Risk Factors for Severe Opioid-Related Adverse Events in a National Cohort of Medical Hospitalizations

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BACKGROUND: Opioids are a leading cause of adverse drug events in the hospital. Guidelines recommend that physicians assess the risks of opioids and discuss them with patients when considering opioid use. There are no studies examining patient- and prescribing-related risk factors for opioid-related adverse drug events (ORADEs) in hospitalized medical patients.

OBJECTIVE: To identify independent risk factors for severe ORADEs in hospitalized medical patients.

DESIGN: Retrospective cohort study.

PATIENTS: Medical patients hospitalized at US, non-federal, and acute care facilities, with at least one pharmacy charge for an opioid during hospitalization. We excluded patients with metastatic malignancy, hospice, or palliative care billing codes.

MAIN MEASURES: We used Cox proportional hazards modeling to identify risk factors for severe ORADEs, defined by a pharmacy charge for naloxone. Candidate risk factors were chosen a priori, based on clinical grounds and prior literature.

KEY RESULTS: Among 731,208 hospitalizations (median age 60, 56.5% female), a severe ORADE occurred in 2727 (0.4%). Independent risk factors included patient characteristics (advanced age, female gender), comorbidities (congestive heart failure, opioid abuse/dependence, non-opioid drug abuse/dependence, psychosis, depression, obstructive sleep apnea), organ failures on admission (respiratory failure, shock/hypotension, renal failure, hepatic failure, acidosis, and neurologic failure), medication co-administrations (antipsychotics and short-acting benzodiazepines), and characteristics of the opioid prescriptions themselves (total dose for the day, parenteral route of administration, and receipt of multiple types of opioids in a day). Although a risk prediction model derived from these factors performed well on stratified *k*-fold cross-validation (average *c*-statistics 0.68–0.71), the low incidence of the outcome limited the positive predictive value of the risk score.

CONCLUSIONS: In this national cohort of medical patients, we identified several risk factors for ORADEs that can be used to inform physician decision-making, conversations with patients about risk, and development and targeting of harm reduction strategies for at-risk populations.

KEY WORDS: opioids; naloxone; adverse effects of opioids; adverse drug events; risk scores; hospitalization.

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INTRODUCTION

Opioid medications are one of the leading causes of adverse drug events in hospitalized patients in the USA.[1, 2] Severe opioid-related adverse drug events (ORADEs), including somnolence, respiratory depression, and cardiopulmonary arrest, have been associated with increased length of stay, higher cost of care, increased risk of 30-day readmission, and increased in-hospital mortality.[3–9]

Identifying risk factors for ORADEs is important because more than half of all medical and surgical patients receive an opioid medication while hospitalized.[3–5] Risk factors identified in the surgical and outpatient literature include *patient-related factors*, like age,[4–6, 10–12] male sex,[4, 6] obesity,[4, 6] chronic obstructive pulmonary disease (COPD),[5, 13] obstructive sleep apnea (OSA),[14–16] reduced renal or hepatic function,[17] pre-surgery opioid use,[4, 5] mental health comorbidities,[18] prior substance use disorders,[18, 19] and higher comorbidity burden,[4, 5, 11] as well as *prescribing-related factors*, such as high doses[6, 8, 14, 15, 20, 21] and co-administration of other sedating medications.[13, 14, 20] Although studies have evaluated risk factors for ORADEs in surgical patients, we are aware of just two prior studies examining risk factors for

ORADEs in hospitalized medical patients.[13, 22] Patients hospitalized for medical reasons are fundamentally different from those hospitalized for surgical reasons with respect to demographics, comorbidities, the conditions prompting opioid use, and even the characteristics of the opioid prescriptions themselves (e.g., type, route, frequency). Of the prior studies examining risk factors in medical hospitalizations, one was limited by small sample size, while the other was limited by reliance on non-specific administrative billing codes for cardiopulmonary arrest to define the outcome, and lack of information on prescribing-related risk factors, such as opioid dose or route of administration.[22]

Developing a better understanding of ORADE risk factors in hospitalized medical patients is crucial to inform the risk-to-benefit calculations and discussions with patients widely advocated by recent guidelines on safe opioid prescribing[23, 24] and to appropriately target interventions to mitigate risk.[25, 26] In this study, we sought to identify independent risk factors for severe ORADEs in a large, national cohort of medically hospitalized patients. We hypothesized that both patient characteristics and characteristics of the opioid administrations themselves (e.g., dose, route) would be associated with severe ORADEs.

