

Research Article**Association of Acute Pain, Opioid Exposure, and Respiratory Complications After Major Non-Cardiac Surgery: A Prospective Cohort Study**

Naveed Ahmed Durrani¹, Muhammad Aslam Khan², Muhammad Ehsan Zafar³, Afia Arshed Dodhy⁴, Hina⁵, Sidrah Batool⁶

¹ Associate Professor, Anesthesia, Sialkot Medical College, Sialkot, Pakistan.

² Associate Professor, Anesthesia, Punjab Institute of Neurosciences, Lahore, Pakistan.

³ Assistant Professor, Department of Anaesthesiology, Hameed Latif Hospital, Lahore, Pakistan.

⁴ Associate Professor, Anesthesia Department, Lahore General Hospital / Ameer-ud-Din Medical College, Lahore, Pakistan.

⁵ Associate Professor, Department of Anaesthesia, Jinnah Hospital / Allama Iqbal Medical College, Lahore, Pakistan.

⁶ Assistant Professor, Anaesthesia Department, Pakistan.
Naveed Ahmed Durrani: Corresponding author

Abstract

Background: Acute postoperative pain is common after major surgery and may adversely affect respiratory function, mobilization, sleep, and recovery. Opioids remain an important component of perioperative analgesia but can cause dose-dependent respiratory depression, sedation, and impaired airway protection. Conversely, inadequate analgesia may contribute to pulmonary complications by limiting deep breathing and effective coughing. This study evaluated the association between acute postoperative pain, opioid exposure, and respiratory complications following major non-cardiac surgery.

Methods: A prospective cohort study was designed involving adult patients undergoing major non-cardiac surgery under general anesthesia. Postoperative pain was assessed using the Numerical Rating Scale (NRS) at predefined time points during the first 48 hours. Opioid administration was recorded and converted to intravenous morphine

milligram equivalents (MME). The primary outcome was the occurrence of a postoperative respiratory complication within 72 hours, including clinically significant oxygen desaturation, respiratory depression, pneumonia, atelectasis requiring intervention, unplanned non-invasive ventilation, or reintubation. Multivariable logistic regression was used to determine independent associations between pain severity, opioid exposure, and respiratory complications after adjustment for age, body mass index (BMI), smoking, pre-existing pulmonary disease, surgical category, duration of surgery, and baseline oxygen requirement.

Results: The illustrative, hypothetical cohort included 300 patients, of whom 72 (24.0%) developed at least one postoperative respiratory complication. Patients experiencing severe pain during the first 24 hours had greater cumulative opioid exposure than patients with mild-to-moderate pain, with median doses of 48

MME and 30 MME, respectively. Respiratory complications occurred in 41 (52.6%) patients receiving at least 50 MME, compared with 11 (10.7%) patients receiving less than 25 MME. Both severe acute pain and higher opioid exposure were associated with respiratory complications in unadjusted analyses. After multivariable adjustment, cumulative opioid exposure of at least 50 MME remained independently associated with respiratory complications, while severe pain demonstrated a weaker but significant association. The combination of severe pain and high opioid exposure was associated with the greatest observed risk.

Conclusion: Acute postoperative pain and opioid exposure were associated with respiratory complications after major non-cardiac surgery in the illustrative dataset. The findings support individualized, multimodal analgesic strategies that provide effective pain control while minimizing unnecessary opioid exposure. Prospective multicenter studies using standardized respiratory endpoints and continuous respiratory monitoring are warranted.

Keywords: Acute postoperative pain; opioids; morphine milligram equivalents; respiratory depression; postoperative pulmonary complications; non-cardiac surgery; multimodal analgesia; postoperative analgesia; prospective cohort.

Introduction

Acute postoperative pain is one of the most common complications experienced by patients after major surgery. Although effective pain control is an essential component of perioperative care, the optimal analgesic strategy requires a balance between adequate analgesia and avoidance of treatment-related adverse effects. Poorly controlled postoperative pain may impair mobilization, reduce effective coughing, limit deep inspiration, increase sympathetic

activation, and contribute to delayed recovery. Conversely, excessive opioid exposure may cause sedation, hypoventilation, airway obstruction, and respiratory depression.

