Am J Transl Res 2025;17(9):7102-7119
www.ajtr.org /ISSN:1943-8141/AJTR0165718

Original Article

Preoperative pupillary metrics as predictors of postoperative acute and chronic pain following thoracoscopic surgery: a prospective study

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Received April 28, 2025; Accepted August 20, 2025; Epub September 15, 2025; Published September 30, 2025

Abstract: Objectives: To elucidate the correlation between preoperative pupillary parameters, obtained via automated pupillometry, and postoperative pain outcomes in patients undergoing thoracoscopic surgery. Methods: Between July and October 2023, 116 patients scheduled for thoracoscopic procedures under general anesthesia were prospectively enrolled. Preoperative pupillary metrics were systematically recorded using an automated pupillometer. Postoperative acute and chronic pain were rigorously assessed using the Numerical Rating Scale (NRS) and structured telephone follow-ups. Logistic regression analyses were employed to examine the association between perioperative pupillary variables and postoperative pain intensity. Receiver operating characteristic (ROC) curve analyses and clinical prediction models were constructed to evaluate the predictive capacity of these parameters. Results: Multivariate analysis identified age, gender, American Standards Association (ASA) classification, minimum pupil diameter [Odd Ratio (OR) = 0.37, P = 0.006], contraction latency (OR = 1.38, P = 0.007), and average dilation velocity (ADV; OR = 15.62, P = 0.003) as independent predictors of acute postoperative pain. The composite clinical prediction model demonstrated good predictive efficacy, with area under the ROC curve values of 0.802 in the training set and 0.819 in the validation cohort. Notably, average dilation velocity (ADV) emerged as a robust independent predictor of both chronic postoperative pain (OR = 223.13, 95% CI = 13.16-3782.33, P < 0.001) and acute-to-chronic pain transition (OR = 59.75, 95% CI = 1.81-1969.32, P = 0.022). Conclusion: This study establishes novel pupillometric biomarkers as independent risk factors for post-thoracoscopic pain, providing valuable insights for targeted pain management strategies.

Keywords: Pupil, acute postoperative pain, chronic postoperative pain, chronicization of acute pain

Introduction

Despite significant advancements in perioperative medicine, postoperative pain management remains a pressing and clinically challenging issue. Postoperative pain is a common concern among surgical patients, leading to substantial discomfort, distress, and considerable burdens on healthcare providers. Consequently, early prediction of postoperative pain is critical for optimizing analgesic strategies and enhancing patient recovery. Prior studies report that approximately 48.2% of surgical patients experience significant pain within 24 hours postoperatively, with 11% reporting severe and 37.2% reporting moderate pain [1]. Acute postoperative pain not only restricts patient mobility and respiratory function but may also exacerbate stress responses, leading to increased release of stress hormones and thereby elevating the risk of chronic pain development [2, 3]. On the other hand, while opioid use is effective in pain relief, it carries risks of adverse effects, including nausea, vomiting, constipation, respiratory depression, and opioid-induced hyperalgesia [4].

Chronic postsurgical pain (CPSP), defined as pain persisting for at least three months beyond normal tissue healing, typically localizes

https://doi.org/10.62347/PRUO9728

to the surgical site or corresponding dermatomal distribution, excluding unrelated pre-existing pain conditions [5]. CPSP exerts profound effects on daily functioning, potentially contributing to insomnia, fatigue, mood disturbances, and appetite suppression, ultimately diminishing patients' quality of life [6-8]. Notably, suboptimal acute pain management may predispose patients to the transition from acute to chronic pain.

Both acute and chronic pain development are influenced by multiple risk factors, including patient-specific characteristics, anesthetic techniques, and surgical factors. Early identification of these predictors and the implementation of targeted interventions are essential for mitigating postoperative pain incidence. Although many studies have attempted to construct predictive models incorporating preoperative and intraoperative variables, the precise risk factors for postoperative pain remain incompletely characterized and are still subject to ongoing debate.

Automated pupillometry is a noninvasive, highly reproducible, and precise modality that provides quantitative assessments of key parameters, including pupil diameter (PD), pupillary reflex dilation (PRD), and pupillary light reflex (PLR). These metrics have been objectively correlated with nociceptive states in prior investigations [9]. Recently, pupillometry has garnered increasing attention in perioperative pain management, demonstrating utility in pain quantification, opioid efficacy monitoring, and analgesic response evaluation [10-12]. Emerging evidence suggests that pupillometry-guided intraoperative analgesia significantly reduces postoperative pain intensity and decreases intraoperative remifentanil consumption compared with conventional analgesia guided by the surgical pleth index [13]. Further studies by David et al. have substantiated the clinical utility of pupillometry in postoperative pain assessment and opioid titration [14].

Given the paucity of research on pupillometric predictors of postoperative pain and limitations associated with single-parameter analyses and model construction, this study hypothesizes that one or more preoperative pupillary variables may serve as reliable predictors for postoperative pain. The novelty of this study lies in the development of a nomogram-based clinical prediction model incorporating baseline patient characteristics and pupillometric parameters. This model aims to facilitate early identification of high-risk patients, addressing the gap in relevant research. It holds promise for guiding personalized analgesic strategies, improving postoperative outcomes, enhancing quality of life, and reducing healthcare expenditures.

Methods

Case selection

This study was conducted in strict adherence to ethical principles of medical research and was approved by the Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University (Approval No: 2023-391). All research activities were conducted in accordance with the principles of the Declaration of Helsinki. The trial was registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR2400082643). All participants provided written informed consent. This study was conducted between July and October 2023 in the wards, operating rooms, and postoperative anesthesia care unit (PACU) of Yantai Yuhuangding Hospital.

Inclusion criteria: (1) Age between 18 and 70 years; (2) American Society of Anesthesiologists (ASA) physical status classification of 1 to 3; (3) Elective procedures including televised thoracoscopic lobectomy, segmental lung resection, or lung wedge resection [15]; (4) Ability to understand the Numeric Rating Scale (NRS) and correctly assess pain levels.

Exclusion criteria: (1) ocular diseases or a history of ocular surgery; (2) neuromuscular disorders; (3) diabetes mellitus; (4) thyroid dysfunction; (5) pupillary deformities; (6) the use of medications affecting pupil size, including dopamine receptor antagonists, neuromuscular blockers, or anticholinergic drugs; (7) planned neurosurgical procedures; (8) sensory dysfunction; or (9) preoperative chronic pain.

During the postoperative follow-up phase, patients were excluded if they experienced any of

the following conditions: metastasis-induced cancer pain, lost to follow-up, deceased, inability to complete the questionnaires, or poor wound healing.

Research methods

Preoperative assessment: Prior to surgery, demographic data including gender, age, and body mass index (BMI) were recorded for each patient, along with their personal and medical history. To assess pupillary function accurately, a PLR-3000™ portable infrared pupillometer was used for the quantitative analysis of pupillary parameters. This device, recognized for its high precision and portability, effectively measures multiple dynamic pupillary indicators, including maximum pupillary diameter (maximum PD before constriction), minimum pupillary diameter (PD at peak constriction), percentage change ((maximum PD - minimum PD)/maximum PD), constriction latency (time from light stimulus onset to the beginning of pupillary constriction), average constriction velocity (ACV), maximum constriction velocity (MCV), average dilation velocity (ADV), and time to 75% recovery (T75, the time for the pupil to return to 75% of its original PD). Each measurement was conducted over a 5-second period by a trained researcher in a dimly lit environment to minimize external light interference. Patients were instructed to fixate straight ahead and cover the contralateral eye to stabilize the pupil position and avoid accommodation reflex effects on the PLR measurements. Measurements were repeated if suboptimal data quality arose due to blinking, head movement, or equipment malfunction.

