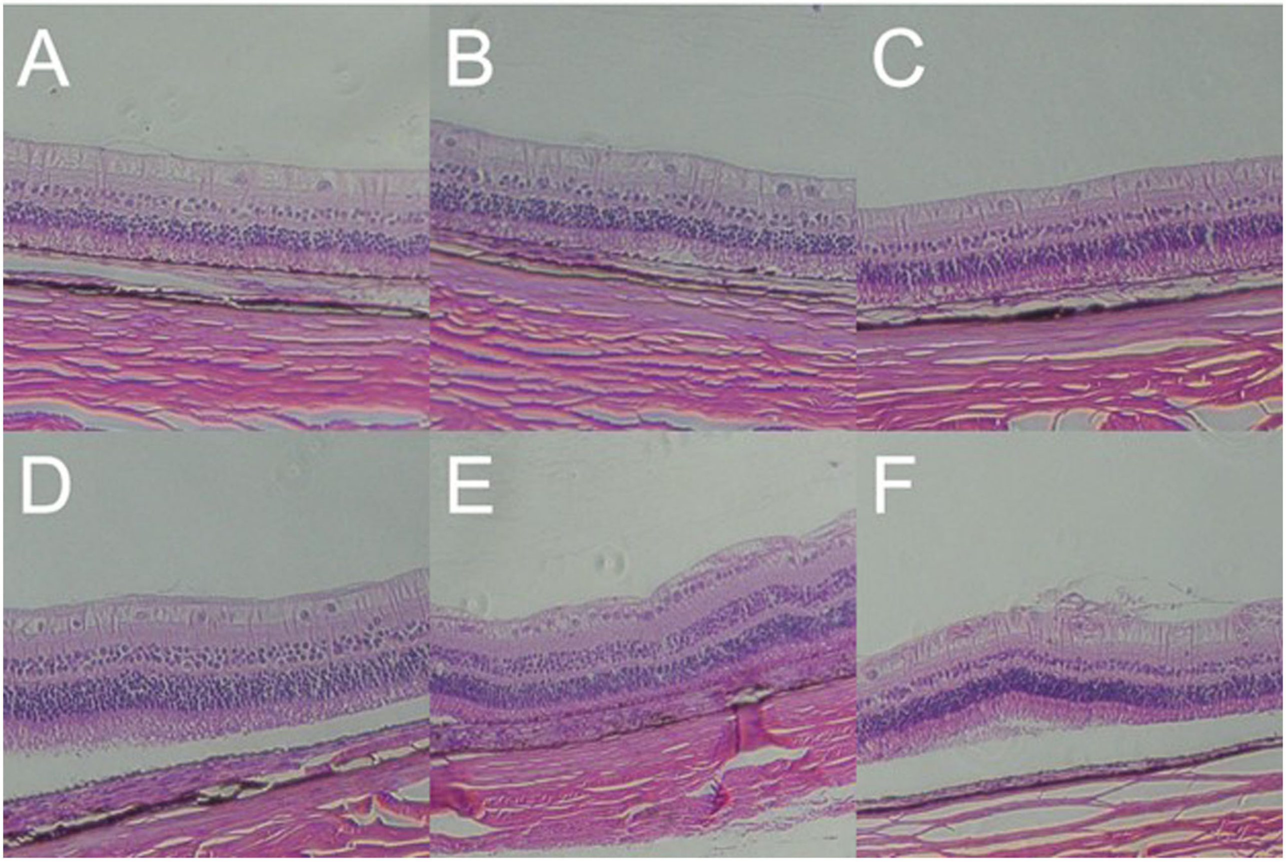

FIGURE 8 | Gross pathology of retinas of animal model with closed globe blast injury at day 7. **(A)**: Blank control group: 10 layers of the retina were integral and well-organized with normal thickness. Morphology of retinal cells were normal (× 100). **(B)** 500 Kpa group: Retinal ganglion cells (RGCs) were arranged in order, and the nucleus were distributed evenly (× 100). **(C)** 1,000 Kpa group: The retinal ganglion cells were arranged neatly, and the nucleus arrangement was tighter than control group (× 100). **(D)** 1,500 Kpa group: The nucleus arrangement was tighter than 1,000 Kpa group (× 100). **(E)** 2,000 Kpa group: The retinal ganglion cells were disordered, and the nucleus were dense (× 100). **(F)** 5,000 Kpa group: RGCs nucleus were karyopyknotic, and like vesicular nucleus (× 100).

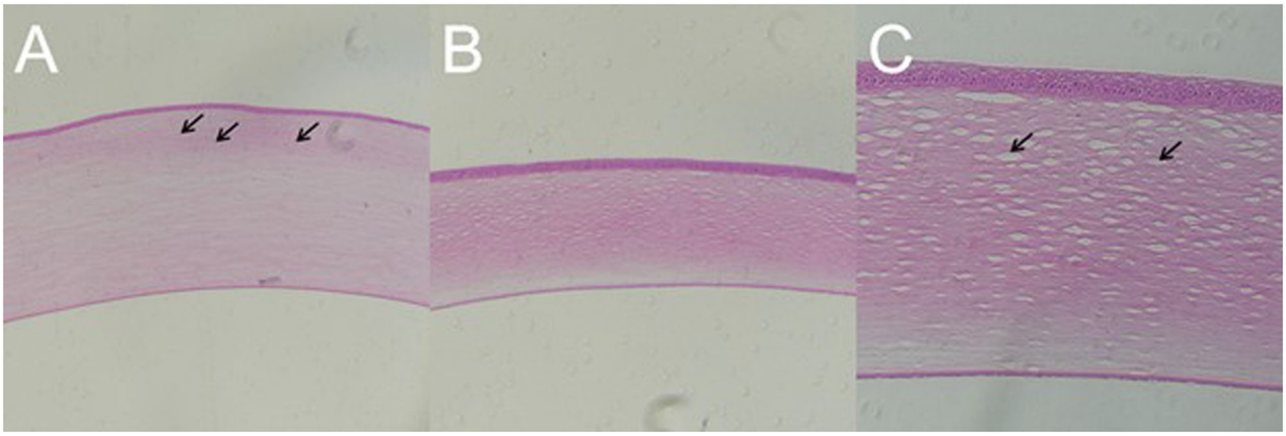

FIGURE 9 | Gross pathology of cornea of animal model with closed globe blast injury at day 7. **(A)**: Eyes with residual corneal edema: The stroma layer was thickened, where the inflammatory cells infiltrated close to the external elastic layer shown by black arrows (× 100). **(B,C)**: Corneal edema occurred immediately after blast and self-healed at day 7: Stromal thickness was normal (× 100), whereas loosen stroma was left at higher magnification shown by black arrow (× 200).

TABLE 1 | Values of IOP in different groups (Median and IOR).

	0 days	1 day	P^a	3 days	P^a	P^b	7 day	P^a	P^b	P^c
对照组	9.50 (9.30, 11.95)	11.15 (9.73, 14.07)	0.144	9.85 (8.70, 13.02)	0.715	0.465	10.35 (7.97, 11.90)	1.000	0.068	0.461
500 KPa	5.85 (3.75, 11.00)	5.65 (4.00, 7.27)	0.916	5.75 (4.92, 12.62)	0.833	0.116	4.35 (3.00, 7.00)	0.462	0.400	0.043
P_1	0.087	0.010		0.199			0.024			
1,000 KPa	6.50 (5.00, 11.00)	4.50 (2.60, 5.40)	0.046	7.00 (3.75, 9.87)	0.674	0.043	4.50 (3.92, 6.40)	0.058	0.498	0.176
P_1	0.257	0.010		0.171			0.010			
P_2	0.589	0.180		0.937			0.699			
1,500 KPa	8.25 (3.75, 12.98)	5.00 (4.52, 14.40)	0.916	6.50 (5.50, 10.57)	0.345	0.752	6.00 (3.82, 12.35)	0.500	0.752	0.686
P_1	0.352	0.352		0.171			0.352			
P_2	0.699	0.818		0.699			0.240			
P_3	0.937	0.310		0.937			0.394			
2,000 KPa	5.65 (4.45, 9.25)	6.35 (4.67, 7.40)	0.753	4.50 (2.92, 9.25)	0.462	0.674	3.65 (3.00, 6.00)	0.248	0.080	0.080
P_1	0.067	0.019		0.114			0.019			
P_2	0.937	0.699		0.132			0.699			
P_3	0.394	0.065		0.589			0.310			
P_4	0.589	0.937		0.240			0.132			
5,000 KPa	6.15 (4.53, 15.35)	8.00 (6.50, 9.22)	0.917	7.65 (4.75, 11.00)	0.917	0.916	4.00 (2.30, 7.00)	0.249	0.207	0.225
P_1	0.476	0.067		0.352			0.114			
P_2	0.818	0.093		0.937			0.699			
P_3	0.937	0.009		0.699			0.485			
P_4	0.937	0.485		0.937			0.240			
P_5	0.699	0.132		0.132			0.937			

P^a compare with 0 days, P^b compare with 1 day, P^c compare with 3 days.
P_1, means compare with control group; P_2, means compare with 500 KPa group; P_3, means compare with 1,000 KPa group; P_4, means compare with 1,500 KPa group; P_5, means compare with 5,000 KPa group.

by the device used is pressure exposed in a controllable and measurable manner by altering the input pressure of the tank. The gas was well-accumulated to the eyes exposed, hitherto, the contralateral eye and other parts of the rabbit body, especially the brain, were not affected during the blast. Superior to the other systems used for the same animal model as reported (10, 17), there was no mortality or open globe injury detected in this study.

Previously, the rodents (C57Bl/6J and DBA/2J and Balb/c mouse strains or rats) were mostly used for the animal model with low costs, whereas less tissue was obtained and higher lethality (18). Additionally, scaling principles have been achieved that injury biomechanical effect caused by blast explosion may differ significantly based on eye size and animal size (19). Although enucleated porcine eyes were also used to overcome the limitations of rodents, the ocular pathological changes could not be observed longitudinally (20). In that case, rabbits with closer anatomical similarities to the human eyes and larger size of eyes were chosen for this study (21). Airflow extruded by the gas shock was dispersed evenly on the rabbit's eyes without affecting the organs close to the eyes (9). Corneal edema, hyphema, and thickened retinal thickness were detected in the rabbit animal model, which might be relevant to clinical vision loss in patients who suffered ocular blast injury.

We set up a gradient of pressure ranging from 500 to 5,000 Kpa to find out the optimum pressure for the blast. Successful rate of the rabbit animal model in each experiment group was 33.3%, 100%, 100%, 66.7%, 83.3%, and in total was 76.7%, which was much higher than the previous animal models reported (30%) (9). There were identical pathological changes on the anterior segment that were commonly found in rabbits' animal models right after the blast exposure. Consistent with the patients or animal models reported, corneal edema occurred within 24 h post-blast was the most common damage (7, 22) due to a sharp decrease of the endothelial cells density, the rate of which in our model was much higher than the one reported by Jones K (23). The majority of corneal edema was receded on day 7, despite the corneal stroma was loosen. The prolonged corneal edema indicated that the dysfunction of endothelial cells in the cornea induced by the blast injury and inflammation shown with inflammatory cells infiltration close to extra elastic layer (23). As Daniel reported, inflammatory factors, such as IL-1b and LIX were elevated between day 1 and 4 weeks after the blast (10), and LIX was associated previously with neutrophil infiltration to the stroma and keratitis (24). The self-healing of corneal edema 7 days post-blast was attributed to the integrity of corneal endothelium shown on the histology slices, since the endothelial cells in rabbits can be regenerated (25), which could be proved by confocal microscopy and Endothelial cell count in the further study.

Clinically, hyphema was a vital sign of iris damage, which occurred frequently in blast induced globe injury (8). However, the present animal models rarely focused on the observation of hyphema after blast (26). In our rabbit animal model, hyphema occurred in eight rabbits, especially in 1,500

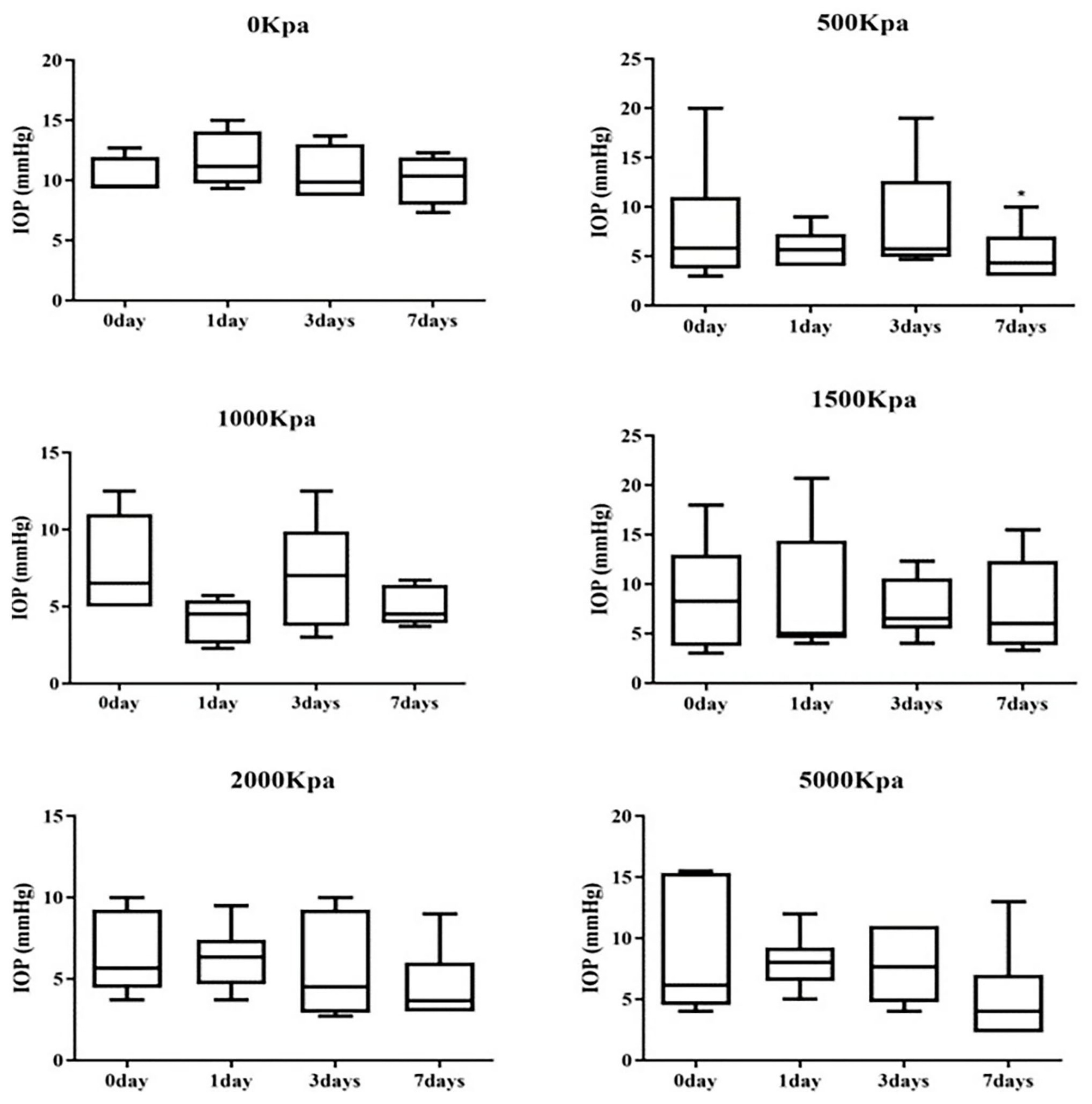

FIGURE 10 | Whisker plot of intraocular pressure (IOP) measured at 0-, 1-, 3-, and 7-days post-blast. *Means $P < 0.05$ compared with day 3.

Kpa group, within 24 h post blast indicating blunt damage to the vessels of the iris. Hyphema in five out of eight rabbits were absorbed without any interventions at day 7 post blast, while the rest were sustained, even to anterior synechia in rabbit, the rate of which conformed to the clinal data collected in veterans (7). Self-absorption of hyphema was relied on less amount of blood and healthy anterior chamber angle. Persistent blood accumulated indicated damage or obstruction to the anterior chamber angle, which could result in the elevation of IOP followed by optic nerve damage, especially in the older patients (27). Moreover, retrospective study about traumatic hyphema from combat ocular injury recorded in Walter Reed Ocular Trauma Database (WRTOD) demonstrated that traumatic hyphema were highly associated with the traumatic cataract formation, retinal detachment, angle recession, and final VA of <20/200 (28). Although none of the rabbit model showed cataract, which may come out as observation prolonged.

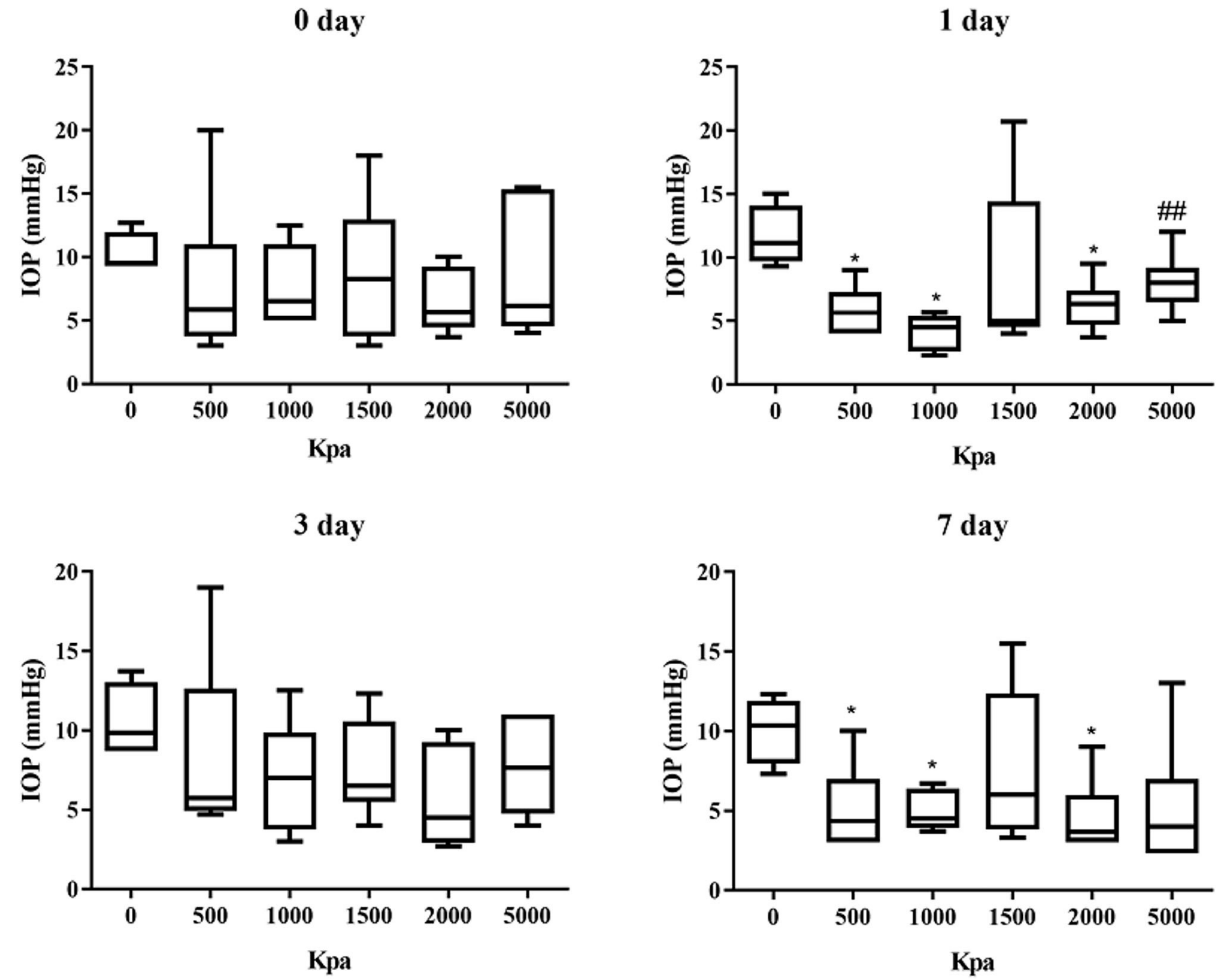

FIGURE 11 | Graphs of changes of IOP with gas pressure detected at the same time point. *Means $P < 0.05$ compared with the blank control group. ##means compared to the 1000 Kpa, the decrease of IOP in eyes exposed to 5000 Kpa was statistically significant with $p < 0.05$.

The changes of IOP about present animal models of ocular blast injury were controversial since multiple factors could have impacts on IOP oppositely. Generally, ketamine anesthesia is proven to elevate IOP, while isoflurane is proven to suppress it (29). Locally, corneal edema, function of ciliary body, and anterior chamber recession may also affect the IOP. Additionally, IOP changes were controversial in different strains of mice, which were elevated in the Balb/c postinjury and decreased in the C57Bl/6J. The reasons could be substantial corneal injuries that occurred in the Balb/c and a spot of corneal injuries in the C57Bl/6J post injury (18). Consistent to the studies of Jessica Hines-Beard and Kirstin Jones, IOP were significantly decreased in rabbits of 500, 1,000, and 2,000 groups at day 1 and day 7 post blast, which was independent of the exposed pressure. The IOP of the rest groups were increased or decreased within 5 mmHg, although there was no statistical significance with this variation. The IOP elevation was attributed to outflow block caused by anterior chamber recession or obstruction, whereas the IOP decrease was due to ciliary muscle dysfunction or corneal edema with a slight negative trend to the IOP measurement (30). IOP changes could be suggestive of traumatic glaucoma, but more improvements should be achieved on the IOP measurement instrument and anterior chamber test with Ultrasound Biomicroscope (UBM) or gonioscope or anterior OCT.

In rabbits exposed to 5,000 Kpa, only one rabbit presented minor vitreous hemorrhage, and another one presented potential commotio retinae with retinal pigmentation left at day 7. There were no obvious clinical signs of increased retinal thickness or detachment on the rest of the rabbit animal models, which was close to the results of the study of Shedd (10). However, there were definite retinal thickening and RGC apoptosis on the retinal sections of eyes exposed to 5,000 Kpa, which indicated that the higher pressure could reach the retina pass through the anterior chamber causing retinal damage proven by the research of Jones (23, 31). Since the retinal thinning and neuron degeneration were observed varied from 2 weeks to 3 months post-injury as literature reported (32). We assume that there will be retinal damages, such as retinal thinning and RGC degeneration will occur in this animal model when the observation time is extended. In addition, electroretinography (ERG)or visual evoked potentials (VEP) could be added to reveal the retinal function as a complement to the structural changes.

Apparently, this study has demonstrated that primary blast itself could induce closed globe injury (2), but the severity of ocular damage is relatively lower for the patients in combats or civilian blast injury (8). Future study may focus on bringing in explosive substances to our blast device on behalf of creating an animal model with blast eye injury closer to the clinics.

In conclusion, we established the rabbit animal model of closed globe blast injury induced by self-developed explosive device under optimized pressure. Eyes exposed to 1,500 Kpa could be an ideal model for traumatic corneal damage and hyphema, whereas the eyes exposed to 5,000 Kpa could serve as a model for traumatic retinal damage. Our research can provide a platform to reveal the underlying mechanism of blast eye injury and verify the new therapeutic interventions preclinically.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The animal study was reviewed and approved by Institute of Radiation Medicine, Chinese Academy of Medical Sciences.

AUTHOR CONTRIBUTIONS

YL, TY, JY, and HY designed this study. YL, TY, ML, and JL collected and measured data. YL and TY analyzed, interpreted the dataset and wrote this article. HY revised the manuscript. All authors contributed to the article and approved the submitted version.

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Clinical Analysis of Adult Severe Open-Globe Injuries in Central China

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Purpose: To describe the characteristics, management, and outcomes of adult severe open-globe injured (OGI) eyes.

Methods: Retrospective chart review of inpatients with initial visual acuity (VA) of light perception (LP) or no light perception (NLP) associated with OGI between 2017 and 2020 at Department of Ophthalmology, Henan Eye Institute, Henan Eye Hospital, Henan provincial People's Hospital.

Results: Six hundred twenty-five eyes of 622 adult patients with initial VA of LP or NLP associated with open-globe injuries (OGIs) were included. The mean age was 47.8 ± 14.1 years with the range from 18 to 91 years. Significant male predominance was noted (81.5%). The most common type of these severe OGIs was rupture (65.8%). Traffic accidents accounted for 13.5% followed by fall/tumble (10.9%) and nail/wire (10.9%) of all the severe OGIs. Almost half of the injuries happened at workplace (47.2%). Initially, 78.7% eyes just received primary debridement and wound closure, while 8.5% eyes with no possible of anatomical reconstruction received evisceration. After initial management, 350 eyes received subsequent operation, including 239 eyes underwent vitrectomy + silicone oil/(+cataract remove). Finally, over 6 months follow-up, 137 eyes (21.9%) were eviscerated, 150 eyes (24.0%) got atrophied, while 132 eyes (21.1%) retain some VA. Fifty-three eyes (8.5%) got VA of 0.3–1.5.

Conclusion: Severe OGIs are most seen in the young, middle-aged, and male working population and remain a serious public health problem, resulting in significant vision loss or Evisceration of eyes. Effective preventive measures should be taken for the individuals in these groups.

Keywords: adult, central China, open-globe injuries, trauma, epidemiology

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INTRODUCTION

Open-globe injuries (OGIs) include a full-thickness break or rupture of the cornea and/or the sclera. OGIs are the major cause of unilateral visual loss. Severe OGIs (initial VA of LP or NLP) not only lead to vision loss but also can cause eye loss. OGIs seem more common in developing countries than in developed countries (1). Henan province is a large agricultural province. It is located in central China with rich labor resources. Latest population census shows that the population of Henan was about one hundred million (99,366 thousands). Henan Eye Hospital is the 1st or the second largest ophthalmic center in Henan Province and received quite a lot of ocular trauma patients every year in Henan Province.

As we know, OGIs are most seen in working population and remain a serious public health problem, resulting in significant vision loss. In severe OGIs, eyes had been destroyed or cannot

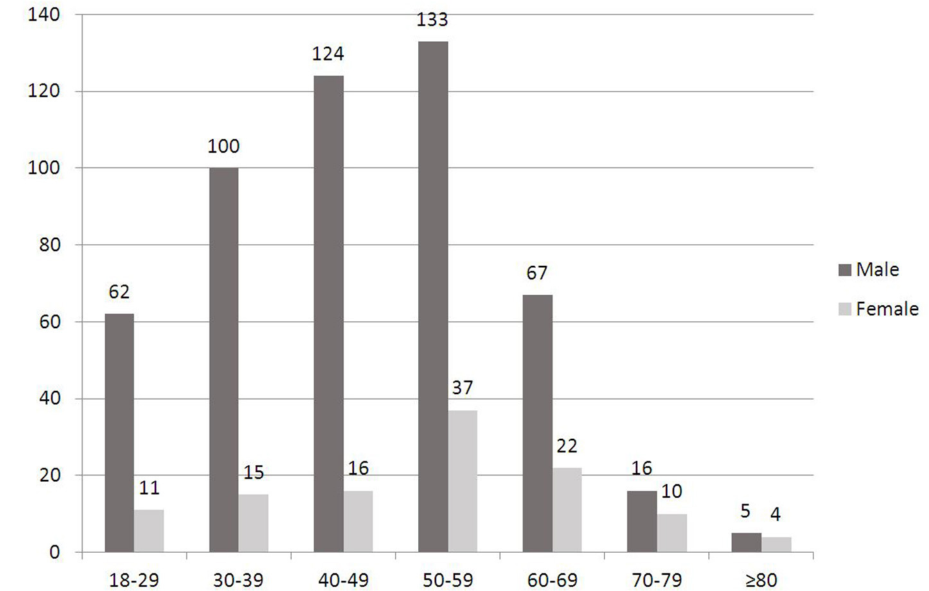

FIGURE 1 | Distribution of gender and age groups of severe adult opened globe injury patients.

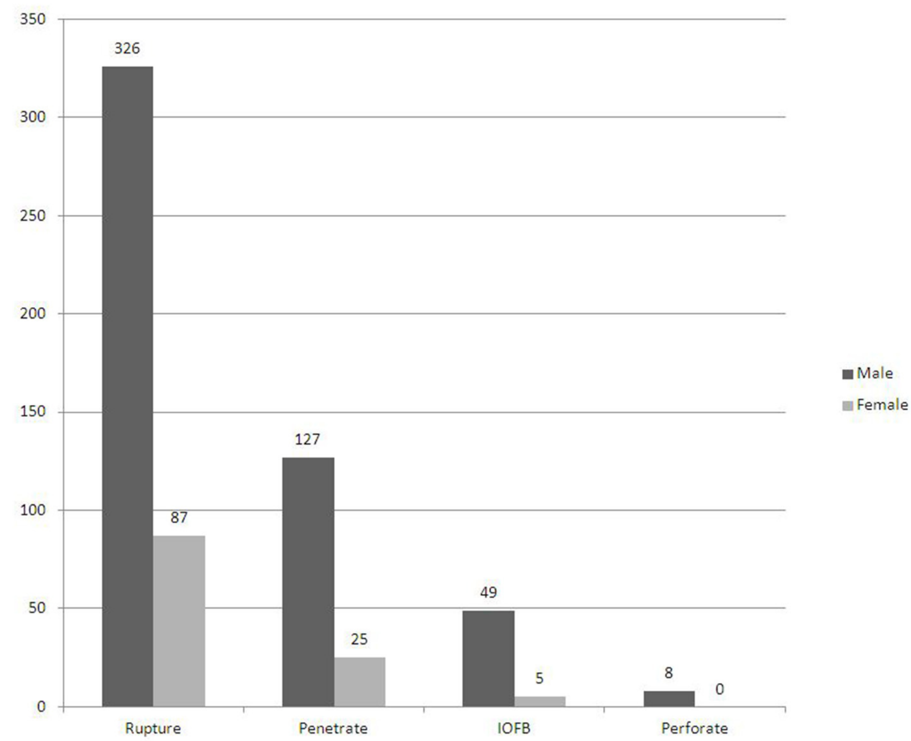

FIGURE 2 | Distribution of gender and types of opened globe injury patients.

be reconstructed. A good understanding of the characteristics of severe OGIs in adults is required for the determination of preventive measures. In this study, we aimed to separately analyze the characteristics of adult severe OGIs diagnosed and treated at Department of Ophthalmology, Henan Eye Institute, Henan Eye Hospital, Henan provincial People's Hospital.

METHODS

We retrospectively chart reviewed all the patients diagnosed and treated at Department of Ophthalmology, Henan Eye Institute, Henan Eye Hospital, Henan provincial People's Hospital between 2017 and 2020. The OGI patients aged over 18 and with initial VA of LP or NLP were included into the study. Age, gender, mechanism of injury, surgical options, and outcomes were analyzed. Ethics approval for the study was granted by Henan Eye Institute, Henan Eye Hospital, Henan provincial People's Hospital Human Research Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki.

Classification

Open-globe injuries were classified according to the Birmingham Eye Trauma Terminology System (2).

The patients were classified into 7 age groups: 18–29, 30–39, 40–49, 50–59, 60–69, 70–79, ≥80 years.

Statistical Analysis

Data were analyzed using Microsoft Office Excel 2007. Continuous and categorical variables were displayed as means ± standard deviation (SD) and percentages, respectively.

The ethics number is HNEECKY-2021(33).

RESULTS

In the 4 years, 1,902 cases (1,908 eyes) of OGI patients (including 1,483 eyes of 1,478 patients older than 17 years) were diagnosed and treated at Department of Ophthalmology, Henan Eye Institute, Henan Eye Hospital, Henan provincial People's Hospital. Of all the OGIs, 622 cases (625 eyes) of adult severe OGIs with initial VA of LP or NLP were included in this study. The mean age at the time of injury was 47.8 ± 14.1 years with the range from 18 to 91 years. Significant male predominance was noted (81.5%). The highest incidence of severe adult OGIs was found in the middle-aged group (50–59, 40–49, 30–39) in male patients (**Figure 1**). The highest incidence of severe adult OGIs was found in 50–59 age group in female patients. Of the 622 patients, 3 cases had bilateral eye injury. In patients with unilateral eye injury, 299 (48.2%) eyes were right eye and 320 (51.2%) were left eye.

