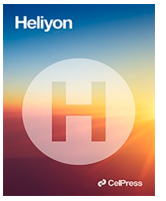
Heliyon 10 (2024) e25160

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Prevalence and time course of postoperative nausea and vomiting and severe pain in patients under general anesthesia with patient-controlled intravenous analgesia

Jie Chen [1], Tingjuan Yang [1], Shuangjiao Cao [1], Xuemei Zheng, Hongni Tian, Yuanjing Chen, Yupei Chen, He Huang, Guangyou Duan [*], Bin Shu [**]

Department of Anesthesiology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, 400010, China

ARTICLE INFO

Keywords:
Postoperative nausea and vomiting
Severe pain
Time course
General anesthesia

ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) and pain are common and distressing complications in patients undergoing surgery. However, it remains uncertain whether timing of the postoperative course or the diel rhythm influences the occurrence of PONV or severe pain. Therefore, we aimed to explore the temporal distribution of PONV and severe pain.

Material and methods: In this prospective observational study, we enrolled patients aged 18–65 years with American Society of Anesthesiologists classifications I–III, who were scheduled for surgery under general anesthesia. Patients were visited postoperatively at regular intervals (every 6 h over a 24-h period). Incidence of PONV was recorded and categorized based on real-time divisions: before dawn (00:00–05:59), morning (06:00–11:59), afternoon (12:00–17:59), and evening (18:00–23:59) and as sequential periods (i.e., 0–6, 6–12, 12–18, and 18–24 h). Severe pain and use of additional remedies were also recorded.

Results: A total of 724 patients were included in the final analysis. Of these, 14.92 % experienced PONV within the first 6 h, and 8.29 % received antiemetic therapy. Occurrence of PONV and administration of remedies declined over the 24-h postoperative period. The lowest rate of PONV was observed during the pre-dawn hours (5.66 %). There was no statistically significant difference in the incidence of PONV 24-h postoperatively between surgeries with different end times. Patients underwent orthopedic surgeries had the highest incidence of PONV during 18:00–23:59, gynecological surgery patients had the highest incidence at 12:00–17:59, and 6:00–11:59 for other surgery patients. All patients had the lowest incidence during 0:00–5:59. During the initial 6-h postoperative period, 24.59 % of patients experienced severe pain, which declined in the remaining episodes. Patients who underwent orthopedic and gynecological surgeries exhibited similar temporal patterns and distribution characteristics of PONV and severe pain.

Discussion: Both PONV and severe pain declined within the 24-h postoperative period, particularly within the first 6 h. Additionally, the onset patterns of PONV vary among patients undergoing different types of surgeries, all patients demonstrated decreased susceptibility to PONV between 00:00–05:59. Our findings enhance prevention and treatment strategies within an optimized timeframe during the postoperative course.

* Corresponding author.
** Corresponding author.
E-mail addresses: duangy@hospital.cqmu.edu.cn (G. Duan), binshu@cqmu.edu.cn (B. Shu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e25160
Received 13 September 2023; Received in revised form 5 January 2024; Accepted 22 January 2024
Available online 26 January 2024

1. Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications associated with general anesthesia. The incidence of PONV in clinical settings ranges from 10 % to 50 % and up to 80 % in high-risk patients [1–3]. It is crucial to comprehensively manage PONV to lower the risks of water-electrolyte balance disorders, wound dehiscence, and aspiration-associated complications to reduce healthcare costs and to improve patient satisfaction [4–6]. The occurrence of PONV is influenced by multiple factors, including sex, type of surgery, and opioids [7]. Severe pain is commonly reported during the postoperative period, which leads to delayed recovery and discharge [8]. However, it is unclear whether the timing of the postoperative period or the diel rhythm can affect the occurrence of PONV and severe pain. This study aimed to explore the temporal distribution patterns of PONV and severe pain in patients undergoing general anesthesia with the goal of identifying reliable evidence for more effective prevention and treatment within an optimized timeframe following surgery.

2. Materials and methods

2.1. Study design and ethics

This prospective, observational study was conducted at the Second Affiliated Hospital of Chongqing Medical University. The study protocol was approved by the Ethics Committee and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100052543; http://www.chictr.org.cn). Written informed consent was obtained from all participants or their legal representatives prior to surgery.

We enrolled patients aged 18–65 years with American Society of Anesthesiologists (ASA) classification I–III who were scheduled for surgery under general anesthesia and postoperative patient-controlled intravenous analgesia (PCIA). We excluded patients who: (i) were unable to communicate clearly; (ii) had long-term use of opioids, analgesics, or sedatives; (iii) received antiemetic therapy or chemotherapy over the past week; (iv) had a history of gastrointestinal obstruction or gastric tube placement; and (v) were admitted to the ICU with an endotracheal tube.

