Pupillary Light Reflex Parameters as Predictors of Postoperative Nausea and Vomiting: A Prospective Study

Ann. Ital. Chir., 2025 96, 5: 681–694
https://doi.org/10.62713/aic.3900

Yawen Zhang[1,2,†], Jin Jin[2,†], Leying Sun[2], Haoyi Ji[1,2], Jinjian Zhu[2,3], Dan Sheng[2,3], Qiang Song[4], Cunxian Shi[2]

[1]The Second School of Clinical Medical of Binzhou Medical University, 264003 Yantai, Shandong, China
[2]Department of Anesthesiology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 264000 Yantai, Shandong, China
[3]School of Anaesthesia, Shandong Second Medical University, 261053 Weifang, Shandong, China
[4]Department of Anesthesiology, PLA 960th Hospital, 250031 Jinan, Shandong, China

AIM: This study aims to investigate whether pupillary light reflex (PLR) parameters in dynamic pupillometry can effectively predict postoperative nausea and vomiting (PONV).

METHODS: In this prospective observational study, patients scheduled to undergo elective lobectomy under general anesthesia were enrolled from 1 August 2023 to 7 October 2023 at Yantai Yuhuangding Hospital, a large regional tertiary hospital in Yantai City, Shandong Province, China. Preoperative pupillary parameters were measured using a portable infrared pupillometer, and the patients were followed up within 24 hours postoperatively to assess postoperative nausea and vomiting (PONV) and recovery quality. Logistic regression analysis and receiver operating characteristics (ROC) curves were used to evaluate the predictive efficacy of pupillary parameters, and mediation analysis was conducted to explore the mediating role of PONV between pupillary parameters and recovery quality.

RESULTS: Forty-six patients (29.9%) who experienced PONV had smaller maximum pupil diameter, average constriction velocity (ACV), maximum constriction velocity (MCV), and percentage pupil change. MCV was identified as an independent predictor of PONV, with each 1-unit increase in MCV reducing the risk of PONV by 87%. Gender was a protective factor, with males having a 65% lower risk of PONV compared to females. The ROC analysis showed that the area under the curve (AUC) value of MCV was 0.831 (95% confidence interval (CI): 0.760–0.902), indicating that the model has strong classification ability when using MCV as a predictor. Thus, PONV plays a full mediating role in the relationship between MCV and postoperative recovery quality.

CONCLUSIONS: MCV is a reliable predictor of PONV, which plays a full mediating role in the relationship between MCV and postoperative recovery quality. Thus, with a capability in predicting PONV occurrence, preoperative MCV measurement can be employed for the purpose of improving patient recovery outcomes.

CLINICAL TRIAL REGISTRATION: Chinese Clinical Trial Registry (ChiCTR2300073869).

Keywords: postoperative nausea and vomiting; anesthesia; pupillary light reflex; maximum constriction velocity; gender; quality of postoperative recovery

Introduction

Nausea and vomiting are among the most common complications during the perioperative period. Nausea is characterized by an unpleasant sensation in the stomach, often leading to the feeling of impending vomiting, accompanied by symptoms such as active dry heaving, tachycardia, and increased salivation [1]. Vomiting, on the other hand, involves the involuntary and forceful expulsion of stomach contents through the mouth and/or nose [2]. Postoperative nausea and vomiting (PONV) persists as distressing complications following surgery, resulting in adverse outcomes such as delayed discharge, increased risk of readmission, prolonged recovery time after discharge, and heightened healthcare costs [3]. PONV is defined as the occurrence of nausea, vomiting, or dry heaving in the post-anesthesia care unit or within 24 hours of surgery [2]. Previous studies indicate that the risk of PONV after elective surgery is approximately 30%, with the incidence rising to 80% in high-risk patients [4–8]. Despite advancements in anesthesiology and the recognition of PONV as a primary management concern, its occurrence remains prevalent. While anesthesiologists prioritize postoperative pain management, preventing PONV is equally crucial from the patient's perspective.

Submitted: 3 December 2024 Revised: 18 February 2025 Accepted: 21 February 2025 Published: 10 May 2025
Correspondence to: Qiang Song, Department of Anesthesiology, PLA 960th Hospital, 250031 Jinan, Shandong, China (e-mail: 181985259@qq.com); Cunxian Shi, Department of Anesthesiology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 264000 Yantai, Shandong, China (e-mail: Shi_cunxian@163.com).
[†]*These authors contributed equally.*

Comfort measures throughout the perioperative period have been a cornerstone of anesthesiology practice, underscoring the importance of addressing PONV alongside postoperative pain. Existing research indicates that the occurrence of PONV is associated with many factors, including patient risk factors such as female gender, history of motion sickness, non-smoking status, and the use of opioids [9,10]. In terms of anesthesia management, the use of inhalational anesthetics is more likely to lead to PONV compared to intravenous anesthetics (e.g., propofol), and prolonged surgical duration can also contribute to PONV. Additionally, genetic factors play a role, as single nucleotide polymorphisms (SNPs) *CHRM3* rs2165870 and *KCNB2* rs349358 have been shown to be significantly associated with PONV in Caucasian populations [11]. Studies have demonstrated that risk assessment for PONV is crucial for reducing its incidence and guiding clinical treatment.

In recent years, researchers have proposed various PONV risk scores and prediction models. Among them, the simplified Apfel risk score is the most widely used predictive tool, which is based on four key variables: female gender, history of motion sickness or PONV, non-smoking status, and postoperative opioid use [12]. Furthermore, the Koivuranta score builds upon the Apfel score by incorporating surgical duration (>60 minutes) as a fifth predictive factor to improve the accuracy of risk assessment. Bourdaud *et al*. [13] proposed a PONV prediction model for pediatric patients by combining multiple risk factors, such as surgical type, anesthesia duration, and postoperative analgesic methods. Xie *et al*. [7] developed a machine learning algorithm to automatically predict PONV, significantly improving prediction accuracy by analyzing large-scale patient data. Currently, all prediction models are based on the Apfel score, and no models predicting PONV from other perspectives have yet emerged. Despite the prevalence and importance of PONV, little is known about the core mechanisms behind it [4].

Vomiting is preceded by a number of characteristic physiologic changes, such as sweating, pallor, salivation, elevated blood pressure, tachycardia, cutaneous vasoconstriction, and decreased gastrointestinal motility, all of which are mediated by the autonomic nervous system (ANS) [1]. Previous studies have shown that an increase in nausea is associated with a decrease in parasympathetic nerves and an increase in sympathetic modulation, which is the main cause of these symptoms [1,14,15]. Additionally, it has been found that while the insula and certain other areas of the brain appear to regulate both sympathetic and parasympathetic responses, there also appears to be a different central control of the autonomic response to nausea and vomiting [16]. Thus, PONV is closely related to the ANS. The functional state of the ANS is challenging to quantify, but recent research suggests that the functional state of the pupil can serve as a reliable indicator. Pupil infrared measurement can quasi-quantify pupil functional parameters, providing insights into ANS activity [15]. Pupillometry, which involves measuring pupil size and reactivity, is a vital component of neurological examinations. The pupillary light reflex (PLR) reflects the functional state of the pupil, with pupil size, dilation, and constriction rates influenced by the ANS. The sympathetic nervous system typically dilates the pupil, while the parasympathetic nervous system tends to constrict it [17]. Advancements in technology have led to the development of portable automated infrared pupillometers (PAIP), enabling objective assessments of PLR by measuring pupil size, constriction, and dilation rates [18]. Numerous studies have demonstrated the utility of PAIP in evaluating clinical disorders affecting the ANS [19–21]. This indicates that the functional state of the pupil reflects the balance between sympathetic and parasympathetic actions, offering insights into the ANS's functional status. Based on these findings, we hypothesize that utilizing PAIP responses to assess patients' autonomic functional status could predict the occurrence of PONV.

To investigate methods for predicting the occurrence of PONV, we conducted a prospective observational study involving patients undergoing thoracoscopic lobectomy. Preoperative pupillary parameters were measured using a pupillometer before anesthesia induction. The aim is to determine whether specific parameters of the PLR could serve as independent predictors of PONV in patients with American Society of Anesthesiologists Physical Status (ASA) grading of I to III undergoing elective surgery.

Materials and Methods

Patients

This prospective observational study was conducted at Yantai Yuhuangding Hospital, a large tertiary teaching hospital in China. The trial has been approved by the Medical Ethics Committee of Yantai Yuhuangding Hospital [2023-266] and registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2300073869, registration date: 24 July 2023). All participating patients provided written informed consent. Eligible patients were individuals aged 18 years or older with ASA physical status I–III scheduled to undergo elective surgery under general anesthesia. Patients with ocular disease, a history of ophthalmic surgery, pupil deformity, use of medications affecting pupil size, use of alpha or beta blockers, neuromuscular dysfunction, thyroid dysfunction, history of cerebral infarction, history of diabetes mellitus, and history of motion sickness, scheduled surgery time <30 minutes or >180 minutes, planned neurosurgery, were excluded. Patients were withdrawn from the study in the events of failed arterial catheterization, loss of PONV data, or loss of pupillary data.

