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SYSTEMATIC REVIEW



Opioid-free general anesthesia in breast surgery: a meta-analysis of randomized trials

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Abstract

Background: Opioid-free general anesthesia (OFGA) is increasingly adopted in clinical settings owing to its potential to reduce opioid-associated adverse events. This systematic review and meta-analysis aimed to evaluate the efficacy of OFGA versus opioid-based general anesthesia (OBGA) in breast surgery patients. **Methods:** We systematically searched Cochrane Library, PubMed, Embase, and Web of Science for randomized controlled trials (RCTs) comparing OFGA with OBGA in breast surgery. The primary focus was postoperative nausea and vomiting (PONV) incidence. Data were analyzed using Review Manager 5.3 and Stata V.12.0. Evidence certainty was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. **Results:** A total of 6 RCTs involving 493 patients were included in this analysis. Compared with the OBGA group, the OFGA group showed a significant reduction in PONV incidence (risk ratio = 0.17, 95% confidence interval (0.09, 0.31); $p \leq 0.05$, $I^2 = 0\%$), and shorter extubation time. Additionally, the OFGA technique was associated with more stable intraoperative hemodynamics and a lower postoperative neutrophil-lymphocyte ratio. **Conclusions:** Current evidence suggests that OFGA may be a promising alternative for patients undergoing breast surgery. However, higher-powered trials are required to confirm these outcomes. **The PROSPERO Registration:** International Prospective Register of Systematic Reviews (PROSPERO) registration number: CRD42024517527.

Keywords

Opioid-free general anesthesia; Nausea and vomiting; Breast surgery; Immune function; Meta-analysis

1. Introduction

As documented in the 2023 Global Cancer Observatory report by the International Agency for Research on Cancer (IARC), breast neoplasms continue to exhibit the highest incidence rates among all gender-specific malignancies affecting the female population. In 2022, the incidence of breast cancer accounted for 11.6% of all new cancer cases worldwide (ranking second), and the number of deaths accounted for 6.9% of the total cancer-related mortality (ranking fourth) [1]. Surgical tumor resection continues to be a standard treatment, yet it is accompanied by moderate to severe pain after surgery [2, 3]. Traditional opioid based general anesthesia (OBGA) is associated with various adverse events after surgery, such as respiratory depression, chest stiffness, pruritus, chills, urinary retention, nausea, and vomiting [4–6]. Moreover, opioid tolerance and opioid-induced hyperalgesia can further increase the demand for opioids, potentially leading to opioid misuse and dependence [7, 8]. Thus, the perioperative analgesia mode, mainly based on opioid drugs, is gradually facing challenges.

In recent years, opioid-free general anesthesia (OFGA) tech-

niques, which utilize a combination of non-opioid analgesics (such as α 2-receptor agonists and N-methyl-D-aspartate antagonists) [9, 10] alongside various regional block techniques have received attention [11–14]. Recent studies suggest that the OFGA protocol combining dexmedetomidine and lignocaine results in better perioperative outcomes than traditional OBGA, with improved hemodynamic stability, reduced anesthetic consumption, optimized recovery trajectories, and diminished postoperative complication rates [15]. Similarly, a retrospective study showed that the combination of ketamine, magnesium, and clonidine was more effective than OBGA in reducing postoperative nausea and vomiting (PONV) and pain scores after breast cancer quadrantectomy [16]. Furthermore, a recent study found that OFGA attenuates perioperative immunosuppression [17]. However, strong, surgery-specific, evidence-based conclusions are still lacking.

Given these considerations, the present investigation was designed to perform a quantitative synthesis of existing evidence regarding OFGA's clinical outcomes in breast oncological procedures through a systematic review methodology with meta-analytic validation.

2. Methods

This evidence synthesis was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standards. PRISMA 2020 Checklist is provided in **Supplementary material 1**. The methodological protocol received prior registration on PROSPERO (International Prospective Register of Systematic Reviews) under identifier CRD42024517527.

2.1 Systematic literature retrieval

An exhaustive database interrogation was conducted across PubMed, Embase, Cochrane Library, and Web of Science, encompassing all records through 30 April 2024, with no linguistic constraints imposed. The complete search syntax for each repository is available in Supplementary Materials. Furthermore, manual scrutiny of bibliographies from the selected publications was implemented to capture potentially omitted relevant studies.

2.2 Criteria for selection

2.2.1 Eligibility criteria

Study selection followed the PICOS framework:

- (1) Participants (P): patients undergoing breast surgery.
- (2) Intervention (I): trials clearly described OFGA technique.
- (3) Comparison (C): traditional OBGA technique.
- (4) Outcome (O): mandatory reporting of PONV incidence.
- (5) Study designs (S): peer-reviewed randomized controlled trials (RCTs).

2.2.2 Exclusion criteria

- (1) Patients had not undergoing general anesthesia.
- (2) Studies lacking extractable outcome data.
- (3) Non-peer reviewed/preliminary reports (conference abstracts, protocols).
- (4) Non-randomized or quasi-experimental study designs.

2.3 Data extraction and outcomes measures

The methodological process was rigorously executed by dual independent reviewers who initially conducted duplicate removal through automated EndNote deduplication complemented by manual verification. Subsequently, a two-phase screening protocol was implemented: preliminary title/abstract triage against PICOS criteria followed by full-text appraisal to confirm final eligibility. Utilizing a standardized extraction template, the reviewers systematically retrieved and cross-validated critical parameters including bibliographic identifiers (author names, publication year), demographic profiles (sample size, age distribution), and detailed anesthetic protocol specifications (OFGA vs. OBGA regimens).

The primary outcome was the incidence of PONV. Secondary outcomes included intraoperative hemodynamic indicators (bradycardia, hypotension and hypertension), postoperative analgesia indicators (pain score, opioid consumption, time for rescue analgesia, and number of patients who required rescue analgesia), recovery indicators (extubation time and

length of post-anesthesia care unit stay), and postoperative immune function indicator (neutrophil-lymphocyte ratio, NLR). For pain scores reported at rest and during movement, only scores during movement were included.

2.4 Quality and risk of bias assessment

The methodological rigor of the included trials was evaluated using the Cochrane collaboration's risk of bias tool across six critical domains: randomization process (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential biases. Studies received categorical ratings of low risk, moderate concern, or high risk through standardized domain-specific algorithms.

Concurrently, the GRADE framework was employed to stratify evidence certainty into four hierarchical tiers: high (indicating strong confidence), moderate (suggesting probable real effect), low (reflecting limited confidence), or very low (denoting uncertain estimates).

2.5 Statistical analysis

Quantitative synthesis was conducted utilizing the Cochrane's RevMan 5.3 (The Nordic Cochrane Centre, Oxford, UK) and Stata 12.0 (StataCorp LP, College station, TX, USA), with dual-platform validation to ensure analytical robustness. Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CIs), while continuous variables were analyzed as mean differences (MDs) for uniform units or standardized mean differences (SMDs) for heterogeneous metrics. When studies reported medians with interquartile ranges (IQR) or ranges, these values were converted to means and standard deviations using established statistical methods [18, 19]. Statistical significance was defined as $p < 0.05$. Heterogeneity in the trials was evaluated using the I^2 statistic, wherein $I^2 > 50\%$ was defined as "highly heterogeneous". Considering multiple factors that contributed to the high clinical heterogeneity in this study, a random-effect model was utilized for the studies with low I^2 values.

Subgroup analyses were stratified by geographic region (China, India, Other) and premedication administration status (Yes/No). Publication bias was evaluated through funnel plot symmetry analysis and Egger's linear regression test. Sensitivity analysis tested the robustness of the primary outcome by iteratively excluding individual studies.