In the present study, the most common type of severe OGIs was rupture (65.8%) no matter in male (326 eyes) or female (87 eyes) (**Figure 2**). Traffic accidents accounted for 13.5% followed by fall/tumble (10.9%) and nail/wire (10.9%) of all the severe OGIs (**Table 1**). Almost half of the injuries happened at workplace (47.2%).

Initially, 492 eyes (78.7%) received primary debridement and wound closure. Fifty three eyes (8.5%) with no possible of anatomical reconstruction received evisceration (**Table 2**). After initial management, 350 eyes received subsequent operation, including 239 eyes underwent vitrectomy + silicone oil/(+cataract remove) and 58 eyes got eviscerated (**Table 3**). Over 6 months of follow-up, 137 eyes (21.9%) were eviscerated, 150 eyes (24.0%) got atrophied, and 132 eyes (21.1%) retain some VA. At the end of follow up, fifty-three eyes (8.5%) got VA of 0.3–1.5 (**Table 4**). Visual recovery was much better in eyes with initial VA of LP than that in eyes with initial VA of NLP. In eyes with initial VA of NLP, final vision improved to light perception/ hand

TABLE 1 | Causes of severe open globe injuries.

Cause	*n*	%
Traffic accident	84	13.5
Fall, tumble	68	10.9
Nail, wire	68	10.9
Wood, branch, bamboo	58	9.3
Fireworks, firecrackers	43	6.9
Emery cutter, grinding wheel, electric saw	37	6
Violence	34	5.5
Metal bar	30	4.8
Metal fragments caused by hammering	23	3.7
Metal block, sheet metal	21	3.4
Scissors, knife	12	1.9
Flying stone	12	1.9
Lighter, bottle, bulb explosion	7	1.1
Glass	5	0.8
Falling objects	4	0.6
Metal hook	3	0.5
Toy bullet	3	0.5
Children head	2	0.3
Battery explosion	2	0.3
Flying object from grass trimmer	1	0.2
Water pump explosion	1	0.2
Tire explosion	1	0.2
Pressure cooker explosion	1	0.2
Gas tank explosion	1	0.2
Cock peck	1	0.2
Horn	1	0.2
Others and unknown	99	15.9
Total	622	100

TABLE 2 | Primary management.

Surgical options	*n*	%
Wound closure	492	78.7
Evisceration	53	8.5
Comprehensive management	46	7.4
Wound closure + cataract removal	23	3.7
No surgery	7	1.1
Other surgeries	4	0.6
Total	625	100

TABLE 3 | Secondary intervention.

Surgical options	*n*	%
Vitrectomy + silicone oil/(+cataract remove)	239	68.3
Evisceration	58	16.6
Vitrectomy/(+cataract remove)	38	10.8
cataract remove/(+IOL implant)	15	4.3
Total	350	100

TABLE 4 | Final outcomes of 625 eyes with severe OGIs.

	LP		NLP	
Outcomes	*n*	%	*n*	%
Loss of follow-up	42	15.4	32	9.1
Evisceration	13	4.8	124	35.2
Atrophy	17	6.2	62	17.6
Atrophy with silicone oil	23	8.4	48	13.6
Silicone oil dependence	31	11.4	49	13.9
NLP-CF	40	14.7	12	3.4
0.01–0.25	60	22	19	5.4
0.3–1.5	47	17.1	6	1.8
Total	273		352	

TABLE 5 | Surgery time of 625 eyes with severe OGIs.

Surgery time	*n*	%
0	7	1.1
1	216	34.6
2	307	49.1
3	80	12.8
4	13	2.1
5	2	0.3
Total	625	100

movement in 6 eyes (1.7%), counting fingers in 5 eyes (1.4%), 0.02–0.8 in 25 eyes (7.1%).

Of all the 625 severe OGIs, almost half eyes (49.1%) received 2 times of surgery (**Table 5**). The average was 1.8 times. Seven eyes were followed up with medical treatment alone and 2 eyes received 5 times surgeries. One eye that underwent 5 times surgeries achieved VA of 0.1. Another eye that underwent 5 times surgeries achieved VA of HM.

Of all the 625 severe OGIs, 53 eyes (8.5%) underwent intraocular lens (IOL) related surgery at last. Thirty-seven eyes underwent IOL implant and 16 eyes underwent sclera suture or intrascleral fixation (3).

Of all the eviscerated 137 eyes, 53 eyes (38.4%) were eviscerated at the primary surgery, 68 eyes (49.6%) were eviscerated at the second surgery, 13 eyes (9.5%) were eviscerated at the third surgery and 3 eyes (2.2%) were eviscerated at the fourth surgery.

Of all the 622 cases of severe OGIs, 2 patients were diagnosed sympathetic ophthalmia. One patient was a 50 year-old male patient who sustained an injury to his right eye when riding a bicycle. Ten weeks later he was diagnosed sympathetic ophthalmia. Another patient was a 41 years old male patient who got his right eye hurt by finger and 8 weeks later he was diagnosed sympathetic ophthalmia.

DISCUSSION

Open globe injury (OGI) remains a significant public health problem both in developed and developing countries due to their outcomes. This type of injury is more commonly seen in underdeveloped and developing countries than in developed countries (1). It is a major and preventable cause of unilateral visual loss.

In spite of medical and technical advancements, severe OGIs result in substantial visual morbidity and lifelong sequelae. Severe OGIs also impose financial burdens on society, company and patients. According to our study, each severe OGI eye need 1.8 times of surgery. Currently, the average medical fee for each severe OGI eye is about 25,000 RMB in Henan Province. In underdeveloped and developing countries, severe OGIs mean disasters to the patients and their families for each patient is the backbone of the family. In our study, the highest incidence of severe adult OGIs was found in the middle-aged group (30–59). The mean age at the time of injury was 47.8 ± 14.1 years.

It seems that patients were younger than those in the study of Fujikawa et al. (4). The mean age of their study populations was 56.7 ± 21.8 years in the LP group and 62.3 ± 21.7 years in the NLP group. This may indirectly reflect the different condition of aging of population of the society. Another interesting difference between our study and Fujikawa et al. (4) is the male to female ratio. In our study, male to female ratio is 81.5% while in the study of Fujikawa et al. (4) it is 66.1%. In other studies, male to female ratio was 73.3–80% (1, 4–12). The highest ratio was found in the study of Supreeyathitikul et al. (13) (88.7%).

In the current study, almost half of the injuries happened at workplace (47.2%) which is similar to the study of Supreeyathitikul et al. (13) (45.8%). In our study, all the severe OGIs cases related to non-wearing of eye protective device. If the patients wear eye protective device, maybe they would not get eyes injured. According to article 54 of <<Safe Production Law of the People's Republic of China>>, the departments in charge of supervising and administering production safety, must strictly check, test or accept the matters concerning production safety, which call for examination and approval, in accordance with the relevant laws and regulations and in conformity with the safety conditions and procedures as required by national standards or trade standards. In fact, Safe Production Law is implemented well in formal company. Safe Production Law seems difficult to enforce when employees work for small unformal company or individuals. Legislation needs improvement to prevent ocular trauma and other traumas.

Of all the 625 severe OGIs, 53 eyes (8.5%) underwent intraocular lens (IOL) related surgery at last. Thirty-seven eyes underwent IOL implant and 16 eyes underwent sclera suture or intrascleral fixation (3). For eyes with combined lens capsular and iris deficiency, glued aniridia IOL and glued IOL with iridoplasty maybe the optimal options (14). Unfortunately, they are unavailable for us.

In our study, 53 eyes were eviscerated at the primary management and 58 eyes were eviscerated at the second intervention. Over 6 months of follow-up, a total of 137 eyes underwent evisceration. The rate of evisceration for severe OGIs in all adult OGIs was 9.2% (137/1,483). It is similar to that of other large series (12, 15, 16). In our study, 124 eyes (35.2%) with initial VA of NLP underwent evisceration. The rate is much lower than that in another small series study (17) in which 21 eyes (84%) were eviscerated in 25 eyes presenting with no light perception (NLP) after open globe injury (OGI). No eyes underwent enucleation in the present study. Zigiotti et al. (18) described a modified standard enucleation.

Before deciding on evisceration/enucleation in severe OGI eyes, reversible causes of vision loss should be excluded including psychological factors (19). Even in situations in which evisceration/enucleation seems inevitable; the ophthalmologist should discuss the possible options with the patient before making a final decision. Primary evisceration/enucleation for severe OGI eyes with NLP in view of risk of sympathetic ophthalmia was a controversial approach. Sympathetic ophthalmia with potential for bilateral blindness is a relative indication for evisceration/enucleation of an injured eye. The use of modern immunosuppressives has also improved treatment and control of sympathetic ophthalmia. In the current study, 2 patients were diagnosed sympathetic ophthalmia after about 2 months later of injury. In consideration of 132 eyes (21.1%) retain some VA and 53 eyes (8.5%) got VA of 0.3–1.5, primary surgical repair should not be abandoned for the risk of sympathetic ophthalmia in eyes with NLP.

In conclusion, this study demonstrated the characteristic, managements, and outcomes of severe OGIs. Severe OGIs are most seen in the young, middle-aged, and male working population and remain a serious public health problem, resulting in significant vision loss or evisceration/enucleation of eyes. Effective preventive measures should be taken for the individuals in these groups. Employers and employees need to be educated on the importance of eye protection. Legislation needs improvement to prevent ocular trauma and other traumas. Finally, we must expand outreach and education to at-risk populations.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Henan Eye Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HC, JH, and XZ organized the database. HC performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to conception and design of the study, manuscript revision, read, and approved the submitted version.

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Relationship of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratio With Visual Acuity After Surgical Repair of Open Globe Injury

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Purpose: To assess the relationship and prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with poor final best-corrected visual acuity (BCVA) after surgical repair of open globe injuries (OGI) in adults.

Design: Retrospective analysis of data from an ongoing prospective cohort of consecutive patients.

Methods: In a tertiary university hospital, 197 eyes of 197 patients were included between 2013 and 2017. NLR and PLR were obtained from pre-operative blood tests to analyze its relationship with poor final BCVA.

Results: Severe visual impairment (SVI) was defined as ≤20/200, and was observed in 96 (48.7%) patients after surgical repair of OGI. SVI patients had higher NLR (7.4 ± 6.6 vs. 4.0 ± 3.2, $p < 0.001$), and PLR (167 ± 92 vs. 139 ± 64; $p = 0.021$) than non-SVI. NLR ≥ 3.47 and PLR ≥ 112.2 were the best cut-off values for SVI, were univariate risk factors for SVI, and had sensitivity: 69.0, 71.4, and specificity: 63.6, 44.8, respectively. In multivariate analysis, only OTS, athalamia, and hyphema remained as risk factors. NLR had significant correlation with ocular trauma score (OTS) ($r = -0.389$, $p < 0.001$) and final BCVA ($r = 0.345$, $p < 0.001$).

Limitations: Simultaneous trauma in other parts of the body that could influence the laboratory findings.

Conclusion: Patients with SVI after a repaired OGI had increased pre-operative NLR and PLR levels. High NLR and PLR are risk factors for SVI in univariate analysis. It is confirmed that low OTS is a risk factor for SVI. High NLR and PLR could be used as a prognostic tool to identify patients at higher risk for SVI after repair of OGI.

Keywords: prognostic, platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), severe visual impairment, ocular injury, ocular trauma, open globe injury (OGI)

INTRODUCTION

Open globe injury (OGI) is defined as a full-thickness wound of the eyewall and represents a vision-threatening ocular injury (1, 2). Global estimations indicate that a total of 1.6 million cases of blindness are due to eye injuries, 2.3 million people with low vision are due to ocular injuries and 19 million cases of monocular blindness are due to eye injuries (3). The importance lies in the fact eye injuries, apart from their visual impact, generate work absenteeism, high cost in health care systems, and a serious impact on the quality of life. Being a preventable problem, there is much to be done to avoid this situation.

Risk factors associated with poor final visual acuity (VA) includes poor initial VA, globe rupture, zone 3 injury, the posterior extension of the wound to rectus insertion, presence of relative afferent pupillary defect (RAPD), vitreoretinal trauma, hyphema, cataract, vitreous loss, and low ocular trauma score (OTS) (4–8). In most cases, the diagnosis of OGI is clinical, however, there are different diagnostic methods such as ultrasonography (US) and computed tomography (CT) that can be of aid when the slit-lamp examination or the evaluation of the fundus are not possible (9). In addition, CT may be useful in the search for orbital fractures, for intraocular foreign bodies (IOFB), and as an aid if an occult OGI is suspected. Likewise, different CT scans findings have been associated with poor visual prognosis, helping in the council of patients (10–12). On the other hand, US and ultrasonic biomicroscopy (UBM) are safe and economical methods that can provide valuable information in case of media opacity for the surgical plan elaboration and as predictors for final vision. However, they are operator dependent, and there is a concern of prolapse of the intraocular tissues, so it should be indicated with caution (13, 14).

The counts of white blood cell (WBC), neutrophil (NEU), and lymphocyte (LYM) as well as the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) are widely used as blood biomarkers associated with inflammation. The NLR and PLR have been used in cardiovascular diseases to predict death and myocardial infarction (15–20), and have been related to inflammatory activity in rheumatologic diseases (21, 22). They have been recognized as indicators of poor prognostic for survival in many solid cancers (23, 24) and renal diseases (25).

The NLR and PLR have been also associated with ocular conditions, such as age-related macular degeneration (26–29), idiopathic acute anterior uveitis (30), diabetic retinopathy (31, 32), keratoconus (33), dry eye disease (34, 35), primary open-angle glaucoma (36), and pseudoexfoliation syndrome (37, 38). However, their relationship with the final VA after a surgical repair of OGI has not been studied. The current study aims to assess the relationship and prognostic value of pre-operative NLR and PLR with poor final VA after repaired OGI.

METHODS

Data were retrospectively analyzed from an ongoing prospective cohort that included all consecutive patients with OGI that had primary repair between January 2013 and December 2017 at the ophthalmology department of the University Hospital from the Faculty of Medicine of the Autonomous University of Nuevo León (UANL), a tertiary care university hospital in Monterrey, Mexico. Patients younger than 18 years of age, primary evisceration or enucleation, secondary OGI repairs, and patients operated elsewhere were excluded. The study received institutional ethics committee approval and was conducted following good clinical practices and the declaration of Helsinki. All patients read and provided written informed consent to participate.

All patients underwent a complete ophthalmic evaluation at presentation and in follow-up visits, including pupillary reflexes, and RAPD. Best-corrected visual acuity (BCVA) was performed with a Snellen chart either with subjective refraction or pinhole. The length and zone of the wound were recorded according to the classification of the Ocular Trauma Classification Group (39). Total raw points of the OTS were calculated using the variables of initial BCVA, globe rupture, endophthalmitis, perforating injury, retinal detachment, and RAPD (6). The type of injury was categorized according to the standardized classification of ocular trauma in globe rupture, penetrating injury, perforating injury, or intraocular foreign body (40, 41). The mechanism of injury was recorded and a detailed examination of the anterior and posterior segment was included. Corneal trauma was defined as follows: central corneal trauma when it occurred in the central 3 mm zone, paracentral when it occurred outside the central zone and inside 8 mm diameter, and peripheral when it occurred outside the paracentral zone and up to the limbus. Total corneal trauma was defined when all 3 zones were involved. Several time intervals relative to the accident were recorded. Patients were divided for analysis based on final visual acuity as patients with severe visual impairment (SVI) or non-SVI (NSVI). Patients with SVI were defined as having a final BCVA of 20/200 or worse in the last visit. Final BCVA better than 20/200 were considered non-SVI (NSVI) (42). Patients were further divided according to the presence or absence of systemic comorbidities and substance use.

Blood tests were performed on all patients before surgery. The blood samples were assessed by flow cytometry using a CELL-DYN® Ruby™ (Abbott Laboratories). All the absolute parameters of the blood tests were included, as well as glucose. The NLR was calculated by dividing neutrophils (NEU) by lymphocytes (LYM) and the PLR was calculated by dividing platelets (PTL) by LYM. The mixed monocyte-basophil-eosinophil (MXD) was calculated by the sum of monocytes (MON), basophils (BAS), and eosinophils (EOS).

Descriptive and inferential statistical analyses were performed. The Chi-square statistics, the *T*-test, and the U-Mann Whitney-test were used for univariate associations. Correlation analysis was performed with Spearman's correlation coefficient. Receiver-operating characteristic (ROC) curve was used for determining cut-off values for NLR and PLR to distinguish between SVI and NSVI, chosen based on the maximal Younden's Index. A linear regression model was used for univariate and multivariate logistic analysis. All variables of known clinical relevance whose univariate analysis resulted in a p-value ≤ 0.001 and with a high OR were considered for multivariable analysis. The odds ratio (OR) and 95% confidence interval (CI) for each independent variable were calculated from the same model. Statistical significance was considered when $p \leq 0.05$. The statistical analysis was performed using Microsoft Office Excel 2013 and SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

RESULTS

Of the 271 patients included in the cohort, 66 patients younger than 18 years old, and 8 with missing worksheets were excluded; 197 eyes of 197 adult patients were included for analysis, 96 (48.7%) developed SVI. Patients with SVI were significantly older (39.5 ± 15.4 vs. 35.3 ± 12.9; $p = 0.043$). Most of the patients were male in SVI (89.6%) as well as in NSVI (90.1%) groups ($p = 1.000$). The median (IQR) follow-up time was significantly longer in NSVI [90 (129) days] than in SVI [30 (80) days] patients ($p < 0.001$). Time intervals between accident and consultation, surgery or blood sample analysis were similar between patients with SVI, and NSVI ($p > 0.05$). Illegal substance use and the presence of systemic comorbidities were significantly more frequent in patients with SVI ($p < 0.05$). The mechanisms of injury had a significantly different distribution between groups; polytrauma, fist/kick and blunt object were observed more often in patients with SVI, whereas metallic objects were observed more often in patients with NSVI. Detailed demographic characteristics, time intervals, and systemic comorbidities are shown in **Table 1**.

TABLE 1 | Demographics, time intervals and mechanism of injury in SVI and NSVI patients.

Characteristics	All ($n = 197$)	SVI ($n = 96$)	NSVI ($n = 101$)	P=
Gender, Men (n, %)	177 (89.8)	86 (89.6)	91 (90.1)	1.000
Age, (mean ± SD) years	37.3 ± 14.3	39.5 ± 15.4	35.3 ± 12.9	**0.043**
Cases < 50 yo (n, %)	163 (82.7)	75 (78.1)	88 (87.1)	0.131
Laterality, left eye (n, %)	109 (55.3)	54 (56.3)	55 (54.5)	0.886
Follow-up (median, IQR) days	75, 120	30, 80	90, 129	**<0.001**
Accident-consultation interval				
Mean hours ± SD	29.0 ± 60.6	28.2 ± 44.9	29.7 ± 72.3	0.872
<24 h (n, %)	116 (70.7)	50 (64.1)	66 (76.7)	0.087
Accident-surgery interval				
Mean hours ± SD	67.7 ± 95.8	60.7 ± 51.6	73.8 ± 121.5	0.358
<24 h (n, %)	29 (17.8)	13 (17.3)	16 (18.2)	1.000
Accident-blood sample interval				
Mean hours ± SD	46.9 ± 84.3	44.4 ± 75.5	49.2 ± 92.3	0.729
<24 h (n, %)	86 (59.3)	42 (60.0)	44 (58.7)	1.000
One or more systemic comorbidities (n, %)	100 (50.8)	58 (60.4)	42 (41.6)	**0.010**
Systemic diseases				
Systemic hypertension (n, %)	14 (7.7)	10 (11.6)	4 (4.1)	0.092
Diabetes mellitus (n, %)	8 (4.4)	5 (5.8)	3 (3.1)	0.478
Other systemic diseases (n, %)	5 (2.5)	2 (2.1)	3 (3.0)	1.000
Substance use				
Tobacco (n, %)	55 (30.2)	26 (30.2)	29 (30.2)	1.000
Alcohol (n, %)	44 (24.2)	25 (29.1)	19 (19.8)	0.167
Illegal substances (n, %)	16 (8.8)	12 (14.0)	4 (4.2)	**0.033**
Mechanism of injury				
Metallic object (n, %)	75 (39.1)	18 (19.6)	57 (57.0)	**<0.001**
Stone (n, %)	19 (9.9)	11 (12.0)	8 (8.0)	0.469
Glass (n, %)	18 (9.4)	8 (8.7)	10 (10.0)	0.808
Polytrauma (n, %)	17 (8.9)	14 (15.2)	3 (3.0)	**0.004**
Fist/kick (n, %)	14 (7.3)	12 (13.0)	2 (2.0)	**0.004**
Blunt object (n, %)	11 (5.7)	10 (10.9)	1 (1.0)	**0.004**
Branch/stick (n, %)	13 (6.8)	4 (4.3)	9 (9.0)	0.256
Knife (n, %)	4 (2.1)	2 (2.2)	2 (2.0)	1.000
Explosives (n, %)	3 (1.6)	3 (3.3)	0 (0.0)	0.108
Others (n, %)	18 (9.2)	10 (10.9)	8 (8.0)	0.622

IQR, Interquartile range; SVI, Severe visually impaired; NSVI, Not-severe visually impaired; OGI, Open globe injury.
Bold means $p < 0.05$. Percentages are relative to the number of patients with available data.

A comparison of the initial clinical presentation of the OGI between patients with SVI and NSVI is shown in **Table 2**. The patients with SVI had significantly lower raw OTS, worse initial BCVA, larger wounds, and more sutures. Furthermore, an initial BCVA 20/200 or worse was significantly associated with patients with the SVI at the last visit. An initial BCVA 20/200 or worse was present in 98.9% of patients that ended with SVI vs. 49.5% of patients that ended with NSVI ($p < 0.001$). Of the 142 patients with initial BCVA 20/200 or worse, 92 (65%) ended with SVI. On the contrary, of the 52 patients with initial BCVA better than 20/200, only 1 (2%) ended with SVI (**Figure 1A**). The patients with SVI showed a significantly higher prevalence of globe rupture, zone 3 injury, total corneal injury, uveal exposure, vitreous exposure, athalamia, hyphema, and anterior chamber fibrin. Whereas, patients with NSVI presented more frequently with penetrating wounds, intraocular foreign body, zone 1 injury, and paracentral corneal injury (**Table 2**).

Twenty-five (12.7%) patients had blood tests performed elsewhere and were excluded from the analysis of blood test parameters because these were not available. The remaining 172 (87.3%) patients had blood tests performed in our hospital and were included for analysis. The differences in blood test parameters between patients with SVI and NSVI are shown in **Table 2**. The patients with SVI had significantly higher LEU and NEU counts, a correspondent lower LYM count, greater NLR and PLR ratios, and higher glucose levels. These significant differences were observed when analyzing all patients together and when separated in patients with comorbidities and without comorbidities, except for PLR that was not significant in patients with comorbidities (**Table 3**). The clinical characteristics of OGI at presentation and its relationship with NLR and PLR ratios are shown in **Table 3**. Patients presenting with globe rupture, zone 3 injury, uveal exposure, vitreous exposure, hyphema or retinal detachment had significantly higher NLR and PLR. Patients presenting with total corneal injury had significantly higher NLR.

TABLE 2 | Clinical characteristics of the OGIs in SVI and NSVI patients.

Characteristics	All (*n* = 197)	SVI (*n* = 96)	NSVI (*n* = 101)	*P*=
Ocular trauma score (OTS) raw points, mean ± SD	60.0 ± 23.2	41.5 ± 14.6	77.0 ± 15.2	**<0.001**
Initial BCVA (LogMAR), mean ± SD	2.6 ± 1.6	3.8 ± 0.9	1.4 ± 1.1	**<0.001**
Initial BCVA 20/200 or worse	142 (73.2)	92 (98.9)	50 (49.5)	**<0.001**
Final BCVA (LogMAR), mean ± SD	2.1 ± 2.0	4.0 ± 1.0	0.2 ± 0.2	**<0.001**
Wound length, millimeter, mean ± SD	16.8 ± 28.0	25.9 ± 36.4	11.2 ± 19.3	**<0.001**
Number of sutures, mean ± SD	8.3 ± 6.0	13.6 ± 6.5	5.9 ± 3.9	**<0.001**
Type of injury				
Globe rupture (*n*, %)	89 (45.2)	76 (79.2)	13 (12.9)	**<0.001**
Penetrating wound (*n*, %)	78 (39.6)	12 (12.5)	66 (65.3)	**<0.001**
Intraocular foreign body (*n*, %)	24 (12.2)	5 (5.2)	19 (18.8)	**0.004**
Perforating wound (*n*, %)	6 (3.0)	3 (3.1)	3 (3.0)	1.000
Zones of injury				
Zone 1 (Cornea and limbus) (*n*, %)	87 (50.6)	20 (28.2)	67 (66.3)	**<0.001**
Zone 2 (<5 mm from limbus) (*n*, %)	42 (24.4)	15 (21.1)	27 (26.7)	0.472
Zone 3 (>5 mm from limbus) (*n*, %)	43 (25)	36 (50.7)	7 (6.9)	**<0.001**
Wounds with corneal injury	137 (69.5)	46 (47.9)	91 (90.9)	**<0.001**
Central corneal (*n*, %)	21 (15.3)	4 (8.7)	17 (18.7)	0.141
Paracentral corneal (*n*, %)	35 (25.5)	2 (4.3)	33 (36.3)	**<0.001**
Peripheral corneal (*n*, %)	42 (30.7)	19 (41.3)	23 (25.3)	0.077
Total corneal (*n*, %)	39 (28.5)	21 (45.7)	18 (19.8)	**0.002**
Siedel + (*n*, %)	92 (56.1)	43 (62.3)	49 (51.6)	0.203
Uveal exposure (*n*, %)	120 (64.9)	74 (88.1)	46 (45.5)	**<0.001**
Vitreous exposure (*n*, %)	51 (29.8)	36 (50.7)	15 (15.0)	**<0.001**
Athalamia (*n*, %)	68 (40.0)	51 (71.8)	17 (17.2)	**<0.001**
Hyphema (*n*, %)	94 (52.5)	65 (82.3)	29 (29.0)	**<0.001**
Anterior chamber fibrin (*n*, %)	51 (34.0)	23 (45.1)	28 (28.3)	**0.046**
Hypopyon (*n*, %)	7 (4.6)	0 (0.0)	7 (7.0)	0.096
Traumatic cataract (*n*, %)	70 (53.4)	19 (55.9)	51 (52.6)	0.842
Anterior capsule rupture (*n*, %)	42 (35.9)	9 (37.5)	33 (35.5)	1.000
Initial retinal detachment (*n*, %)	6 (8.5)	1 (9.1)	5 (8.3)	1.000

SVI, Severe visual impairment; NSVI, Non-SVI; OGI, Open globe injury; SD, standard deviation.
Bold means p < 0.05. Percentages at each parameter are relative to the number of patients with available data.

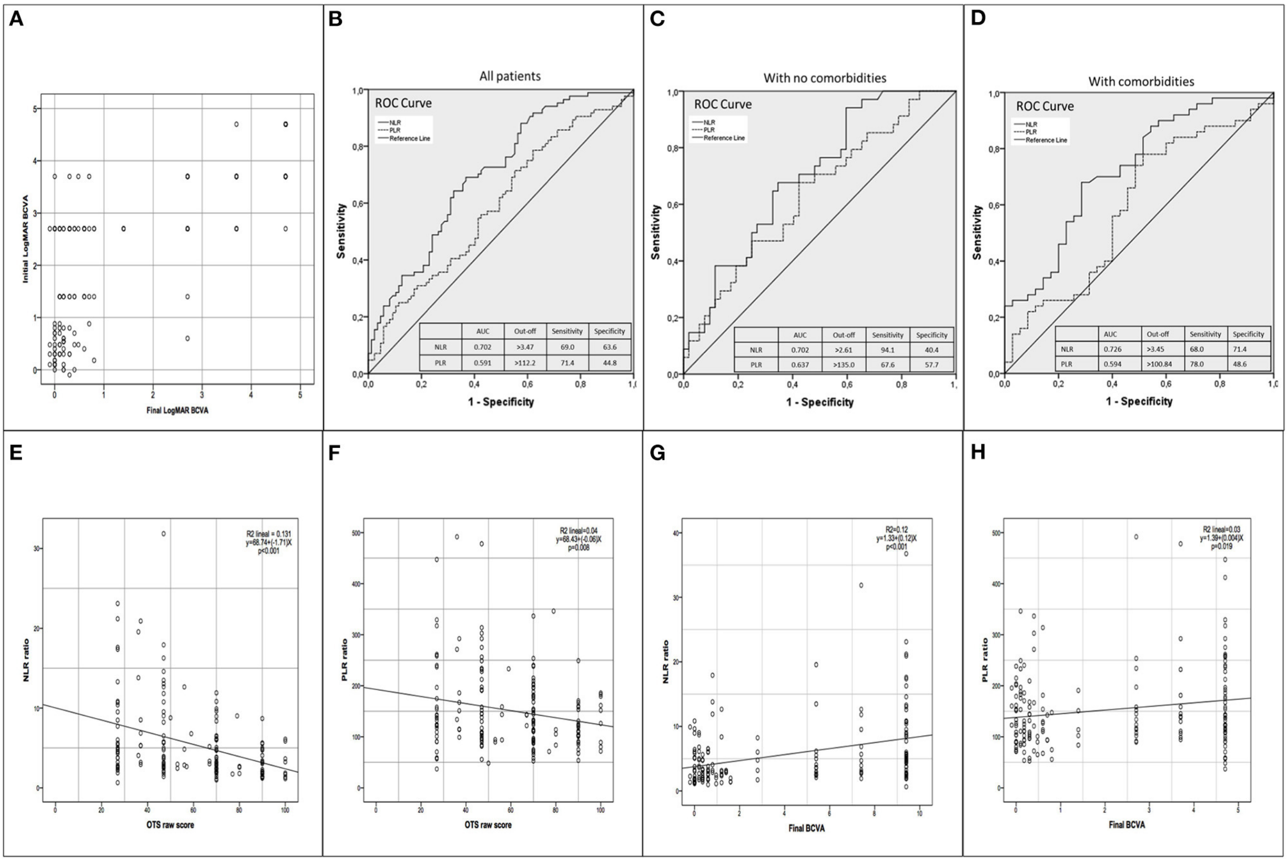

FIGURE 1 | (A) Scatterplot of the initial LogMAR best corrected visual acuity (BCVA) with the final LogMAR BCVA. Patients with better initial BCVA were more likely to have better final BCVA. The majority that ended with severe visual impairment (SVI) had poor initial BCVA (LogMAR >2.00 equivalent to count fingers or worst). Only 2 patients with initial BCVA better than count fingers ended with SVI. **(B)** Receiver Operating Characteristics (ROC) curve analysis for discrimination between patients with SVI and Non-SVI (NSVI) in all patients. **(C)** ROC curve analysis for discrimination between patients with SVI and NSVI only in patients with no comorbidities. **(D)** ROC curve analysis for discrimination between patients with SVI and NSVI only in patients with comorbidities. **(E)** Scatterplot and linear regression of neutrophil to lymphocyte ratio (NLR) with the ocular trauma score (OTS) raw points. **(F)** Scatterplot and linear regression of platelet to lymphocyte ratio (PLR) with the OTS raw points. **(G)** Scatterplot and linear regression of NLR with the final BCVA. **(H)** Scatterplot and linear regression of PLR with the final BCVA.

Whereas, those presenting with intraocular foreign body, zone 1 injury, paracentral corneal injury, or hypopyon had significantly lower NLR and PLR, and patients with penetrating wounds had significantly lower NLR (**Table 4**). When analyzing only patients without comorbidities, the same result was observed except for total corneal injury. Likewise, when analyzing patients with comorbidities, the same was found, except for globe rupture, intraocular foreign body, paracentral and total corneal injury, vitreous exposure, and hypopyon (**Table 4**).