Pupil Measurement

All patients remained in the pre-anesthesia room before entering the operating theater for induction of anesthesia. Pupillometry measurements were conducted by a profes-

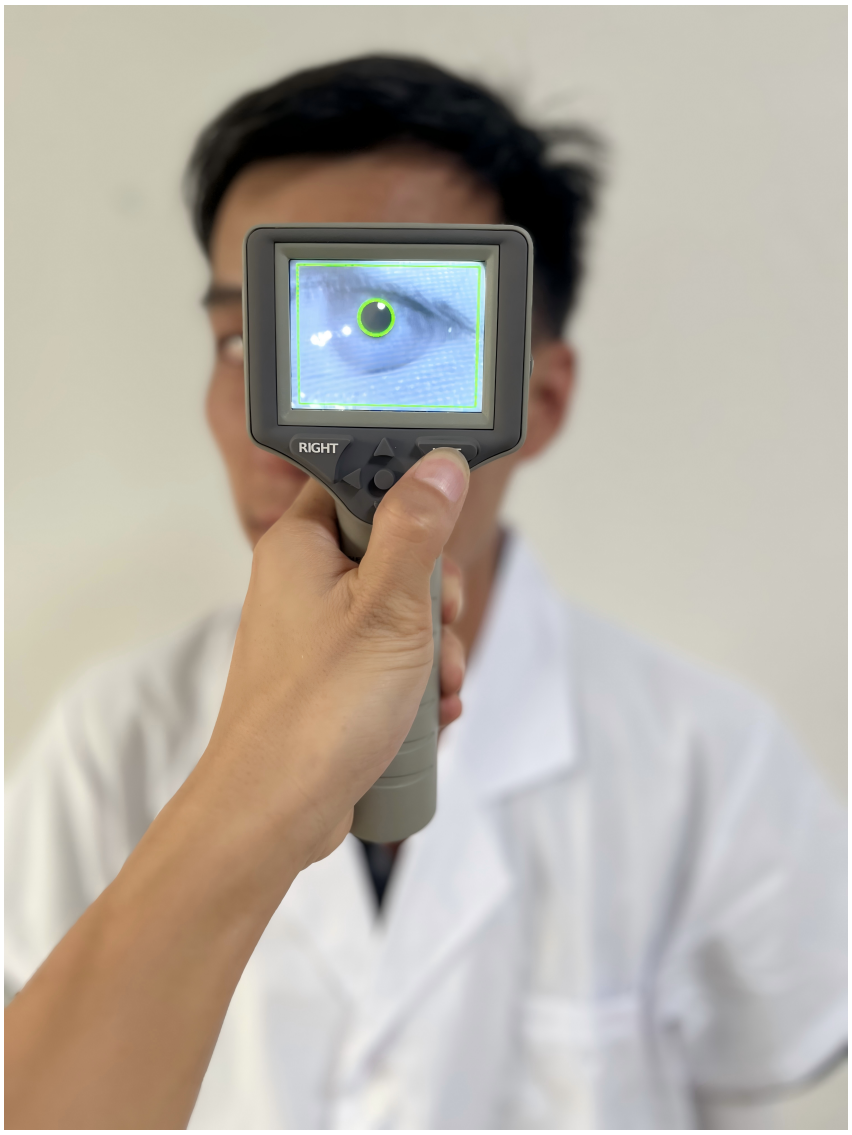

Fig. 1. Schematic diagram of operating a pupillometer (PLR-3000™, Neuroptics, Inc., Laguna Hills, CA, USA).

sionally trained researcher between 8:00 AM and 10:00 AM in the pre-anesthesia room with the curtains drawn. The left pupil was uniformly measured using a pupillometer (PLR-3000, NeurOptics, Inc, Laguna Hills, CA, USA). During the measurement, the ambient light was kept relatively dim to minimize interference from external light on the natural state of the pupil. Patients were instructed to look straight ahead to stabilize the pupil position and avoid the influence of the accommodation reflex on the PLR measurement (Fig. 1). Additionally, patients were guided to cover the contralateral eye to eliminate any potential impact of contralateral vision on the measurement results. If any issues such as blinking, head movement, or technical malfunctions occurred during the measurement process, leading to data quality that did not meet the requirements, the scan result would be immediately discarded, and repeated measurement was conducted to ensure the accuracy and reliability of the data. After computer recording completion, the following parameters were recorded: maximum pupil diameter, minimum pupil diameter, percentage pupil change, pupil constriction delay, maximum constriction velocity (MCV), and average constriction velocity (ACV).

Anesthesia Management

The day before surgery, patients were visited to obtain general clinical information. The experimental study and anesthesia procedure were explained to the patients, and informed consent was obtained for both. Patients were required to fast, avoiding food and drink, after 10:00 PM. Upon entering the operating room, patients were connected to cardiac monitoring. Intraoperative monitoring included cuff pressure, invasive arterial pressure, respiratory rate, oxygen saturation, pulse, electrocardiogram (ECG), body temperature, airway pressure, end-tidal carbon dioxide, tidal volume, and minute ventilation. Ten minutes after entering the operating room, patients underwent radial artery

puncture to monitor arterial blood pressure. Five minutes after puncture, anesthesia was induced using the standard rapid sequence induction protocol: midazolam 0.04 mg/kg, sufentanil 0.3 μg/kg, etomidate 0.3 mg/kg, cisatracurium 0.15 mg/kg, or rocuronium bromide 0.6 mg/kg. Mask ventilation was performed for 5 minutes, followed by tracheal intubation by an experienced anesthesiologist under video laryngoscopy. All patients were intubated with a reinforced tracheal tube (size 7.5) and had a bronchial blocker inserted. The position of the blocker was adjusted using a fiberoptic bronchoscope. After successful placement, patients were positioned in the lateral decubitus position and underwent an erector spinae plane block under ultrasound guidance. Twenty milliliters of ropivacaine at a concentration of 0.375% was injected. At the end of the surgery, a fiberoptic bronchoscope was used again to ensure the correct position of the bronchial blocker for one-lung ventilation. During the operation, anesthesia was maintained with remifentanil and sevoflurane. Norepinephrine or phenylephrine was used to increase blood pressure if necessary, and no morphine was administered throughout the perioperative period.

Data Collection

Patient characteristics were retrieved from the hospital V6 system, including age, gender, body mass index (BMI), ASA classification, hemoglobin level, total protein level, potassium ions, sodium ions, calcium ions, history of smoking, history of hypertension, history of cardiac disease, use of analgesic pumps, hypotension after induction of anesthesia, and intraoperative hypothermia. Mean arterial pressure (MAP) was recorded within 10 minutes from the start of induction of anesthesia, including tracheal intubation. Post-induction hypotension was defined as MAP <65 mmHg or a 30% reduction from baseline MAP, which was recorded 1 minute before induction of anesthesia, during the interval from induction to 10 minutes after intubation. Intraoperative hypothermia was defined as a body temperature below 36 °C during a period from induction of anesthesia to the end of anesthesia.

PONV was defined as the symptom of nausea and vomiting within 24 hours after completion of the procedure, and the patients were divided into the PONV group and the non-PONV group according to whether or not they experienced nausea and vomiting during the first postoperative day. The Quality of Recovery-15 (QoR-15) scale was used to assess the quality of recovery on the first postoperative day. The occurrence of PONV in this study was assessed primarily through two methods. First, ward nurses evaluated PONV at three time points postoperatively: 2 hours, 12 hours, and 24 hours, using a PONV assessment scale [2,22]. Second, a specialized anesthesiologist conducted a ward follow-up at 24 hours postoperatively, inquiring about the patient's and family's experiences to gather information.

Calculation of Sample Size

The test level was set at $\alpha = 0.05$, test efficacy $(1 - \beta)$ was set at 90%, and a two-sided test (s = 2) was utilized. Based on previous study indicating that PONV occurs in up to 30% of patients after surgery under general anesthesia, with a known incidence of 30%, the minimum number of cases required to construct a logistic regression model (Model 1) was determined to be 122 [23]. Considering a dropout rate of 20%, a minimum of 154 patients would need to be included in the study to ensure an adequate sample size.

Statistical Analysis

Data collection was conducted using Microsoft Excel. The normality of all data was tested using the Kolmogorov–Smirnov test. Normally distributed results were reported as mean ± standard deviation (SD) and compared using the independent samples *t*-test. Non-normally distributed data were reported as median (interquartile range) and compared using the Mann–Whitney *U* test. Categorical data were compared using the chi-square test (or Fisher's exact test) and reported as numbers (%).

