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Title: Predicting Opioid Induced Oversedation in Hospitalized Patients: A Multicenter Observational Study

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ABSTRACT (300 words)

Objectives: Opioid-induced respiratory depression (OIRD) and oversedation are rare but potentially devastating adverse events in hospitalized patients. We investigated which features predict an individual patient's risk of OIRD or oversedation; and developed a risk stratification tool that can be used to aid point-of-care clinical decision-making.

Design: Retrospective observational study

Setting: Twelve acute care hospitals in a large not-for-profit integrated delivery system

Participants: All inpatients ≥18 years admitted between July 1, 2016 and June 30, 2018 who received an opioid during their stay (163,190 unique hospitalizations).

Main outcome measures: The primary outcome was occurrence of sedation or respiratory depression severe enough that emergent reversal with naloxone was required, as determined from medical record review; if naloxone reversal was unsuccessful or if there was no evidence of hypoxic encephalopathy or death due to oversedation, it was not considered an oversedation event.

Results: Age, sex, body mass index, chronic obstructive pulmonary disease, concurrent sedating medication, renal insufficiency, liver insufficiency, opioid naïvety, sleep apnea, and surgery were significantly associated with risk of oversedation. The strongest predictor was concurrent administration of another sedating medication (adjusted hazard ratio, 95%CI = 3.88, 2.48-6.06); the most common such medications were benzodiazepines (29%), antidepressants (22%), and gamma-aminobutyric acid analog (14.7%). The c-statistic for the final model was 0.755. The 24-point Oversedation Risk Criteria (ORC) score developed from the model stratifies patients as high (>20%, 22-24 points), moderate (11-20%, 18-21 points), and low risk (≤10%, <18 points).

Conclusions: The ORC risk score identifies patients at high risk for OIRD or oversedation from routinely collected data, enabling targeted monitoring for early detection and intervention. It can also be applied to preventive strategies – for example, clinical decision support offered when concurrent prescriptions for opioids and other sedating medications are entered that shows how the chosen combination impacts the patient's risk.

Keywords: oversedation, opioid-induced respiratory distress, risk score

Strengths and limitations of this study

- This multi-hospital study is the first large study to develop a risk score for oversedation/opioid-induced respiratory depression that is applicable to all adult hospitalized patients prescribed opioids.
- All predictors used to build the novel 24-point Oversedation Risk Criteria (ORC) score presented here are routinely collected and readily available from the electronic medical record; thus, implementation will not add to clinicians' data collection burden.
- The predictors include both patient characteristics that cannot be modified and treatment choices that can; it can therefore both facilitate targeted monitoring for early detection and intervention on oversedation/opioid-induced respiratory distress events, and be used in clinical decision support tools, providing information regarding the impact of concomitant medication choice on a patient's risk for such an event.
- This is a novel risk score that should be validated in other, external case series.

INTRODUCTION

Opioid-induced respiratory depression (OIRD) and oversedation are rare but frequently devastating side effects of opioid analgesia in hospitalized patients. In an analysis of closed malpractice claims, more than half the OIRD events resulted in death, and another 22% in severe brain damage.[1] Furthermore, such events are highly preventable with improved monitoring and response.[1 2] The challenge, however, lies in ensuring appropriate monitoring is provided. Opioid analgesia is the primary pharmacologic intervention for managing pain in hospitalized patients,[3] and more than half of all non-surgical patients admitted to hospitals,[4] and almost all patients who undergo surgery,[5 6] receive opioids during their stay. At these large volumes, continuous monitoring of all patients receiving opioids is not feasible: even if hospitals were to invest in the equipment necessary to provide pulse oximetry and capnography electronic monitoring[7] for all patients receiving opioids, issues related to alarm fatigue and staff burden[8] would remain significant barriers to effective monitoring.

Acknowledging the challenges to continuously monitoring all patients receiving opioids, clinical practice guidelines (for example, from the American Society of Anesthesiologists[9] and the American Society for Pain Management Nursing[10]), as well as the Joint Commission accreditation requirements addressing safe use of opioids for pain management,[11] include the step of identifying patients at high risk of OIRD or oversedation for enhanced monitoring. However, there is currently no agreed-upon method for assessing that risk. Multiple factors that increase patient risk – including patient demographic characteristics (such as older age[12-14] and female sex[12 15 16]), clinical characteristics (such as cardiac disease,[12 17 18] pulmonary disease,[12 17] sleep apnea,[12 15-20] diabetes,[18 20] impaired kidney function,[12 15 16 18] and obesity[12 14 15]), and opioid-related factors (higher opioid dosage,[12 17 19 20] route of administration[12 16] and concomitant use of other medications with sedative effects[12 13 19 21]). Survey data indicates that, while at least some of these factors are considered by most hospitals in identifying patients at high risk for OIRD and oversedation, there is substantial variation in which criteria are used.[8] Furthermore, simply considering the list of possible risk factors does not help clinicians quantify actual

risks for patients with multiple factors present, as it does not provide information regarding the extent to which they may be additive.

Some previous work has been done to synthesize multiple patient risk factors into clinically-useful risk scores. The PRODIGY trial, for example, developed a 5-variable prediction model for OIRD, using data from a prospective trial in which participants were monitored continuously via capnography and pulse oximetry, but was limited to patients receiving parenteral opioids, treated on the general care floor, and able to wear the continuous monitoring equipment.[22 23] Another risk scoring system for severe opioid-related adverse events (including somnolence, respiratory depression, and cardiopulmonary arrest) was developed from a US national cohort of medical hospitalizations, but did not consider surgical or trauma admissions.[24] A risk index has also been developed and validated for serious OIRD or overdose among outpatients with opioid prescriptions,[25 26] but has not been tested for the inpatient setting (where dosages, routes of administration, and the degree of control the patient has over when and how much of the medication to take, differ significantly).[25 26] What is thus currently missing from the literature is a risk score that is applicable to all hospitalized patients. Using data from our multi-hospital system, we sought to address this gap and 1) determine which features predict an individual patient's risk of OIRD or oversedation; and 2) develop a risk stratification tool to determine which patients are low, moderate, and high risk for OIRD or oversedation that can be used at the point-of-care to aid clinical decision-making.

METHODS

This study was approved by the Baylor Scott & White Research Institute's institutional review board with a waiver of informed consent.

Study population: We considered all adult (≥18 years) patients admitted to one of the 12 [health care system] acute care hospitals in north Texas between July 1, 2016 and June 30, 2018 who received an opioid during their inpatient stay.

Outcomes: The outcome of interest ("oversedation") was defined as an occurrence of sedation or respiratory depression severe enough that the primary care team felt emergent reversal with naloxone was indicated. Cases in which naloxone was administered were identified from the electronic medical record and individually reviewed by one of two healthcare providers via a standardized review process. Discrepancies between reviewers were discussed until both reviewers agreed with final determination. If naloxone administration successfully reversed the sedation event or opioid medication administered as part of inpatient care was determined to be the causative etiology of sedation, the case was considered an oversedation event. Cases in which reversal with naloxone was not successful or in which the patient did not have evidence of hypoxic encephalopathy or death due to oversedation were not considered to be oversedation events. Patients who received naloxone during the course of procedural sedation were excluded from this analysis.

Data collection: All data were extracted from the electronic medical record. Data were collected on patient demographics, medical history, and clinical and admission characteristics considered to be potential risk factors for oversedation, as identified in national guidelines.[3] Patient outcomes (discharge disposition and length of stay) were also collected. All variables are listed in Table 1.

Statistical analysis:

Patients' demographic characteristics, medical history and outcomes were summarized for the over-sedated and not-oversedated groups. Continuous variables were summarized by mean and standard deviation or median with interquartile range, while categorical variables were summarized by frequency and percent. Differences in the characteristics were assessed by t-tests or Kruskall-Wallis tests for continuous data, and Chi-square tests for categorical data.

Cox proportional hazards regression model was developed to predict in-hospital risk of oversedation. Survival times were defined as time from hospital admission to oversedation for patients

that experienced oversedation, or time from hospital admission to discharge for patients that were never oversedated during their hospital stay. To develop the risk model, we first examined a full model with all potential risk factors of interest. Risk factors considered included age, sex, race, ethnicity, body mass index (BMI), smoking history, indicator of concurrent administration of sedating medication, surgery, antihistamine, renal insufficiency, liver insufficiency, COPD, heart failure (HF), thoracic, sleep apnea, live alone, untreated sleep apnea, opioid naïve, and PCA basal rate. Body mass index was fitted with restricted cubic splines to account for any non-linear relationship with the outcome.[27] The backward variable selection algorithm was implemented and risk factors significant at 0.25 level ($p<0.25$) were initially retained. The final model was fitted using only previously retained variables and risk factors significant at 0.10 level ($p < 0.10$) were retained. The risk score was developed from retained risk factors in the final model. A bootstrap approach with 1000 resamples was used to validate the model, and a discriminative index calculated.[28]

Data analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.0 (The R Foundation for Statistical Computing) statistical programs.

