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Contributing factors to short-term intraocular pressure elevation following intravitreal anti-VEGF injections

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Abstract

Background Short-term intraocular pressure (IOP) elevation is a common complication following intravitreal injection (IVI) of anti-VEGF drugs, potentially posing risks to retinal health. This study aimed to identify key factors influencing short-term IOP elevation and provide actionable insights for its prediction and effective management in clinical practice.

Methods An observational study was conducted on 64 postoperative measurements from patients who underwent IVI of anti-VEGF drugs at Yidu Central Hospital of Weifang between 2023 and 2024. Data on patient demographics (e.g., age, sex), clinical characteristics (e.g., lens status, diabetes), and pre- and postoperative IOP values were collected. A linear mixed-effects model was applied to evaluate factors associated with IOP elevation 5 min post-injection.

Results The baseline IOP was 14.64 ± 2.71 mmHg, increasing to 43.33 ± 7.70 mmHg at 5 min post-injection and subsequently decreasing to 19.25 ± 3.80 mmHg at 30 min post-injection. Statistically significant differences were observed between the baseline and postoperative IOP values ($p < 0.0001$). At 30 min post-injection, 68.8% of the measured IOP values were ≤ 21 mmHg, and all were ≤ 30 mmHg. The linear mixed-effects model revealed that older age ($p < 0.001$), native crystalline lens ($p < 0.001$), and diabetes ($p = 0.009$) were significant predictors of greater IOP elevation at 5 min post-injection.

Conclusions Short-term IOP elevation following intravitreal anti-VEGF injections is associated with older age, a native crystalline lens, and diabetes. Individualized preventive strategies may effectively mitigate the risk of postoperative IOP elevation in high-risk patients.

Keywords Intravitreal injection, Anti-VEGF, Intraocular pressure, Diabetes, Pseudophakia

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Introduction

IVI of anti-VEGF agents has become a cornerstone treatment for various retinal diseases. However, owing to the limited ocular volume, the injected medication often results in a rapid spike in IOP immediately following the procedure [1, 2], with reported IOP levels ranging from 41.6 mmHg to 81 mmHg within the first minute [3–5]. While studies have demonstrated that elevated IOP typically normalizes within 30 to 60 min [6], transient IOP spikes may still pose risks to the retinal nerve fiber layer (RNFL) [4, 7], with potential cumulative damage following repeated treatments [6, 8].

To predict and manage the risk of IOP elevation after intravitreal anti-VEGF injections, it is crucial to monitor short-term IOP fluctuations. Additionally, identifying the contributing factors plays a key role in effective management. This approach facilitates preoperative risk assessment and supports the development of individualized IOP management strategies. However, standardized protocols for managing post-IVI IOP have yet to be established [1]. While previous studies have identified factors such as age, axial length, and the injection procedure as contributors to short-term IOP changes [1, 9–12], uncertainties remain regarding other variables. For example, the impact of intraocular lens (IOL) implantation on postoperative IOP remains controversial, with studies reporting inconsistent findings [1, 6]. Additionally, the role of systemic conditions, such as diabetes, in short-term IOP elevation remains unexplored, with no substantial evidence currently available.

Our study aimed to explore the potential influence of systemic and ocular factors such as age, IOL implantation, and diabetes on IOP elevation within 5–30 min post-IVI [13, 14]. The findings are intended to provide insights for predicting and mitigating IOP spikes following intravitreal anti-VEGF injections.

Methods

Data collection

Data were collected from adult patients at Yidu Central Hospital of Weifang who underwent intravitreal injection of anti-VEGF agents between 2023 and 2024. The exclusion criteria included baseline IOP > 21 mmHg; a personal or family history of glaucoma; narrow or closed anterior chamber angles; intraocular or periocular triamcinolone injection; dexamethasone implantation; other conditions potentially affecting long-term IOP within six months prior to anti-VEGF treatment; and intraoperative findings of reflux at the injection site or anterior chamber paracentesis for decompression. A total of 64 postoperative measurements from 51 eyes of 51 patients were analyzed. The collected data included age, sex, diagnosis, number of injections, type of anti-VEGF drug (conbercept or aflibercept), lens status (phakic or pseudophakic), diabetes status (diabetic or non-diabetic), axial length, baseline IOP, IOP at 5 min post-injection, and IOP at 30 min post-injection.