Predictors of PONV likelihood were tested using two multivariate logistic regression models. Pupil parameters showing significant differences in the PONV group were added to the logistic regression model, and regression analyses were performed using the input method. Age was included as a separate variable in Model 1 due to its strong correlation with pupil parameters [24]. Additionally, based on the study results and previous large-scale retrospective analyses, variables such as age, analgesic pump use, gender, smoking history were adjusted for inclusion in Model 2 for multifactorial regression analysis [25,26]. Receiver operating characteristics (ROC) curves were used to assess pupil functional state parameters and their ability to predict PONV based on these analyses. The relationship between MCV and quality of postoperative recovery was analyzed using Spearman correlation analysis before mediation analysis. The mediating effect of PONV in MCV and quality of postoperative recovery was tested using Bootstrap method with 5000 repeated samples (95% confidence interval (CI)). All statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA), and $p < 0.05$ was considered statistically different.

Results

Initially, 178 patients were enrolled in this study. Among them, two patients with a history of dizziness, four patients with a history of cerebral infarction, three patients with thyroid dysfunction, and four patients with missing PONV data were excluded. Additionally, 11 patients withdrew from the study, including six patients with partially missing pupil data, three patients with operation time of less than 30 minutes, and two patients with operation time of more than 180 minutes. Ultimately, data from 154 patients were analyzed, among whom 46 (29.9%) experienced PONV. The distri-

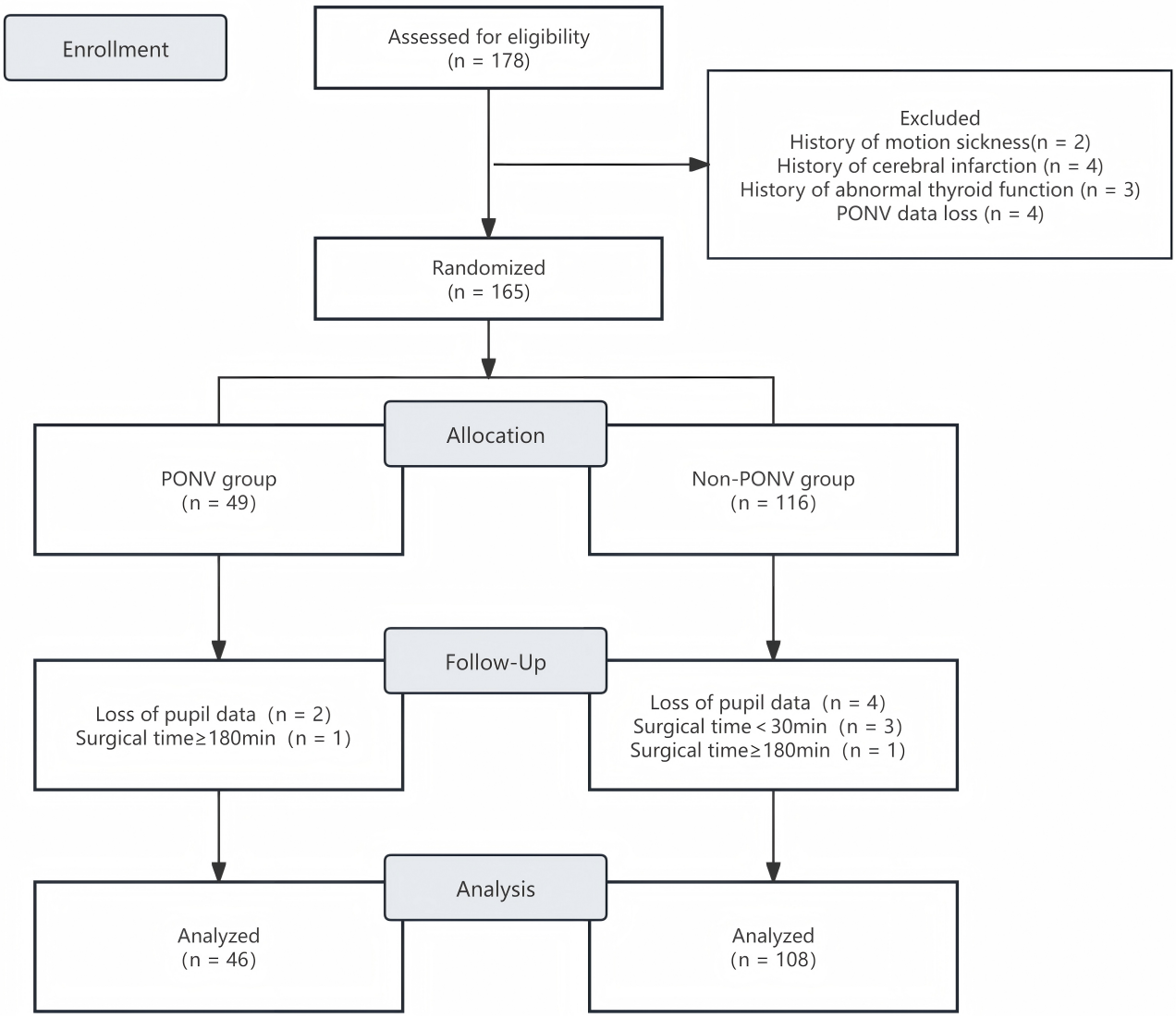

Fig. 2. Flow chart depicting the screening and grouping of participants, as well as analysis process, in this study [27–29]. The specific steps are as follows: During the screening phase (Enrollment), a total of 178 patients were assessed for eligibility. Exclusion criteria included patients with a history of motion sickness (n = 2), patients with a history of cerebral infarction (n = 4), patients with a history of abnormal thyroid function (n = 3), and patients with missing postoperative nausea and vomiting (PONV) data (n = 4). In the randomization phase (Randomized), a total of 165 patients met the criteria and were randomized into two groups: the PONV group (n = 49) and the non-PONV group (n = 116). During the follow-up phase (Follow-Up), in the non-PONV group, there were patients with missing pupil data (n = 4), patients with surgical time <30 minutes (n = 3), and patients with surgical time ≥180 minutes (n = 1). In the PONV group, there were patients with missing pupil data (n = 2) and patients with surgical time ≥180 minutes (n = 1). In the analysis phase (Analysis), the final number of patients included in the analysis was 46 in the PONV group and 108 in the non-PONV group.

bution of ASA grades among these patients was as follows: ASA grade I (n = 4), ASA grade II (n = 131), and ASA grade III (n = 19) (Fig. 2, Ref. [27–29]).

Out of 178 initially assessed participants, 165 were deemed eligible and subsequently divided into the PONV and non-PONV groups. During data processing, some data were lost or deemed ineligible due to various reasons. Consequently, data from 46 participants in the PONV group and 108 participants in the non-PONV group were analyzed. This grouping and screening process helps ensure the reliability of the data and the validity of the experimental results.

Patient Data

In the cohort of enrolled patients, 29.9% (46/154) experienced PONV. Among these patients, 33 were female and 13 were male. Twenty-four patients had used analgesic pumps, while 21 had not. In the PONV group, the proportion of female patients was significantly higher than that of male patients (71.74% vs. 28.26%, p = 0.013), indicating that female patients are more likely to experience PONV compared to male patients. The proportion of patients in the non-PONV group using analgesic pumps was significantly higher than that in the PONV group (70.09% vs. 53.33%, p

Table 1. Basic characteristics between the PONV group and non-PONV groups.

	Non-PONV (n = 108)	PONV (n = 46)	z/χ^2	p
Age (years)	59.00 (55.00, 65.25)	63.50 (58.00, 68.00)	–1.69	0.091
BMI (kg/m^2)	24.73 (22.48, 27.22)	23.89 (22.27, 26.20)	–1.28	0.201
Gender, n (%)			6.20	0.013*
Female	54 (50.00)	33 (71.74)		
Male	54 (50.00)	13 (28.26)		
HGB (g/L)	133.00 (123.75, 142.00)	131.50 (124.25, 142.75)	–0.29	0.773
Total protein (g/L)	66.23 (63.03, 68.40)	67.26 (64.34, 70.65)	–1.81	0.058
K^+ (mmol/L)	3.98 (3.84, 4.16)	3.88 (3.68, 4.11)	–1.65	0.100
Ca^{2+} (mmol/L)	2.28 (2.23, 2.34)	2.30 (2.25, 2.35)	–1.15	0.250
Na^+ (mmol/L)	141.25 (139.93, 142.20)	141.25 (140.20, 142.00)	–0.16	0.874
ASA, n (%)				0.646
I	2 (1.85)	2 (4.35)		
II	93 (86.11)	38 (82.61)		
III	13 (12.04)	6 (13.04)		
Smoking history, n (%)			0.56	0.454
No	86 (79.63)	39 (84.78)		
Yes	22 (20.37)	7 (15.22)		
History of hypertension, n (%)			0.06	0.801
No	75 (69.44)	31 (67.39)		
Yes	33 (30.56)	15 (32.61)		
History of heart disease, n (%)			3.22	0.073
No	104 (96.30)	40 (86.96)		
Yes	4 (3.70)	6 (13.04)		
Analgesic pump, n (%) (n = 152)			3.92	0.048*
No	32 (29.91)	21 (46.67)		
Yes	75 (70.09)	24 (53.33)		
Post-induction hypotension, n (%)			0.18	0.673
No	81 (75.00)	33 (71.74)		
Yes	27 (25.00)	13 (28.26)		
Intraoperative hypothermia, n (%)			0.03	0.863
No	65 (60.19)	27 (58.70)		
Yes	43 (39.81)	19 (41.30)		

Notes: Post-induction hypotension means a 20% fall in systolic blood pressure or a MAP <65 mmHg within 15 minutes of induction of anaesthesia. *$p < 0.05$, compared with the non-PONV group.