2.2. Anesthesia and analgesia

Peripheral venous access was obtained upon admission. Electrocardiography (ECG), heart rate, invasive blood pressure, and pulse oxygen saturation were routinely monitored. A SedLine® Legacy monitor (Masimo, Mexico) was used to continuously monitor the depth of anesthesia. Experienced anesthesiologists administered the same anesthetic regimen to patients. Atropine (0.5 mg) and dexamethasone (5–10 mg) were sequentially administered as pre-anesthesia medications. Anesthesia was induced intravenously with midazolam (0.04 mg/kg), propofol (2–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and rocuronium bromide (0.6 mg/kg). After endotracheal intubation, anesthesia was maintained with an intravenous infusion of remifentanil (0.1–0.2 μg/kg/min), propofol (1–4 mg/kg/h), and sevoflurane (1 %) inhalation, within the desired levels (Patient State Index of 25–50), and heart rate and blood pressure within 20 % of baseline values, according to the anesthesiologist judgment based on monitoring parameters. Rocuronium bromide was administered as a loading dose depending on surgical needs.

All patients received a nerve block or local infiltration analgesia at the end of the procedure. A patient-controlled intravenous analgesia (PCIA) pump was routinely used postoperatively. The 100-mL PCIA solution contained sufentanil (1 μg/kg), flurbiprofen ester (2 mg/kg), ondansetron (12 mg), and 0.9 % normal saline. The volumes of the loading and patient-controlled doses for the PCIA pump were 2 mL, the background infusion rate was 2 mL/h, and the lockout duration was 15 min.

The tracheal catheter was removed after the patient reached the indication for extubation, and the patients were monitored until their vital signs met the discharge criteria and then transferred to the general wards.

2.3. PONV and pain assessment and remedies

During the postoperative period, the patients in the ward were visited by the investigator every 6 h for 24 h after surgery. The patients were required to describe whether and when they had nausea and vomiting, as well as pain, during the past 6 h. Numerical rating scale were rated and a score of >4 was defined as severe pain. If the patient experiences PONV, metoclopramide (10 mg) was administered depending on the clinical needs of the patients and according to the surgeon's judgment. The rescue analgesics in the ward include flurbiprofen ester, tramadol, and dezocine.

2.4. Data collection

The baseline data included sex, age, body mass index, comorbidities, history of smoking, PONV, and motion sickness. Intraoperative data included the duration of anesthesia and operations, volumes of fluids infused, urine output, doses of anesthetic drugs and other adjuvant drugs, and the incidence of intraoperative hypertension or hypotension.

Whether patients were prescribed antiemetics or opioids were confirmed by the electronic medical system during every episode. Incidence of PONV was categorized and classified into two distinct time courses. The first time course was based on real-time events within a 24-h postoperative period (i.e., before dawn: 00:00–5:59, morning: 06:00–11:59, afternoon: 12:00–17:59, and evening:

18:00–23:59). The second time course consisted of sequential periods of (i.e., 0–6, 6–12, 12–18, and 18–24 h) after surgery.

2.5. Statistical analysis

2.5.1. Sample size

The primary outcome was the incidence of PONV. In our preliminary study, the incidence of PONV was 15.5 % and 22.4 % in the morning and afternoon, respectively. Assuming the significance (α-value) of 0.05, the power (β-value) of 0.8, and considering a loss-to-follow-up rate of about 10 %, we needed to enroll 720 patients. The sample size was calculated using PASS software (version 15.0, Stata Corp. LP, College Station, TX, USA).

2.5.2. Data analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), depending on the distribution traits, using the Shapiro–Wilk test. When comparing two independent groups, continuous variables with a Gaussian distribution were compared using a two-tailed Student's t-test; otherwise, the Mann–Whitney *U* test was applied. Categorical variables are represented as frequencies and ratios and were analyzed using the chi-square test. Pearson's Chi-squared test was used when comparing the four periods after surgery. The adjusted p-value of multiple comparisons of all pairwise groups was calculated based on the Bonferroni method. A subgroup analysis was conducted based on the type of surgery performed. For all hypotheses, p-values or adjusted p-values <0.05 were considered statistically significant. Statistical analyses were performed using the SPSS statistical package, version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

Between October 1, 2021, and February 28, 2022, 724 participants were included in this observational study and final analysis (Fig. 1). There were 231 (31.9 %) and 493 (68.1 %) patients with and without PONV, respectively. The two groups were comparable in terms of baseline variables, Apfel simplified risk scores, anesthesia, surgery duration, and drugs for PCIA, whereas the incidence of PONV varied with the type of surgery ($p = 0.005$; Table 1).

3.1. Prevalence and time course of PONV

Surgeries were mainly performed in the afternoon (386, 53.3 %), followed by evening (181, 25 %), morning (137, 18.92 %), and very rarely at dawn (20, 2.76 %). The prevalence of PONV during the 24-h postoperative period between surgeries concluded at different time periods was not statistically significant (dawn: 25 %, morning: 28.47 %, afternoon: 33.16 %, evening: 32.6 %, $p = 0.681$; Fig. 2A). The different surgical subgroups showed similar temporal distributions (Fig. 2B–F).