Trial sequential analysis (TSA) was performed using TSA software (0.9.5.10 beta, Copenhagen Trial Unit, Copenhagen, Denmark) to control false-positive risks. Stopping boundaries were predefined as: Type I error (α) = 5% (two-sided), and Power ($1 - \beta$) = 80%. The cumulative Z-curve crossing either the monitoring boundary or reaching the required information size (RIS) threshold indicated sufficient evidence.

3. Results

3.1 Screening and eligibility assessment

The systematic search initially yielded 518 potentially eligible records. Following duplicate removal ($n = 202$), 297 studies were excluded through title/abstract screening based on the PICOS criteria. Full-text assessment of the remaining 19 articles led to the exclusion of 13 studies for the following reasons: OFGA protocol contamination in control groups ($n = 2$) [20, 21], non-randomized study designs ($n = 4$) [22–25], conference abstracts without full methodology ($n = 4$) [26–29], unavailable outcome metrics ($n = 3$) [30–32]. Six randomized controlled trials [15, 33–37] ultimately met the predefined inclusion criteria. The complete selection workflow is visually summarized in the PRISMA flow diagram (Fig. 1), with

critical study characteristics detailed in Table 1.

3.2 Risk of bias

The risk of bias evaluation revealed methodological limitations across the included trials: two studies [15, 33] lacked blinding of outcome assessors, resulting in “unclear risk” ratings for detection bias, while two additional trials [36, 37] omitted double-blind designs, leading to “unclear risk” classifications for performance bias. Furthermore, one trial [36] failed to report sample size calculations, introducing “unclear risk” of selection bias. These methodological constraints are comprehensively visualized in the risk of bias summary (Fig. 2).

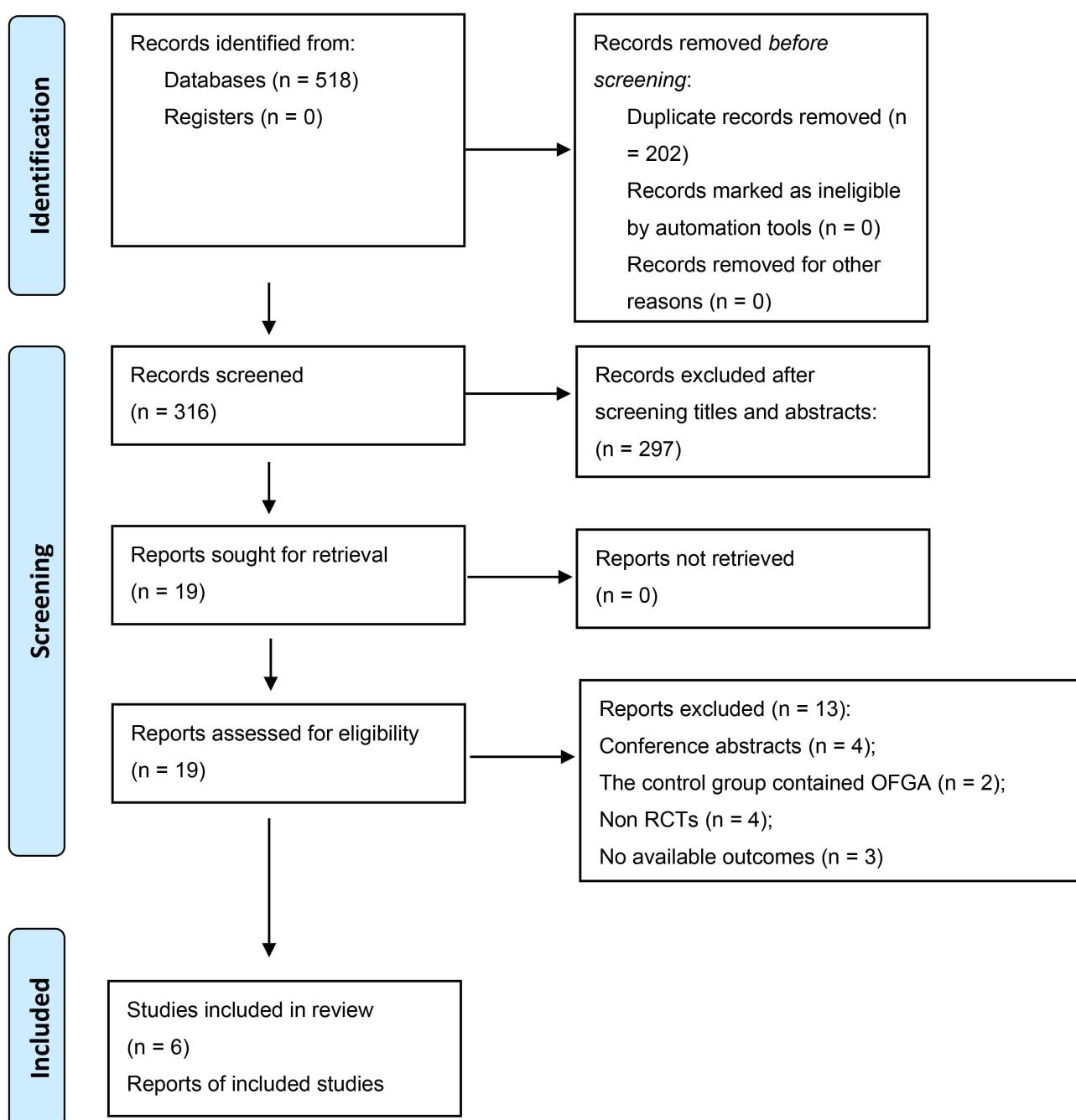


FIGURE 1. PRISMA flow diagram of literature selection process. OFGA, Opioid-free general anesthesia; RCTs, randomized controlled trials.

TABLE 1. Details of included studies.

Study	Country	Type of surgery	Sample size	Premedication	OFGA	OBGA	Postoperative analgesia
Jose 2023	India	Modified radical mastectomy	OFGA: 60 OBGA: 60	Glycopyrrolate 0.004 mg/kg and midazolam 0.02 mg/kg.	Dexmedetomidine 1 μ g/kg for 10 min, followed with 0.5 μ g/kg/h; lidocaine 1.5 mg/kg, followed with 1.5 mg/kg/h.	Morphine 0.15 mg/kg.	Not reported.
Li 2024	China	Breast cancer surgery	OFGA: 39 OBGA: 40	No Premedication.	Dexmedetomidine 1 μ g/kg, lidocaine spray, paravertebral nerve block with 0.25% ropivacaine 20 mL.	Sufentanil 0.4 μ g/kg; remifentanil 1–2 ng/mL.	PCIA: sufentanil.
Qian 2023	China	Lumpectomy	OFGA: 37 OBGA: 37	Dexamethasone 5 mg and penehyclidine hydrochloride 0.01 mg/kg.	Dexmedetomidine 0.5 μ g/kg over 10 min, esketamine 0.1 mg/kg, lidocaine 1.5 mg/kg, followed with dexmedetomidine 0.1–0.2 μ g/kg/h, esketamine 0.1–0.2 mg/kg/h, lidocaine 1–1.5 mg/kg/h.	Sufentanil 0.2–0.4 μ g/kg, remifentanil 0.1–0.3 μ g/kg/min.	Desocine for rescue analgesia.
Sarma 2024	India	Breast Cancer Surgery	OFGA: 50 OBGA: 50	No Premedication.	Dexmedetomidine 0.5 μ g/kg/h over 10 min, followed with 0.3–0.7 μ g/kg/h, magnesium sulfate 40 mg/kg, erector spinae plane block with 0.5% ropivacaine 0.5 mL/kg.	Fentanyl 2 μ g/k, followed with 1 μ g/kg after every hour intraoperatively.	PCIA: morphine.
Yilmaz 2021	Turkey	Breast Cancer Surgery	OFGA: 30 OBGA: 30	No Premedication.	Pectoral nerve I block with 0.25% bupivacaine 10 mL, pectoral nerve II block with 0.25% bupivacaine 20 mL.	Remifentanil 0.2–0.5 μ g/kg/min.	Tramadol for rescue analgesia.
Zhang 2023	China	Breast cancer surgery	OFGA: 40 OBGA: 40	Midazolam 2 mg.	Lidocaine 1.5 mg/kg; paravertebral nerve block with 0.4% ropivacaine 20 mL.	Sufentanil 0.2–0.3 μ g/kg, sufentanil 0.05–0.1 μ g/kg during surgery.	Flurbiprofen.