Axial length was measured preoperatively via a Lenstar LS900 optical biometer. All IVI procedures were performed using a 29-gauge needle to inject 0.05 ml of aflibercept or conbercept solution 4 mm posterior to the limbus in phakic eyes or 3.5 mm in pseudophakic eyes, at a site within the 9–11 o'clock position, avoiding any visible previous injection sites. No IOP-lowering medications were administered preoperatively or postoperatively. Patients whose visual acuity was immediately reduced to hand motion or worse were treated with anterior chamber paracentesis (excluded from the analysis per the study criteria). Postoperative IOP measurements were collected at 5 and 30 min via a standardized non-contact tonometer (TOPCON CT-80). Each IOP value was calculated as the mean of three measurements taken at the specified time point, 5 s before, and 5 s after.

Statistical analysis

Statistical analyses were performed via GraphPad Prism (version 10.1.1; GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics (version 29.0.1.0; IBM Corp., Armonk, NY, USA). Figures were generated via both GraphPad Prism and Python (Matplotlib library, version 3.8.0). Continuous variables are presented as the means ± standard deviations, whereas categorical data are expressed as percentages. A p value < 0.05 was considered to indicate statistical significance.

Repeated-measures one-way ANOVA in GraphPad Prism was used to compare IOP differences at baseline and postoperative time points, with the results visualized graphically. The linear mixed-effects model in SPSS was applied to analyze factors influencing the increase in IOP at 5 min post-injection (calculated as the postoperative IOP at 5 min minus the baseline IOP). Patient ID was defined as the subject variable, with repeated measures set as the injection count for each patient. The covariance type was specified as compound symmetry (CS).

Univariate linear mixed-effects models were initially applied to screen potential influencing factors, including age, type of anti-VEGF drugs, lens status, diabetes status, and axial length. Diagnosis was also evaluated, and due to the limited sample size of other diagnoses, only patients with neovascular age-related macular degeneration (nAMD, 23 patients) and diabetic macular edema (DME, 18 patients) were included. Variables with $p < 0.2$ in the univariate analysis were included in the final multivariate model. Factors were subsequently added stepwise to optimize the final model.

All collected data were handled with strict confidentiality. Patient identifiers were anonymized and used solely for research purposes. The study results did not involve

individual patient data. Informed consent was obtained from all participants. The study was approved by the Ethics Committee of Yidu Central Hospital of Weifang (YDCH2024-160) and adhered to the principles of the Declaration of Helsinki.

Results

Demographic and clinical characteristics

A total of 64 postoperative measurement samples were obtained from the 51 patients (51 eyes) included in this study. The mean age was 63.1 ± 13.1 years, with 25 (49%) male and 26 (51%) female patients. Among these, 47.1% (24 patients) had diabetes, and 52.9% (27 patients) did not. Regarding lens status, 25.5% (13 patients) were pseudophakic and 74.5% (38 patients) were phakic. In terms of diagnosis, nAMD accounted for the largest proportion (45.1%), followed by DME (35.3%). Other diagnoses included cystoid macular edema/branch retinal vein occlusion (CME/BRVO, 9.8%), vitreous hemorrhage/diabetic retinopathy (VH/DR, 5.9%), choroidal neovascularization (CNV, 2.0%), and cystoid macular edema/central retinal vein occlusion (CME/CRVO, 2.0%) (Table 1). Among the anti-VEGF agents administered, conbercept accounted for 73.8% of the injections, while aflibercept was used in 24.6%. The mean axial length of the eyes was 23.20 ± 1.45 mm.