Intraoperative management: Upon arrival in the operating room, the patient's vital signs were monitored, including invasive arterial pressure, electrocardiogram, blood pressure, pulse, heart rate, airway pressure, respiratory rate, and end-expiratory CO_2. Anesthesia was induced with 0.04 mg/kg midazolam (H20031037, Jiangsu Nhwa Pharmaceutical Co., Ltd.), 0.3 μg/kg sufentanil (H20237165, Yichang Humanwell Pharmaceutical Co., Ltd.), 0.3 mg/kg etomidate (H32022999, Jiangsu Nhwa Pharmaceutical Co., Ltd.), and 0.15 mg/kg cisatracurium (H20183042, Jiangsu Hengrui Pharmaceuticals Co., Ltd.) or 0.6 mg/kg rocuronium (H20103495, North China Pharmaceutical Corporation Limited) followed by endotracheal intubation. After 10 minutes, a nerve blocker was inserted and adjusted as necessary, and patients were positioned laterally for a combined paravertebral nerve block using 0.375% ropivacaine. After intubation, mechanical ventilation with volume control was initiated, maintaining end-expiratory CO_2 levels between 35 and 45 mmHg. Intravenous infusion of propofol (50-100 μg/kg/min, H20010368, Xi'an Libang Pharmaceutical Co., Ltd.) and remifentanil (0.1-1 μg/kg/min, H20030197, Yichang Humanwell Pharmaceutical Co., Ltd.) was administered, with an additional intravenous bolus of 0.1 μg/kg sufentanil given 30 minutes before the end of the surgery for preemptive analgesia.

Postoperative assessment: In the PACU, pain intensity was assessed 10 minutes after the patient regained consciousness. The NRS, a 10 cm visual analogue scale ranging from "0" (no pain) to "10" (worst pain imaginable), was employed for pain assessment. Patients were instructed to mark the point on the scale that best represented their pain level, and a nurse subsequently recorded the score based on the marked position. Patients with an NRS score ≥ 3 were classified into the acute postoperative pain group, while those with an NRS score < 3 were classified into the non-acute postoperative pain group. Three months postoperatively, a telephone follow-up was conducted to inquire about the presence of chronic postoperative pain. Pain severity was again assessed using the NRS, with scores ≥ 1 indicating chronic postoperative pain and scores < 1 classified as non-chronic postoperative pain.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 25.0) for primary data processing and R software (version 3.3.3) for predictive model development and visualization. Continuous variables with a normal distribution were expressed as mean ± standard deviation (M ± SD) and compared using independent samples t-tests. Categorical data were presented as frequency counts and analyzed using χ^2 tests. Univariate logistic regression analysis was initially conducted to identify

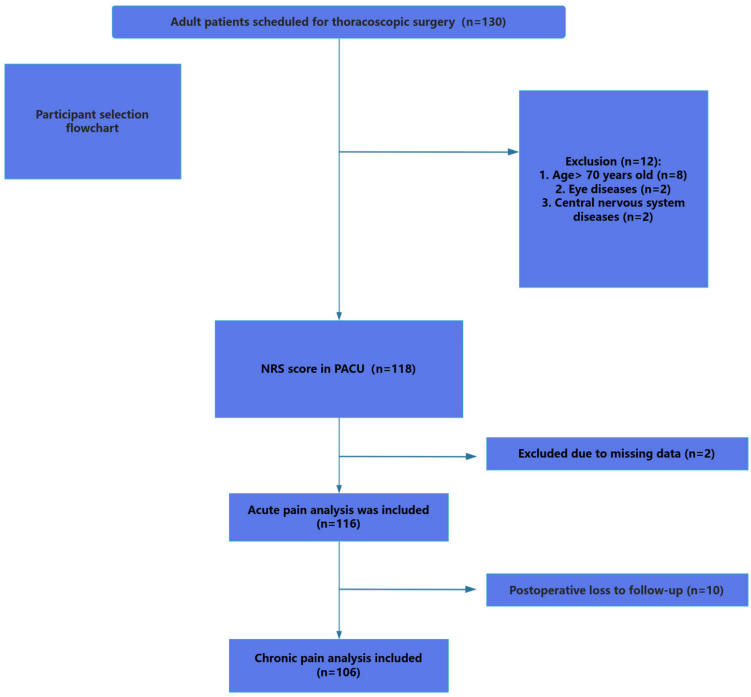

Figure 1. Flowchart of participant selection. NRS: Numerical Rating Scale; PACU: Post-Anesthesia Care Unit.

potential confounders and variables of interest, with NRS ≥ 3 serving as the primary outcome measure. Variables demonstrating statistical trends ($P < 0.1$) in univariate analysis were subsequently incorporated into multivariate logistic regression models, maintaining consistent exposure variables and outcomes across all analytical stages. Statistical significance was defined as a two-tailed *p*-value < 0.05.

The predictive performance of the models was evaluated using receiver operating characteristic (ROC) curve analysis with corresponding area under the curve (AUC) values, precision-recall (PR) curves for postoperative pain screening, calibration curves for assessing model fit, and decision curve analysis for evaluating clinical utility. Advanced model interpretation was achieved through decision plot visualization, SHAP (SHapley Additive exPlanations) value interpretation plots, correlation coefficient heatmaps, and additional machine learning-based feature importance analyses.

SHAP is an additive feature attribution originally proposed by Lundberg and Lee [16], designed to explain feature contributions in artificial intelligence and machine learning models, specifically in the area of explainable artificial intelligence (XAI). Recently, SHAP has shown promise in feature selection, offering valuable insights by explaining the contribution of each feature to model accuracy. This model-agnostic method can be applied to any machine learning or deep learning model, ensuring robust evaluation of both statistical performance and clinical applicability throughout the analytical processes.

Results

Pupil metrics and acute postoperative pain

A total of 130 patients underwent eligibility screening, with 116 ultimately included (**Figure 1**). Demographic and clinical characteristics of this cohort revealed a male predominance (70/116; 60%), a high proportion classified as ASA II (97/116; 84%), a majority without hypertension history (82/116; 71%), and a predominance of non-smokers (91/116; 78%). The mean age of enrolled patients was 59.57 ± 6.68 years, with a mean BMI of 24.33 ± 3.44. Among these, 45 patients (39%) reported NRS scores ≥ 3, indicating postoperative acute pain, whereas 71 patients (61%) exhibited NRS scores < 3 (**Table 1**).

Demographic analysis revealed significant disparities in age ($P = 0.053$), sex ($P = 0.045$), and ASA classification ($P = 0.017$) between the acute postoperative pain group (NRS ≥ 3) and non-acute postoperative pain group (NRS < 3) (**Table 1**). Pupillometric evaluation revealed differences in minimum pupil diameter ($P = 0.068$), contraction latency ($P = 0.035$), and ADV ($P < 0.001$) between groups (**Table 2**). Univariate logistic regression incorporating these pupillary metrics alongside age, sex, and ASA classification identified all six variables as potential predictors of postoperative acute pain (**Table 3**).