Patient and Public Involvement:

There was no patient or public involvement in setting the research question or the outcome measures, in the design and implementation of the study, or dissemination of results.

RESULTS

Between July 2016 and June 2018, a total of 163,190 unique inpatient hospitalizations had documentation of opioid administration. Naloxone was found to have been administered in 961 cases. As shown in Figure 1, following exclusion of patients who received naloxone during procedural sedation, to treat a pre-admission overdose, or for an indication other than oversedation, we identified 293 (0.18%) hospitalizations with opioid administration that resulted in oversedation.

Table 1 compares patients characteristics between oversedated and non oversedated groups. Bivariate analysis showed significant differences existed for most of the characteristics, except sex, race, ethnicity, average BMI, and having a thoracic or large incision that interferes with adequate ventilation. In the multivariable model, age, sex, BMI, COPD, concurrent administration of sedating medication, renal insufficiency, liver insufficiency, opioid naïvety, sleep apnea, and surgery were significantly associated with risk of oversedation (Table 2). The strongest predictor of oversedation was concurrent administration of another medication with sedative properties (adjusted hazard ratio, 95%CI = 3.88, 2.48-6.06); Table 3 shows the medication types most frequently implicated. Older age was also significantly associated with increased risk of oversedation: patients' aged 60 years were more than 1.5 times higher likely to be oversedated when compared to those < 50 years. BMI exhibited a non-linear relationship with the outcome, with low decreasing BMI (< 20) and high increasing BMI (>35) both associated with significant increase in risk of oversedation. (Figure 2). Opioid naivety had a protective effect against oversedation.

Table 4 presents the points scores for risk factors in the final model. Point scores ranged from 0 to 10 while total risk score points ranged from 0 to 24. The predictive ability of the final model was very good with c-statistic = 0.755.

DISCUSSION

In this study of 163,191 hospitalized patients receiving opioids, we observed an incidence of oversedation of 0.18%. The strongest predictor of oversedation was concurrent administration of other medications with sedative properties. Other strong predictors included older age, female sex, BMI, COPD, liver insufficiency, renal insufficiency, undergoing surgery, and a history of sleep apnea or positive sleep apnea screen. Opioid naivety was protective against oversedation in our population. The predictive model developed showed good performance and was used to develop a points-based risk score, the Oversedation Risk Criteria (ORC) that can quickly inform clinicians regarding a patient's level of risk for oversedation.

Several of the predictors identified have good face validity for increasing risk for oversedation or respiratory distress. For example, COPD, in which the respiratory system is already compromised, and liver and renal insufficiency, in which clearance of some opioids or their metabolites may be reduced, increasing drug bioavailability to unsafe levels at dosages and frequencies that would be safe in the absence of dysfunction.[29 30] Likewise, concurrent use of other medications with sedating effects makes intuitive sense, as it complicates the balance of cumulative sedation against management of the pain, nausea, or other symptoms each drug is prescribed to address. In the outpatient setting, co-administration of sedating agents has been shown to increase risk for overdose.[31] Increasing age, presence of sleep apnea, and undergoing surgery, have all been previously identified as risk factors in the literature. [17] In the case of age, physiological changes occur with aging that affect how medicines are handled, including alterations in volumes of drug distribution, metabolism and clearance which can prolong half-life, increasing potential for drug toxicity and the likelihood of adverse drug reactions.[32] Possible mechanisms that have been proposed for the impact of surgery include a combination of the residual effects of anaesthetic medications, as the risk appears to be greatest during the first 12 to 24 hours following surgery.[17] With respect to sleep apnea, it is a prevalent characteristic among patients who die due to critical respiratory events during the first 24 hours following surgery,[18] and among patients who suffer postoperative OIRD.[1] The intermittent hypoxia that is a component of obstructive sleep apnea has been shown to both increase pain and enhance opioid effects; in addition, opioids attenuate the arousal response to hypoxia and prolong airway obstruction, a combination of effects that has been hypothesized as explaining the association between sleep apnea and risk for OIRD.[17 33] Our findings regarding the risk associated with BMI are unique in that, while previous studies have found increased risk of oversedation or OIRD with obesity,[12] ours is the first to elucidate the J-shaped curve in which risk increases as BMI values move away in either direction from the point of inversion at 26 $kg.m^{-2}$ – although a similar relationship between BMI and risk for adverse outcomes has been shown in other contexts.[27]

The low incidence of oversedation observed here was in line with previous reports examining similarly severe opioid-related adverse events (ie, necessitating the administration of a reversal agent such as naloxone). The frequency of such events varies according to the population studied – for example, reported at 0.4% in hospitalized medical patients receiving opioids,[24] 0.1% for postoperative patients, [34] 0.3% for patients undergoing major surgery,[35] and ≤0.07% in women who had undergone caesarean.[36] Previous studies have also set out to develop risk prediction models for OIRD or oversedation. These include a small case-control study from a US community hospital considering all hospitalized patients receiving opioids,[16] a large observational study of medical patients hospitalized in the United States receiving opioids,[24] and a risk score developed from an international prospective trial (PRODIGY) of the use of continuous capnography and oximetry to monitor patients receiving opioids on general inpatient wards.[22] One additional case-control study by Pawasaukas et al[37] did not develop a risk model *per* se, but identified a set of risk factors and found that patients with a higher number of these factors were more likely to experience oversedation. Predictors included in these previous models both overlapped with and differed from the predictors used in our risk score. Older age was consistently identified as a risk factor, and some measure related to sleep apnea was included as a risk factor (sleep disorders,[22] untreated sleep apnea,[16] or obstructive sleep apnea[24]) in all but Pawasaukas et al.[37] Two of the previous risk models, as well as Pawasaukis et al,[37] included factors related to the renal insufficiency variable in our risk model (comorbid renal disease[16] and renal failure on admission[24]), but only Pawasaukas et al[37] (hepatic disease) and the risk model developed for medical hospitalizations (hepatic failure on admission[24]) included any measure similar to the liver insufficiency variable in our model. These were also the only two models to include measures related to our strongest predictor of oversedation: concurrent administration of other medications with sedative properties (concurrent sedating medications,[37] and short-acting benzodiazepine exposure and antipsychotic exposure[24]). While sex was included in all models except Pawasaukas et al[37], two of the previous studies identified female sex as associated with increased risk[16 24] (as in our model) while the third identified male sex as being so associated.[22] Similarly, opioid naivety was included in the

PRODIGY risk score as a risk factor,[22] while in our model, and in Pawasaukas et al,[37] it was a protective characteristic. Of the remaining predictors in our model, Pawasaukas et al[37] was the only previous model to include BMI and respiratory disease. None of the previous models included surgery (understandable for the risk model targeting medical hospitalizations only[24]), or PCA basal rate (although one did identify receipt of long-acting oxycodone or as-needed hydromorphone as a risk factor, which is physiologically similar).[16] Risk factors they identified and included that were not a part of our model include congestive heart failure,[22 24] psychosis or depression,[24] opioid abuse/dependence,[24] non-opioid drug abuse/dependence,[24] and presence on admission of respiratory failure, shock/hypotension on admission, acidosis, or neurologic failure.[24] Despite these differences, the performance of our risk model and the previous models is similar: both the PRODIGY model reported and the risk model targeting medical hospitalized patients reported c-statistics of 0.68-0.71,[22 24] which our model modestly out-performed at 0.755, while the remaining risk model, which was developed from a small single center study, achieved a c-statistic of 0.86.[16] The PRODIGY score showed greater separation in risk for OIRD between its low, medium, and high risk score categories (24%, 42%, and 65%[22] compared to our <5%, 5-15%, and >15%), but this is likely explained by their having examined respiratory depression detected by continuous pulse oximetry and capnography monitoring, rather than the clinically relevant potentially life-threatening events requiring naloxone reversal we examined.

Some limitations should be kept in mind when interpreting our results. First, while our study sample was large and drawn from 12 acute care hospitals, it was nonetheless drawn from a single health care system. To the extent that risk for oversedation is affected by institutional prescribing policies or clinical decision support tools, monitoring schedules/equipment/staffing resources, and similar structural considerations governed at the health care system level, our findings may be less generalizable to all other settings. The differences noted in the risk factors included among the risk scores that have been developed to date – with all models showing good discrimination – indicates that there is further work to be done explain these discrepancies. Second, as was noted by the developers

of a previous risk score focusing on oversedation or OIRD events identified through naloxone reversal,[24] the rarity of this adverse outcome keeps the positive predictive value of even a risk score with good discrimination relatively low. Thus, while the risk score offers important value in terms of identifying patients at increased risk for OIRD or oversedation, care must still be taken in selecting mechanisms for mitigating that risk, to avoid issues such as alarm fatigue that have been reported as barriers to increased monitoring (human or electronic) to catch earlier signs of oversedation and prevent its progression.[8]

Recommendations included in national guidelines on monitoring for OIRD and oversedation include that "all patients who will receive opioids undergo a comprehensive assessment of level of individual risk before initiation of opioid therapy."[10] While the guidelines go on to suggest that a risk factor checklist be integrated into the electronic health record to assist with this comprehensive assessment and its documentation, no guidance is provided on how clinicians should judge cumulative risk for patients in whom multiple risk factors are present. The ORC risk score we have developed is a tool to achieve this, and unlike previous studies, is applicable to all adult patients admitted to an acute care hospital. Future research should include evaluation of the ORC risk score for use in ambulatory centers: as more procedures that have traditionally been performed in the high resource setting of acute care hospitals transition to such settings,[38] where the availability of staff and resources to monitor patients for or respond to events of OIRD or oversedation may be more limited, identification of high-risk patients may be even more critical for maintaining patient safety.