Abbreviations: ASA, American Society of Anesthesiologists Physical Status; BMI, body mass index; HGB, hemoglobin; MAP, mean arterial pressure.

Table 2. Pupil parameters between the PONV group and non-PONV groups.

	Non-PONV (n = 108)	PONV (n = 46)	t/z	p
Maximum pupillary diameter (mm)	4.08 ± 0.83	3.73 ± 0.83	2.42	0.017*
Minimum pupillary diameter (mm)	3.25 (2.90, 3.60)	3.00 (2.52, 3.60)	–1.70	0.090
Pupil constriction delay (mm/s)	0.23 (0.23, 0.27)	0.23 (0.23, 0.27)	–2.53	0.673
ACV (mm/s)	1.92 (2.38, 1.44)	1.42 (2.14, 1.08)	–2.54	0.011*
MCV (mm/s)	2.75 (3.41, 2.40)	1.79 (2.09, 1.44)	–6.49	<0.001**
Percentage pupil change	0.19 (0.16, 0.24)	0.15 (0.12, 0.24)	–0.42	0.011*

Note: *$p < 0.05$, **$p < 0.01$, compared with the non-PONV group.

Abbreviations: ACV, average constriction velocity; MCV, maximum constriction velocity.

= 0.048). No significant differences were observed between patients who experienced PONV and those who did not in terms of preoperative hemoglobin counts, albumin counts, electrolyte concentrations (including potassium ions, serum calcium ions, and sodium ions), BMI, ASA classification, presence of a history of smoking, history of cardiac disease, post-induction hypotension, and intraoperative hypothermia. In addition, there were no statistically significant dif-

Table 3. Univariate regression analysis.

Variables	β	SE	z	p	OR (95% CI)
ASA, *n* (%)					
I					
II	–0.90	1.02	–0.88	0.379	0.41 (0.06–3.01)
III	–0.77	1.12	–0.69	0.488	0.46 (0.05–4.11)
Smoking history, *n* (%)					
No					
Yes	0.35	0.47	0.75	0.456	1.43 (0.56–3.62)
History of hypertension, *n* (%)					
No					
Yes	–0.10	0.38	–0.25	0.801	0.91 (0.43–1.91)
History of heart disease, *n* (%)					
No					
Yes	–1.36	0.67	–2.03	0.052	0.26 (0.07–0.96)
Use of analgesic pump, *n* (%)					
No					
Yes	0.72	0.37	1.96	0.050	2.05 (1.01–4.20)
Gender, *n* (%)					
Female					
Male	–0.93	0.38	–2.45	0.014*	0.39 (0.19–0.83)
Post-induction hypotension, *n* (%)					
No					
Yes	0.17	0.40	0.42	0.673	1.18 (0.54–2.57)
Intraoperative hypothermia, *n* (%)					
No					
Yes	0.06	0.36	0.17	0.863	1.06 (0.53–2.15)
HGB (g/L)	–0.00	0.01	–0.25	0.805	1.00 (0.97–1.02)
Total protein (g/L)	0.07	0.04	1.99	0.056	1.08 (1.01–1.16)
K^+ (mmol/L)	–0.78	0.54	–1.44	0.151	0.46 (0.16–1.33)
Na^+ (mmol/L)	–0.01	0.08	–0.13	0.894	0.99 (0.84–1.17)
Ca^{2+} (mmol/L)	1.93	1.52	1.27	0.206	6.86 (0.35–135.69)
BMI (kg/m^2)	–0.06	0.05	–1.23	0.218	0.94 (0.85–1.04)
Age (years)	0.03	0.02	1.29	0.197	1.03 (0.99–1.07)
Maximum pupillary diameter (mm)	–0.53	0.23	–2.35	0.019*	0.59 (0.38–0.92)
Minimum pupillary diameter (mm)	–0.33	0.25	–1.30	0.192	0.72 (0.44–1.18)
Pupil constriction delay (mm/s)	0.16	0.19	0.88	0.381	1.18 (0.82–1.69)
Percentage pupil change	–1.84	3.24	–0.57	0.571	0.16 (0.00–91.80)
ACV (mm/s)	–0.63	0.24	–2.58	0.010*	0.54 (0.33–0.86)
MCV (mm/s)	–1.58	0.31	–5.15	<0.001**	0.21 (0.11–0.38)

Note: *$p < 0.05$, **$p < 0.01$ compared with the non-PONV group. Post-induction hypotension means a 20% fall in systolic blood pressure or a MAP <65 mmHg within 15 minutes of induction of anaesthesia. The results were considered statistically significant at $p < 0.05$.
Abbreviations: CI, confidence interval; SE, standard error; OR, odds ratio.

ferences in age and history of hypertension between the groups (Table 1).

Data on Pupil Function Parameters

Compared to patients who did not develop PONV, patients who developed PONV had smaller maximum pupil diameters at rest ($p = 0.017$), smaller average constriction velocity (ACV) values ($p = 0.011$), smaller maximum constriction velocity (MCV) values ($p < 0.001$), and smaller percentage pupil change ($p = 0.011$) (Table 2).

Regression Analysis

Univariate regression analysis revealed the relationship of PONV occurrence with maximum pupil diameter at rest,

Table 4. Predictors for PONV occurrence.

	Predictors	β	SE	Wald χ^2	OR (95% CI)	p
Unadjusted analysis	Maximum pupillary diameter (mm)	–0.09	0.32	0.078	0.92 (0.49–1.71)	0.783
	ACV (mm/s)	0.76	0.45	2.79	2.13 (0.87–5.12)	0.096
	MCV (mm/s)	–2.06	0.41	25.50	0.13 (0.06–0.28)	<0.001**
	Gender, *n* (%)					
	Female					
	Male	–1.09	0.48	–2.27	0.34 (0.13–0.86)	0.023*
Model 1	Maximum pupillary diameter (mm)	–0.03	0.33	0.001	0.97 (0.51–1.85)	0.923
	ACV (mm/s)	0.80	0.46	2.99	2.23 (0.90–5.52)	0.083
	MCV (mm/s)	–2.08	0.41	25.50	0.12 (0.06–0.28)	<0.001**
	Gender, *n* (%)					
	Female					
	Male	–1.09	0.48	–2.29	0.34 (0.13–0.85)	0.022*
Model 2	Maximum pupillary diameter (mm)	0.08	0.34	0.063	1.09 (0.56–2.13)	0.804
	ACV (mm/s)	0.75	0.47	2.53	2.11 (0.84–5.29)	0.111
	MCV (mm/s)	–2.07	0.42	24.50	0.13 (0.06–0.29)	<0.001**
	Gender, *n* (%)					
	Female					
	Male	–1.04	0.48	–2.16	0.35 (0.14–0.91)	0.030*

Note: *$p < 0.05$, **$p < 0.01$. Model 1: Adjusted for age; Model 2: Adjusted for age, analgesic pump use, gender, smoking history.

