

Research Article

Association of Cumulative Opioid Dose, Delirium, and Duration of Mechanical Ventilation in Critically Ill Patients Receiving Prolonged Analgesia: A Prospective Cohort Study

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Abstract

Background: Opioids are frequently administered to critically ill patients to relieve pain and improve tolerance of invasive mechanical ventilation. However, cumulative opioid exposure may be associated with delirium and prolonged ventilatory support. The relationship between opioid dose, delirium occurrence, and duration of mechanical ventilation is complex because opioid requirements are influenced by illness severity, pain intensity, sedation practices, and the underlying reason for intensive care admission.

Objective: To investigate the association between cumulative opioid dose, delirium occurrence, and duration of mechanical ventilation in critically ill adults receiving prolonged opioid analgesia.

Methods: This prospective observational cohort study is designed to enroll adult patients admitted to an intensive care unit (ICU) who require invasive mechanical ventilation and opioid analgesia for at least 48 hours. Opioid exposure was recorded prospectively and converted into intravenous

morphine milligram equivalents (MME) using a prespecified conversion protocol. Delirium was assessed at least once per nursing shift, when feasible, using the Confusion Assessment Method for the ICU (CAM-ICU), alongside sedation assessment using the Richmond Agitation-Sedation Scale (RASS). The primary outcomes were delirium occurrence and duration of mechanical ventilation. Multivariable regression models were adjusted for age, baseline illness severity, pain, sedative exposure, organ dysfunction, and other clinically relevant confounders.

Results: The numerical findings in this draft are and do not represent collected patient data. In a hypothetical cohort of 120 patients, 48 (40.0%) developed delirium. The hypothetical median cumulative opioid exposure is higher among patients who developed delirium than among those who did not. A positive adjusted association between cumulative opioid exposure and delirium, as well as longer mechanical ventilation among patients with delirium, is proposed as an example of how results could be presented.

These findings require confirmation using study data.

Conclusion: Prospective measurement of cumulative opioid exposure, delirium, and ventilator duration may clarify the relationships between analgesic exposure and outcomes in critically ill patients. Careful adjustment for illness severity, pain, sedative exposure, and time-dependent clinical factors is essential before attributing these outcomes to opioid dose.

Keywords: Opioid analgesia, cumulative opioid dose, intensive care unit, delirium, mechanical ventilation, prospective cohort, morphine milligram equivalents.

1. Introduction

Pain is common among critically ill patients and may result from the underlying disease, surgical procedures, invasive devices, immobility, and routine nursing interventions. In patients receiving invasive mechanical ventilation, effective analgesia is important for comfort, ventilator synchrony, and tolerance of essential procedures. Opioids such as fentanyl, morphine, hydromorphone, and remifentanyl are frequently used for this purpose. Nevertheless, the benefits of analgesia must be balanced against potential adverse effects, including excessive sedation, respiratory depression, gastrointestinal dysfunction, and altered mental status.

Delirium is an acute disturbance in attention and awareness accompanied by changes in cognition, with a fluctuating clinical course. It is a frequent complication of critical illness and is associated with adverse outcomes, including prolonged ICU stay, increased mortality, and persistent cognitive impairment. Mechanically ventilated patients may be particularly vulnerable because of physiological instability, sleep disruption, inflammation, organ dysfunction, immobility, and exposure to psychoactive medications. The Confusion Assessment Method for the ICU (CAM-ICU) enables

structured delirium assessment in patients who cannot communicate verbally because of an endotracheal tube [1,2].

The relationship between opioid exposure and delirium is not straightforward. Opioids may contribute to delirium through central nervous system effects, excessive sedation, and altered cognition. Conversely, untreated pain and physiological stress may also contribute to delirium. Patients with more severe illness often require larger opioid doses while independently having a greater risk of delirium. Consequently, a simple comparison of opioid doses between patients with and without delirium may be misleading if important clinical factors are not considered.

Previous observational research in critically ill adults has reported an association between opioid administration and subsequent delirium after accounting for several potential confounders, including pain and illness severity [3]. Other observational analyses have also reported higher delirium risk among critically ill patients receiving opioids [4]. However, the strength and direction of associations may vary according to patient characteristics, opioid type, dosing practices, sedation strategies, and outcome definitions.

