Risk factors for intraocular pressure rise after pars plana vitrectomy with silicone oil tamponade

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Article

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Abstract

Purpose:

To evaluate risk factors for intraocular pressure elevation after vitreoretinal surgery with silicone oil tamponade and further develop predictive models to support clinical management.

Methods:

A retrospectively analyzed 824 eyes of 824 consecutive patients that presented to the Jiangsu Province Hospital between December 2015 and August 2019, the IOP was measured from the preoperative visit and at the 1-week, 1-month, 3-month, and 6-month visits, and the final postoperative visit before silicone oil removal. Predictors were selected based on the p-value results of the univariate analysis.

Results

Elevated intraocular pressure developed in 39.2% of the eyes postoperatively. The prediction model reached an accuracy of 0.7349. Single factor analysis revealed that age ($p<0.001$), myopia ($p<0.001$, OR=2.02[1.46-2.81]), retinal detachment ($p=0.007$, OR=5.97[1.41-53.42]), macular hole ($p=0.009$, OR=1.99[1.14-3.48]), lens status ($p<0.001$) and biological parameter (Axial Length $p<0.01$, Anterior Chamber Depth $p=0.001$, Lens Thickness $p=0.028$, White-to-White $p=0.02$) were risk factors, meanwhile the prediction model further found that hypertension, diabetes, the use of intraoperative laser and silicone oil viscosity can also influence the development of postoperative IOP elevation.

Conclusions

Age, myopia, retinal detachment, macular hole and biological parameters have influence on postoperative intraocular pressure elevation for patients with silicone oil tamponade after pars plana vitrectomy. This may have some reference significance for reducing the incidence of high intraocular pressure after pars plana vitrectomy combined with silicone oil filling.

Introduction

Silicone oil (SO) has become an indispensable intraocular tamponading agent in vitreoretinal surgery owing to its high surface tension since it was introduced by Cibis in 1962. Although silicone oil has been successfully used by retina surgeons for decades, many complications have been associated with SO endotamponade, including increased intraocular pressure (IOP), ocular hypotony, cataract formation in phakic eyes, band keratopathy in corneas, and silicone oil emulsification. Among all these complications, the IOP elevation is one of the most common and severe.
The incidence of elevated IOP varies from 2.2–56.0% related to SO endotamponade in different studies.\textsuperscript{6–9} It may be related to the different definitions of ocular hypertension, the time point of different postoperative periods, and different retinal diseases. Each study had a different set of inclusion criteria and exclusion criteria. The pathologic mechanisms behind IOP elevation are multiple and not yet clearly known, and could be secondary to an overfill of silicone oil, anterior chamber inflammatory activity, a pupillary block, anterior migration of SO, and preexisting glaucoma.\textsuperscript{10–13}

Because the occurrence of postoperative IOP elevation is the result of multiple factors, conventional single-factor analysis does not allow for a comprehensive analysis, and there is no consensus result on any of the postoperative risk factors derived from the current study analysis.

With the development of data science, an increasing number of machine learning models have been applied to predictive tasks in various domains, including healthcare. However, the medical field has particularly high requirements for model interpretability, and some interpretable predictive models have been proposed for clinical analysis. In this study\textsuperscript{2,14}, we introduce a predictive model for further analysis to provide clinical reference. Our model not only provides assistance to doctors through predicted values, but also outputs the importance of different features through its interpretability, offering more precise clinical reference.

We retrospectively analyzed 824 patients who underwent pars plana vitrectomy (PPV) with silicone oil tamponade, including surgical indication, the use of laser and perfluorocarbon liquid intraoperatively, lens status, especially the biological parameters like axial length, central corneal thickness, anterior chamber depth, and white-to-white of the eyes that have not been reported before. Based on this, we used p-values from hypothesis testing to screen features and combined them with four different machine learning methods to establish predictive models for IOP elevation.

**Materials and methods**

This study was approved by the ethics of committees of The First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) and conducted in accordance with the tenets of the Declaration of Helsinki. As this is a retrospective study with data processed anonymously, informed consent was waived.