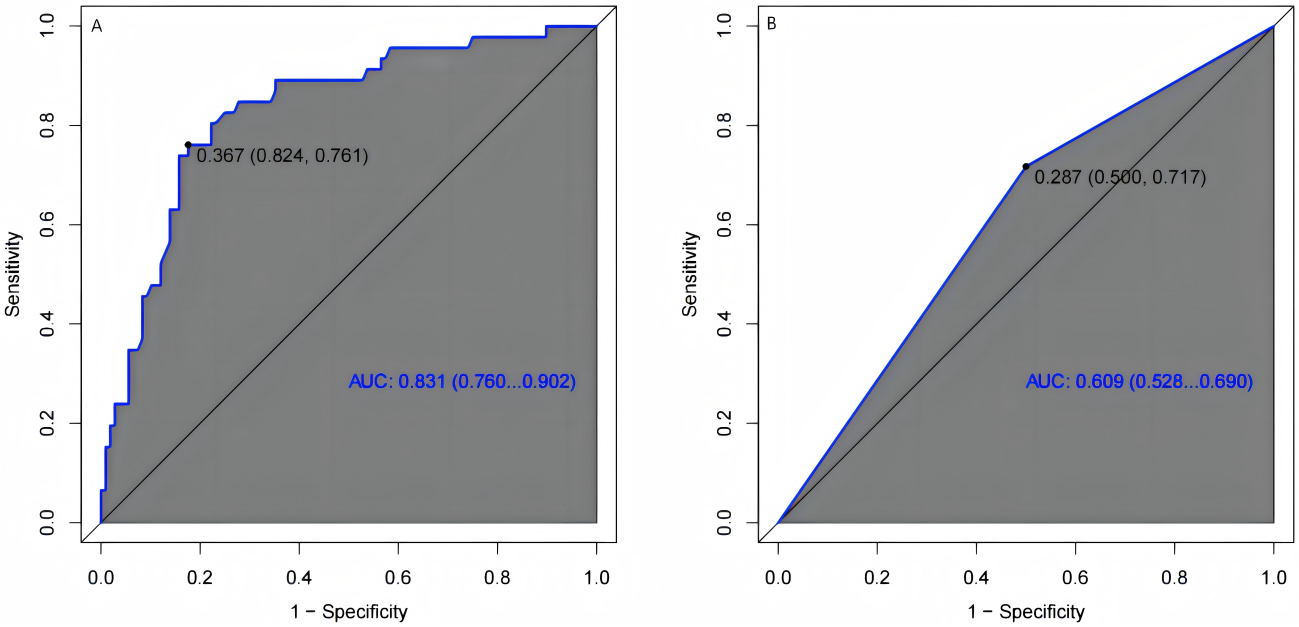

Fig. 3. ROC curves. (A) ROC curve for MCV. The blue curve indicates the ROC curve for MCV, with an AUC = 0.831, demonstrating the diagnostic performance of MCV at different thresholds. The AUC value of 0.831 indicates that MCV has good diagnostic ability. The black line represents the ROC curve for random guessing, with an AUC = 0.50. The curve represents the performance of random guessing, with an AUC value of 0.50, indicating that the model has no diagnostic ability. (B) ROC curve for gender. The blue curve indicates the ROC curve for gender, with an AUC = 0.609, demonstrating the diagnostic performance of gender at different thresholds. The AUC value of 0.609 indicates that gender has some diagnostic ability. The black line represents the ROC curve for random guessing, with an AUC = 0.50. This curve represents the performance of random guessing, with an AUC value of 0.50, indicating that the model has no diagnostic ability. Abbreviations: AUC, area under the curve; ROC, receiver operating characteristics.

ACV, MCV, and gender (Table 3). Considering that age is an important factor influencing pupillary reflexes according to existing studies, age was included in Model 1 of the multivariate regression analysis [27–29]. After adjustment, only two variables showed significant correlations with PONV: MCV ($p < 0.001$) and gender ($p = 0.022$),

Table 5. Spearman correlation analysis.

Variable 1	Variable 2	ρ	p
PONV	MCV	–0.523	<0.05*
PONV	QoR-15	–0.803	<0.05*
MCV	QoR-15	0.379	<0.05*

Note: This table shows correlation results from a sample of 154, which were generated from the Spearman correlation analysis. *$p < 0.05$.
Abbreviations: QoR-15, Quality of Recovery-15.

Table 6. Model analysis for mediating effects.

	QoR-15	PONV	QoR-15
Constant	44.548	1.197	68.732
MCV	5.412	–0.291	–0.468
PONV			–20.198
R^2	0.184	0.234	0.895
Adjusted R^2	0.175	0.226	0.893
F	22.065	29.906	412.303

while the remaining variables did not show statistically significant differences between the PONV and non-PONV groups. Based on current literature suggesting that the use of analgesic pumps and smoking history also affect PONV [6,8,30,31], these factors were further included in Model 2. After adjustment, significant differences remained between the PONV and non-PONV groups for MCV values ($p < 0.001$) and gender ($p = 0.030$). Therefore, MCV values (odds ratio (OR) 0.13, 95% CI 0.06–0.29; $p < 0.001$) were identified as significant independent predictors of PONV. Gender (OR 0.35, 95% CI 0.14–0.91; $p = 0.030$) also showed a correlation, albeit a weak one (Table 4). We assessed multicollinearity among the predictors. The variance inflation factor (VIF) was used to measure multicollinearity, and the VIF values for all experimental independent variables were less than 5.

ROC Curve Analysis

Based on the results of logistic regression, we analyzed the predictive power of MCV as well as gender on PONV and performed ROC curve analysis. MCV demonstrated good diagnostic value when used as a predictor (area under the curve (AUC): 0.831, 95% CI: 0.760–0.902; $p < 0.001$) (Fig. 3A). The sensitivity and specificity of the best diagnostic value (0.367 mm/s) were 82.4% and 76.1%, respectively. Gender also exhibited some diagnostic value (AUC: 0.609, 95% CI: 0.528–0.690; $p = 0.030$) (Fig. 3B), with an optimal diagnostic value of 0.287. The sensitivity and specificity values were 50.0% and 71.7%, respectively.

Correlation Between the Occurrence of PONV, Maximum Pupil Constriction Velocity and the Quality of Postoperative Recovery

To further explore the relationships among PONV, MCV, and QoR-15, we performed Spearman correlation analysis (Table 5). The results showed a significant negative correlation between PONV and MCV ($\rho = –0.5252$, $p < 0.05$), indicating that lower MCV values are associated with a higher risk of PONV. Additionally, PONV was significantly negatively correlated with the QoR-15 ($\rho = –0.8026$, $p < 0.05$), suggesting that the occurrence of PONV significantly reduces the quality of postoperative recovery. On the other hand, MCV was significantly positively correlated with QoR-15 ($\rho = 0.3789$, $p < 0.05$), indicating that higher MCV values are associated with better postoperative recovery quality. These findings further support the importance of MCV as a predictive indicator of PONV and reveal the mediating role of PONV between MCV and postoperative recovery quality.

Analysis of the Mediating Effect of the Occurrence of PONV in the Maximum Pupillary Constriction Velocity and the Quality of Postoperative Recovery

Maximum pupil constriction velocity was used as the independent variable (X), PONV as the mediating variable (M), and quality of postoperative recovery as the dependent variable (Y): the predicted effect value of X on M was a; the predicted effect value of M on Y was b; the predicted effect value of X on Y was c; and the predicted direct effect value of adding M was c' (i.e., c' = c-ab). The results of this study showed that the occurrence of PONV had a fully mediated effect between MCV and postoperative recovery quality, and the mediating effect accounted for 100% of the total effect ratio, i.e., 100% of the predicted effect of MCV on postoperative recovery quality was indirectly influenced by PONV. Bootstrap method was further applied to test the mediating effect of PONV, and the results showed that the mediating effect value of PONV was 0.481, 95% CI did not include 0 (0.341, 0.590), indicating that the mediating effect of PONV was significant and that the hypothesis of mediating effect was valid (Tables 6,7; Fig. 4).

Discussion

PONV continues to be a prevalent and distressing problem after surgery, despite the fact that postoperative pain control has been given priority for clinical management for decades. Previous data have shown that the incidence of nausea and vomiting can be as high as 80% in high-risk populations undergoing general surgery [25]. From the patient's perspective, its significance is similar to avoiding postoperative pain. The treatment of PONV is complicated by the fact that various antiemetics have different pharmacokinetics, efficacy, and side effects [9]. Recognizing the importance of early prevention and treatment of PONV is critical to avoiding postoperative complications, improving patient satisfaction, and facilitating the development of outpatient and expedited surgery [32]. Consensus guidelines provide some direction but have limited applicability to all patient populations and to all aspects of nausea and vomiting prevention [9]. The physiologic mechanisms

Table 7. Analysis of mediating effects.

Effect model	Effect	95% CI		SE	Efficiency ratio
		LLCI	ULCI		
Total effect	5.412	3.154	7.671	1.152	
Direct effect	–0.468	–1.400	0.463	0.475	
Total indirect effect	0.481	0.341	0.590	0.064	
MCV→PONV→QoR-15	0.481	0.341	0.590	0.064	100%

Abbreviations: LLCI, lower limit of the confidence interval; ULCI, upper limit of the confidence interval.

