


# BMJ Open Predicting opioid-induced oversedation in hospitalised patients: a multicentre observational study

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## ABSTRACT

**Objectives** Opioid-induced respiratory depression (OIRD) and oversedation are rare but potentially devastating adverse events in hospitalised 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 1 July 2016 and 30 June 2018 who received an opioid during their stay (163 190 unique hospitalisations).

**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 apnoea and surgery were significantly associated with risk of oversedation. The strongest predictor was concurrent administration of another sedating medication (adjusted HR, 95% CI=3.88, 2.48 to 6.06); the most common such medications were benzodiazepines (29%), antidepressants (22%) and gamma-aminobutyric acid analogue (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.

## INTRODUCTION

Opioid-induced respiratory depression (OIRD) and oversedation are rare but

## 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 hospitalised patients prescribed opioids.
- All predictors used to build the novel 24-point Oversedation Risk Criteria 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.

frequently devastating side effects of opioid analgesia in hospitalised patients. In an analysis of closed malpractice claims, more than half the OIRD events resulted in death, and another 22% in severe brain damage.<sup>1</sup> Furthermore, such events are highly preventable with improved monitoring and response.<sup>1 2</sup> The challenge, however, lies in ensuring appropriate monitoring is provided. Opioid analgesia is the primary pharmacological intervention for managing pain in hospitalised patients,<sup>3</sup> and more than half of all non-surgical patients admitted to hospitals,<sup>4</sup> and almost all patients who undergo surgery,<sup>5 6</sup> 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<sup>7</sup> for all patients receiving opioids, issues related to

alarm fatigue and staff burden<sup>8</sup> would remain significant barriers to effective monitoring.

Acknowledging the challenges to continuously monitoring all patients receiving opioids, clinical practice guidelines (eg, from the American Society of Anesthesiologists<sup>9</sup> and the American Society for Pain Management Nursing,<sup>10</sup>) as well as the Joint Commission accreditation requirements addressing safe use of opioids for pain management,<sup>11</sup> 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<sup>12–14</sup> and female sex,<sup>12 15 16</sup>) clinical characteristics (such as cardiac disease,<sup>12 17 18</sup> pulmonary disease,<sup>12 17</sup> sleep apnoea,<sup>12 15–20</sup> diabetes,<sup>18 20</sup> impaired kidney function,<sup>12 15 16 18</sup> and obesity<sup>12 14 15</sup>) and opioid-related factors (higher opioid dosage,<sup>12 17 19 20</sup> route of administration<sup>12 16</sup> and concomitant use of other medications with sedative effects<sup>12 13 19 21</sup>). 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.<sup>8</sup> 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 synthesise multiple patient risk factors into clinically-useful risk scores. The PRODIGY trial (PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY), for example, developed a five-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.<sup>22 23</sup> 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 hospitalisations, but did not consider surgical or trauma admissions.<sup>24</sup> A risk index has also been developed and validated for serious OIRD or overdose among outpatients with opioid prescriptions,<sup>25 26</sup> 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).<sup>25 26</sup> What is thus currently missing from the literature is a risk score that is applicable to all hospitalised 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 ( $\geq 18$  years) patients admitted to 1 of the 12 (healthcare system) acute care hospitals in North Texas between 1 July 2016 and 30 June 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 standardised 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 aetiology 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.<sup>3</sup> 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 summarised for the oversedated and not-oversedated groups. Continuous variables were summarised by mean and SD or median with IQR, while categorical variables were summarised by frequency and per cent. Differences in the characteristics were assessed by t-tests or Kruskal-Wallis tests for continuous data, and  $\chi^2$  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

