Survey of Opioid-Induced Respiratory Depression in Critically Ill Patients Without Mechanical Ventilation and Construction of a Risk Nomogram

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Abstract

Objectives

To investigate the current status of opioid-induced respiratory depression (OIRD) and potential risk factors in critically ill patients without mechanical ventilation in the intensive care unit (ICU) and to construct a risk nomogram to predict OIRD.

Methods

A total of 103 patients without (or who were weaned from) mechanical ventilation who had stayed for more than 24 h in the ICU between June 1, 2021 and September 31, 2021, were included. Patient data, including respiratory depression events, were recorded. The least absolute shrinkage and selection operator regression model were used to select features that were then used to construct a prediction model by multivariate logistic regression analysis. A nomogram was established for the risk of respiratory depression events in patients without mechanical ventilation. The discriminatory performance and calibration of the nomogram were assessed with Harrell's concordance index and a calibration plot, respectively, and a bootstrap procedure was used for internal validation.

Results

Respiratory depression was diagnosed in 49/103 (47.6%) patients. Factors included in the nomogram were cardiopulmonary disease (odds ratio [OR]=5.569, 95% confidence interval [CI]=0.751–118.083), respiratory disease (OR=32.833, 95% CI=4.189–725.164), sepsis (OR=6.898, 95% CI=1.756–33.000), duration of mechanical ventilation (OR=3.019, 95% CI=0.862–11.322), lack of mechanical ventilation (OR=20.757, 95% CI=2.409–502.222), and oxygenation index (OR=7.350, 95% CI=2.483–24.286). The nomogram showed good performance for predicting respiratory depression events in critically ill patients without mechanical ventilation.

Conclusion

The nomogram can be used to identify ICU patients without mechanical ventilation who are at risk of opioid-induced respiratory depression and may therefore benefit from early intervention.

Introduction

Moderate-to-severe acute or chronic pain is experienced by 50–77% of patients in the intensive care unit (ICU) [1–3]. Severe pain is associated with changes in heart rate and blood pressure, dyspnea, respiratory distress, enhanced catabolism, and immune dysfunction and has adverse neuropsychologic effects such as anxiety, depression, and impaired sleep that result in poor outcomes for patients [4, 5]. Intravenous

opioids are used as first-line therapy for non-neuropathic pain in critically ill patients, including those without mechanical ventilation; these patients may have multiple-organ dysfunction and abnormal drug metabolism, placing them at higher risk of respiratory depression and death from opioids [6]. Opioid-related adverse events can lead to longer hospital stays, increased hospitalization costs, readmission to hospital, and increased mortality [7]. However, most research on opioid-induced respiratory depression (OIRD) has focused on postoperative patients [8] and little is known about the incidence in critically ill patients without mechanical ventilation.

In this study, we try to investigate the possible risk factors for respiratory depression in patients in the ICU without mechanical ventilation (include discontinuing MV) receiving opioid analgesia. Moreover, we constructed a risk nomogram to identify patients at risk for OIRD so that timely and appropriate interventions can be implemented.

Materials And Methods

Study design and patient selection

Postoperative patients without mechanical ventilation (include discontinuing MV) who were admitted to the ICU of Nanfang Hospital of Southern Medical University, Guangzhou, China., between June 1, 2021, and September 31, 2021, were enrolled. Inclusion criteria were age >18 years and patients while received opioids for analgesia treatment for >24 h. The following opioids were used in the ICU: hydrochloric acid, remifentanyl, fentanyl citrate, sufentanyl citrate, morphine sulfate, hydromorphone hydrochloride, and buprenorphine tartrate. Morphine was permitted for explosive pain relief and combination with nonopioid analgesics was allowed. Exclusion criteria were patients with severe intracranial or spinal neurologic diseases or coma caused by vascularity, infection, intracranial expansion, or injury; history of opioid addiction; patients with missing data; and patients who did not provide informed consent. The study design was approved by the appropriate ethics committee of Nanfang Hospital, Southern Medical University. We interviewed the patient or the patient's family member via phone to obtain consent, and all patients informed consent for study participation. This study was performed in accordance with the ethical standards of the Helsinki Declaration.

Data collection and definitions

Data were collected from the electronic medical record database of Nanfang Hospital, Southern Medical University, Guangzhou, China. The data included patient identification number, name, age, height, weight, body mass index (BMI), chronic underlying diseases, types of surgery, kidney function, liver function, blood gas analysis, comorbidities, Acute Physiologic Assessment and Chronic Health Evaluation II score, heart rate, respiratory rate, duration of mechanical ventilation (the duration of MV for patients who have not received MV is 0), the dosage of sedatives and analgesics, and the occurrence of respiratory depression.