The correlations of NLR and PLR ratios with continuous variables are shown in **Table 4**. NLR and PLR had a significant negative correlation with raw OTS and accident-blood sample interval, a significant positive correlation with initial LogMAR BCVA, and the number of sutures. NLR had a significant positive correlation with final LogMAR BCVA and wound length. In general, NLR showed stronger and more consistent correlations than PLR. NLR and PLR had stronger correlations in patients without comorbidities. PLR showed no significant differences in patients with comorbidities (**Table 5**). The univariate logistic regression analysis found many variables had an increased risk for SVI. A detailed description is shown in **Table 5**, those with OR > 5 were polytrauma (OR = 5.80), trauma with fist/kick (OR = 7.35), blunt objects (OR = 12.07), globe rupture (OR = 25.72), zone 3 injury (OR = 13.81), uveal exposure (OR = 8.84), vitreous exposure (OR = 5.83), hyphema (OR = 11.37), and athalamia (OR = 12.30). Also, the risk to end with SVI showed a 4-fold increase when NLR $\geq$ 3.47 (OR = 3.90) and a 2-fold increase when PLR $\geq$ 112.2 (OR = 2.03) (**Table 6**). However, when included in the multivariate analysis only athalamia [OR = 3.75, (1.04–13.45), $p = 0.042$], hyphema [OR = 4.92 (1.38–17.45), $p = 0.014$] and lower OTS [OR = 1.09 (1.04–1.14), $p < 0.0001$] retained its statistical significance as risk factor for SVI.

The ROC analysis of NLR and PLR for SVI and NSVI is shown in **Figures 1B–D**. In all patients, the area under the ROC (AUROC) value for NLR and PLR that distinguish between SVI and NSVI was 0.702 (CI 0.624–0.779, $p < 0.001$) and 0.591 (CI 0.506–0.676, $p = 0.040$) respectively. The best cut-off value for NLR was 3.47 (sensitivity of 69.0% and a specificity of 63.6%) and

TABLE 3 | Blood test parameters in SVI and NSVI patients with and without comorbidities.

Parameter (Mean ± SD)	All patients (n = 172)			Without comorbidities (n = 87)			With comorbidities (n = 85)		
	SVI (n = 84)	NSVI (n = 88)	P=	SVI (n = 34)	NSVI (n = 53)	P=	SVI (n = 50)	NSVI (n = 35)	P=
Accident-blood sample interval (hours)	44.4 ± 76	49.2 ± 92	0.731	57.0 ± 100	39.1 ± 55	0.363	33.1 ± 42	64.8 ± 131	0.171
Hemoglobin (g/dL)	15.0 ± 1.8	15.3 ± 1.2	0.177	15.1 ± 1.8	15.3 ± 1.3	0.408	14.9 ± 1.8	15.2 ± 0.9	0.309
Hematocrit (%)	45.0 ± 5.0	45.9 ± 3.4	0.136	45.1 ± 4.4	46.2 ± 3.8	0.243	44.9 ± 5.5	45.6 ± 2.8	0.485
Leucocytes (K/uL)	11.7 ± 4.0	9.4 ± 3.0	**<0.001**	11.5 ± 3.6	9.3 ± 2.7	**0.001**	11.9 ± 4.2	9.6 ± 3.3	**0.002**
Neutrophils (K/uL)	9.2 ± 4.1	6.7 ± 3.0	**<0.001**	9.2 ± 3.9	6.7 ± 2.9	**0.002**	9.2 ± 4.3	6.6 ± 3.1	**0.001**
Lymphocytes (K/uL)	1.7 ± 0.9	2.1 ± 0.9	**0.014**	1.5 ± 0.5	1.9 ± 0.8	**0.006**	1.8 ± 1.0	2.3 ± 0.9	**0.011**
Platelets (K/uL)	249.0 ± 96	244.7 ± 54	0.709	249.7 ± 61	241.4 ± 48	0.495	249 ± 115	249.8 ± 62	0.954
NLR	7.4 ± 6.6	4.0 ± 3.2	**<0.001**	7.7 ± 6.6	4.4 ± 3.5	**0.001**	7.2 ± 6.7	3.5 ± 2.6	**<0.001**
PLR	167.2 ± 92	139.0 ± 64	**0.021**	189 ± 100	146.0 ± 63	**0.018**	152.7 ± 85	128.5 ± 65	0.160
MXD	0.8 ± 0.4	0.8 ± 0.3	0.304	0.7 ± 0.3	0.7 ± 0.3	0.830	0.9 ± 0.4	0.8 ± 0.4	0.508
Glucose (mg/dL)	124.8 ± 50	106.5 ± 35	**<0.001**	115.1 ± 36	99.0 ± 15	0.070	130.2 ± 56	117.4 ± 51	**0.019**

SVI, Severe visual impairment; NSVI, Non-SVI; OGI, Open globe injury; SD, Standard deviation; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio. Bold means $p < 0.05$.

for PLR 112.2 (sensitivity of 71.4% and a specificity of 44.8%). The positive predictive value (PPV) and the negative predictive value (NPV) for NLR were 64.4 and 68.3%, respectively. For PLR, the PPV and NPV were 55.6 and 61.9%, respectively. Furthermore, the NLR $\geq$ 3.47 and PLR $\geq$ 112.2 together had a sensitivity of 57.1%, specificity of 65.9%, PPV of 61.5%, and NPV of 61.7%, for distinguishing between SVI and NSVI. The relationship between NLR and PLR with OTS is shown in **Figures 1E,F**. Patients with higher pre-operative NLR or PLR were more likely to have lower OTS. The relationship between NLR and PLR with final LogMAR BCVA is shown in **Figures 1G,H**. Patients with higher pre-operative NLR or PLR were more likely to have greater LogMAR BCVA; a greater LogMAR value means worse vision.

DISCUSSION

Almost half of the patients ended with SVI after OGI repair. To the best of our knowledge, this study shows for the first time that patients with repaired OGI that ended with SVI had increased pre-operative NLR and PLR levels compared to patients that achieved a better vision. NLR showed a positive correlation with final LogMAR BCVA in all patients with or without comorbidities, but this was stronger in patients without comorbidities, which means that the higher the pre-operative NLR, the worse the final visual acuity. PLR showed a positive correlation with final LogMAR BCVA only in patients without comorbidities. The correlation of PLR in patients with comorbidities was absent. NLR and PLR were considered risk factors for SVI after OGI repair in a univariate analysis. Furthermore, a known prognostic score for poor final BCVA after OGI, the OTS, showed a negative correlation with NLR and PLR, which means that higher NLR and PLR were associated with lower OTS and poor final BVCA in this study. Even more, ROC analysis found that NLR $\geq$ 3.47 and PLR $\geq$ 112.2 were the best cut-off values to predict SVI after OGI repair. The risk to develop SVI showed a 4-fold increase when NLR $\geq$ 3.47 and a 2-fold increase when PLR $\geq$ 112.2 in univariate analysis. However, on multivariate analysis, only athalamia, hyphema, uveal exposure, and lower OTS remained as risk factors for SVI after OGI repair. In addition, we evaluated demographics characteristics, mechanism of injury, OTS, initial BCVA, wound characteristics, and blood test parameters to look for associations with high NLR, high PLR, and risk factors for SVI after OGI repair.

In OGI the natural ocular barriers have been trespassed, and appropriate control of immune tolerance and regulation may not be achieved, resulting in increased local and systemic inflammation, and damage. However, it is not clear if OGI has a systemic inflammatory effect. The NLR and the PLR are non-specific parameters for systemic inflammation. This is the first study to describe its relationship with OGI and final visual acuity. We believe that traumatic ocular damage can lead to a systemic inflammatory response, which can be detected by NLR and PLR.

Higher LEU, NEU and glucose, and lower LYM counts were all associated with SVI in univariate analysis. The fact that the NLR, PLR, and NEU levels were elevated and LYM levels were reduced indicating a systemic inflammation with poor regulation (15). In this study, OGI presenting with globe rupture, zone 3 injury, uveal exposure, vitreous exposure, hyphema or retinal detachment, had higher NLR and PLR. These clinical characteristics were associated with increased damage of globe structure and worse visual outcome, in previous studies (4, 5, 7, 8).

As previously mentioned, a proportional correlation between NLR and PLR with initial and final LogMAR visual acuity was observed. That means that the higher the NLR and PLR, the worse the initial and final BCVA. However, the majority of these were weak correlations ($r < 0.4$), the stronger and more significant correlations were observed when analyzing the NLR or the group without comorbidities where moderate correlations (r = 4–6) of NLR with OTS, NLR with initial BCVA, and PLR with OTS were found. High pre-operative NLR or PLR could

TABLE 4 | Clinical characteristics of OGI and its relationship with NLR and PLR.

Characteristics		All patients (*n* = 172)			Without comorbidities (*n* = 87)			With comorbidities (*n* = 85)		
		n*	**NLR mean ± SD**	**PLR mean ± SD**	***n****	**NLR mean ± SD**	**PLR mean ± SD**	***n****	**NLR mean ± SD**	**PLR mean ± SD**
Globe rupture	No	91	4.4 ± 4.4	139 ± 64	51	3.7 ± 2.4	136 ± 53	40	5.2 ± 6.0	142 ± 77
	Yes	81	7.2 ± 6.0	169 ± 93	36	8.5 ± 6.5	202 ± 101	45	6.1 ± 5.3	143 ± 79
	P=		**<0.001**	**0.015**		**<0.001**	**<0.001**		0.442	0.959
Penetrating wound	No	107	6.6 ± 5.6	159 ± 88	52	7.0 ± 6.1	176 ± 94	55	6.1 ± 5.0	143 ± 80
	Yes	65	4.3 ± 4.9	144 ± 66	35	3.7 ± 2.4	145 ± 57	30	5.0 ± 6.7	142 ± 76
	P=		**<0.001**	0.205		**0.002**	0.061		**0.032**	0.976
Intraocular foreign body	No	149	5.8 ± 5.7	157 ± 82	71	6.1 ± 5.6	174 ± 86	78	5.7 ± 5.8	142 ± 76
	Yes	23	4.3 ± 2.7	127 ± 63	16	3.8 ± 2.5	118 ± 36	7	5.5 ± 3.1	146 ± 103
	P=		**0.038**	**0.047**		**0.014**	**0.005**		0.939	0.904
Zone 1 injury	No	74	7.2 ± 6.2	183 ± 93	41	7.8 ± 6.4	200 ± 95	33	6.4 ± 5.9	160 ± 87
	Yes	75	3.7 ± 2.5	124 ± 49	44	3.7 ± 2.6	126 ± 44	31	3.7 ± 2.3	121 ± 56
	P=		**<0.001**	**<0.001**		**<0.001**	**<0.001**		**0.018**	**0.039**
Zone 2 injury	No	113	5.5 ± 5.0	151 ± 82	67	5.7 ± 5.5	157 ± 85	46	5.4 ± 4.5	142 ± 78
	Yes	36	5.0 ± 4.7	161 ± 73	18	5.6 ± 4.2	182 ± 70	18	4.4 ± 5.2	141 ± 72
	P=		0.552	0.481		0.916	0.220		0.490	0.953
Zone 3 injury	No	111	4.1 ± 3.4	136 ± 60	62	4.2 ± 3.2	142 ± 58	49	4.0 ± 3.6	129 ± 63
	Yes	38	9.2 ± 6.8	203 ± 106	23	9.5 ± 7.4	216 ± 110	15	8.8 ± 5.9	184 ± 100
	P=		**<0.001**	**<0.001**		**<0.001**	**0.001**		**0.001**	**0.023**
Central corneal injury	No	104	4.4 ± 3.1	139 ± 56	56	4.3 ± 2.9	137 ± 50	48	4.5 ± 3.2	142 ± 64
	Yes	16	4.4 ± 3.1	123 ± 63	9	4.4 ± 3.2	147 ± 70	7	4.3 ± 3.1	95 ± 44
	P=		0.947	0.358		0.947	0.708		0.873	0.071
Paracentral corneal injury	No	90	4.8 ± 3.2	144 ± 59	44	4.9 ± 3.1	149 ± 56	46	4.8 ± 3.3	140 ± 62
	Yes	30	3.1 ± 2.2	114 ± 45	21	3.2 ± 2.1	114 ± 33	9	3.0 ± 2.6	113 ± 69
	P=		**0.002**	**0.005**		**0.013**	**0.003**		**0.032**	0.254
Peripheral corneal injury	No	81	4.4 ± 3.2	133 ± 56	49	4.3 ± 3.0	137 ± 52	32	4.7 ± 3.6	126 ± 61
	Yes	39	4.3 ± 2.9	146 ± 60	16	4.5 ± 2.9	141 ± 52	23	4.2 ± 2.9	149 ± 65
	P=		0.860	0.252		0.789	0.767		0.601	0.195
Total corneal injury	No	85	3.9 ± 2.7	130 ± 57	46	3.9 ± 2.7	130 ± 49	39	4.0 ± 2.9	131 ± 65
	Yes	35	5.6 ± 3.6	152 ± 56	19	5.4 ± 3.3	157 ± 55	16	5.8 ± 3.9	147 ± 58
	P=		**0.015**	0.053		0.054	0.051		0.053	0.403
Positive Seidel test	No	59	5.0 ± 4.3	147 ± 70	36	4.5 ± 3.2	147 ± 57	23	5.8 ± 5.7	146 ± 88
	Yes	85	5.6 ± 5.2	156 ± 88	43	6.5 ± 6.4	175 ± 103	42	4.8 ± 3.5	138 ± 66
	P=		0.408	0.476		0.077	0.142		0.458	0.690
Uveal exposure	No	57	3.8 ± 2.9	127 ± 56	36	3.9 ± 2.5	137 ± 53	21	3.7 ± 3.5	110 ± 58
	Yes	104	6.6 ± 6.2	166 ± 84	50	7.1 ± 6.2	182 ± 94	54	6.2 ± 6.2	151 ± 72
	P=		**<0.001**	**0.001**		**0.009**	**0.025**		**0.006**	**0.004**
Vitreous exposureo	No	100	4.5 ± 4.0	136 ± 60	55	4.4 ± 3.8	141 ± 59	45	4.6 ± 4.4	131 ± 60
	Yes	50	7.4 ± 6.0	185 ± 95	28	8.6 ± 6.7	210 ± 104	22	5.8 ± 4.7	152 ± 72
	P=		**<0.001**	**0.001**		**<0.001**	**0.001**		0.285	0.206
Athalamia	No	87	4.5 ± 3.4	145 ± 62	54	4.5 ± 3.4	146 ± 58	33	4.4 ±3.4	143 ± 68
	Yes	62	5.5 ± 5.1	151 ± 94	24	6.7 ± 6.7	184 ± 113	38	4.8 ± 3.7	131 ± 73
	P=		0.163	0.625		0.059	0.052		0.671	0.464
Hyphema	No	73	3.4 ± 2.3	130 ± 58	43	3.5 ± 2.3	132 ± 51	30	3.3 ± 2.3	128 ± 68
	Yes	83	6.9 ± 5.7	165 ± 88	39	7.2 ± 6.3	186 ± 95	44	6.6 ± 5.3	146 ± 77
	P=		**<0.001**	**0.004**		**<0.001**	**0.001**		**<0.001**	0.307
Anterior chamber fibrin	No	91	4.8 ± 4.8	143 ± 80	53	5.2 ± 5.4	152 ± 89	38	4.3 ± 3.7	130 ± 65
	Yes	41	4.9 ± 2.8	154 ± 50	20	4.7 ± 2.8	155 ± 45	21	5.1 ± 2.9	152 ± 56
	P=		0.066	0.345		0.601	0.841		**0.029**	0.192

(Continued)

TABLE 4 | Continued

Characteristics		All patients (n = 172)			Without comorbidities (n = 87)			With comorbidities (n = 85)		
		n*	NLR mean ± SD	PLR mean ± SD	n*	NLR mean ± SD	PLR mean ± SD	n*	NLR mean ± SD	PLR mean ± SD
Hypopyon	No	128	4.9 ± 4.3	148 ± 72	69	5.2 ± 4.9	157 ± 80	59	4.6 ± 3.4	138 ± 62
	Yes	6	3.0 ± 0.6	108 ± 29	5	3.1 ± 0.7	112 ± 31	1	2.4	90
	P=		**<0.001**	**0.019**		**0.002**	**0.029**		0.537	0.444
Traumatic cataract	No	53	4.2 ± 2.9	138 ± 65	28	4.9 ± 3.4	152 ± 68	25	3.3 ± 2.0	122 ± 59
	Yes	61	4.3 ± 3.6	145 ± 70	39	4.3 ± 3.9	148 ± 75	22	4.2 ± 3.0	141 ± 62
	P=		0.858	0.539		0.483	0.813		0.211	0.283
Anterior capsule rupture	No	67	4.2 ± 3.2	147 ± 73	36	4.8 ± 3.9	158 ± 80	31	3.6 ± 2.1	134 ± 63
	Yes	34	4.2 ± 3.7	135 ± 59	23	4.1 ± 3.8	135 ± 58	11	4.4 ± 3.8	136 ± 63
	P=		0.952	0.403		0.514	0.207		0.414	0.911
Retinal detachment	No	52	3.5 ± 2.9	133 ± 57	34	4.1 ± 3.4	147 ± 62	18	2.4 ± 1.3	107 ± 38
	Yes	5	10.2 ± 6.8	286 ± 148	3	13.4 ± 6.4	332 ± 140	2	5.5 ± 5.0	218 ± 182
	P=		**0.015**	**0.018**		**0.004**	**0.006**		**0.028**	**0.017**

OG0, Open globe injury; SVI, Severe visual impairment; NSVI, Non-SVI; SD, Standard deviation; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio.
**Number of patients with available data.*
Bold means $p < 0.05$.

TABLE 5 | Spearman's correlation coefficient between NLR and PLR and the studied variables.

	All (n = 172)				Without comorbidities (n = 87)				With comorbidities (n = 85)			
	NLR		PLR		NLR		PLR		NLR		PLR	
	σ	P	σ	P	σ	P	σ	P	σ	P	σ	P
OTS, raw points	−0.389	**<0.001**	−0.166	**0.031**	−0.562	**<0.001**	−0.442	**<0.001**	−0.246	**0.026**	-0.009	0.936
Initial BCVA (LogMAR)	0.392	**<0.001**	0.157	**0.042**	0.477	**<0.001**	0.349	**0.001**	0.334	**0.002**	0.055	0.624
Final BCVA (LogMAR)	0.345	**<0.001**	0.123	0.108	0.383	**<0.001**	0.283	**0.008**	0.364	**0.001**	0.077	0.481
Wound length, (millimeter)	0.173	**0.046**	0.091	0.301	0.261	**0.025**	0.180	0.127	0.100	0.451	0.043	0.744
Number of sutures	0.379	**<0.001**	0.260	**0.004**	0.444	**<0.001**	0.390	**0.001**	0.361	**0.009**	0.193	0.169
Accident-blood sample interval	−0.392	**<0.001**	−0.286	**0.001**	−0.451	**<0.001**	−0.338	**0.003**	−0.334	**0.007**	-0.245	0.051

OTS, Ocular trauma score; OGI, Open globe injury; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; BCVA, Best corrected visual acuity.
Correlation analysis with Spearman's correlation coefficient.
Bold means $p < 0.05$.

be considered as an aid in the identification of patients with a higher risk for SVI before the OGI is repaired. This can be helpful to identify patients that might benefit from pre-operative counseling about their poor visual prognosis. In agreement with that, as the levels of NLR and PLR were increased, the raw OTS was reduced, indicating a worse OTS category and a worse prognosis for final visual acuity, as observed in **Figures 1E–H**. Furthermore, the risk to develop SVI showed a 4-fold increase when NLR $\geq$ 3.47, a 2-fold increase when PLR $\geq$ 112.2. The univariate logistic regression analysis demonstrates that NLR, and in a lesser manner the PLR are directly related to the severity of trauma and with the final visual prognosis after OGI repair. These findings also confirm the role of the OTS as a great prognostic tool in OGI (**Table 6**). However, the OTS oftentimes cannot be performed adequately because of missing information like ultrasound evaluation, retinal detachment, and RAPD. In these cases, the NLR and PLR have the advantage that can be used as a complementary index to assess visual prognosis when not all the variables required to perform the OTS are available. It can be performed easily before or after OGI repair because it only requires standard pre-operative blood tests.

A higher prevalence of initial BCVA 20/200 or worse was found in patients with final SVI. Two-thirds of patients with initial BCVA 20/200 or worse ended with SVI, on the contrary, only 2% of those with initial BCVA better than 20/200, ended with SVI (**Figure 1A**). Other parameters found to be associated with SVI were globe rupture, zone 3 injuries, longer wounds with a greater number of sutures, total corneal injury, uveal exposure, vitreous exposure, athalamia, hyphema, and anterior chamber fibrin. These clinical findings are similar to those found in other studies (43–46). Okamoto et al. recently described worse initial and final BCVA in ruptured globes in comparison with laceration and also found that greater wound length was significantly correlated with worse final BCVA (43). The results found in the present study correlate with previous studies that described the presence of hyphema, uveal and vitreous exposure at initial

TABLE 6 | Univariate logistic regression analysis for severe visual impairment.

Variable	*n* (%)	OR	C.I. 95%	*P*=
Gender, men	86 (89.6)	1.06	0.42–2.67	0.905
Age (mean ± SD) years	39.5 ± 15.4	1.021	1.00–1.04	**0.044**
Follow-up days (median, IQR)	30, 80	1.00	0.99–1.00	0.685
Systemic comorbidities				
Illegal substance abuse	12 (14.0)	3.73	1.16–12.04	**0.028**
Hypertension	10 (11.6)	3.06	0.92–10.14	0.067
Diabetes	5 (5.8)	1.93	0.45–8.34	0.376
Mechanism of injury				
Metallic object trauma	18 (18.8)	0.18	0.96–0.35	**<0.001**
Polytrauma	14 (14.6)	5.80	1.61–20.92	**0.007**
Fist/kick trauma	12 (12.5)	7.35	1.60–33.80	**0.010**
Blunt objects trauma	12 (12.5)	12.07	1.51–96.29	**0.019**
Explosives trauma	4 (4.2)	–	–	0.999
OTS raw points (mean ± SD)	41.5 ± 14.6	1.138	1.10–1.18	**<0.001**
Wound length, millimeters (mean ± SD)	25.9 ± 36.4	1.022	1.01–1.04	**0.007**
Number of sutures	13.6 ± 6.5	1.333	1.21–1.47	**<0.001**
Type and zones of injury				
Penetrating wound	12 (12.5)	0.76	0.36–0.16	**<0.001**
Globe rupture	76 (79.2)	25.72	11.99–55.15	**<0.001**
Zone 3 trauma (>5 mm from limbus)	36 (50.7)	13.81	5.62–33.89	**<0.001**
Peripheral corneal injury	19 (41.3)	2.08	0.98–4.42	0.057
Total corneal injury	21 (45.7)	3.41	1.57–7.40	**0.002**
Clinical characteristics of OGI				
Intraocular foreign body	5 (5.2)	0.24	0.85–0.66	**0.006**
Uveal exposure	74 (88.1)	8.84	4.10–19.06	**<0.001**
Vitreous exposure	36 (50.7)	5.83	2.83–11.96	**<0.001**
Hyphema	65 (82.3)	11.37	5.52–23.38	**<0.001**
Athalamia	51 (71.8)	12.30	5.89–25.65	**<0.001**
Anterior chamber fibrin	23 (45.1)	2.08	1.03–4.21	**0.041**
Initial retinal detachment	1 (9.1)	1.10	0.12–10.43	0.934
Blood test parameters				
Neutrophil to lymphocyte ratio (NLR) ≥ 3.47	58 (64.4)	3.90	2.07–7.36	**<0.001**
Platelet to lymphocyte ratio (PLR) ≥ 112.2	60 (55.6)	2.03	1.08–3.83	**0.029**
Absolute leucocyte count (mean ± SD)	11.7 ± 3.9	1.23	1.11–1.37	**<0.001**
Absolute neutrophil count (mean ± SD)	9.2 ± 4.1	1.24	1.12–1.37	**<0.001**
Absolute lymphocyte count (mean ± SD)	1.7 ± 0.9	0.59	0.39–0.86	**0.008**
Glucose (mean ± SD)	124.8 ± 50	1.01	1.00–1.02	**0.027**

OTS, Ocular trauma score; BCVA, best corrected visual acuity; IQR, Interquartile range; SVI, Severe visual impairment; NSVI, Non-SVI; OGI, Open globe injury.
Bold means $p < 0.05$.
Percentages are relative to the number of patients with available data.

presentation to be associated with poor VA and ocular prognosis (44–46). The initial BCVA was significantly worse in patients with SVI, which is in agreement with previous publications that consider it as a risk factor for poor final visual outcome (43–50). Older age was also associated with poor final VA and is in agreement with Agrawal et al. that found worse final visual outcome with increasing age (51). This could be due to reduced wound healing potential, decreased corneal and scleral collagen crimp (52), increase in non-enzymatic crosslinking, decrease in hydration stability, and glycosaminoglycans, and more overall globe stiffness (53). The mechanism of injury more frequently observed in patients with SVI were polytrauma, fist/kick, blunt object, and explosives. They all share in common a high probability of producing a contuse blunt blow trauma instead of a puncture or cut and consequently a globe rupture injury.

On the other hand, more than half of the patients with NSVI had an OGI that was generated with a metallic object that resulted in a penetrating wound that involved zone 1 or paracentral cornea. Penetrating, metallic object trauma had reduced risk for SVI in univariate analysis. Penetrating wounds, zone 1 and paracentral corneal injury had significantly lower NLR. The patients with NSVI had longer median follow-up, this might be because they had better visual acuity and required closer and longer follow-up to take care of the eye and visual rehabilitation. On the contrary, those patients with SVI showed lower median follow-up probably because they needed fewer follow-up examinations and only palliative care of the eye. The NLR and PLR showed a weak significant negative correlation with the accident-blood sample interval, which means that the NLR tends to decrease as more time passes between the accident and the collection of blood samples. In cases with longer accident-blood sample intervals, the sensibility of NLR or PLR as a predictor of poor final visual acuity might be reduced. However, this correlation was weak, and since the hypothesis of this study is that higher levels of NLR or PLR area are associated with SVI, this might not affect the specificity to detect those at high risk for SVI.

The strengths of this study are that it is the first to correlate the NLR and the PLR in acute ocular trauma. In addition, this study included all consecutive patients who arrived with an OGI. Analyzing patients separately with and without comorbidities addressed the bias that systemic comorbidities can have in the interpretation of the NLR and PLR. These parameters are already present in the report of the CBC and could be used in patients with OGI to aid in the assessment of the risk of ending with SVI.

We acknowledge several limitations in our study. Firstly that simultaneous trauma in the orbit, face, or other parts of the body could have influenced the laboratory findings and were not addressed in this study. We believe that the mechanisms of trauma and characteristics of the injuries could affect the inflammation parameters if the orbit, facial or other parts of the body were traumatized and consequently releasing higher levels of glucocorticoids, inflammatory, vasoactive, and chemotactic substances, capable of changing the NLR and the PLR in this population. In addition, the associations identified between laboratory findings and the OTS and other ocular parameters that mostly indicate the magnitude of the eye damage would not be expected to be present if the laboratory findings were caused by trauma in other parts of the body. However, the aim of this study was to use the NLR and the PLR in all cases. Given the conditions of consecutive enrollment of patients, all types of mechanisms for OGIs that were surgically repaired were included, only the minority were polytraumatized and those treated with primary evisceration or enucleation were excluded. A similar limitation lies in the heterogeneity of the patients in this case series of consecutive patients since we included all types of OGIs such as globe rupture, IOFB, penetrating and perforating wounds; and the type of OGI was not evenly distributed between SVI and NSVI groups. Further studies should evaluate the impact of NLR and PLR in predicting final SVI by type and zone of injury. Secondly, C-reactive protein (CRP) and globular sedimentation rate (GSR) tests were not analyzed, which are the most commonly used parameters of systemic inflammation. The reason for this is that these studies are not done routinely as part of the pre-operative evaluations of eye wounds; however, it is worthwhile to carry further studies with more systemic inflammatory markers to confirm our findings. Thirdly, in the univariate and multivariate logistic analysis, initial BCVA was not included, the reason for this is that our population included very heterogeneous initial visual acuities to use this regression analysis.

In conclusion, this study reports for the first time that NLR and PLR were correlated with visual outcomes after OGI repair. Higher NLR and PLR were correlated with low OTS and SVI after OGI repair. NLR $\geq$ 3.47 or PLR $\geq$ 112.2 increases the risk for SVI 4 and 2 folds, respectively. NLR and PLR could be used as prognostic biomarkers for SVI after OGI repair. These findings pave the pad to further investigate the role of NLR and PLR as a prognostic tool for final visual acuity after surgical repair of OGI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética en Investigación, Hospital Universitario Dr. José E. González y Facultad de Medicina, Universidad Autónoma de Nuevo León, Avenida Francisco I. Madero Avenida Jose Eleuterio Gonzalez Gonzalitos Colonia Mitras Centro, C.P. 64460, monterrey, Nuevo León, México. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KM-N: conceptualization, patient evaluation, formal analysis, investigation, methodology, project administration, supervision, roles/writing—original draft, writing—review and editing, data curation, supervision, and validation. AT-H: conceptualization, data curation, patient evaluation, formal analysis, investigation, methodology, roles/writing—original draft, writing—review and editing, data curation, supervision, and validation. JM-N: conceptualization, patient evaluation, formal analysis, investigation, methodology, supervision, validation, visualization, and review and editing. BV-S: formal analysis, investigation, software, roles/writing—original draft, and writing—review and editing. VM-P: investigation, data curation, formal analysis, patient evaluation, roles/writing—original draft, and writing—review and editing. DG-V: data curation, patient evaluation, and investigation. DR-M and AS-S: data curation. GV-M and JG-C: patient evaluation and review and editing. RE-O: supervision, validation, and review and editing. SG-L: supervision, validation, resources, and review and editing. JM-H: project administration, resources, investigation, methodology, supervision, validation, and review and editing. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Visual Loss Caused by Central Retinal Artery Occlusion After Bee Sting: A Case Report

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A bee sting can lead to an extremely rare case of visual loss caused by central retinal artery occlusion (CRAO). In this study, we report a 66-year-old healthy woman who was referred to our Eye Center because of visual loss, which had occurred after bee sting 2 days earlier. The visual acuity was no light perception (NLP). Examination revealed left eyelid edema, conjunctiva congestion, a 6-mm fixed pupil, scattered retinal hemorrhage, and white-appearing ischemic retina with one small area of the normal-appearing retina temporal to the optic disk. Fundus fluorescein angiography revealed CRAO with one cilioretinal artery sparing. Her systemic workup revealed hypersensitivity, hypercoagulable state, myocardial damage, and hepatic damage. After topical and systemic treatments, the visual acuity was still NLP with improved systemic workup. In brief, CRAO may occur after bee sting, and visual acuity should be monitored for early diagnosis.

Keywords: bee sting, central retinal artery occlusion, thrombosis, venom, case report

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INTRODUCTION

Sudden visual loss is an ophthalmologic emergency. Central retinal artery occlusion (CRAO), one of the common etiological factors, can lead to sudden visual loss (1, 2). Systemic conditions play an important role in the development of CRAO (3). Bee sting may lead to local and systemic reactions due to sensitization of the patient. A symptomatic spectrum of a bee sting ranges from mild local reaction to death (4). Inflammation caused by bee stings, such as keratopathy and endophthalmitis, has been well-reported (5–8). Recently, Pujari et al. described a patient with CRAO after bee sting; this patient was treated with systemic steroids and his systemic workup was normal at 1 week following the incidence, the exact pathogenesis of CRAO in this case is not clear (9). In this study, we present another case of visual loss caused by CRAO after bee sting, which was accompanied with hypersensitivity, hypercoagulable state, myocardial damage, and hepatic damage.