Variables exhibiting $P < 0.1$ in univariate logistic regression analysis were subsequently inte-

Table 1. Comparison of demographic characteristics between acute pain and non-acute pain cohorts

Variables	Acute pain group (NRS < 3; n = 71)	Non-acute pain group (NRS ≥ 3; n = 45)	χ^2/t	P
Age, years	60.52 ± 6.13	58.07 ± 7.28	1.949	0.053
BMI (kg/cm^2)	24.63 ± 3.45	23.85 ± 3.42	0.655	0.236
Sex			4.032	0.045
Male	48 (67.61)	22 (48.89)		
Female	23 (32.39)	23 (51.11)		
ASA			5.681	0.017
II	64 (90.14)	33 (73.33)		
III	7 (9.86)	12 (26.67)		
History of smoking			1.264	0.261
No	53 (74.65)	38 (84.44)		
Yes	18 (25.35)	7 (15.56)		
History of hypertension			0.073	0.788
No	49 (69.01)	33 (73.33)		
Yes	22 (39.99)	12 (26.67)		

Note: Values are presented as M ± SD, median (interquartile range), or n (%); ASA: American Society of Anesthesiologists; BMI: body mass index.

Table 2. Comparison of perioperative pupil parameters between acute pain and non-acute pain cohorts

Variables	Acute pain group (NRS < 3; n = 71)	Non-acute pain group (NRS ≥ 3; n = 45)	t	P
Maximum pupillary diameter	4.06 ± 0.89	3.89 ± 0.84	1.024	0.322
Minimum pupillary diameter	3.34 ± 0.75	3.07 ± 0.75	1.889	0.068
Percentage change	0.18 ± 0.06	0.21 ± 0.11	1.898	0.112
Constriction latency	25.63 ± 2.15	26.53 ± 2.32	2.130	0.035
ACV	1.83 ± 0.79	1.85 ± 0.79	0.133	0.908
MCV	2.64 ± 0.98	2.96 ± 1.38	1.459	0.142
ADV	0.73 ± 0.22	0.90 ± 0.31	3.452	<0.001
T75	1.02 ± 0.85	1.12 ± 0.92	0.598	0.542

Note: Values are presented as M ± SD. ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; T75: time to 75% recovery.

Table 3. Univariate logistic regression analysis of factors associated with acute postoperative pain

Variables	P	OR (95% CI)
Age, years	0.057	0.95 (0.89-1.00)
Minimum pupillary diameter	0.071	0.62 (0.37-1.04)
Constriction latency	0.038	1.20 (1.01-1.43)
ADV	0.002	12.90 (2.47-67.44)
Sex	0.046	2.18 (1.01-4.70)
ASA	0.021	3.32 (1.20-9.24)

Note: 95% CI: 95% confidence interval; ADV: average dilation velocity; ASA: American Society of Anesthesiologists.

grated into a multivariate model, identifying age (odds ratios (OR) = 0.93, 95% confidence intervals (CI) = 0.87-0.99, P = 0.036), sex (OR = 4.48, 95% CI = 1.66-12.13, P = 0.003), ASA classification (OR = 3.59, 95% CI = 1.10-11.71, P = 0.034), minimum pupil diameter (OR = 0.37, 95% CI = 0.18-0.76, P = 0.006), contraction latency (OR = 1.38, 95% CI = 1.09-1.74, P = 0.007), and ADV (OR = 15.62, 95% CI = 2.50-97.48, P = 0.003) as independent predictors for postoperative acute pain (**Table 4**).

A clinical prediction model was developed using these independent predictors. The cohort was randomly partitioned into training and vali-

Table 4. Multivariate logistic regression analysis of risk factors for acute postoperative pain

Variables	P	OR (95% CI)
Age, years	0.020	0.92 (0.86-0.99)
Minimum pupillary diameter	0.006	0.37 (0.18-0.76)
Constriction latency	0.007	1.38 (1.09-1.74)
ADV	0.003	15.62 (2.50-97.48)
Sex	0.003	4.48 (1.66-12.13)
ASA	0.034	3.59 (1.10-11.71)

Note: ADV: average dilation velocity; ASA: American Society of Anesthesiologists.

dation sets (7:3 ratio), with model performance rigorously evaluated. Statistical analysis revealed most *P*-values exceeded 0.05, indicating satisfactory model fit (**Table 5**). A nomogram was constructed, assigning weighted scores to each predictor (age, minimum pupil diameter, contraction latency, ADV, ASA classification, and sex). The aggregate score corresponded to a probability scale estimating postoperative pain risk (**Figure 2**), enabling effective patient stratification. Calibration curves demonstrated close alignment with the ideal line in low-risk strata, with minor deviations in moderate-to-high-risk ranges, supporting clinical utility (**Figure 3**).

The model's discriminative capacity was assessed via ROC analysis, yielding AUC values of 0.802 (training set) and 0.819 (validation set), with optimal thresholds of 0.43 (sensitivity 69.7%, specificity 81.3%, accuracy 76.5%) and 0.34 (sensitivity 83.3%, specificity 73.9%, accuracy 77.1%), respectively (**Figure 4**). Precision-recall curves further validated robust performance (training AP = 0.79; validation AP = 0.75), confirming reliable identification of high-risk patients (**Figure 5**).

SHAP value analysis highlighted ASA classification and ADV as key predictors (mean SHAP~0.4-0.5), whereas sex contributed minimally (**Figures 6**, **7**). Individualized SHAP plots facilitated patient-specific risk interpretation (**Figure 8**). Correlation heatmaps and decision-path analysis revealed inverse relationships between age, minimum pupil diameter, and pain risk, whereas ADV and ASA classification exhibited positive associations (**Figures 9**, **10**).

Decision curve analysis (DCA) demonstrated clinical net benefit within the 20%-50% threshold range, outperforming extreme strategies (**Figure 11**). This model not only enhances postoperative pain prediction but also provides a framework for timely clinical intervention and severity assessment.

Pupil metrics and chronic postoperative pain

Among the 116 patients included in the acute pain analysis, 10 were lost to follow-up, yielding a final cohort of 106 patients for chronic pain assessment (**Figure 1**). Demographic and clinical characteristics of this subset demonstrated a male predominance (67/106; 63.2%), a high proportion classified as ASA II (90/106; 84.9%), a majority without hypertension history (74/106; 71.6%), and a predominance of non-smokers (82/106; 78.1%). The mean age was 59.43 ± 6.78 years, with a mean BMI of 24.32 ± 3.39. At the three-month follow-up, 31 patients (29%) reported chronic postoperative pain (NRS ≥ 1), while 75 patients (71%) did not (**Table 5**).

Comparative demographic analysis between the chronic and non-chronic pain cohorts revealed no significant differences. However, pupillometric assessment identified disparities in mean ADV (P < 0.001), percentage change (P = 0.011), contraction latency (P = 0.061), MCV (P = 0.043), and minimum pupil diameter (P = 0.091) (**Table 6**). These five pupillary variables were incorporated into univariate and multivariate logistic regression models, with ADV emerging as the sole independent predictor of chronic postoperative pain (OR = 223.13, 95% CI = 13.16-3782.33, P < 0.001) (**Table 7**).

To further evaluate the predictive capacity of ADV for chronic postoperative pain, ROC analysis was performed. The AUC for ADV was 0.86 (95% CI = 0.78-0.93), with an optimal cutoff value of 0.785, sensitivity of 75%, and specificity of 90% (**Figure 12**). These findings underscore the utility of ADV as a robust predictor of chronic postoperative pain.