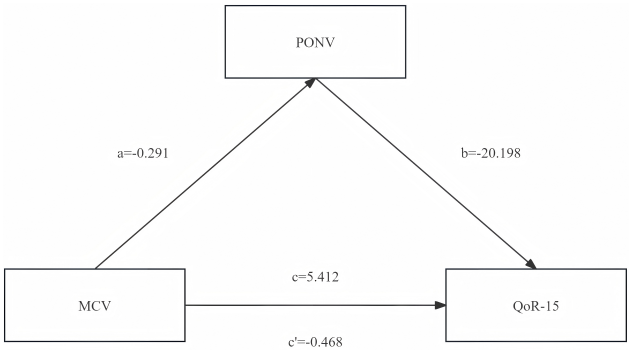

Fig. 4. Diagram depicting PONV-mediated path between MCV and QoR-15, illustrating the mediating effect of PONV between MCV and Quality of Recovery-15 (QoR-15). The values represent the standardized regression coefficients (β) for each path: (1) Path a (MCV → PONV): β = –0.291. This indicates that higher MCV values are significantly associated with a lower risk of PONV. (2) Path b (PONV → QoR-15): β = –20.198. This indicates that the occurrence of PONV is significantly associated with poorer postoperative recovery quality. (3) Path c (MCV → QoR-15): β = 5.412. This indicates that higher MCV values are significantly associated with better postoperative recovery quality. (4) Path c' (MCV → QoR-15, after accounting for PONV): β = –0.468. This indicates the direct effect of MCV on QoR-15 after controlling for the mediating effect of PONV. Note: The mediating effect of PONV fully explains the relationship between MCV and QoR-15, as the direct effect (c') becomes non-significant after accounting for PONV.

of nausea and vomiting involve intricate interactions between the central nervous system, the ANS, and the enteric nervous system [1,33]. This complexity highlights the need for reliable indicators applicable to different populations in order to minimize adverse effects and economic burden while using antiemetics effectively. The PLR is regulated by the ANS, reflecting the balance between the sympathetic and parasympathetic nervous systems. Based on this understanding, our study aimed to explore potential neurally mediated pathways connecting the PLR and PONV. Evidence suggests that there is a common neural basis of pupil function with nausea and vomiting, and thus we sought to identify parameters of pupil function that could predict PONV [1,15,16]. Specifically, we aimed to investigate whether parameters such as maximal constriction velocity could serve as predictors of PONV, which capitalized on insights from previous studies that emphasized the sensitivity of pass pupil MCV and relative constriction amplitude in the assessment of parasympathetic dysfunction. By examining the relationship between pupillary function parameters and PONV, our study aims to facilitate the development of non-invasive predictive tools for PONV. Such tools could facilitate personalized risk assessment and targeted intervention strategies, ultimately improving patient prognosis and resource utilization in perioperative care. PONV remains a significant problem in modern anesthesia practice because it poses risks that affect the quality of postoperative recovery, such as increased rates of wound dehiscence, dehydration, pulmonary aspiration, and unplanned hospitalization. Therefore, preventive measures have been taken to minimize the occurrence of PONV according to the risk level. However, in patients who are at low risk for PONV, preventive measures are not recommended unless their medical history indicates a risk of vomiting [25]. This further emphasizes the importance of identifying ways to predict PONV and implementing individualized preventive measures.

In this study, we explored the potential clinical application of PLR parameters to predict PONV. Although the relationship between PLR and PONV has been extensively studied in the previous literature, there is still a notable gap in research on whether PLR parameters can be used as an indicator of nausea and vomiting and to predict their occurrence. A significant association was found between MCV and PONV, a result that may be closely related to the functional state of the ANS, which plays a key role in the regulation of both the PONV and the PLR. The onset of PONV is usually associated with an imbalance of the ANS, especially sympathetic and parasympathetic activity. dysregulation of the ANS. Studies have shown that the occurrence of nausea and vomiting is associated with the inhibition of parasympathetic activity and the enhancement of sympathetic activity [1,14,15]. Enhanced parasympathetic activity is related to gastrointestinal motility and emptying functions, while increased sympathetic activity may lead to gastrointestinal dysfunction, thereby increasing the risk of PONV. The PLR is a sensitive indicator of the functional state of the ANS. Pupil constriction is mainly innervated by parasympathetic

nerves, whereas pupil dilation is regulated by sympathetic nerves. MCV, as a key parameter of PLR, reflects the ability of the pupil to rapidly constrict in response to light stimulation, and its changes may directly reflect the level of parasympathetic nerve activity. In this study, the MCV of patients with PONV was significantly reduced, suggesting that their parasympathetic function may be inhibited or abnormally regulated. The diminished parasympathetic function may be associated with the occurrence of PONV, as decreased parasympathetic activity indicates weakened ability to promote gastrointestinal motility and emptying, leading to gastrointestinal dysfunction and thereby increasing the risk of PONV. In addition, changes in MCV may reflect abnormal regulation of the ANS by the central nervous system (CNS). Studies have shown that the development of PONV is associated with activation of the brainstem vomiting center, which is also an important center for regulating the PLR [1,15,34]. Therefore, the decrease in MCV may not only be a reflection of abnormal ANS function, but also a result of dysregulation of ANS regulation by the CNS. This dual role of the central and peripheral nervous system may further explain the association between MCV and PONV.

Although we controlled for known confounders (e.g., age, sex, ASA classification, history of motion sickness, etc.), individual patient differences (e.g., genetic factors, psychological status, preoperative anxiety level, etc.) may have an impact on the occurrence of PONV, which were not measured in this study and may have biased the results somewhat. Although we included patients with ASA class I–III and controlled for the duration of surgery and the use of anesthetic drugs, subtle differences in the type of surgery and anesthetic management (e.g., degree of surgical trauma, depth of anesthesia, etc.) may influence the occurrence of PONV. These factors were not documented in detail in the study and may have had some influence on the results. The quality of postoperative care, the frequency and dosage of analgesic medications, and the use of postoperative antiemetic medications may influence the occurrence of PONV. These factors were not documented in detail in this study and may also have some confounding effect on the results. We suggest that more potential confounding factors, such as patients' genetic background, psychological status, and degree of surgical trauma, be further included in future studies to more comprehensively assess the predictors of PONV, and that, to reduce the possible bias due to the single-center nature of research design, multicenter studies could be considered in future studies to increase the diversity of samples and the generalizability of results.

Our study found that MCV is a reliable predictor of PONV. Initially, 178 patients were enrolled, and unreliable data such as patient's own factors and data collection factors were excluded according to the exclusion criteria, and the study finally included 154 cases, of which 46 (29.9%) developed PONV. In the between-group analysis of variance, we found a correlation between PONV and analgesic pump use, which is consistent with previous findings that opioid analgesic pumps increase the likelihood of nausea and vomiting [8,31]. However, after adjusting for other factors in Model 2, the significance of analgesic pump use was reduced, possibly because concomitant antiemetic use masked this effect. Previously, it has been well established that age has an independent effect on pupillary data [35]. Therefore, in Model 1, the effectiveness of the correlation between the pupillary constriction velocity parameter and PONV was reduced by including age as an independent variable. After adjusting for indicators that may influence nausea and vomiting in Model 2 [8,30,31], pupil MCV remained statistically significant in predicting efficacy for PONV (OR 0.13, 95% CI 0.06–0.29; $p < 0.001$). The results are also of great significance in clinical applications.

In this study, the OR of MCV was 0.13 (95% CI: 0.06–0.29), indicating that for every 1 mm/s increase in MCV, the risk of PONV in patients decreased by 87%. This high OR suggests that preoperative measurement of MCV may help anesthesiologists identify patients at increased risk for PONV with high accuracy, and then take preventive measures (such as administering antiemetic drugs or adjusting the anesthesia regimen) to reduce the incidence of PONV and improve the quality of postoperative recovery. In addition, the study also found that women were more likely than men to experience PONV, which corroborated previous findings. Mediating effect analysis showed that PONV played a significant mediating role between MCV and postoperative recovery quality (mediating effect value: 0.481, 95% CI: 0.341–0.590). This result supports the hypothesis that MCV influences the quality of postoperative recovery by influencing the occurrence of PONV. However, this finding needs to be interpreted with caution. Despite having controlled for known confounders, we believe that unmeasured confounders, such as genetic background and preoperative anxiety, hold high potential in influencing the results. In addition, MCV may influence the quality of postoperative recovery through other unmeasured pathways (e.g., ANS function). Therefore, future studies need to further validate this mediating effect and explore other potential mechanisms. The ROC curves for MCV with an AUC value of 0.831 (95% CI: 0.760–0.902) suggest that MCV has a good predictive capability in predicting PONV. Specifically, the optimal diagnostic threshold for MCV was 0.367 mm/s, with a sensitivity of 82.4%, and a specificity of 76.1%. This means that MCV correctly identified 82.4% of patients who actually presented with PONV. This suggests that maximal systolic velocity is highly accurate in identifying high-risk patients and can help clinicians identify patients who may experience nausea and vomiting even before surgery. In addition, MCV correctly excluded 76.1% of patients who would not have experienced nausea and vomiting, suggesting that MCV can excellently exclude low-risk patients for the purpose of minimizing unnecessary prophylactic treatments. By measuring MCV preoperatively, clin-