CASE REPORT

A 66-year-old healthy woman was in a coma for 2 h after a bumble bee had stung the left side of her face. When she woke up, she immediately reported obvious eyelid edema and blurred vision in left eye. In addition, some systemic symptoms, such as dizziness, headache, nausea and vomiting, and multiple diarrhea were also reported. The patient was treated with methylprednisolone, compound glycyrrhizin injection, and ceftriaxone sodium at a local hospital.

FIGURE 1 | The findings of anterior segment image, fundus image, and fundus fluorescein angiography. Anterior segment photograph shows conjunctiva congestion and a 6-mm fixed pupil **(A)**. Fundus image reveals scattered retinal hemorrhage and retinal whiting with one small area of the normal-appearing retina temporal to the optic disk **(B)**. Fundus fluorescein angiography 40 s after injection of the dye showed rapid filling of one cilioretinal vessel and delayed filling of the central retinal artery **(C)**.

Forty-eight hours later, visual loss in left eye was observed by an ophthalmologist. She was referred to our Eye Center. On presentation, the visual acuity was 20/32 in right eye and no light perception (NLP) in left eye. The intraocular pressure was 16 mmHg in right eye and 19.5 mmHg in left eye. Examination of left eye revealed eyelid edema, conjunctiva congestion, a 6-mm fixed pupil (**Figure 1A**), scattered retinal hemorrhage, and white-appearing ischemic retina with one small area of the normal-appearing retina temporal to the optic disk (**Figure 1B**). The CRAO with one cilioretinal artery sparing was identified by fundus fluorescein angiography (**Figure 1C**). Except for mild cortical cataract, the ocular examination was unremarkable in right eye.

She was admitted to the emergency department of our hospital and systemic workup was performed. Increased total immunoglobulin E 910 IU/ml (reference 0–100 IU/ml) indicated hypersensitivity. Decreased activated partial thromboplastin time 25 s (reference 30–45 s) and increased D-dimer 590 ug/L (reference 0–500 μg/L) indicated a hypercoagulable state. Increased creatine kinase 3,340 U/L (reference 0–145 U/L) and creatine kinase-MB 68 U/L (reference 0–24 U/L), decreased left ventricular diastolic function by cardiac Doppler ultrasound and T wave change in the left anterior wall by ECG were observed, which revealed myocardial damage. Increased alanine aminotransferase 97 U/L (reference 0–34 U/L) and aspartate aminotransferase 200 U/L (reference 0–34 U/L) indicated hepatic damage. Increased lactate dehydrogenase 507 U/L (reference 140–271 U/L) may be associated with the myocardial damage and hepatic damage. Other systemic workups including blood test (routine, C reactive protein, erythrocyte sedimentation rate, electrolyte routine, procalcitonin, B-type natriuretic peptide, immunoglobulin, complement, and renal function), color Doppler ultrasound (bilateral thyroid and cervical lymph nodes, liver, gallbladder, pancreas, spleen, bilateral kidney, ureter, and bladder), cranial MRI, and high-resolution CT (orbital and chest) were within normal limits. The patient received treatments including dilation of the central retinal artery (sublingual isosorbide nitrite), reduction of intraocular pressure (intravenous mannitol), topical eye drops (Tobramycin and Dexamethasone eye drops, Pranoprofen eye drops, and Olopatadine eye drops), and systemic treatment (methylprednisolone, compound glycyrrhizin, ceftriaxone sodium, and glutathione). After 5 days of treatment, the visual acuity was still NLP in left eye with mildly decreased activated partial thromboplastin time 28.8 s (reference 30–45 s) and mildly increased D-dimer 510 ug/L (reference 0–500 ug/L), normal creatine kinase 37 U/L (reference 0–145 U/L) and creatine inase-MB 20 U/L (reference 0–24 U/L), normal aspartate aminotransferase 26 U/L (reference 0–34 U/L), mildly increased alanine aminotransferase 46 U/L (reference 0–34 U/L), and lactate dehydrogenase 351 U/L (reference 140–271 U/L).

DISCUSSIONS

Bee stings are common environmental injuries, generally resulting in some limited discomfort and swelling at the site of the sting with minimal residual effect. Occasionally they cause severe adverse reactions such as anaphylaxis, cardiovascular collapse, and death (10). Bee venom contains a complex mixture of biogenic amines, enzymes, and polypeptide toxins (11). A sudden release of highly concentrated biogenic amines, such as histamine in the venom, produces vasodilatation and increase in capillary permeability and an immunologic reaction to high molecular weight enzymes in the venom-induced type 1 hypersensitivity response mediated by immunoglobulin E (12–14). The patient was in coma for 2 h after bumble bee sting. When she woke up, left eyelid edema and blurred vision of the left eye were reported, following dizziness, headache, nausea and vomiting, multiple diarrhea, which indicated that the bee venom caused serious systemic symptoms. Ansotegui et al. suggest that immunoglobulin E testing is the basis for the diagnosis and evaluation of suspected allergic diseases (15); significantly increased total immunoglobulin E was observed in this patient, which provided evidence for the allergic reaction in this patient. As bee venom activates some inflammatory and vascular events resulting in occlusion in vessels or diseases in the electrical system of the heart, it may cause myocardial infarction or atrial fibrillation (16). Decreased activated partial thromboplastin time and increased D-dimer, which indicated hypercoagulable state, may attribute to the myocardial damage that was revealed by increased creatine kinase and creatine kinase-MB, ECG, and cardiac Doppler ultrasound.

Local reactions, such as pain, wheal, flare, edema, and swelling, are common and generally self-limiting. The lesions of the eye after bee stings may be caused by toxic and allergic reactions (17). Ocular features after bee sting include conjunctivitis, corneal infiltrates, cataract formation, acute iritis with keratic precipitates, hyphema, lens subluxation, and rarely retinal damage (12–14, 18). In this patient, blurred vision and visual loss in left eye were reported 2 and 48 h, respectively, after being stung, which were consistent with the fundus fluorescein angiography examination showing CRAO with one cilioretinal artery sparing. Recently, one study reported the first case of CRAO following multiple bee stings (9). The exact pathogenesis of CRAO in this case is not clear, because the systemic workup including blood investigations, carotid Doppler, and echocardiography was within normal range at 1 week following the incidence, which might be attributed to steroid-induced resolution of allergic and toxic reactions. A transient vasospasm of the central retinal artery *via* the Kounis reaction following bee stings appears as the most likely mechanism of CRAO. A transient hypercoagulable state caused by large-dose envenomation is another possible mechanism. Thrombotic events either due to direct toxin effect or toxic vasculitis may also be responsible for this vascular complication (8). In our case, hypersensitivity, hypercoagulable state, myocardial damage, and hepatic damage were observed 2 days after bee sting. After 5 days of systemic treatment, her systemic workup was within normal range 1 week after the bee sting.

CONCLUSIONS

In conclusion, although the exact pathological mechanism of bee-sting-related CRAO is unclear, there is a possibility that the thrombosis, which was induced by a component of the venom at the early stage of bee sting, blocks the central retinal artery. A further study with early systemic workup may explain the pathogenesis of CRAO after bee sting. This case emphasizes that CRAO may occur after the bee sting, and clinicians should pay attention to the visual acuity in the event of eyelid swelling.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZS: conception, design, image interpretation, and manuscript preparation. ZH: data collection and analysis and manuscript preparation. LW: systemic examination collection and interpretation. YW: image interpretation and diagnosis. XF: patient treatment and data collection. PY: conception and design. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Vitrectomy vs. Spontaneous Closure for Traumatic Macular Hole: A Systematic Review and Meta-Analysis

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Objective: This systematic review and meta-analysis aimed to determine the traumatic macular hole (TMH) closure rate and visual acuity (VA) improvement rate by comparing two treatment methods for TMH: vitrectomy and observation for spontaneous closure.

Methods: PubMed, Cochrane, Web of Science Library, Embase, CNKI, Wanfang, VIP, and Sino Med were systematically searched from their inception to June 10, 2021. Studies in the surgery group ($n = 32$) and studies in the observation group ($n = 12$) were meta-analyzed. The primary outcomes were the TMH closure and VA improvement rates in the surgery and observation groups. The secondary outcomes were best-corrected visual acuity (BCVA) improvement in the surgery group. Stata software (version 15.1) was used for the analyses.

Results: Thirty-six studies that included 1,009 eyes were selected for this meta-analysis, among which 33 were retrospective studies and 3 were prospective studies. The meta-analysis showed that the random-model pooled event rate for TMH closure was 0.37 (95% confidence interval [CI], 0.26–0.48) in the observation group, while it was 0.9 (95% CI, 0.85–0.94) in the surgery group. The fixed-model pooled event rate for VA improvement was 0.39 (95% CI, 0.33–0.45) in the observation group, while the random-model pooled event rate of VA improvement for the surgery group was 0.72 (95% CI, 0.63–0.80). The pooled event rate for BCVA improvement in the surgery group was 0.39 (95% CI, 0.33–0.46).

Conclusions: This meta-analysis suggests that TMH hole closure and VA improvement rates in the surgery group were significantly higher than those in the observation group. Vitrectomy is an effective method for treating TMH. However, further randomized controlled trials (RCTs) are required to evaluate the efficacy and safety of surgery and observation for TMH treatment.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/#recordDetails, identifier: CRD42021276684.

Keywords: traumatic macular hole, closure rate, visual acuity improvement, vitrectomy, spontaneous closure, meta-analysis

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INTRODUCTION

A macular hole (MH) is a defined as a full-thickness defect of the neuroretina in the macular foveal area. Traumatic macular holes (TMH) represent approximately 10% of MHs and may result in permanent significant vision loss (1). TMH is often found in young men, as the condition it is frequently associated with sport- and work-related accidents (2). The functional outcomes are often unclear because of the accompanying trauma-induced retinal pathologies, such as vitreous hemorrhage, retinal detachment, retinal hemorrhage, choroidal fracture, subretinal choroidal neovascularization, and fibrosis.

However, the posttraumatic approach is controversial. To date, no clinical guidelines have been established for this vision-threatening disease. Treatment includes vitrectomy surgery and observation, as well as spontaneous closure (1). Vitrectomy has been reported to improve anatomical and visual outcomes in eyes with TMH (3, 4). Currently, surgical techniques include removing the posterior vitreous cortex and epiretinal membranes, with or without internal limiting membrane (ILM) peeling, and intraocular gas or silicone oil tamponade. Various adjuvant therapies, including transforming growth factor-beta (TGF-β), biological tissue adhesives, and platelet concentrate, have been investigated with varying degrees of success (5, 6). However, there are many unanswered questions about the necessity of surgery because spontaneous hole closure has been commonly reported (7). Many studies have reported that spontaneous closure usually occurs between 1 and 6 months after the trauma incident (8, 9). While a number of studies have discussed the anatomical and visual outcomes of surgery and observation on TMH, a previous systemic review and meta-analysis, which included only 10 studies, lacked sufficient detail (10). Therefore, in this systematic review and meta-analysis, we systematically and statistically determined the improvement rates with TMH closure and visual acuity (VA) by comparing the two methods of treating TMH.

MATERIALS AND METHODS

This systematic review and meta-analysis was performed according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (11). Ethical approval was not necessary for the study as it used published data. Four databases in English, including PubMed, Cochrane, Web of Science Library, and Embase, and four databases in Chinese, including CNKI, Wanfang, VIP, and Sino Med, were searched from their inception to June 10, 2021. Google Scholar and Baidu Scholar were also searched to find studies missing in those databases. A manual search was conducted to identify published studies. In the case of unpublished studies, the database was searched for their abstracts, and their authors were also contacted. EndNote was used to merge retrieved citations and eliminate duplications.

Two independent researchers (QZ and HYF) separately assessed the eligibility, extracted the data, and assessed the quality of the included studies, and a third author (HJY) determined the final criteria for any inconsistencies.

Search Strategy

The search strategy included the following search terms: "retinal perforations," "retinal hole," "retinal tear," "retinal break," "macular hole," "traumatic macular hole," "vitrectomy," "pars plana vitrectomy," "surgical management," "observation," "treatment," and "spontaneous closure." The search terms are shown in the **Supplementary Material**.

Inclusion Criteria

Articles were included if they (1) included studies on patients with TMH; (2) used closure rate and VA improvement rate as the treatment endpoints; (3) provided clinical statistics on age, sex, best-corrected visual acuity (BCVA) expressed in the logarithm of the minimal angle of resolution (logMAR), MH size, follow-up data, operation, interval from injury to surgery, TMH closure rate, and VA improvement rate; and (4) were published in Chinese or English full text.

Exclusion Criteria

Articles were excluded if they (1) reported duplicated or overlapping data; (2) were designed as "reviews," "case reports," "letters" or "conference articles" with no data to extract; (3) focused on patients diagnosed with idiopathic MH, myopic MH, or TMH with retinal detachment; and (4) were not published in Chinese or English full text.

Data Extraction

According to the inclusion and exclusion criteria, two researchers (QZ and HYF) independently read the full text of the articles and selected the qualified studies. The following information was extracted from eligible studies: first author and publication year, study design, country, follow-up time, sex, number of participants, BCVA logMAR before and after TMH closure, size of TMH (μm), closure rate, and VA improvement rate. For the surgery group patients, data on the interval from the injury to the surgery were extracted. For the observation group patients, data on the time of hole closure were extracted.

Quality Assessment

To accurately evaluate the methodological quality of eligible studies, two researchers independently used the Newcastle-Ottawa Scale, which is a nine-point system including participant selection (0–4 points), comparability (0–2 points), and exposure (0–3 points) (12). Scores of 0–3, 4–6, and 7–9 points were regarded as low, moderate, and high quality, respectively. All included studies were identified to be of moderate or high methodological quality (**Supplementary Material**).

Statistical Analysis

The primary outcomes were TMH closure rate and VA improvement rate in both groups. BCVA improvement in the surgery group was defined as a secondary outcome.

Continuous data are presented as mean ± standard deviation. The descriptive statistics (BCVA logMAR improvement, TMH closure, and VA improvement rate) were analyzed with a 95% confidence interval (CI). The Cochran Q test and I^2 statistic were used to identify heterogeneity among the studies. When there was

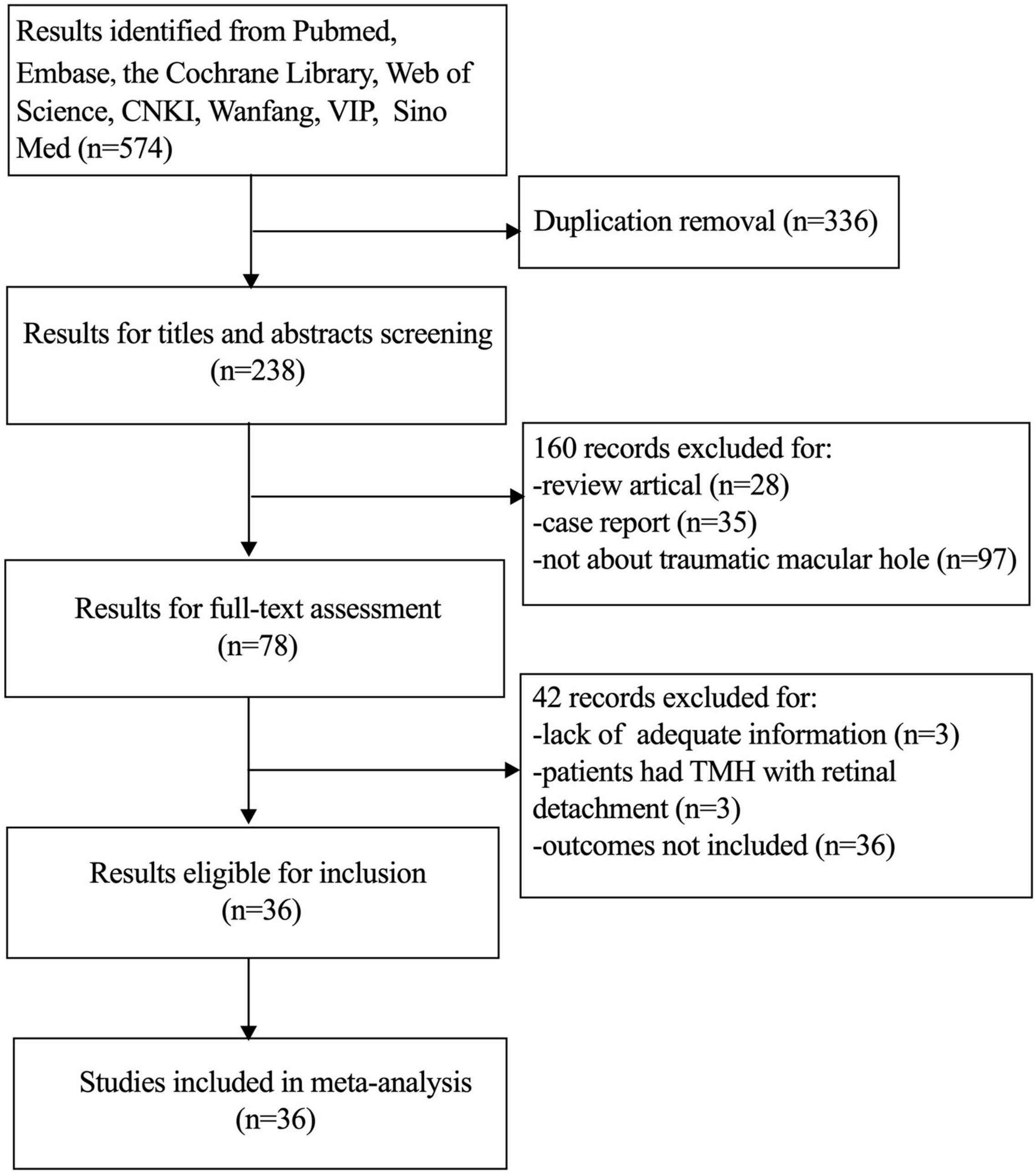

FIGURE 1 | Flow chart of the study selection (through June 10, 2021).

no significant heterogeneity ($I^2 < 50\%$ or $P > 0.05$), we applied a fixed-effect model to estimate the pooled effect size; otherwise, a random-effect model was employed. Funnel plots were used to detect potential publication bias. A sensitivity analysis was performed to test the robustness of the analysis. A subgroup analysis was conducted to explore the potential heterogeneity among patients in the surgery according to the different surgical procedures. All data synthesis and analysis were performed using Stata version 15.1.

RESULTS

Literature Search and Study Selection

A total of 574 records were identified with the initial search strategy. After removing 336 duplicates, 238 studies were assessed by title and abstract. Thirty-six studies, including 33 retrospective studies and three prospective studies, were selected for our meta-analysis according to the inclusion and exclusion criteria. The details of the search strategy are shown in **Figure 1**.

TABLE 1 | Study design and baseline patient characteristics of the surgery group studies.

References	Design	Country	Follow-up (months)	No. of eyes	Mean age (years)	Gender (Male/ Female)	BCVA±SD logMAR (pre/post)	Size of Macular hole (μm)	Interval from injury to surgery	Operation	Closure Rate	VA improvement Rate
Kunikata et al. (3)	Retrospective	Japan	12.9	18	18.3	15/3	0.65 ± 0.08/0.21 ± 0.07	312.5 ± 170.8	71.7 ± 44.2 days	PPV + ILM peeling or ILM flap + SF6	0.9444	1.0000
Chang et al. (13)	Prospective	China	3.56 ± 1.32	32	31.02 ± 5. 98	22/10	0.59 ± 0.12/0.14 ± 0.06	650.28 ± 34.19	1–4 months	PPV + ILM Peeling	0.9063	0.9375
Ghoraba et al. (14)	Retrospective	Egypt	37±45	28	21.4 ± 13	23/5	NA	757 ± 221	9 ± 23.5 months	PPV + ILM peeling	0.7500	NA
Chen et al. (7)	Prospective	China	6	25	31.0 ± 12.5	22/3	1.00 ± 0.35/0.56 ± 0.36	512.4 ± 315.1	20.8 ± 8.8 days	PPV + ILM peeling + C3F8/air filling	1.0000	0.8800
Fan et al. (15)	Retrospective	China	3	33	37.02 ± 1.35	17/16	NA	NA	NA	PPV	0.7879	0.4242
Tang et al. (16)	Retrospective	Australian and New Zealand	12	23	43.2	NA	NA	374	117 days	PPV + ILM peeling (21 cases) + C3F8/SF6	0.9130	0.4783
Li et al. (17)	Retrospective	China	12	25	28.5 ± 10.1	NA	NA	281.3 ± 111.3	NA	PPV + ILM peeling+air	0.8000	0.2800
Li et al. (17)	Retrospective	China	12	28	26.1 ± 12.9	NA	NA	397.6 ± 98.2	NA	PPV + ILM peeling + C3F8	0.8214	0.3214
Fu et al. (18)	Retrospective	China	4.6 ± 0.5	30	36.4 ± 3.7	NA	0.12 ± 0.06/NA	648.5 ± 105.3	8.5 ± 5.7 days	PPV + ILM peeling + C3F8	0.8667	0.5000
Li et al. (19)	Retrospective	China	10	16	12–45	16/0	0.07 ± 0.01/0.33 ± 0.02	477 ± 183	NA	PPV + ILM peeling + air	0.8125	0.9375
Browne et al. (20)	Retrospective	Egypt	6	16	29.95 ± 9.98	14/2	1.1 ± 0.2/0.2 ± 0.13	401.44 ± 34.8	NA	PPV + ILM peeling + C3F8	0.9375	NA
Brennan et al. (21)	Retrospective	Switzerland	12	13	14.15 ± 2.882	10/3	0.91 ± 0.43/0.50 ± 0.17	NA	5.38 ± 3.5 months	PPV + ILM peeling + C3F8	0.9231	0.9231
Li et al. (22)	Retrospective	China	12	34	34.1 ± 7.4	NA	0.12 ± 0.07/NA	653.6 ± 123.9	40.8 ± 20.6 days	PPV + ILM peeling + C3F8	0.7059	0.3824
Zhu et al. (23)	Retrospective	China	6	28	29.01 ± 7.33	22/6	0.086 ± 0.101/0.202 ± 0.171	NA	NA	PPV + ILM peeling + C2F6	0.8571	0.6786
Abou Shousha et al. (24)	Prospective	Egypt	9	12	23.25±14.11	8/4	NA	696 ± 445	3.75 ± 1.06 months	PPV + ILM flap + SF6	1.0000	0.9167
Chen et al. (25)	Retrospective	China	4–12	11	26.36 ± 8.43	8/3	NA	NA	4–14 months	PPV + ILM peeling + air	0.6364	0.4545
Yuan et al. (26)	Retrospective	China	12	26	32.4 ± 9.7	NA	0.13 ± 0.07/0.15 ± 0.07	643.3 ± 125	NA	PPV + ILM peeling + C3F8	0.6923	0.2692
Tian et al. (27)	Retrospective	China	12	10	44.6	6/4	NA	607.13	NA	PPV + ILM peeling + intraocular tamponade	0.8000	0.5000
Hou et al. (28)	Retrospective	China	1–27	54	27.2 ± 12.4	48/6	1.06 ± 0.39/0.84 ± 0.43	598 ± 227	1–156 months	PPV + ILM peeling + C3F8/SF6/C2F6 + platelet concentrate	0.8889	0.5185
Wan et al. (29)	Retrospective	China	6–14	24	NA	22/2	NA	623 ± 303	4–24 months	PPV + ILM peeling + C3F8	0.9167	0.7083

(Continued)

TABLE 1 | Continued

References	Design	Country	Follow-up (months)	No. of eyes	Mean age (years)	Gender (Male/ Female)	BCVA±SD logMAR (pre/post)	Size of Macular hole (μm)	Interval from injury to surgery	Operation	Closure Rate	VA improvement Rate
Ghoraba et al. (30)	Retrospective	Egypt	14.46 ± 3.43	13	26.54 ± 5.68	9/4	0.061/0.433	NA	NA	PPV+ILM peeling+C3F8	0.9231	NA
Qu et al. (31)	Retrospective	China	96 ± 131 days	95	26.6 ± 13.5	87/8	1.1 ± 0.45/0.83 ± 0.40	644.2 ± 270.5	9.8 ± 21.8 months	PPV + ILM peeling (90 cases) or not + C3F8/SF6/C2F6 + platelet concentrate (85 cases)	1.0000	0.7263
Ovali et al. (32)	Retrospective	Turkey	NA	14	40.4 ± 14.4	NA	NA	425	NA	PPV + ILM peeling + C3F8 (13 cases)/silicone-oil (1 case)	0.9286	0.8571
Chen et al. (33)	Retrospective	China	8	11	NA	NA				PPV + ILM peeling+air	0.6364	0.7273
Gong (34)	Retrospective	China	3–12	14	37.93 ± 12.92	12/12	0.058 ± 0.044/0.22 ± 0.21	628.79 ± 183.33	45.36 ± 45.24 days	PPV + ILM peeling	1.000	0.7143
Wu et al. (35)	Retrospective	America	12.5 ± 16.4	13	10	10/3	NA	NA	2.9 ± 2.0 months	Plasmin Enzyme-Assisted PPV + ILM peeling (3 cases) + C3F8/ silicone-oil	0.9231	0.9167
Ma et al. (36)	Retrospective	China	3–6	8	24.13	7/1	NA	NA	NA	PPV + ILM peeling + C3F8	0.8750	0.7500
Liu and Gong (37)	Retrospective	China	4-24	12	18–65	9/3	NA	NA	3–12 months	PPV + ILM peeling (3 cases) + C3F8/SF6	0.8333	0.7500
Kuhn et al. (38)	Retrospective	Hungary	14	17	26	15/2	NA	NA	2.5 months	PPV + ILM peeling + SF6	1.0000	0.9412
Johnson et al. (39)	Retrospective	America	11	25	23	20/5	NA	NA	NA	PPV + ILM peeling + C3F8	0.9600	0.8400
García-Arumí et al. (40)	Retrospective	Spain	13	14	19	11/3	NA	NA	1–6 weeks	PPV + platelet concentrate + SF6	0.9286	0.9286
Rubin et al. (41)	Retrospective	America	12.1	12	15	11/1	NA	NA	19 weeks	PPV + TGF-β + C3F8	0.9167	0.6667

BCVA, best-corrected visual acuity; C2F6, hexafluoroethane; C3F8, perfluoropropane; SF6, sulfur hexafluoride; ILM, internal limiting membrane; logMAR, logarithm of the minimal angle of resolution; NA, not available; PPV, pars plana vitrectomy; VA, visual acuity.

TABLE 2 | Study design and baseline patient characteristics of observation group studies.

References	Design	Country	Follow-up (months)	No. of Patients	Mean age (years)	Gender (male/female)	BCVA ± SD logMAR (pre/post)	Size of macular hole (μm)	Time of hole closure	Closure Rate	VA improvement Rate
Chen et al. (7)	Prospective	China	6	15	33.1 ± 11.6	14/1	1.11 ± 0.48/0.75 ± 0.4	423.2 ± 242.9	2.5 ± 1.6 months	0.6667	0.4667
Fan et al. (15)	Retrospective	China	3	30	37.28 ± 1.40	16/14	NA	NA	NA	0.5667	0.4333
Fu et al. (18)	Retrospective	China	4.6 ± 0.5	26	35.9 ± 3.4	NA	0.13 ± 0.08/NA	653.8 ± 94.7	12 months	0.4231	0.4615
Li et al. (22)	Retrospective	China	12	27	31.2 ± 5.5	19/8	0.13 ± 0.06/NA	632.5 ± 82.4	NA	0.4074	0.4074
Yuan et al. (26)	Retrospective	China	12	21	26.1 ± 10.0	NA	NA	490 ± 86.9	51.0 ± 12.6 days	0.3333	0.3333
Chen et al. (42)	Retrospective	China	6	27	26.2 ± 10.7	23/4	1.36 ± 0.74/1.01 ± 0.60	NA	NA	0.3704	0.3333
Tian et al. (27)	Retrospective	China	12	12	35	8/4	NA	NA	NA	0.6667	0.5000
Hou et al. (43)	Retrospective	China	16	30	32	27/3	NA	NA	NA	0.1000	0.4000
Chen et al. (33)	Retrospective	China	12	30	NA	NA	NA	NA	2.83 months	0.3000	0.3667
Li et al. (44)	Retrospective	China	14	28	30.1	25/3	NA	NA	4–5 months	0.1071	0.2857
Jin et al. (45)	Retrospective	China	20.72 ± 11.61	11	19.55 ± 8.18	10/1	NA	NA	NA	0.2727	0.2727
Yamashita et al. (46)	Retrospective	Japan	8.4	18	14.6	NA	NA	NA	1 week to 4 months	0.4444	0.4444

BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; NA, not available; VA, visual acuity.

Characteristics of the Study Samples

Thirty-two studies, as shown in **Table 1**, reported data on patients ($n = 734$) who underwent vitrectomy. For the surgery group patients, vitrectomies were performed using adjunctive therapies, including ILM peeling or flap, platelet concentrate or TGF-β, and gas or silicon oil tamponade. Most of the patients were males, with a similar proportion in both groups. The mean age of the surgery group patients was 26.95 years ($n = 671$; range, 1–69 years). The mean follow-up time was 10.41 ± 6.48 months ($n = 662$; median, 12; range, 3–45 months). The interval from injury to surgery ranged from 1 week to 120 months, and the average size of the TMH was 628.84 μm ($n = 358$; range, 64–1,588 μm). The mean preoperative and postoperative BCVA were 0.87 logMAR ($n = 247$) and 0.48 logMAR ($n = 247$), respectively. The pooled event rate for BCVA improvement in the surgery group was 0.39 (95% CI, 0.33–0.46).

For the observation group, 12 studies and 275 patients were analyzed (**Table 2**). The average age of the observation group patients was 30.36 years ($n = 157$; range, 9–49 years), the mean follow-up time was 10.56 ± 5.15 months ($n = 275$, median, 12; range, 3–48 months), and the average size of the TMH was 561.10 μm ($n = 93$; range, 553.6–681.4 μm). The percentage of patients who achieved TMH closure in <6 months was > 80%.

Pooled Rates of Closure and VA Improvement for the Surgery Group

In the surgery group, the pooled rates of TMH closure and VA improvement were reported in 31 studies (709 eyes) and 28 studies (651 eyes), respectively. The random-model pooled rate for TMH closure was 0.9 (95% CI, 0.85–0.94, **Figure 2A**), while that for VA improvement was 0.72 (95% CI, 0.63–0.80). There was high heterogeneity between the studies ($I^2 = 64.19\%$, $P < 0.05$; $I^2 = 81.13\%$, $P < 0.05$, **Figure 2B**). The Funnel plots did not reveal evidence of publication bias (**Supplementary Material**). For the TMH closure rate, sensitivity analysis suggested that one study (31) may have been a potential source of heterogeneity (**Supplementary Material**). After excluding this study, the pooled rate of TMH closure in the remaining 30 studies was 0.89 (95% CI, 0.85–0.92, $I^2 = 40.10\%$, $P < 0.05$).

The results of the subgroup analyses are shown in **Table 3**. There was no significant difference in TMH closure rate between subgroups stratified by different types of operation. Statistically significant effects of the subgroups were identified for VA improvement rate and BCVA logMAR improvement ($P < 0.05$ for heterogeneity between groups).

The pooled event rate of TMH closure was higher in the pars plana vitrectomy (PPV) + ILM peeling + perfluoropropane (C_3F_8)/sulfur hexafluoride (SF_6)/hexafluoroethane (C_2F_6) group (0.88, 95% CI: 0.82–0.93, $I^2 = 37.22\%$, **Table 3**) than in the PPV + ILM peeling + air group (0.75, 95% CI: 0.63–0.86, $I^2 = 0\%$, **Table 3**). However, there was still unexplained heterogeneity ($I^2 > 50\%$) between subgroups in the VA improvement rate, which the subgroup analysis could not completely explain. For BCVA logMAR improvement, the patients in the PPV+ILM peeling + platelet concentrate + intraocular tamponade group had a better BCVA improvement (0.25, 95% CI: 0.16–0.35, $I^2 = 0\%$, **Table 3**) than those in the PPV + ILM peeling + intraocular tamponade group (0.45, 95% CI: 0.41–0.48, $I^2 = 0\%$, **Table 3**). Meta-regression revealed that different types of operations affected the results of BCVA logMAR improvement.