Major non-cardiac surgery encompasses a heterogeneous group of procedures, including abdominal, thoracic, orthopedic, vascular, urological, gynecological, and other operations. These procedures differ considerably in the intensity and duration of postoperative pain and in their baseline risk for pulmonary complications.

Postoperative pulmonary and respiratory complications remain important contributors to morbidity following major surgery. They may include atelectasis, pneumonia, hypoxemia, respiratory failure, the need for non-invasive ventilation, and unplanned reintubation. A prospective cohort study of major non-cardiac surgery demonstrated the importance of perioperative respiratory physiology in the development of postoperative pulmonary complications, emphasizing that respiratory complications are multifactorial rather than attributable to a single perioperative exposure.

Opioids remain effective analgesic medications and are widely used in the perioperative setting. However, their adverse effects include sedation, respiratory depression, nausea, vomiting, ileus, urinary retention, and impaired psychomotor function. The respiratory effects are particularly concerning because clinically significant opioid-induced respiratory depression may occur in patients receiving postoperative opioids, especially when additional risk factors are present.

Patients with obstructive sleep apnea, obesity, older age, pre-existing pulmonary disease, opioid-naïve status, renal dysfunction, concurrent sedative medication

use, and higher opioid doses may be particularly vulnerable to respiratory adverse effects.

At the same time, simply minimizing opioid administration without providing adequate alternative analgesia may not be appropriate. Severe pain can impair respiratory mechanics, particularly after thoracic and upper abdominal surgery, and may prevent effective coughing and pulmonary physiotherapy.

Therefore, the relationship between pain, opioid exposure, and respiratory complications is potentially bidirectional and clinically complex.

Modern postoperative analgesia increasingly emphasizes multimodal approaches that combine different analgesic classes and regional techniques to reduce opioid requirements. The PROSPECT collaboration specifically advocates procedure-specific analgesia based on evidence regarding pain relief, functional recovery, and adverse effects.

Recent recommendations also emphasize the role of regional and fascial-plane techniques in reducing postoperative opioid requirements for several major surgical categories. Updated 2026 American Society of Anesthesiologists guidance recommends fascial-plane blocks for selected open cardiothoracic, abdominal, retroperitoneal, pelvic, and breast procedures to reduce postoperative pain and opioid requirements. Continuous respiratory monitoring may also be relevant in patients receiving postoperative opioids. A systematic review and meta-analysis found that continuous pulse oximetry and capnography can facilitate the detection of postoperative respiratory depression and respiratory deterioration, although the clinical impact of monitoring strategies depends on implementation and patient population.

An important unresolved question is whether postoperative respiratory complications are more strongly related to pain severity, opioid exposure, or the interaction between these factors. A patient with severe pain may receive more opioids, creating a potential confounding relationship between pain and respiratory complications. Conversely, clinicians may reduce opioid administration in patients who develop respiratory compromise, producing reverse causation in observational datasets.

Prospective measurement of pain before subsequent opioid administration and respiratory outcomes can help clarify these temporal relationships.

The present study was designed to evaluate the association between acute postoperative pain, cumulative opioid exposure, and respiratory complications during the early postoperative period following major non-cardiac surgery.

Objectives

Primary objective

To determine the association between postoperative opioid exposure and respiratory complications within 72 hours following major non-cardiac surgery.

Secondary objectives

1. To determine the association between acute postoperative pain severity and respiratory complications.
2. To quantify the relationship between cumulative opioid exposure and respiratory complications.
3. To compare respiratory outcomes among patients receiving low, moderate, and high opioid doses.
4. To assess whether severe postoperative pain combined with high opioid exposure is associated with a greater risk of respiratory complications.

5. To identify independent clinical predictors of postoperative respiratory complications.

Materials and Methods

Study design

A prospective observational cohort study was designed.

Participants would be enrolled before major non-cardiac surgery and followed prospectively throughout the first 72 postoperative hours.

Study setting

The study would be conducted in the departments of Anesthesiology, Surgery, and Postoperative or High-Dependency Care of a tertiary-care hospital.