Pupil metrics and the chronicization of acute postoperative pain

In 45 patients with acute postoperative pain, 8 of them were lost of follow up, then, a cohort of

Table 5. Test for balance between training and testing sets

Variables	Total (n = 116)	test (n = 35)	train (n = 81)	χ^2/t	P
Age, years	59.57 ± 6.68	58.91 ± 6.62	59.85 ± 6.72	1.353	0.490
Minimum pupillary diameter	3.23 ± 0.76	3.49 ± 0.67	3.12 ± 0.77	0.150	0.016
Constriction latency	25.98 ± 2.25	26.34 ± 2.33	25.83 ± 2.21	0.454	0.259
ADV	0.80 ± 0.27	0.81 ± 0.25	0.80 ± 0.28	0.055	0.861
Sex				0.604	0.437
Male	70 (60.34)	23 (65.71)	47 (58.02)		
Female	46 (39.66)	12 (34.29)	34 (41.98)		
ASA				0.897	0.344
II	97 (83.62)	31 (88.57)	66 (81.48)		
III	19 (16.38)	4 (11.43)	15 (18.52)		

Note: ADV: average dilation velocity; ASA: American Society of Anesthesiologists.

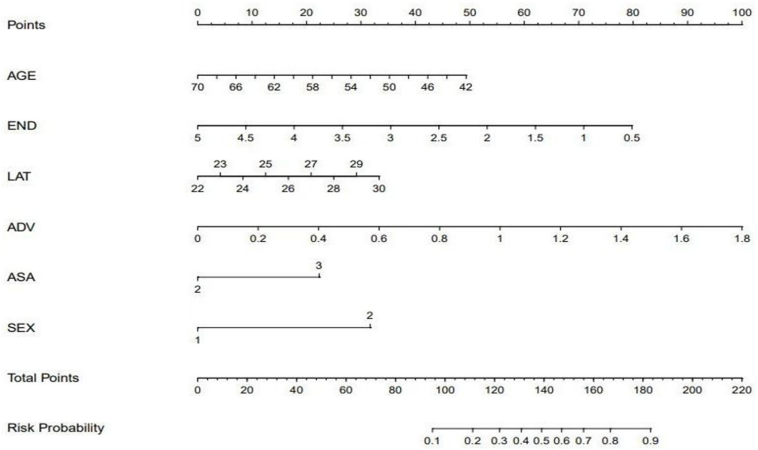

Figure 2. Nomogram for the clinical prediction model of acute postoperative pain. Note: END: minimum pupillary diameter; LAT: constriction latency; ADV: average dilation velocity; ASA: American Society of Anesthesiologists.

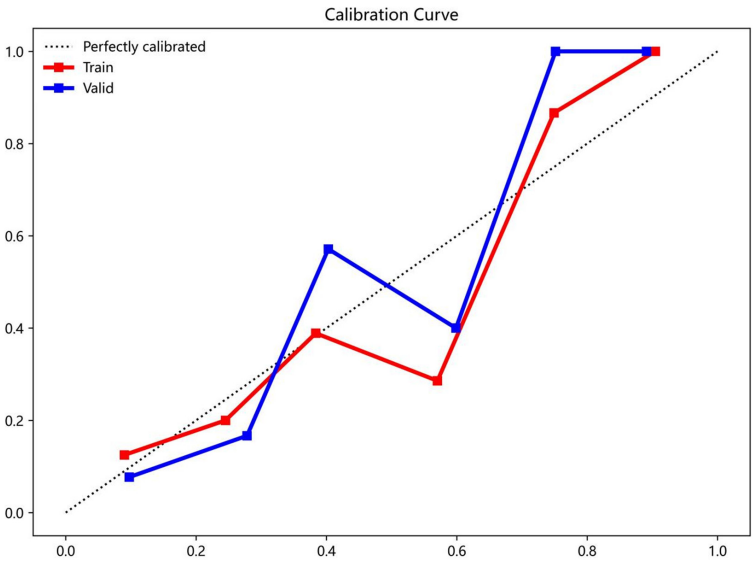

Figure 3. Calibration curve of the model.

37 patients who developed acute postoperative pain was enrolled in this study. Demographic and clinical characteristics of this subgroup demonstrated a male predominance (20/37; 54%), with most patients classified as ASA II (28/37; 75.7%), having no history of hypertension (27/37; 73%), and being non-smokers (31/37; 84%). The mean age was 57.57 ± 7.65 years with a mean BMI of 23.85 ± 3.42. At the three-month follow-up, 22 patients (59%) experienced chronification of acute postoperative pain, while 15 patients (41%) did not.

Initial analysis revealed no significant demographic differences between patients who developed chronic pain and those who did not. However, pupillometric evaluation demonstrated significant between-group differences in mean ADV (P = 0.010) (**Table 8**). Subsequent univariate and multivariate logistic regression analyses identified ADV as an independent predictor of pain chronification (OR = 59.75, 95% CI 1.81-1969.32, P = 0.022) (**Table 9**).

ROC curve analysis was performed to further evaluate

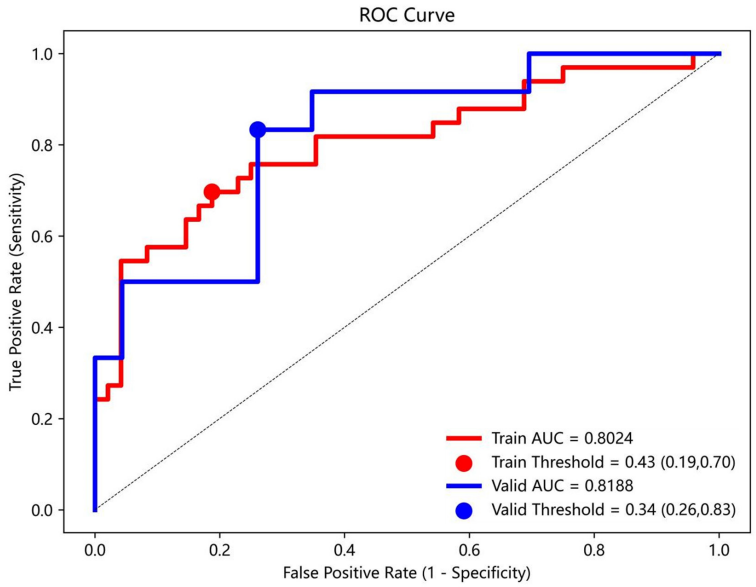

Figure 4. ROC curves for the predictive model in both the training and validation sets. Note: ROC: receiver operating characteristic; AUC: area under the curve.

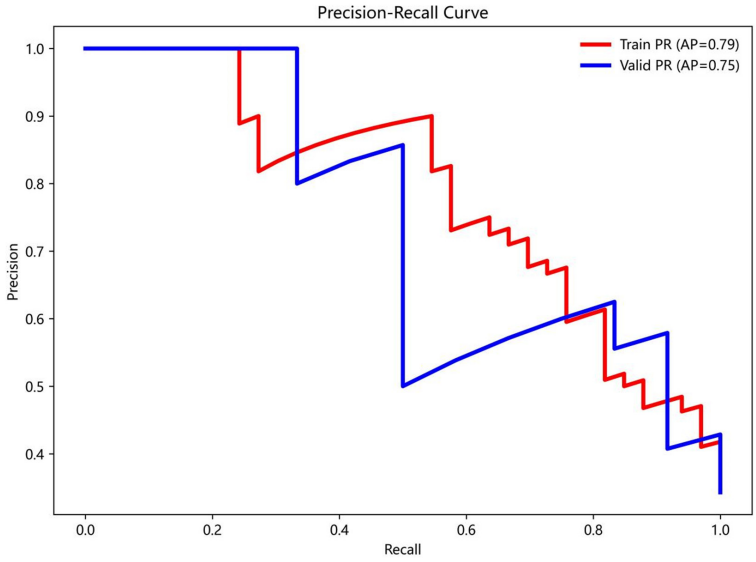

Figure 5. Precision-Recall (PR) curve analysis for the predictive model in both the training and validation cohorts.