Pooled Rates of Closure and VA Improvement for the Observation Group

For the observation group, the rate of TMH closure and VA improvement was reported in 12 studies (275 eyes). The random-model pooled rate for TMH closure was 0.37 (95% CI, 0.26–0.48). There was high heterogeneity among the studies ($I^2 = 71.07\%$, $P < 0.05$) (**Figure 3A**). The included studies were not randomized controlled trials (RCTs), which may be a potential source of heterogeneity. Publication bias was not assessed. Sensitivity analysis showed that the results were robust (**Supplementary Material**). The pooled event rate for VA improvement was 0.39 (95% CI, 0.33–0.45; fixed model) with no heterogeneity between the studies ($I^2 = 0.00\%$, $P > 0.05$) (**Figure 3B**).

Adverse Effects

Mild vitreous hemorrhage was noted in one patient one day after vitrectomy surgery, which resolved within 1 week (40). Vitreoretinal surgery combined with the use of intraocular gases can result in elevated postoperative intraocular pressure (IOP) and cataract formation. Three studies reported increased IOP after surgery, but it was controlled within the normal range after medication (30, 37). In six studies, 24 patients developed cataract formation or acceleration during the follow-up period (17, 23, 29, 30, 37). After the operation, three patients from two studies developed retinal detachment (17, 31). One of the reasons for this was an improper surgical operation. None of the patients in these studies developed endophthalmitis. In the observation group, 17 eyes developed obvious hole enlargement and two eyes had retinal detachment (43, 44).

DISCUSSION

Summary of the Main Results

We obtained several results by combining the existing evidence. First, although the studies included in our meta-analysis were of moderate or high methodological quality, there were no RCTs of TMH treatment, which may have led to a lack of convincing results. Second, the rates of TMH closure and VA improvement were significantly higher in the surgery group than in the observation group. This evidence may represent the best available support for treating patients with vitrectomy. Third, TMH patients were younger and mainly males, and over 80% of them showed closure with observation in <6 months. Raised IOP and cataracts are common postoperative complications, but these will not be severely adverse if immediate and proper treatment is adopted.

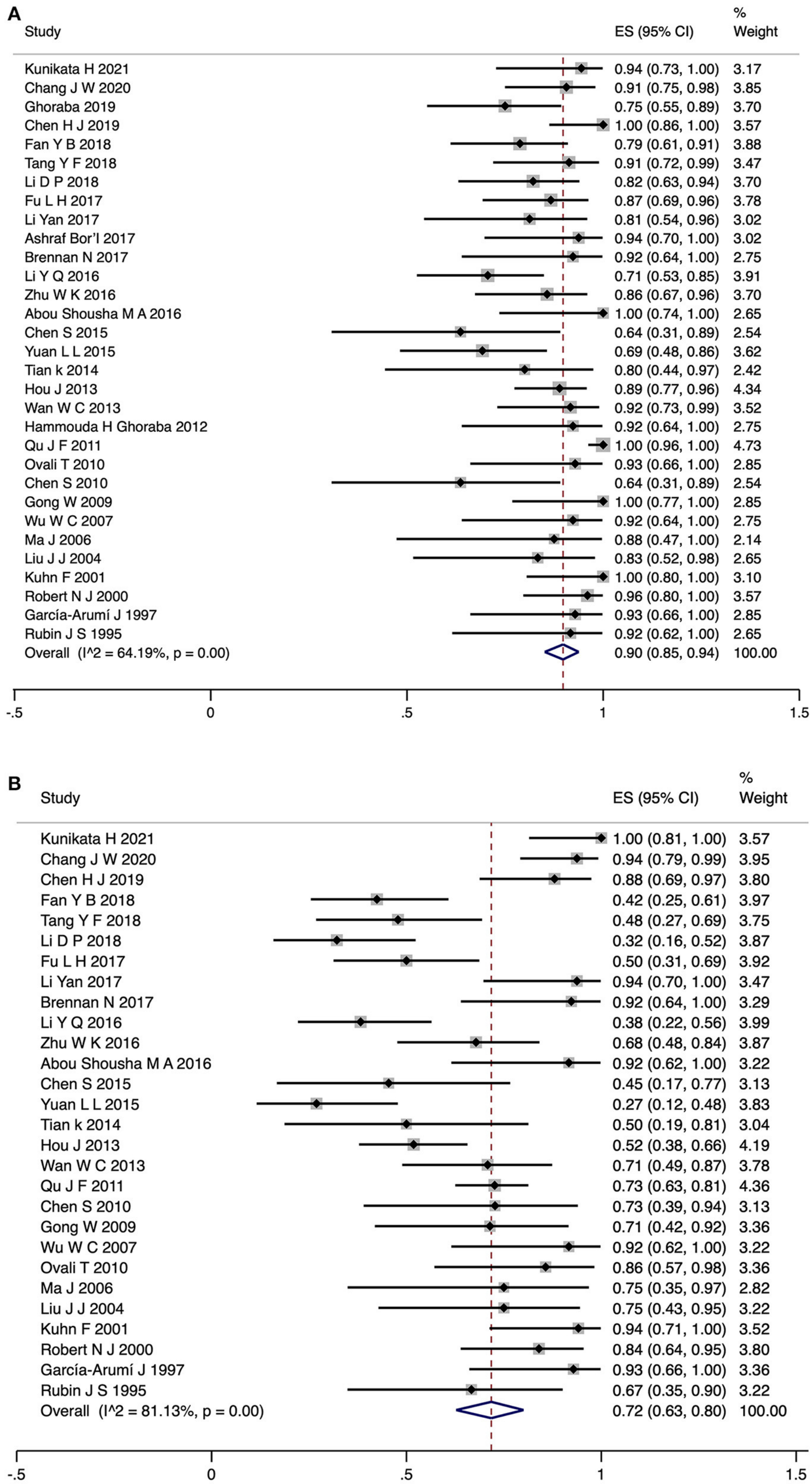

FIGURE 2 | Forest plot for TMH closure rate **(A)** and VA improvement rate **(B)** of surgery group patients. TMH, traumatic macular hole; VA, visual acuity.

TABLE 3 | Subgroup analysis for outcomes.

	No. of comparisons	Results	*P* value for overall effect	I^2	*P* value for subgroup difference
Type of operation	17	TMH closure rate (95% CI)		39.01%	0.05
PPV + ILM peeling + air	4	0.75 (0.63–0.86)	0.57	0%	
PPV + ILM peeling + C3F8/SF6/C2F6	13	0.88 (0.82–0.93)	0.09	37.22%	
Type of operation	14	VA improvement rate (95% CI)		81.85%	0.00
PPV + ILM peeling + air	4	0.61 (0.27–0.91)	0	86.10%	
PPV+ILM peeling+C3F8/SF6/C2F6	10	0.62 (0.48–0.76)	0	82.00%	
Type of operation	7	BCVA logMAR improvement (95% CI)		59.4%	0.022
PPV + ILM peeling + intraocular tamponade	5	0.45(0.41–0.48)	0.990	0%	
PPV + ILM peeling + platelet concentrate + intraocular tamponade	2	0.25(0.16–0.35)	0.022	0%	

BCVA, best-corrected visual acuity; C3F8, perfluoropropane; SF6, sulfur hexafluoride; C2F6, hexafluoroethane; ILM, internal limiting membrane; logMAR, logarithm of the minimal angle of resolution; PPV, pars plana vitrectomy; TMH, traumatic macular hole; VA, visual acuity.

Rate of Closure and VA Improvement According to Vitrectomy Surgery

In this systematic review, the TMH closure rate ranges from 0.63 to 1.0 with a pooled event rate of 0.90, while the VA improvement rate ranges from 0.28 to 1.0, with a pooled event rate of 0.72 in patients undergoing surgery. According to the study by Wang and Peng (47), the closure and VA improvement rates were 0.83 and 0.84, respectively, so that our results are similar to theirs, and showed that vitrectomy surgery seems to be a more effective method than observation for TMH treatment. The widespread use of optical coherence tomography (OCT) can offer further insight into the nature of TMH and shed light on the possible reasons for this Miller et al. (2) reported that an intact ellipsoid zone in closed holes tended to correlate with improved final visual acuity. A multicenter prospective comparative study showed that there were no significant differences in the length of the photoreceptor IS/OS junction (ellipsoid zone) defect and the final BCVA between the surgically closed cases and spontaneously closed cases, with 80% of the patients showing spontaneous hole closure within 3 months (7). Thus a 3-month observation period after injury may be an alternative modality for TMH management. Therefore, many researchers suggested that vitreous surgery should be carried out in 3 months to prevent severe photoreceptor damages. The closure rate was higher than the VA improvement rate in the surgery group, and the differences between anatomical and functional outcomes may be associated with different preoperative retinal pathologies and ocular complications (1). The study by Qu et al. (31), which reported a TMH closure rate of 1.0, may be a potential source of heterogeneity. The reason for the high closure rate may be associated with the use of adjunctive therapy (platelet concentrate).

The underlying mechanism of TMH formation is unclear. One type forms immediately after ocular trauma, with the foveal rupture causing acute vision loss. Another type may result from the development of macular edema and cysts, which may induce delayed-onset TMH formation. With the regression of macular edema, shrinkage and closure of the hole may occur. Glial cell proliferation and epiretinal membrane formation are often the causes of a persistent open hole. Therefore, vitrectomy with membrane peeling might be helpful and is a standard surgical procedure for treating TMH (6). Currently, PPV, ILM peeling or flap, and intraocular gas or silicone oil tamponade are the most commonly employed surgical procedures for TMH treatment (5). Ghoraba et al. concluded that gas tamponade is more successful than silicone oil tamponade for the anatomical closure and VA improvement of TMH (30). Intraocular gas tamponade is a crucial component of the surgical procedure for TMH repair. Higher rates of TMH closure were observed with C3F8, SF6, or C2F6 ocular tamponades, which could result from the extended amount of time the C3F8, SF6, or C2F6 lasts in the vitreous cavity. In this meta-analysis, the TMH closure rate and VA improvement rate in the C3F8/SF6/C2F6 tamponade group showed better outcomes than that in the air tamponade group.

Adjunctive therapies are often used together with surgery to accelerate hole closure (28, 40, 41). Rubin et al. used TGF-β2 in 12 eyes during vitrectomy and finally achieved a closure rate of 67% in eight eyes (41). Garca-Arum et al. found that the intraoperative application of platelet concentrate in combination

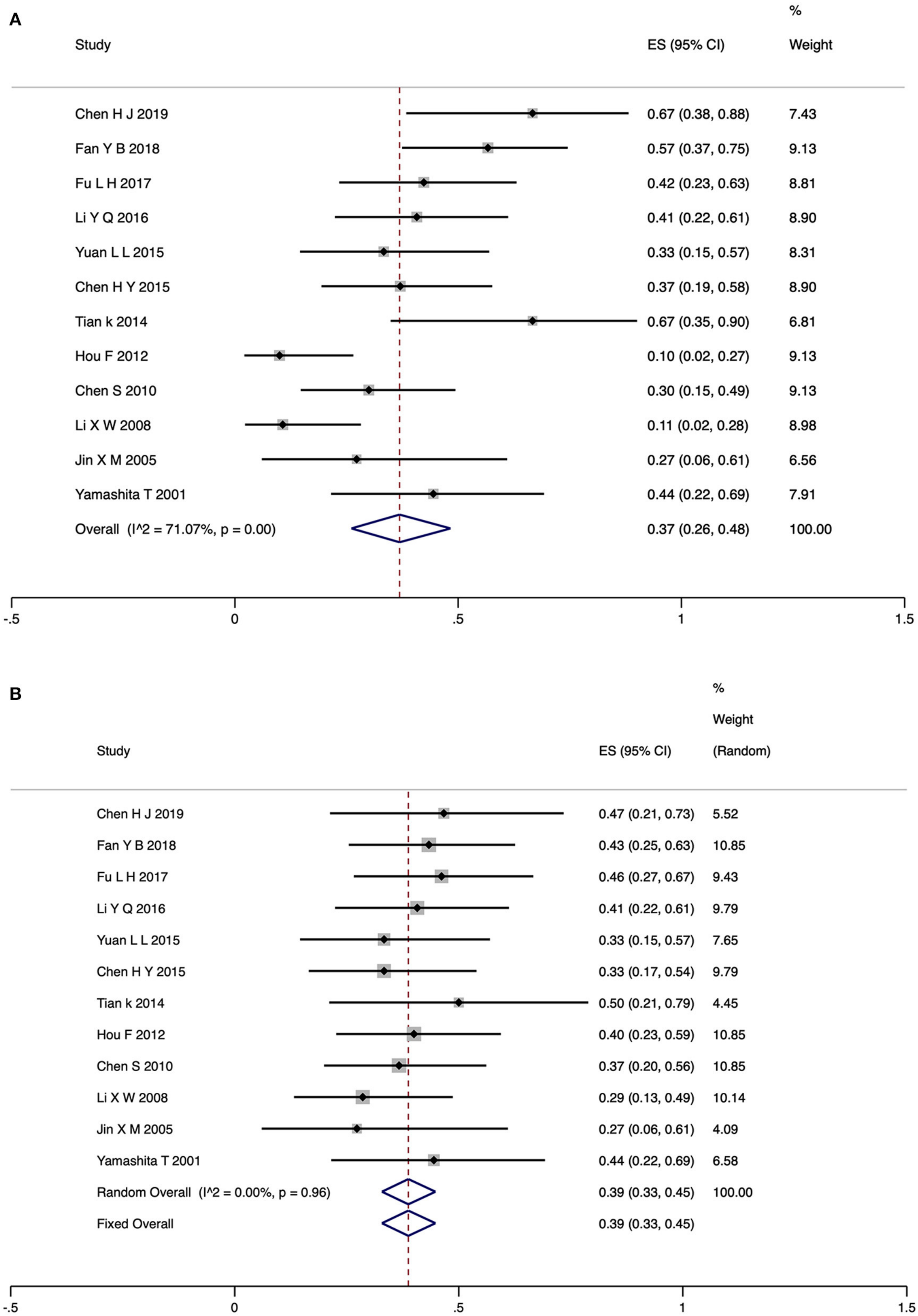

FIGURE 3 | Forest plot for TMH closure rate **(A)** and VA improvement rate **(B)** of observation group patients. TMH, traumatic macular hole; VA, visual acuity.

with vitrectomy may help improve anatomic and visual outcomes (40). As shown by our meta-analysis, platelet concentrate was a potential factor that affected visual improvement. However, studies are unlikely to be designed to evaluate adjunctive therapies, which are also seldom implemented today.

Spontaneous TMH Closure

TMH has been shown to close without any treatment, usually between 1 and 6 months after the trauma incident (8, 9). The closure and VA improvement rates were 0.37 and 0.39, respectively, similar to those reported in previous publications. In our meta-analysis, over 80% of the patients with TMH achieved closure within 6 months. The mechanism of spontaneous closure is of great interest. Why does TMH have a higher spontaneous closure rate than other types of MH? The fact that TMH patients are young and have a healthy vitreous gel and a firm vitreofoveal attachment may account for the high rate of spontaneous closure. Indeed, young age, small hole size, cystic edema at the edge of the MH, and no posterior vitreous detachment have been recognized as possible features affecting spontaneous closure (7, 48).

In addition, it should be noted that 17 eyes developed obvious hole enlargement and two eyes showed retinal detachment (43, 44). In five studies, 134 patients received supportive drugs (such as Sanqi Panax notoginseng for injection, compound anisodine hydrobromide injection, inosine tablets, or iodizedlecithin) to prepare the optic nerve and promote retinal microcirculation. However, experimental or clinical proof about their efficacy is lacking.

Limitations

This meta-analysis has some limitations. First, high heterogeneity existed in some outcomes, and many factors could have led to heterogeneity, such as the size of MH, different types of surgery, and interval from injury to surgery. However, the complete data were hardly accessed for subgroup analysis, and the factors were relative to treatment decisions. Second, since the studies included were retrospective and prospective observational studies and not RCTs, the comparison between the surgery and observation groups was based on data with a discrepant baseline. Therefore, given the limitations mentioned above, RCTs are needed in the future to evaluate the effectiveness and safety of surgery and observation for TMH. Therefore, we will update our meta-analysis if RCTs are performed in future.

CONCLUSIONS

In conclusion, our systematic review and meta-analysis provides evidence that, compared with observation, surgery leads to higher TMH closure and VA improvement rates. Vitrectomy is an effective and safe treatment method for TMH. The management guidelines for TMH in pediatric patients and the factors affecting the related outcomes need further clarification.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

QZ, YX, and HL: conceptualization and design. QZ, HF, and ZF: literature search, data extraction, quality assessment, and statistical analysis. QZ: manuscript writing. HY: supervision. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.735968/full#supplementary-material

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COVID-19 Changed Prevalence, Disease Spectrum and Management Strategies of Ocular Trauma

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The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted the health of people around the world and has reshaped social behaviors and clinical practice. The purpose of this perspective is to provide epidemiologists and clinicians with information about how the spectrum of ocular trauma diseases changed, as well as to optimize management for improving patient prognosis during this crisis. Analysis of current studies revealed that the prevalence of eye trauma decreased overall, with a trend of delayed medical treatment during the COVID-19 era. Irregular epidemic prevention and control measures, unprotected home activities, and unusual mental states are the main causes of ocular trauma. Strategies for reducing morbidity are also discussed, including popularizing the use norms of prevention and control supplies, taking heed to the safety of family activities, highlighting the special status of child protection, and paying attention to previous case data to implement region-specific precautions. The procedure of ophthalmological emergency and outpatient management should also be optimized, and mental health should be emphasized during this pandemic.

Keywords: COVID-19, ocular trauma, prevalence, management, disinfectants

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has demonstrated wide-ranging effects on the society and the healthcare system. Many countries have executed strong "Shelter-in-Place" policies to curb its spread. However, such measures have significantly impacted the mental preference and behavioral pattern of individuals, which has led to further changes in the disease spectrum (1, 2). It has been proven that during this pandemic, there exists an increasing trend in interpersonal violence-related trauma and traffic-related trauma due to anxiety, irritability, and cancellation of public transportation (3–6). The pandemic has also significantly disrupted scheduled medical activities, through the redeployment of more healthcare resources to COVID-19 patients and addition of COVID-19 screening for infection control before treatment (7, 8). In addition, patients grew more reluctant to seek health care, for fear of nosocomial infection, and even delay treatment (9).

Ocular trauma is an acute and severe disease in ophthalmology, and is an important cause of monocular blindness, which has a huge socioeconomic burden (10–12). Work-related injuries such as intraocular foreign body (IOFB) caused by machine elements and corneal burn caused by chemical reagents are the most common mechanisms of ocular trauma, followed by the tools used in the home and fireworks in festival activities (13–15). Seasonal trends in the incidence of ocular trauma were also observed, being higher in spring and summer, owing to the increase in outdoor activities (16, 17). Prompt diagnosis with a high standard of emergency management can provide patients with better visual outcomes and prognoses (18, 19). Considering the paradigm shift in all aspects of life and healthcare during the ongoing COVID-19 pandemic, we assumed that the disease spectrum and care paths of ocular trauma would change. This perspective narratively reviewed the COVID-19-related changes in the morbidity and disease spectrum of ocular trauma and discussed its potential prevention and control measures with the aim of optimizing the emergent treatment and management in the COVID era.

METHODS

The impact of the COVID-19 pandemic on the morbidity and management of ocular trauma were determined through literature search in the databases of Web of Science, Embase, Cochrane and PubMed, and presented as a narrative review owing to the novelty of related studies (20). The search terms were identified as Birmingham Eye Trauma Terminology, "Coronavirus," "COVID-19," "SARS-Cov-2," "Ocular trauma," "Eye injury" and their variations. The search was conducted in November 2021, and all the references of included articles were reviewed to prevent missing associated research. All literatures fitting the theme were included regardless of their article types, and the searching and screening were performed independently by three reviewers (MX, HY, and YZ) while the disagreements were resolved by a fourth investigator (YF). A total of 467 records were retrieved, of which 56 were included through title and abstract analysis and further full-text content assessment for eligibility (**Figure 1**).

RESULTS

Impact on Morbidity and Patient Characteristics

Several studies have reported an overall decreasing trend in the morbidity of ocular trauma, and the number of emergency eye services has also decreased during the COVID-19 era, especially for traffic and work-related trauma. Meanwhile, interpersonal violence-related injuries were at a relatively high level (21–27). A case-control study in the United Kingdom noted that within the first month after the national lockdown order was issued, the total number of ophthalmological emergency visits decreased by 53.1% compared with the same period the year before. Likewise, the ocular trauma-related presentations decreased by 43.9%, which could be mainly attributed to fewer outdoor activities due to movement restrictions and social distancing (28). A similar finding was reported in India, where the incidence decreased by 58.5% during the lockdown. However, upon the lifting of the lockdown, the number of emergency visits due to ocular trauma increased monthly (29).

During quarantine, men were still the most frequent victims, and in some studies, the proportion of male patients presenting with ocular trauma has increased further (30, 31). There was a disputable change in the mean age of patients with ocular trauma before and after the outbreak, which may have resulted from the differences in the age composition of the population and economic structure between cities. A review in the United States reported a 2.4-year increase in the average age of patients, and in Italy, a 2.6-year increase was also reported (31, 32). However, there was a significant reduction in the average age of patients in India, with a decreased proportion of patients aged >50 years and an increased proportion of patients aged between 16 and 50 years (29, 33, 34). Moreover, the prevalence of serious ocular trauma, such as eyelid laceration, open globe injury, and traumatic retinal detachment, was reported to be higher during the COVID-19 era, which could be attributed to the changes in the behavioral pattern of individuals and reduced likelihood of patients with mild trauma seeking healthcare (35). The widespread use of online ophthalmic consultation services during the outbreak further confirmed this view (28). In addition, there was a trend of delay in emergency department visits for ocular trauma, and Stedman et al. (36) revealed that the delay between onset and visit increased from 0.33 days to 1.1 days before and after COVID-19, respectively.

Impact on Disease Spectrum

Table 1 summarizes the changes in the mechanisms of ocular trauma during the COVID-19 pandemic. There was an increase in the ocular trauma associated with the prevention and control of virus transmission during the pandemic, mainly including keratoconjunctivitis photoelectrica caused by ultraviolet (UV) disinfection, and chemical ocular injuries caused by disinfection products such as hand sanitizers. Keratoconjunctivitis photoelectrica has been a typical occupational injury since before COVID-19, occurring mostly in industries with high UV exposure such as electric welding. A large number of non-occupational cases appeared after the outbreak, which nearly doubled compared with the same period the year before (37). With the general use of UV-C rays to prevent airborne virus transmission, acute exposure to high-dose UV radiation arising from proximity to the light source, and lack of self-protection has emerged as a key risk factor that could induce topical inflammation and cause damage to corneal and conjunctival epithelial cells (57, 58). Symptoms usually appear a few hours after exposure, from the earliest gritty sensation to ocular pain or discomfort, conjunctival congestion, photophobia, and tearing (59). Fortunately, most cases were mild with a good visual prognosis, requiring only supportive treatment to promote epithelial repair, resist infection, and prevent scarring (60). Leung and Ko (39) reported that three adults developed photophobia, ocular pain, and decreased visual acuity after direct exposure to a UV germicidal lamp; no corneal epithelial staining was found, and the symptoms were relieved after receiving lubricating eye drops. Sengillo et al. (40) reported seven patients presenting with ocular pain, conjunctival congestion, and punctiform corneal epithelial erosion following overexposure to UV. They all recovered well after treatment with artificial tears, topical antibiotics, or steroids.

Regular use of disinfectants and hand sanitizers is also recommended for the prevention of COVID-19, although the

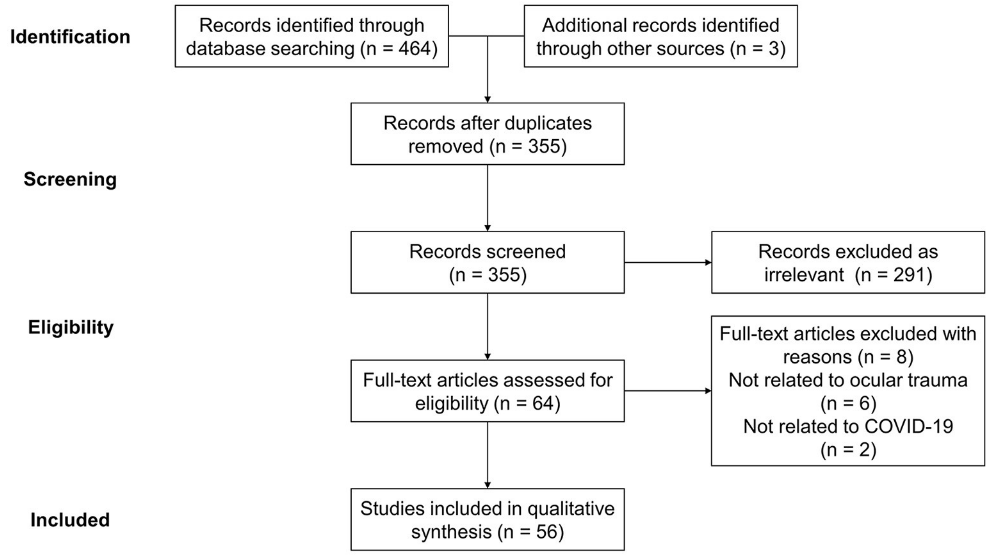

FIGURE 1 | Flow diagram of literature searching and selecting.

TABLE 1 | Changes in disease spectrum of ocular trauma before and after COVID-19.

Mechanism	Changes in ocular trauma cases per mechanism
Irregular epidemic prevention and control measures	• Cases associated with UV overexposure were tripled in China (37) • 109 cases of photokeratitis in a hospital in China within 8 weeks after the outbreak, increased nearly four times (38) • 3 and 7 cases of UV-photokeratitis were reported, respectively (39, 40) • In Croatia, the consultations related to exposure to disinfectants and hand sanitizers were doubled and ten-fold respectively (41). Some relevant cases were reported (42) • A seven-fold increase in pediatric cases related to hand sanitizers in France (43) • 9 pediatric cases related to hand sanitizers in Israel, which was not seen last year (44) • 2 pediatric cases of toxic keratopathy related to hand sanitizers (45) • 9 cases related to masks in China (46)
Home accidents	• A 42.4% increase in the cases occurring at home in India, and 5.5% in the U.S. (29, 32) • 23 cases occurring at home per week, in comparison to 10 in 2019 (47) • 4 cases related to home accidents in Jorden (48) • 4.6% and 2.2% increase in cases related to home activities and gardening in Italy, respectively (31) • A 28% increase in cases related to home improvement in the U.S. (35) • Many cases related to gardening was reported (49, 50) • DIY-related cases were three-fold compared to normal days (36) • 2 cases related to "bow and row" in India (51) • 2 cases secondary to exercise resistance band were reported respectively (52, 53)
Outdoor accidents	• A 37.9% decrease in the cases occurring in the workplace in India, and 4.3% in the U.S., (29, 32) • 5.5 and 3% decrease in cases related to falls and outdoor sports in Italy, respectively (31)
Interpersonal violence	• A 5% increase in call-outs and 75% increase in Internet searches related to intimate partner violence, even as overall crime dropped 40% in Australia; a 32–36% increase in intimate partner violence complaints in France, and 21–35% in the U.S. after quarantine measures (54) • 45% of intimate partner violence injuries involved eyes (55) • A 5% increase in the cases related to intimate partner violence in North India (33) • Cases related to pepper spray in protest march against COVID-19 restrictions (56) • A 1.2% increase in the cases related to interpersonal violence (31)

hypochlorous acid and alcohol compounds contained therein could lead to concentration-dependent corneal and limbal toxicity, including superficial epithelial denudation, topical inflammation, and stem cell deficiency (61, 62). Both direct and indirect contact through the volatilization of disinfectant components in the air could induce ocular inflammation, especially in patients with chronic allergies, compromised ocular surfaces, and previous ocular surface diseases like dry eyes (63). Babić et al. (41) reported that exposure to disinfectants and hand sanitizers during the COVID-19 outbreak was, respectively, twice and 10 times that of the same period the previous year in Croatia. Adults were at high risk of exposure to disinfectants, while children were at high risk of exposure to hand sanitizers. In France, it was also found that the incidence of ocular trauma caused by alcohol-based hand sanitizer in children increased by seven times compared with the same period in 2019, with nearly 38% of patients with corneal ulcers involving over 50% of the ocular surface and nearly 13% of patients requiring amniotic membrane transplantation (43). Chemical ocular injuries caused by hand sanitizers in children usually have a good prognosis after treatment. Wasser et al. (44) reviewed nine cases of ocular chemical injuries caused by hand disinfectants and indicated that after washing and topical antibiotics, hormones, and lubricants, 67% of the children were discharged and the others with more severe ocular surface injuries involving over 85% cornea and 30–75% conjunctiva received an average of 7 days of hospitalization and were healed within 19 days, with good visual recovery and no irreversible damage. Yangzes et al. (45) also reported two cases of toxic keratopathy in children caused by hand disinfectants during the COVID-19 outbreak. One patient presented with a large central corneal defect combined with conjunctival edema and ischemia, and the other presented with superficial punctate keratopathy. After receiving antibiotics, glucocorticoids, topical lubricants, as well as additional antibiotics and vitamin C orally, the ocular surface of both patients recovered well.

Given the impact of the pandemic and related containment strategies, the lifestyle and workstyle of individuals underwent a great shift, and correspondingly, the prevalence of ocular trauma occurring in domestic settings was significantly higher than in the workplace (64–66). Pellegrini et al. (31) reported that during quarantine, the proportion of ocular trauma caused by falls and sports decreased significantly by ∼5.5 and 3%, respectively. On the other hand, the percentage of ocular trauma caused by home activities and gardening, respectively, increased from 12.4 and 8.5% in 2019 to 17.0 and 10.7%. The surge of ocular trauma occurring at home could be mainly attributed to gardening, do-it-yourself (DIY) activities, home improvement, and exercise. Although most cases were mild, there were also open globe injuries with a high risk of blindness, constituting the majority of severe ocular injuries during the COVID-19 era. Several studies have reported a variety of types of ocular trauma caused by gardening, including epithelial defects or fungal keratitis caused by leaf scratches, corneal or conjunctival burns caused by improper use of herbicides, and open-global injuries or perieyelid injuries caused by splashes of plant debris or stones thrown by lawnmowers (67). A case of ocular trauma in a 58-year-old man caused by gardening during this COVID-19 period was reported by Nocini et al. (50), in which a nail thrown by the lawnmower pierced his left upper eyelid and penetrated the superior rectus and lateral rectus muscles, leading to restricted globe movement. Sputtering particles from DIY and amateur home improvement activities are also the leading causes of serious ocular trauma.

A retrospective cohort analysis in the United Kingdom noted that the number of serious ocular traumas, including rupture, lid lacerations, and IOFB, was three times the average over the past 5 years, with a 400% increase in hospital admissions due to DIY activities after the outbreak (36). Wu et al. (35) also reported a nearly 30% increase in the proportion of serious ocular trauma caused by home improvement during the COVID-19 pandemic. Exercise resistance bands, mainly used for strength training and a good substitute for gymnasiums, were the most reported sources of exercise-related ocular trauma occurring at home during COVID-19. Sibley et al. (52) first reported two cases of ocular trauma caused by exercise resistance bands during the lockdown in the United Kingdom. A 41-year-old woman had a 0.8-mm hyphema in the right eye, 1.0-mm in the left eye, and peripheral commotio retinae after being hit in both eyes. The other case was a 19-year-old young man presenting with red blood cell deposition on the inferior corneal endothelium and commotio retinae in the right eye, and a 1-mm hyphema, vitreous and intraretinal hemorrhages, and retinal break in the left eye. Both patients presented with binocular involvement and asymmetrical injuries, with the left eye being more severe than the right eye. Al-Khersan et al. (53) further reviewed 11 cases of ocular trauma caused by exercise resistance bands during the COVID-19 era and reported a wide range of subsequent ocular injuries, including corneal epithelial defects, iris defects, iritis, hyphema, vitreous hemorrhage, retinal tear, commotio retinae, macular hole, and permanent vision loss.