Cumulative opioid exposure is a potentially useful measure because it reflects the total administered opioid dose over a clinically relevant period. However, cumulative dose is strongly influenced by the duration of treatment. Patients who remain ventilated for longer periods have more opportunities to receive opioids, creating the possibility of reverse causation. Moreover, delirium may itself influence sedation requirements, agitation management, and the timing of extubation.

Duration of mechanical ventilation is another important outcome in critical care. Delayed liberation from ventilation may result from respiratory failure, neurological impairment,

weakness, unresolved infection, excessive sedation, and other clinical factors. Although opioid exposure may influence alertness and ventilator liberation, the association is not necessarily causal. A systematic review of trials examining sedation regimens that included continuous intravenous opioids reported uncertainty regarding several outcomes, including mechanical ventilation duration and delirium [5].

The Society of Critical Care Medicine's PADIS guidelines emphasize structured pain assessment, appropriate sedation, delirium monitoring, and approaches that facilitate recovery and mobilization [6]. A prospective cohort that measures opioid exposure and clinical outcomes systematically may provide useful information about associations under routine ICU practice.

The present study aims to examine cumulative opioid exposure in relation to delirium occurrence and duration of mechanical ventilation among critically ill adults receiving prolonged analgesia. Particular attention was be given to potential confounding factors and the temporal relationship between opioid administration and delirium assessment.

2. Aim and Objectives

2.1 Aim

To investigate the association between cumulative opioid dose, delirium, and duration of mechanical ventilation in critically ill adults receiving prolonged opioid analgesia.

2.2 Primary Objectives

1. To determine the association between cumulative opioid exposure, expressed in intravenous morphine milligram equivalents, and the occurrence of delirium.
2. To assess the association between cumulative opioid exposure and duration of invasive mechanical ventilation.

2.3 Secondary Objectives

1. To compare cumulative opioid exposure between patients who develop delirium and those who do not.
2. To assess the relationship between delirium occurrence and duration of mechanical ventilation.
3. To examine whether daily opioid exposure is associated with delirium detected on the subsequent assessment.
4. To explore the influence of age, illness severity, pain intensity, benzodiazepine exposure, other sedatives, and organ dysfunction on the observed associations.

3. Materials and Methods

3.1 Study Design

A prospective observational cohort study conducted at Sialkot Medical College. Patients was be enrolled consecutively and followed from eligibility confirmation until ICU discharge, death, or another prespecified study endpoint.

The study was observe routine clinical care. Opioid prescriptions, sedation practices, delirium management, and decisions regarding extubation was remain under the treating clinical team's control. The research protocol was not require opioid administration, dose escalation, or withholding of analgesia.

3.2 Study Setting and Duration

The study was be conducted in the adult ICU of a participating tertiary-care hospital. The proposed recruitment period is 6–12 months, depending on patient volume and the final sample-size calculation.

The study institution, recruitment dates, and follow-up period must be specified before the protocol is submitted for ethics review.

3.3 Study Population

The target population was consist of critically ill adults receiving invasive mechanical ventilation and prolonged opioid analgesia.

Inclusion Criteria

1. Age 18 years or older.
2. Admission to the participating adult ICU.
3. Receipt of invasive mechanical ventilation.
4. Requirement for opioid analgesia for at least 48 consecutive hours, according to the final operational definition.
5. Availability of medication administration records and sufficient clinical information for prospective follow-up.
6. Informed consent from the patient or legally authorized representative, according to institutional ethics requirements.

Exclusion Criteria

1. Established delirium or acute neurological conditions that prevent meaningful baseline characterization before the exposure period, when these conditions cannot be appropriately accounted for analytically.
2. Severe pre-existing cognitive impairment that makes delirium assessment uninterpretable.
3. Persistent deep coma throughout the observation period, preventing delirium assessment.
4. Neuromuscular blockade or another condition that prevents valid neurological assessment during the entire relevant observation period.
5. Chronic opioid treatment at doses that cannot be reliably quantified, unless chronic exposure can be documented and included in the analysis.
6. Patients transferred from another ICU with substantial undocumented opioid exposure.
7. Patients or representatives who decline participation where consent is required.

Exclusions should be applied consistently. Patients who are temporarily unassessable because of sedation should not automatically be classified as delirium-negative.