ADV's predictive capacity for pain chronification. The optimal ADV cutoff value of 0.785 yielded an AUC of 0.81 (95% CI 0.63-0.98), with 73% sensitivity and 91% specificity. These findings suggest ADV's potential utility as a predictor for the chronification of acute postoperative pain within three months (**Figure 13**).

Discussion

This study systematically examined the potential correlations between preoperative pupillary parameters and the occurrence of both acute and chronic postoperative pain. In the analysis of acute pain, data from 116 patients were used. Through comprehensive multivariate logistic regression analysis, we identified six independent predictors of acute postoperative pain: minimum pupil diameter, contraction latency, ADV (a composite pupillary variable), along with patient age, ASA classification, and gender. A clinical prediction model incorporating these six variables demonstrated moderate but clinically meaningful predictive accuracy for acute postoperative pain development. In parallel, our evaluation of pupillary characteristics in 106 patients experiencing chronic postoperative pain revealed ADV as the sole independent predictive factor. This finding underscores the potential clinical utility of ADV in forecasting long-term pain outcomes. Furthermore, in a supplementary analysis of 37 patients who transitioned from acute to chronic postoperative pain, ADV again emerged as a significant predictor, further supporting its role in understanding the mechanisms underlying pain chronification.

The physiological basis for using pupillary measurements in pain assessment lies in pain's profound impact on autonomic nervous system homeostasis. Nociceptive stimuli disrupt autonomic balance through two primary mechanisms: activation of the sympathetic nervous system and concurrent inhibition of parasympathetic tone. These autonomic perturbations manifest through measurable changes in several physi-

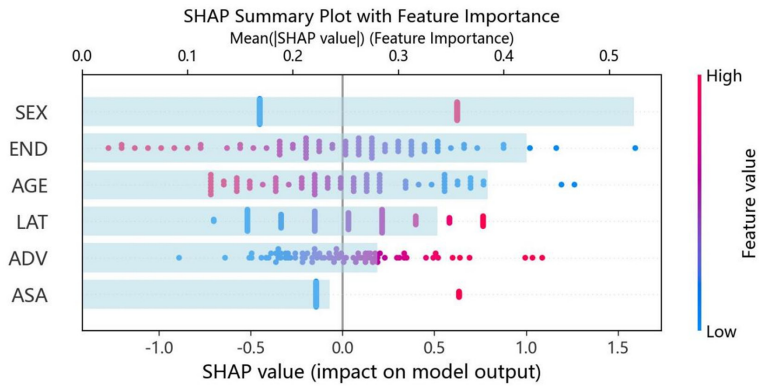

Figure 6. SHAP-based analysis of feature importance and directional impact in predictive modeling. SHAP: SHapley Additive exPlanations.

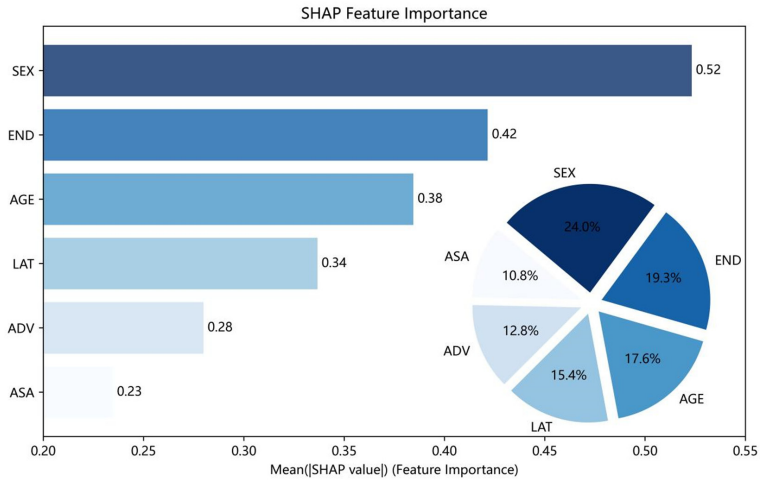

Figure 7. SHAP-based feature importance ranking. SHAP: SHapley Additive exPlanations.

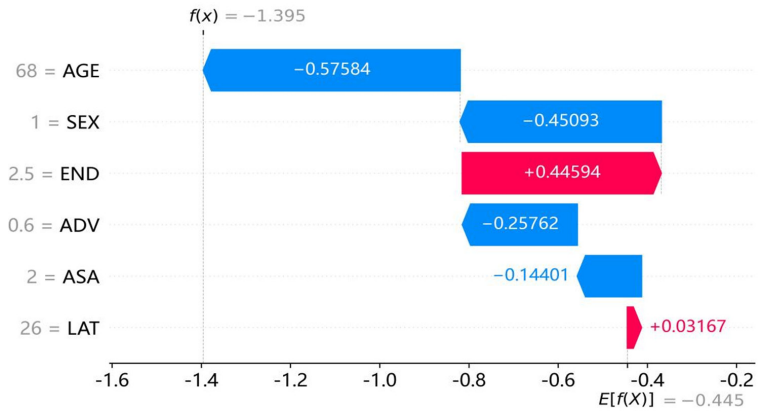

Figure 8. SHAP plot for patient-specific risk prediction. SHAP: SHapley Additive exPlanations.

ological parameters, including heart rate variability, arterial blood pressure fluctuations, and alterations in respiratory rate - all of which reflect the dynamic regulatory processes of the autonomic nervous system [17]. Of particular relevance, the iris musculature represents a unique anatomical site where the sympathetic and parasympathetic systems interact in a complex, reciprocal manner to produce characteristic pupillary oscillations. The dilator pupillae muscle is predominantly innervated by the sympathetic nervous system, while the sphincter pupillae is primarily under parasympathetic control [18]. Painful stimuli trigger a sympathetically-mediated pupillary dilation response, with the magnitude of dilation showing a positive dose-response relationship with the intensity of the nociceptive stimulus [19]. Pupillary reflex dilation during anesthesia is produced by inhibition of the Edinger-Westphal nucleus, without sympathetic involvement [18]. When the Edinger-Westphal nucleus is inhibited, the pupil is passively dilated, and sphincter tone is lost. This index has been previously used to assess postoperative pain [10]. In one study [20], PRD measurements were performed once the patient's responsiveness had returned. However, in contrast to the PRD in unconscious patients, which is a supraspinal parasympathetic reflex, the PRD in unanesthetized patients is predominantly a sympathetic reflex. This neurophysiological relationship establishes pupillometry as a robust and physiologically grounded tool for assessing the dynamic balance between sympathetic and parasympathetic activity in the context of pain perception.

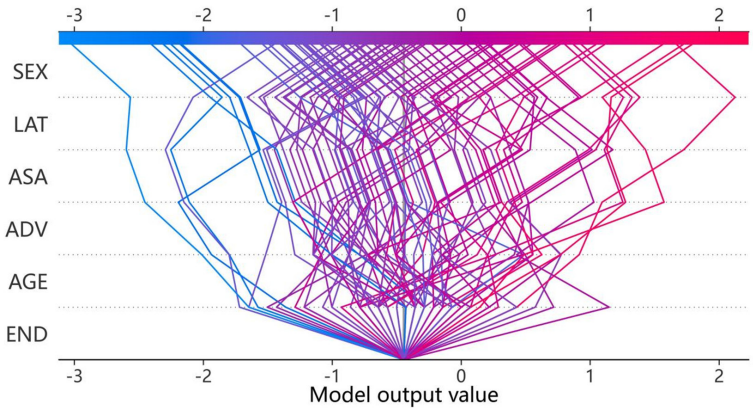

Figure 9. Decision-path analysis.