Beyond application to targeted monitoring of high-risk patients for early detection of and intervention to prevent progression of OIRD and oversedation events, our results suggest opportunities for prevention through interventions aimed at prescribing clinicians – for example, clinical decision support utilizing the ORC offered when concurrent prescriptions for opioids and other sedating medications are entered. Such preventive approaches will be critical to achieving sustained improvement, as the high rate of false positive alarms – even among patients at high risk for OIRD and

oversedation – leave strategies that focus exclusively on monitoring and early detection vulnerable to alarm fatigue and competing priorities for attention among staff tasked with responding.

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Contributions of the authors:

Garrett (study guarantor): study concept, study design, data analysis, data interpretation, drafting the manuscript

Vanston: data collection, data management, revising the manuscript

da Graca: literature search, drafting the manuscript

Ogola: data collection, data analysis, figures and tables, drafting the manuscript

Kouznetsova: study concept, revising the manuscript

Cassity: data collection, revising the manuscript

Hall: data collection, data management, revising the manuscript

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Transparency declaration: I, Dr. John Garrett, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned) have been explained.

Data sharing: Please contact the corresponding author with any requests.

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Figure Legends

Figure 1. Inclusion and exclusion of hospital encounters for the development of the Oversedation Risk Criteria (ORC) score.

ED = emergency department; OB = Obstetric; OR = operating room

Figure 2. Risk of opioid-induce respiratory depression or oversedation by body mass index (BMI)

Figure 3. Risk of opioid-induce respiratory depression or oversedation by Oversedation Risk Criteria (ORC) score.

TABLES

Table 1. Patient demographic and clinical characteristics and outcomes for inpatients who did vs did not experience an opioid-related oversedation event

	Oversedation (N=293)	No Oversedation (N=162,897)	P-value
Age (years)			< 0.001
<50	52 (17.7%)	63361 (38.9%)	
50-59	54 (18.4%)	26319 (16.2%)	
60-69	74 (25.3%)	31329 (19.2%)	
70+	113 (38.6%)	41888 (25.7%)	
Sex (Female)	191 (65.2%)	99562 (61.1%)	0.154
Race			0.618
White	230 (78.5%)	124351 (76.3%)	
Black	46 (15.7%)	29139 (17.9%)	
Other	17 (5.8%)	9407 (5.8%)	
Hispanic ethnicity	34 (11.6%)	25330 (15.5%)	0.063
BMI - Mean ± SD ($kg.m^2$)	30.1 ± 10.3	30.0 ± 8.2	0.745
Concurrent administration of sedating medication	267 (91.1%)	95495 (58.6%)	< 0.001
Antihistamine	73 (24.9%)	29952 (18.4%)	0.004
Renal Insufficiency diagnosis	141 (48.1%)	46415 (28.5%)	< 0.001
Liver Insufficiency diagnosis	189 (64.5%)	67917 (41.7%)	< 0.001
Chronic obstructive pulmonary disease	73 (24.9%)	20592 (12.6%)	< 0.001
Heart failure	72 (24.6%)	25506 (15.7%)	< 0.001
Thoracic or large incision that interferes with adequate ventilation	20 (6.8%)	8577 (5.3%)	0.232
Positive sleep apnea screen: Snore	95 (32.9%)	40018 (24.9%)	< 0.001
Positive sleep apnea screen: Doze off	76 (26.3%)	22167 (13.8%)	< 0.001
Live alone	4 (1.4%)	603 (0.4%)	0.018
Smoking History			0.014
Non-Smoker	152 (51.9%)	95410 (58.6%)	
Former Smoker	90 (30.7%)	38785 (23.8%)	
Current Smoker	40 (13.7%)	24733 (15.2%)	
Unknown/Missing	11 (3.8%)	3969 (2.4%)	
Surgery	148 (50.5%)	55262 (33.9%)	< 0.001
Untreated obstructive sleep apnea	55 (19.4%)	18846 (12.0%)	< 0.001
Opioid Naive	155 (52.9%)	105519 (64.8%)	< 0.001
PCA basal	7 (2.4%)	1066 (0.7%)	< 0.001
Days on opioids - Median (Q1, Q3)	7.0 (4.0, 13.0)	3.0 (2.0, 5.0)	< 0.001
Disposition			< 0.001
Expired	20 (6.8%)	4743 (2.9%)	
Home	140 (47.8%)	128709 (79.0%)	
Transferred to other facilities	133 (45.4%)	29445 (18.1%)	
Length of Stay (days) - Median (Q1, Q3)	9.0 (5.0, 15.0)	3.0 (2.0, 6.0)	< 0.001

BMI – body mass index; SD – standard deviation; Q - quartile

Table 2. Associations between risk factors included in the full and reduced models for predicting opioid-induced respiratory depression or oversedation.

	HR (95%CI) and P-value	
Risk factors	**Full Model**	**Reduced Model**
Age (years)		
50-59	1.39 (0.91 - 2.13) p = 0.13	1.39 (0.91 - 2.12) p = 0.13
60-69	1.52 (1.01 - 2.28) p = 0.04	1.54 (1.03 - 2.30) p = 0.03
70+	1.69 (1.13 - 2.52) p = 0.01	1.75 (1.19 - 2.57) p = <.01
Sex (Female vs. Male)	1.59 (1.21 - 2.09) p = <.01	1.60 (1.23 - 2.09) p = <.01
Race		
Black vs White	0.83 (0.57 - 1.20) p = 0.31	
Other vs White	1.21 (0.70 - 2.10) p = 0.49	
Hispanic ethnicity	1.06 (0.71 - 1.58) p = 0.78	
Smoking History		
Former vs Never	1.03 (0.77 - 1.38) p = 0.84	
Current vs Never	0.86 (0.58 - 1.28) p = 0.47	
BMI (kg/m^2)		
(BMI<26)	1.02 (1.00 - 1.03) p = 0.07	1.02 (1.00 - 1.04) p = 0.05
(BMI >= 26)	0.68 (0.48 - 0.96) p = 0.03	0.69 (0.49 - 0.97) p = 0.03
Antihistamine	0.91 (0.68 - 1.22) p = 0.53	
Chronic obstructive pulmonary disease	1.57 (1.14 - 2.15) p = <.01	1.48 (1.10 - 1.99) p = <.01
Concurrent administration of sedating medication	3.89 (2.48 - 6.10) p = <.01	3.88 (2.48 - 6.06) p = <.01
Heart Failure	0.89 (0.64 - 1.22) p = 0.47	
Live alone	2.55 (0.63 - 10.29) p = 0.19	
Liver insufficiency diagnosis	1.60 (1.21 - 2.10) p = <.01	1.62 (1.23 - 2.12) p = <.01
Opioid Naive	0.76 (0.59 - 0.97) p = 0.03	0.74 (0.58 - 0.95) p = 0.02
PCA Basal	1.87 (0.82 - 4.26) p = 0.13	1.96 (0.87 - 4.46), p = 0.10
Renal insufficiency	1.40 (1.07 - 1.85) p = 0.02	1.35 (1.03 - 1.76) p = 0.03
Positive sleep apnea screen (Snore or Doze-off)	1.42 (1.08 - 1.87) p = 0.01	1.45 (1.11 - 1.88) p = <.01
Surgery	1.57 (1.20 - 2.04) p = <.01	1.53 (1.18 - 1.98) p = <.01
Thoracic or large incision that interferes with adequate ventilation	0.68 (0.41 - 1.12) p = 0.13	
Untreated obstructive sleep apnea	1.18 (0.84 - 1.66) p = 0.34	