Study population

Adult patients undergoing major non-cardiac surgery under general anesthesia would be eligible.

Major surgery would be defined according to institutional classification based on the expected duration, physiological stress, tissue injury, and requirement for postoperative inpatient care.

Sample size

For this manuscript model, a hypothetical sample of 300 patients was used.

The actual sample size should be calculated using the expected incidence of postoperative respiratory complications and the anticipated effect of high opioid exposure on the primary outcome.

For example, if the expected respiratory complication rate is approximately 20% and the study aims to detect a clinically meaningful increase in risk among patients with higher opioid exposure, an appropriate sample size should be calculated with a significance level of 0.05, statistical power of at least 80%, and allowance for loss to follow-up or incomplete data.

Inclusion criteria

Patients would be included if they fulfilled all of the following criteria:

1. Age 18 years or older.
2. Elective or urgent major non-cardiac surgery.
3. General anesthesia used for the procedure.
4. Expected postoperative hospitalization of at least 48 hours.
5. Ability to communicate pain intensity using the NRS.
6. Written informed consent.

Exclusion criteria

Patients would be excluded if they had:

1. Cardiac surgery.
2. Emergency surgery requiring immediate life-saving intervention where baseline assessment was impossible.
3. Preoperative mechanical ventilation.
4. Preoperative severe respiratory failure.
5. Altered consciousness preventing reliable pain assessment.
6. Chronic opioid therapy exceeding the predefined institutional threshold.
7. Known opioid use disorder.
8. Severe cognitive impairment.
9. Refusal to participate.
10. Incomplete postoperative opioid records.

Patients receiving neuraxial or regional analgesia could be included, provided that the opioid contribution and technique were accurately recorded.

Baseline assessment

Before surgery, the following variables would be recorded: age, sex, BMI, smoking status, American Society of Anesthesiologists (ASA) physical status, diabetes mellitus, chronic kidney disease, chronic pulmonary disease, obstructive sleep apnea, preoperative oxygen saturation, baseline respiratory rate, preoperative opioid exposure, type of

surgery, planned surgical approach, and expected duration of surgery.

Surgical classification

For analysis, procedures would be categorized into the following major groups:

1. Major abdominal surgery.
2. Thoracic surgery.
3. Major orthopedic surgery.
4. Major gynecological surgery.
5. Major urological surgery.
6. Major vascular surgery.
7. Other major non-cardiac procedures.

Pain intensity would be assessed using an 11-point Numerical Rating Scale (NRS), defined as follows:

NRS score Pain severity

0	No pain
1–3	Mild pain
4–6	Moderate pain
7–10	Severe pain

Pain would be recorded at the following time points:

1. Postoperative recovery.
2. 6 hours.
3. 12 hours.
4. 24 hours.
5. 36 hours.
6. 48 hours.

The primary pain exposure would be the maximum NRS score during the first 24 postoperative hours.

For secondary analysis, the area-under-the-curve approach could be used to estimate overall pain burden during the first 48 hours.

Opioid exposure

Surgical duration and intraoperative blood loss would also be recorded.

Anesthetic variables

The following perioperative variables would be collected: type of general anesthesia, intraoperative opioid dose, intraoperative non-opioid analgesics, regional anesthesia or nerve block, neuromuscular blocking agents, reversal strategy, intraoperative hypotension, duration of anesthesia, duration of surgery, and extubation status.

Assessment of postoperative pain

All postoperative opioid doses would be recorded from medication administration records.

Different opioids would be converted to intravenous morphine milligram equivalents (MME) using an institutional or validated conversion framework.

The following opioid exposure measures would be calculated:

1. Intraoperative opioid exposure.
2. First 24-hour postoperative opioid exposure.
3. First 48-hour postoperative opioid exposure.
4. Cumulative 72-hour opioid exposure.

For the primary analysis, postoperative opioid exposure during the first 24 hours would be categorized as follows:

Opioid exposure category Dose

Low	Less than 25 MME
Moderate	25–49 MME
High	50 MME or greater

The continuous opioid dose in MME would also be analyzed to avoid information loss associated with categorization.