Multiple studies have indicated that the prevalence of ocular trauma associated with interpersonal violence is high during this pandemic, which could be mainly attributed to mental anxiety and depression arising from movement restrictions (35, 68). Sissoko et al. (68) reported a striking increase in ocular trauma related to interpersonal conflicts, especially quarrels and protest marches after the stay-at-home order was initiated, with corneal and maxillofacial injuries as major symptoms. Intimate partner violence also emerged as a leading cause of ocular trauma, which was severe and worsened with scleral laceration, vision loss, and ultimately enucleation (69). Previous studies have illustrated a 27% increase in domestic violence reports received by police in the United States since the travel restriction orders were issued, of which the proportion of serious injuries nearly doubled, suggesting higher severity (70, 71). In addition, the incidence of pediatric ocular trauma increased markedly, and children aged 13–18 years became a high-risk group for open-globe injuries during the pandemic rather than preschoolers (72). Apart from the aforementioned risk factors of epidemic prevention, home activities, and interpersonal violence, children's imitation of risky behaviors on entertainment programs could also result in ocular trauma. Bapaye et al. (51) reported that within 4 days after the broadcast of an Indian TV program, two Indian children suffered ocular trauma while imitating the "archery" part of the program. The first one presented with epithelial defects after being hit by a rubber arrow, and the other developed traumatic cataract and endophthalmitis after an arrow made from a broom stick shot the cornea and entered into the eye. However, related cases were rare prior to the COVID-19 outbreak.

DISCUSSION

Despite a decreased incidence of ocular trauma during the COVID-19 pandemic, the proportion of serious cases has increased, with a significant shift in risk and pathogenesis. Fortunately, most ocular traumas are preventable, which underscores the need for targeted precautions. First, since products against viruses, including disinfectants, hand sanitizers, and UV germicidal lamps, have become widely available and have led to an increased incidence of related ocular trauma, it is necessary for the media and local businesses to clarify the potential hazards to the public and popularize the use norms of these (37, 41). Further, wearing goggles or sports glasses is central to the prevention of ocular trauma due to home activities, such as gardening, DIY activities, and exercise, although it remains unpopular to date (53, 73). As individuals were confined to their homes and engaged in more home activities during the lockdown, great importance should be attached to the education on the risk of ocular trauma and the promotion of associated protective measures. In addition to the goggles, it is also effective to encourage the media to broadcast home leisure activities and exercise instruction programs.

Further, parents should strengthen the supervision and protection of children, especially in the use of prevention and control supplies and potentially dangerous items, to prevent accidental ocular trauma due to mental immaturity (45, 72). Moreover, given the temporal and spatial specificity of ocular trauma, it is critical to collate previous cases and summarize the region-specific pathogenic characteristics of ocular trauma before formulating regional preventive strategies. All preventive measures contribute to reducing the incidence and severity of ocular trauma and the burden on the national healthcare system.

Since ocular trauma often leads to poor visual prognosis and blindness, timely treatment is important. The lag between onset and presentation was common during the lockdown, which may further worsen the symptoms, such as a large corneal ulcer (36, 47). Reduced access to healthcare may be a key factor in the lag. Thus, it is recommended that the healthcare system optimizes the procedure of ophthalmological emergency and outpatient care to ensure timely treatment of ocular trauma despite limited medical resources. Remote ophthalmic services may be an effective strategy to provide specialized health care in time and have been implemented in many countries. This could tilt medical resources toward emergency patients with serious ocular trauma, and also decrease the risk of viral infection and transmission by avoiding visits of non-emergency patients (28, 29).

Widespread psychological problems, such as anxiety, depression, and distrust caused by social distancing during the pandemic, should be taken seriously, as they are considered to be the main reasons for the surge of ocular trauma cases associated with interpersonal conflicts (35). Home activities and online communication are both effective in alleviating panic and anxiety and maintaining mental health during quarantine. Moreover, it is necessary to promptly disclose information associated with the pandemic, as misinformation distributed by social media could trigger a cascade of fear and anxiety among the public (74). On the other hand, the same psychological problem also existed among medics, partly owing to a particularly high risk of infection. Authorities concerned should emphasize the mental health of medics and provide timely psychological counseling through online psychological consultation or other methods.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HY and MX conceived and designed the entire study and wrote the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Novel Suturing Methods for the Management of Traumatic Choroidal Avulsion in Globe Injuries

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Purpose: To explore the long-term efficacy of novel choroidal suturing methods including trans-scleral mattress suturing (TSS) and intraocular suturing (IOS) in the treatment of choroidal avulsion.

Design: Prospective cohort, hospital-based study.

Methods: A total of 24 patients who were diagnosed with choroidal avulsion were enrolled in this study. The demographic characteristics, baseline information of trauma, best-corrected visual acuity (BCVA), and intraocular pressure (IOP) were collected before surgery, and the anatomic abnormities of the globe were recorded before or during surgery. All patients were diagnosed with choroidal avulsion and underwent choroid suturing treatment during vitrectomy, postoperative functional variables including BCVA and IOP, anatomic variables including retinal and choroidal reattachment rate, and silicone oil migration rate, which were recorded at the regular follow-ups at least 1 year after surgery.

Results: All patients with open globe injury involved zone III, 70.8% of the patients presented with two quadrants of the avulsed choroid, and 29.2% with one quadrant involved; moreover, all patients had complications with retinal detachment (RD), of which 58.3% of patients had closed funnel retinal detachment. TSS was applied in nineteen patients and IOS in five patients. Postoperatively, a significant improvement on LogMAR BCVA was observed at each follow-up from 3.57 ± 0.69 before surgery to 2.82 ± 0.98 at the last follow-up ($p < 0.05$), and the proportion of no light perception (NLP) was also reduced from 69.6 to 37.5%. IOP was markedly elevated from 6.4 ± 4.1 mmHg preoperatively to 11.3 ± 4.3 mmHg at the last follow-up ($p < 0.05$). Choroidal reattachment was achieved in 91.7% of patients; two patients were observed with silicone oil migration at 3 months after surgery and underwent drainage of suprachoroidal silicone oil and sclera buckling. Meanwhile, retinal attachment was observed in 95.8% of patients, only one patient developed partial RD due to postoperative proliferative vitreoretinopathy, and secondary vitrectomy was performed; all patients were observed with complete retinal and choroidal attachment at the last follow-up. Eventually, four patients were silicone oil-free, and 20 patients were silicone oil-dependent.

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Conclusions: Choroidal suturing proved to be an effective method to fix the avulsed choroid, which greatly improved the BCVA and maintained the IOP, and efficiently increased the choroidal and retinal reattachment rate and preservation of the eyeball.

Keywords: choroidal avulsion, ocular trauma, trans-scleral mattress suturing, intraocular suturing, no light perception

INTRODUCTION

Ocular trauma remains one of the major causes of visual impairment and even blindness in the working population worldwide, especially when the posterior segment is involved (1, 2). In addition to retinal injuries, traumatic choroidal injuries are also severe complications and are closely associated with the prognosis of ocular trauma. It was reported that choroidal injuries were observed in 69.7% of all the eyes with no light perception and were estimated as a predictor of poor prognosis (3). Traumatic choroidal injuries are not uncommon in clinical practice, and a variety of choroidal injuries have been reported (4–7). In our recent study (8), we summarized traumatic choroidal injuries into nine categories, including suprachoroidal effusion, suprachoroidal hemorrhage, massive suprachoroidal hemorrhage, choroidal avulsion, traumatic chorioretinal rupture, choroidal rupture, choroidal loss, choroidal hole, and choroidal damage at the wound site, and a classification system for traumatic choroidal injuries was proposed. Among the nine categories, choroidal avulsion was one of the most catastrophic, and it was found that 92.2% of eyes with choroidal avulsion had unfavorable outcomes (8).

The concept of choroidal avulsion was first brought up by *Bordeianu* in 1984, and we have recently redefined the term as a sudden severe hemorrhagic separation of the choroid from the sclera, accompanied by discontinuity of the detached choroid or, sometimes, choroid and ciliary body avulsed at scleral spur as a whole unit (8, 9). It has been nearly half a century since the concept was raised; however, literature focusing on choroidal avulsion is scant, mainly because of the lack of effective treatment. Despite the development and refinement of vitreoretinal microsurgical techniques, eyes with choroidal avulsion can hardly be repaired. They are almost always complicated with persistent hypotony, which results from the connection of the vitreous cavity and the suprachoroidal cavity after uveal injuries, leading to the free flow of the aqueous humor and all intraocular tamponade between these two compartments, which lowers the intraocular pressure. Moreover, the formation of the two compartments significantly reduces the volume of the vitreous cavity, which results in the decreased possibilities of retinal reattachment. Therefore, without effective treatment, eyes with choroidal avulsion usually end in phthisis bulbi and cannot be preserved.

Surgical treatment of choroidal avulsion should be full of challenges. Very few surgical techniques have been reported in the literature (6, 7). In the present study, novel suturing methods including trans-scleral mattress suturing (TSS) and intraocular suturing (IOS) were developed to refix the avulsed choroid and the postoperative conditions were evaluated.

SUBJECTS AND METHODS

Study Design and Participants

This study was a prospective cohort study conducted following the principles of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of Peking University Third Hospital. All information was collected from the database of Eye Injury Vitrectomy Study (EIVS), which has been a hospital-based multicenter, prospective cohort study since January 1997. Patients in the present study were recruited from the Department of Ophthalmology at Peking University Third Hospital, consecutively, between April 2013 and July 2017. Informed consent was obtained from all patients or their direct relatives if the patient was under 18.

The study included patients who were diagnosed with choroidal avulsion in the surgery and received TSS or IOS refixation of the avulsed choroid suturing treatment. Since nearly all cases with choroidal avulsion were complicated with severe intraocular hemorrhage, it was difficult to identify the choroidal avulsion before the surgery. The decisions of suturing were made intraoperatively. All cases with choroidal avulsion found during surgery were sutured unless the extension of choroidal avulsion was >2 quadrants, and/or there was total retinal loss. For this study, patients with the following conditions were excluded including primary ocular diseases other than refractive errors and cataract (especially uveitis or other inflammatory diseases, which might influence the function of the choroid); intraocular surgeries before ocular injury; patients over 80; and patients without regular follow-ups for half a year. Eventually, 24 patients were enrolled in this study.

Clinical Evaluation

The clinical evaluation of all the enrolled patients was performed in the following order: demographic information (including age, sex), baseline information of trauma (including injured eye, type of injury, time interval from trauma to the primary surgery, time interval from trauma to the vitrectomy), and routine ophthalmic examinations (including best-corrected visual acuity (BCVA), intraocular pressure (IOP), and intraocular complications of the injured eye, which was assessed during exploratory vitrectomy surgery by two chief surgeons (MZZ and CHJ). The evaluation procedure was carried out following a standardized "Register of Eye Injury" form as reported in the previous study (10). The VA was converted to LogMAR for analysis. Counting fingers at 1-meter vision was converted to 1.87 LogMAR, Hand motions vision to 2.3 LogMAR, and light perception vision to 2.8 LogMAR, for those with no light perception, 4. LogMAR was applied (11).

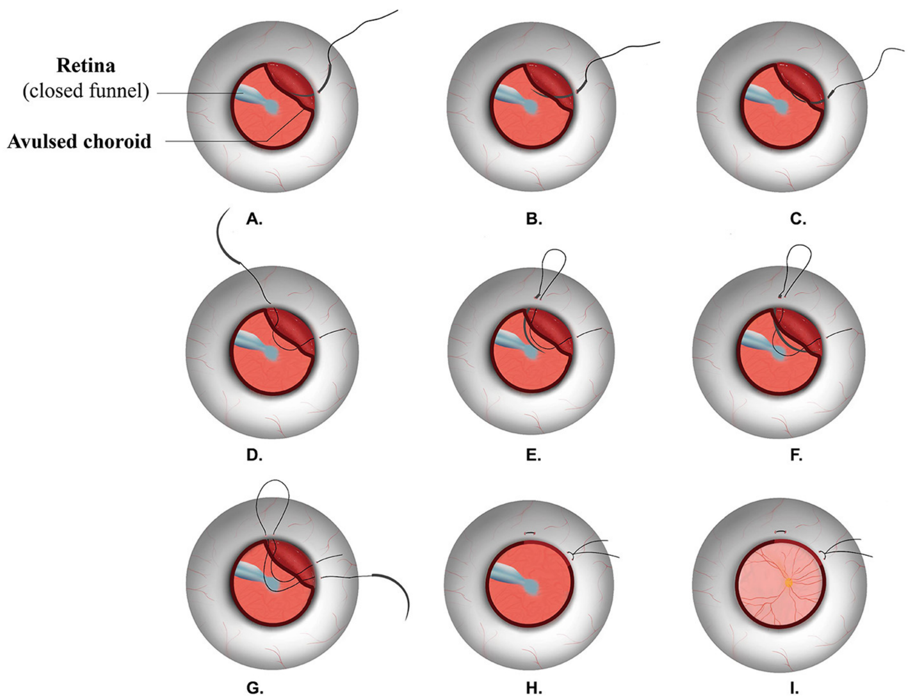

FIGURE 1 | Surgical procedures of TSS. TSS: trans-scleral mattress suturing. A long-curved needle with a 10-0 polypropylene suture **(A)** was inserted at the sclera 6 mm posterior to the limbus, **(B,C)** passed through the avulsed choroid, **(D)** exited from the sclera, **(E)** a U-turn was made, and the needle was reinserted near the exit site; **(F,G)** the suturing maneuver was repeated, passing through near the insertion site, **(H)** a knot was tied, **(I)** a retinal funnel was unfolded, and retina was reattached.

Postoperative follow-ups were regularly performed, and BCVA, IOP, retinal and choroidal reattachment rates, percentage of the silicone oil migration to suprachoroidal cavity, and postoperative complications were assessed at each follow-up. Subsequent treatment was applied according to the clinical findings at each follow-up.

Surgical Procedure

All patients received a standard 3-port 20-gauge pars plana vitrectomy under general anesthesia. After the removal of intraocular hemorrhage and other opacities in ocular media, the extension of the avulsed choroid was assessed, and the corresponding location was marked on the sclera. Suturing techniques, TSS or IOS, were applied to reattach the avulsed choroid to the sclera. IOS was chosen if the anterior part of the avulsed choroid was missing and/or the choroid was highly detached, making the suturing unreachable from the outside of the eye. The description of the two suturing techniques is as follows:

For patients receiving TSS (**Figure 1**), a long-curved needle with a 10-0 polypropylene suture (Alcon laboratories, Inc. 8065307901) was inserted into the eye at the sclera 6 mm posterior to the limbus, passed through the avulsed choroid, exited from the sclera, approximately 8- to 10-mm wide apart from the insertion site, and then a U-turn was made, the needle was reinserted near the exit site, and the suturing maneuver was repeated, passing through near the insertion site, and a knot was made. The passing route of the suture paralleled with the limbus. Several pairs of sutures were made to cover the extent of the choroidal avulsion.

For patients undergoing IOS (**Figure 2**), chandelier illumination was used to assist bimanual manipulation. A needle with 8-0 polyglactin 910 suture (ETHICON, LLC. EMW9560) was introduced into the vitreous cavity through the right port of 20G sclerotomy and was placed in the center of the vitreous cavity; two intraocular forceps (MR-G113T, Suzhou Mingren Medical Equipment Co., Ltd., China) were inserted through the sclerotomy on both sides, with the right forceps holding the needle and the left one capturing the anterior margin of the avulsed choroid to accomplish the suturing. The needle passed through the full-thickness choroid, lamellar sclera, and through the choroid again, trying to minimize sliding of the suture through the choroid, which can cause a cutting effect on the choroid. Then, the suture at the needle side was cut, and a needle was taken out of the eye before a knot was made by the two intraocular forceps. For each stitch, a new needle with a suture was used. Usually, three stitches were necessary to cover a 180° avulsion.

After the repair of the choroidal avulsion, the retinal funnel was unfolded, and the retina was reattached by additional procedures such as epiretinal or subretinal membrane peeling, retinotomy and retinectomy, use of perfluorocarbon

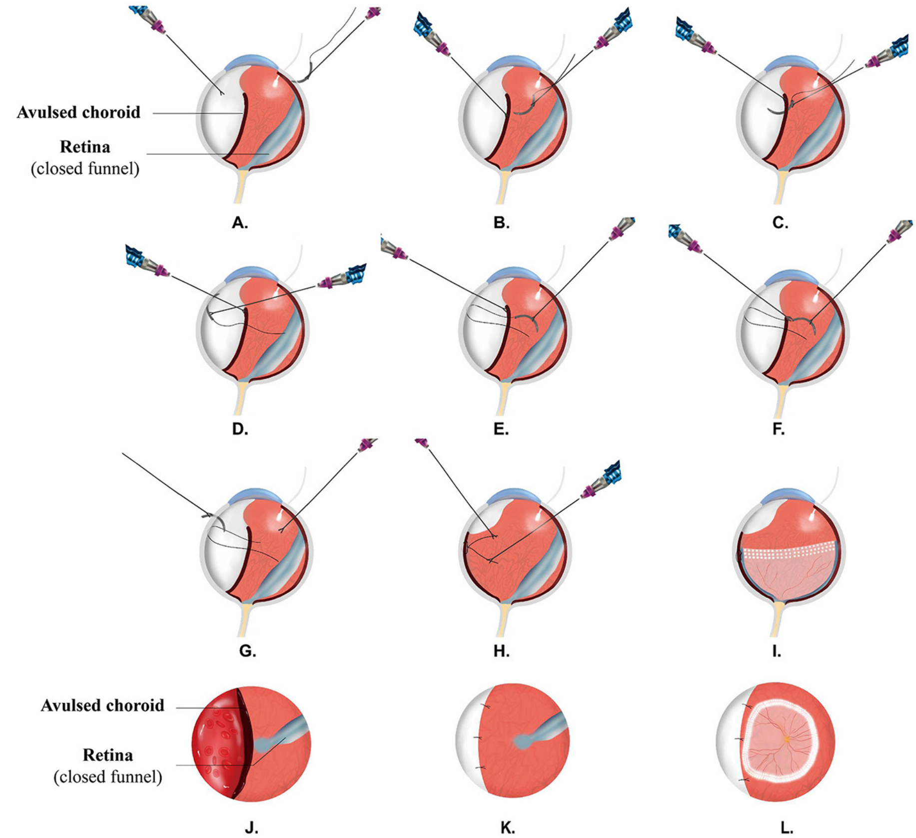

FIGURE 2 | Surgical procedures of IOS. IOS: intraocular suturing. **(A-I)** presents the sideview. Chandelier illumination was used to assist bimanual manipulation, **(A)** a needle with 8-0 polyglactin suture was introduced into the vitreous cavity through the right port of 20-G sclerotomy, **(B)** two intraocular forceps were inserted, with the right forceps holding the needle and the left one capturing the anterior margin of the avulsed choroid to accomplish the suturing. The needle passed through the full-thickness choroid **(C)**, lamellar sclera **(D)**, and through the choroid again **(E)**; suture at the needle side was cut **(F)**, and a needle was taken out of the eye **(G)** before a knot was tied **(H)** by the two intraocular forceps, **(I)** a retinal funnel was unfolded, and retina was reattached. **(J-L)** presents the front view. **(J)** Showing avulsed choroid with closed funnel retinal detachment, **(K)** the avulsed choroid was refixed to the sclera with intraocular-interrupted suturing, and the connection of vitreous cavity and suprachoroidal cavity was blocked, **(L)** the retinal funnel was unfolded, and retina was reattached.

liquid (PFCL), retinal photocoagulation, and silicon oil or gas tamponade.

Statistical Analyses

Statistical analyses were performed using SPSS software version 22.0 (SPSS, Inc., Chicago, IL). For each variable, grouped and overall analyses were conducted. Basic characteristics in all enrolled patients were described using descriptive statistics including means ± standard deviations for continuous variables, and frequencies (proportions) for categorical variables. Paired *t*-test was used to evaluate the differences of BCVA, IOP at follow-ups from the baseline. A $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and Preoperative Information

A total of 24 patients' eyes with choroidal avulsion (aged from 5 to 72) who underwent vitrectomy with choroidal suturing at Peking University Third Hospital between the period of April 2013 and July 2017 were enrolled, of which 19 patients underwent TSS and 5 patients with IOS. All patients finished the 1-year follow-up, and the mean overall follow-ups were 460 ± 83 days. Demographic and preoperative information, including age, sex, types of injury, and disease progression, is shown in **Table 1**.

In this study, 91.7% of patients were injured in a uniocular manner, 8.3% were binocularly injured, while only one eye suffered from choroidal avulsion and underwent choroid suturing procedures. Of all the enrolled patients, rupture constituted the majority of the injury types (91.7%), penetrating (4.2%), and contusion (4.2%) were also observed, all patients with open globe injury involved zone III. Additionally, all patients with open-globe injuries underwent primary globe repair in 48 h (ranged from 1 to 2 days) and received vitrectomy in an average of 24.8 ± 23.8 days (ranged from 1 to 120 days), with 26.1 ± 26.7 days in the TSS group (ranged from 1 to 120 days) and 27.3 ± 9.2 days in the IOS group (ranged from 17 to 36 days).

TABLE 1 | Basic characteristics of enrolled subjects.

Objectives	ALL ($n = 24$)	TSS ($n = 19$)	IOS ($n = 5$)
Age, mean ± SD	40.8 ± 15.0	40.8 ± 15.6	40.6 ± 9.1
Sex, *n* (%)			
Male	16 (66.7%)	11 (57.9%)	5 (100.0%)
Female	8 (33.3%)	8 (42.1%)	0 (0%)
Type of injury, *n* (%)			
Rupture	22 (91.7%)	17 (89.5%)	5 (100.0%)
Penetrating	1 (4.2%)	1 (5.3%)	0 (0%)
Contusion	1 (4.2%)	1 (5.3%)	0 (0%)
Traumatic zone, n (%)			
I/ II	0 (0%)	0 (0%)	0 (0%)
III	23 (100.0%)	18 (100.0%)	5 (100.0%)
Primary time interval, mean±SD (days)	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.0
Total time interval, mean±SD (days)	24.8 ± 23.8	26.1 ± 26.7	27.3 ± 9.2

TSS, transcleral suturing; IOS, intraocular suturing; n, number; SD, standard deviation; primary time interval, time interval between the occurrence of trauma and primary repairment of the globe; total time interval, time interval between the occurrence of trauma and vitrectomy.

TABLE 2 | Ocular characteristics and surgical interventions.

	ALL ($n = 24$)	TSS ($n = 19$)	IOS ($n = 5$)
Cornea wound/opacity, *n* (%)	17 (70.8%)	14 (73.7%)	3 (60.0%)
Irisdefect, *n* (%)	23 (95.8%)	18 (94.7%)	5 (100.0%)
Ciliary body defect (more than two quadrants involved), *n* (%)	13 (54.2%)	11 (57.9%)	2 (40.0%)
Hyphema, *n* (%)	21 (87.5%)	16 (84.2%)	5 (100.0%)
Lens, *n* (%)			
Extrusion	19 (79.2%)	14 (73.7%)	5 (100.0%)
Dislocation	2 (8.3%)	2 (10.5%)	0 (0%)
Subluxation	2 (8.3%)	2 (10.5%)	0 (0%)
Phakia	1 (4.2%)	1 (4.2%)	0 (0%)
Choroid avulsed extent, n (%)			
1 quadrant	7 (29.2%)	7 (36.8%)	0 (0%)
2 quadrants	17 (70.8%)	12 (63.2%)	5 (100.0%)
Severe intraocular hemorrhage, n (%)	24 (100.0%)	19 (100.0%)	5(100.0%)
Retina, n (%)			
Partial RD	5 (20.8%)	5 (26.3%)	0 (0%)
Total RD	5 (20.8%)	4 (21.1%)	1 (20.0%)
F-RD	14 (58.3%)	10 (52.6%)	4 (80.0%)
PVR, *n* (%)	14 (58.3%)	10 (52.6%)	4 (80.0%)
Surgical interventions, *n* (%)[a]			
Temporary keratoprosthesis	8 (33.3%)	5 (26.3%)	3 (60.0%)
Lensectomy	4 (16.7%)	4 (21.1%)	0 (0%)
Unfold of F-RD	14 (58.3%)	10 (52.6%)	4 (80.0%)
Retinotomy/retinectomy	20 (83.3%)	15 (78.9%)	5 (100.0%)
Membrane peeling	11 (45.8%)	8 (42.1%)	3 (60.0%)
C3F8	1 (4.2%)	1 (5.3%)	0 (0%)
SO	23 (95.8%)	18 (94.7%)	5 (100.0%)

n, number; RD, retinal detachment; F-RD, closed funnel retinal detachment; SO, silicone oil.
[a]*All cases underwent 20-gauge PPV; laser and perfluorocarbon were used in all.*

Intraoperative Findings

During the vitrectomy surgeries, quadrants of the avulsed choroid were assessed after the removal of vitreous hemorrhage, and the results are shown in **Table 2**. Complicated findings, including cornea wound or opacity, iris, and ciliary body injuries, lens conditions, retinal detachment, and proliferation were also recorded. All the patients underwent 20-gauge PPV; additional treatment procedures, such as temporary keratoprosthesis, phacoemulsification, and intraocular tamponade, were applied accordingly and shown in **Table 2**.

Anatomical Rehabilitation and Postoperative Interventions

Reattachment of the avulsed choroid was observed in twenty-two patients (91.7%) after choroid suturing throughout the follow-ups; the other two cases without reattachment were both from the TSS group, who were found to be complicated with silicone oil migration into the suprachoroidal space at 3 months after vitrectomy. Both patients further underwent drainage of the suprachoroidal silicone oil and scleral buckling to block the remaining connection between the vitreous and suprachoroidal cavity, and at the last follow-up, the choroids were attached. Retinal reattachment was accomplished in all patients 1 day after the surgery, while partial retinal detachment due to postoperative PVR was found in one case in the TSS group at 1 month, revision vitrectomy was performed, and at the last follow-up, all patients were found with retina attached. At the last visit, four eyes (16.7%) were silicone oil-free, including one eye with primary C3F8 tamponade. Two eyes received IOL suspension. Meanwhile, 83.3% (20/24) of the eyes were silicone oil-dependent, but none of the eyes developed atrophia bulbi.

Functional Rehabilitation at Each Follow-Up

Figure 3A shows the BCVA before the surgery and at each follow-up in all patients. Since one patient in the TSS group aged 5, at the time of trauma, could not cooperate at the sight examination, we only recorded the BCVA of this patient at the last follow-up. Overall, compared with the preoperative BCVA (3.57 ± 0.69), a significant improvement on LogMAR BCVA was observed at each follow-up after vitrectomy (3.07 ± 0.73 at Day 1, 2.90 ± 0.70 at Day 7, 2.95 ± 0.74 at Month 1, 2.97 ± 0.81 at Month 3, 2.89 ± 1.01 at Month 6, and 2.90 ± 1.06 at Year 1, and 2.82 ± 0.98 at the last visit, all with $p < 0.05$). A small fluctuation was observed during follow-ups; however, there were no significant differences among each follow-up (all with $p > 0.05$). The proportion of NLP was also observed to be reduced (**Figure 3B**) from 69.6% (16/23) before surgery to 34.8% (8/23) at Day 1, 21.7% (5/23) at Day 7, 30.4% (7/23) at Month 1, 34.8% (8/23) at Month 3, 39.1% (9/23) at Month 6, 39.1% (9/23) at Year 1, and, eventually, 37.5% (9/24) at the last follow-up.

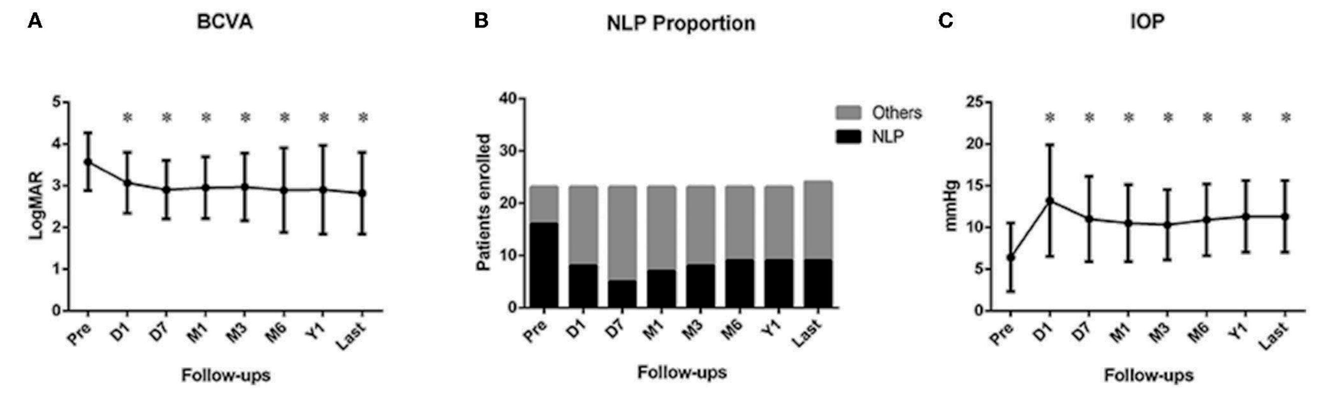

FIGURE 3 | Changes of best-corrected visual acuity (BCVA), intraocular pressure (IOP), and proportion of NLP at each follow-up. **(A)** Compared with the preoperative BCVA, a significant improvement in LogMAR BCVA was observed at each follow-up after vitrectomy (all with $p < 0.05$), **(B)** Proportion of NLP was observed to be reduced from before surgery at each follow-up. **(C)** Compared with the preoperation, IOP at each postoperative follow-up was significantly increased (all with $p < 0.05$). Pre: preoperation; D1: 1 day after vitrectomy; D7: 1 week after vitrectomy; M1: 1 month after vitrectomy; M3: 3 months after vitrectomy; M6: 6 months after vitrectomy; Y1: 1 year after vitrectomy; last: last follow-up. $^{*}p < 0.05$ compared with preoperation.

A significant elevation of IOP after vitrectomy was also observed (shown in **Figure 3C**). Compared with the preoperation (6.4 ± 4.1 mmHg), IOP at each postoperative follow-up, including Day 1 (13.2 ± 6.7 mmHg), Day 7 (11. ± 5.1 mmHg), Month 1 (10.5 ± 4.6 mmHg), Month 3 (10.3 ± 4.2 mmHg), Month 6 (10.9 ± 4.3 mmHg), Year 1 (11.3 ± 4.3 mmHg), and the last follow-up (11.3 ± 4.3 mmHg), was significantly increased (all with $p < 0.05$). Mean IOP at follow-ups after 1 month stayed rather stable, which indicates a long-term stable state in the patients undergoing choroidal suturing.

DISCUSSION

Choroid avulsion was one of the most severe traumatic conditions, which can lead to atrophia bulbi without treatment. The mechanism of choroidal avulsion has not been elucidated before. We speculate that the expulsive suprachoroidal hemorrhage leads to the separation of the choroid from the sclera first, and then the sudden increase of pressure and the shearing force in the suprachoroidal space cause the discontinuity of the detached choroid or sometimes, choroid and ciliary body disruption at the scleral spur as a whole unit, releasing the pressure in the suprachoroidal space by connection with the vitreous cavity. Meanwhile, external contusion or compression forces on the injured globe may further exacerbate the extent of the avulsion.