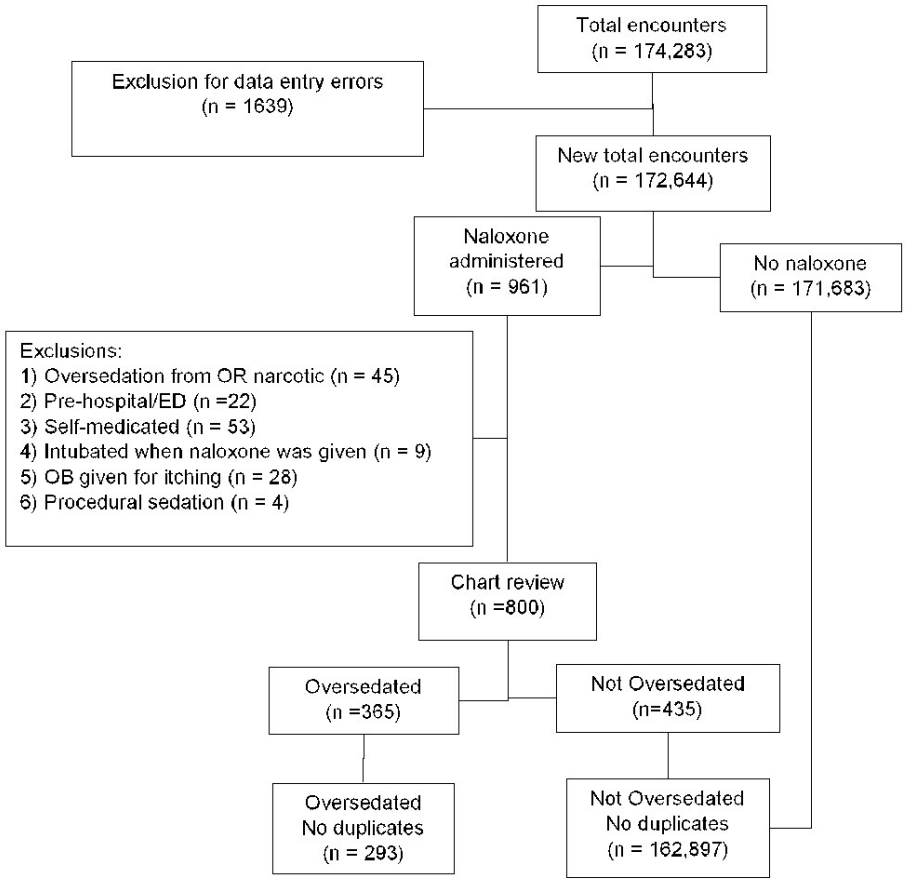
BMI – body mass index; CI – confidence interval; HR – hazard ratio

Table 3. Medications with sedating properties prescribed concomitantly with opioids in patients who experienced an opioid-related oversedation event

Drug type/category	n (%)
Benzodiazepine	245 (29.0)
Antidepressants	186 (22.0)
Gamma-aminobutyric acid analog	124 (14.7)
Miscellaneous anxiolytic, sedative and hypnotic (sleep aids)	86 (10.2)
Antipsychotic	69 (8.2)
Antihistamine	68 (8.0)
Anticonvulsant	38 (4.5)
Dopaminergic anti-Parkinsonism agents	15 (1.8)
Barbiturate	6 (0.7)
Phenothiazine antiemetics	5 (0.6)
Carbonic anhydrase inhibitor	3 (0.4)

Table 4. Points assigned per risk factor in the Oversedation Risk Criteria (ORC) score

Risk factor	Points
Age (years)	
< 50	0
50-59	1
60+	2
Sex - Female	2
BMI (kg/m^2)	
10	5
20	2
30	0
40	1
50	2
60	3
70	4
80	5
90	6
100	7
110	8
120	9
130	10
Concurrent administration of sedating medication	5
Renal Insufficiency	1
Liver Insufficiency	2
Chronic obstructive pulmonary disease	1
Sleep Apnea	2
Surgery within 24 hours	2
Not Opioid Naive	1
PCA Basal	3
BMI – body mass index	



Inclusion and exclusion of hospital encounters for the development of the Oversedation Risk Criteria (ORC) score.

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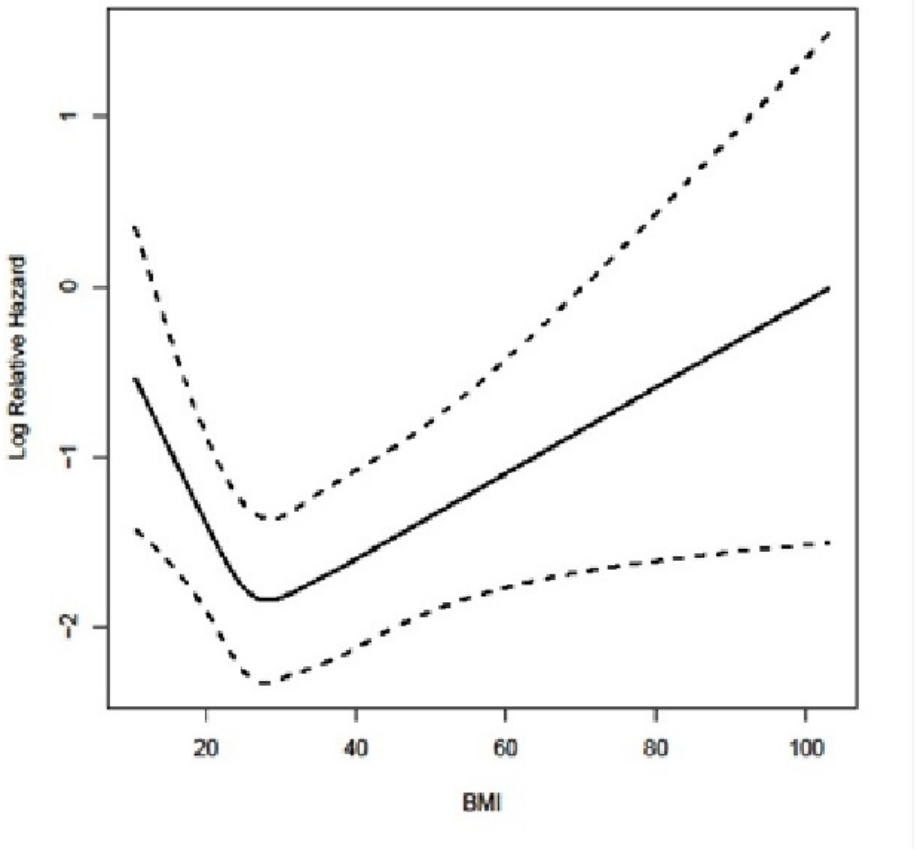

Risk of opioid-induce respiratory depression or oversedation by body mass index (BMI)

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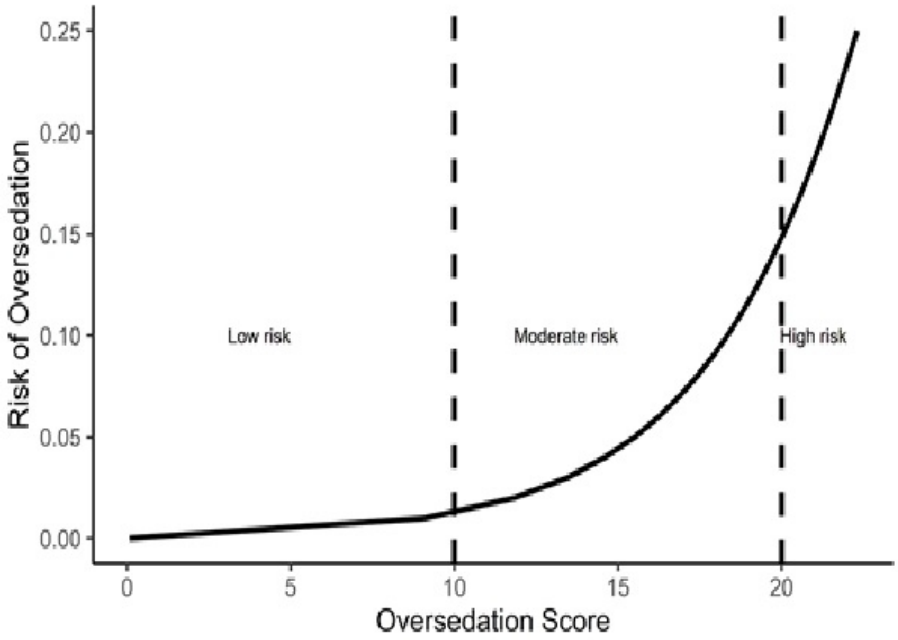

Risk of Oversedation	ORC Score
>20% (high risk)	22-24
11-20% (moderate risk)	18-21
0-10% (low risk)	< 18

Risk of opioid-induce respiratory depression or oversedation by Oversedation Risk Criteria (ORC) score.

56x53mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	23
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	27, Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Tables 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title: Predicting Opioid Induced Oversedation in Hospitalized Patients: A Multicenter Observational Study

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ABSTRACT (300 words)

Objectives: Opioid-induced respiratory depression (OIRD) and oversedation are rare but potentially devastating adverse events in hospitalized patients. We investigated which features predict an individual patient's risk of OIRD or oversedation; and developed a risk stratification tool that can be used to aid point-of-care clinical decision-making.