OFGA, opioid-free general anesthesia; OBGA, opioid-based general anesthesia; PCIA, patient controlled intravenous analgesia.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Jose 2023	+	+	+	?	+	+	+
Li2024	+	+	+	+	+	+	+
Qian2023	+	+	+	+	+	+	+
Sarma2024	+	+	+	?	+	+	+
Yilmaz2021	+	+	?	+	+	+	?
Zhang2023	+	+	?	+	+	+	+

FIGURE 2. Methodological quality assessment for included studies. +, low risk; ?, unclear risk.

3.3 Outcomes

3.3.1 Primary outcome

All the six included trials consistently reported PONV incidence. Meta-analytic synthesis (Fig. 3) demonstrated a statistically significant reduction in PONV occurrence within the OFGA cohort compared to OBGA, yielding a RR of 0.17 (95% CI: 0.09–0.31; $p < 0.05$). Notably, the analysis exhibited negligible interstudy heterogeneity ($I^2 = 0\%$), indicating remarkable consistency across trials. Subgroup stratification by geographic region and premedication status aligned with the primary findings, as detailed in **Supplementary Figs. 1,2**.

3.3.2 Secondary outcomes

3.3.2.1 Intraoperative hemodynamic indicators

Four trials assessed the incidence of intraoperative bradycardia. As presented in Fig. 4A, the results indicated a significantly lower incidence in the OFGA group (RR = 0.28, 95% CI: 0.10–0.75, $p < 0.05$), with low heterogeneity ($I^2 = 0\%$). Moreover, four trials assessed the incidence of intraoperative hypotension. The results, as depicted in the forest plot (Fig. 4B), indicated a significantly lower incidence in the OFGA group (RR = 0.24, 95% CI: 0.10–0.59, $p < 0.05$), with low heterogeneity ($I^2 = 0\%$). Additionally, two trials reported the incidence of intraoperative hypertension. The forest plot (Fig. 4C) indicated no significant difference in incidence between the OFGA group and the OBGA group.

3.3.2.2 Postoperative analgesia indicators

Three trials evaluated pain scores at 24 hours postoperatively. As shown in Fig. 5A, there was no statistically significant difference between the OFGA and OBGA groups (MD = -0.25, 95% CI: -0.95 to 0.44, $p = 0.48$, Fig. 5A), although substantial heterogeneity was observed ($I^2 = 76\%$). Two trials reported postoperative opioid consumption. As illustrated in the forest plot (Fig. 5B), there was no significant difference between the OFGA group and OBGA group (SMD = -0.03, 95% CI: -0.48 to 0.42, $p = 0.89$), with moderate heterogeneity observed ($I^2 = 57\%$). Two trials evaluated the time to first rescue analgesia, and the forest plot (Fig. 5C) showed no significant difference between the OFGA and OBGA groups. Two trials assessed the number of patients who required rescue analgesia, and the forest plot (Fig. 5D) also demonstrated no significant difference in incidence between the two groups.

3.3.2.3 Recovery indicators

Two trials reported extubation time. The result indicated a significantly shortened extubation time in the OFGA group (MD = -2.84 minutes, 95% CI: -4.26 to -1.41; $p < 0.05$, Fig. 6A), with substantial heterogeneity ($I^2 = 61\%$). Moreover, three trials reported the length of post-anesthesia care unit stay, and the results indicated no significant difference between the two groups (Fig. 6B).

3.3.2.4 Immune function indicator

Two trials reported postoperative NLR. The result indicated a significantly lower NLR in the OFGA group (MD = -2.09, 95% CI: -3.12 to -1.05, $p < 0.05$), with low heterogeneity ($I^2 = 6\%$) as shown in Fig. 7.

3.3.3 Evidence certainty and analytical robustness

The GRADE framework stratified evidence certainty across trials, ranging from low to high confidence levels as systematically documented in Table 2. Simultaneously, publication bias evaluation demonstrated a qualitatively symmetric funnel plot configuration for the primary outcome (**Supplementary Fig. 3**), corroborated by nonsignificant Egger's regression results ($p > 0.05$), collectively indicating no statistically significant small-study effects. Sensitivity analysis, employing iterative exclusion methodology, consistently replicated the primary effect estimates (Fig. 8), confirming analytical stability and reinforcing the conclusiveness of the meta-analytic findings.

3.3.4 TSA result

While the cumulative Z-score trajectory failed to attain the required information size (RIS) threshold, its breach of the trial sequential monitoring boundary ($\alpha = 5\%$, power = 80%) demonstrates conclusive evidence adequacy within the accrued dataset, as graphically substantiated in Fig. 9.

4. Discussion

This meta-analysis constitutes the first comprehensive evidence synthesis systematically evaluating OFGA protocols in mammary surgical interventions. Our findings indicate that OFGA is associated with a significant reduction in PONV, improved intraoperative hemodynamic stability, shorter extubation times, and reduced postoperative NLR.

Current international consensus guidelines on PONV management persistently identify female gender and postoperative opioid administration as key predictive determinants in adult populations [38]. Andrews *et al.* [39] suggest that opioid induced PONV may be associated with the activation of chemical trigger receptors in the brainstem. A prospective observational study indicated that a robust positive correlation exists between postoperative opioid dosage escalation and both PONV frequency and escalation [40]. A recent study reported that even when treated with some intervention measures (electrical acupoint stimulation or dexamethasone), the incidence of PONV in breast surgery patients receiving OBGA treatment is still approximately 30% [41]. PONV is associated with a range of postoperative adverse events, including electrolyte imbalance, postoperative bleeding, and decreased sleep quality. In this meta-analysis, we found that the OFGA technique significantly reduced the incidence of PONV compared with OBGA (4.1% vs. 27.9%), consistent with previous meta-analyses [42–44].