METHODS

Setting and Patients

We conducted a retrospective cohort study using data from all US, non-federal, and acute care facilities contributing to the Premier database (Premier Healthcare Solutions, Inc., Charlotte, NC, USA). This database, created to measure healthcare utilization and quality of care, is drawn from voluntarily participating hospitals and contains data on approximately 20% of hospital discharges nationwide.[27] Participating hospitals are similar in geographic distribution and metropolitan status to hospitals nationwide, although large teaching hospitals, and hospitals in the Southern USA are overrepresented. The database contains patient demographics, *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification* (*ICD-10-CM*) codes, and a date-stamped log of all charges, including medications. Because the data do not contain identifiable information, the Baystate Medical Center Institutional Review Board determined that this study did not constitute human subjects research.

All medical hospitalizations for patients at least 18 years of age at participating hospitals from January 1, 2016 to December 31, 2016 with at least one pharmacy charge for an opioid medication were eligible for inclusion. We defined a medical hospitalization as one that had a Medicare Severity-Diagnosis Related Group (MS-DRG) flagged as medical and did not have operating room charges. Because the goals of opioid therapy in the setting of cancer-related pain or palliative care are unique, we excluded hospitalizations of patients with metastatic malignancy (defined by presence of an *ICD-10-CM* code indicative of metastatic malignancy as defined by the Healthcare Cost and Utilization Project (HCUP) comorbidity measures)[28] and patients admitted from hospice (where admission source is "transfer from hospice") or with a palliative care code (*ICD-10-CM* Z51.5) classified as present on admission. We also excluded hospitalizations with missing information on opioid dose or extreme opioid doses, defined as presence of any hospitalization days with a total oral morphine equivalent dose > 99th percentile (660 mg in oral morphine equivalents), since these are likely to represent erroneous data entries. We excluded hospitalizations with a naloxone charge prior to the first opioid charge and those with a naloxone charge more than 1 day from the last opioid charge since these circumstances make the event less likely to be attributable to in-hospital opioid use. Finally, we excluded hospitalizations with unknown gender.

Opioid Exposure

We defined opioid exposure as presence of any pharmacy charge where the drug class was defined as "opioids" in the Premier dataset (codeine, buprenorphine, butorphanol, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, tapentadol, tramadol).

Severe ORADEs

We defined occurrence of a severe ORADE by presence of a charge for naloxone, since naloxone is almost exclusively used for treatment of a suspected severe opioid-related adverse event, including sedation or respiratory depression. In addition, naloxone is one of the Institute for Healthcare Improvement's (IHI) "triggers" for identifying adverse drug events.[29] A study assessing the positive predictive value of naloxone for adverse drug events in adult patients in a hospital setting found a high positive predictive value of 91%.[30]

Candidate Risk Factors

We chose candidate risk factors based on clinical grounds and previously demonstrated associations in other patient populations and settings of care, hypothesizing that each would be associated with severe ORADEs. They included the following:

- *Demographics*: age, gender
- *Comorbidities*: congestive heart failure, chronic pulmonary disease, obesity, alcohol abuse, drug abuse (separated into two variables representing opioid abuse/dependence and non-opioid drug abuse/dependence), psychoses, and depression, all defined by the HCUP comorbidity measures,[28] and obstructive sleep apnea and dementia, defined using *ICD-9/10-CM* codes in any position, listed in Online Appendix Table 1
- *Organ failure present on admission*: hematological, respiratory, cardiovascular (shock/hypotension), renal,

hepatic, acidosis, and neurologic, defined and operationalized in prior analyses using *ICD-9-CM* codes flagged as present on admission,[31] which we converted to *ICD-10-CM* codes using a publicly available conversion tool from the Centers for Medicare and Medicaid Services[32] (Online Appendix Table 1)