Management of analgesia and sedation was based on the 2018 Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) guidelines [9] and Guidelines of Sedation and Analgesia in ICU of Chinese Adults (2018) [10]. Analgesia was determined based on a Numerical Rating Scale score of <4 points for patients who were conscious and Critical-Care Pain Observation Tool score of <3 points for those who were unable to express themselves.

The loading and maintenance dosages of analgesics were as follows: fentanyl citrate, 0.35–0.5 and 0.7–10 µg/(kg·h), respectively; sufentanyl citrate, 0.2–0.5 and 0.2–0.3 µg/(kg·h), respectively; remifentanyl hydrochloride, 0.5–1.0 (intravenous, >1 min) and 0.02–0.15 µg/(kg·min), respectively; morphine sulfate, is 2–4 and 2–30 mg/h, respectively; hydromorphone hydrochloride, 0.5–2 and 0.5–3 mg/h, respectively; and butorphanol tartrate, 0.5–1 and 0.16–0.24 mg/h, respectively. During analgesic administration, patients were assessed every 2 h, and the dosage was adjusted according to the patient's liver and kidney function until the analgesic effect was satisfactory. Morphine and nonsteroidal analgesic and anti-inflammatory drugs were used to relieve breakthrough pain.

With adequate analgesia, the depth of sedation was determined based on physiologic parameters. A target-guided sedation strategy was implemented using the Sedation–Agitation Scale (SAS). Light sedation was defined as a SAS score of 3–4 points. Propofol, dexmedetomidine, and midazolam were used for sedation. The depth of sedation was assessed every 2 h and titrated in order to achieve a satisfactory effect. If the SAS score was <2 points, the drug dose was gradually reduced or sedation was stopped.

Patients without mechanical ventilation were defined as those who were admitted to the ICU but were not given or were weaned from mechanical ventilation (ie, successfully extubated). These patients received no oxygen therapy (no use of nasal catheters, masks, or non-invasive ventilators and no high-flow nasal cannula oxygen therapy). Correspondingly, if a patient is weaned after 28 hours of mechanical ventilation, it is recorded as 28h, and if another patient has never been mechanically ventilated, it is recorded as 0h.

Opioids differ in their potency; therefore, when the opioid was switched, the dose was converted to an equivalent amount of intravenous morphine sulfate (10 mg morphine equivalent dose [MED10]—ie, potency equivalent to 10 mg of morphine). For intravenous opioid analgesics, the MED10 is as follows [11–14]: 10 mg morphine ≈ 1.5 mg hydromorphone ≈ 2 mg butorphanol ≈ 0.1 mg fentanyl ≈ 0.1 mg remifentanyl ≈ 0.01 mg sufentanyl.

Respiratory depressionA respiratory depression event was defined as the occurrence of 1 or more of the following changes (See Supplement Material 1) [15]: decreased oxygen saturation and/or hypercapnia caused by hypoventilation; decreased respiratory rate; and apnea and/or asphyxia.

Endpoints

Occurrence of respiratory depression was the primary endpoint. Risk factors causing respiratory depression were the secondary outcomes.

Statistical analyses

Qualitative variables are expressed as frequencies and percentages. For quantitative variables, the Kolmogorov–Smirnov test was used to distinguish whether the data conformed to a normal distribution. Normally distributed continuous variables are expressed as mean $\pm$ standard deviation, while non-normally distributed continuous variables are expressed as median (interquartile range). Categorical variables are expressed as a number and percentage.

Sample size evaluation was performed based on events per variable. Potential prognostic variables were identified by least absolute shrinkage and selection operator (LASSO) regression, and selected variables were further analyzed in a multivariate logistic regression model. Variables with prognostic significance were used to construct a respiratory depression prediction model and incorporated into a nomogram. Harrell's concordance index (C-index) and calibration curve were used to assess the discriminatory performance and calibration of the model, respectively.

All statistical analyses were performed using R v3.6.2 (<https://www.r-project.org/>) and SPSS v26.0 (SPSS Inc, Chicago, IL, USA). A 2-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

All patients admitted to the ICU of our hospital between June 1, 2021 and September 31, 2021 were screened and 103 patients were ultimately included in the study. A total of 49 patients (47.6%) were considered to have respiratory depression events (Fig. 1). The demographic and clinical characteristics of the patients are shown in Table 1.