Due to the different histological compositions between choroid and retina, the avulsed choroid is less compliant than the detached retina to be reattached by the routine methods we use to treat retinal detachment. Very few surgical treatments have been attempted to repair choroidal avulsion. Jiang YR et al. reported a case in which medical fibrin glue was injected into the suprachoroidal cavity before the injection of the silicone oil, and the long-term outcome showed the retina and choroid were well attached (6). However, the fibrin glue can only be applied after fluid-air exchange in the non-water operation environment, which limited its use because, in many cases, the avulsed choroid should be repaired before the retina can be reattached. Meanwhile, Ma J et al. reported a suturing method in which a full-thickness scleral incision as long as the extension of the avulsion was made at the equator, and the avulsed choroid was incarcerated into the scleral incision and sutured together. They found 76.2% of eyes reached a complete choroid reattachment at 1 month after the surgery (7). Nevertheless, this suturing technique might lead to uveal exposure, which may further cause sympathetic ophthalmia. Besides, a full-thickness scleral incision at the equator may disrupt the integrity of the eyewall. Therefore, the current surgical procedures for choroidal avulsion all have their limitations.

In this study, we explored novel mattress suturing methods to repair the avulsed choroid. In both TSS and IOS, the avulsed choroid was refixed to the inner surface of the sclera. Our results indicated that these therapies had good effects on the restoration of ocular structures, with 91.7% of cases (22/24) accomplishing a successful choroid reattachment after primary vitrectomy and choroid suturing, and 8.3% (2/24) acquiring choroidal reattachment with secondary scleral buckling. On the other hand, reattachment of the choroid increased the rate of retinal attachment (95.8%); only one patient was complicated with PVR and partial retinal detachment at 1 month after the surgery, and the second vitrectomy accomplished the reattachment of retina, and at the last follow-up, all patients were observed with the full attached retina.

Visual improvement was directly correlated with the reattachment of the retina and choroid, with a significant improvement on LogMAR BCVA from 3.57 ± 0.69 before surgery to 2.82 ± 0.98 at the last follow-up ($p < 0.05$), and the proportion of NLP was also reduced from 69.6 to 37.5%. Eyes that were still NLP at the last follow-up might be owing to the ischemic injuries of the optic nerve, since the wide avulsion of short posterior ciliary arteries would shut the blood supply from its branches to the optic nerve (12).

Meanwhile, the IOP of the injured eye significantly increased from 6.4 ± 4.1 mmHg preoperatively to 11.9 ± 5.1 mmHg at the last visit ($p < 0.05$). We assume that suturing of the choroid contributes to the postoperative improvement of IOP, owing to the blockage of the abnormal passage between the vitreous cavity and the suprachoroidal cavity. However, since there was no control group in this study and silicone oil was not finally removed in twenty eyes, and the scleral buckle was also applied in two eyes, we cannot estimate exactly how beneficial the suturing techniques have on the maintenance of IOP. But, based on our previous experience, if choroidal avulsion is left untreated, phthisis will ensue despite silicone oil tamponade. Moreover, suturing of the choroid can only prevent aqueous humor passage through the suprachoroidal space but has little effect on aqueous humor production, unless the ciliary body is detached along with the choroid as a whole. In this series, therefore, twenty patients (83.3%) were silicone oil-dependent at the last visit. Dysfunction of the ciliary body complicated with severe ciliary body injury should be the main reason for silicone oil dependence in these eyes.

In this study, among the two techniques, IOS was more innovative. To our knowledge, we were the first to report putting the needle into the vitreous cavity to suture the choroid. This technique was chosen if the anterior part of the avulsed choroid was missing and/or the choroid was highly detached, making the suturing unreachable from the outside of the eye. Regarding this technique, several issues need to be noted here. First, when performing IOS, after the needle passes through the full-thickness choroid, lamellar sclera, and through the choroid again, it is advisable to cut the suture at the needle side and take the needle out of the eye before a knot is made, which decreases sliding of the suture through the choroid and minimizes the cutting effect on the choroid, as well as avoids additional damage to the intraocular tissue by the sharp needle. We suggest that a new needle with a suture is used for each stitch. Second, the blood circulation in the choroid is severely affected after avulsion occurs; therefore, suturing the avulsed choroid seldom causes bleeding, and, if it does, it is controllable with the endo-diathermy. Third, although the suture used in IOS was absorbable, we did not find postoperative suture failure in our cases. The avulsion did not recur after the suture was absorbed, implying that adhesion between choroid and sclera was generated, which assured the long-term attachment of the choroid. Last, although our results showed that intraocular suturing of the avulsed choroid was technically feasible, it takes experience and proficiency to perform this technique. Currently, there are no surgical instruments specifically designed for this suturing technique. The average operating time of vitrectomy combined with IOS in trauma cases is relatively long (∼4 h).

There were also some limitations of this study: firstly, due to the relatively low incidence of choroidal avulsion, the number of the enrolled cases were limited, especially for the IOS group, and we did not analyze the influence factors of the prognosis, nor the difference between groups; long-term enrollment of patients is required in the future. Secondly, since some of the patients were from remote areas across China other than our city, part of the follow-up examinations was performed at the local hospital, and the follow-up information was acquired by a telephone interview, which might lead to some extent of information bias, which we should be aware of when interpreting our results.

CONCLUSIONS

In conclusion, the current study explored two different suturing methods in the treatment of choroidal avulsion, which is one of the most severe ocular traumatic conditions. The follow-up results presented a high retinal and choroidal reattachment rate and significant improvements for the visual function and IOP stabilization, demonstrating these techniques may provide a much better prognosis for such severely injured eyes which otherwise cannot be preserved.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research and Ethics Committee of Peking University Third Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ZM and HC supervised the project. JY and HC wrote the manuscript. JY and KF conducted the statistical analysis. CW, HC, XF, and ZM collected the data. All the authors contributed to the article and approved the submitted version.

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Pediatric Open Globe Injury in Central China

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Purpose: To describe the characteristics, managements, and outcomes of pediatric open globe injury (OGI) in central China.

Methods: Retrospective chart review of pediatric diagnosis in patients with OGI between 2017 and 2020 at Henan Eye Hospital. Four hundred and one eyes of the patients younger than 17 years were included in this study. Open globe injury was classified according to the Birmingham Eye Trauma Terminology system (BETT). Age, sex, history, cause, month of trauma, treatment received, and outcomes were recorded. Visual acuity was documented according to standard visual acuity chart (decimals).

Results: Four hundred and one eyes of patients were included in the study. The mean age was 6.6 ± 3.4 years with the range from 8 months to 16 years. Open globe injuries (OGIs) occurred most frequently in the 2–8 year age and significant male predominance was noted (70.8%). The incidence of pediatric OGIs was lowest in summer months while it increased in the winter months. The most common type of pediatric OGI was penetration (89%). Scissors/knife accounted for 22%, followed by pen/pencil (15.2%), and wood/bamboo sticks (14.5%) of all the pediatric OGIs. Among the injuries, the most frequently involved is the zone I (76.1%). Initially, 70.8% of the eyes received primary debridement and wound closure without any additional intervention, while only one eye has no possibility of anatomical reconstruction when it received an evisceration. After the initial management, 198 eyes received subsequent operation, including 44 eyes that underwent cataract removal + intraocular lens (IOL) implantation, and 24 eyes underwent IOL implantation. Finally, over 6 months of follow-up, 129 eyes (32.2%) got visual acuity (VA) of 0.3–1.5 and, 63 eyes (15.7%) got VA of 0.01–0.25, while 11 eyes (2.7%) were eviscerated.

Conclusion: This study showed that pediatric OGIs in central China are most seen in 2–8-year age group with significant male predominance. Scissors/knife, pen/pencil, and wood/bamboo sticks accounted for over half of all cases. Pediatric OGIs often result in significant vision loss. In some severe cases (2.7%), evisceration was ultimately performed. We should call on the public to pay more attention to their children and build a safer environment for them.

Keywords: pediatric, Central China, open-globe injury, trauma, epidemiology

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INTRODUCTION

Open globe injury (OGI) refers to the ocular trauma with full thickness wound of the eyewall (1). It is a major cause of non-congenital monocular visual loss in the pediatric population (2–4) and it can cause a lifelong impact on children. In spite of medical and technical advancements, pediatric OGIs may result in substantial visual morbidity and lifelong sequelae. Severe pediatric OGIs also impose financial burdens on society and families. In addition to the primary impact by the trauma itself, OGIs can result to amblyopia in younger children. Children are the most prone to getting their eyes hurt because of lesser ability to recognize hazards and less focused moves.

Henan province is a major agricultural province that lies in central China. Latest population census shows that the population of Henan was about 100 million (99,366 thousands) and the population of 0–15 years old was about 24,406 thousands. Henan Eye Hospital is one of the largest ophthalmic centers in Henan Province and receives large numbers of patients with pediatric ocular trauma every year.

With regards to ocular trauma, prevention is more important than treatment. In order to develop ocular safety education and injury prevention programs, it is important to understand the epidemiology and characteristics of OGI in pediatric patients. The aim of this study was to investigate the characteristics, treatments, and outcomes of pediatric OGIs diagnosed and treated at Henan Eye Hospital.

METHODS

We retrospectively reviewed all the patients who were admitted and treated at Henan Eye Hospital between 2017 and 2020. Most self-sealed globe injuries with low risk of infection will be treated by eye drops (antibiotics and others) and will not be admitted to hospital. However, self-sealed globe injuries but with high risk of infection and severe open globe injuries will be admitted to hospital for surgery or observation. Attending doctors will deal with simple OGI such as wound closure, ocular injection, and so on. Senior surgeon on duty will perform for complex surgery such as vitrectomy + IOFB removal, and so on. Patients will be referred to Ocular Trauma center if necessary after the primary treatment.

Four hundred and one eyes of 401 patients younger than 17 years were included in the study, with the cut-off age of 16, and were consistent with prior studies (5–7). The OGIs were classified according to the Birmingham Eye Trauma Terminology system (BETT) (1). This classification consists of rupture (full-thickness wound of the eyewall, caused by a blunt object), penetrating injury (entrance wound/s only, caused by sharp object/s), intraocular foreign body (IOFB), or perforating injury (separate entrance and exit wounds) (8). The zone of injury was defined as zone I (wound involves only cornea), zone II (wound extends into anterior 5 mm of sclera), and zone III (wound involves sclera extending more than 5 mm from the limbus) (8).

Visual acuity was documented according to the standard visual acuity chart (decimals).

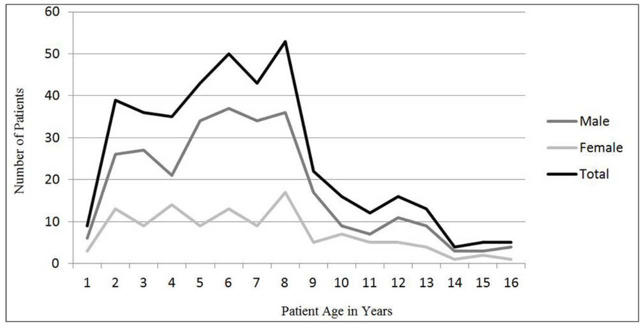

FIGURE 1 | Sex and age distribution of OGI in children.

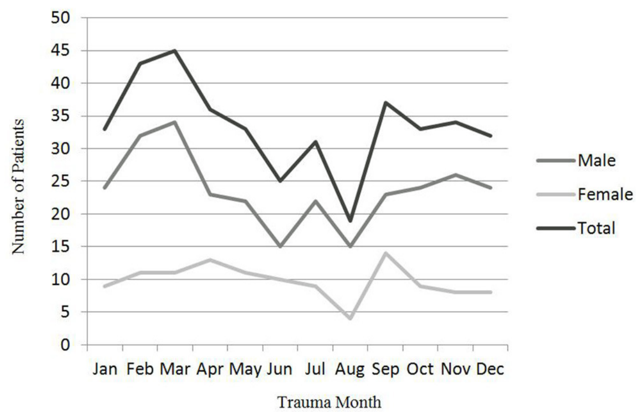

FIGURE 2 | Sex and trauma month distribution of OGI in children.

Data were analyzed using Microsoft Office Excel 2007 (Microsoft, USA). Continuous and categorical variables were displayed as means ± standard deviation (SD) and percentages, respectively.

Ethics approval for the study was granted by Henan Eye Institute, Henan Eye Hospital, Henan Provincial People's Hospital Human Research Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki.

RESULTS

In the 4 years between 2017 and 2020, 1,902 cases (1,908 eyes) of patients with OGI were admitted and treated at Henan Eye Hospital. Of all the OGIs, 401 eyes (21.0%) of 401 patients younger than 17 years were included in our analyses. The mean age was 6.6 ± 3.4 years with the range from 8 months to 16 years. The right eye was injured in 218 (54.4%) cases. Most frequently, OGIs occur in the 2–8 years age (**Figure 1**) and these patients aged 2–8 years accounted for 74.6% (299 patients) of all cases. Significant male predominance was noted (70.8%). Male-female ratio was 2.43. The incidence of pediatric OGI was low in summer months and was lowest in August (**Figure 2**).

Causative objects of the OGIs are listed in **Table 1**. Injuries were most often caused by scissors and knife (22.0%). Sixty-seven

TABLE 1 | Causes of pediatric open globe injuries.

Cause	*n*	%
Scissors, knife	88	22.0
Pen, pencil	61	15.2
Wood or bamboo stick	58	14.5
Metal wire, metal stick	32	8.0
Fall, tumble	31	7.7
Toy	24	6.0
Glass	23	5.7
Fireworks, firecrackers	17	4.2
Needle, syringe	6	1.5
Flying stone	6	1.5
Key	3	0.8
Traffic accident	3	0.8
Lighter explosion	3	0.8
Straw	3	0.8
Door	3	0.8
Book	2	0.5
Beak of cock	2	0.5
Violence	2	0.5
Others* and unknown	34	8.2
Total	401	100.0

*Others include unusual causes such as fitness equipment, fishing line, and so on.

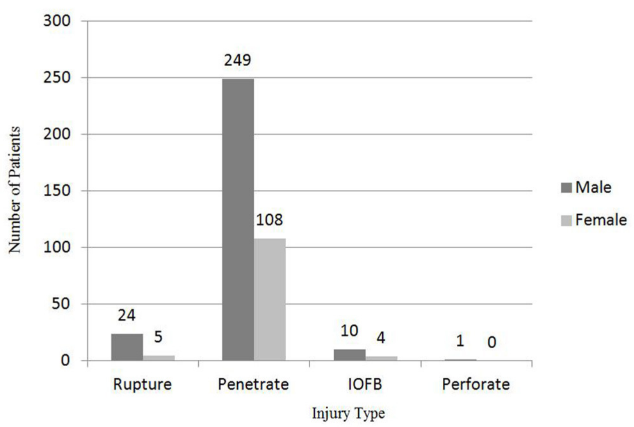

FIGURE 3 | Sex and injury type distribution of OGI in children.

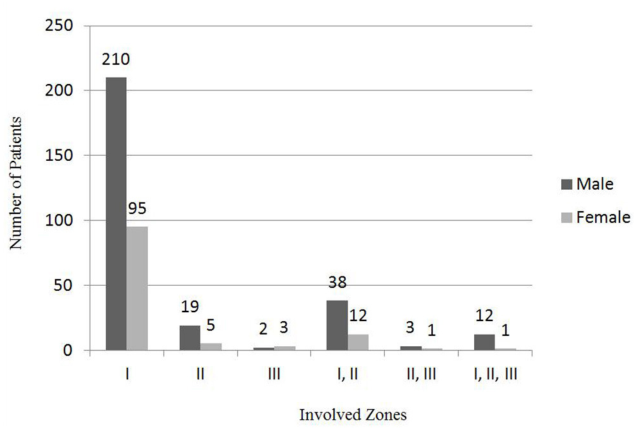

FIGURE 4 | Distribution of gender and zones involved in pediatric OGI.

eyes (16.7%) were injured by scissors. Pen and pencil accounted for 15.2% cases (88 eyes) of pediatric OGIs.

In the present study, the most common type of pediatric OGI was penetration (89%) (**Figure 3**). There was only one case of perforation in the present study. It was a 2-year old boy whose right eye was injured by a wood stick. Perforation was diagnosed during the secondary surgery (cataract removal +vitrectomy + silicone oil) 40 days after the wound closure. Fortunately, silicone oil was safely removed 3 months after the second surgery. Of all the 11 intraocular foreign body (IOFB) cases, IOFB was eyelash in 7 eyes.

Injuries most frequently involved zone I (76.1%; $n = 305$) (I group) (**Figure 4**). Fifty pediatric OGIs (12.5%) involved zones I and II (I, II groups), and 24 eyes (12.5%) involved zone II (II group). Thirteen eyes (3.2%) involved zones I, II, and III (I, II, III group). Five eyes (1.2%) involved zone III (III group) and 4 eyes (1%) involved zones II and III (II, III group).

Initially, 70.8% eyes received primary debridement and wound closure without additional intervention, and only one eye has no possibility of anatomical reconstruction received evisceration (**Table 2**). Twenty-nine eyes (7.2%) received wound closure and cataract removal, while 16 eyes received wound closure and intraocular injection (antibiotics). Nine eyes (2.2%) received wound closure, cataract removal, and anterior vitrectomy. Seven eyes (1.8%) only received intraocular injection (antibiotics) because the injuries were self-sealed, and the infection was under control. Comprehensive management, at least, included vitrectomy, silicone oil tamponade, and other management such as wound closure, cataract removal, intraocular injection, and IOFB removal. Six eyes (1.5%) received comprehensive management as the primary surgery.

After the initial management, 198 eyes (49.4%) received subsequent operation (**Table 3**), including 44 eyes (22.2%) that underwent cataract removal + IOL implantation, while 24 eyes (12.1%) underwent IOL implantation. Twenty-two eyes (11.1%) received vitrectomy and silicone oil tamponade, and 21 eyes (10.6%) received cataract removal, vitrectomy, and silicone oil tamponade at the secondary intervention. Seven eyes got eviscerated at the secondary intervention. Another three eyes were eviscerated at the third, fourth, and fifth intervention, respectively. Eleven eyes were eviscerated eventually (including one eye that got eviscerated at the first intervention).

Finally, over 6 months of follow-up, 129 eyes (32.2%) got visual acuity (VA) of 0.3–1.5, and 63 eyes (15.7%) got VA of 0.01–0.25, while 11 eyes (2.7%) were eviscerated (**Table 4**).

Of all the 401 pediatric OGI cases, 18 eyes (4.5%) had never received any surgery because they were self-sealed globe injuries. Almost half (49.4%; $n = 198$) of the eyes sampling

TABLE 2 | Primary surgery.

Surgical options	*n*	%
Wound closure	284	70.8
Wound closure + cataract removal	29	7.2
Wound closure + intraocular injection	16	4.0
Wound closure + cataract removal + anterior vitrectomy	9	2.2
Wound closure + cataract removal + IOL implantation	2	0.5
Wound closure + cataract removal + IOFB removal	2	0.5
Wound closure + IOFB removal	2	0.5
Wound closure + cataract removal+IOFB removal	2	0.5
Wound closure + intraocular injection + IOFB removal + intraocular injection	1	0.25
Wound closure + cataract removal + anterior vitrectomy + IOFB removal+intraocular injection	2	0.5
Wound closure + anterior vitrectomy	1	0.25
Cataract removal + IOL implantation	3	0.75
Cataract removal + anterior vitrectomy + IOL implantation	3	0.75
Comprehensive management	6	1.5
Intraocular injection	7	1.8
Evisceration	1	0.25
Re-formation of anterior chamber	1	0.25
No surgery	30	7.5
Total	401	100

IOL, intraocular lens; IOFB, intraocular foreign body.

TABLE 3 | Secondary intervention.

Surgical options	*n*	%
Cataract removal + IOL implantation	44	22.2
IOL implantation	24	12.1
Vitrectomy + silicone oil	22	11.1
Cataract removal + vitrectomy+silicone oil	21	10.6
Cataract removal	15	7.6
Cataract removal + anterior vitrectomy+IOL	14	7.1
Cataract removal + vitrectomy	12	6.1
Cataract removal + anterior vitrectomy	9	4.6
Intraocular injection	6	3.0
IOL implantation + anterior vitrectomy	5	2.5
IOL implantation + silicone oil removal	3	1.5
Anterior vitrectomy	3	1.5
Vitrectomy + IOFB removal+silicone oil	2	1.0
Cataract removal + vitrectomy + IOFB removal + intraocular injection	1	0.5
Cataract removal + vitrectomy + intraocular injection	1	0.5
Vitrectomy + intraocular injection	1	0.5
Evisceration	7	3.5
Others*	8	4.1
Total	198	100

**Others include unusual intervention such treatment of iris cysts, iris and ciliary body surgery.*
IOL, intraocular lens; IOFB, intraocular foreign body.

TABLE 4 | Final outcomes of 401 eyes of pediatric OGIs.

Outcomes	*n*	%
0.3–1.5	129	32.2
0.01–0.25	63	15.7
HM-CF	8	2.0
Silicone oil dependence	30	7.5
Atrophy	5	1.3
Evisceration	11	2.7
Loss of follow-up	57	14.2
Others*	98	24.4
Total	401	100

**Others include patients who was too young to test vision acuity.*
HM, hand movement; CF, counting fingure.

received only once surgery (**Figure 5**). One hundred and twenty-four eyes (30.9%) underwent the surgeries twice and 44 eyes (11.0%) underwent the surgeries for three times. Thirteen (3.2%) and four eyes (1%) received four times and five times of surgeries, respectively.

In this study, 36 eyes (9%) were diagnosed with endophthalmitis. One case developed endophthalmitis 2 years after the ocular trauma by scissors due to the reopening and the leakage of the primary limbus wound. Twenty eyes (5%) were diagnosed with endophthalmitis at first management and received an intraocular injection (antibiotics) or comprehensive management. Three eyes were eviscerated at the second, third, and fifth intervention, respectively. One eye got atrophic after six interventions. One eye of a 2-year old boy got atrophic after the primary wound closure without further ocular treatment because of high fever and poor general condition. The infection was controlled at pediatric department. Ten eyes received intraocular injection (antibiotics) and/or comprehensive management. One eye achieved VA of 0.8 at the end of follow-up.

Two eyes (0.5%) developed iris cyst and 1 eye (0.25%) developed sympathetic ophthalmia 3 weeks after the ocular trauma.

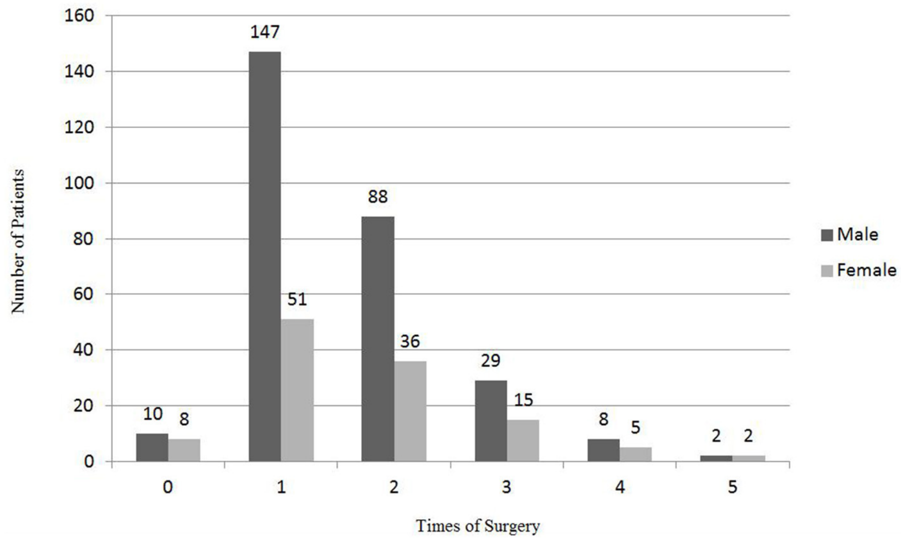

FIGURE 5 | Distribution of gender and times of surgery for pediatric OGI.

DISCUSSION

The Birmingham Eye Trauma Terminology system (BETT) provides an unambiguous, consistent, simple, and comprehensive system to describe any types of mechanical globe trauma. According to BETT, open-globe injury (OGI) refers to the ocular trauma with full thickness wound of the eyewall (1) and it consists of a rupture, penetrating and perforating IOFB.

In this study, 21% of all OGIs were children younger than 17 years old. The proportion of pediatric OGI was 9.26–22.99% in other previous studies from other countries (9–12). However, in the study of Batur et al. (13), the proportion was 67.7%. Similarly, it was 43.1–68.9% in other studies conducted in Turkey (14, 15). The high proportion of pediatric OGI in children could be attributed to the high population growth rate and high proportion of the children.

The male-female ratio was 2.43 in our study. The male-female ratio was 1.44–5.13 in other previous studies (11–13, 16–22). The differences of male-female ratio among different regions or countries could be related to many factors.

Compared to the study of Batur et al. (13), there were many similarities and other differences. Both studies have evaluated patients aged 16 years or younger. The mean age of the patients was 7 ± 3.7 years in the study of Batur et al. (13), and it was 6.6 ± 3.4 years in our study. According to the study of Batur et al. (13), OGI occurred most frequently in the 3-to-7-year age group, and it was 2-to-8-year age group in our study. Except the difference of proportion of OGIs in children, another interesting difference was the month of distribution of OGI in children. The incidence of OGI decreased in winter months and increased in summer months in the study of Batur et al. (13), starting in May and reaching a peak in August. Conversely, our study showed that the incidence of pediatric OGI was low in summer months and it was lowest in August (4.7%; $n = 19$) (**Figure 2**). It was highest in March (11.2%; $n = 45$). The reason of the difference between the two studies was unclear. Temperature in Henan, China is similar to that in Sanliufa, Turkey and it is highest in August every year.

Causative objects of the ocular trauma in our study were scissors, knives, pen/pencil, sticks, and other sharp objects. It was consistent with other previous studies (11, 13, 17).

The primary repair to maintain the integrity of the globe is the appropriate choice for initial treatment of OGIs (13). Simple primary repair was performed in 70.8% of eyes in our study. In some complicated cases such as cataract with rupture of capsule, IOFB, vitreous prolapse, and suspect of endophthalmitis, wound closure combined with other procedures were carried out in 18% of eyes.

Of all the 401 pediatric OGI cases, 18 eyes (4.5%) with self-sealed globe injuries had never received any surgery and almost half (49.4%) of the eyes received one surgery. One hundred and twenty-four eyes (30.9%) underwent surgeries for two times and 44 eyes (11.0%) underwent surgeries for three times. Thirteen (3.2%) and four eyes (1%) received surgeries for 4 times and 5 times, respectively. It was a little different from the result of Batur et al. (13). In the study of Batur et al. (10), 64.4% of the eyes required one surgical procedure, 26.1% required two, and 6.2% required three separate procedures.

One of the major differences between pediatric and adult OGIs is the difficulty of assessing VA in children immediately after the trauma and at the follow-up. It is more difficult to assess VA immediately after trauma in children because of pain, discomfort, and fear among them. Additionally, manipulation of the globe may cause further damage and expulsion of intraocular contents. Almost half of the patients could not provide VA assessment initially and 24.4 patients could not carry out VA assessment at follow-up. In the present study, 129 eyes (32.2%) got visual acuity (VA) of 0.3–1.5 and 63 eyes (15.7%) got VA of 0.01–0.25.

In this study, except one case developed endophthalmitis 2 years after the ocular trauma by scissors due to the reopening and leakage of the primary limbus wound, 35 eyes (8.7%) were diagnosed with endophthalmitis at primary or secondary management. In the study of Behbehani et al. (19), only one eye (1.1%) developed endophthalmitis of all the pediatric 95 patients. In the study of Lesniak et al. (8), there was no one who developed endophthalmitis of all the pediatric 89 patients. In another study, of all the 213 patients, eight (3.7%) eyes had the clinical diagnosis of posttraumatic endophthalmitis (16). While in the study of Choovuthayakorn et al. (12), endophthalmitis occurred in 15 of the 49 patients (30.6 %). The incidence of post-traumatic endophthalmitis is higher in the subjects living in rural areas (23).

This study reviewed the characteristics, managements, and outcomes of pediatric open globe injury (OGI) in central China. It has several potential limitations. First, this is a retrospective study in nature. Second, the data were collected in a single institution. Third, the differences in patient selection and surgical technique between experts could lead to bias. Thus, a prospective study is warranted in the future.

Nonetheless, to our knowledge, the present study is the first to demonstrate the characteristics, managements, and outcomes of pediatric open globe injury (OGI) in central China. It is helpful to carry out preventive program to reduce the occurrence of ocular trauma in children. The authors of this study usually published relevant publicity and education through WeChat, the website of the hospital and other We-Media. The authors had also been invited to the local TV show and broadcast programs every year to educate the public how to prevent ocular trauma in children. However, it seems far from enough. The parents or guardians should pay more attention to the children and build much safer environment for their growth. However, the left-behind children in rural areas do not usually get intensive care from their grandparents or other guardians. Fortunately, the government had realized the problem of these left-behind children. More and more of these children will stay with their parents.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Henan Eye Institute, Henan Eye Hospital, Henan Provincial People's Hospital Human Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XZ and HC organized the database. HC performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to conception, design of the study, manuscript revision, read, and approved the submitted version.

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Exploring Minimum Secondary Injury for the Treatment of Ocular Trauma With Giant Intraocular Foreign Bodies

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Purpose: To investigate the clinical therapy for giant intraocular foreign bodies (IOFBs) and evaluate the best treatment method with minimum secondary injury.

Methods: We retrospectively analyzed the data of 73 eyes of 73 patients with ocular trauma caused by giant IOFBs between January 2016 and December 2018. The IOFB size, localization, shape, and magnetic properties were recorded. The best corrected visual acuity (BCVA), ocular tissue injuries, entrance wound, interval time from injury to second phase surgery, silicone oil removal, and globe recovery were also observed. The cases were divided into three groups based on the following IOFB extraction paths: limbus path, the pars plana path, and the entrance wound path. The BCVA, IOFB size and shape, the wound, endophthalmitis, and silicone oil removal were compared among the three groups.

Results: The IOFBs were 46 cases of magnetic and 27 cases of nonmagnetic, with a shape of thin flat in 19 cases, thick flat in 12 cases, long in seven cases, and irregular in 35 cases. Multiple damages were caused by the giant IOFBs, mainly involving the severe cornea, lens, and retina injuries. The postoperative BCVA increased compared with the preoperative BCVA ($z = -6.06$, $P < 0.01$). The rate of recovery from blindness was 40.85% (29/71). The thin flat IOFB and long IOFB resulted in a better postoperative BCVA than the other two IOFB shapes (all $P < 0.05$). The irregular IOFB had a poorer silicone oil removal rate than the other three IOFB shapes (all $P < 0.05$). The IOFB extraction followed the limbus path in 18 cases, pars plana path in 27 cases, and entrance wound path in 28 cases. The IOFB length and width in the pars plana path group were significantly lower than that in the limbus path group (all $P < 0.05$), the preoperative BCVA of the pars plana path group was superior to that of the limbus path group ($P < 0.05$), and the IOFB length, width, and entrance wound length in the pars plana path group were significantly lower than in the entrance wound path group (all $P < 0.05$). But the postoperative BCVA in the pars plana path group was not better than that in the other two groups (all $P > 0.05$). The postoperative BCVA of the entrance wound path group was significantly superior to that of the limbus path group ($z = -2.01$, $P = 0.04$), while there was no difference between the two groups in IOFB length, width, entrance wound length, or preoperative BCVA (all $P > 0.05$).

Conclusion: The entrance wound path would benefit to minimize secondary injury in giant IOFB extraction procedure, compared with the limbus and pars plana path.