This retrospective study enrolled 824 eyes of 824 consecutive patients that presented to the Jiangsu Province Hospital between December 2015 and August 2019. These cases were confirmed by experienced researchers (ST Yuan and W Fan with 25, and 10 years of experience, respectively). All eyes had a vitreoretinal condition treated by PPV with SO endotamponade. Eyes with corneal pathology, a previous history of glaucoma or preoperative ocular hypertension (IOP > 21mmHg), or patients with severe data deficiencies were excluded. Demographic data, a detailed ocular and systemic history, and the etiology of the PPV were recorded for each patient preoperatively. (Fig. 1.)
Indications for vitro-retinal surgery included retinal detachment (RD), macular hole (MH), choroidal detachment, vitreous hemorrhage (VH) and proliferative diabetic retinopathy (PDR). All eyes were operated under assisted local or general anesthesia. PPV, air/uid exchange, and SO were performed in all patients. At the end of the surgery, eyes were kept slightly hypotonic with IOP evaluated by manual palpation.

Patient age, sex, lens status, presence of diabetes, presence of hypertension, biological measurement parameters of the eyes, surgical indication and surgical factors were recorded. The IOP measured by Canon TX-20 automatic non-contact tonometer were obtained for both the operative and fellow eyes from the preoperative visit and at the 1-week, 1-month, 3-month, 6-month visits, and at the nal postoperative visit. The follow-up ended after silicone oil removal. Silicone Oil was removed about 3–6 months after implantation. Due to early equipment problems, some patients had missing IOP values, so we retrospectively determined whether a patient had postoperative IOP elevation by combining the prescription of IOP-lowering medication with IOP values in the medical prescription. IOP less than 21 mmHg was predefined as normal. Commonly used IOP-lowering drugs include Brinzolamide and Timolol Maleate Eye Drops, Carteolol Hydrochloride Eye Drops, Brimonidine Tartrate Eye Drops and Travoprost Eye Drops. For patients whose IOP is not effectively controlled with IOP-lowering medications, we may perform further operations or surgeries to control IOP, such as paracentesis of anterior chamber, trabeculectomy and drainage valve implantation.

Data were analyzed using Python 3.6.9 with package: SciPy (1.2.1), Statsmodels (0.11.1), NumPy (1.19.4) and scikit-learn (0.24.1). Continuous variables were expressed as means (standard deviations), and were compared with the Mann-Whitney U test. Categorical variables were expressed as number (%) and compared by χ² test. A p-value of less than 0.05 was considered a statistically signicant difference. Four machine learning methods were used to carried out the prediction of IOP elevation: Decision Tree, Logistic Regression, Random Forest, and Gradient-Boosted Decision Trees (GBDT). Among these, GBDT achieved the best predictive performance. The selection of predictive features was based on the p-value from the above hypothesis testing.

Results

Baseline characteristics of the study cohort are summarized in Table 1. A total of 824 patients (mean age, 55.97 years ± 13.02; age range, 11–88 years) with pars plana vitrectomy were included. 446 (54.13%) patients were men, and 378 (45.87%) were women. Diabetes mellitus was present in 92 patients (11.17%), systemic hypertension was present in 179 patients (21.72%), and myopia was present in 216 patients (26.21%). The most common indication for surgery in the study eye was retinal detachment in 804 patients (97.57%) followed by vitreous hemorrhage in 71 patients (8.62%) and macular hole in 62 patients (7.52%).