Design: Retrospective observational study

Setting: Twelve acute care hospitals in a large not-for-profit integrated delivery system

Participants: All inpatients ≥18 years admitted between July 1, 2016 and June 30, 2018 who received an opioid during their stay (163,190 unique hospitalizations).

Main outcome measures: The primary outcome was occurrence of sedation or respiratory depression severe enough that emergent reversal with naloxone was required, as determined from medical record review; if naloxone reversal was unsuccessful or if there was no evidence of hypoxic encephalopathy or death due to oversedation, it was not considered an oversedation event.

Results: Age, sex, body mass index, chronic obstructive pulmonary disease, concurrent sedating medication, renal insufficiency, liver insufficiency, opioid naïvety, sleep apnea, and surgery were significantly associated with risk of oversedation. The strongest predictor was concurrent administration of another sedating medication (adjusted hazard ratio, 95%CI = 3.88, 2.48-6.06); the most common such medications were benzodiazepines (29%), antidepressants (22%), and gamma-aminobutyric acid analog (14.7%). The c-statistic for the final model was 0.755. The 24-point Oversedation Risk Criteria (ORC) score developed from the model stratifies patients as high (>20%, ≥21 points), moderate (11-20%, 10-20 points), and low risk (≤10%, <10 points).

Conclusions: The ORC risk score identifies patients at high risk for OIRD or oversedation from routinely collected data, enabling targeted monitoring for early detection and intervention. It can also be applied to preventive strategies – for example, clinical decision support offered when concurrent prescriptions for opioids and other sedating medications are entered that shows how the chosen combination impacts the patient's risk.

Keywords: oversedation, opioid-induced respiratory distress, risk score

Strengths and limitations of this study

- This multi-hospital study is the first large study to develop a risk score for oversedation/opioid-induced respiratory depression that is applicable to all adult hospitalized patients prescribed opioids.
- All predictors used to build the novel 24-point Oversedation Risk Criteria (ORC) score presented here are routinely collected and readily available from the electronic medical record; thus, implementation will not add to clinicians' data collection burden.
- The predictors include both patient characteristics that cannot be modified and treatment choices that can; it can therefore both facilitate targeted monitoring for early detection and intervention on oversedation/opioid-induced respiratory distress events, and be used in clinical decision support tools, providing information regarding the impact of concomitant medication choice on a patient's risk for such an event.
- This is a novel risk score that should be validated in other, external case series.

INTRODUCTION

Opioid-induced respiratory depression (OIRD) and oversedation are rare but frequently devastating side effects of opioid analgesia in hospitalized patients. In an analysis of closed malpractice claims, more than half the OIRD events resulted in death, and another 22% in severe brain damage.[1] Furthermore, such events are highly preventable with improved monitoring and response.[1 2] The challenge, however, lies in ensuring appropriate monitoring is provided. Opioid analgesia is the primary pharmacologic intervention for managing pain in hospitalized patients,[3] and more than half of all non-surgical patients admitted to hospitals,[4] and almost all patients who undergo surgery,[5 6] receive opioids during their stay. At these large volumes, continuous monitoring of all patients receiving opioids is not feasible: even if hospitals were to invest in the equipment necessary to provide pulse oximetry and capnography electronic monitoring[7] for all patients receiving opioids, issues related to alarm fatigue and staff burden[8] would remain significant barriers to effective monitoring.

Acknowledging the challenges to continuously monitoring all patients receiving opioids, clinical practice guidelines (for example, from the American Society of Anesthesiologists[9] and the American Society for Pain Management Nursing[10]), as well as the Joint Commission accreditation requirements addressing safe use of opioids for pain management,[11] include the step of identifying patients at high risk of OIRD or oversedation for enhanced monitoring. However, there is currently no agreed-upon method for assessing that risk. Multiple factors that increase patient risk – including patient demographic characteristics (such as older age[12-14] and female sex[12 15 16]), clinical characteristics (such as cardiac disease,[12 17 18] pulmonary disease,[12 17] sleep apnea,[12 15-20] diabetes,[18 20] impaired kidney function,[12 15 16 18] and obesity[12 14 15]), and opioid-related factors (higher opioid dosage,[12 17 19 20] route of administration[12 16] and concomitant use of other medications with sedative effects[12 13 19 21]). Survey data indicate that, while at least some of these factors are considered by most hospitals in identifying patients at high risk for OIRD and oversedation, there is substantial variation in which criteria are used.[8] Furthermore, simply considering the list of possible risk factors does not help clinicians quantify actual

risks for patients with multiple factors present, as it does not provide information regarding the extent to which they may be additive.

Some previous work has been done to synthesize multiple patient risk factors into clinically-useful risk scores. The PRODIGY trial, for example, developed a 5-variable prediction model for OIRD, using data from a prospective trial in which participants were monitored continuously via capnography and pulse oximetry, but was limited to patients receiving parenteral opioids, treated on the general care floor, and able to wear the continuous monitoring equipment.[22 23] Another risk scoring system for severe opioid-related adverse events (including somnolence, respiratory depression, and cardiopulmonary arrest) was developed from a US national cohort of medical hospitalizations, but did not consider surgical or trauma admissions.[24] A risk index has also been developed and validated for serious OIRD or overdose among outpatients with opioid prescriptions,[25 26] but has not been tested for the inpatient setting (where dosages, routes of administration, and the degree of control the patient has over when and how much of the medication to take, differ significantly).[25 26] What is thus currently missing from the literature is a risk score that is applicable to all hospitalized patients. Using data from our multi-hospital system, we sought to address this gap and 1) determine which features predict an individual patient's risk of OIRD or oversedation; and 2) develop a risk stratification tool to determine which patients are low, moderate, and high risk for OIRD or oversedation that can be used at the point-of-care to aid clinical decision-making.

METHODS

Study population: We considered all adult (≥18 years) patients admitted to one of the 12 [health care system] acute care hospitals in north Texas between July 1, 2016 and June 30, 2018 who received an opioid during their inpatient stay.

Outcomes: The outcome of interest ("oversedation") was defined as an occurrence of sedation or respiratory depression severe enough that the primary care team felt emergent reversal with naloxone

was indicated. Distinction was not made between three mechanisms through which opioid-induced ventilatory impairment (OIVI) occurs: depression of the respiratory centre in the brain stem, depression of the hypothalamus leading to increased arousal thresholds and sedation, and decreased upper airway muscle tone leading to airway obstruction. Cases in which naloxone was administered were identified from the electronic medical record and individually reviewed by one of two healthcare providers via a standardized review process. Discrepancies between reviewers were discussed until both reviewers agreed with final determination. If naloxone administration successfully reversed the sedation event or opioid medication administered as part of inpatient care was determined to be the causative etiology of sedation, the case was considered an oversedation event. Cases in which reversal with naloxone was not successful or in which the patient did not have evidence of hypoxic encephalopathy or death due to oversedation were not considered to be oversedation events. Patients who received naloxone during the course of procedural sedation were excluded from this analysis.

Data collection: All data were extracted from the electronic medical record. Data were collected on patient demographics, medical history, and clinical and admission characteristics considered to be potential risk factors for oversedation, as identified in national guidelines.[3] Patient outcomes (discharge disposition and length of stay) were also collected. All variables are listed in Table 1.

Statistical analysis:

Patients' demographic characteristics, medical history and outcomes were summarized for the over-sedated and not-oversedated groups. Continuous variables were summarized by mean and standard deviation or median with interquartile range, while categorical variables were summarized by frequency and percent. Differences in the characteristics were assessed by t-tests or Kruskall-Wallis tests for continuous data, and Chi-square tests for categorical data.

Cox proportional hazards regression model was developed to predict in-hospital risk of oversedation. Survival times were defined as time from hospital admission to oversedation for patients

that experienced oversedation, or time from hospital admission to discharge for patients that were never oversedated during their hospital stay. To develop the risk model, we first examined a full model with all potential risk factors of interest. Risk factors considered included age, sex, race, ethnicity, body mass index (BMI), smoking history, indicator of concurrent administration of sedating medication (defined as sedating medications administered either before or after administration of the opioid medication where the time that elapsed between administration was less than the predicted timeframe of the mechanism of action for the medication that was administered first), surgery, antihistamine, renal insufficiency, liver insufficiency, COPD, heart failure (HF), thoracic, sleep apnea, live alone, untreated sleep apnea, opioid naïve, and PCA basal rate. Body mass index was fitted with restricted cubic splines to account for any non-linear relationship with the outcome.[27] The backward variable selection algorithm was implemented and risk factors significant at 0.25 level ($p<0.25$) were initially retained. The final model was fitted using only previously retained variables and risk factors significant at 0.10 level ($p < 0.10$) were retained. The final prediction model was implemented in a nomogram to develop a risk score calculator for estimating probabilities of oversedation during hospitalization for each individual. Predictive performance of the nomogram was validated for discrimination and calibration on the original data using 1000 bootstrap resamples. Discrimination was assessed by bootstrap-adjusted Harrell's concordance index (C-index) with 95% confidence intervals.[28] Nomogram was developed using rms package of R version 3.5.0. Distribution of the relationship between probabilities of oversedation and risk scores were assessed and stratified as high, moderate and low risk.