Table 1 Demographic and clinical characteristics

Variable	No. of patients (%)
Age (years) ($n=51$)	
21–40	4 (7.8)
41–60	11 (21.6)
61–80	34 (66.7)
81–90	2 (3.9)
Gender ($n=51$)	
Male	25 (49.0)
Female	26 (51.0)
Type of drugs ($n=64$)	
conbercept	48 (73.8)
aflibercept	16 (24.6)
Diagnoses ($n=51$)	
nAMD	23 (45.1)
DME	18 (35.3)
CME/BRVO	5 (9.8)
VH/DR	3 (5.9)
CNV	1 (2.0)
CME/CRVO	1 (2.0)
Diabetic ($n=51$)	
Yes	24 (47.1)
No	27 (52.9)
Pseudophakic ($n=51$)	
Yes	13 (25.5)
No	38 (74.5)

Postoperative IOP changes

The baseline IOP for all 64 measurements was 14.64 ± 2.71 mmHg. Five minutes after surgery, the IOP increased to 43.33 ± 7.70 mmHg and subsequently decreased to 19.25 ± 3.80 mmHg at 30 min after surgery. Repeated-measures one-way ANOVA revealed statistically significant differences among the three time points ($p<0.0001$) (Fig. 1). These results indicate a significant increase in IOP at 5 min postoperatively compared with baseline, with IOP levels not returning to baseline by 30 min postoperatively.

The average increase in IOP for all 64 measurements at 5 min postoperatively was 29.12 ± 7.81 mmHg, whereas the average decrease at 30 min postoperatively (relative to IOP at 5 min) was 24.43 ± 7.63 mmHg. At 30 min postsurgery, 44 measurements (68.8%) showed IOP recovery to ≤ 21 mmHg, 60 measurements (93.8%) recovered to ≤ 25 mmHg, and all 64 measurements (100.0%) recovered to ≤ 30 mmHg.

Linear mixed-effects model analysis

In the initial univariate analysis, age, type of anti-VEGF drugs, lens status, diabetes status, axial length, and diagnosis were evaluated as independent variables. Type of drug ($p=0.255$), axial length ($p=0.344$), and diagnosis ($p=0.209$) showed no statistically significant effects. Based on the selection criteria, the final multivariate model included age, lens status, and diabetes status as independent variables.

Fixed effects.

Age: A positive correlation was observed between age and postoperative IOP increase. For each additional year of age, the IOP increased by an average of 0.283 mmHg ($p<0.001$) (Table 2; Fig. 2).

Lens status: Compared with pseudophakic patients, patients with native crystalline lenses presented significantly greater IOP increases, with an estimated difference of 9.809 mmHg ($p<0.001$) (Table 2; Fig. 2).

Diabetes status: Diabetic patients presented significantly greater IOP increases than non-diabetic patients did, with an estimated difference of 5.502 mmHg ($p=0.009$) (Table 2).

Random effects.

The analysis indicated significant variability among the measurement samples ($p=0.014$ for the compound symmetry diagonal shift). Additionally, compound symmetry covariance was statistically significant ($p=0.020$), suggesting a correlation between repeated measurements within the same patient group (Table 2).

Discussion

This study investigated the impact of factors such as age, lens status, and diabetes on short-term IOP elevation following IVI of anti-VEGF agents. The findings revealed