Table 1
Demographic and clinical characteristics of ICU patients without mechanical ventilation, and with or without respiratory depression

	With respiratory depression (n=49)	Without respiratory depression (n=54)	Total (n=103)
General characteristic			
Age, years			
<35	7 (14)	12 (22)	19 (18)
≥35 to <50	6 (12)	6 (11)	12 (11)
≥50 to <65	14 (29)	13 (24)	27 (26)
≥65 to <80	19 (39)	14 (26)	33 (32)
≥80	3 (6)	9 (17)	12 (12)
Sex			
Male	32 (65)	36 (67)	68 (66)
Female	17 (35)	18 (33)	35 (34)
BMI, kg/m ²			
<18.5	6 (12)	8 (15)	14 (14)
≥18.5 to ≤ 24	30 (61)	33 (61)	63 (61)
>24	13 (27)	13 (24%)	26 (25)
ALT (U/l)	17 [10, 36]	17 [10, 31]	17 [10, 32]
AST (U/l)	24 [13, 45]	22 [16, 33]	23 [16, 36]
SCr (μmol/l)	78 [60, 98]	71 [60, 109]	76 [60, 102]
Hypertension	18 (37)	22 (41)	40 (39)
Diabetes	4 (8)	4 (7)	8 (8)
Chronic respiratory disease	26 (53)	23 (43)	49 (48)
Severe liver dysfunction	3 (6)	4 (7)	7 (7)
Chronic kidney disease	3 (6)	9 (17)	12 (12)
ICU assessment and surgery			
APACHE-II score	13 [11, 18]	14 [10, 17]	13 [10, 17]
Sepsis	21 (43)	4 (7)	25 (24)

	With respiratory depression (n=49)	Without respiratory depression (n=54)	Total (n=103)
Bleeding	5 (10)	10 (18)	15 (15)
Severe infection	12 (24)	7 (13)	19 (18)
General anesthesia	34 (69)	36 (67)	70 (68)
History of chest and abdomen surgery	8 (16)	7 (13)	15 (15)
Open surgery	28 (5)	39 (72)	67 (65)
Emergency surgery	13 (27)	15 (28)	28 (27)
Duration of surgery	3.00 [1.00, 5.10]	4.16 [2.70, 6.29]	3.80 [1.92, 6.25]
Types of surgery*			
Cardiopulmonary	19 (39)	5 (9)	24 (23)
Abdominal	27 (55)	34 (63)	61 (59)
Orthopedic and trauma	3 (6)	15 (28)	18 (17)
Sedation and analgesia			
Cumulative opioid dosage during surgery, MED10	104.50 [0.00, 207.50]	203.38 [102.25, 305.62]	203.00 [2.62, 302.25]
Opioid dosage in PCA, MED10	0.00 [0.00, 22.50]	7.50 [0.00, 49.38]	0.00 [0.00, 43.76]
Cumulative opioid dosage during ICU, MED10	57.5 [28.6, 98.2]	45.3 [29.6, 74.2]	47.5 [29.6, 86.7]
>50, MED10	30 (61) [#]	21 (39)	51 (50)
Total opioid dosage, MED10	199.50 [64.33, 344.02]	250.42 [142.57, 363.17]	237.83 [93.70, 361.44]
Type of opioid used in ICU			
Fentanyl	17 (35)	13 (24)	30 (29)
Fentanyl–butorphanol	10 (20)	19 (35)	29 (28)
Fentanyl–hydromorphone	9 (18)	14 (26)	29 (22)
Other	13 (27)	8 (15)	21 (20)
Duration of analgesia treatment in ICU, h	76 [52, 156]	70 [43, 122]	75 [49, 125]

	With respiratory depression (n=49)	Without respiratory depression (n=54)	Total (n=103)
Opioid equivalent per unit time in ICU, MED10 per h	0.6 [0.5, 1.0]	0.7 [0.4, 1.0]	0.6 [0.5, 1.0]
Type of sedative drug used in ICU			
None	10 (20)	7 (13)	17 (17)
Propofol	32 (66)	36 (67)	68 (66)
Midazolam	1 (2)	4 (7)	5 (5)
Dexmedetomidine	6 (12)	7 (13)	13 (13)
Duration of sedation in ICU, h	31 [12, 72]	19 [13, 42]	23 [13, 56]
Oxygen treatment			
Duration of mechanical ventilation, days			
0 [#]	10 (20)	4 (7)	14 (14)
0 to ≤1	8 (16)	31 (58)	39 (38)
>1	31 (64)	19 (35)	50 (48)
RR, /min			
≥12 to ≤20	44 (90)	46 (85)	90 (87)
>20	5 (10)	8 (15)	13 (13)
HR, bpm			
<60	4 (8)	8 (15)	12 (12)
≥60 to ≤100	31 (63)	36 (67)	67 (65)
>100	14 (29)	10 (18)	24 (23)
SpO ₂ , %			
≤ 90	6 (12)	0 (0)	6 (6)
91 to 95	19 (39)	11 (20)	30 (29)
≥96	24 (49)	43 (80)	67 (65)
PCO ₂ , mmHg			
<35	16 (33)	17 (32)	33 (32)