Definition of respiratory complications

The primary outcome would be the occurrence of one or more clinically significant respiratory complications within 72 hours.

These would include the following:

1. Clinically significant hypoxemia
Sustained oxygen saturation below the predefined institutional threshold despite appropriate supplemental oxygen or requiring escalation of oxygen therapy.
2. Opioid-related respiratory depression
Respiratory rate below 8 breaths per minute, significant sedation with hypoventilation, or

clinically significant hypercapnia temporally associated with opioid administration.

3. Atelectasis requiring intervention
Radiologically or clinically identified atelectasis requiring active treatment beyond routine postoperative care.

4. Pneumonia
Clinically diagnosed postoperative pneumonia based on appropriate clinical, radiological, and laboratory findings.

5. Non-invasive ventilation
Unplanned postoperative requirement for continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) because of respiratory deterioration.

6. Reintubation
Unplanned tracheal reintubation following initial postoperative extubation.

Respiratory monitoring

Routine postoperative monitoring would include respiratory rate, oxygen saturation, level of consciousness or sedation, and oxygen requirement.

Where clinically indicated or available, capnography would be used for patients considered at elevated risk.

Continuous pulse oximetry and capnography have been investigated as strategies for detecting postoperative respiratory depression and respiratory deterioration in patients receiving opioids.

Multimodal analgesia

The study would document the use of the following interventions:

1. Paracetamol or acetaminophen.
2. Non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors.
3. Regional nerve blocks.
4. Epidural analgesia.
5. Local wound infiltration.
6. Ketamine.
7. Dexmedetomidine.
8. Other opioid-sparing interventions.

The study would not mandate a particular analgesic protocol because it is observational.

This is important because current procedure-specific recommendations generally favor multimodal analgesia and increasingly reserve systemic opioids for rescue treatment when appropriate.

Statistical analysis

Data would be analyzed using SPSS version 26.0 or equivalent statistical software.

Continuous variables would be reported as mean $\pm$ standard deviation or median with

interquartile range, depending on distribution. Categorical variables would be presented as frequencies and percentages.

The chi-square test or Fisher's exact test would be used for categorical comparisons. The independent-samples t-test or Mann–Whitney U test would be used for continuous variables, as appropriate.

For the primary analysis, logistic regression would evaluate the association between opioid exposure and respiratory complications.

Potential confounders would include age, sex, BMI, smoking, ASA status, chronic pulmonary disease, obstructive sleep apnea, surgical category, surgery duration, intraoperative opioid exposure, regional analgesia, and baseline oxygen requirement. Adjusted odds ratios (aORs) with 95% confidence intervals would be reported.

An interaction term between severe pain and high opioid exposure would be considered to determine whether their combined effect differed from either exposure alone.

A two-sided p-value below 0.05 would be considered statistically significant.

Results

All results in this section are illustrative and hypothetical and must be replaced with actual study data before submission.

Baseline characteristics

A hypothetical total of 300 patients were included. The mean age was 56.2 ± 13.1 years, and 164 (54.7%) patients were male. The most common surgical category was major abdominal surgery.

Table 1. Baseline Characteristics of the Study Population

Variable	Overall (n = 300)
Age, years	56.2 ± 13.1
Male sex	164 (54.7%)
Female sex	136 (45.3%)
BMI, kg/m ²	28.1 ± 4.6
Current or former smoker	88 (29.3%)
ASA I	48 (16.0%)
ASA II	161 (53.7%)
ASA III	87 (29.0%)
ASA IV	4 (1.3%)
Chronic pulmonary disease	39 (13.0%)
Obstructive sleep apnea	27 (9.0%)
Diabetes mellitus	82 (27.3%)
Preoperative oxygen requirement	12 (4.0%)
Major abdominal surgery	128 (42.7%)
Thoracic surgery	34 (11.3%)
Major orthopedic surgery	55 (18.3%)
Gynecological surgery	27 (9.0%)
Urological surgery	25 (8.3%)
Vascular surgery	18 (6.0%)
Other major surgery	13 (4.3%)
Duration of surgery, minutes	174 ± 68

Illustrative data only.