The total incidence of PONV varied between the two time courses (Fig. 3A, $p < 0.001$; Fig. 4A, $p < 0.001$). The rate of PONV was the

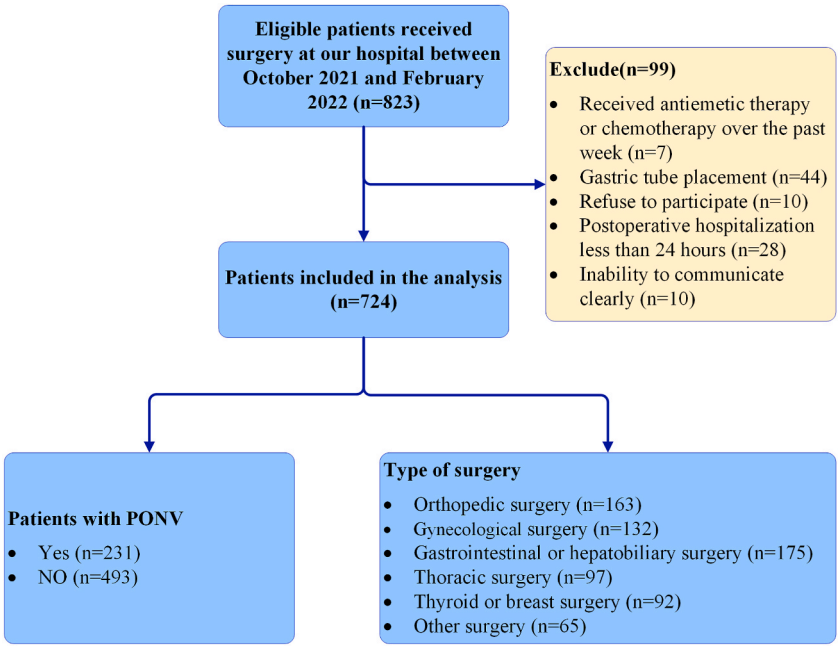


Fig. 1. Flow diagram representing patient enrollment.

Table 1
Demographic characteristics and intraoperative and postoperative data of the two groups.

Characteristic	PONV (n = 231)	Absence of PONV (n = 493)	*p* value
Age, mean (SD), year	46 (12)	46 (12)	0.378[a]
Height, mean (SD), cm	162.0 (7.8)	162.2 (7.6)	0.809[a]
Weight, mean (SD), kg	62.8 (11.5)	62.3 (10.8)	0.542[a]
Apfel simplified risk scores, median (IQR)	3 (2, 4)	3 (2, 4)	0.776[b]
Apfel simplified risk scores >2, frequency (%)	149 (64.5)	322 (65.3)	0.831[b]
Anesthesia duration, median (IQR), min	159 (110, 217)	171 (111, 236)	0.123[b]
Surgery duration, median (IQR), min	110 (75, 169)	120 (74, 185)	0.430[b]
Types of surgeries			0.005[c]
Orthopedic surgeries, frequency (%)	49 (37.4)	130 (72.6)	
Gynecological surgeries, frequency (%)	36 (27.3)	96 (72.7)	
Gastrointestinal or hepatobiliary surgeries, frequency (%)	55 (31.4)	120 (68.6)	
Thoracic surgeries, frequency (%)	40 (41.2)	57 (58.8)	
Thyroid or breast surgeries, frequency (%)	41 (44.6)	51 (55.4)	
Other surgeries, frequency (%)	10 (20.4)	39 (79.6)	
Fluid infusion, median (IQR), ml	1700 (1150, 2200)	1700 (1245, 2250)	0.421[b]
Fluid output, median (IQR), ml	350 (150, 800)	410 (165, 803)	0.396[b]
Dosage of PCIA			
Sufentanil, median (IQR), μg	100 (50, 100)	100 (60, 100)	0.305[b]
Flurbiprofen, median (IQR), mg	120 (100, 150)	100 (100, 150)	0.891[b]
Ondansetron, median (IQR), mg	12 (12, 16)	12 (12, 16)	0.888[b]

PONV, Postoperative Nausea and Vomiting; PCIA, patient-controlled intravenous analgesia.
Data are presented as the mean (SD), median (IQR), or number of patients (%).
[a] Two-tailed Student *t*-test.
[b] Mann-Whitney *U* test.
[c] Pearson's Chi-squared test.

lowest before dawn (5.66 %) when compared with the other three periods (Fig. 4A). Of the 724 participants, 108 (14.92 %) reported PONV and 60 (8.29 %) received antiemetic therapies during the first 6-h episode after surgeries, which declined in occurrence and episodes of remedies over the following 24-h postoperative period (Fig. 3A–Table 2).

A total of 179 patients who underwent orthopedic surgery had similar time courses and distribution traits compared to the overall group (Figs. 3B and 4B). A total of 132 patients underwent gynecological surgeries. Among these participants, the incidence of PONV varied with time and reached its peak within 0–6 h after surgery, whereas PONV most likely occurred between 12:00–17:59 (Figs. 3C and 4C). Among gastrointestinal or hepatobiliary surgeries, thoracic surgeries, and thyroid or breast surgeries, the frequency and