- *Medication co-administrations*: benzodiazepines (grouped as short- and long-acting), and antipsychotics
- *Probable opioid-maintenance therapy*: defined by presence of charges within the first 2 days of hospitalization for once daily methadone or any buprenorphine
- *Probable pre-existing long-term opioid therapy*: defined by presence of charges within the first 2 days of hospitalization for any long-acting opioid except once daily methadone (which would count as "probable opioid-maintenance therapy")
- *Prescription characteristics*: total opioid dose during calendar day in oral morphine equivalents (OME), route of administration (oral/rectal, parenteral/transdermal), and number of types of opioids during calendar day (single or multiple, defined by presence of at least 2 different opioid drugs [e.g., morphine and hydromorphone], or different formulations of the same drug [e.g., long-acting and short-acting morphine])

Statistical Analysis

We report cohort characteristics and outcomes stratified by presence or absence of a severe opioid-related ADE and calculated standardized mean differences (SMD) to gauge differences between groups, with SMD > 0.10 considered meaningful.[33]

We used Cox proportional hazards modeling to identify independent predictors of severe ORADEs. We chose this approach to account for the time-varying nature of several of our candidate risk factors, including medication co-administrations and opioid prescription characteristics, which can change daily. We defined time zero as the day of the first opioid administration, excluding from the analysis any time prior to opioid administration since patients are not at risk for an in-hospital ORADE until they are exposed in the hospital. Observations were censored at hospital discharge or 15 days after the first opioid administration to avoid inclusion of outlier time, which would not be representative of the typical medical patient. We hypothesized that the relationship between opioid dose and severe ORADEs would be impacted by pre-hospitalization opioid use, so assessed for effect modification of dose by pre-hospitalization long-term opioid use.

To increase the usability of the model, we took steps to make it parsimonious. First, we combined candidate risk factors that were clinically similar, had a similar magnitude of effect, and where a test of contrast yielded a p value > 0.05. On this basis, we combined probable opioid-maintenance therapy and probable pre-existing long-term opioid therapy into a single variable representing probable pre-hospitalization long-term opioid use. We also combined psychoses and depression into a single variable representing psychoses/depression. Finally, we retained only those variables with $p < 0.05$ in the final model.

We used stratified k-fold cross-validation to assess the internal validity of our model.[34] Using this methodology, we divided the data into 5 segments ("folds") stratified by outcome to achieve approximately the same rate of outcome in each stratum. We then refit the model we developed on the full cohort in 4 of the "folds" (80% data) and validated it on the remaining fold (20% data). This was performed a total of 5 times, leaving out a different "fold" each time. We computed c-statistics as a measure of model fit for each validation "fold" and computed the mean and standard deviation of the five c-statistics obtained in this manner.

We used our final model to develop a point scoring system for daily risk calculation.[35] To do so, we first ranked predictor variables based on their regression coefficients. We then set the largest beta coefficient to a point score of 10 and sequentially assigned point values for other predictors based on their relative coefficients. We grouped age into discrete categories and rounded to whole numbers to simplify computation of the score. We calculated test characteristics based on different point thresholds and used these values to derive receiver operating curves (ROC) by day for the first 3 days.

All analyses were carried out using the SAS software, version 9.4, Cary, NC.