A key concern for anesthesiologists is whether OFGA can provide adequate analgesia during the perioperative period. Our findings suggest that OFGA offers comparable analgesic efficacy to OBGA, with lower incidences of bradycardia and hypotension, and no increase in hypertension, indicating stable hemodynamic profiles. Unfortunately, due to insufficient data, we were unable to analyze the difference in intraoperative opioid consumption between the two groups. Moreover, postoperative pain score, opioid consumption, and time for rescue analgesia were of no significant difference between

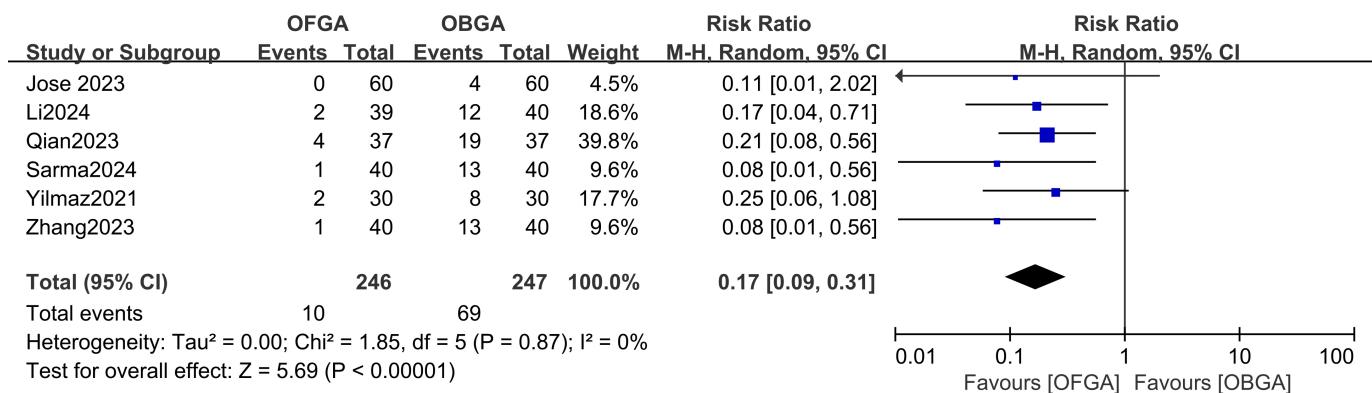


FIGURE 3. Forest plot of postoperative nausea and vomiting (PONV) incidence: opioid-free general anesthesia (OFGA) versus opioid-based general anesthesia (OBGA). CI, confidence interval; M-H, Mantel–Haenszel.

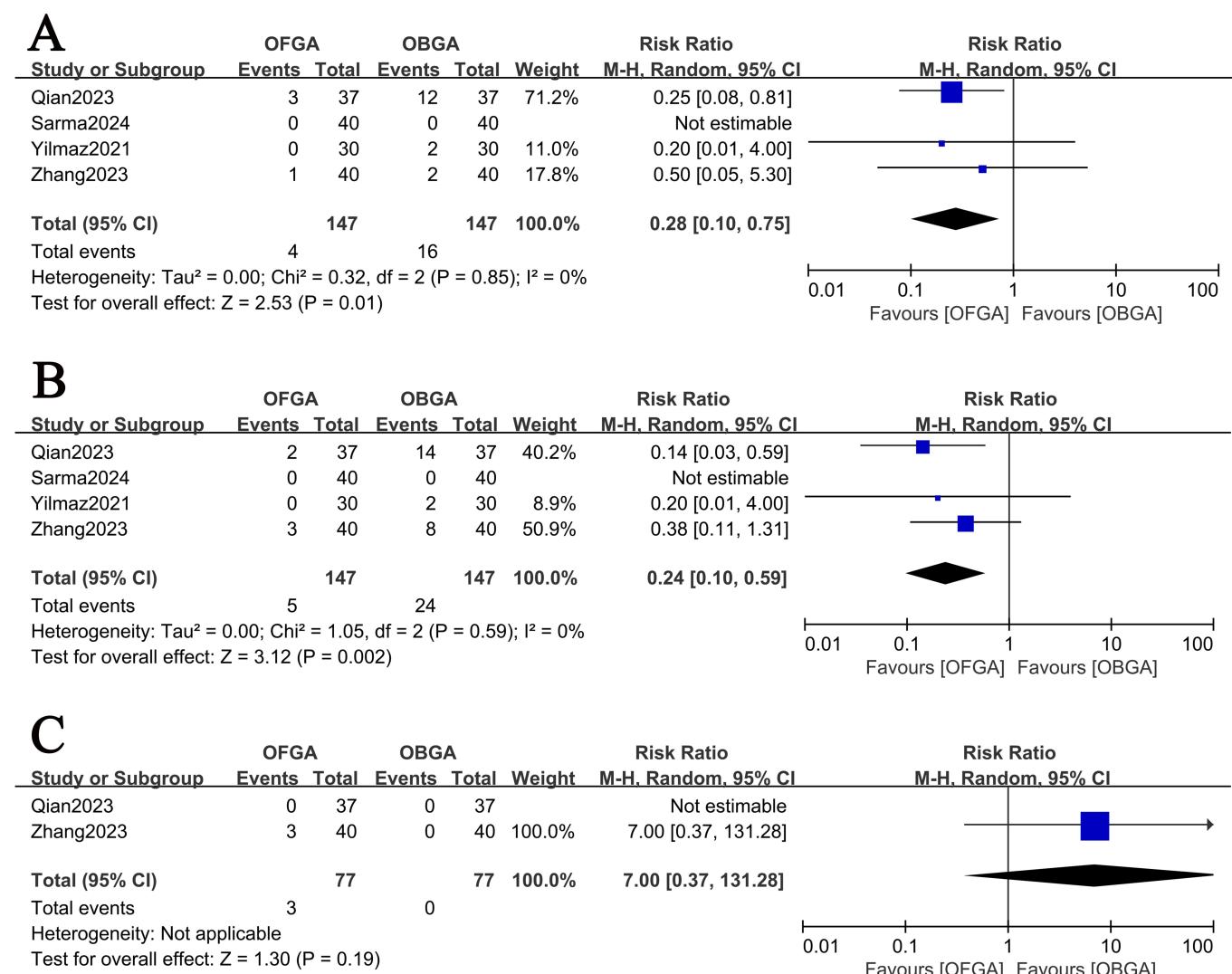
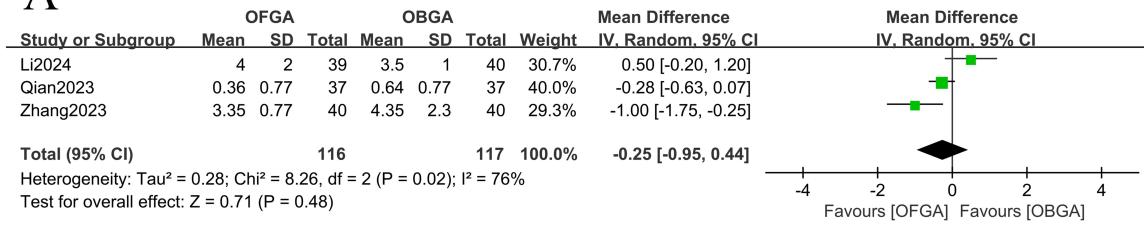
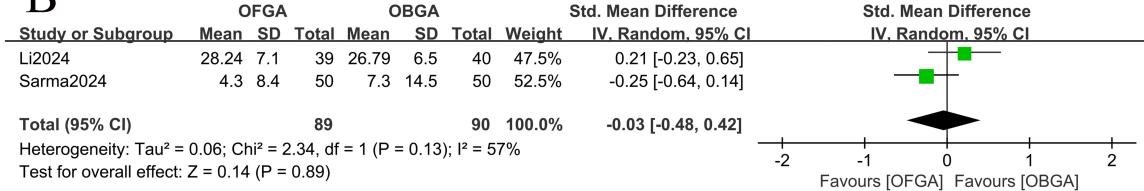


FIGURE 4. Meta-analytic comparison of perioperative hemodynamic outcomes. (A) Bradycardia risk assessment. (B) Hypotension incidence analysis. (C) Hypertension occurrence evaluation between opioid-free general anesthesia (OFGA) and opioid-based general anesthesia (OBGA) cohorts. CI, confidence interval; M-H, Mantel–Haenszel.