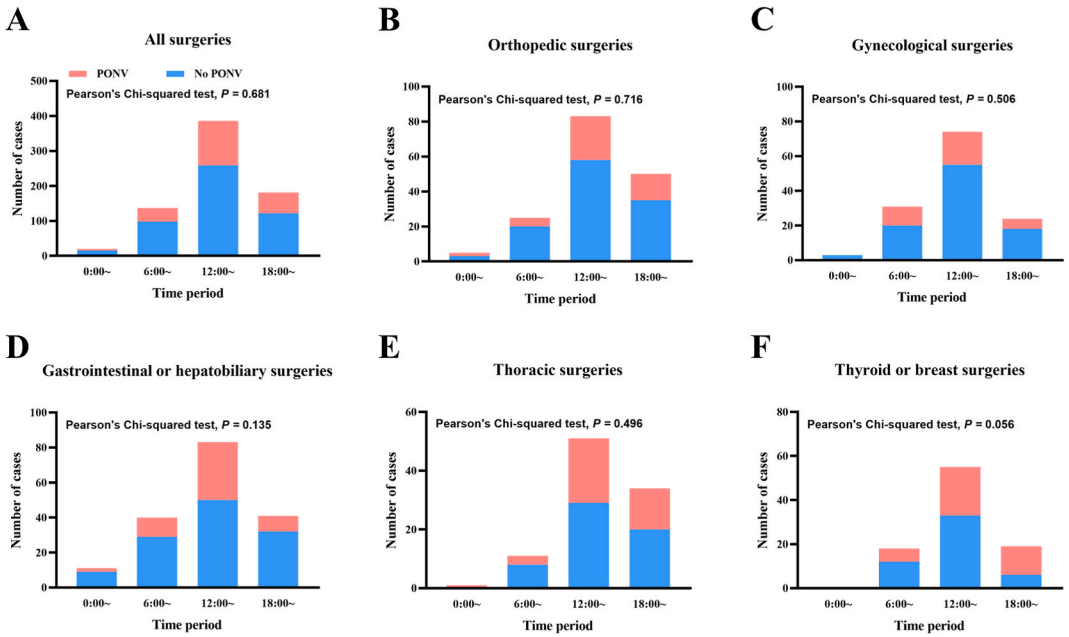


Fig. 2. The prevalence of postoperative nausea and vomiting (PONV) during the 24-h postoperative period between surgeries concluded at different time periods. Time distribution of surgery completion and PONV occurrence of all surgeries (A) and subgroup analysis of different types of surgeries (B–F). Pearson's Chi-squared test was used when comparing the four periods after surgery.

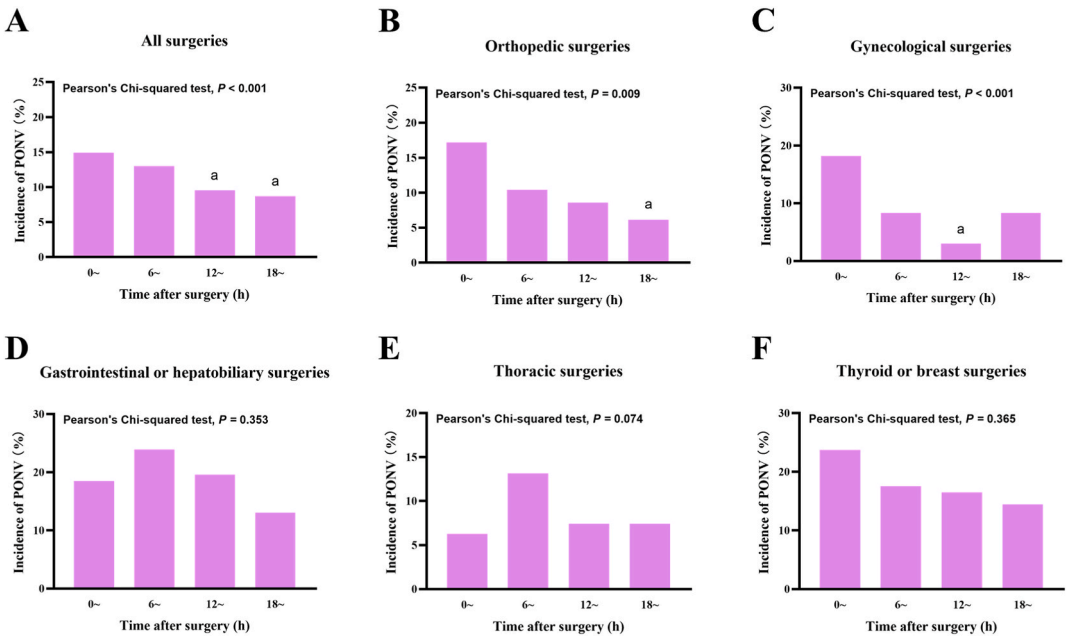


Fig. 3. Prevalence and postoperative time course of postoperative nausea and vomiting (PONV). Postoperative time distribution of PONV occurrence of all surgeries (A) and subgroup analysis of different types of surgeries (B–F). 0~: 0–6 h; 6~: 6–12 h; 12~: 12–18 h; 18~: 18–24 h. Pearson's Chi-squared test was used when comparing the four periods after surgery, Bonferroni correction was used for multiple comparisons. [a] $P < 0.05$ vs 0–6 h.