The analysis of preoperative risk factors for IOP elevation is shown in Table 2. Of all 824 patients, 323(39.2%) developed postoperative IOP elevation, 501(60.8% showed normal postoperative IOP. We
compared the different variables of all the patients. Age at surgery, high myopia, retinal detachment and macular hole all conferred a higher risk for increased IOP. All other characteristics were not found to be associated with the development of increased IOP. The age of people who developed IOP elevation was significantly lower than those had normal IOP ($p < 0.001$). No significant difference was found between the gender ($p = 0.242$, OR = 1.18[0.88–1.58]). In patients with IOP elevation, the underlying ocular diseases necessitating PPV included retinal detachment, macular hole, choroidal detachment, vitreous hemorrhage, and diabetic retinopathy. The types of ocular disease were not significantly different between the two groups. We can see that patients with retinal detachment ($p = 0.007$, OR = 5.97[1.41–53.42]), macular hole ($p = 0.009$, OR = 1.99[1.14–3.48]) and myopia ($p < 0.001$, OR = 2.02[1.46–2.81]) were more prone to develop an increase in IOP. Patients with diabetes, hypertension, vitreous hemorrhage, silicone oil filling eye did not seem to influence the risk for elevated IOP. Among the 323 patients, 120 developed IOP elevation 1–2 weeks postoperatively and 92 developed within one week postoperatively. The relevant data are shown in Figure S1.

Effects of surgical factors are shown in Table 3. Among all 824 patients, 656 patients were with phakic, 34 patients were aphakic, 134 patients were pseudophakic. Lens status had significant statistical differences. Besides, other continuous variables were also included, such as axial length (AL), anterior chamber depth (ACD), lens thickness (LT), central corneal thickness (CCT), white-to-white value (WTW). Eyes with longer axial length, deeper AC depth, thicker corneal CCT and higher WTW measurements were significantly associated with elevated IOP. Among patients with elevated IOP, the mean AL (24.88 ± 3.80) was significantly longer than patients with normal IOP (23.80 ± 3.01) ($p < 0.001$). The same is true for ACD ($p = 0.001$), LT ($p = 0.028$), and WTW ($p = 0.02$). No significant difference was found in CCT between two groups ($p = 0.072$).

A total of 23(2.79%) patients had 1000cSt silicone oil implanted, and other 801 (97.21%) patients implanted 5000cSt. SO viscosity was not found to be associated with the development of increased IOP ($p = 0.799$), with 1,000 cSt OR = 0.10[0.38–2.51] and 5,000 cSt OR = 1.01[0.40–2.66]. Meanwhile, pars plana vitrectomy combined cataract extraction conferred a reduced risk for increased IOP ($p < 0.001$, OR = 0.48[0.36–0.65]).

For the prediction of IOP elevation, the clinical experience of senior doctors and the results of data analysis from earlier in this study were used to filter out redundant feature information. The data was split into a training set and a testing set at a ratio of 9:1. By using the clinical experience of senior doctors, as well as the support of authoritative ophthalmology literature to identify necessary features and the features with p-values less than 0.2 from hypothesis testing, the Gradient-Boosted Decision Trees (GBDT) model achieved the highest accuracy of 0.7349. For detailed experimental results and feature selection, please refer to the Appendix section.

The feature importance provided by the prediction model is shown in the Fig. 2. The vertical axis represents the feature name, and the horizontal axis represents the value of feature importance. It should be noted that the sum of the importance of all features equals to 1, we can see that the model assigns
higher importance to some features compared to others in the prediction process, the results of the prediction model showed that factors such as age, biological parameters, and lens status play a more important role: Age-0.159, AL-0.169, ACD-0.113, LT-0.101, CCT-0.129, WTW-0.097, Phakic-0.011, Aphakia 0.004, Cataract 0.009, Pseudophakic 0.014. This is consistent with the results of our single-factor analysis above. More details were showed in supplementary information.

**Discussion**

This study aimed to evaluate risk factors and incidence for postoperative IOP elevation after vitreoretinal surgery with silicone oil tamponade in eyes without a previous history of glaucoma or ocular hypertension, and a predictive model was developed based on this, in the hope of early detection and treatment of the patients concerned. Preexisting glaucoma is considered a very important risk factor for IOP elevation after PPV and SO tamponade. It had described that approximately 5.9%-7% of patients with elevated IOP after surgery had a history of preoperative glaucoma or ocular hypertension in previous studies.

We excluded patients with the history of glaucoma or ocular hypertension from our study to detect risk factors other than it. Patients most often have elevated IOP in the first week after surgery. During this period, patients should be closely monitored and followed up, and appropriate treatment should be taken to control IOP at an early stage to achieve better treatment and prognosis.