RESULTS

Cohort Characteristics

There were 5,240,538 adult hospitalizations at 516 participating hospitals from January 1, 2016 to December 31, 2016. After exclusions (Online Appendix Figure 1), 731,208 medical hospitalizations were included in our analytic cohort (see Table 1 for cohort characteristics). The median age was 60, and females represented 56.5% of the cohort. The most common primary diagnoses overall, based on the Agency for Healthcare Research and Quality Clinical Classification System,[36] were septicemia (7.1%), skin and subcutaneous tissue infections (4.2%), and congestive heart failure (3.5%). The most common diagnoses among hospitalizations with a severe ORADE were septicemia (9.2%), cardiac dysrhythmias (5.2%), and poisoning by other medications and drugs (5.2%). The most commonly used opioid was morphine (323,956, 44.3%), followed by hydrocodone (221,447, 30.3%) and oxycodone (196,694, 26.9%).

Unadjusted Associations Between Candidate Risk Factors and Severe ORADEs

A severe ORADE occurred in 2727 (0.4%) hospitalizations, with 1635 (60%) occurring on day 1 of opioid exposure, 532

Table 1 Cohort Characteristics and Outcomes Stratified by Presence or Absence of a Severe Opioid-Related Adverse Drug Event (ORADE; *N* = 731,208)

Characteristics	No ORADE	Severe ORADE	SMD
	n = 728,481(99.6%)	*n* = 2727(0.4%)	
Demographics			
Age in years—median (Q1–Q3)	60 (46–73)	61 (49–74)	0.06
Female—*n* (%)	411,600 (56.5)	1637 (60.0)	0.07
Comorbidities—*n* (%)			
Congestive heart failure	137,980 (18.9)	644 (23.6)	0.11
Chronic pulmonary disease	208,622 (28.6)	903 (33.1)	0.10
Obesity	129,406 (17.8)	522 (19.1)	0.04
Alcohol abuse	51,509 (7.1)	216 (7.9)	0.03
Opioid abuse/dependence	26,115 (3.6)	353 (12.9)	0.34
Non-opioid drug abuse/dependence	40,468 (5.6)	260 (9.5)	0.15
Psychoses	39,467 (5.4)	244 (8.9)	0.14
Depression	119,503 (16.4)	623 (22.8)	0.16
Obstructive sleep apnea	68,010 (9.3)	330 (12.1)	0.09
Dementia	45,555 (6.3)	215 (7.9)	0.06
Organ failure present on admission—*n* (%)			
Hematological†	35,704 (4.9)	162 (5.9)	0.05
Respiratory	8177 (1.1)	69 (2.5)	0.11
Cardiovascular (shock/hypotension)	31,480 (4.3)	304 (11.1)	0.26
Renal (acute)	105,168 (14.4)	560 (20.5)	0.16
Hepatic	5695 (0.8)	49 (1.8)	0.09
Acidosis	32,722 (4.5)	217 (8.0)	0.14
Neurologic‡	26,498 (3.6)	325 (11.9)	0.31
Medication co-administrations§—*n* (%)			
Long-acting benzodiazepine	36,267 (5.0)	128 (4.7)	0.01
Short-acting benzodiazepine	245,065 (33.6)	1132 (41.5)	0.16
Antipsychotic	59,692 (8.2)	300 (11.0)	0.10
Probable pre-existing long-term opioid therapy—*n* (%)	36,705 (5.0)	320 (11.70)	0.24
Probable opioid-maintenance therapy—*n* (%)	10,170 (1.4)	85 (3.1)	0.12
Opioid prescription characteristics			
Total opioid dose per calendar day in mg oral morphine equivalents—mean (median, Q1–Q3)	39 (19, 8–43)	61 (30, 15–72)	0.30
Oral/rectal§—*n* (%)	501,243 (68.8)	1539 (56.4)	0.26
Parenteral/transdermal§—*n* (%)	482,832 (66.3)	1955 (71.7)	0.19
Multiple opioid types in single day¶—*n* (%)	269,849 (37.0)	983 (36.0)	0.02
Outcomes			
Length of hospitalization in days—mean (median, Q1–Q3)	3.6 (3, 2–4)	4.4 (3, 2–6)	0.23
Total charges—mean (median, Q1-Q3)	28,548 (22,358, 14,395–34,869)	37,240 (28,970, 17,843–45,603)	0.31
Readmission within 30 days—*n* (%)	79,826 (11.0)	335 (12.3)	0.04
In-hospital mortality—*n* (%)	8136 (1.1)	168 (6.2)	0.27