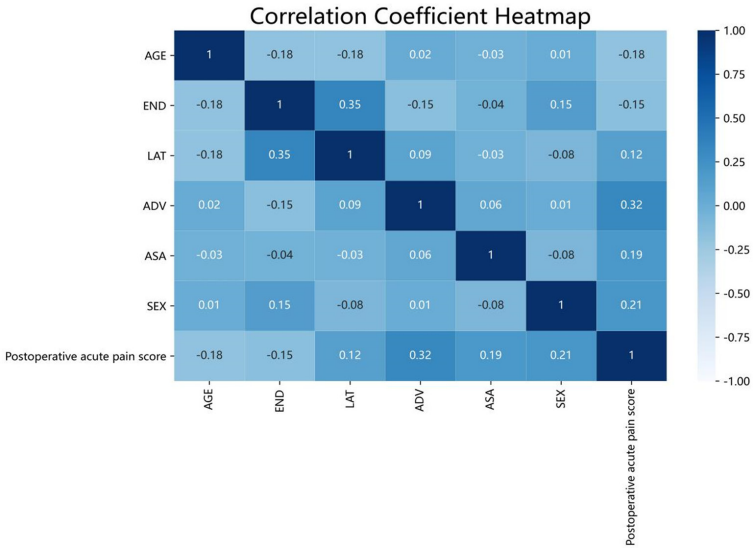

Figure 10. Correlation coefficient heatmap.

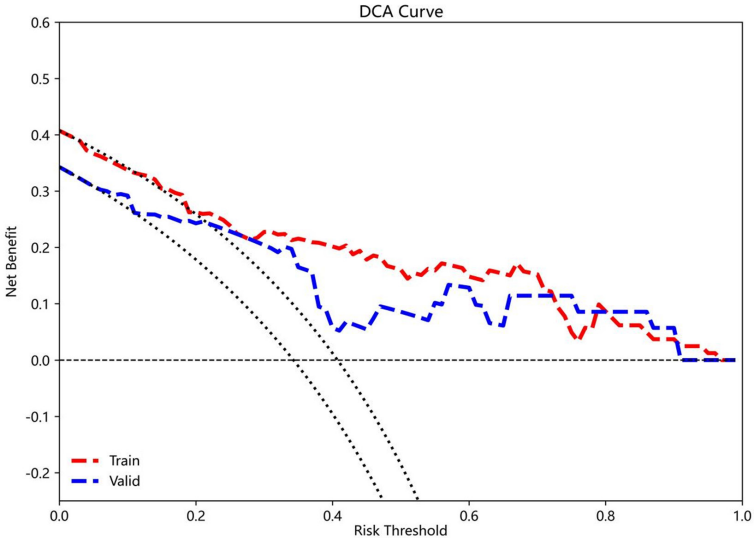

Figure 11. Decision curve analysis (DCA) for the predictive model.

Contemporary automated pupillometry devices provide a noninvasive, highly reproducible, and precise methodology for quantifying several key pupillary parameters that have demonstrated utility in nociception assessment. These parameters include static PD, dynamic PRD responses, and characteristics of the PLR - all of which have been empirically validated as objective indicators of nociceptive state and pain processing. A growing body of evidence supports a positive correlation between subjective pain intensity ratings and objectively measured pupillary dilation magnitude, with multiple studies confirming that more intense pain stimuli elicit proportionally greater pupillary dilation responses [20, 21]. Recent clinical investigations have further demonstrated that anesthesia protocols incorporating pupillometry-guided intraoperative analgesic administration result in superior pain outcomes compared to conventional approaches, including significant reductions in immediate postoperative pain intensity scores and decreased intraoperative remifentanil requirements when compared to surgical pleth index-guided analgesia [13]. Additional rigorous studies have corroborated the clinical utility of pupillary measurements in postoperative pain assessment and opioid dose titration, establishing their role in perioperative pain management protocols [14]. The scientific rationale for investigating pupillary parameters as potential predictors of postoperative pain stems from their shared neuroanatomical substrates with pain pathways. The pupillary light reflex, being regulated by

Table 6. Comparison of demographic characteristics and perioperative pupil parameters between chronic pain and non-chronic pain cohorts

Variables	Total (n = 106)	No Chronic Pain (n = 75)	Chronic Pain (n = 31)	χ^2/t	P
Age, years	59.43 ± 6.78	59.40 ± 7.18	59.52 ± 5.80	0.083	0.937
Maximum pupillary diameter	3.98 ± 0.87	3.98 ± 0.92	3.98 ± 0.77	0.016	0.987
Minimum pupillary diameter	3.22 ± 0.77	3.30 ± 0.78	3.02 ± 0.71	1.724	0.089
Percentage change	0.19 ± 0.09	0.17 ± 0.06	0.24 ± 0.12	4.00	0.011
Constriction latency	25.92 ± 2.24	25.65 ± 2.13	26.55 ± 2.41	1.903	0.061
ACV	1.83 ± 0.80	1.77 ± 0.80	1.99 ± 0.79	1.293	0.195
MCV	2.74 ± 1.15	2.60 ± 1.04	3.09 ± 1.33	2.028	0.043
ADV	0.78 ± 0.26	0.70 ± 0.21	0.99 ± 0.24	6.199	< .001
BMI	24.32 ± 3.39	24.68 ± 3.50	23.65 ± 3.12	1.421	0.139
T75	1.08 ± 0.90	0.95 ± 0.53	1.40 ± 1.43	2.372	0.107
Sex, n (%)				0.069	0.792
Male	67 (63.21)	48 (64.00)	19 (61.29)		
Female	39 (36.79)	27 (36.00)	12 (38.71)		
ASA, n (%)				0.621	0.624
II	90 (84.91)	65 (86.67)	25 (80.65)		
III	16 (15.09)	10 (13.33)	6 (19.35)		
History of smoking, n (%)				1.306	0.253
No	82 (77.36)	60 (80.00)	22 (70.97)		
Yes	24 (22.64)	15 (20.00)	9 (29.03)		
History of hypertension, n (%)				2.093	0.148
No	74 (69.81)	55 (73.33)	19 (61.29)		
Yes	32 (30.19)	20 (26.67)	12 (38.71)		

Note: ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; BMI: body mass index; ASA: American Society of Anesthesiologists.

integrated autonomic pathways, provides a window into the ongoing balance between sympathetic and parasympathetic tone. This physiological understanding motivated our systematic investigation to identify specific pupillometric variables that might serve as reliable predictors for both acute and chronic postoperative pain outcomes, with the ultimate translational goal of developing practical, noninvasive tools for preoperative risk stratification that could facilitate personalized perioperative pain management strategies and optimize resource allocation.