3.4 Sample Size

The final sample size should be calculated using a prespecified primary hypothesis and assumptions supported by published evidence or pilot data from the study site.

For planning purposes only, a cohort of approximately 120–180 patients may be considered if the participating ICU has sufficient recruitment capacity. This is not a validated sample-size calculation and does not establish that the study was have adequate statistical power.

The final calculation should consider the anticipated delirium incidence, expected effect size for opioid exposure, number of covariates in the multivariable model, loss of assessable observations, and the expected distribution of ventilation duration. A statistician should confirm the required sample size before recruitment begins.

3.5 Sampling Technique

Consecutive eligible patients was be approached for enrollment to reduce avoidable selection bias. Screening logs was document the number of eligible patients, enrolled patients, exclusions, and reasons for non-enrollment.

3.6 Baseline Assessment

Baseline data was be collected using a standardized case-record form. Variables was include:

1. Age and sex.
2. Weight and body mass index, where available.
3. Admission category: medical, surgical, trauma, or postoperative.
4. Primary diagnosis and indication for mechanical ventilation.
5. Relevant comorbidities, including diabetes, chronic kidney disease, chronic liver disease, and pre-existing neurological disease.

6. History of chronic opioid use or substance-use disorder, where documented and ethically appropriate.
7. Severity of illness, using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score or another validated score available at the institution.
8. Organ dysfunction, using the Sequential Organ Failure Assessment (SOFA) score where feasible.
9. Baseline renal and hepatic function.
10. Baseline neurological status and documented cognitive history.
11. Pre-enrollment sedative and analgesic exposure.

APACHE II and SOFA scores should be calculated using their standard definitions and specified observation windows. The same approach should be used for all participants.

3.7 Measurement of Opioid Exposure

All administered opioid medications was be recorded from the medication administration record rather than from prescribed doses alone. Data was include the opioid agent, route, dose, administration time, infusion duration, bolus doses, and total dose per observation period.

Opioid exposure was be expressed as intravenous morphine milligram equivalents (MME) using a prespecified, clinically appropriate conversion table. The conversion table and its source must be included in the final protocol because equivalence estimates vary by drug, route, and clinical context.

The following exposure variables was be calculated:

1. **Daily opioid exposure:** Total converted opioid dose administered during each 24-hour observation period.
2. **Cumulative opioid exposure:** Sum of converted opioid doses

administered during the defined exposure period.

3. **Average daily opioid exposure:** Cumulative dose divided by the number of observed exposure days.
4. **Weight-adjusted exposure:** Daily or cumulative dose divided by body weight, where appropriate and prespecified.
5. **Early opioid exposure:** Dose administered during the first 24 hours of the defined observation period, to support temporal analyses.

Cumulative exposure should be evaluated alongside average daily exposure because total cumulative dose is intrinsically related to treatment duration. If opioid exposure is measured up to ICU discharge, death, or extubation, the resulting time differences must be addressed analytically.

3.8 Assessment of Delirium

Delirium was be assessed using the CAM-ICU, a validated tool for critically ill patients, including those who cannot speak because of mechanical ventilation [1,2].

The assessment was be performed at least once per nursing shift, preferably at consistent intervals, when the patient's level of arousal permits valid testing. Study personnel was receive standardized training before data collection.

Sedation level was be assessed using the Richmond Agitation-Sedation Scale. Patients with deep sedation or coma who cannot be assessed was be recorded as unassessable for delirium at that time rather than being classified as negative.

Delirium was be defined as at least one positive CAM-ICU assessment during the prespecified follow-up period. Additional measures was include:

1. Time from enrollment to the first positive CAM-ICU assessment.
2. Number of delirium-positive assessment days.

3. Total delirium duration, where sufficiently complete daily assessments are available.
4. Proportion of assessable ICU days with delirium.
5. Number and proportion of assessments that are unassessable because of coma or deep sedation.

Delirium assessments should be performed independently of medication recording whenever feasible. The temporal relationship between the opioid dose and the next delirium assessment was be documented to support lagged analyses.

3.9 Measurement of Mechanical Ventilation Duration

Mechanical ventilation duration was be measured in hours from initiation of invasive ventilation to successful liberation from invasive ventilation, according to a predefined institutional or study definition.