SMD standardized mean difference, Q quartile
† Includes platelet and/or coagulation defects (see Online Appendix Table 1 for specific ICD-10-CM codes)
‡ Includes delirium/encephalopathy, psychiatric disorders due to underlying medical illness, anoxic brain injury, and altered level of consciousness (see Online Appendix Table 1 for specific ICD-10-CM codes)
§At any point during the hospitalization
¶Includes administration of more than one type of opioid (i.e., morphine and hydromorphone) and/or different formulations of the same opioid (i.e., short-acting and long-acting morphine)

(20%) on day 2, and 230 (8%) on day 3. Compared to hospitalizations without a severe ORADE, hospitalizations with a severe ORADE had higher rates of each of the HCUP-defined comorbidities, notably opioid abuse/dependence (3.6% vs 12.9%) and depression (16.4% vs 22.8%), higher rates of in-hospital benzodiazepine (36.1% vs 44.7%) and antipsychotic use (8.2% vs 11.0%), greater total daily opioid doses on average (39 vs 61 mg OME), and a greater incidence of parenteral opioid administration (65.4% vs 70.0%; Table 1).

Adjusted Associations Between Candidate Risk Factors and Severe ORADEs

In multivariable Cox proportional hazards modeling, we identified several significant predictors of a severe ORADE (Table 2), the strongest of which were opioid abuse/dependence (HR 2.8, 95% CI 2.4–3.1), cardiovascular organ failure (shock/hypotension) present on admission (HR 2.2, 1.9–2.5), neurologic organ failure present on admission (HR 2.8, 2.4–3.1), and receipt of more than one type of opioid in the same day (HR 2.1, 1.5–2.7). The model performed well on stratified *k*-fold cross-validation, with average *c*-statistics of 0.68–0.71 for all derivation and validation "folds" (Online Appendix Table 2).

Severe ORADE Risk Score

The scoring system derived from the associated model coefficients is presented in Table 3. Hospitalizations with a severe ORADE had greater mean point scores than hospitalizations without a severe ORADE on all days examined (Online Appendix Table 3). The relationship between risk score on day

Table 2 Adjusted Association Between Characteristics and Severe Opioid-Related Adverse Drug Events in the Final Model (n = 731,208)

Characteristics	Beta coefficient	Hazard ratio	95% CI
Demographics			
Age in years (per 10 years)	0.04	1.04	1.01–1.06
Female	0.17	1.2	1.1–1.3
Comorbidities			
Congestive heart failure	0.20	1.2	1.1–1.3
Opioid abuse/dependence	1.02	2.8	2.4–3.1
Non-opioid drug abuse/dependence	0.36	1.4	1.2–1.6
Psychoses/depression	0.20	1.2	1.1–1.3
Obstructive sleep apnea	0.24	1.3	1.1–1.4
Organ failure present on admission			
Respiratory	0.52	1.7	1.3–2.1
Cardiovascular (shock/hypotension)	0.80	2.2	1.9–2.5
Renal	0.20	1.2	1.1–1.3
Hepatic	0.43	1.5	1.1–2.0
Acidosis	0.26	1.3	1.1–1.5
Neurologic*	1.02	2.8	2.4–3.1
Medication co-administrations			
Short-acting benzodiazepine	0.58	1.8	1.6–1.9
Antipsychotic	0.20	1.2	1.1–1.4
No pre-hospitalization long-term opioid use			
Total opioid dose on calendar day in 10 mg oral morphine equivalents	0.01	1.0	1.0–1.0
Probable pre-hospitalization long-term opioid use			
Total opioid dose on calendar day in 10 mg oral morphine equivalents	0.83	2.3	1.9–2.7
Opioid prescription characteristics			
Oral/rectal	− 0.31	0.7	0.6–0.9
Parenteral/Transdermal	0.24	1.3	1.1–1.5
One opioid type on calendar day	0.59	1.8	1.4–2.2
Multiple opioid types on calendar day†	0.74	2.1	1.5–2.7