Postoperative pain and opioid exposure

The median maximum pain score during the first 24 hours was reported as 6 (IQR 4–8). Patients with severe pain received greater cumulative opioid doses.

Table 2. Postoperative Pain and Opioid Exposure

Variable	Overall (n = 300)
Maximum NRS pain score, 0–10	6.1 ± 2.0
Mild pain, n (%)	48 (16.0%)
Moderate pain, n (%)	164 (54.7%)
Severe pain, n (%)	88 (29.3%)
24-hour opioid exposure, MME	36.8 ± 29.4
Less than 25 MME	103 (34.3%)
25–49 MME	119 (39.7%)
50 MME or greater	78 (26.0%)
Regional analgesia	94 (31.3%)
Regular paracetamol	279 (93.0%)
NSAID or COX-2 inhibitor	216 (72.0%)
Rescue opioid administration	246 (82.0%)

Illustrative data only.

Respiratory complications

In the hypothetical cohort, 72 patients (24.0%) developed at least one respiratory complication. The most common complication was clinically significant hypoxemia, followed by atelectasis requiring additional intervention.

Table 3. Postoperative Respiratory Complications Within 72 Hours

Respiratory outcome	n (%)
Any respiratory complication	72 (24.0%)
Clinically significant hypoxemia	51 (17.0%)
Opioid-related respiratory depression	24 (8.0%)
Atelectasis requiring intervention	31 (10.3%)
Postoperative pneumonia	17 (5.7%)
Unplanned non-invasive ventilation	11 (3.7%)
Unplanned reintubation	4 (1.3%)

Some patients experienced more than one complication.

Illustrative data only.

Relationship between opioid exposure and respiratory complications

Respiratory complications occurred more frequently among patients receiving at least 50 MME.

Table 4. Respiratory Complications According to 24-Hour Opioid Exposure

Opioid exposure	Respiratory complication	No complication	Total
Less than 25 MME	11 (10.7%)	92 (89.3%)	103
25–49 MME	20 (16.8%)	99 (83.2%)	119
50 MME or greater	41 (52.6%)	37 (47.4%)	78
Overall	72 (24.0%)	228 (76.0%)	300

Illustrative p-value below 0.001.

Relationship between pain severity and respiratory complications

Severe pain was also associated with a higher frequency of respiratory complications.

Table 5. Respiratory Complications According to Maximum Postoperative Pain Severity

Maximum NRS score Respiratory complication No complication Total

Mild (0–3)	6 (12.5%)	42 (87.5%)	48
Moderate (4–6)	31 (18.9%)	133 (81.1%)	164
Severe (7–10)	35 (39.8%)	53 (60.2%)	88
Overall	72 (24.0%)	228 (76.0%)	300

Illustrative p-value below 0.001.

Multivariable analysis

After adjustment for clinically relevant confounders, high opioid exposure remained independently associated with respiratory complications. Severe pain also demonstrated an independent association, although the magnitude was lower than that associated with high opioid exposure.

Table 6. Illustrative Multivariable Logistic Regression Analysis

Predictor	Adjusted OR 95% CI		p-value
Opioid exposure ≥50 MME	3.21	1.78–5.79	Below 0.001
Severe pain, NRS ≥7	1.86	1.05–3.30	0.033
Age ≥65 years	1.74	1.01–3.00	0.046
BMI ≥30 kg/m ²	1.48	0.84–2.61	0.172
Chronic pulmonary disease	2.41	1.19–4.87	0.015
Obstructive sleep apnea	2.63	1.18–5.84	0.018
ASA III–IV	1.91	1.10–3.31	0.021
Surgery duration >180 minutes	1.67	1.00–2.78	0.049
Regional analgesia	0.71	0.41–1.23	0.219

Illustrative regression model only.

Discussion

This prospective cohort model investigated the relationship between acute postoperative pain, opioid exposure, and respiratory complications following major non-cardiac surgery. The principal finding in the illustrative dataset was that patients receiving higher opioid doses had a substantially greater frequency of postoperative respiratory complications. Severe postoperative pain was also associated with respiratory complications, highlighting the complex relationship between pain, analgesic requirements, and respiratory outcomes.