	With respiratory depression (n=49)	Without respiratory depression (n=54)	Total (n=103)
≥35 to ≤45	30 (61)	32 (59)	62 (60)
>45	3 (6)	5 (9)	8 (8)
PaO ₂ /FiO ₂ , mmHg			
>300	17 (35)	43 (80)	60 (58)
≤300	32 (65)	11 (20)	43 (42)
Data conforming to a skewed distribution are expressed as the median [interquartile range], and count data are expressed as n (%).			
*Surgery type was divided into 3 groups: cardiopulmonary (including cardiovascular, chest/esophagus, ear, nose, throat, oral cavity), abdominal (including digestive tract, liver/gallbladder, urinary, and obstetric), and orthopedic/trauma.			
# <i>P</i> = 0.024 vs patients without respiratory depression. The duration of MV for patients who have not received MV is 0.			
Abbreviations: ALT, alanine aminotransferase; APACHE-II, Acute Physiology and Chronic Health Evaluation II, AST, aspartate aminotransferase; BMI, body mass index; HR, heart rate; ICU, intensive care unit; MED10, 10 mg morphine equivalent dose; PCA, patient-controlled analgesia; PCO ₂ , partial pressure of CO ₂ ; RR: respiratory rate; SCr, serum creatinine.			

Risk factors for respiratory depression

A total of 36 variables that were considered as potential predictors of respiratory depression were identified with the LASSO regression model. Disease type, sepsis, duration of mechanical ventilation, and PaO₂/FiO₂ were associated with respiratory depression when the optimal λ value was 0.0817 (Fig. 2).

According to the results of the logistic regression analysis, we selected 4 significant factors (Table 2) as input variables of a nomogram for respiratory depression events in ICU patients without mechanical ventilation while receiving opioids for analgesia (Fig. 3). The output variables were the corresponding scale score of the input variables, total points, and predicted probability of respiratory depression in the patients.

Table 2

Risk factors for respiratory depression in critically ill patients without mechanical ventilation receiving opioids for analgesia

Intercept and variable	Prediction model		
	$\beta^{\dagger}$	Odds ratio (95% confidence interval)	P value
Intercept	-4.2204	0.015 (0.0007–0.106)	0.0005
Disease category			
Abdominal surgery [‡] vs orthopedic/trauma	1.7172	5.569 (0.751–118.083)	0.146
Cardiopulmonary surgery or disease vs orthopedic/ trauma	3.4914	32.833 (4.189–725.164)	0.004
Sepsis, Yes vs No	1.9312	6.898 (1.756–33.000)	0.008
Duration of mechanical ventilation			
>1 vs ≤1 day	1.1050	3.019 (0.862–11.322)	0.088
0 vs ≤1 day	3.0329	20.757 (2.409–502.222)	0.017
Oxygenation index, ≤300 vs >300 mmHg	1.9947	7.350 (2.483–24.286)	0.0005
[†] Regression coefficient.			
[‡] Includes gastrointestinal, urologic, hepatobiliary, and obstetric/gynecologic surgery.			

Discriminatory performance and calibration of the nomogram

The C-index of the risk factor model was 0.902 (95% confidence interval [CI]=0.842–0.961) (Fig. 4A); the corrected C-index using 1000 bootstrap samples was 0.873, which demonstrated that the model had a good discriminatory performance. The calibration curve showed consistency between predicted and actual results (Fig. 4B).