CI confidence interval
**Includes delirium/encephalopathy, psychiatric disorders due to underlying medical illness, anoxic brain injury, altered level of consciousness (see Online Appendix Table 1 for specific ICD-9-CM/ICD-10-CM codes)*
†Includes administration of more than one type of opioid (i.e., morphine and hydromorphone) and/or different formulations of the same opioid (i.e., short-acting and long-acting morphine)

1 of opioid receipt and the incidence of a severe ORADE is demonstrated in Figure 1a. The proportion of hospitalizations falling into each risk category on hospital day 1 is demonstrated in Figure 1b. Hospitalizations with a score of 12 or more on hospital day 1 had a risk of severe ORADE of 1.1% and represented 3.8% of the cohort, while hospitalizations with a score of 15 or more had a risk of severe ORADE of 1.7% and represented 0.6% of the cohort.

For each day of opioid receipt, we calculated the sensitivity, specificity, and positive predictive value of different point score thresholds, and used these values to derive ROC curves. Table 4 demonstrates these test characteristics for day 1 of opioid receipt (see Online Appendix Table 4 for test characteristics for days 1, 2, and 3 and Online Appendix Figure 2 for the corresponding ROC curves). Based on these test characteristics, using a point score cutoff of 3 or more to define "high risk" would identify 100% of the severe ORADEs but would be associated with less than 1% specificity (i.e., high false-positive rate). Using a point score cutoff of 12 or more would be associated with greater than 95% specificity but less than 20% sensitivity for detecting severe ORADEs (i.e., high false-negative rate). The cutoff that simultaneously maximizes sensitivity and specificity is a point score of 8 or more, resulting in 61% sensitivity, 71% specificity, and a positive predictive value of 0.46%.

DISCUSSION

In this large cohort of medical hospitalizations across the USA, we identified several independent predictors of severe ORADEs, including patient characteristics (advanced age, female gender), comorbid diseases (congestive heart failure, opioid abuse/dependence, non-opioid drug abuse/dependence, psychosis, depression, obstructive sleep apnea), organ failures at the time of admission (respiratory failure, shock/hypotension, renal failure, hepatic failure, acidosis, and neurologic failure), medication co-administrations (antipsychotics and short-acting benzodiazepines), and characteristics of the opioid prescriptions themselves (total dose for the day, parenteral

Table 3 Scoring System for Severe Opioid-Related Adverse Drug Events

Risk factor	Points
Age 30–74	1
Age 75+	2
Female	1
Congestive heart failure	1
Opioid abuse/dependence	4
Non-opioid drug abuse/dependence	1
Psychosis or depression	1
Obstructive sleep apnea	1
Respiratory failure present on admission	2
Shock/hypotension present on admission	3
Renal failure present on admission	1
Hepatic failure present on admission	2
Acidosis present on admission	1
Neurologic failure present on admission*	4
Antipsychotic exposure	1
Short-acting benzodiazepine exposure	2
No pre-hospitalization long-term opioid use	0
Total opioid dose for the day	0.005† dose in mg OME
Parenteral only	4
Oral only	2
Parenteral and oral	3
Pre-hospitalization long-term opioid use	4
Total opioid dose for the day	− 0.01† dose in mg OME
Parenteral only	3 (+ 1 if multiple parenteral agents‡)
Oral only	1 (+ 1 if multiple oral agents‡)
Parenteral and oral	3

**Includes delirium/encephalopathy, psychiatric disorders due to underlying medical illness, anoxic brain injury, altered level of consciousness (see Online Appendix Table 1 for specific ICD-9-CM/ICD-10-CM codes)*
†Score must be updated daily to account for changes in medications
‡Includes administration of more than one type of opioid (i.e., morphine and hydromorphone), as well as different formulations of the same opioid (i.e., short-acting and long-acting morphine)