Data analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.0 (The R Foundation for Statistical Computing) statistical programs.

Patient and Public Involvement:

There was no patient or public involvement in setting the research question or the outcome measures, in the design and implementation of the study, or dissemination of results.

RESULTS

Between July 2016 and June 2018, a total of 163,190 unique inpatient hospitalizations had documentation of opioid administration. Naloxone was found to have been administered in 961 cases. As shown in Figure 1, following exclusion of patients who received naloxone during procedural sedation, to treat a pre-admission overdose, or for an indication other than oversedation, we identified 293 (0.18%) hospitalizations with opioid administration that resulted in oversedation.

Table 1 compares patients characteristics between oversedated and non oversedated groups. Bivariate analysis showed significant differences existed for most of the characteristics, except sex, race, ethnicity, average BMI, and having a thoracic or large incision that interferes with adequate ventilation. In the multivariable model, age, sex, BMI, COPD, concurrent administration of sedating medication, renal insufficiency, liver insufficiency, opioid naïvety, sleep apnea, and surgery were significantly associated with risk of oversedation (Table 2). The strongest predictor of oversedation was concurrent administration of another medication with sedative properties (adjusted hazard ratio, 95%CI = 3.88, 2.48-6.06); Table 3 shows the medication types most frequently implicated. Older age was also significantly associated with increased risk of oversedation: patients' aged 60 years were more than 1.5 times higher likely to be oversedated when compared to those < 50 years. BMI exhibited a non-linear relationship with the outcome, with low decreasing BMI (< 20) and high increasing BMI (>35) both associated with significant increase in risk of oversedation. (Figure 2). Opioid naivety had a protective effect against oversedation.

Table 4 presents the points scores for risk factors in the final model. Point scores ranged from 0 to 10 while total risk score points ranged from 0 to 24. Figure 3 shows the risk of OIRD by Oversedation Risk Criteria (ORC) score. The predictive ability of the final model was very good with c-statistic = 0.755.

DISCUSSION

In this study of 163,191 hospitalized patients receiving opioids, we observed an incidence of oversedation of 0.18%. The strongest predictor of oversedation was concurrent administration of other medications with sedative properties. Other strong predictors included older age, female sex, BMI, COPD, liver insufficiency, renal insufficiency, undergoing surgery, and a history of sleep apnea or positive sleep apnea screen. Opioid naivety was protective against oversedation in our population. The predictive model developed showed good performance and was used to develop a points-based risk score, the Oversedation Risk Criteria (ORC) that can quickly inform clinicians regarding a patient's level of risk for oversedation.

Several of the predictors identified have good face validity for increasing risk for oversedation or respiratory distress. For example, COPD, in which the respiratory system is already compromised, and liver and renal insufficiency, in which clearance of some opioids or their metabolites may be reduced, increasing drug bioavailability to unsafe levels at dosages and frequencies that would be safe in the absence of dysfunction.[29 30] Likewise, concurrent use of other medications with sedating effects makes intuitive sense, as it complicates the balance of cumulative sedation against management of the pain, nausea, or other symptoms each drug is prescribed to address. In the outpatient setting, co-administration of sedating agents has been shown to increase risk for overdose.[31] Increasing age, presence of sleep apnea, and undergoing surgery, have all been previously identified as risk factors in the literature. [17] In the case of age, physiological changes occur with aging that affect how medicines are handled, including alterations in volumes of drug distribution, metabolism and clearance which can prolong half-life, increasing potential for drug toxicity and the likelihood of adverse drug reactions.[32] Possible mechanisms that have been proposed for the impact of surgery include a combination of the residual effects of anaesthetic medications, as the risk appears to be greatest during the first 12 to 24 hours following surgery.[17] With respect to sleep apnea, it is a prevalent characteristic among patients who die due to critical respiratory events during the first 24 hours following surgery,[18] and among patients who suffer postoperative OIRD.[1] The intermittent hypoxia that is a component of obstructive

sleep apnea has been shown to both increase pain and enhance opioid effects; in addition, opioids attenuate the arousal response to hypoxia and prolong airway obstruction, a combination of effects that has been hypothesized as explaining the association between sleep apnea and risk for OIRD.[17 33] Our findings regarding the risk associated with BMI are unique in that, while previous studies have found increased risk of oversedation or OIRD with obesity,[12] ours is the first to elucidate the J-shaped curve in which risk increases as BMI values move away in either direction from the point of inversion at 26 $kg.m^{-2}$ – although a similar relationship between BMI and risk for adverse outcomes has been shown in other contexts.[27]

The low incidence of oversedation observed here was in line with previous reports examining similarly severe opioid-related adverse events (ie, necessitating the administration of a reversal agent such as naloxone). The frequency of such events varies according to the population studied – for example, reported at 0.4% in hospitalized medical patients receiving opioids,[24] 0.1% for postoperative patients, [34] 0.3% for patients undergoing major surgery,[35] and ≤0.07% in women who had undergone caesarean.[36] Previous studies have also set out to develop risk prediction models for OIRD or oversedation. These include a small case-control study from a US community hospital considering all hospitalized patients receiving opioids,[16] a large observational study of medical patients hospitalized in the United States receiving opioids,[24] and a risk score developed from an international prospective trial (PRODIGY) of the use of continuous capnography and oximetry to monitor patients receiving opioids on general inpatient wards.[22] One additional case-control study by Pawasaukas et al[37] did not develop a risk model *per* se, but identified a set of risk factors and found that patients with a higher number of these factors were more likely to experience oversedation. Predictors included in these previous models both overlapped with and differed from the predictors used in our risk score. Older age was consistently identified as a risk factor, and some measure related to sleep apnea was included as a risk factor (sleep disorders,[22] untreated sleep apnea,[16] or obstructive sleep apnea[24]) in all but Pawasaukas et al.[37] Two of the previous risk models, as well as Pawasaukis et al,[37] included factors related to the

renal insufficiency variable in our risk model (comorbid renal disease[16] and renal failure on admission[24]), but only Pawasaukas et al[37] (hepatic disease) and the risk model developed for medical hospitalizations (hepatic failure on admission[24]) included any measure similar to the liver insufficiency variable in our model. These were also the only two models to include measures related to our strongest predictor of oversedation: concurrent administration of other medications with sedative properties (concurrent sedating medications,[37] and short-acting benzodiazepine exposure and antipsychotic exposure[24]). While sex was included in all models except Pawasaukas et al[37], two of the previous studies identified female sex as associated with increased risk[16 24] (as in our model) while the third identified male sex as being so associated.[22] Similarly, opioid naivety was included in the PRODIGY risk score as a risk factor,[22] while in our model, and in Pawasaukas et al,[37] it was a protective characteristic. This discordance between studies requires further investigation, including into the relative opioid doses received by naïve vs non-naïve patients, and the default dosing applied in the clinical setting being studied. It may be that opioid naivety is protective in the real-world practice settings where clinicians know to utilize a lower default starting dosage to effectively control pain in patients who have not developed tolerance. In contrast, non-opiate naïve patients may have experienced increased risk of OIVI from higher starting doses and increased rate of escalating supplemental doses needed to control pain. Of the remaining predictors in our model, Pawasaukas et al[37] was the only previous model to include BMI and respiratory disease. None of the previous models included surgery (understandable for the risk model targeting medical hospitalizations only[24]), or PCA basal rate (although one did identify receipt of long-acting oxycodone or as-needed hydromorphone as a risk factor, which is physiologically similar).[16] Risk factors they identified and included that were not a part of our model include congestive heart failure,[22 24] psychosis or depression,[24] opioid abuse/dependence,[24] non-opioid drug abuse/dependence,[24] and presence on admission of respiratory failure, shock/hypotension on admission, acidosis, or neurologic failure.[24] Despite these differences, the performance of our risk model and the previous models is similar: both the PRODIGY model reported and the risk model targeting medical hospitalized patients reported c-statistics of 0.68-0.71,[22 24] which

our model modestly out-performed at 0.755, while the remaining risk model, which was developed from a small single center study, achieved a c-statistic of 0.86.[16] The PRODIGY score showed greater separation in risk for OIRD between its low, medium, and high risk score categories (24%, 42%, and 65%[22] compared to our <5%, 5-15%, and >15%), but this is likely explained by their having examined respiratory depression detected by continuous pulse oximetry and capnography monitoring, rather than the clinically relevant potentially life-threatening events requiring naloxone reversal we examined.