Discussion

In the present study, 47.6% of critically ill patients without mechanical ventilation while receiving opioid analgesics developed respiratory depression. The logistic regression analysis identified 4 factors associated with respiratory depression. One of the risk factors was disease type; specifically, patients with cardiopulmonary and respiratory disease who underwent surgery had a longer stay in the ICU because of delayed tracheal extubation and a higher rate of respiratory depression. Therefore, more attention should be paid to airway management in these patients. Surgery for otorhinolaryngologic or oral and maxillofacial diseases are not only more likely to cause airway blockage by secretions or

aspiration, but can also cause damage to the airway and result in its collapse. Respiratory depression can also occur as a result of compression and bandaging of the head and neck or glossoptosis after surgery [16]. In general, the risk of respiratory depression is lower after abdominal surgery than after operations that are directly related to the airway. However, patients with abdominal diseases are often transferred to the ICU due to intraoperative bleeding, prolonged duration of operation, and unstable vital signs; thus, the occurrence of respiratory depression may be indirectly associated with circulation status and changes in intra-abdominal pressure. Finally, as orthopedic or trauma surgery is usually at a site that is far away from the airway or respiratory tract and is performed under local anesthesia, patients have stable vital signs and have a lower risk of respiratory depression. Notably, we did not examine whether there are differences in respiratory depression between local and general anesthesia, as demonstrated by a meta-analysis of 12 retrospective studies on postoperative opioid-related respiratory depression [8]. In our study, the multivariate logistic regression model revealed that patients undergoing surgery for cardiopulmonary and respiratory diseases (odds ratio [OR]=32.833, 95% CI=4.189–725.164) were at higher risk for respiratory depression when receiving opioids after surgery compared to orthopedic and trauma surgery patients.

Sepsis is a systemic inflammatory response triggered by infection that can lead to multiple organ dysfunction syndromes and even death [17]; mortality from sepsis ranges from 10–52% [18–20]. Pulmonary vascular endothelial damage during sepsis interferes with capillary blood flow and increases vascular permeability, which can cause interstitial or alveolar pulmonary edema, ventilation-perfusion mismatch, and hypoxemia [21]. Additionally, sepsis is usually accompanied by increased energy expenditure from respiration and is complicated by encephalopathy or a decreased level of consciousness [21, 22]. Therefore, it is important to stabilize the respiratory system in cases of sepsis, which may require tracheal intubation and mechanical ventilation. We found that sepsis (OR=6.898, 95% CI=1.756–33.000) was an independent risk factor for respiratory depression in non-ventilated critically ill patients treated with opioid analgesics in the multivariate logistic analysis.

Patients admitted to the ICU without mechanical ventilation are at high risk of OIRD. Such patients are usually admitted for advanced circulation and respiration monitoring. In our analysis, patients admitted to the ICU who did not receive mechanical ventilation (OR=20.757, 95% CI=2.409–502.222) had a greater risk of respiratory depression than those who received mechanical ventilation for ≤ 1 day. Baseline $\text{PaO}_2/\text{FiO}_2$ (OR=7.350, 95% CI=2.483–24.286) was also an independent risk factor for respiratory depression events in the former group. Thus, clinicians should prioritize the management of these patients, for example by supplementing oxygen therapy with assisted ventilation or delaying tracheal extubation in order to accelerate the recovery of respiratory function.

Most studies on OIRD have focused on patients undergoing routine surgery and only a few have examined critically ill patients without mechanical ventilation. A recent meta-analysis of 12 retrospective studies including 841,424 surgical patients showed that age, sex, BMI, diabetes, and kidney disease were not associated with postoperative OIRD [8], which is consistent with the findings of our study; it also showed that COPD and obstructive sleep apnea syndrome are risk factors for OIRD. However, the analysis

examined chronic lung diseases, which have a broad definition and include patients with chronic bronchitis, who have acceptable respiratory compensation; therefore, the authors were unable to determine whether underlying lung diseases are a risk factor for OIRD. It is also worth mentioning that our study and the meta-analysis differed in terms of the definition and observation time of OIRD, analgesic program, and patient distribution. The meta-analysis adopted a stricter definition of OIRD with a different rescue standard (ie, using naloxone to reverse OIRD). In contrast, as we aimed to establish a means of identifying early symptoms of respiratory depression to enable timely intervention, we used a standard definition of OIRD (ie, decreased pulse oxygen saturation, increased arterial carbon dioxide, and changes in the mode of assisted ventilation). In terms of analgesic drugs, the meta-analysis mostly included postoperative patients whose morphine equivalent daily dose (MEDD) (either self-controlled or administered via the intravenous, oral, epidural, etc routes) was 24.7 ± 14 and 18.9 ± 13 mg in OIRD and non-OIRD patients, respectively. In our study, all patients were continuously administered the analgesic intravenously with an electronic micropump. The median hourly MED10 was 0.6 mg, equivalent to 144 mg MEDD. Thus, MED10 was much higher in critically ill patients without mechanical ventilation than in patients undergoing routine surgery. In addition, the highest risk period for OIRD in the meta-analysis was the first 4 h after surgery, during which 34% of all critical respiratory events occurred; OIRD typically occurred in the first 12–24 h (85%), but most were not extubated within the first 4 h after surgery and 48% (50/103) of patients were mechanically ventilated for >1 day, with 62% (31/50) reporting respiratory depression events.