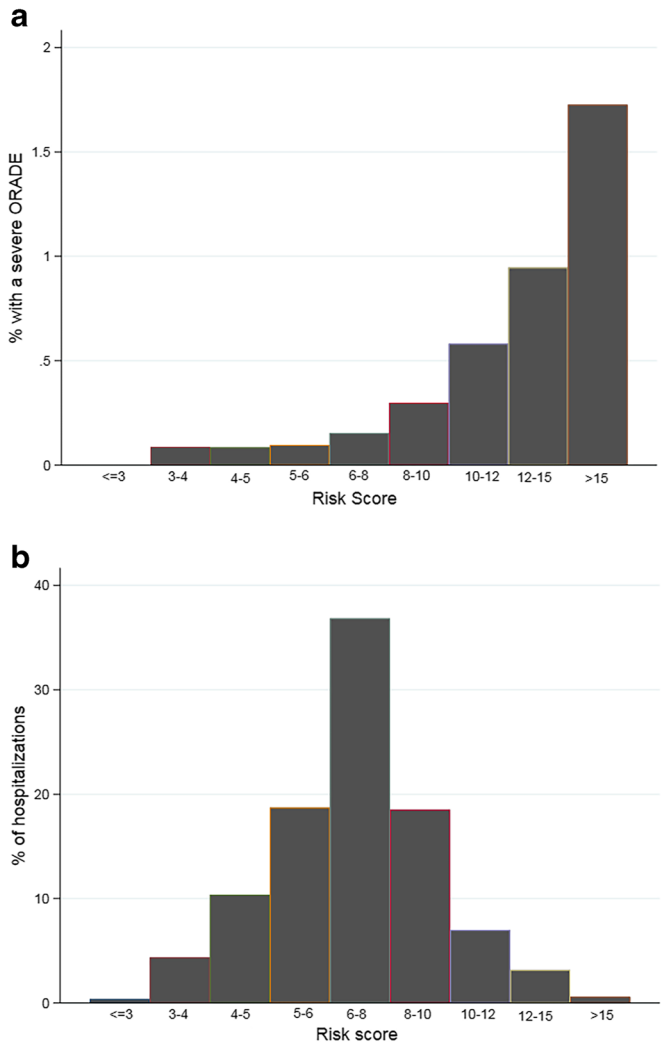

Figure 1 a Bar graph of the percentage of hospitalizations with a severe opioid-related adverse drug event (ORADE) by risk score on day 1 of opioid receipt. b Histogram of the percentage of hospitalizations falling into each risk score category.

route of administration, and receipt of multiple types of opioids in a day). Although a risk prediction model derived from these factors performed well on internal validation, the low incidence of the outcome limited the positive predictive value of the risk score. Awareness of the risk factors themselves, however, may help physicians, hospital systems, and researchers identify patients at higher risk for a severe ORADE, to inform decisions around dosing, sedative co-administration, conversations with patients, and development or deployment of risk-mitigation strategies.

Prior analyses have demonstrated increased risk of cardiopulmonary and respiratory arrest in hospitalized patients exposed to opioids.[22, 37, 38] We are aware of just two prior studies examining risk factors for these outcomes among hospitalized

Table 4 Test Characteristics of Point Scoring System on Day 1 of Opioid Receipt (n = 731,208)

Point score	Sensitivity	Specificity	PPV	TP	FP	TN	FN
≥ 1	1.00	0.00	0.22%	1635	729,505	68	0
≥ 2	1.00	0.00	0.22%	1635	729,438	135	0
≥ 3	1.00	0.00	0.22%	1635	726,821	2752	0
≥ 4	0.98	0.05	0.23%	1607	695,089	34,484	28
≥ 5	0.94	0.15	0.25%	1543	619,420	110,153	92
≥ 6	0.86	0.34	0.29%	1409	482,722	246,851	226
≥ 7	0.75	0.55	0.37%	1219	331,611	397,962	416
≥ 8	0.61	0.71	0.46%	998	213,721	515,852	637
≥ 9	0.48	0.82	0.60%	788	131,165	598,408	847
≥ 10	0.36	0.89	0.75%	595	78,335	651,238	1040
≥ 11	0.26	0.94	0.89%	418	46,693	682,880	1217
≥ 12	0.18	0.96	1.07%	297	27,497	702,076	1338