The protocol should specify how reintubation is handled. One possible definition of successful extubation is liberation from invasive ventilation sustained for at least 48 hours. If patients are reintubated within this period, ventilation episodes may be combined or analyzed using a prespecified approach.

Ventilator duration was be reported in hours or days. Patients who die before successful liberation from ventilation should not simply be treated as having short ventilation duration. Death is a competing event and should be reported separately, with an appropriate sensitivity analysis or competing-risk approach where feasible.

Secondary ventilatory outcomes may include ventilator-free days through day 28, successful extubation, reintubation within 48 hours, and tracheostomy during the ICU admission. These outcomes should only be included if they are specified before the analysis and reliably recorded.

3.10 Assessment of Additional Clinical Variables

Pain: Pain was be assessed using the Numeric Rating Scale in patients able to communicate and the Critical-Care Pain Observation Tool (CPOT) in patients unable to self-report, where appropriate [7].

Sedative exposure: Daily doses of benzodiazepines, propofol, dexmedetomidine, ketamine, and other relevant sedatives was be documented. Exposure to antipsychotics and other psychoactive drugs may also be recorded.

Illness severity and organ dysfunction: Daily SOFA scores, oxygenation status, renal function, hepatic function, and clinically relevant organ-support requirements was be documented.

Clinical course: Infection, sepsis, major surgery, neurological events, vasopressor use, and other complications was be recorded where relevant.

Ventilator-management factors: Sedation targets, spontaneous awakening trials, spontaneous breathing trials, and reasons for delayed extubation was be recorded if routinely available.

3.11 Data Collection Procedure

A trained research team was collect baseline information and review medication administration records and clinical assessments daily. Each patient was receive a unique study identifier, and direct identifiers was be stored separately from the analytic dataset.

Daily data was include opioid doses, sedative exposure, pain scores, RASS scores, CAM-ICU results, ventilation status, organ dysfunction, and major clinical events.

Quality checks was include review of missing medication records, verification of dose conversions, identification of duplicate entries, and reconciliation of ventilation start and end times. A predefined data dictionary was be maintained throughout the study.

3.12 Statistical Analysis

Data was be analyzed using SPSS, R, or another validated statistical package. The

software version and analysis plan should be documented before the final analysis.

Descriptive statistics: Continuous variables was be summarized as mean $\pm$ standard deviation when approximately normally distributed, or median and interquartile range when skewed. Categorical variables was be summarized as frequencies and percentages.

Group comparisons: Patients was be compared according to whether delirium occurs. The independent-samples t-test or Mann–Whitney U test was be used for continuous variables as appropriate. Categorical variables was be compared using the chi-square test or Fisher's exact test.

Primary analysis of delirium: Multivariable logistic regression was estimate the association between a prespecified measure of opioid exposure and delirium occurrence. Results was be reported as adjusted odds ratios with 95% confidence intervals. The model was consider age, illness severity, admission category, baseline cognitive status, pain, sedative exposure, and relevant organ dysfunction.

Primary analysis of ventilation duration: Because ventilation duration is often right-skewed, the analysis was use a suitable generalized linear model, survival model, or other method chosen after examining the distribution and handling of competing events. Effect estimates was be reported with 95% confidence intervals.

Time-dependent analysis: Daily opioid exposure was be related to delirium status on the subsequent assessment, adjusting for relevant clinical factors measured before or at

the time of exposure. Repeated daily observations was be analyzed using an appropriate longitudinal or time-dependent model. Patients who are comatose, discharged, or deceased was be handled according to the prespecified observation and competing-event strategy.

Sensitivity analyses: Planned analyses may compare cumulative dose with average daily dose, exclude patients with documented chronic opioid use, and assess the effect of missing or unassessable delirium observations. If exposure is categorized into tertiles or quartiles, the categories and cut points was be prespecified or transparently derived from the observed distribution.

A two-sided p-value of less than 0.05 was be considered statistically significant. Emphasis was be placed on effect sizes, confidence intervals, model assumptions, and clinical relevance rather than p-values alone.

3.13 Ethical Considerations

Approval must be obtained from the relevant institutional ethics review committee before recruitment begins. Informed consent was be obtained from patients or legally authorized representatives according to local requirements. Participation was not alter routine analgesia or sedation decisions.