**Table 1** Patient demographic and clinical characteristics and outcomes for inpatients who did versus 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%)	63 361 (38.9%)	
50–59	54 (18.4%)	26 319 (16.2%)	
60–69	74 (25.3%)	31 329 (19.2%)	
70+	113 (38.6%)	41 888 (25.7%)	
Sex (female)	191 (65.2%)	99 562 (61.1%)	0.154
Race			0.618
White	230 (78.5%)	124 351 (76.3%)	
Black	46 (15.7%)	29 139 (17.9%)	
Other	17 (5.8%)	9 407 (5.8%)	
Hispanic ethnicity	34 (11.6%)	25 330 (15.5%)	0.063
BMI—mean±SD (kg/m <sup>2</sup> )	30.1±10.3	30.0±8.2	0.745
Concurrent administration of sedating medication	267 (91.1%)	95 495 (58.6%)	<0.001
Antihistamine	73 (24.9%)	29 952 (18.4%)	0.004
Renal insufficiency diagnosis	141 (48.1%)	46 415 (28.5%)	<0.001
Liver insufficiency diagnosis	189 (64.5%)	67 917 (41.7%)	<0.001
Chronic obstructive pulmonary disease	73 (24.9%)	20 592 (12.6%)	<0.001
Heart failure	72 (24.6%)	25 506 (15.7%)	<0.001
Thoracic or large incision that interferes with adequate ventilation	20 (6.8%)	8 577 (5.3%)	0.232
Positive sleep apnoea screen: Snore	95 (32.9%)	40 018 (24.9%)	<0.001
Positive sleep apnoea screen: Doze off	76 (26.3%)	22 167 (13.8%)	<0.001
Live alone	4 (1.4%)	603 (0.4%)	0.018
Smoking history			0.014
Non-smoker	152 (51.9%)	95 410 (58.6%)	
Former smoker	90 (30.7%)	38 785 (23.8%)	
Current smoker	40 (13.7%)	24 733 (15.2%)	
Unknown/missing	11 (3.8%)	3 969 (2.4%)	
Surgery	148 (50.5%)	55 262 (33.9%)	<0.001
Untreated obstructive sleep apnoea	55 (19.4%)	18 846 (12.0%)	<0.001
Opioid naïve	155 (52.9%)	105 519 (64.8%)	<0.001
PCA basal	7 (2.4%)	1 066 (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%)	4 743 (2.9%)	
Home	140 (47.8%)	128 709 (79.0%)	
Transferred to other facilities	133 (45.4%)	29 445 (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; PCA, Patient Controlled Analgesia; Q, quartile.

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, chronic obstructive pulmonary disease (COPD), heart failure

(HF), thoracic, sleep apnoea, live alone, untreated sleep apnoea, opioid naïve and Patient Controlled Analgesia (PCA) basal rate. BMI was fitted with restricted cubic splines to account for any non-linear relationship with the outcome.<sup>27</sup> 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 hospitalisation 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% CIs.<sup>28</sup> Nomogram was developed using rms package of R V.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 V.9.4 (SAS Institute) and R V.3.5.0 (The R Foundation for Statistical Computing) statistical programmes.

### 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 hospitalisations 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 preadmission overdose, or for an indication other than oversedation, we identified 293 (0.18%) hospitalisations with opioid administration that resulted in oversedation.

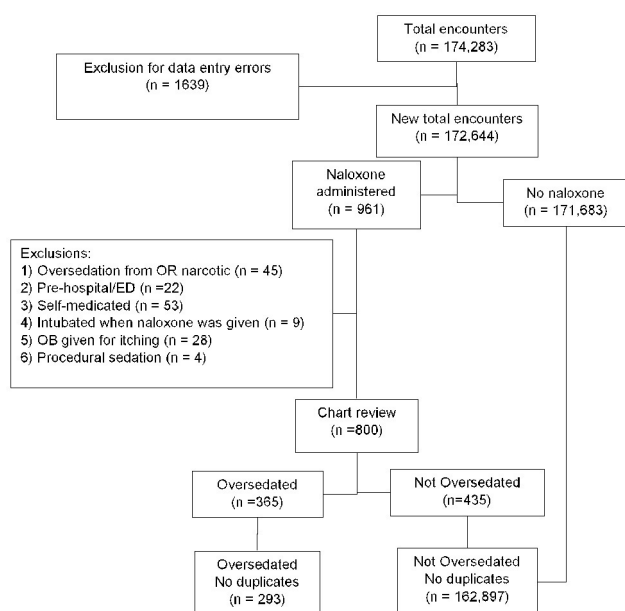
[Table 1](#) compares patients characteristics between oversedated and non-oversedated groups. Bivariate analysis showed significant differences existed for most of the characteristics, except sex, race, ethnicity, average BMI and having a thoracic or large incision that interferes with adequate ventilation. In the multivariable model, age, sex, BMI, COPD, concurrent administration of sedating medication, renal insufficiency, liver insufficiency, opioid naïvety, sleep apnoea 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 HR, 95%CI=3.88, 2.48 to 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 with 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 naïvety 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 hospitalised 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 apnoea or positive sleep apnoea screen. Opioid naïvety 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 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.<sup>29 30</sup> Likewise,



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

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

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

BMI, body mass index; PCA, Patient Controlled Analgesia.