icians can more accurately identify patients at high risk for nausea and vomiting and develop individualized prevention strategies. The high sensitivity and specificity of maximal constriction can help optimize the use of healthcare resources by avoiding unnecessary prophylactic treatments in low-risk patients, thereby reducing medication side effects and healthcare costs. Early recognition and prevention of nausea and vomiting can reduce postoperative complications, improve the quality of patient recovery, shorten the length of hospital stay, and increase patients' satisfaction, all of which have important practical clinical implications. Although the AUC value for gender was relatively low, it still showed some predictive value in multiple regression analysis (OR 0.35, 95% CI 0.14–0.91; $p = 0.030$), suggesting that gender can be used as a co-predictor that, when combined with other predictors (e.g., MCV), improves the overall accuracy of the PONV prediction model. Therefore, female patients may require more attention and preventive measures in clinical practice, especially in the absence of other strong predictors. Female patients are more likely to experience PONV than male patients, which is consistent with previous findings [3,36,37]. Potential reasons for this include women's greater sensitivity to opioids, greater pharmacodynamic response to morphine, and gender differences in pharmacokinetics (e.g., drug metabolism and distribution) and the CNS [37]. Premenopausal women are more likely to experience nausea and vomiting, suggesting that sex hormones (e.g., estrogen and progesterone) may also influence the efficacy and side effects of opioids. Nausea and vomiting are associated with activation of 5-HT3 receptors, to which women may be more sensitive. Women may also be more susceptible to opioid-induced inhibition of gastrointestinal motility, which can lead to nausea and vomiting.

The diagnostic value of MCV demonstrated by the study has advantages over existing risk prediction tools for PONV, such as the Apfel score, a widely used clinical PONV prediction tool that is based on four key variables: female gender, history of motion sickness or PONV, nonsmoking status, and postoperative opioid use. The team's findings suggest that the Apfel score is an excellent diagnostic tool to predict the risk of PONV in women [9,12]. Although the Apfel score is widely used in clinical practice, its AUC values typically range from 0.70 to 0.75 and have relatively low sensitivity and specificity (approximately 70%) [9,12]. In contrast, the AUC value for pupil MCV was higher, suggesting that it has greater predictive power in identifying high-risk patients. In addition, the Apfel score is largely dependent on the patient's clinical characteristics and medical history, whereas MCV is a noninvasive predictive parameter based on objective pupillometric data. This physiologically based predictive tool provides clinicians with a more accurate individualized risk assessment, especially if the patient's medical history is unclear or difficult to obtain. Combining MCV with traditional prediction tools such as the Apfel score may further improve the overall accuracy of PONV prediction models. Future studies could explore the possibility of combining MCV with Apfel score. For example, MCV could be used as a complementary metric to the Apfel score to further identify high-risk patients. Such a multifactorial predictive model could provide greater predictive accuracy in clinical practice, thereby optimizing the use of antiemetic medications, reducing unnecessary prophylactic treatments, and improving the quality of a patient's postoperative recovery. First, the cost of pupillometers may be a major limiting factor. Currently, high-quality portable infrared pupillometers are relatively expensive, which may limit their widespread use in resource-limited healthcare settings. Second, the operation of pupillometers requires specialized training to ensure data accuracy and consistency. This may require additional training resources and time investment. In addition, the variability of pupillometry data may be affected by factors such as equipment accuracy and inter-individual differences.

Despite the strengths of our study, there are some limitations. First, the relatively small sample size ($n = 154$) and the single-center research design may limit the generalizability and extrapolation of the results obtained. Although this study provides preliminary evidence for MCV as a predictive tool for PONV, its findings are primarily applicable to ASA class I–III patients undergoing thoracoscopic lobectomy. The generalizability of the results is constrained by the type of surgery, patient population, and anesthesia modality. Future research should expand the sample size to include a wider range of surgical types and patient populations to validate the broader applicability of MCV. Second, the variability in pupillometry data may be influenced by the measurement environment, device accuracy, and inter-individual differences. Although we implemented standardized measurement procedures, there may still be some measurement errors. Furthermore, this study did not account for other potential confounding factors, such as the patients' genetic background, preoperative anxiety levels, and the extent of surgical trauma, which may have some impact on the occurrence of PONV. Future research should be conducted in larger, multicenter settings to further validate the predictive efficacy of MCV and explore its combined application with other predictive tools, such as the Apfel score. Despite these limitations, MCV, as a physiologically based predictive tool, demonstrates potential advantages in predicting PONV. When combined with traditional predictive tools, MCV may provide clinicians with more accurate individualized risk assessments, thereby optimizing the use of antiemetic medications, reducing unnecessary preventive treatments, and improving patients' postoperative recovery quality. Future studies should further explore the clinical application value of MCV and validate its role in multifactorial prediction models.

Conclusions

This study provides preliminary evidence that MCV and gender are reliable predictive indicators for PONV in ASA class I–III patients undergoing elective thoracoscopic surgery, with the predictive efficacy of MCV being superior to that of gender. The high AUC value of MCV (0.831) and its relatively high sensitivity and specificity (82.4% and 76.1%, respectively) demonstrate its significant advantage in identifying high-risk PONV patients. Additionally, given that PONV fully mediates the relationship between MCV and patients' postoperative recovery quality, preoperative measurement of MCV can be leveraged to predict PONV occurrence, thereby improving patients' postoperative recovery outcomes.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the first author if needed.

Author Contributions

YWZ, CXS: conceived and designed the experiments; analyzed and interpreted the data; provided the experimental tools as well as the platform for data analysis and wrote the paper. HYJ, JJZ, DS: recruited subjects and collected data. QS, JJ, LYS: analyzed and interpreted the data, and critically revised the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study has been approved by the Ethics Committee of Yantai Yuhuangding Hospital, with the approval number 2023-266. This study was conducted in adherence to the Declaration of Helsinki. During the research process, we obtained informed consent from all patients, and patient data were sourced exclusively from the hospital's case system.

Acknowledgment

We would like to extend our deepest gratitude to all those who have contributed to this research. We would also like to express our appreciation to all the patients who participated in the study, without whose participation, this study could not have been realized.

Funding

This study is supported by 2021 Shandong Medical Association Clinical Research Fund—Qilu Special Project (No.YXH2022ZX02102).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Zhong W, Shahbaz O, Teskey G, Beever A, Kachour N, Venketaraman V, *et al*. Mechanisms of Nausea and Vomiting: Current Knowledge and Recent Advances in Intracellular Emetic Signaling Systems. International Journal of Molecular Sciences. 2021; 22: 5797. https://doi.org/10.3390/ijms22115797.

[2] Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. F1000Research. 2020; 9: F1000 Faculty Rev-983. https://doi.org/10.12688/f1000research.21832.1.

[3] Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, *et al*. Consensus guidelines for the management of postoperative nausea and vomiting. Anesthesia and Analgesia. 2014; 118: 85–113. https://doi.org/10.1213/ANE.0000000000000002.

[4] Jin Z, Gan TJ, Bergese SD. Prevention and Treatment of Postoperative Nausea and Vomiting (PONV): A Review of Current Recommendations and Emerging Therapies. Therapeutics and Clinical Risk Management. 2020; 16: 1305–1317. https://doi.org/10.2147/TCRM.S256234.

[5] McCracken G, Houston P, Lefebvre G, Society of Obstetricians and Gynecologists of Canada. Guideline for the management of postoperative nausea and vomiting. Journal of Obstetrics and Gynaecology Canada. 2008; 30: 600–600–7, 608–16. https://doi.org/10.1016/s1701-2163(16)32895-x.

[6] Kovac AL. Postoperative Nausea and Vomiting in Pediatric Patients. Paediatric Drugs. 2021; 23: 11–37. https://doi.org/10.1007/s40272-020-00424-0.

[7] Xie M, Deng Y, Wang Z, He Y, Wu X, Zhang M, *et al*. Development and assessment of novel machine learning models to predict the probability of postoperative nausea and vomiting for patient-controlled analgesia. Scientific Reports. 2023; 13: 6439. https://doi.org/10.1038/s41598-023-33807-7.

[8] Hsieh CY, Poon YY, Ke TY, Chiang MH, Li YY, Tsai PN, *et al*. Postoperative Vomiting Following Laparoscopic Cholecystectomy Is Associated with Intraoperative Fluid Administration: A Retrospective Cohort Study. International Journal of Environmental Research and Public Health. 2021; 18: 5305. https://doi.org/10.3390/ijerph18105305.

[9] Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, *et al*. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. Anesthesia and Analgesia. 2020; 131: 411–448. https://doi.org/10.1213/ANE.0000000000004833.