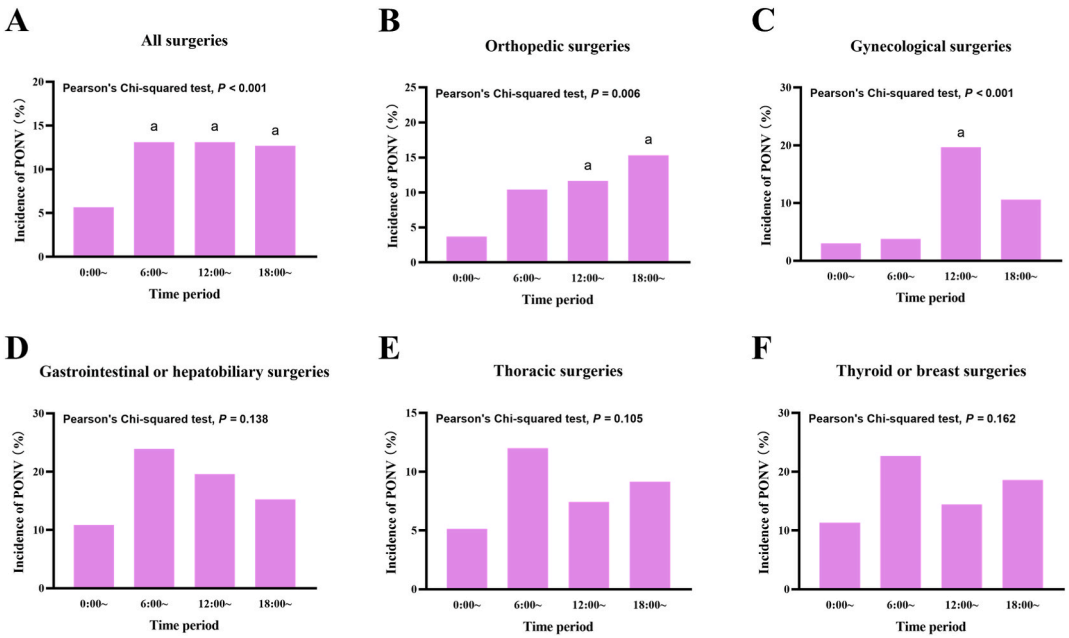


Fig. 4. Prevalence and real-time divisions of postoperative nausea and vomiting (PONV). Real-time divisions of PONV occurrence of all surgeries (A) and subgroup analysis of different types of surgeries (B–F). 0:00~: 00:00~5:59; 6:00~: 6:00~11:59; 12:00~: 12:00~17:59; 18:00~: 18:00~23:59. Pearson's Chi-squared test was used when comparing the four periods after surgery, Bonferroni correction was used for multiple comparisons. [a] $P < 0.05$ vs 00:00~5:59.

remedies for PONV revealed insignificant fluctuations in the different timeline, with sample sizes of 175 (Figs. 3D and 4D) and 97 (Figs. 3E and 4E) and 92 (Figs. 3F and 4F) cases, respectively. The incidence of PONV remained the lowest from 0:00–5:59, although there were no statistically significant differences among the time courses in these three subgroups (Fig. 4D–F).

Table 2
Episodes of remedy and postoperative sequential time course of PONV.

Hours after surgeries	0~	6~	12~	18~	*p* value[a]
Types of surgeries rowhead					
All surgeries	60 (8.29)	45 (6.22)	27 (3.73)	37 (5.11)	0.001
Orthopedic surgeries	20 (11.17)	9 (5.03)	7 (3.91)	10 (5.59)	0.013
Gynecological surgeries	4 (3.03)	4 (3.03)	1 (0.76)	5 (3.79)	0.392
Gastrointestinal or hepatobiliary surgeries	10 (5.71)	10 (5.71)	8 (4.57)	5 (2.86)	0.511
Thoracic surgeries	16 (16.49)	11 (11.34)	3 (3.09)	12 (12.73)	0.010
Thyroid or breast surgeries	5 (5.43)	10 (10.87)	6 (6.52)	2 (2.17)	0.101

PONV, Postoperative Nausea and Vomiting.
Data are presented as number of patients (%).
[a] Pearson's Chi-squared test.

We performed regression analyses of the overall and different natural time period PONV profiles, incorporating variables such as type of surgery (orthopedic, gynecological, gastrointestinal or hepatobiliary, thoracic, thyroid or breast), time of surgery completion (00:00~05:59, 06:00~11:59, 12:00~17:59, 18:00~23:59), female, age >45, BMI >24, nonsmoking, history of PONV, ASA