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, coadministration of sedating agents has been shown to increase risk for overdose.<sup>31</sup> Increasing age, presence of sleep apnoea and undergoing surgery, have all been previously identified as risk factors in the literature.<sup>17</sup> In the case of age, physiological changes occur with ageing 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.<sup>32</sup> Possible

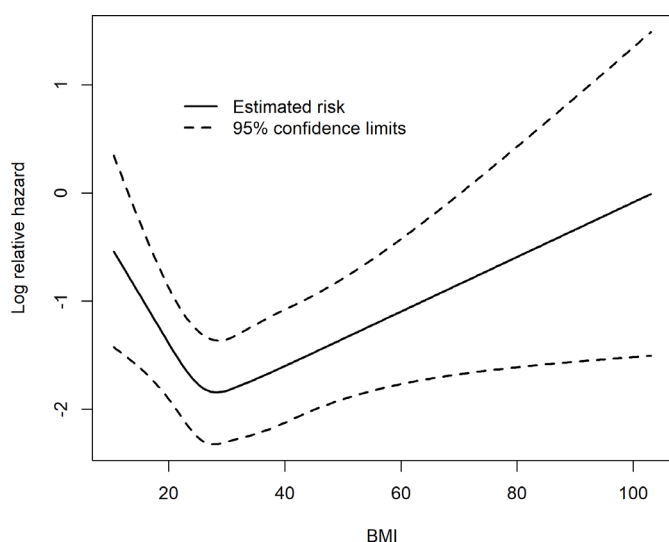
mechanisms that have been proposed for the impact of surgery include a combination of the residual effects of anaesthetic medications, as the risk appears to be greatest during the first 12–24 hours following surgery.<sup>17</sup> With respect to sleep apnoea, it is a prevalent characteristic among patients who die due to critical respiratory events during the first 24 hours following surgery,<sup>18</sup> and among patients who suffer postoperative OIRD.<sup>1</sup> The intermittent hypoxia that is a component of obstructive sleep apnoea 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 hypothesised as explaining the association between sleep apnoea and

**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 analogue	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)

risk for OIRD.<sup>17,33</sup> 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,<sup>12</sup> 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<sup>2</sup>—although a similar relationship between BMI and risk for adverse outcomes has been shown in other contexts.<sup>27</sup>

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 hospitalised medical patients receiving opioids,<sup>24</sup> 0.1% for postoperative patients,<sup>34</sup> 0.3% for patients undergoing major surgery<sup>35</sup> and ≤0.07% in women who had



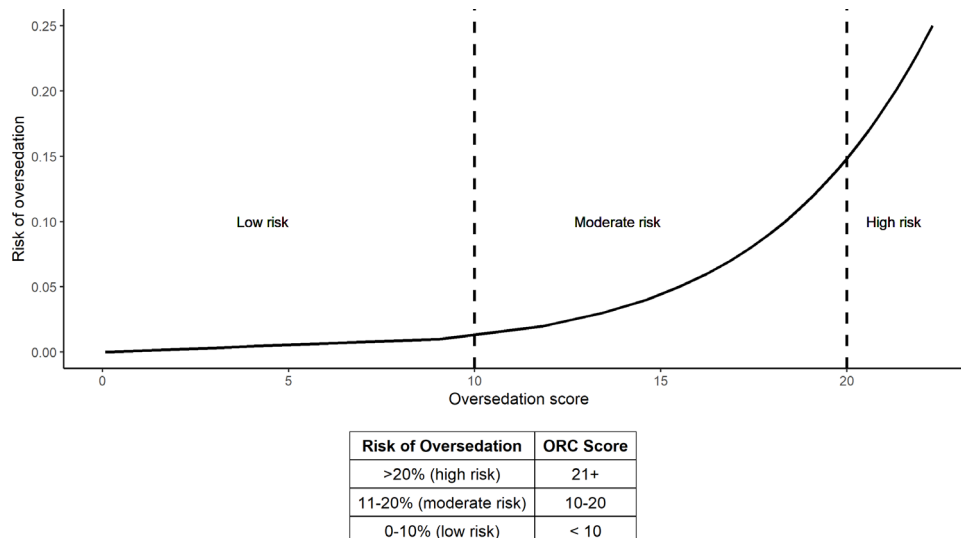
**Figure 2** Risk of opioid-induced respiratory depression or oversedation by body mass index (BMI).