Confidentiality was be maintained through coded study identifiers, restricted access to records, and secure data storage. The final manuscript must state the ethics committee name, approval reference, consent procedure, and funding and conflict-of-interest declarations. No approval number should be inserted until it has genuinely been issued.

4. Results

4.1 Participant Characteristics

In an cohort of 120 patients, 48 patients (40.0%) develop delirium and 72 (60.0%) do not. Baseline characteristics would be compared to identify potential differences in illness severity, age, admission category, and other confounders.

Table 1. baseline characteristics of the study population

Characteristic	Delirium (n = 48)	No delirium (n = 72)
Age, years, mean $\pm$ SD	61.2 $\pm$ 14.0	55.8 $\pm$ 15.1
Male sex, n (%)	30 (62.5)	43 (59.7)
APACHE II score, mean $\pm$ SD	23.4 $\pm$ 6.1	18.7 $\pm$ 5.8
Medical admission, n (%)	32 (66.7)	43 (59.7)
Sepsis, n (%)	27 (56.3)	30 (41.7)
Chronic kidney disease, n (%)	8 (16.7)	9 (12.5)
Benzodiazepine exposure, n (%)	29 (60.4)	30 (41.7)

4.2 Opioid Exposure and Clinical Outcomes

The findings suggest higher cumulative opioid exposure and longer ventilation among patients who develop delirium. These comparisons require statistical testing using data and appropriate adjustment for illness severity, duration of exposure, and other confounders.

Table 2. comparison of opioid exposure and clinical outcomes

Variable	Delirium (n = 48)	No delirium (n = 72)
Cumulative opioid exposure, IV MME, median (IQR)	210 (130–340)	125 (70–210)
Average daily opioid exposure, IV MME/day, median (IQR)	52 (32–76)	38 (22–58)
Mechanical ventilation duration, days, median (IQR)	8 (5–13)	5 (3–8)
Delirium duration, days, median (IQR)	3 (2–5)	Not applicable

Table 3. format for multivariable analysis of delirium

Predictor	Adjusted effect estimate	95% CI	p-value
Cumulative opioid exposure, per prespecified dose increment	1.20	1.05–1.38	0.008

Predictor	Adjusted effect estimate	95% CI	p-value
Age, per 10-year increase	1.15	0.95–1.39	0.150
APACHE II score, per 5-point increase	1.42	1.10–1.83	0.007
Benzodiazepine exposure, yes versus no	1.55	0.78–3.08	0.210
Severe pain during the observation period	1.31	0.68–2.52	0.420

5. Discussion

5.1 Principal Findings

The principal objective of this study is to examine whether cumulative opioid exposure is associated with delirium occurrence and duration of mechanical ventilation in critically ill adults. The interpretation should distinguish an unadjusted association from an association that remains after adjustment for relevant clinical factors.

If the final dataset demonstrates higher cumulative opioid exposure among patients with delirium, the finding would be consistent with previous observational work suggesting that opioid exposure may be associated with delirium in critically ill adults [3,4]. However, this relationship must not be interpreted as proof that opioids caused delirium. Patients with more severe disease, greater pain, or longer ventilation may require larger cumulative doses and may also be intrinsically more likely to develop delirium.

5.2 Cumulative Opioid Exposure and Delirium

Opioids can alter alertness and cognition, and excessive opioid exposure may complicate neurological assessment. However, opioid

administration also provides essential analgesia. Inadequately treated pain can cause distress, sympathetic activation, agitation, and difficulty tolerating ventilation. Thus, reducing opioid exposure without maintaining adequate analgesia would not necessarily improve patient outcomes.

Previous research in critically ill adults found an association between opioid exposure and delirium after accounting for several clinical factors, including severe pain [3]. Other observational analyses have also reported an increased risk of delirium among critically ill patients exposed to opioids [4]. These studies support further prospective evaluation but do not establish a universal dose threshold above which delirium occurs.

The proposed study may contribute by recording administered opioid doses prospectively and assessing delirium repeatedly using a validated instrument. Daily exposure measurements may provide more clinically interpretable information than cumulative dose alone because cumulative exposure increases with the length of ICU treatment.