Postoperative pain and respiratory function are closely interconnected. Severe pain can reduce inspiratory effort, inhibit coughing, restrict chest wall movement, and impair mobilization. These effects can contribute to atelectasis and secretion retention, particularly following thoracic and upper abdominal procedures.

At the same time, opioids can suppress respiratory drive and reduce the ventilatory response to hypercapnia and hypoxemia. Opioid-related sedation can further compromise airway protection. Thus, a patient with severe pain may simultaneously have an increased need for analgesia and an increased susceptibility to opioid-related respiratory adverse effects.

The present findings support the concept that opioid exposure should not be considered independently of pain severity. Simply identifying a high opioid dose without accounting for the severity of surgical pain could produce misleading conclusions because patients undergoing more painful procedures may naturally require greater analgesia.

The prospective design provides an important methodological advantage because pain was measured during the

postoperative period before subsequent respiratory outcomes were assessed. Nevertheless, the observational nature of the study means that residual confounding remains possible.

The relationship between opioid dose and respiratory complications is biologically plausible. Higher opioid exposure can produce greater sedation and respiratory depression, particularly in susceptible patients. A systematic review and meta-analysis by Khanna et al. highlighted the clinical importance of postoperative respiratory monitoring for the detection of opioid-induced respiratory depression and respiratory deterioration.

However, not every episode of postoperative hypoxemia in a patient receiving opioids should be classified as opioid-induced respiratory depression. Postoperative respiratory complications have multiple potential causes, including residual anesthetic effects, atelectasis, fluid overload, pneumonia, pulmonary edema, airway obstruction, diaphragmatic dysfunction, aspiration, and underlying pulmonary disease.

For this reason, the present study distinguishes opioid-related respiratory depression from the broader category of postoperative respiratory complications.

This distinction is clinically important and improves the conceptual clarity of the study. The finding that severe pain was associated with respiratory complications is also clinically plausible. Inadequately controlled pain can prevent deep breathing and coughing and reduce participation in respiratory physiotherapy. Thus, an opioid-sparing strategy should not become an opioid-avoidance strategy that leaves patients with severe, uncontrolled pain.

Modern perioperative analgesia therefore increasingly emphasizes multimodal

analgesia. PROSPECT recommendations focus on procedure-specific combinations of analgesics and regional techniques rather than reliance on systemic opioids alone.

The 2026 American Society of Anesthesiologists guideline similarly supports fascial-plane blocks for selected major surgical procedures because they can reduce postoperative pain and opioid requirements.

Regional analgesia may therefore represent an important strategy for reducing opioid exposure without sacrificing analgesic efficacy.

The thoracic surgery population deserves particular attention. Thoracic operations can produce substantial pain and respiratory compromise simultaneously. Updated 2026 PROSPECT recommendations for open thoracotomy recommend thoracic epidural analgesia or paravertebral blockade as first-line regional analgesic options, combined with basic systemic analgesia.

Similarly, current procedure-specific recommendations for other surgical categories increasingly emphasize paracetamol, NSAIDs or COX-2 inhibitors, local or regional techniques, and opioid rescue rather than routine high-dose systemic opioid therapy.

The present study also identified several clinical variables that may increase respiratory risk, including older age, chronic pulmonary disease, obstructive sleep apnea, higher ASA class, and prolonged surgery. These factors are consistent with the multifactorial nature of postoperative pulmonary complications.

A particularly important consideration is obstructive sleep apnea. Patients with OSA may have increased susceptibility to opioid-related respiratory events because opioids can worsen upper-airway collapsibility and alter ventilatory responses. Therefore,

postoperative opioid prescribing should be individualized in this population.

BMI and obesity also warrant consideration. Although BMI was not independently associated with respiratory complications in the illustrative model after adjustment, obesity can coexist with OSA, restrictive respiratory physiology, and other risk factors. The present findings also have implications for postoperative monitoring. Continuous pulse oximetry can detect oxygen desaturation, but supplemental oxygen may mask hypoventilation. Capnography may provide additional information regarding ventilation in selected high-risk patients. The evidence base supports consideration of enhanced respiratory monitoring, particularly in patients receiving opioids who have multiple risk factors.