**Table 4** Points assigned per risk factor in the Oversedation Risk Criteria score

Risk factor	Points
Age (years)	
<50	0
50–59	1
60+	2
Sex—female	2
Body mass index (kg/m <sup>2</sup> )	
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 apnoea	2
Surgery within 24 hours	2
Not opioid naïve	1
PCA basal	3

PCA, Patient Controlled Analgesia.

undergone caesarean.<sup>36</sup> 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 hospitalised patients receiving opioids,<sup>16</sup> a large observational study of medical patients hospitalised in the USA receiving opioids<sup>24</sup> 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.<sup>22</sup> One additional case–control study by Pawasauskas *et al*<sup>37</sup> 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 apnoea was included as a risk



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

factor (sleep disorders,<sup>22</sup> untreated sleep apnoea<sup>16</sup> or obstructive sleep apnoea<sup>24</sup>) in all but Pawasauskas *et al.*<sup>37</sup> Two of the previous risk models, as well as Pawasauskas *et al.*,<sup>37</sup> included factors related to the renal insufficiency variable in our risk model (comorbid renal disease<sup>16</sup> and renal failure on admission<sup>24</sup>), but only Pawasauskas *et al.*<sup>37</sup> (hepatic disease) and the risk model developed for medical hospitalisations (hepatic failure on admission<sup>24</sup>) 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,<sup>37</sup> and short-acting benzodiazepine exposure and antipsychotic exposure<sup>24</sup>). While sex was included in all models except Pawasauskas *et al.*,<sup>37</sup> two of the previous studies identified female sex as associated with increased risk<sup>16 24</sup> (as in our model) while the third identified male sex as being so associated.<sup>22</sup> Similarly, opioid naïvety was included in the PRODIGY risk score as a risk factor,<sup>22</sup> while in our model, and in Pawasauskas *et al.*,<sup>37</sup> it was a protective characteristic. This discordance between studies requires further investigation, including into the relative opioid doses received by naïve versus non-naïve patients, and the default dosing applied in the clinical setting being studied. It may be that opioid naïvety is protective in the real-world practice settings where clinicians know to use 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, Pawasauskas *et al.*<sup>37</sup> 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 hospitalisations only<sup>24</sup>), 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).<sup>16</sup> Risk factors they identified and included that were not a part of our model include congestive HF,<sup>22 24</sup> psychosis or depression,<sup>24</sup> opioid abuse/dependence,<sup>24</sup> non-opioid drug abuse/dependence<sup>24</sup> and presence on admission of respiratory failure, shock/hypotension on admission, acidosis or neurological failure.<sup>24</sup> 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 hospitalised patients reported c-statistics of 0.68–0.71,<sup>22 24</sup> which our model modestly outperformed at 0.755, while the remaining risk model, which was developed from a small single centre study, achieved a c-statistic of 0.86.<sup>16</sup> The PRODIGY score showed greater separation in risk for OIRD between its low, medium and high risk score categories (24%, 42% and 65%<sup>22</sup> compared with 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 healthcare 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 healthcare system level, our findings may be less generalisable 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,<sup>24</sup> 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.<sup>8</sup> 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-world 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'.<sup>10</sup> 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 centres: as more procedures that have traditionally been performed in the high resource setting of acute care hospitals transition to such settings,<sup>38</sup> 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 using 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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