Keywords: intraocular foreign body, giant, secondary injury, extraction, surgery, ocular trauma

INTRODUCTION

Ocular trauma is a major cause of blindness (1). Intraocular foreign body (IOFB) is a common type of open global injury with an occurrence rate of 28.60% (2). It was one of the chief causes of poor visual acuity prognosis in open globe injuries (3). IOFBs can cause mechanical, chemical, and biological injuries to the eye (4). The manifestations and prognosis of IOFB injuries vary depending on IOFB size, characteristics, and environment. Furthermore, the severity of mechanical eye damage by IOFB is related to its own size, weight, and kinetic energy (5), and the risk of poor visual acuity prognosis has been reported to increase 1.21-fold for every 1 mm of addition in IOFB length (6). Giant IOFBs cause both penetrating and blunt eye injuries including prolapse of intraocular contents and severe retinal and choroidal damage. Surgery for the extraction of giant IOFBs is one of the most difficult operations for eye injuries, as secondary injuries inevitably occur during the extraction procedure (7). A combined surgery with minimal incision pars plana vitrectomy (PPV) and giant IOFB extraction has been developed with the aim of decreasing secondary injury during IOFB extraction (8, 9). In this study, we analyzed the clinical manifestation and treatment of giant IOFB injuries using various extraction paths to discuss the best methods for decreasing secondary injuries during surgical extraction of giant IOFBs.

MATERIALS AND METHODS

General Materials

We conducted a retrospective cohort study on a series of giant IOFB injuries. Seventy-three patients with giant IOFB injuries (73 eyes) were hospitalized for surgical therapy in the Fundus/Ocular Trauma Diseases Department at the First Affiliated Hospital of Zhengzhou University between January 2016 and December 2018. This study met the requirements of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and the patients had provided informed consent.

The inclusion criteria were the following: First, the IOFB must be giant, defined as that with a length $\geq$10 mm, width $\geq$4 mm, (or) thickness $\geq$3 mm (10). Second, the patient's required first-aid therapy at our hospital after the eye injury, or the patients were transferred to our hospital within 5 days after debridement and suture surgery at other hospitals. Third, the patients had no other severe eye disease, except for IOFB eye injury. Fourth, none of the patients had any systemic diseases. The patients with any of the following manifestations were excluded from our observation group. First, the IOFB was incarcerated in the entrance wound so that part of it was exposed outside the eyeball. Second, the patients underwent evisceration during emergency debridement and suture surgery. Third, the patients had manifested most or all the retina prolapsed out of the injured eye in primary or secondary surgery. Fourth, the length of the IOFB entrance wound $\leq$3 mm. Fifth, the patients with concomitant diseases such as craniocerebral injury or other systemic organ injuries, systemic organic diseases, primary eye diseases, or cases lost to follow-up.

Abbreviations: IOFB, intraocular foreign body; BCVA, best corrected visual acuity; IOP, intraocular pressure; NLP, no light perception; LP, light perception; HM, hand movement; CF, counting finger; OCT, optical coherence tomography.

Surgical Method and IOFB Extraction Path

The patients routinely underwent emergency debridement and suture procedures after the injury. The second phase of giant IOFB extraction combined with vitrectomy and global reconstruction was performed subsequently. This included the following surgical procedures according to the necessity of global reconstruction, such as giant IOFB extraction, vitrectomy, lensectomy, epiretinal membrane peeling, retinal photocoagulation/cryocoagulation, and intraocular silicone oil tamponade. All patients accepted silicone oil tamponade because of the severe ocular damage.

If proliferative vitreoretinopathy was observed during follow-up, the third surgery for epiretinal membrane peeling would be performed. The silicone oil removal surgery was performed when the globe was stable and the retina was restored for $\geq$3 months. All patients in this study were followed up for $\geq$6 months after the latest surgery.

There were three paths for IOFB extraction in this study: the limbus path, the pars plana path, and the entrance wound path. In the limbus path procedure, a limbus tunnel incision was prepared after vitrectomy and lensectomy. The IOFB was then lifted into the anterior chamber or the pupil area using intraocular forceps, and another forceps was placed into the anterior chamber from the limbus tunnel incision to relay the IOFB and pull it out of the eyeball. A magnetic IOFB could also be relayed and extracted using a magnetic rod. Part of the patients underwent IOFB extraction using a pars plana incision path. After vitrectomy, the proliferating membrane around the IOFB was released. The pars plana incision for vitrectomy was enlarged, and the IOFB was extracted from this incision using forceps or a magnetic rod. As to the entrance wound path for IOFB extraction, vitrectomy and lensectomy were performed first; then, the IOFB was released from its surrounding proliferative membrane, and the wound suture of the stitched cornea (or the partial anterior sclera) was removed. The IOFB was subsequently lifted into the anterior

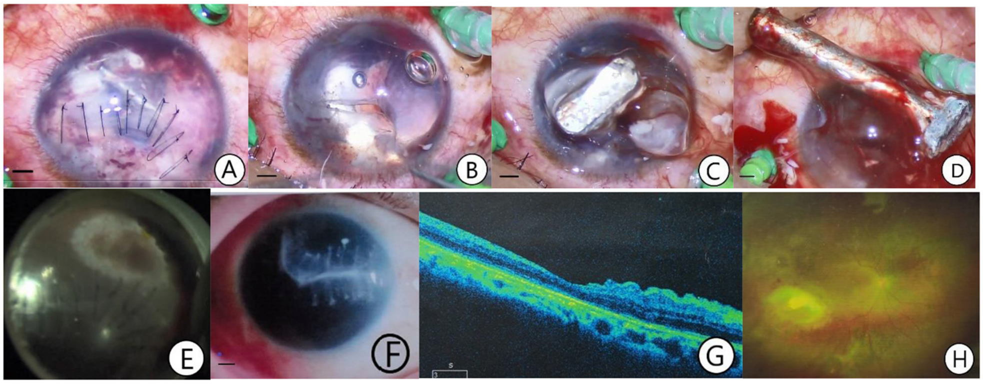

FIGURE 1 | A case of giant IOFB extracted from the entrance wound path. The patient was a 41-year-old man admitted to the hospital 8 h after an eye injury caused by a nail. An emergency debridement and suture procedure were performed, and the combined second phase surgery of giant IOFB extraction from the entrance wound path, pars plana vitrectomy, retinectomy, retinal photocoagulation, and silicone oil tamponade was performed 24 h after the injury **(A–E)**. The silicone oil was removed in 4 months. The retina was recovered with a scar formation at the retinal wound caused by the IOFB. A postoperative BCVA of 0.1 was achieved **(F–H)**. **(A)** One end of the giant IOFB was exposed after the infiltration and the cortex of the ruptured lens was removed. **(B)** The exposed IOFB end was visible after the wound sutures were removed. **(C)** After intraocular viscoelastic solution injection and loosening the giant IOFB from the intraocular tissue, the head of the IOFB floated out of the wound. **(D)** The giant IOFB was extracted through the entrance wound. **(E)** Retinal photocoagulation was performed at the site of the retinal wound due to the IOFB. **(F)** Corneal scar formation at the IOFB entrance wound. **(G)** Optical coherence tomography macular image after silicone oil removal. **(H)** Fundus photograph after silicone oil removal showing that the retina had reattached stably with a scar formed at the retinal wound site (The length of the bar: 1 mm).

chamber using the above method, except that the IOFB was extracted from the eye through the reopened entrance wound. After IOFB extraction, the wound was sutured. After that, the subsequent surgical procedures were finished. If the giant IOFB was so large that it impeded intraocular operation (**Figure 1**), the IOFB could be extracted before vitrectomy. Intraocular viscoelastics injection could be helpful for the IOFB extraction procedure under that condition.

Observation Items and Groups

The best corrected visual acuity (BCVA), intraocular pressure (IOP), ocular tissue injuries, wound location and length, and intraoperative and postoperative complications were evaluated, together with the IOFB size, localization, shape, and magnetic properties. The interval time from injury to the second phase of IOFB extraction and ocular reconstruction, the IOFB extraction path, the rate of silicone oil removal, and globe recovery were also recorded for statistical analysis.

The patients in this study were divided into three groups according to the giant IOFB extraction path: the limbus path group, pars plana path group, and entrance wound path group. The IOFB size, shape, and magnetic properties as well as the preoperative and postoperative BCVA, length of the entrance wound, endophthalmitis, and rate of silicone oil removal were compared among the three groups.

In addition, to evaluate the IOFB shape distribution in the three IOFB extraction paths, the patients were also divided into four groups according to the giant IOFB shape: the thin flat IOFB group, the thick flat IOFB group, the long IOFB group, and the irregular IOFB group. IOFBs with a thickness < 1 mm and a width ≥ 5 mm were classified into the thin flat IOFB group. IOFBs with a thickness of 1–3 mm and a width ≥ 4 mm were classified into the thick flat IOFB group. IOFBs with a thickness ≥ 3 mm and a width > 3 mm were classified into irregular IOFB groups. Finally, IOFBs in which both the width and thickness were $<$ 3 mm with a length ≥ 10 mm were classified into the long IOFB group. The preoperative and postoperative BCVAs and silicone oil removal of the four groups were compared.

Statistical Analysis

The statistical analysis was completed using Statistical Package for Social Sciences software, version 21.0 (IBM, Chicago, IL). Quantitative data are provided in the form of [mean $\pm$ SD]. The BCVA, recorded in decimal form, was transformed into quantitative data by the logarithmic minimum angle of resolution (log MAR) for statistical analysis. Quantitative data meeting the normal distribution were analyzed using a t-test for comparison of paired samples, a t-test for group-designed two-sample mean comparison, or one-way ANOVA. Non-normally distributed quantitative data were tested using a nonparametric test (Kruskal-Wallis H test; Wilcoxon test). Qualitative data were tested using the chi-square test (χ^2-test). Statistical significance was set at a $P < 0.05$.

RESULTS

IOFB Characteristics and Eye Injuries

This study included 68 men and 5 women. Forty-three patients were injured in the right eye and 30 in the left eye. The average age of the patients was 34 $\pm$ 15 years, ranging between 1 and 63 years. In addition, 67.12% of all patients were aged between 21 and 50 years.

The giant IOFBs were magnetic and nonmagnetic in 46 and 27 cases, respectively. There were 19 cases of thin flat IOFBs, 12 cases of thick flat IOFBs, 7 cases of long IOFBs, and 35 cases of irregular IOFBs. The average IOFB length was 11.80 $\pm$ 4.85 mm, and the average IOFB width was 5.27 ± 1.85 mm. The average length of the entrance wound was 8.45 ± 3.95 mm (**Table 1**).

Most cases in this study suffered multiple damages to the eye, including the cornea, iris, lens, vitreous body, retina, and choroid. Damage by giant IOFBs manifested as combined injuries of the anterior and posterior segments. The giant IOFBs caused corneal wounds in 54 patients (73.97%), mostly located in the vitreous cavity (95.89%, 70/73), among which 55 (75.34%, 55/73) cases had a direct wound on the retina. Those IOFBs hit the retina and were incarcerated in the inner wall of the globe, or fell into the vitreous after colliding with the retina. Most IOFBs caused multiple damages to the anterior and posterior segments of the eye, including the cornea, iris, lens, vitreous, and retina. Only two cases had no retinal damage in this study. The injuries to the eye are listed in **Table 1**.

Surgeries and Outcomes

After emergency debridement and suture surgery, all patients underwent a combined surgery of IOFB extraction, vitrectomy, retinal photocoagulation (or cryocoagulation), and silicone oil tamponade. By the end of the follow-up period, 47 patients maintained a normal globe shape and had a stable recovery from the injury after the last silicone oil removal surgery. However, 25 patients did not undergo silicone oil removal because of a poor ocular condition, and one patient required ocular evisceration because of bullous keratopathy.

The cause for the failure to remove silicone oil from the globe was severe eye damage. Nine patients had large corneal wounds running through the center of the cornea combined with serious post-polar retinal injury, which resulted in poor postoperative visual acuity, with difficulties in postoperative fundus observation and postoperative proliferation management. Eight cases had a massive globe rupture due to the giant IOFBs, combined with prolapse of intraocular contents and destruction of intraocular structures. Five patients had severe corneal stroma opacity and edema, which delayed the second phase surgery for ocular reconstruction and created difficulty in globe reconstruction because of serious proliferative vitreoretinopathy. Two patients had serious endophthalmitis, intraocular empyema, and ocular tissue necrosis. One patient developed persistent ocular hypotension and *atrophia bulbi* because of anterior proliferative vitreoretinopathy and cyclitic membrane formation.

Other postoperative complications included postoperative proliferation and epiretinal membrane formation, retinal detachment, corneal endothelial decompensation, and secondary glaucoma. Twelve patients were complicated with postoperative epiretinal membrane, which was removed in a secondary surgery without recurrence. Four patients had complicated postoperative retinal detachment with proliferative epiretinal membrane, they had undergone subsequent surgery of retinal reattachment, epiretinal membrane peeling and silicone oil tamponade, and a stable retina reattachment was achieved after final silicone oil removal surgery. One patient with mild corneal endothelial decompensation after surgery had recovered after medical therapy and silicone oil removal. In addition, three cases with postoperative glaucoma had restored normal IOP after antiglaucoma drug treatment or silicone oil removal.

TABLE 1 | Characteristics of giant intraocular foreign bodies (IOFBs) and injuries to the eye.

Observation items	Classification	Cases (n)	%
MAGNETIC PROPERTIES OF GIANT IOFBs			
Magnetic	Iron pieces	35	47.95
	Nails	11	15.07
Nonmagnetic	Glass	12	16.44
	Plastics	9	12.33
	Stone	3	4.11
	Copper pieces	2	2.74
	Bamboo	1	1.37
SHAPE OF GIANT IOFBs			
	Thin flat IOFBs	19	26.03
	Thick flat IOFBs	12	16.44
	Long IOFBs	7	9.59
	Irregular IOFBs	35	47.95
IOFB LOCALIZATION			
	Anterior segment	1	1.37
	Vitreous cavity	70	95.89
	Subretinal space	2	2.74
INJURIES TO THE EYE			
	Corneal wound	54	73.97
	Iris prolapse/incarceration	29	39.73
	Hyphemia	45	61.64
	Hypopyon/anterior chamber inflammation	27	36.99
	Broken of lens	54	73.97
	Dislocation/hemidislocation of lens	9	12.33
	Vitreous hemorrhage	69	94.52
	Vitreous abscess	15	20.55
	Retinal wound with subretinal hemorrhage	55	75.34
	Retinal detachment	46	63.01
	Retinal infection	25	34.25
	Retinal ischemia	7	9.59
	Endophthalmitis	27	36.99

Preoperative and Postoperative BCVA

The preoperative BCVA in this study showed no light perception (NLP) in three cases, from light perception (LP) to hand movement (HM) in 63 cases, from counting fingers (CF) to 0.04 in 5 cases, and from 0.05 to 0.25 in 2 cases. The average preoperative BCVA (logMAR) was 2.46 ± 0.33 (**Table 2**). The postoperative BCVA showed NLP in 3 cases, from LP to HM in 26 cases, from CF to 0.04 in 13 cases, from 0.05 to 0.25 in 29 cases, and > 0.3 in 2 cases. The average postoperative BCVA (logMAR) was 1.73 ± 0.79, and the rate of freedom from blindness was 40.85% (29/71; **Table 2**). Therefore, the BCVA significantly improved after surgical treatment ($z = -6.06$, $P < 0.01$; **Table 2**).

In addition, the preoperative and postoperative BCVAs compared in the three different IOFB extraction path groups showed that the postoperative BCVA was significantly better than

TABLE 2 | Comparison of the preoperative and postoperative BCVAs for all and each giant IOFB extraction path.

Groups	Cases (n)	Preoperative BCVA(n)					Postoperative BCVA (n)					Z^a	P^a
		NLP	LP ~HM	CF ~0.04	0.05~0.25	≥0.3	NLP	LP ~HM	CF ~0.04	0.05~ 0.25	≥0.3		
Limbus path group	18	2	16	0	0	0	2	8	4	4	0	−2.53	0.01
Pars plana path group	27	0	20	5	2	0	1	10	2	7	2	−3.62	< 0.01
Entrance wound path group	28	0	28	0	0	0	0	8	8	12	0	−4.13	< 0.01
Total	73	3	63	5	2	0	3	26	13	29	2	−6.06	< 0.01

[a]*Comparison between the logMAR value of preoperative BCVA and postoperative BCVA, Wilcoxon signed-rank test; NLP, no light perception; LP, light perception; HM, hand movement; CF, counting finger.*

the preoperative BCVA in each group (all $P < 0.05$; **Table 2**). In IOFB shape-based groups, the postoperative BCVA was also significantly better than the preoperative BCVA in each group (all $P < 0.05$; **Table 3**).

Comparison of BCVA and Silicone Oil Removal According to IOFB Shape

The preoperative BCVA, postoperative BCVA, and rate of silicone oil removal were significantly different among the four IOFB shape-based groups (all $P < 0.05$). The preoperative and postoperative BCVAs of the thin flat IOFB group were better than those of the thick flat group and the irregular IOFB group, respectively ($P < 0.05$). The postoperative BCVA of the long IOFB group was better than that of the thick flat group and the irregular IOFB group, respectively ($P < 0.05$). In addition, the rate of silicone oil removal in the irregular IOFB group was lower than that in the other three IOFB shape groups ($P < 0.05$; **Table 3**).

Comparison Among Extraction Paths

There were significant differences among the three extraction path groups in preoperative and postoperative BCVA, IOFB length and width, and the entrance wound length (all $P < 0.05$; **Tables 4**, **5**). Whereas, there was no difference in terms of age, left or right side of the eye, interval time from injury to the second phase surgery, entrance wound location, endophthalmitis, magnetic properties, and silicone oil removal among extraction paths (all $P > 0.05$; **Tables 4**, **5**).

Comparing between the pars plana path and the limbus path, both IOFB length ($z = -2.59$, $P = 0.01$) and width ($z = -3.32$, $P < 0.01$) in the pars plana path group were significantly lower than that in the limbus path group (all $P < 0.05$), and the preoperative BCVA of the pars plana path group was significantly better than that of the limbus path group ($z = -2.46$, $P = 0.01$). But no difference was identified between the two groups ($P > 0.05$; **Tables 4**, **5**).

Comparing between the pars plana path and the entrance wound path, IOFB length ($z = -2.01$, $P = 0.04$), IOFB width ($z = -3.65$, $P < 0.01$), and the entrance wound length ($z = -2.80$, $P < 0.01$) in the pars plana path group were significantly smaller than that in the entrance wound path group ($P < 0.05$). But no difference was identified between the two groups ($P > 0.05$; **Tables 4**, **5**).

Comparing between the limbus path and the entrance wound path, no difference was identified between the two groups in IOFB length or width, entrance wound length, or preoperative BCVA (all $P > 0.05$). But Wilcoxon test showed that the postoperative BCVA of the entrance wound path group was significantly better than that of the limbus path group ($z = -2.01$; $P = 0.04$; **Tables 4**, **5**).

As to the IOFB shape distribution comparison, all of the long IOFBs were extracted from the pars plana path in this study. After eliminating the long IOFBs, no difference in the distribution of the remaining three shape IOFBs on extraction paths was observed ($\chi^2 = 1.35$, $P = 0.85$; **Table 4**).

In the 38 cases where the end of the entrance wound was limited to area I (the wounds did not involve the global wall outside of the cornea), the entrance wound lengths in the limbus path group, pars plana path group, and the entrance wound path group were 5.60 ± 0.52 mm, 6.40 ± 1.99 mm, and 8.67 ± 2.61 mm, respectively, with significant difference ($\chi 2 = 8.25$; $P = 0.02$) among them. The entrance wound in the entrance wound path group was longer than that in the limbus and pars plana path groups ($z = -2.604$; $P = 0.009$; $z = -2.296$, $P = 0.022$), but there was no difference between the latter two groups ($z = -0.812$; $P = 0.417$).

DISCUSSIONS

The intraocular foreign bodies are different in their mass, size, kinetic energy, chemical and magnetic properties, and microorganism contamination. The variety of IOFB injuries makes difference in prognosis. Sometimes, a small IOFB that damages the optic nerve or macula can cause severe visual loss, while a large IOFB may have a better vision prognosis if important structures are free from injury. However, less probability of damaging important structures occurred in small and slender IOFBs, while more probability occurred in large IOFBs. To avoid biased judgment in this study, all giant IOFBs were selected strictly to meet the inclusion criteria size, and the IOFB incarcerated in the entrance wound was also excluded. The characteristics of this case series were a large proportion of huge

TABLE 3 | Preoperative BCVA, postoperative BCVA, and rate of silicone oil removal in different IOFB shape groups.

Groups	Cases (n)	BCVA (logMAR)				Silicone oil removal[d] (n)	
		Preoperative[a]	Postoperative[b]	Z^c	P^c	Yes	No
Thin flat IOFB group	19	2.36 ± 0.44	1.10 ± 0.41	−3.83	<0.01	18	1
Thick flat IOFB group	12	2.55 ± 0.17	2.07 ± 0.62	−2.41	0.02	10	2
Long IOFB group	7	2.16 ± 0.57	1.21 ± 0.84	−2.21	0.03	6	1
Irregular IOFB group	35	2.56 ± 0.18	2.05 ± 0.75	−3.55	<0.01	13	22
$\chi^{2\ e}$		8.89	20.96			22.29	
P		0.03	< 0.01			< 0.01	

[a]Preoperative BCVA of the thin flat IOFB group compared with that of the thick flat IOFB group and the irregular IOFB group, respectively (z = −2.04,P = 0.04;z = −2.34,P = 0.02); [b]postoperative BCVA of the thin flat IOFB group compared with that of the thick flat IOFB group and the irregular IOFB group, respectively (z = −3.88,P < 0.01;z = −3.76,P < 0.01). The postoperative BCVA of the long IOFB group compared with that of the thick flat IOFB group and the irregular IOFB group, respectively (z = −2.10,P = 0.04;z = −2.36,P = 0.02); [c]Wilcoxon signed-rank test for the paired data of the preoperative BCVA and postoperative BCVA in each IOFB shape group; [d]silicone oil removal of the irregular IOFB group compared with the long IOFB group, the thin flat IOFB group, and the thick flat IOFB group using Fisher's exact probability test (P < 0.01; P < 0.01; P = 0.03); [e]comparison between the four IOFB shape groups, Kruskal-Wallis H-test for the logMAR value of preoperative BCVA and postoperative BCVA, chi-square test for the silicone oil removal.

TABLE 4 | Best corrected visual acuity (BCVA), age, side of eye, interval time from injury to second phase surgery, entrance wound location, endophthalmitis, and silicone oil removal of giant IOFB according to extraction path.

Groups	N	Preoperative BCVA[b] (logMAR) (mean ± SD)	Postoperative BCVA[c] (logMAR) (mean ± SD)	Age (years, [mean ± SD])	Side of the eye (n)		Interval time (day, [mean ± SD])	Entrance wound location (n)			Endophthalmitis (n)		Silicone oil removal (n)	
					Right	Left		I	II	III	Yes	No	Yes	No
Limbus path group	18	2.60 ± 0.15	2.06 ± 0.78	31.22 ± 17.31	6	12	7.56 ± 4.53	10	6	2	4	14	10	8
Pars plana path group	27	2.31 ± 0.48	1.63 ± 0.88	29.89 ± 16.40	12	15	7.41 ± 4.22	16	7	4	9	18	17	10
Entrance wound path group	28	2.51 ± 0.14	1.61 ± 0.66	39.07 ± 10.22	12	16	7.29 ± 4.72	12	14	2	14	14	20	8
Total	73	2.46 ± 0.33	1.73 ± 0.79	33.74 ± 15.01	30	43	7.40 ± 4.43	38	27	8	27	46	47	26
$\chi^{2\ a}$		7.03,	4.33	5.07	0.61		0.03	3.75			3.87		1.24	
P^a		0.03	0.12	0.08	0.74		0.98	0.44			0.14		0.54	

[a]Comparison between the three IOFB extraction path groups (Kruskal-Wallis H test); [b]pairwise comparison between the three IOFB extraction path groups, the preoperative BCVA in the pars plana path group was better than that in the limbus path group (z = −2.46, P = 0.01), no statistical difference between the other paired groups (P > 0.05); [c]pairwise comparison between the three IOFB extraction path groups, the postoperative BCVA in the entrance wound path group was better than that in the limbus path group (z = −2.01, P = 0.04), no statistical difference between the other paired groups (P > 0.05).

cornea wound, lens broken, and retinal wound, which made the data comparable for IOFB extraction path analysis.

Similar to the previous reports (11–13), the giant IOFBs caused serious ocular structural damage in this study. Giant IOFB injuries mostly occurred in young and middle-aged men in this series, with 67.12% of them aged 21–50 years. Only 64.38% of the cases in this study underwent silicone oil removal surgery and maintained a stable ocular shape with partial restoration of visual acuity. The patients who recovered from blindness (final BCVA ≥0.05) accounted for 40.85% of all patients. Despite severe damage to the eyes, visual acuity improved in most cases after surgery. Therefore, improving management options for IOFB extraction may improve the prognosis.

At present, the treatment for IOFB injury includes single IOFB extraction surgery, or a combined IOFB extraction surgery, PPV, and other procedures for ocular reconstruction. IOFB extraction paths include the posterior scleral path through the IOFB location site, the pars plana incision path, the limbus tunnel incision path, and the IOFB entrance wound path (13–15).

Reducing secondary damage during giant IOFB extraction is important for improving visual prognosis. There were two main ways to reduce the secondary injury during IOFB extraction: one was to reduce the size of the incision for extracting the IOFB, and the other one was choosing the best incision site. Since the incision length was related to IOFB size, it was usually slightly wider than the IOFB width, leaving little room for intervention in this area. Therefore, the incision site selection was chosen to decrease the injury. A suitable incision site would allow smoother IOFB extraction with milder injury (15). The incision selection should consider the IOFB location, entrance wound location and size, the transparency of the cornea, and the condition of the lens (4). Previously, expanding the pars plana incision of PPV would be ideal for cases with an intact lens, while limbus incision would be preferred in cases with an injured lens (16).

TABLE 5 | Intraocular foreign bodies size, shape, magnetic properties, and entrance wound length according to IOFB extraction.

Groups	N	FB length[b] (mm, [mean ± SD])	FB width[c] (mm, [mean ± SD])	Entrance wound length[d] (mm, [mean ± SD])	FB shape[e] (n)				FB properties (n)	
					Thin flat	Thick flat	Long	Irregular	Magnetic	Nonmagnetic
The limbus path group	18	12.83 ± 4.20	6.00 ± 1.75	8.22 ± 3.62	4	4	0	10	10	8
The pars plana path group	27	9.65 ± 3.13	4.11 ± 1.55	7.22 ± 3.62	5	4	7	11	15	12
The entrance wound path group	28	13.21 ± 5.89	5.93 ± 1.65	9.79 ± 4.17	10	4	0	14	22	6
Total	73	11.80 ± 4.85	5.27 ± 1.85	8.45 ± 3.95	19	12	7	35	47	26
χ^2 [a]		7.25	16.92	7.27	12.48	3.99				
P [a]		0.03	< 0.01	0.03	0.04	0.14				

[a]Comparison between the three extraction path groups, Kruskal-Wallis H test for quantitative data, chi-square test for qualitative data; [b]pairwise comparison between the three IOFB extraction path groups, the IOFB length in the pars plana path group was shorter than that in the limbus path group and the entrance wound path group, respectively ($z = -2.59$, $P = 0.01$; $z = -2.01$, $P = 0.04$), no difference between the latter two groups ($P > 0.05$); [c]pairwise comparison between the three IOFB extraction path groups, the IOFB width in the pars plana path group was shorter than that in the limbus path group and the entrance wound path group, respectively ($z = -3.32$, $P < 0.01$; $z = -3.65$, $P < 0.01$), no difference between the latter two groups ($P > 0.05$); [d]pairwise comparison between the three IOFB extraction path groups, the entrance wound length in the pars plana path group was shorter than that in the entrance wound path group ($z = -2.80$, $P < 0.01$), no difference was found between the other paired groups ($P > 0.05$); [e]Fisher's exact probability test. After eliminating long IOFB cases, no difference in shape distribution among the three IOFB extraction path groups ($\chi^2 = 1.35$, $P = 0.85$).

The pars plana path extraction incision could avoid cornea injury and iris prolapse (17). But excessively large incision for a large IOFB increased the risk of retinal prolapse (18) and caused sudden and severely low IOP, which could induce corneal depression and deformation. An over-enlarged incision might also increase the risk of subchoroidal hemorrhage, ora serrata dialysis, retinal detachment, ciliary body injury, and postoperative low IOP (19). The limbus tunnel path provided a wide and direct view of the operation, avoiding injuries to the ciliary body or the ora serrata (14, 20). However, the lens must be removed for this extraction, and a large limbus incision could worsen corneal and anterior chamber angle injuries. Secondary glaucoma is more likely to occur in patients with anterior chamber angle trauma. Furthermore, limited by the anterior chamber depth, irregular IOFBs would abrade the endothelial cells of the cornea. The entrance wound path had more room for IOFB extraction, hence, no need of making a new incision (21). Thinking about the giant IOFB size, the secondary injury of an incision should not be ignored. However, the sutured entrance wound should be reopened and re-sutured, which spent more operational time. Occasionally, corneal wound leakage might occur in cases of corneal wound lysis.

When comparing the advantages of the three IOFB extraction paths in giant IOFB injury, still other prognostic factors should be considered. The wound length was consistent with the size of the IOFB and was associated with visual prognosis (2, 11). A poorer preoperative BCVA in giant IOFBs injuries would result in a poorer postoperative BCVA, and the larger the IOFB width/wound length, the poorer the visual acuity outcome (10). Damage to the eyes varied because of the different IOFB shapes in this series. The eyes injured by thin flat or long IOFBs have a better visual prognosis, but an irregular IOFB injury would result in a poor prognosis both in terms of visual acuity and global shape recovery.

In this series, the IOFB size and shape and the preoperative BCVA in the pars plana path group indicated a better prognosis. However, the postoperative BCVA and the rate of silicone oil removal in this group had no advantage over the limbus path group or the entrance wound path groups. The limbus path and the entrance wound path would be better choices for the extraction of giant IOFBs compared with the pars plana path.

When making a comparison between the limbus path and entrance wound path groups, no difference was found in the preoperative BCVA, IOFB size, IOFB shape, or the wound length. In the 38 cases in which the end of the wound was limited to the cornea, the IOFB length of the entrance wound path was longer than that of the limbus path group. However, the postoperative BCVA of the entrance wound path group was better than that of the limbus path group. Hence, an entrance wound path IOFB extraction would be more advantageous for a better prognosis.

The IOFB was a flying object before it entered the eye. It kept its long axis along its flight path, which reduced frictional resistance. As a result, the long axis of the IOFB was more likely perpendicular to the wound plane. An IOFB extraction from the entrance wound was coincident with this condition, avoiding new damage of another incision. Furthermore, most of the entrance wounds were in the anterior segment of the eye (zones I and II) in this case series, which facilitates this procedure. In particular, for very large IOFBs, the entrance wound path is the only choice. Two cases of very large IOFBs in this study had an unexpectedly good visual acuity by using the entrance wound path IOFB extraction, considering their severe eye damage.

Extraction of IOFB from the entrance wound path needs an in-time secondary phase surgery; otherwise, it would be difficult to reopen the sutured wound. The in-time surgery for IOFB extraction and ocular reconstruction could be beneficial for the success of retinal reattachment (16), as it would interrupt the continuous mechanical and chemical injury of IOFBs, and resolve the hemorrhage, retinal detachment, proliferation membrane, and endophthalmitis in the eye (22, 23). This might be another cause for a better prognosis in the entrance path group.

CONCLUSION

In summary, giant IOFB injury can cause severe damage to the eye and result in a poor prognosis. However, postoperative BCVA could be improved after intensive treatment. IOFB extraction should obey the rule of minimum damage, considering the IOFB size, shape, and properties. IOFBs with a large width are not suitable for pars plana path extraction, whereas the entrance wound path would be more advantageous for giant IOFB extraction. In this study, we encountered several problems. The giant IOFBs are various in size and shape, which made the comparison difficult. Though we defined the giant IOFB size, there are still some inconformities in ocular damage caused by each IOFB. The lack of enough cases for analysis in this study would make us lose valuable information for judgment. Hence, more studies and discussions should be conducted on the surgical design and postoperative management to decrease secondary injury in patients with giant IOFB injuries.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JM had finished the statistical analysis and manuscript. All authors had taken part in the clinical procedure and data collection and agree to be accountable for the content of the study.

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