Some limitations should be kept in mind when interpreting our results. First, while our study sample was large and drawn from 12 acute care hospitals, it was nonetheless drawn from a single health care system. To the extent that risk for oversedation is affected by institutional prescribing policies or clinical decision support tools, monitoring schedules/equipment/staffing resources, and similar structural considerations governed at the health care system level, our findings may be less generalizable to all other settings. The differences noted in the risk factors included among the risk scores that have been developed to date – with all models showing good discrimination – indicates that there is further work to be done explain these discrepancies. Second, as was noted by the developers of a previous risk score focusing on oversedation or OIRD events identified through naloxone reversal,[24] the rarity of this adverse outcome keeps the positive predictive value of even a risk score with good discrimination relatively low. Thus, while the risk score offers important value in terms of identifying patients at increased risk for OIRD or oversedation, care must still be taken in selecting mechanisms for mitigating that risk, to avoid issues such as alarm fatigue that have been reported as barriers to increased monitoring (human or electronic) to catch earlier signs of oversedation and prevent its progression.[8] Another factor to be kept in mind with identifying OIRD events through naloxone reversal in an retrospective study is that staff may have had inherent biases related to their perceptions of patients' risk that made them more likely to diagnose oversedation and administer naloxone in some groups than others that cannot be captured in our data. However, such effects are

likely to be small, and do reflect the real-word setting in which this risk score was developed and will be applied.

Recommendations included in national guidelines on monitoring for OIRD and oversedation include that "all patients who will receive opioids undergo a comprehensive assessment of level of individual risk before initiation of opioid therapy."[10] While the guidelines go on to suggest that a risk factor checklist be integrated into the electronic health record to assist with this comprehensive assessment and its documentation, no guidance is provided on how clinicians should judge cumulative risk for patients in whom multiple risk factors are present. The ORC risk score we have developed is a tool to achieve this, and unlike previous studies, is applicable to all adult patients admitted to an acute care hospital. Future research should include evaluation of the ORC risk score for use in ambulatory centers: as more procedures that have traditionally been performed in the high resource setting of acute care hospitals transition to such settings,[38] where the availability of staff and resources to monitor patients for or respond to events of OIRD or oversedation may be more limited, identification of high-risk patients may be even more critical for maintaining patient safety.

Beyond application to targeted monitoring of high-risk patients for early detection of and intervention to prevent progression of OIRD and oversedation events, our results suggest opportunities for prevention through interventions aimed at prescribing clinicians – for example, clinical decision support utilizing the ORC offered when concurrent prescriptions for opioids and other sedating medications are entered. Such preventive approaches will be critical to achieving sustained improvement, as the high rate of false positive alarms – even among patients at high risk for OIRD and oversedation – leave strategies that focus exclusively on monitoring and early detection vulnerable to alarm fatigue and competing priorities for attention among staff tasked with responding.

Ethical Statement:

This study involves human participants and was approved the Baylor Scott & White Research Institute Institutional Review Board (IRB 018-761) with a waiver of informed consent.

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Contributions of the authors:

Garrett (study guarantor): study concept, study design, data analysis, data interpretation, drafting the manuscript

Vanston: data collection, data management, revising the manuscript

da Graca: literature search, drafting the manuscript

Ogola: data collection, data analysis, figures and tables, drafting the manuscript

Kouznetsova: study concept, revising the manuscript

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Transparency declaration: I, Dr. John Garrett, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned) have been explained.

Data sharing: Please contact the corresponding author with any requests.

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Figure Legends

Figure 1. Inclusion and exclusion of hospital encounters for the development of the Oversedation Risk Criteria (ORC) score.

Figure 2. Risk of opioid-induce respiratory depression or oversedation by body mass index (BMI)

Figure 3. Risk of opioid-induce respiratory depression or oversedation by Oversedation Risk Criteria (ORC) score.

TABLES

Table 1. Patient demographic and clinical characteristics and outcomes for inpatients who did vs did not experience an opioid-related oversedation event

	Oversedation (N=293)	No Oversedation (N=162,897)	P-value
Age (years)			< 0.001
<50	52 (17.7%)	63361 (38.9%)	
50-59	54 (18.4%)	26319 (16.2%)	
60-69	74 (25.3%)	31329 (19.2%)	
70+	113 (38.6%)	41888 (25.7%)	
Sex (Female)	191 (65.2%)	99562 (61.1%)	0.154
Race			0.618
White	230 (78.5%)	124351 (76.3%)	
Black	46 (15.7%)	29139 (17.9%)	
Other	17 (5.8%)	9407 (5.8%)	
Hispanic ethnicity	34 (11.6%)	25330 (15.5%)	0.063
BMI - Mean ± SD ($kg.m^2$)	30.1 ± 10.3	30.0 ± 8.2	0.745
Concurrent administration of sedating medication	267 (91.1%)	95495 (58.6%)	< 0.001
Antihistamine	73 (24.9%)	29952 (18.4%)	0.004
Renal Insufficiency diagnosis	141 (48.1%)	46415 (28.5%)	< 0.001
Liver Insufficiency diagnosis	189 (64.5%)	67917 (41.7%)	< 0.001
Chronic obstructive pulmonary disease	73 (24.9%)	20592 (12.6%)	< 0.001
Heart failure	72 (24.6%)	25506 (15.7%)	< 0.001
Thoracic or large incision that interferes with adequate ventilation	20 (6.8%)	8577 (5.3%)	0.232
Positive sleep apnea screen: Snore	95 (32.9%)	40018 (24.9%)	< 0.001
Positive sleep apnea screen: Doze off	76 (26.3%)	22167 (13.8%)	< 0.001
Live alone	4 (1.4%)	603 (0.4%)	0.018
Smoking History			0.014
Non-Smoker	152 (51.9%)	95410 (58.6%)	
Former Smoker	90 (30.7%)	38785 (23.8%)	
Current Smoker	40 (13.7%)	24733 (15.2%)	
Unknown/Missing	11 (3.8%)	3969 (2.4%)	
Surgery	148 (50.5%)	55262 (33.9%)	< 0.001
Untreated obstructive sleep apnea	55 (19.4%)	18846 (12.0%)	< 0.001
Opioid Naive	155 (52.9%)	105519 (64.8%)	< 0.001
PCA basal	7 (2.4%)	1066 (0.7%)	< 0.001
Days on opioids - Median (Q1, Q3)	7.0 (4.0, 13.0)	3.0 (2.0, 5.0)	< 0.001
Disposition			< 0.001
Expired	20 (6.8%)	4743 (2.9%)	
Home	140 (47.8%)	128709 (79.0%)	
Transferred to other facilities	133 (45.4%)	29445 (18.1%)	
Length of Stay (days) - Median (Q1, Q3)	9.0 (5.0, 15.0)	3.0 (2.0, 6.0)	< 0.001

BMI – body mass index; SD – standard deviation; Q - quartile

Table 2. Associations between risk factors included in the full and reduced models for predicting opioid-induced respiratory depression or oversedation.

	HR (95%CI) and P-value	
Risk factors	**Full Model**	**Reduced Model**
Age (years)		
50-59	1.39 (0.91 - 2.13) p = 0.13	1.39 (0.91 - 2.12) p = 0.13
60-69	1.52 (1.01 - 2.28) p = 0.04	1.54 (1.03 - 2.30) p = 0.03
70+	1.69 (1.13 - 2.52) p = 0.01	1.75 (1.19 - 2.57) p = <.01
Sex (Female vs. Male)	1.59 (1.21 - 2.09) p = <.01	1.60 (1.23 - 2.09) p = <.01
Race		
Black vs White	0.83 (0.57 - 1.20) p = 0.31	
Other vs White	1.21 (0.70 - 2.10) p = 0.49	
Hispanic ethnicity	1.06 (0.71 - 1.58) p = 0.78	
Smoking History		
Former vs Never	1.03 (0.77 - 1.38) p = 0.84	
Current vs Never	0.86 (0.58 - 1.28) p = 0.47	
BMI (kg/m^2)		
(BMI<26)	1.02 (1.00 - 1.03) p = 0.07	1.02 (1.00 - 1.04) p = 0.05
(BMI >= 26)	0.68 (0.48 - 0.96) p = 0.03	0.69 (0.49 - 0.97) p = 0.03
Antihistamine	0.91 (0.68 - 1.22) p = 0.53	
Chronic obstructive pulmonary disease	1.57 (1.14 - 2.15) p = <.01	1.48 (1.10 - 1.99) p = <.01
Concurrent administration of sedating medication	3.89 (2.48 - 6.10) p = <.01	3.88 (2.48 - 6.06) p = <.01
Heart Failure	0.89 (0.64 - 1.22) p = 0.47	
Live alone	2.55 (0.63 - 10.29) p = 0.19	
Liver insufficiency diagnosis	1.60 (1.21 - 2.10) p = <.01	1.62 (1.23 - 2.12) p = <.01
Opioid Naive	0.76 (0.59 - 0.97) p = 0.03	0.74 (0.58 - 0.95) p = 0.02
PCA Basal	1.87 (0.82 - 4.26) p = 0.13	1.96 (0.87 - 4.46), p = 0.10
Renal insufficiency	1.40 (1.07 - 1.85) p = 0.02	1.35 (1.03 - 1.76) p = 0.03
Positive sleep apnea screen (Snore or Doze-off)	1.42 (1.08 - 1.87) p = 0.01	1.45 (1.11 - 1.88) p = <.01
Surgery	1.57 (1.20 - 2.04) p = <.01	1.53 (1.18 - 1.98) p = <.01
Thoracic or large incision that interferes with adequate ventilation	0.68 (0.41 - 1.12) p = 0.13	
Untreated obstructive sleep apnea	1.18 (0.84 - 1.66) p = 0.34	