[10] Stephenson SJ, Jiwanmall M, Cherian NE, Kamakshi S, Williams A. Reduction in post-operative nausea and vomiting (PONV) by preoperative risk stratification and adherence to a standardized anti emetic prophylaxis protocol in the day-care surgical population. Journal of Family Medicine and Primary Care. 2021; 10: 865–870. https://doi.org/10.4103/jfmpc.jfmpc_1692_20.

[11] Klenke S, Frey UH. Genetic variability in postoperative nausea and vomiting: A systematic review. European Journal of Anaesthesiology. 2020; 37: 959–968. https://doi.org/10.1097/EJA.0000000000001224.

[12] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999; 91: 693–700. https://doi.org/10.1097/00000542-199909000-00022.

[13] Bourdaud N, Devys JM, Bientz J, Lejus C, Hebrard A, Tirel O, *et al*. Development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients: the VPOP score. Paediatric Anaesthesia. 2014; 24: 945–952. https://doi.org/10.1111/

pan.12428.
[14] LaCount LT, Barbieri R, Park K, Kim J, Brown EN, Kuo B, *et al*. Static and dynamic autonomic response with increasing nausea perception. Aviation, Space, and Environmental Medicine. 2011; 82: 424–433. https://doi.org/10.3357/asem.2932.2011.
[15] Ferencová N, Višňovcová Z, Bona Olexová L, Tonhajzerová I. Eye pupil - a window into central autonomic regulation via emotional/cognitive processing. Physiological Research. 2021; 70: S669–S682. https://doi.org/10.33549/physiolres.934749.
[16] Sclocco R, Kim J, Garcia RG, Sheehan JD, Beissner F, Bianchi AM, *et al*. Brain Circuitry Supporting Multi-Organ Autonomic Outflow in Response to Nausea. Cerebral Cortex. 2016; 26: 485–497. https://doi.org/10.1093/cercor/bhu172.
[17] Hall CA, Chilcott RP. Eyeing up the Future of the Pupillary Light Reflex in Neurodiagnostics. Diagnostics. 2018; 8: 19. https://doi.org/10.3390/diagnostics8010019.
[18] Robba C, Moro Salihovic B, Pozzebon S, Creteur J, Oddo M, Vincent JL, *et al*. Comparison of 2 Automated Pupillometry Devices in Critically III Patients. Journal of Neurosurgical Anesthesiology. 2020; 32: 323–329. https://doi.org/10.1097/ANA.0000000000000604.
[19] Park KW, Choi N, Ryu HS, Kim MS, Lee EJ, Chung SJ. Pupillary dysfunction of multiple system atrophy: Dynamic pupillometric findings and clinical correlations. Parkinsonism & Related Disorders. 2019; 65: 234–237. https://doi.org/10.1016/j.parkreldis.2019.05.003.
[20] Bista Karki S, Coppell KJ, Mitchell LV, Ogbuehi KC. Dynamic Pupillometry in Type 2 Diabetes: Pupillary Autonomic Dysfunction and the Severity of Diabetic Retinopathy. Clinical Ophthalmology. 2020; 14: 3923–3930. https://doi.org/10.2147/OPTH.S279872.
[21] de Rodez Benavent SA, Nygaard GO, Harbo HF, Tønnesen S, Sowa P, Landrø NI, *et al*. Fatigue and cognition: Pupillary responses to problem-solving in early multiple sclerosis patients. Brain and Behavior. 2017; 7: e00717. https://doi.org/10.1002/brb3.717.
[22] Darvall J, Handscombe M, Maat B, So K, Suganthirakumar A, Leslie K. Interpretation of the four risk factors for postoperative nausea and vomiting in the Apfel simplified risk score: an analysis of published studies. Canadian Journal of Anaesthesia. 2021; 68: 1057–1063. https://doi.org/10.1007/s12630-021-01974-8.
[23] Meco BC, Ozcelik M, Yildirim Guclu C, Beton S, Islamoglu Y, Turgay A, *et al*. Does Type of Pharyngeal Packing during Sinonasal Surgery Have an Effect on PONV and Throat Pain? Otolaryngology–Head and Neck Surgery. 2016; 154: 742–747. https://doi.org/10.1177/0194599815626126.
[24] Sharma S, Baskaran M, Rukmini AV, Nongpiur ME, Htoon H, Cheng CY, *et al*. Factors influencing the pupillary light reflex in healthy individuals. Graefe's Archive for Clinical and Experimental Ophthalmology. 2016; 254: 1353–1359. https://doi.org/10.1007/s00417-016-3311-4.
[25] Kienbaum P, Schaefer MS, Weibel S, Schlesinger T, Meybohm P, Eberhart LH, *et al*. Update on PONV-What is new in prophylaxis and treatment of postoperative nausea and vomiting?: Summary of recent consensus recommendations and Cochrane reviews on prophylaxis and treatment of postoperative nausea and vomiting. Der Anaesthesist. 2022; 71: 123–128. https://doi.org/10.1007/s00101-021-01045-z. (In German)
[26] Li M, Chen J, Deng Y, Yan T, Gu H, Zhou Y, *et al*. Risk prediction models based on hematological/body parameters for chemotherapy-induced adverse effects in Chinese colorectal cancer patients. Supportive Care in Cancer. 2021; 29: 7931–7947. https://doi.org/10.1007/s00520-021-06337-z.
[27] Ishikawa M. Clinical factors affecting pupillary light reflex parameters: a single-centre, cross-sectional study. Ophthalmic & Physiological Optics. 2021; 41: 952–960. https://doi.org/10.1111/opo.12858.
[28] Fotiou DF, Brozou CG, Tsiptsios DJ, Fotiou A, Kabitsi A, Nakou M, *et al*. Effect of age on pupillary light reflex: evaluation of pupil mobility for clinical practice and research. Electromyography and Clinical Neurophysiology. 2007; 47: 11–22.
[29] Eto T, Higuchi S. Review on age-related differences in non-visual effects of light: melatonin suppression, circadian phase shift and pupillary light reflex in children to older adults. Journal of Physiological Anthropology. 2023; 42: 11. https://doi.org/10.1186/s40101-023-00328-1.
[30] Rashad AE, El Hefnawy E, Elmorshedi M, Abuyousif YA, Salem A, Attia M, *et al*. Prevalence, Risk Factors, and Management of Postoperative Nausea and Vomiting After Laparoscopic Sleeve Gastrectomy (a Retrospective Multicentric Study). Obesity Surgery. 2023; 33: 3237–3245. https://doi.org/10.1007/s11695-023-06803-z.
[31] Qian Y, Zhu JK, Hou BL, Sun YE, Gu XP, Ma ZL. Risk factors of postoperative nausea and vomiting following ambulatory surgery: A retrospective case-control study. Heliyon. 2022; 8: e12430. https://doi.org/10.1016/j.heliyon.2022.e12430.
[32] Veiga-Gil L, Pueyo J, López-Olaondo L. Postoperative nausea and vomiting: physiopathology, risk factors, prophylaxis and treatment. Revista Espanola De Anestesiologia Y Reanimacion. 2017; 64: 223–232. https://doi.org/10.1016/j.redar.2016.10.001.
[33] Pandey P, Ray S. Pupil dynamics: A potential proxy of neural preparation for goal-directed eye movement. The European Journal of Neuroscience. 2021; 54: 6587–6607. https://doi.org/10.1111/ejn.15453.
[34] Li N, Liu L, Sun M, Wang R, Jin W, Liu C, *et al*. Predominant role of gut-vagus-brain neuronal pathway in postoperative nausea and vomiting: evidence from an observational cohort study. BMC Anesthesiology. 2021; 21: 234. https://doi.org/10.1186/s12871-021-01449-9.
[35] Guillon M, Dumbleton K, Theodoratos P, Gobbe M, Wooley CB, Moody K. The Effects of Age, Refractive Status, and Luminance on Pupil Size. Optometry and Vision Science: Official Publication of the American Academy of Optometry. 2016; 93: 1093–1100. https://doi.org/10.1097/OPX.0000000000000893.
[36] Hayase T, Sugino S, Moriya H, Yamakage M. TACR1 gene polymorphism and sex differences in postoperative nausea and vomiting. Anaesthesia. 2015; 70: 1148–1159. https://doi.org/10.1111/anae.13082.
[37] Salazar-Parra M, Guzman-Ramirez BG, Pintor-Belmontes KJ, Barbosa-Camacho FJ, Bernal-Hernández A, Cruz-Neri RU, *et al*. Gender Differences in Postoperative Pain, Nausea and Vomiting After Elective Laparoscopic Cholecystectomy. World Journal of Surgery. 2020; 44: 4070–4076. https://doi.org/10.1007/s00268-020-05744-3.