In previous studies, risk factors for IOP elevation after PPV combined with silicone oil tamponade include diabetes, aphakic eye, and silicone oil viscosity. In our study, single factor analysis revealed that age, myopia, retinal detachment, macular hole, biological parameter significant were risk factors for elevated IOP after PPV. Moreover, in the prediction model, we further found that hypertension, diabetes, type of IOL, the use of intraoperative laser and silicone oil viscosity can also influence the development of postoperative IOP elevation.

Our results indicated that younger patients have more tendency to develop high IOP postoperatively. This finding is comparable with Pillai et al which considered that the increased incidence of trabeculitis and anterior chamber inflammation may account for the high IOP symptoms in younger patients after surgery because they are more likely to develop an inflammatory response. However, there is no clear evidence to confirm this conclusion in our study, which requires further studies to be conducted subsequently.

Although biological parameters significantly affected the postoperative IOP in our study, few studies evaluated the effect of biological parameter such as AL, ACD, CCT, LT and WTW for IOP elevation after vitreoretinal surgery with silicone oil filling. Previous studies had found a positive correlation between CCT and IOP values. The tendency of higher IOP readings with longer axial length had also been reported. Meanwhile, Hoffmann et al. highlighted the high correlation of IOP measures with thicker central cornea, a thicker lens, and a longer posterior segment length. WTW was positively correlated with ACD, which can explain that WTW has a positive association with IOP. These studies only reported the correlation between biological parameters and intraocular pressure, did not analyze the impact on the occurrence of elevated IOP after vitrectomy and silicone oil tamponade. Our study is the first to discuss
this factor and finds a high positive correlation between postoperative IOP elevation and AL, ACD and WTW, as well as a negative correlation with LT. The correlation between biological parameters and IOP needs to be further explored and explained subsequently.

Many articles have reported that aphakic is a strong risk factor for IOP elevation after PPV and SO tamponade,\textsuperscript{15,26} this result is demonstrated in our article as well. We also found that patients with pseudophakia is also a risk factor for IOP elevation. Chang\textsuperscript{27} first presented that the main reason for IOP elevation in vitrectomized eye was the diffusion of oxygen from the vitreous cavity to the anterior chamber. This caused alterations in the trabecular meshwork leading to reduced aqueous outflow with increase in IOP and glaucoma.\textsuperscript{28,29} Since the crystalline lens contains proteins which metabolize oxygen,\textsuperscript{30,31} it has the potential to reduce the oxidative stress on the trabecular meshwork and prevent the oxidative damage. In addition, it also acts as a barrier to prevent oxygen from entering the anterior chamber. This could explain why the model estimates that lens status is one of the major factors influencing postoperative IOP elevation.

Comparing with PPV alone, previous studies\textsuperscript{32–34} agreed that combined phacoemulsification and intraocular lens implantation (PE & IOL) seems to exert an additive effect on transient IOP elevation after PPV, which shows the same results with our prediction model. Then the long-term IOP lowering effect of cataract surgery may lead to decreased IOP in the late postoperative period. This may be due to cataract surgery inducing more inflammation in the trabecular meshwork, leading to elevated IOP in the first few days after surgery, while PPV combined with cataract surgery may also cause anterior segment inflammation and disruption of the blood-water barrier.\textsuperscript{26,35–37} The long-term IOP reduction after cataract surgery has been explained by the improvement of outflow facility, deepening of the anterior chamber and posteriorization of the lens-iris diaphragm after cataract surgery.\textsuperscript{38,39}

Patients with RD or MH were strongly associated to develop an IOP rise in our study. Fujikawa et al. \textsuperscript{40} reported the same conclusion that MH group was significantly at high risk of IOP increase after vitrectomy. The result of recent study\textsuperscript{41} had suggested that because the vitreous lacks a diffusion barrier for the oxygen, the partial oxygen pressure is highly elevated in the vitreous cavity. For patients with RD and MH, we performed a more thorough vitrectomy removing the peripheral vitreous completely but core vitrectomy for other patients, it would increase oxygen stress to the trabecular meshwork\textsuperscript{42} in eyes with RD which may cause the IOP elevation.