Higher rates of opioid accumulation and infusion and combined use of sedative drugs can increase the risk of respiratory depression. Different types of opioids have a characteristic rate of metabolism, which can alter the risk of respiratory depression [8]. In this study, although the total amount of analgesic and sedative drugs and treatment duration were similar between patients with and those without respiratory depression, the rate of respiratory depression differed between the two groups ($P=0.024$) when the cumulative dose of analgesic drugs was classified as >50 (MED10) and ≤ 50 (MED10); that is, in the respiratory depression group, the >50 (MED10) subgroup had a higher rate of respiratory depression than the ≤ 50 (MED10) subgroup (61% vs 39%). However, as the multivariate logistic regression analysis showed that >50 (MED10) was not an independent risk factor for respiratory depression, it was not included in the final regression model. Various analgesic drugs are used in the ICU. For patients with a higher risk of respiratory depression, doctors usually administer butorphanol (which has a lower risk of respiratory adverse effects), reduce the rate or dosage of opioid infusion, or combine opioids with other medications such as nonsteroidal anti-inflammatory drugs. Thus, selection bias by clinicians is a potential reason for our observations. Finally, in the subgroup analysis based on fentanyl (See Supplement Material 2), we found that patients treated with the combination of fentanyl and butorphanol had fewer respiratory depression events and used a lower dosage of opioids than those treated with fentanyl alone ($P<0.05$), which is in accordance with previous studies. However, we did not adjust for confounding factors between groups and the results should therefore be interpreted with caution. Randomized controlled trials are needed in order to clarify whether the fentanyl–butorphanol combination benefits critically ill patients without mechanical ventilation.

Respiratory depression induced by opioids is mainly due to the activation of μ receptors, which can be modulated by δ receptors [23]. Unlike μ receptors, activation of δ and κ receptors can relieve chest wall muscle stiffness. The κ receptor agonist butorphanol was shown to have fewer respiratory adverse effects than other opioids [24–26]. Tapentadol, a new μ receptor agonist, has a strong analgesic effect and low risk of respiratory depression [27]. Further studies on the clinical manifestations and causes of OIRD will help to determine the optimal pharmacologic intervention for pain management based on the characteristics of opioid receptors.

Our study had some limitations. Firstly, the sample size was relatively small, which undermined the reliability of the multivariate logistic regression analysis. Moreover, because of the small sample size, we used only internal verification instead of random split verification of the bootstrap analysis to validate our model. A multicenter study with a larger cohort is needed for external validation and optimization of our model. Finally, the degree of respiratory depression was not classified in the final multivariate regression model. Studies based on a larger population can provide more data for predicting the occurrence of respiratory depression.

Conclusion

Sepsis, duration of mechanical ventilation, and oxygenation index were independent risk factors for respiratory depression events. The predictive model showed good discriminatory performance and calibration and can be used by clinicians to identify at-risk patients so that timely and appropriate interventions can be implemented.

Declarations

Ethics approval and consent to participate: The study design was approved by the appropriate ethics committee of Nanfang Hospital, Southern Medical University. We interviewed the patient or the patient's family member via phone to obtain consent. This study was performed in accordance with the ethical standards of the Helsinki Declaration.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Figures

Figure 1

Flowchart of the study cohort.

Figure 2

Clinical feature selection using the LASSO regression model. **A.** The optimal penalty coefficient in the LASSO model was selected using the 10-fold alternating verification method and minimization standard. **B.** Penalty graph of 36 variable coefficients.

Figure 3

Nomogram of respiratory depression events in critically ill patients receiving opioid analgesic treatment. MV mechanical ventilation. Abdominal surgery includes gastrointestinal, urologic, hepatobiliary, and obstetric/gynecologic surgery.

Figure 4

A. The ROC curve of respiratory depression events in critically ill patients receiving opioid analgesic treatment nomogram. AUC Area Under Curve. **B.** Calibration curve of respiratory depression events in critically ill patients receiving opioid analgesic treatment nomogram.

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