An important strength of this study is the simultaneous assessment of pain, opioid exposure, and respiratory outcomes. Many postoperative studies focus on pain scores or opioid consumption separately. Studying the three variables together provides a more clinically relevant framework.

The study nevertheless has several limitations.

First, it is observational and cannot prove that opioid exposure directly caused respiratory complications.

Second, opioid dose is strongly influenced by procedure type, baseline pain, clinician practice, regional anesthesia, and patient factors. Although multivariable adjustment can reduce confounding, it cannot eliminate it completely.

Third, conversion of different opioids into MME is an approximation and does not perfectly represent pharmacodynamic equivalence between agents.

Fourth, postoperative respiratory complications are heterogeneous. Hypoxemia from atelectasis is

mechanistically different from opioid-induced hypoventilation or pneumonia.

Fifth, pain scoring is subjective and can be influenced by patient expectations, anxiety, communication, and analgesic timing.

Finally, the use of intermittent rather than continuous respiratory monitoring could underestimate transient respiratory depression.

Future studies should incorporate continuous capnography, standardized sedation scores, objective respiratory depression definitions, procedure-specific pain assessment, and detailed multimodal analgesic exposure.

Clinical implications

The findings support several clinically relevant principles:

1. Adequate pain control remains essential.
2. High opioid exposure should trigger increased attention to respiratory risk.
3. Opioid dose should be interpreted in relation to pain severity and surgical procedure.
4. Patients with OSA, pulmonary disease, older age, obesity, or prolonged surgery may require enhanced monitoring.
5. Multimodal analgesia can reduce reliance on systemic opioids.
6. Regional and fascial-plane analgesic techniques may be particularly useful after major painful procedures.
7. Respiratory complications should not automatically be attributed to opioids because postoperative pulmonary complications are multifactorial.

Strengths

The study has several methodological strengths. These include prospective collection of pain and opioid exposure data,

direct evaluation of the relationship between pain, opioids, and respiratory outcomes, standardized opioid conversion into MME, clinically relevant 72-hour postoperative follow-up, multivariable adjustment for important respiratory risk factors, and inclusion of both opioid-specific and broader respiratory outcomes.

The study may have practical applicability to multidisciplinary anesthesiology and surgical practice.

Limitations

The study has several limitations. The observational design limits causal inference. The heterogeneity of surgical procedures may influence the relationship between pain, opioid exposure, and respiratory complications. Potential confounding by indication for opioid administration cannot be completely excluded. MME conversion is an approximation, and respiratory complications have multiple etiologies.

Intermittent monitoring may miss transient respiratory events, while pain assessment is subjective. Single-center recruitment may limit generalizability. Chronic opioid users may also be underrepresented because of the exclusion criteria.

Conclusion

Acute postoperative pain and opioid exposure are closely interconnected determinants of early postoperative outcomes following major non-cardiac surgery. In the illustrative cohort, severe pain and higher opioid exposure were associated with increased respiratory complications, with high opioid exposure remaining independently associated with respiratory morbidity after adjustment for important patient and surgical factors.

The findings emphasize the importance of balancing effective analgesia with opioid-related safety. Multimodal and procedure-specific analgesic strategies, including

appropriate regional techniques, may reduce unnecessary opioid exposure while maintaining adequate pain control. High-risk patients should receive individualized respiratory monitoring and analgesic planning.

Large prospective multicenter studies incorporating continuous respiratory monitoring and standardized definitions of opioid-induced respiratory depression are needed to clarify the causal relationship between postoperative opioid exposure and respiratory morbidity.

Declarations

Ethical approval

The study protocol should be approved by the institutional ethics review committee before commencement of participant recruitment.

Informed consent

Written informed consent should be obtained from all participants before enrollment.

Conflict of interest

The authors should declare any actual or potential conflicts of interest.

Funding

The authors should disclose all sources of funding. If no external funding was received, this should be explicitly stated.

Data availability

The data availability statement should comply with institutional and journal requirements.

Author contributions

To be completed according to the actual contributions of each author.

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