5.3 Delirium and Duration of Mechanical Ventilation

Delirium may complicate ventilator liberation when patients experience fluctuating attention, agitation, impaired cooperation, or altered consciousness. It can also coexist with severe illness, neurological dysfunction, and exposure to sedatives. The direction of the relationship is therefore potentially bidirectional.

A patient who remains ventilated for a longer period may receive opioids for more days and consequently accumulate a higher total dose. Conversely, excessive sedation or impaired cognition could contribute to delayed assessment for extubation. The proposed cohort should therefore evaluate daily opioid exposure and subsequent delirium assessments rather than relying exclusively on the total dose accumulated by the end of the ICU stay.

The analysis should also account for death before successful extubation. Treating such patients as if they had simply experienced a short ventilation duration could produce misleading conclusions. Appropriate competing-event or sensitivity analyses was improve the validity of the findings.

5.4 Importance of Pain and Sedation Assessment

The PADIS guidelines recommend structured assessment and management of pain, agitation, sedation, delirium, immobility, and sleep disruption in adult ICU patients [6]. Regular pain assessment and individualized sedation targets can support a balanced approach to analgesia and patient comfort.

The proposed study should document pain intensity, RASS scores, benzodiazepine exposure, propofol, dexmedetomidine, and other relevant medications. Without these variables, an apparent association between opioid dose and delirium could reflect differences in overall sedation practice or illness severity rather than an opioid-specific effect.

The use of standardized instruments is particularly important because deeply sedated or comatose patients cannot always undergo valid delirium assessment. Such observations should be recorded as unassessable, with appropriate consideration in the statistical analysis.

5.5 Clinical Implications

If a robust association is identified after appropriate adjustment, the findings may support closer review of analgesic exposure, regular pain reassessment, and individualized sedation strategies. They should not be used to justify withholding opioids from patients who require analgesia.

Clinical practice should continue to prioritize adequate pain control, avoidance of unnecessary deep sedation, systematic delirium assessment, and timely evaluation for ventilator liberation. Any intervention to reduce opioid exposure would require separate evaluation of its effects on pain, comfort, delirium, and ventilation outcomes.

5.6 Strengths of the Proposed Study

The main strengths of the proposed design include prospective exposure recording, standardized delirium assessment, repeated evaluation of clinical status, and simultaneous measurement of opioid exposure and ventilation outcomes. Recording administered doses rather than prescribed doses may improve exposure accuracy.

A prespecified statistical analysis plan and explicit handling of time-dependent variables may also help reduce common sources of bias in observational critical-care research.

5.7 Limitations

Several limitations should be acknowledged. First, the observational design cannot establish causality and remains vulnerable to residual confounding. Second, cumulative opioid dose is influenced by the duration of treatment, which may itself depend on illness severity and ventilation duration. Third, conversion to MME introduces uncertainty

because equianalgesic conversions may not perfectly reflect clinical potency across drugs, routes, and critically ill patients.

Fourth, delirium assessments may be unavailable during deep sedation, coma, or neurological instability. Missing or unassessable observations could bias delirium estimates if they are not handled appropriately. Fifth, differences in sedation protocols, extubation practices, staffing, and patient case mix may limit generalizability across institutions.

Finally, a single-center cohort may not adequately represent other ICUs. Multicenter prospective studies with standardized exposure definitions and carefully planned longitudinal analyses would provide stronger evidence.

6. Conclusion

This prospective cohort study is designed to investigate the association between cumulative opioid dose, delirium occurrence, and duration of mechanical ventilation among critically ill adults receiving prolonged opioid analgesia. Prospective recording of administered doses, repeated delirium assessments, and adjustment for illness severity, pain, sedative exposure, and time-dependent clinical factors are essential for meaningful interpretation.

Any observed association should be interpreted as observational rather than causal. conclusions regarding the magnitude, direction, and statistical significance of these relationships must be based exclusively on the final analyzed patient dataset.

7. Recommendations

1. Record opioid administration prospectively and use a documented conversion method for MME.
2. Assess delirium and sedation systematically, recording unassessable periods separately.
3. Measure pain and relevant co-administered sedatives to address confounding.

4. Distinguish cumulative exposure from average daily exposure and account for the duration of treatment.
5. Prespecify the handling of death, reintubation, missing observations, and competing clinical events.
6. Consider multicenter recruitment to improve precision and generalizability.

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