Our analytical results confirmed several key hypotheses regarding pupillary predictors of acute postoperative pain. As anticipated, three pupillary-specific variables - minimum pupil diameter, contraction latency, and the composite measure ADV - emerged as statistically significant predictors of acute postoperative pain development. Additionally, three non-pupillary patient characteristics (age, gender, and ASA classification) maintained their predictive value in our multivariate models, consistent with existing literature. The predictive validity of PRD merits particular attention. First described by Budge in 1852 as a sympathetically-mediated physiological response, our findings substantially extend this historical observation by establishing its prognostic value in acute pain prediction. Previous clinical investigations had demonstrated significant correlations between the Pupillary Pain Index (PPI, a derived metric incorporating PRD measurements) and standard pain rating scales in specific patient populations, including neurosurgical patients [22] and pediatric cohorts [23]. Our current research advances this scientific understanding by demonstrating that preoperative pupillary characteristics can predict postoperative pain outcomes, rather than simply showing reactive correlations with concurrent pain states. The

Table 7. Logistic regression analyses for postoperative chronic pain

Variables	Univariate					Multivariate				
	β	S.E	Z	P	OR (95% CI)	β	S.E	Z	P	OR (95% CI)
Minimum pupillary diameter	-0.49	0.29	-1.67	0.095	0.61 (0.34-1.09)	-0.12	0.44	-0.27	0.790	0.89 (0.37-2.11)
Percentage change	11.73	3.89	3.02	0.003	124862.00 (61.43-253784888.53)	7.83	6.44	1.22	0.224	2512.58 (0.01-761035658.53)
Constriction latency	0.19	0.10	1.85	0.064	1.20 (0.99-1.46)	0.26	0.13	2.06	0.139	1.30 (1.01-1.68)
ADV	6.24	1.43	4.37	< .001	514.87 (31.24-8486.16)	5.41	1.44	3.74	< .001	223.13 (13.16-3782.33)
MCV	0.36	0.19	1.90	0.058	1.44 (0.99-2.10)	-0.06	0.35	-0.17	0.865	0.94 (0.48-1.86)

Notes: ADV: average dilation velocity; MCV: maximum constriction velocity.

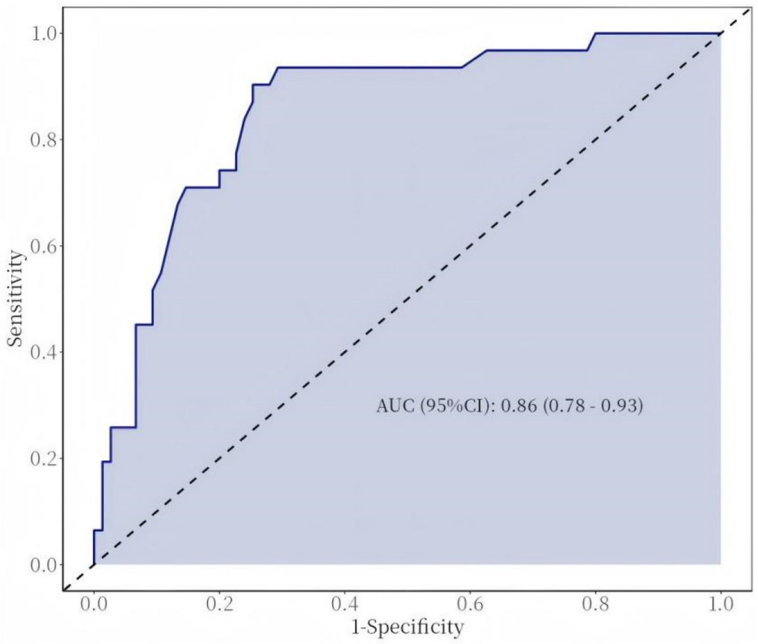

Figure 12. ROC curve for ADV in predicting postoperative chronic pain.

clinical prediction model we developed, which integrates both pupillary and non-pupillary variables, exhibited statistically significant associations with postoperative NRS scores, thereby reinforcing and extending previous correlational findings. An independent study of 50 patients undergoing thoracoabdominal surgical procedures similarly identified significant associations between preoperative pupillary light reflex latency parameters and postoperative pain scores in PACU [24]. However, this particular investigation failed to identify other pupillary parameters as significant predictors, possibly attributable to their relatively low rate of rescue analgesic administration (26% versus 43.3% in comparable studies), which may have reduced the incidence of severe pain events and consequently attenuated observable correlations. The modest sample size in that study may have further limited its statistical power to detect significant associations. In contrast, our investigation specifically enrolled patients undergoing thoracoscopic surgery, a procedure associated with characteristically high postoperative pain intensity, which enhanced our ability to detect meaningful predictive relationships.

The existing literature presents some apparent inconsistencies regarding the role of pupillary parameters in pain prediction that warrant careful consideration. Several well-designed studies have failed to demonstrate significant correlations between either preoperative or postoperative pain ratings and static pupil diameter measurements or NRS scores [25, 26]. These discrepancies likely reflect important methodological differences, particularly regarding the timing of pupillometric assessments relative to nociceptive stimuli and whether measurements were obtained during active noxious stimulation [12, 18]. Our study intentionally obtained preoperative pupillary measurements in a carefully controlled environment devoid of acute noxious stimuli, suggesting that baseline pupillary characteristics may reflect inherent neurological susceptibility to pain development rather than simply representing reactive responses to immediate painful stimuli. An important physiological consideration is that general anesthetic agents, particularly propofol and opioids, significantly suppress spontaneous pupillary oscillations [18, 27]. Previous studies have shown that higher pain levels within the first three days post-surgery are associated with an increased risk of chronic pain [28, 29]. Our findings highlight that ADV serves as a predictor of the chronicization of acute postoperative pain, filling a gap in research on pupil function and chronic pain, providing new insights into predicting postoperative chronic pain.

The prediction of postoperative pain has emerged as a critical focus in contemporary surgical care, with extensive global research dedicated to optimizing pain management outcomes. Current evidence demonstrates that postoperative pain development correlates with multifactorial determinants, including patient-specific characteristics, surgical variables, and anesthetic techniques [30, 31]. Established demographic predictors include BMI, age, gender, and prior pain history [32, 33], while psychological factors such as pain catastrophizing, have been significantly associated with

Table 8. Comparison of demographic and pupillometric parameters between patients with chronicization and non-chronicization of acute postoperative pain

Variables	Total (n = 37)	Non-chronicization of acute Pain (n = 15)	Chronicization of acute Pain (n = 22)	χ^2/t	P
BMI (kg/cm^2)	23.85 ± 3.42	24.25 ± 3.88	23.65 ± 3.21	0.513	0.611
Age, years	57.57 ± 7.65	55.73 ± 9.38	58.82 ± 6.13	1.214	0.233
Maximum pupillary diameter	3.77 ± 0.83	3.71 ± 0.96	3.82 ± 0.76	0.388	0.700
Minimum pupillary diameter	2.97 ± 0.74	3.09 ± 0.78	2.89 ± 0.72	0.802	0.428
Percentage change	0.21 ± 0.12	0.17 ± 0.05	0.24 ± 0.14	1.851	0.073
Constriction latency	26.51 ± 2.29	26.40 ± 2.10	26.59 ± 2.46	0.244	0.808
ACV	1.79 ± 0.84	1.59 ± 0.83	1.92 ± 0.84	1.179	0.246
MCV	2.88 ± 1.44	2.63 ± 1.26	3.04 ± 1.55	0.849	0.404
ADV	0.88 ± 0.28	0.74 ± 0.31	0.97 ± 0.22	2.644	0.010
T75	1.16 ± 1.00	1.00 ± 0.80	1.28 ± 1.12	0.833	0.411
Sex, n (%)				0.457	0.554
Male	20 (54.05)	7 (46.67)	13 (59.09)		
Female	17 (45.95)	8 (53.33)	9 (40.91)		
ASA, n (%)				0.256	0.613
II	28 (75.68)	12 (80.00)	16 (72.73)		
III	9 (24.32)	3 (20.00)	6 (27.27)		
History of smoking, n (%)				1.693	0.193
No	31 (83.78)	14 (93.33)	17 (77.27)		
Yes	6 (16.22)	1 (6.67)	5 (22.73)		
History of hypertension, n (%)				0.632	0.427
No	27 (72.97)	12 (80.00)	15 (68.18)		
Yes	10 (27.03)	3 (20.00)	7 (31.82)		

Note: BMI: body mass index; ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; ASA: American Society of Anesthesiologists.