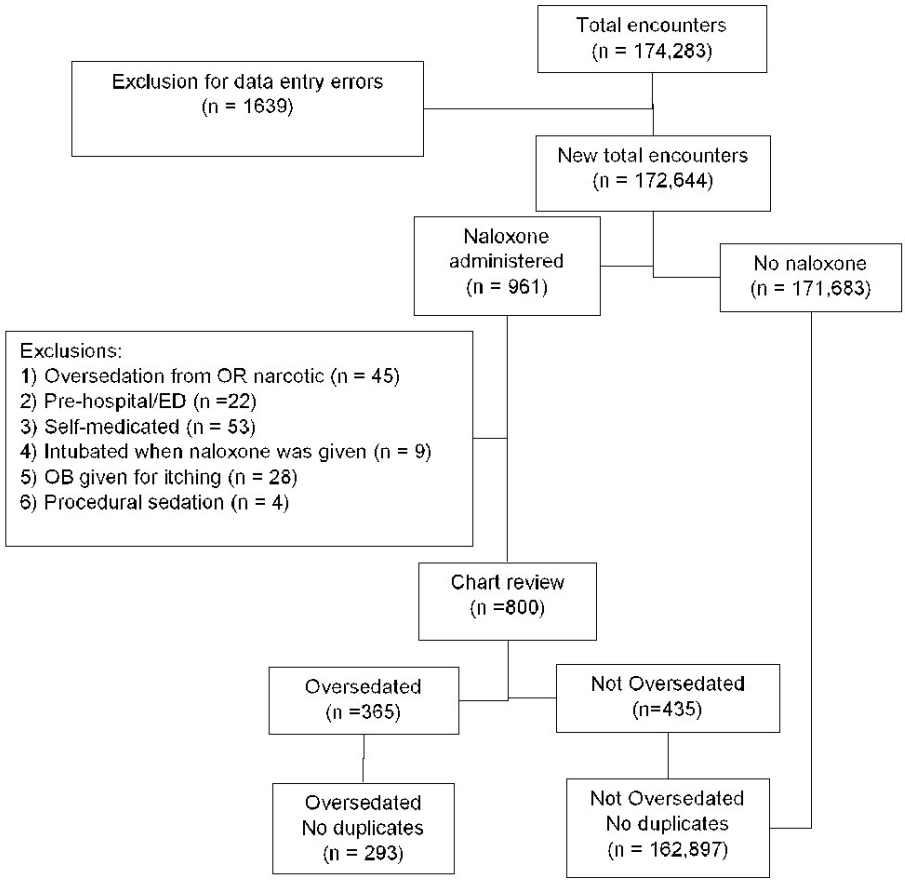
BMI – body mass index; CI – confidence interval; HR – hazard ratio

Table 3. Medications with sedating properties prescribed concomitantly with opioids in patients who experienced an opioid-related oversedation event

Drug type/category	n (%)
Benzodiazepine	245 (29.0)
Antidepressants	186 (22.0)
Gamma-aminobutyric acid analog	124 (14.7)
Miscellaneous anxiolytic, sedative and hypnotic (sleep aids)	86 (10.2)
Antipsychotic	69 (8.2)
Antihistamine	68 (8.0)
Anticonvulsant	38 (4.5)
Dopaminergic anti-Parkinsonism agents	15 (1.8)
Barbiturate	6 (0.7)
Phenothiazine antiemetics	5 (0.6)
Carbonic anhydrase inhibitor	3 (0.4)

Table 4. Points assigned per risk factor in the Oversedation Risk Criteria (ORC) score

Risk factor	Points
Age (years)	
< 50	0
50-59	1
60+	2
Sex - Female	2
BMI (kg/m^2)	
10	5
20	2
30	0
40	1
50	2
60	3
70	4
80	5
90	6
100	7
110	8
120	9
130	10
Concurrent administration of sedating medication	5
Renal Insufficiency	1
Liver Insufficiency	2
Chronic obstructive pulmonary disease	1
Sleep Apnea	2
Surgery within 24 hours	2
Not Opioid Naive	1
PCA Basal	3



Inclusion and exclusion of hospital encounters for the development of the Oversedation Risk Criteria (ORC) score.

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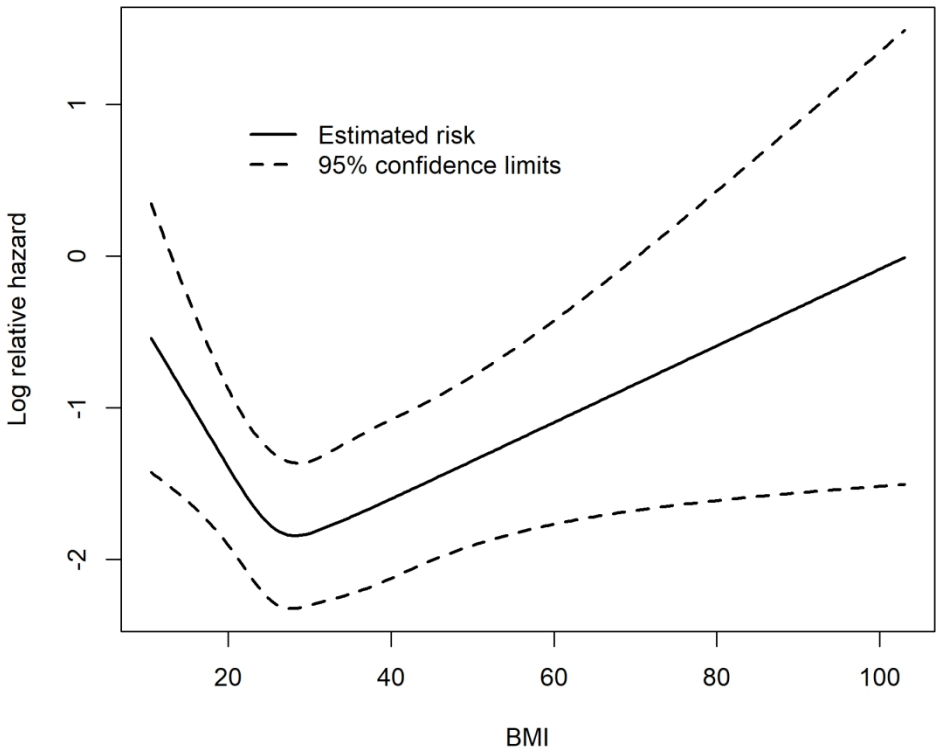

Figure 2. Risk of opioid-induce respiratory depression or oversedation by body mass index (BMI)

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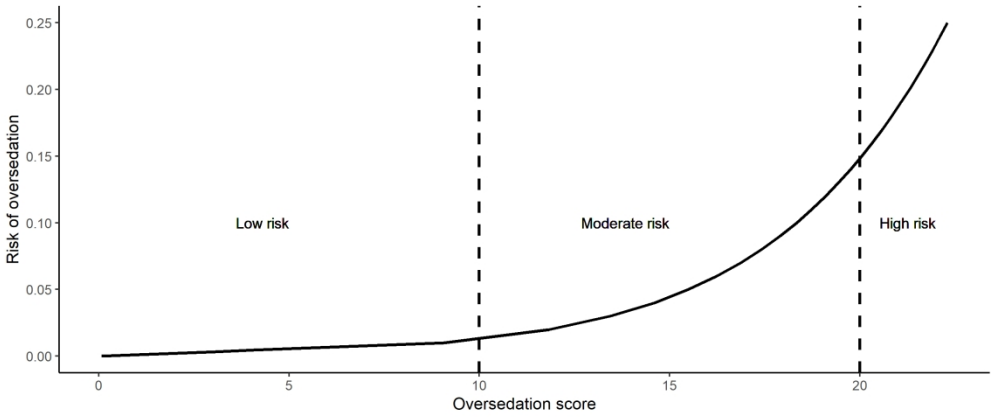

Risk of Oversedation	ORC Score
>20% (high risk)	21+
11-20% (moderate risk)	10-20
0-10% (low risk)	< 10

Figure 3. Risk of opioid-induce respiratory depression or oversedation by Oversedation Risk Criteria (ORC) score.

237x135mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	23
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	27, Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	Tables 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.