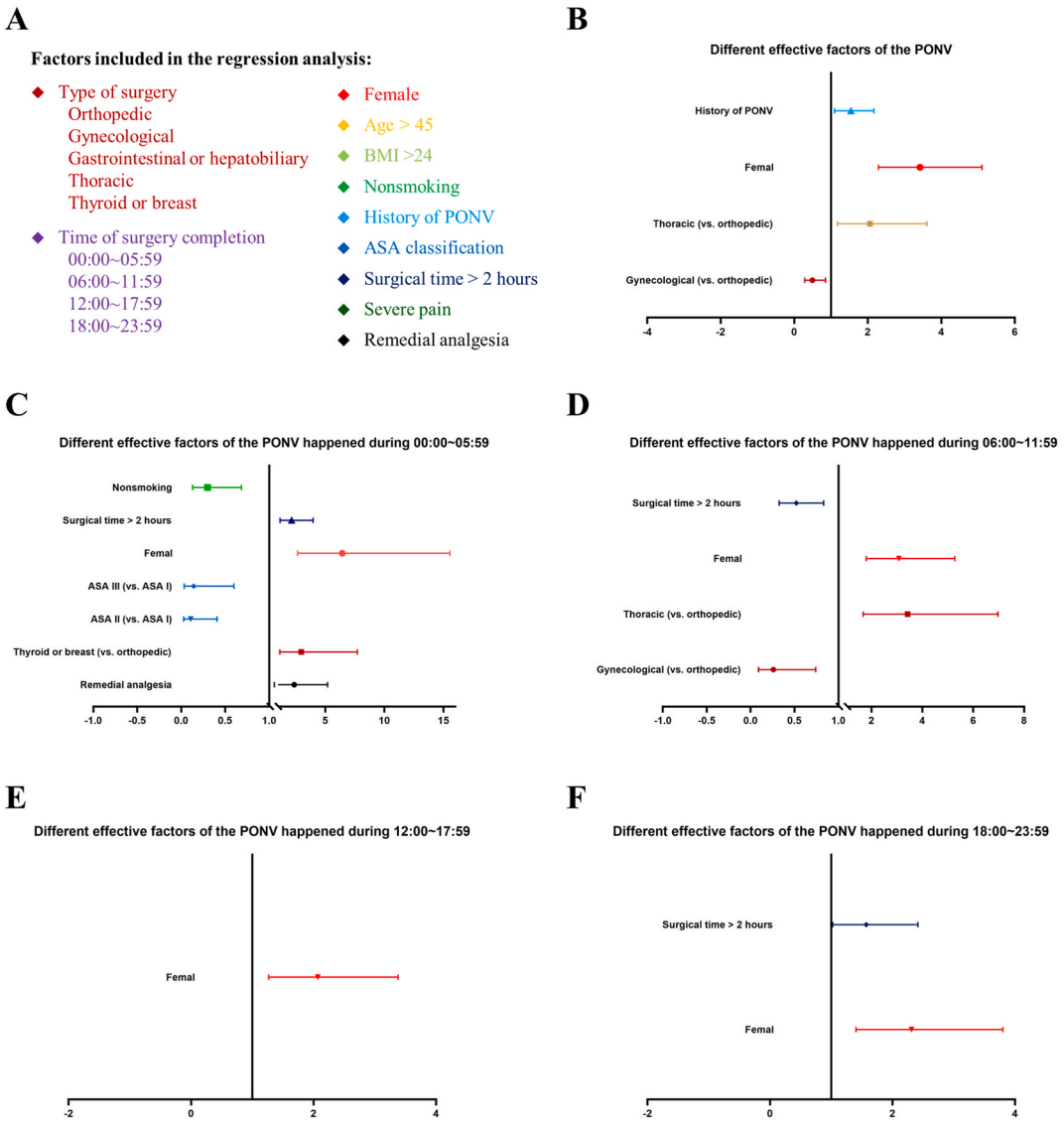


Fig. 5. Regression analyses of different effective factors of postoperative nausea and vomiting (PONV). The incorporating variables (A) and regression analyses of the overall (B) and different natural time period (C–F) PONV profiles.

classification, surgical time >2 h, severe pain, and remedial analgesia (Fig. 5A). Regression analysis showed that history of PONV (OR = 1.09), female (OR = 2.29), and thoracic surgery (OR = 1.17 vs. orthopedic surgery) were risk factors for overall PONV, gynecological surgery (OR = 0.28 vs. orthopedic surgery) was a protective factor (Fig. 5B). The subgroup analyses of different natural time periods yielded mixed results. Nonsmoking (OR = 0.30), ASA II (OR = 0.11 vs. ASA I), ASA III (OR = 0.14 vs. ASAI), thyroid or breast surgery (OR = 1.17 vs. orthopedic surgery), and remedial analgesia (OR = 2.37) were incorporated only in time period during 00:00∼05:59 (Fig. 5C). Thoracic surgery (OR = 1.17 vs. orthopedic surgery) and gynecological surgery (OR = 0.28 vs. orthopedic surgery) were incorporated in time period during 06:00∼11:59 (Fig. 5D). Surgical time >2 h were incorporated in time periods of 00:00∼05:59 (OR = 2.14, Figs. 5C), 06:00∼11:59 (OR = 0.33, Figs. 5D), and 18:00∼23:59 (OR = 1.03, Fig. 5F). Female (OR = 6.43, 1.80, 1.27, and 1.41 respectively) was risk factor in all 4 time periods (Fig. 5C–F).

3.2. Prevalence and time course of postoperative severe pain

Unlike PONV, the incidence of severe pain in patients 24 h postoperatively varied for surgeries that ended at different time periods. It was significantly higher in patients whose surgery ended in the evening (41.44 %) than in those whose surgery ended in the morning (20.44 %), although subgroup analyses of different surgery types showed no significant differences (Fig. 6A–F).

Of the 724 patients, 178 (24.59 %) reported severe pain during the first 6 h postoperatively, while a significant decrease in pain intensity was observed in the remaining three episodes (Fig. 7A). Severe pain in patients who underwent orthopedic surgeries (Fig. 7B), obstetric and gynecological surgeries (Fig. 7C), gastrointestinal or hepatobiliary surgeries (Fig. 7D), and thoracic surgeries (Fig. 7E) also showed similar trends and gradually worsened during the last 6 h. This phenomenon was not observed in thyroid or breast surgeries (Fig. 7F), which might have been due to patients experiencing milder tissue injuries and pain.