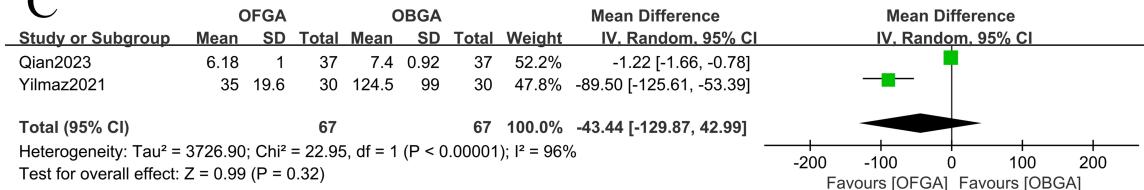
A



B



C



D

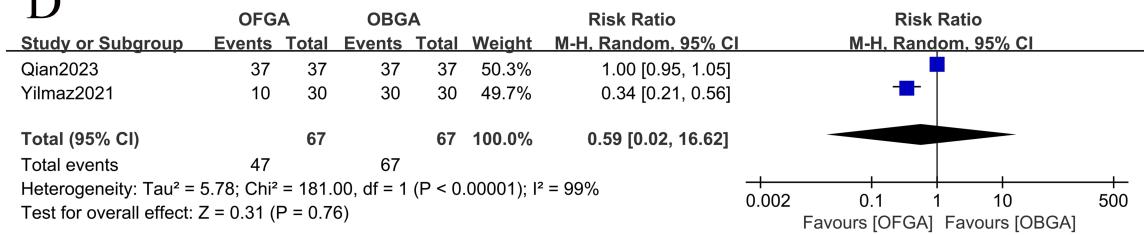
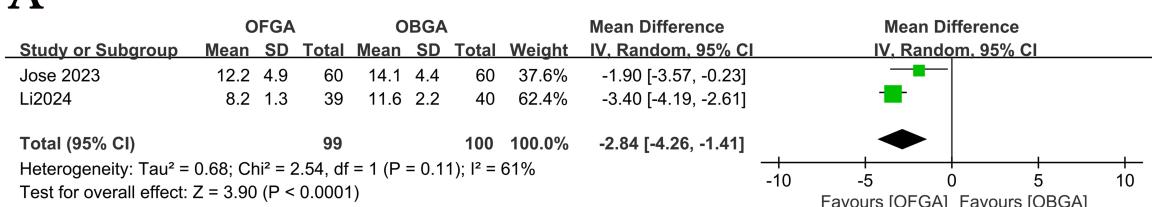


FIGURE 5. Meta-analytic evaluation of postoperative pain management outcomes. (A) 24-hour postoperative pain scores. (B) Opioid consumption. (C) Time to first rescue analgesia. (D) Frequency of rescue analgesia administration. Forest plots compare outcomes between opioid-free general anesthesia (OFGA) and opioid-based general anesthesia (OBGA) cohorts. CI, confidence interval; SD, standard deviation; M-H, mantel–haenszel; IV, inverse variance.

A



B

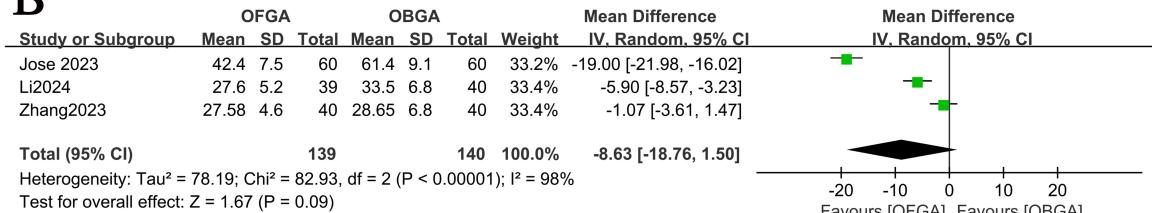


FIGURE 6. Meta-analysis of postoperative recovery metrics. (A) Tracheal extubation time. (B) Post-anesthesia care unit (PACU) duration. Forest plots compare opioid-free general anesthesia (OFGA) and opioid-based general anesthesia (OBGA) cohorts, presenting pooled mean differences (MD) with 95% confidence intervals. CI, confidence interval; SD, standard deviation; IV, inverse variance.

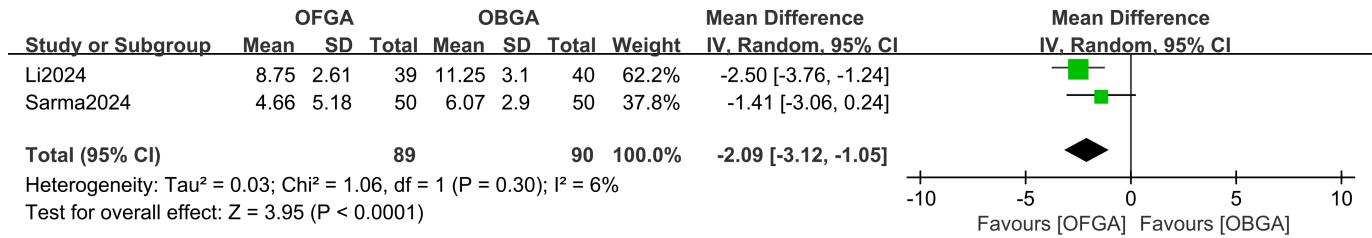


FIGURE 7. Meta-analytic comparison of neutrophil-lymphocyte ratio (NLR) between opioid-free (OFGA) and opioid-based general anesthesia (OBGA) cohorts. CI, confidence interval; SD, standard deviation; IV, inverse variance.

TABLE 2. Summary of GRADE for included studies.

Outcome	Included studies (n)	Patients (n)	Quality of evidence	Reasons
Incidence of PONV	6	493	⊕⊕⊕○ MODERATE	“Risk of bias” was downgraded to “serious”.
Incidence of bradycardia	4	294	⊕⊕⊕⊕ HIGH	NONE.
Incidence of hypotension	4	294	⊕⊕⊕⊕ HIGH	NONE.
Incidence of hypertension	2	154	⊕⊕⊕⊕ HIGH	NONE.
Pain score at postoperative 24 hour	3	233	⊕⊕○○ LOW	“Risk of bias” and “Imprecision” were downgraded to “serious”.
Postoperative opioid consumption	2	179	⊕⊕○○ LOW	“Imprecision” and “Inconsistency” were downgraded to “serious”.
Time to first rescue analgesia	2	134	⊕⊕⊕○ MODERATE	“Imprecision” was downgraded to “serious”.
Number of patients in need of rescue analgesia	2	114	⊕⊕⊕⊕ HIGH	NONE.
Extubation time	2	199	⊕⊕⊕○ MODERATE	“Imprecision” was downgraded to “serious”.
Post-anesthesia care unit stay	3	279	⊕⊕⊕○ MODERATE	“Imprecision” was downgraded to “serious”.
Neutrophil-lymphocyte ratio	2	179	⊕⊕⊕○ MODERATE	“Risk of bias” was downgraded to “serious”.