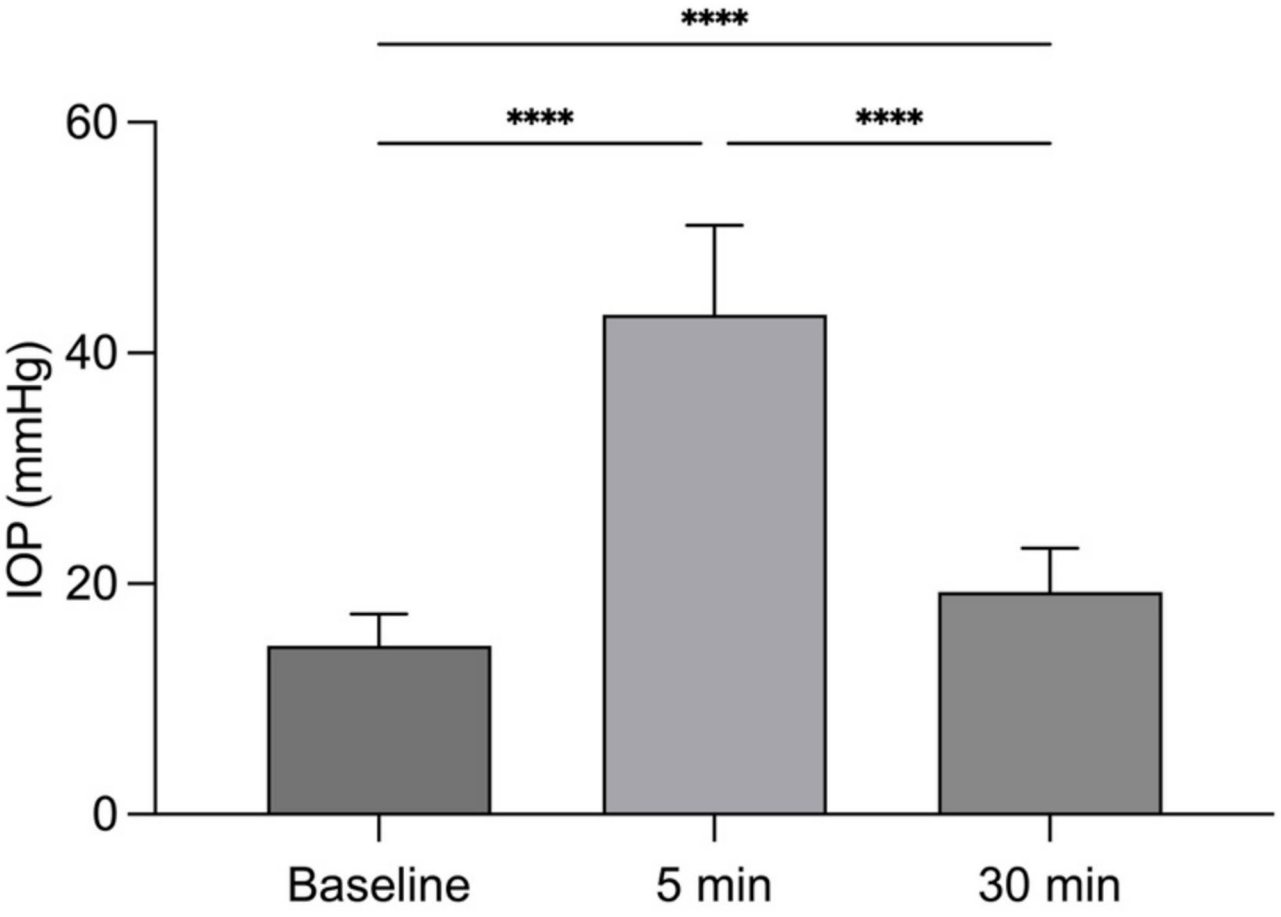

Fig. 1 IOP at different time points. Bar graph showing IOP at baseline, 5 min, and 30 min post-injection. Error bars show standard error. **** indicates $p < 0.0001$

Table 2 Parameters in the linear mixed-effects model

Effect	Estimate (95% CI)	Standard Error	*p*-value
Fixed Effects			
Age	0.283 (0.136, 0.429)	0.073	< 0.001
Phakic (vs. Pseudophakic)	9.809 (5.254, 14.364)	2.264	< 0.001
Non-diabetic (vs. Diabetic)	-5.502 (-9.545, -1.459)	2.018	0.009
Random Effects			
CS Diagonal Shift	17.759 (7.989, 39.476)	7.238	0.014
CS Covariance	24.500 (3.830, 45.170)	10.546	0.020

that older age, native crystalline lenses, and diabetes were significantly associated with more pronounced IOP increases at 5 min post-injection. In contrast, no significant associations were observed for axial length or drug type. Notably, IOP increased sharply at 5 min postoperatively, and although it decreased substantially within 30 min, it did not return to baseline levels.