4. Discussion

The pathogenesis of PONV is intricately caused by multiple factors involving the central and peripheral nervous systems and is related to various neural transduction pathways and receptors [9]. Mechanical stimuli (e.g., traction or oppression by operations) and chemical stimuli (e.g., drugs, humoral changes, and inflammatory mediators) can excite the vomiting center by stimulating mechanoreceptors and chemoreceptors, respectively [10].

In the present study, we observed a PONV incidence of 31.9 % in the overall sample, which is consistent with previous literature [3]. Across the surgical procedures, the prevalence of PONV varied from 27.3 % to 44.6 %, with obstetric and gynecological surgeries and thyroid or breast surgeries, respectively. The discrepancy between these two types of surgeries is challenging and contradictory to explain, given that the surgical cohorts consisted predominantly of women, who are considered a high-risk group owing to their physiological and genetic susceptibility [11]. Several studies have reported high occurrences of PONV (44 %–64 %) in patients undergoing thyroid surgeries [12,13]. Cervical hyperextension was the standard position during thyroid surgeries, which was often accompanied by local vascular compression, vagal stimulation, or traction during surgical manipulation, which together can contribute to PONV. Inflammatory infiltration and edema surrounding the tissues in the neck during the postoperative course also evoked vagal reflex and induced PONV [14].

In our study, PONV occurred more frequently in the early postoperative course (i.e., postoperative 0–6 h). This time-related trait was more evident in patients undergoing orthopedic, gynecological, and obstetric surgeries. Our results are supported by those of previous studies in which the incidence of PONV reached 40.4 % during the first 2 h and remained as high as 35.6 % during the subsequent 4 h postoperatively. One potential explanation for the notable incidence of PONV within the initial 6-h period is the presence of residual opioids and inhaled anesthetics administered during surgery. Additionally, our study revealed that patients most frequently experienced severe pain during this period, which could exacerbate PONV by necessitating increased opioid usage [15]. Conversely, we observed decreased susceptibility to PONV between 00:00–06:00, possibly attributable to inherent circadian rhythms, although further investigation is warranted to fully understand this phenomenon.

Most importantly, the onset patterns of PONV vary among patients undergoing different types of surgeries. Patients underwent orthopedic surgeries had the highest incidence of PONV during 18:00–23:59, gynecological surgery patients had the highest incidence at 12:00–17:59, and 6:00–11:59 for other surgery patients. All patients had the lowest incidence during 0:00–5:59. These time course traits of PONV could help clinicians better prevent PONV by prescribing antiemetic drugs in advance at the optimal time.

This study has limitations as follows: first, although this was a prospective study with data of the primary outcome from investigator follow-up, there were still some outcome data from anesthesia record sheets and electronic medical systems; therefore, confounding factors could not be effectively eliminated. Studies have revealed a negative correlation between intraoperative crystal infusion volume and the occurrence of PONV [16]. For laparoscopic cholecystectomy surgery, the incidence of PONV is lower at a high intraoperative crystal infusion rate ($\geq$2 mL/kg/h) than at a lower infusion rate (<2 mL/kg/h) [17]. The intravenous-inhalation combined anesthesia was used in this study, as the intravenous-inhalation combined anesthesia is a prevalent approach in China [18,19]. In addition, although the overall sample size of this study was large, the sample size of the subgroups divided by surgery type was less than 200, which made the results of the subgroup analysis heterogeneous. Nevertheless, based on our current results, randomized controlled trials should be conducted to explore the effect of antiemetic drugs in different postoperative courses to reduce PONV occurrence.