Table 9. Logistic regression analysis of chronicization of acute postoperative pain

Variables	P	OR (95% CI)
ADV	0.022	59.75 (1.81-1969.32)

pain severity [34]. Various statistical methodologies have been employed to develop predictive models, with machine learning algorithms demonstrating particular utility in identifying critical pain-associated variables through clinical data analysis [35, 36]. These advanced models enhance predictive accuracy while facilitating personalized analgesic strategies to improve postoperative recovery [37]. Representative studies analyzing 500+ patient datasets have successfully identified predictive physiological and psychological parameters [38]. Our integrated predictive model combining pupillometric indices with conventional risk factors offers novel opportunities for tailored analgesia and pain prevention.

Expanding research across surgical specialties reveals procedure-specific predictors of preoperative pain. For example, preoperative pain scores and functional status significantly predict pain outcomes in joint arthroplasty [39, 40], while abdominal surgery outcomes correlate with preoperative anxiety, operative duration, and intraoperative blood loss [31]. These findings highlight the need for further investigation into pupillometric parameters' predictive validity across diverse surgical procedures. Concurrent advances in pain pathophysiology have identified novel biomarkers, including inflammatory mediators (TNF, IL-6) that contribute to pain pathogenesis [28, 33]. Systematic monitoring of these biomarkers may facilitate early identification of high-risk patients for targeted intervention. Our current model warrants expansion to incorporate additional variables, including surgical duration, blood loss, and cytokine profiles, to improve predictive robustness while controlling for potential confound-

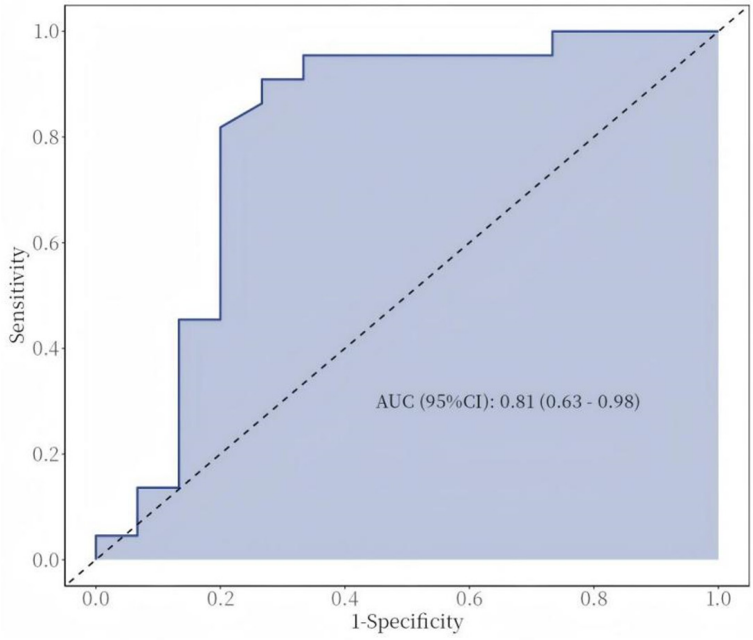

Figure 13. ROC curve for ADV in predicting chronicization of acute postoperative pain.

ers. These collective advances hold the potential to revolutionize pain management through precision medicine approaches.

While our findings present several clinically relevant insights, certain methodological limitations should be recognized. The moderate sample size, while adequate for our primary analyses, may limit the generalizability of some findings and suggests the need for larger-scale validation studies. Pupillometric measurements can be influenced by various environmental factors, including ambient light conditions, though we implemented rigorous protocols to minimize these potential confounders. As an observational study, our research can identify statistically significant associations but cannot definitively establish causal relationships - a limitation that future randomized controlled trials should address.

Of note, extremely high odds ratios (OR) and extremely wide confidence intervals (CI) were observed when analyzing mean expansion velocity (ADV) as a predictor of chronic postoperative pain and its chronicity. This statistical phenomenon most likely reflects model instability caused by the small relative sample size of chronic pain events in our study, particularly events in the subgroup of chronic pain. Therefore, we should be cautious in interpreting the specific values of ors rather than directly interpreting them as precise multiples of risk. In the future, our findings need to be validated in larger prospective cohort studies.

In addition, although we used multivariable models to adjust for underlying patient characteristics, our study was limited by our failure to include several key intraoperative variables as covariates. These variables included the specific type of surgery (e.g., the difference between lobectomy and wedge resection), the duration of the procedure, and the total amount of opioids consumed during the procedure.

These factors are recognized as critical in determining the degree of surgical trauma, the intensity of the inflammatory response, and the potential for central sensitization, and a reasonable hypothesis is that the more complex and time-consuming procedure itself may result in greater physiological stress and sympathetic excitation that can affect the pupil parameters measured preoperatively. The associations we observed between pupil parameters and postoperative pain may have been partially influenced by the confounding effects of these unmeasured variables. Therefore, the independent predictive contribution of preoperative pupillometry that we report may be overestimated and the effect size may be affected by confounding factors.

Despite these limitations, our comprehensive analyses provide compelling evidence that specific pupillary parameters, particularly the ADV metric, show significant promise as clinically accessible predictors of both acute and chronic postoperative pain outcomes. These findings contribute to the growing body of evidence supporting the development of personalized, physiologically-informed approaches to perioperative pain management and risk stratification.

Conclusion

In summary, our study demonstrates that minimum pupil diameter, contraction latency, ADV,

along with age, ASA classification and gender are independent predictors of acute postoperative pain. Specifically, ADV has been validated as an independent predictor for both acute and chronic pain following thoracoscopic surgery. The clinical prediction model developed from these variables demonstrates moderate predictive efficacy for acute postoperative pain. These pupillometric parameters enable anesthesiologists to more accurately anticipate and manage postoperative pain, potentially improving patient outcomes and quality of life. However, further research is warranted to address the limitations of this study and to more precisely define the role of pupillometry in comprehensive pain management strategies.

Clinical perspectives

Despite the remarkable advancements in perioperative medicine, the management of postoperative pain remains a formidable and intricate clinical challenge. The transition from acute to chronic pain, particularly in the context of surgical procedures, significantly impairs patients' recovery and quality of life. In recent years, pupillometry has emerged as a promising tool in perioperative pain management, offering novel insights into pain quantification, opioid effect monitoring, and analgesic response assessment.

This study extends the current body of knowledge by specifically investigating whether preoperative pupillary variables can serve as predictive indicators for postoperative pain. Our findings not only support the utility of pupillometry in predicting acute postoperative pain but also establish ADV as a key independent predictor of both chronic postoperative pain and the chronicization of acute postoperative pain.

By incorporating pupillary indicators into preoperative assessments, anesthesiologists can predict and manage postoperative pain more effectively. This provides valuable guidance for alleviating postoperative discomfort and improving the efficacy of pain prediction and intervention strategies.

Acknowledgements

This research was supported by the 2021 Shandong Medical Association Clinical Research Fund - Qilu Special Project (No. YXH2022ZX02102).

Disclosure of conflict of interest

None.

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