Unlike previous studies that focused primarily on absolute postoperative IOP levels, this research emphasized the magnitude of IOP elevation as the primary outcome. By adopting this approach, we provided a more objective and dynamic assessment of postoperative IOP changes. Few studies [6, 15] have directly examined postoperative IOP elevation in this manner, underscoring the novelty and contribution of our findings.

Nonetheless, the accuracy of IOP measurements depends on the tonometric method used. In our study, we employed a non-contact tonometer (NCT), which offers practical advantages and avoids potential contamination of the ocular surface in the immediate post-injection period. While NCT has shown moderate to good agreement with Goldmann applanation tonometer (GAT) in normotensive eyes [16, 17], studies have reported a tendency to slightly overestimate IOP, particularly in eyes

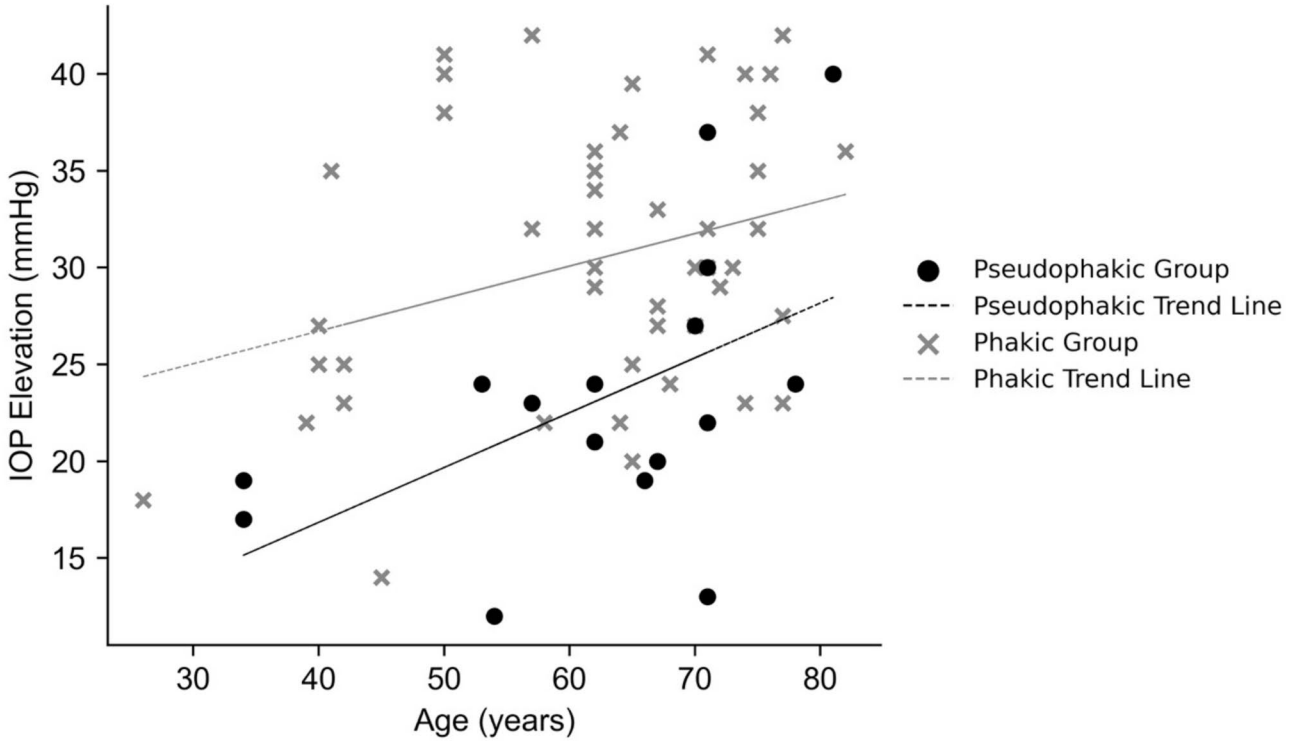

Fig. 2 Effect of age and lens status on IOP elevation. Scatter plot showing age versus IOP elevation 5 min post-injection. Trend lines represent pseudophakic and phakic groups

with higher pressures or thicker corneas [18, 19]. By focusing on IOP changes rather than absolute values, we mitigated much of this potential bias. Therefore, while this limitation should be kept in mind, our findings still offer valuable insights that may inform clinical assessment and decision-making.