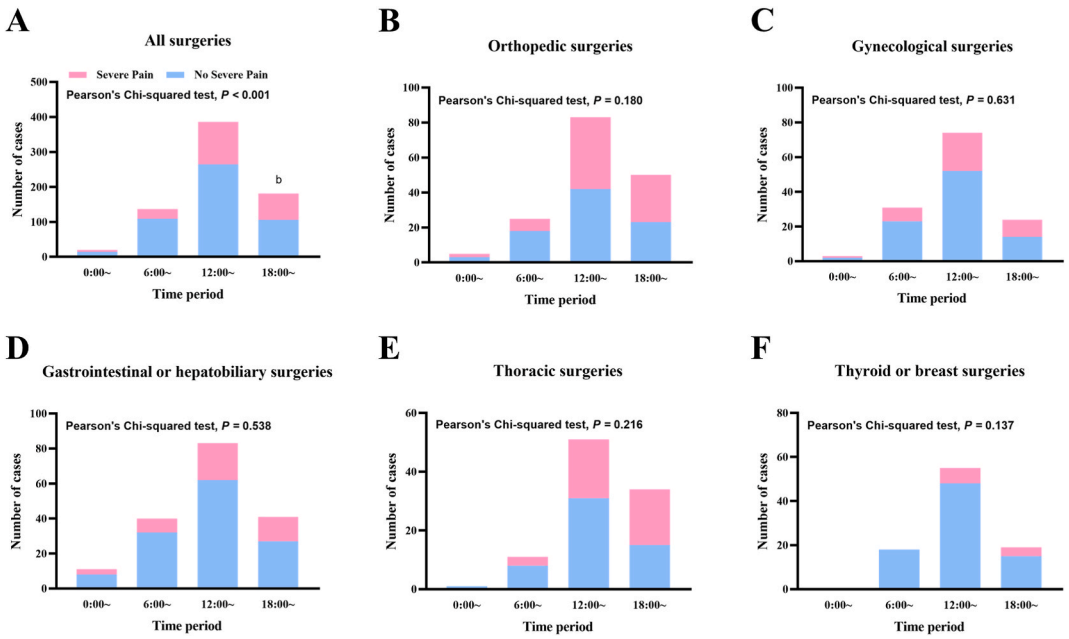


Fig. 6. The prevalence of postoperative severe pain during the 24-h postoperative period between surgeries concluded at different time periods. Time distribution of surgery completion and severe pain occurrence of all surgeries (A) and subgroup analysis of different types of surgeries (B–F). 0:00~: 00:00~5:59; 6:00~: 6:00~11:59; 12:00~: 12:00~17:59; 18:00~: 18:00~23:59. Pearson's Chi-squared test was used when comparing the four periods after surgery, Bonferroni correction was used for multiple comparisons. [b] $P < 0.05$ vs 6:00~11:59.

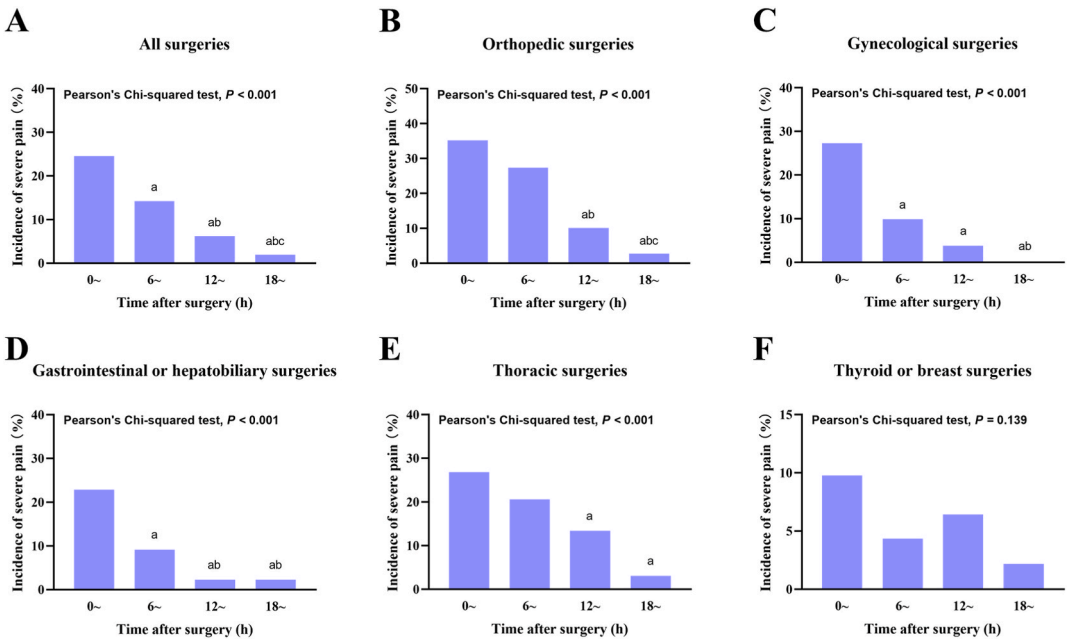


Fig. 7. Prevalence and time course of postoperative severe pain. Prevalence of severe pain occurrence in different time post operation (A) and subgroup analysis (B–F). 0~: 0–6 h; 6~: 6–12 h; 12~: 12–18 h; 18~: 18–24 h. Pearson's Chi-squared test was used when comparing the four periods after surgery, Bonferroni correction was used for multiple comparisons. [a] $P < 0.05$ vs 0–6 h, [b] $P < 0.05$ vs 6–12 h, [c] $P < 0.05$ vs 12–18 h. Pearson's Chi-squared test.

Conclusion

The onset patterns of PONV vary among patients undergoing different types of surgeries. Both PONV and severe pain after surgery were observed within the initial 6 h and exhibited a decreasing pattern over the subsequent 24 h in patients under general anesthesia with PCIA. Additionally, patients demonstrated reduced susceptibility to PONV between midnight and 6:00 a.m. These findings support the implementation of more effective strategies for the prevention and management of PONV and pain within a specific timeframe following surgery.

Ethics statement

This study involving human participants was reviewed and approved by the Medical Ethics Committee of The Second Affiliated Hospital of Chongqing Medical University, with the approval number: No.2021-91-1. All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82171210), Chongqing Natural Science Foundation (Grant No. CSTC2021JCYJ-MSXMX0188 and CSTB2022NSCQ-BHX0015), and Science and Technology Program of Chongqing Municipal Education Commission (No. KJQN202000409).

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Jie Chen: Writing – original draft, Resources, Investigation, Formal analysis. **Tingjuan Yang:** Investigation. **Shuangjiao Cao:** Writing – original draft, Investigation, Formal analysis. **Xuemei Zheng:** Resources, Data curation. **Hongni Tian:** Methodology, Data curation. **Yuanjing Chen:** Resources, Methodology. **Yupei Chen:** Methodology, Conceptualization. **He Huang:** Writing – review & editing, Methodology, Conceptualization. **Guangyou Duan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Bin Shu:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the subjects' selfless contribution to this work.

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