PONV, postoperative nausea and vomiting.

the two groups. However, these inconsistencies may be explained by differences in study protocols. Specifically, Qian *et al.* [35] did not specify whether pain scores were assessed at rest or during movement, whereas both Li *et al.* [34] and Sarma *et al.* [15] clearly reported pain scores during movement. In addition, opioid consumption differed in definition and administration: Li *et al.* [34] utilized patient-controlled intravenous analgesia with sufentanil, while Sarma *et al.* [15] employed patient-controlled intravenous analgesia with morphine postoperatively. These disparate approaches to rescue analgesia and variation in surgery type (lumpectomy *vs.* broader breast cancer surgery) likely contributed to the observed heterogeneity in analgesic outcomes. These findings also require validation through further standardized research. Hyperalgesia is an important reason for poor postoperative pain control after opioid use [45]. After infusion of remifentanil at a rate of 0.05–0.3 μ g/kg/min for 60–90 minutes, the

degree and range of postoperative incision pain increase, and the incidence of hyperalgesia is much higher than with other opioid analgesics [46, 47]. In contrast, our study revealed that OFGA techniques frequently utilized long-acting local anesthetics such as ropivacaine in conjunction with regional nerve blocks (*e.g.*, erector spinae, pectoral, or paravertebral blocks), enhancing analgesic effects without opioid-related risk.

Although our meta-analysis demonstrated a statistically significant decrease in extubation time with OFGA (MD = -2.84 minutes), the clinical importance of this reduction remains uncertain. A time difference of less than 3 minutes may lack practical relevance in routine clinical settings. Notably, Zhang *et al.* [48] reported comparable extubation times between OFGA and OBGA groups. Conversely, a separate RCT observed a marginal prolongation of tracheal extubation in patients receiving OFGA [49]. These conflicting findings

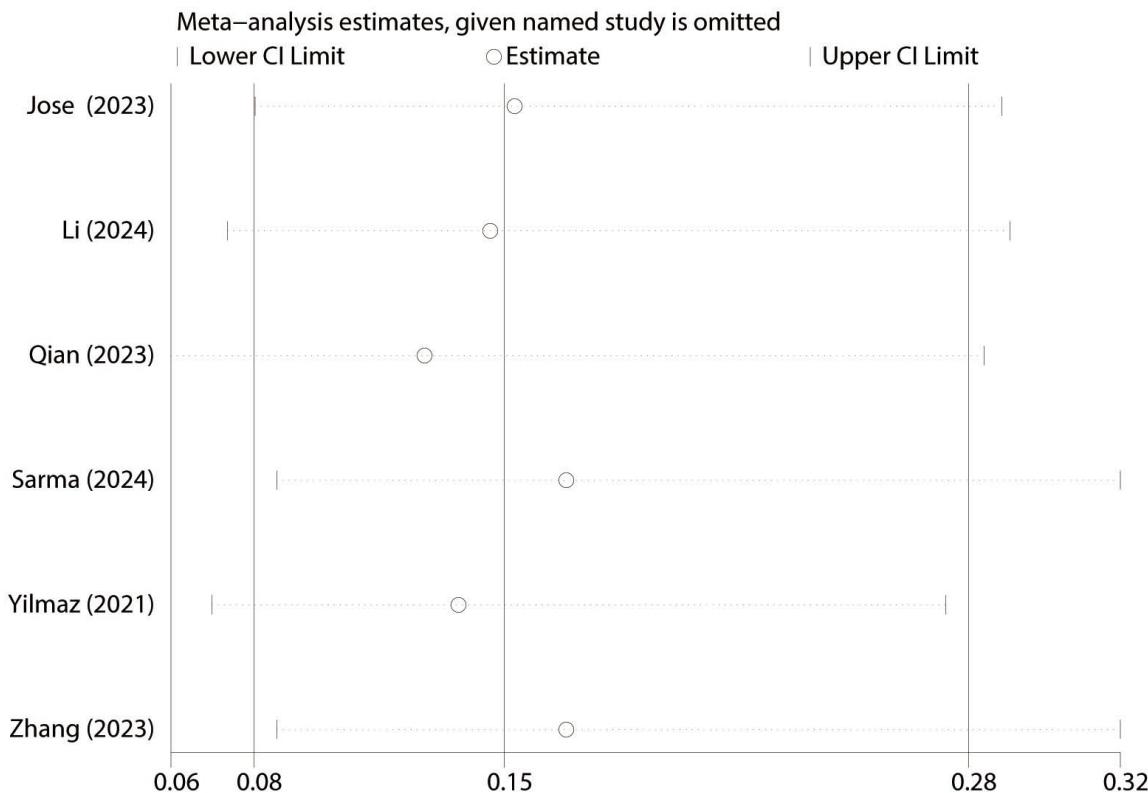


FIGURE 8. Sensitivity analysis for the incidence of PONV. A leave-one-out sensitivity analysis was conducted to assess the influence of individual studies on the pooled effect size and test result robustness. PONV, postoperative nausea and vomiting; CI, confidence interval.

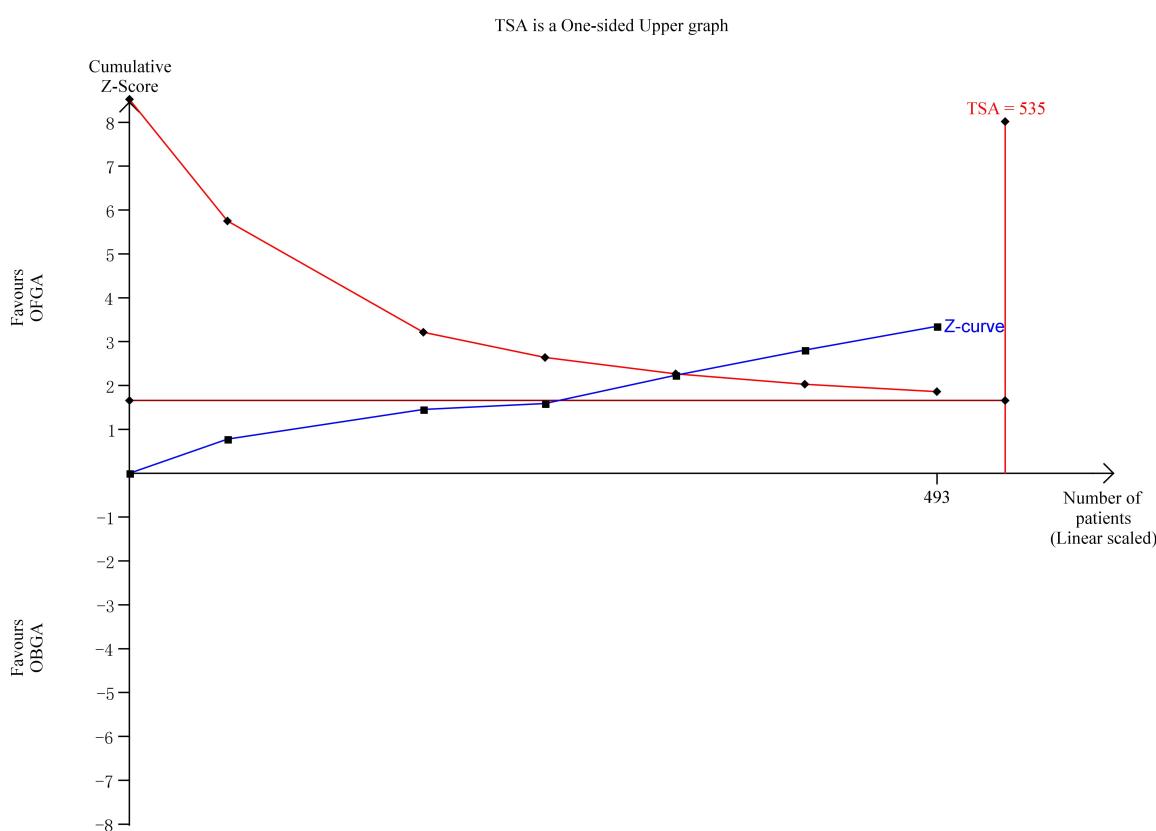


FIGURE 9. TSA for the incidence of PONV. TSA, trial sequential analysis; PONV, postoperative nausea and vomiting; OFGA, opioid-free general anesthesia; OBGA, opioid-based general anesthesia.