Our analysis included 64 postoperative measurements from 51 patients, a sample size comparable to that of prior studies. For example, Hu et al. investigated IOP changes after conbercept IVI in 40 patients via a linear mixed-effects model, demonstrating its effectiveness in handling repeated measurements [6]. Another study analyzed sustained IOP elevation after anti-VEGF injections in 55 patients (58 eyes) via univariate and multivariate logistic regression [20]. By employing a linear mixed-effects model in this study, we accounted for random effects, addressing the repeatability of some data and the variability between measurement samples. The variability observed may result from minor dosage discrepancies during drug preparation or undetectable slow reflux at the injection site.

Short-term IOP elevation is a common occurrence after IVI. Studies suggest that transient IOP spikes may pose risks to retinal ganglion cells. Li et al. demonstrated that transient IOP increases after IVI could cause structural changes in the retinal microvasculature [21]. These findings emphasize that while short-term IOP elevation may be temporary, its potential harm should not be underestimated, particularly in high-risk patients. Therefore, personalized prevention strategies are crucial for mitigating excessive postoperative IOP [22].

In clinical practice, preoperative interventions such as topical IOP-lowering medications (e.g., brinzolamide or timolol) or systemic treatments (e.g., oral acetazolamide or intravenous mannitol) can effectively reduce preoperative IOP and minimize postoperative fluctuations [23]. Additionally, anterior chamber paracentesis during surgery is a viable method for managing acute IOP spikes but carries inherent risks, including infection, bleeding, and damage to intraocular structures [24]. In addition, decompressive techniques such as scleral indentation or digital ocular massage before or after IVI have demonstrated efficacy in reducing post-injection IOP spikes and may offer a less invasive alternative to paracentesis [25].

Future studies may benefit from comparing short-term IOP responses between patients who receive prophylactic IOP-lowering medications prior to IVI and those who do not, to better quantify the efficacy of such interventions. Consequently, while existing strategies partially address short-term IOP elevation, further optimization of predictive models and the development of individualized intervention protocols are essential to reduce potential complications in high-risk populations. For these patients, more vigilant postoperative care may be

warranted, including close monitoring of IOP, visual acuity, pupil response, and anterior chamber status. Additionally, intraoperative strategies such as slower injection speed may help mitigate acute IOP spikes [26], although these approaches require further validation in prospective studies.

Our study demonstrated that older age, diabetes, and native crystalline lenses were significantly associated with greater IOP elevation following IVI of anti-VEGF agents. Research has suggested that age and axial length may influence postoperative IOP changes, with older patients and those with shorter axial lengths being more prone to IOP elevation after injection [6, 27]. Consistent with these findings, our results confirmed the correlation between age and IOP changes. However, we did not observe a significant association between axial length and IOP changes. Unlike earlier studies that measured IOP changes within 5 min post-injection [6, 28], our measurements began at 5 min post-injection. Although previous studies have assessed IOP at multiple time points after IVI, including 5 min, they found a significant correlation between shorter axial length and IOP elevation only at 5 s post-injection [13]. By this time, IOP may have already decreased compared with immediate postoperative levels, potentially mitigating the influence of globe volume, as reflected by axial length, on IOP.

The association between older age and greater post-injection IOP elevation observed in our study may be explained by age-related changes in ocular biomechanics. Previous studies have indicated that ocular rigidity increases with age, and that higher rigidity is associated with more pronounced IOP spikes following intravitreal injection [6]. Furthermore, experimental evidence indicates that the intact natural vitreous plays a biomechanical damping role during transient IOP fluctuations [29]. With age-related vitreous liquefaction, this damping function may diminish, increasing strain transmission to the sclera and optic nerve head.