Although features such as hypertension, diabetes, types of IOL, intraoperative laser and silicone oil viscosity were not statistically significant in the univariate analysis, their importance in the prediction model accounted for a certain percentage. Due to the fact that postoperative IOP elevation is the result of a multifactorial interaction and a common univariate analysis is rather homogeneous, whereas the prediction model performs the analysis as a whole therefore yielding a more comprehensive risk factor.

Silicone oil viscosity may interact with the lens, lower silicone oil viscosity is more likely to result in silicone oil emulsification into the anterior chamber in patients with aphakic or IOL eyes, leading to high
postoperative IOP. In patients undergoing vitrectomy combined with cataract ultrasound emulsification and IOL implantation, IOL is risk factor due to its weak barrier effect and inability to consume oxygen, therefore in the prediction model, different types of lens also influence the development of postoperative IOP elevation. The roles of diabetes and hypertension in IOP elevation had also been discussed in many studies, but the conclusion remains controversial, further observation and analysis are necessary in the follow-up study.

This study has several limitations. The retrospective nature of the study means it contains some bias due to poor patient adherence and incomplete data. We missed the specific IOP values of some patients, basing on the doctor prescribed intraocular pressure lowering drugs to determine whether the patients have postoperative high IOP, which will also lead to statistical errors. Meanwhile, although the prediction model is interpretable, the accuracy is still weak, an updated algorithm is needed to build a more reliable model.

IOP elevation is one of the most common and severe complications of PPV with silicone oil tamponade in eyes. If a patient's high IOP is not effectively controlled after surgery, the clinical option is usually to control IOP by using IOP-lowering eye drops or removing intraocular silicone oil early to prevent optic nerve damage, but the early removal of silicone oil may lead to secondary problems such as recurrent retinal detachment. Therefore, it is clinically relevant to investigate the risk factors that may lead to postoperative hypertension and to take interventions to reduce the incidence of postoperative hypertension accordingly. Also, due to the high prevalence of myopia and cataract in China, our study innovatively included biological parameters as factors for a systematic analysis. The larger amount of data in this study allows for a more comprehensive and accurate analysis of the risk factors that may be associated with postoperative high IOP. Meanwhile, the statistical results and prediction model can provide a basis for our subsequent prospective study.

**Conclusion**

In conclusion, IOP elevation is a common complication following PPV with SO tamponade. We found the risk factors for IOP elevation following PPV and SO tamponade would be age, myopia, retinal detachment, macular hole, and biological parameters, while pars plana vitrectomy combined cataract extraction was found to be protective factors against IOP elevation. Furthermore, we carried out the Gradient-Boosted Decision Trees (GBDT) model prediction of IOP elevation, with an accuracy of 0.7349. Knowledge of incidence, risk factors, and mechanism of IOP rise following PPV is crucial in the follow-up and management of patients after surgery.

**Summary**

What was known before

- Intraocular pressure elevation is one of the most common complications after silicone oil filling.
Many studies have found that diabetes, preoperative high intraocular pressure, lens state and silicone oil viscosity can affect the occurrence of postoperative intraocular hypertension.

What this study adds

- The first study to develop predictive models to evaluate risk factors for intraocular pressure rise after pars plana vitrectomy with silicone oil tamponade.
- Biological parameters were included for analysis for the first time.

Declarations

Conflict of Interest: None of the authors has any financial/conflicting interests to disclose.

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Research Ethics Approval: This study involves human participants and was approved by the ethics committee of the The First Affiliated Hospital of Nanjing Medical University, 2022-SR-200. Exception to the requirement of informed consent.

References


**Tables**

Tables 1 to 3 are available in the Supplementary Files section.

**Figures**
Figure 1
Flow chart of study patients

Figure 2
Feature importance provided by prediction model

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.xlsx
- FigureS1.pdf
- FigureS2.pdf
- FigureS3.pdf
- FigureS4.pdf
- Table1.xlsx
- Table2.xlsx
- table3.xlsx