PPV positive predictive value, TP true positives, FP false positives, TN true negatives, FN false negatives

medical patients.[13, 22] One was a small, single-center case-control analysis that presented only unadjusted associations.[13] The other also used data from Premier, but differed from ours in that their outcome was defined using *ICD-9-CM* codes for cardiopulmonary arrest, respiratory arrest, and cardiopulmonary resuscitation, precluding determination of the day of hospitalization upon which the adverse event occurred, and increasing the chance of bias in their observed associations owing to lack of specificity in their outcome definition. They focused on patient-level predictors and did not examine prescribing-related predictors. The risk factors identified in our analysis have good face validity in that they are consistent with those demonstrated by others in surgical patient populations,[4, 5, 8, 10, 13–15] and the outpatient setting.[20, 21, 23, 39–44]

We chose to focus on severe ORADEs, rather than all ORADEs, for several reasons. First, we did not feel it made clinical sense to group multiple types of ORADEs together (e.g., nausea, constipation, delirium, and opioid-related respiratory depression), since the severity, implications, and predictors of these events are likely to differ. Second, naloxone administration is likely to be more specific to an opioid-related complication relative to other types of adverse events; for example, the causes of delirium are numerous.

Using naloxone administration as a marker of a possible adverse event was originally proposed by Classen et al.,[45] who observed that use of an antidote such as naloxone is one of the most common signals of a subsequently confirmed adverse drug reaction. Naloxone use was subsequently incorporated into the IHI's "adverse drug event trigger tool."[29] A study assessing the positive predictive value of naloxone for adverse drug events in adult patients in a hospital setting found a high positive predictive value of 91%.[30] The high specificity of this outcome definition helps to assure unbiased effect estimates,[46] while simultaneously providing a "date-stamp" for the occurrence of the ORADE, which would not have been available had we used diagnosis codes to define ORADEs.

Despite generally good discriminative ability of our model, the low prevalence of severe ORADEs in this patient population limits the positive predictive value of the scoring system. This poses challenges for application of risk modification strategies, since fewer than 2% of patients experienced a severe ORADE even in the highest risk category. An intervention would have to be low cost, easily adoptable, and not associated with any detrimental secondary effects to be useful in such a scenario. Electronic health record-based alerts for high risk patients being prescribed opioids is an example of a low cost, flexible intervention that, rather than prohibiting opioid prescribing, could provide important clinical information at the point of care to inform the risk-to-benefit assessment widely advocated by recently released opioid prescribing guidelines.[23, 24] Knowledge of factors that place a patient at heightened risk for a severe ORADE can also be used to facilitate conversations with patients and caregivers about the risks, as recommended in the guidelines.[23, 24]

There are additional limitations of this analysis. The lack of information on pre-admission medication use in the Premier database necessitated use of proxy variables to measure long-term pre-admission opioid medication use, including charges for long-acting opioids in the first 2 days of the hospitalization. This approach would have missed pre-admission use of short-acting opioids, which could be another important predictor of ORADEs. Additionally, our reliance on diagnosis codes to identify some risk factors could have resulted in misclassification and makes prospective operationalization more difficult. Nevertheless, physicians are typically aware of comorbidities and organ failures present at the time of admission.

In conclusion, in this large, national cohort of medical hospitalizations, we identified several risk factors for severe ORADEs, which can be used to inform physician decision-making around pain management, conversations with patients or to target at-risk populations for design and testing of interventions to mitigate opioid-associated risk.

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