The impact of IOL on postoperative IOP remains contentious. Some studies reported no significant differences in IOP changes between pseudophakic and phakic eyes [6, 30]. Chehab et al. reported higher IOP levels at 1 min postoperatively in pseudophakic patients than in phakic patients, which contrasts with our findings [30]. However, their study relied on the Mann-Whitney U test without adjusting for potential confounders. In contrast, Kerimoglu et al. reported no significant differences between the two groups at 3 min postoperatively but noted a faster IOP reduction in pseudophakic eyes after 3 min [31]. Our study, which focused on IOP changes at 5 min postoperatively, aligns with these observations. Previous research has proposed that pseudophakic eyes may exhibit wider anterior chamber angles, facilitating faster IOP reduction [32]. We speculate that shorter measurement intervals may reduce the observable impact of wider anterior chamber angles on IOP reduction. Additionally, the smaller intraocular volume occupied by IOLs than by native crystalline lenses may increase the vitreous cavity volume, potentially influencing the immediate postoperative IOP.

Although prior studies have reported more pronounced RNFL thinning in DME patients following IVI [15], and others have linked elevated glycated hemoglobin levels to a greater risk of sustained IOP elevation [20], the role of diabetes as a risk factor for short-term IOP elevation remains underexplored. Our findings indicate that diabetic patients experienced significantly greater IOP elevation at 5 min post-surgery. We hypothesize that impaired aqueous humor outflow in diabetic patients [33, 34] may contribute to this effect, suggesting that diabetes could be a potential risk factor for postoperative IOP elevation.

Several limitations of this study should be acknowledged. First, while the analysis jointly evaluated multiple covariates, more granular subgroup analyses were not performed in this study and may offer additional clinical insight in future research. Second, IOP was measured using a NCT rather than the gold-standard GAT. While NCT offers practical advantages and avoids corneal contact in the immediate post-injection period, it may slightly overestimate IOP, particularly in eyes with higher pressure or thicker corneas. To reduce this potential bias, we focused on IOP elevation rather than absolute values. Third, this was a single-center study, which may affect generalizability. Finally, although diabetes was included as a systemic factor, other conditions such as hypertension and cardiovascular disease were not comprehensively evaluated and should be addressed in future research. Despite these limitations, our findings may still contribute to improving risk assessment and individualized care for patients undergoing intravitreal anti-VEGF therapy.

Conclusion

In conclusion, our results identify age, lens status, and diabetes as significant factors influencing short-term IOP changes after intravitreal anti-VEGF injections. These findings hold clinical relevance for preoperative risk assessment and individualized postoperative management. By employing a linear mixed-effects model, we accounted for repeated measurements and inter-individual variability, providing robust estimates. Future studies should include larger sample sizes, incorporate systemic comorbidities and ocular structural assessments, and explore the effects of prophylactic interventions or varied injection techniques to better refine risk stratification and management strategies.

Abbreviations

AMD	Age-related macular degeneration
BRVO	Branch retinal vein occlusion
CNV	Choroidal neovascularization
CRVO	Central retinal vein occlusion
DME	Diabetic macular edema
DR	Diabetic retinopathy
GAT	Goldmann applanation tonometer
IOP	Intraocular pressure
IVI	Intravitreal injection
NCT	Non-contact tonometer
nAMD	Neovascular age-related macular degeneration
RNFL	Retinal nerve fiber layer
VEGF	Vascular endothelial growth factor
VH	Vitreous hemorrhage

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Author contributions
Yanchen Liu conceptualized and designed the study, conducted patient recruitment, and collected the clinical data. Ting Wang was responsible for the statistical analysis, data interpretation, and preparation of the figures and tables. Xiaohong Zhang assisted in the clinical procedures and data validation. Xuefeng Wang supervised the study, provided methodological guidance, and critically revised the manuscript. Mengyun Li, Li Han, Xianhai Lan, and Li Wang supported data management, patient follow-up, and manuscript review.

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Data availability
The datasets used and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of the Yidu Central Hospital of Weifang (Approval No.YDCH2024-160). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable. This manuscript does not contain data from any individual person that could be identified.

Competing interests
The authors declare no competing interests.

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