underscore the need for larger, standardized trials to clarify the impact of OFGA on postoperative recovery metrics. In addition, we found that OFGA decreased the NLR, which indicated less inflammation or improved cell-mediated immunity [50]. A systematic review demonstrated that an NLR exceeding 5 holds significant prognostic value in clinical oncology, and elevated preoperative NLR levels are independently associated with increased postoperative recurrence risk [51]. Previous studies have shown that opioids may suppress immune function [52, 53]. A retrospective study found that, compared with inhalational agent-opioid anesthesia, propofol-paravertebral block anesthesia attenuated the postoperative increase in the NLR after breast surgery [54]. Our study only evaluated the NLR as an immune marker. To fully assess the impact of OFGA on immune function, future research should incorporate broader biomarkers.

Several limitations of this meta-analysis should be acknowledged. First, although we conducted a comprehensive search, the sample size included in this meta-analysis was relatively small. Second, most of the included studies were conducted in China and India, which may affect generalizability. Third, the OFGA techniques included in the study exhibited significant heterogeneity, which may lead to potential biases. Fourth, the surgical procedures included in the analysis also varied widely; this broad clinical spectrum adds further heterogeneity and may limit the generalizability of the findings. Despite applying a random-effects model, the variability in anaesthetic approaches and surgical types necessitates cautious interpretation of the findings.

5. Conclusions

Our study suggests that OFGA is a promising alternative to OBGA in breast surgery, offering effective pain relief, reduced adverse effects, and benefits for postoperative NLR. However, to establish its role definitively, future research should focus on standardized OFGA protocols applied in specific surgical contexts to validate and optimize its clinical application.

AVAILABILITY OF DATA AND MATERIALS

The datasets supporting the conclusions of this article are supplemented along with the article.

AUTHOR CONTRIBUTIONS

LX—conceptualization, methodology, writing—original draft. YZL and YFS—project administration, resources, supervision. LX and QHS—formal analysis, investigation, validation. QHS—project administration.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.signavitae.com/mre-signavitae/article/2019691504757293056/attachment/Supplementary%20material.zip>.

REFERENCES

- [1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2024; 74: 229–263.
- [2] Guo H, Zhang X, Wang JG, Kalika P, Ran R, Xie YB. S-ketamine infusion on chronic postoperative pain following breast cancer surgery: a randomized double-blind placebo-controlled trial. *Clinical Breast Cancer*. 2024; 24: e605–e612.
- [3] Sowa Y, Nakayama I, Toyohara Y, Higai S, Yoshimura K. Pain-relieving effects of autologous fat grafting in breast cancer surgery: a scoping review. *Plastic and Reconstructive Surgery—Global Open*. 2024; 12: e5909.
- [4] Robinson S, Gregory GA. Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. *Anesthesia & Analgesia*. 1981; 60: 331–334.
- [5] Fan YZ, Duan YL, Chen CT, Wang Y, Zhu AP. Advances in attenuating opioid-induced respiratory depression: a narrative review. *Medicine*. 2024; 103: e38837.
- [6] Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Schgal N, *et al.* Opioid complications and side effects. *Pain Physician Journal*. 2008; 11: S105–S120.
- [7] Gooding SW, Whistler JL. A balancing act: learning from the past to build a future-focused opioid strategy. *Annual Review of Physiology*. 2024; 86: 1–25.
- [8] Henshaw DS, Turner JD, Khanna AK. Opioid abuse and perioperative care: a new medical disease. *Current Opinion in Anesthesiology*. 2022; 35: 401–408.
- [9] Yu DH, Shen X, Lai L, Chen YJ, Liu K, Shen QH. Application of dexametadomidine as an opioid substitute in opioid-free anesthesia: a systematic review and meta-analysis. *Pain Physician Journal*. 2023; 26: E635–E649.
- [10] Léger M, Perrault T, Pessiot-Royer S, Parot-Schinkel E, Costerousse F, Rineau E, *et al.* Opioid-free anesthesia protocol on the early quality of recovery after major surgery (SOFA trial): a randomized clinical trial. *Anesthesiology*. 2024; 140: 679–689.
- [11] Dai J, Li S, Weng Q, Long J, Wu D. Opioid-free anesthesia with ultrasound-guided quadratus lumborum block in the supine position for lower abdominal or pelvic surgery: a randomized controlled trial. *Scientific Reports*. 2024; 14: 4652.
- [12] Davis S, Batan T. The efficacy and safety of opioid-free anesthesia combined with ultrasound-guided intermediate cervical plexus block vs.

opioid-based anesthesia in thyroid surgery: a randomized controlled trial. *Journal of Anesthesia*. 2024; 38: 572.

[13] Kamel AAF, Fahmy AM, Medhat MM, Ali Elmesallamy WAE, Salem DAE. Retrolaminar block for opioid-free anaesthesia and enhanced recovery after posterior lumbar discectomy: a randomised controlled study. *Indian Journal of Anaesthesia*. 2024; 68: 261–266.

[14] Liu Z, Bi C, Li X, Song R. The efficacy and safety of opioid-free anesthesia combined with ultrasound-guided intermediate cervical plexus block vs. opioid-based anesthesia in thyroid surgery—a randomized controlled trial. *Journal of Anesthesia*. 2023; 37: 914–922.

[15] Sarma R, Gupta N, Gupta A, Kumar V, Mishra S, Bharati SJ, *et al.* Effect of opioid-free general anesthesia versus opioid-based general anesthesia on postoperative pain and immune response in patients undergoing breast cancer surgery: a randomized controlled trial. *Indian Journal of Surgical Oncology*. 2024; 15: 901–908.

[16] Di Benedetto P, Pelli M, Loffredo C, La Regina R, Pollicastro F, Fiorelli S, *et al.* Opioid-free anesthesia versus opioid-inclusive anesthesia for breast cancer surgery: a retrospective study. *Journal of Anesthesia, Analgesia and Critical Care*. 2021; 1: 6.

[17] Liu W, Ou C, Xue R, Yang X, Ye Y, Wang X, *et al.* Opioid-free anesthesia attenuates perioperative immunosuppression by regulating macrophages polarization in gastric cancer patients treated with neoadjuvant PD-1 inhibitor. *Frontiers in Immunology*. 2024; 15: 1438859.

[18] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Statistical Methods in Medical Research*. 2018; 27: 1785–1805.

[19] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*. 2014; 14: 135.

[20] Mohasseb AM, Elebiedy MG, Mohammed MN. A randomised comparative study of erector spinae plane block versus low-dose ketamine-dexmedetomidine intravenous infusion as intraoperative opioid-free analgesia for modified radical mastectomy. *Indian Journal of Anaesthesia*. 2024; 68: 651–657.

[21] Naja MZ, Ziade MF, Lönnqvist PA. Nerve-stimulator guided paravertebral blockade vs. general anaesthesia for breast surgery: a prospective randomized trial. *European Journal of Anaesthesiology*. 2004; 20: 897–903.

[22] Afonso A, Oskar S, Tan KS, Disa JJ, Mehrara BJ, Ceyhan J, *et al.* Is enhanced recovery the new standard of care in microsurgical breast reconstruction? *Plastic and Reconstructive Surgery*. 2017; 139: 1053–1061.

[23] Bайлارد NS, Flores RA. Could opioid sparing, rather than a direct non-steroidal anti-inflammatory drug effect, be responsible for improved survival after conservative breast surgery? *British Journal of Anaesthesia*. 2015; 114: 527.

[24] El Ayoubi S, Ghannam A, El Ahmadi B, Belkadir Z. ESRA19-0639 The ultrasound-guided erector spinae plane block allows opioid free anesthesia in the modified radical mastectomy with axillary dissection: a pilot study about 14 cases. *Regional Anesthesia & Pain Medicine*. 2019; 44: A264.

[25] Santonastaso DP, de Chiara A, Russo E, Musetti G, Lucchi L, Sibilio A, *et al.* Single shot ultrasound-guided thoracic paravertebral block for opioid-free radical mastectomy: a prospective observational study. *Journal of Pain Research*. 2019; 12: 2701–2708.

[26] Abdallah FW, Morgan PJ, Cil T, McNaught A, Escalon J, Semple J, *et al.* Paravertebral blocks for ambulatory breast tumour resection: effects of an inhalational gas- and opioid-free anesthetic on the quality of recovery. Randomized controlled trial. *Canadian Journal of Anesthesia*. 2013; 60: S40.

[27] Kaniyil S, Jose A, Raveendran R. Dexmedetomidine–lignocaine infusion compared to morphine for intraoperative hemodynamic stability in modified radical mastectomy. *Anesthesia & Analgesia*. 2021; 133: 715.

[28] Lecluyse V, Nadeau C, Boisvert C, Medicis ÉD, Masse MH. Effect of opioids replacement by beta-blockers on post mastectomy pain. *Canadian Journal of Anesthesia*. 2014; 61: S31.

[29] Sarma R, Gupta N, Kumar V, Mishra S, Bhatnagar S. To compare the efficacy of opioid free general anesthesia with opioid based general anesthesia on post-operative morphine consumption in patients undergoing breast cancer surgery: a prospective randomized control study. *Anesthesia & Analgesia*. 2021; 133: 1454.

[30] Aboalsoud RAHE-d, Arida EAM, Sabry LAA, Elmolla AF, Ghoneim HEM. The effect of opioid free versus opioid based anaesthesia on breast cancer pain score and immune response. *Egyptian Journal of Anaesthesia*. 2021; 37: 472–482.

[31] Krishnasamy Yuvaraj A, Gayathri B, Balasubramanian N, Mirunalini G. Patient comfort during postop period in breast cancer surgeries: a randomized controlled trial comparing opioid and opioid-free anesthesia. *Cureus*. 2023; 15: e33871.

[32] Naik S, Bhosale A, Kale D, Patil PB. Opioid-based vs. opioid-free anesthesia in breast cancer surgery. *Journal of Pharmacy and Bioallied Sciences*. 2023; 15: S1033–S1035.

[33] Jose A, Kaniyil S, Ravindran R. Efficacy of intravenous dexmedetomidine-lignocaine infusion compared to morphine for intraoperative haemodynamic stability in modified radical mastectomy: a randomised controlled trial. *Indian Journal of Anaesthesia*. 2023; 67: 697–702.

[34] Li W, Zhang W, Xie H. Effects of opiate-free general anesthesia on perioperative pain and immune function in patients undergoing breast cancer surgery. *Chinese Journal of Endocrine Surgery*. 2024; 18: 217–221. (In Chinese)

[35] Qian XL, Li P, Chen YJ, Xu SQ, Wang X, Feng SW. Opioid free total intravenous anesthesia with Dexmedetomidine-Esketamine-Lidocaine for patients undergoing lumpectomy. *Journal of Clinical Medicine Research*. 2023; 15: 415–422.

[36] Yilmaz F, Bas K, Zengel B. Comparative study of postoperative analgesia and opioid requirement using pectoral nerve blocks with general analgesia. *Indian Journal of Surgery*. 2021; 83: 440–445.

[37] Zhang Q, Wu Y, An H, Feng Y. Postoperative recovery after breast cancer surgery: a randomised controlled trial of opioid-based versus opioid-free anaesthesia with thoracic paravertebral block. *European Journal of Anaesthesiology*. 2023; 40: 552–559.

[38] 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 & Analgesia*. 2020; 131: 411–448.

[39] Andrews PL. Physiology of nausea and vomiting. *British Journal of Anaesthesia*. 1992; 69: 2S–19S.

[40] Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. *Anesthesia & Analgesia*. 2005; 101: 1343–1348.

[41] Zhang Y, Li Y, Ji F, Zhang K, Lou Y, Xu H. Transcutaneous electrical acupoint stimulation versus dexamethasone for prophylaxis of postoperative nausea and vomiting in breast surgery: a non-inferiority randomized controlled trial. *Surgery*. 2023; 174: 787–793.

[42] Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia*. 2019; 74: 651–662.

[43] Ao Y, Ma J, Zheng X, Zeng J, Wei K. Opioid-sparing anesthesia versus opioid-free anesthesia for the prevention of postoperative nausea and vomiting after laparoscopic bariatric surgery: a systematic review and network meta-analysis. *Anesthesia & Analgesia*. 2024; 140: 385–396.

[44] Feenstra ML, Jansen S, Eshuis WJ, van Berge Henegouwen MI, Hollmann MW, Hermanides J. Opioid-free anesthesia: a systematic review and meta-analysis. *Journal of Clinical Anesthesia*. 2023; 90: 111215.

[45] Mangutov E, Pradhan AA. Tiam1 is part of a novel mechanism for morphine tolerance and hyperalgesia. *Brain*. 2024; 147: 2264–2266.

[46] Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005; 103: 147–155.

[47] Shin SW, Cho AR, Lee HJ, Kim HJ, Byeon GJ, Yoon JW, *et al.* Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *British Journal of Anaesthesia*. 2010; 105: 661–667.

[48] Zhang Z, Li C, Xu L, Sun X, Lin X, Wei P, *et al.* Effect of opioid-free anesthesia on postoperative nausea and vomiting after gynecological surgery: a systematic review and meta-analysis. *Frontiers in Pharmacology*. 2023; 14: 1330250.

[49] Wang D, Sun Y, Zhu YJ, Shan XS, Liu H, Ji FH, *et al.* Comparison

of opioid-free and opioid-inclusive propofol anaesthesia for thyroid and parathyroid surgery: a randomised controlled trial. *Anaesthesia*. 2024; 79: 1072–1080.

[50] Thompson D, Perry LA, Renouf J, Vodanovich D, Hong Lee AH, Dimiri J, *et al.* Prognostic utility of inflammation-based biomarkers, neutrophil-lymphocyte ratio and change in neutrophil-lymphocyte ratio, in surgically resected lung cancers. *Annals of Thoracic Medicine*. 2021; 16: 148–155.

[51] Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Critical Reviews in Oncology/Hematology*. 2013; 88: 218–230.

[52] Chen S, Liu J, Huang S. Effect of repeated intraperitoneal injections of different concentrations of oxycodone on immune function in mice. *Frontiers in Pharmacology*. 2024; 15: 1370663.

[53] Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M. Review article: the role of the perioperative period in recurrence after cancer surgery. *Anesthesia & Analgesia*. 2010; 110: 1636–1643.

[54] Ni Eochagáin A, Burns D, Riedel B, Sessler DI, Buggy DJ. The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. *Anaesthesia*. 2018; 73: 603–611.

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