Opioid-Induced Respiratory Depression Increases Hospital Costs and Length of Stay in Patients Recovering on the General Care Floor

Ashish Khanna (ashish@or.org)  
Wake Forest School of Medicine

Leif Saager  
Universitätsmedizin Göttingen

Sergio Bergese  
Stony Brook Medicine

Carla Jungquist  
University at Buffalo School of Nursing

Hiroshi Morimatsu  
Okayama University Hospital

Shoichi Uezono  
Jikei University School of Medicine

Lian Kah Ti  
National University of Singapore

Roy Soto  
Beaumont Hospital

Wei Jiang  
Medtronic Inc.

Wolfgang Buhre  
University Medical Center

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Abstract

**Background:** Opioid-induced respiratory depression is common on the general care floor. However, the clinical and economic burden of respiratory depression is not well-described. The PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial created a prediction tool to identify patients at risk of respiratory depression. The purpose of this retrospective sub-analysis was to examine healthcare utilization and hospital cost associated with respiratory depression.

**Methods:** 1,335 patients (N=769 United States patients) enrolled in the PRODIGY trial received parenteral opioids and underwent continuous capnography and pulse oximetry monitoring. Cost data was retrospectively collected for 420 United States patients. Differences in healthcare utilization and costs between patients with and without ≥1 respiratory depression episode were determined. The impact of respiratory depression on hospital cost per patient was evaluated using a propensity weighted generalized linear model.

**Results:** Patients with ≥1 respiratory depression episode had a longer length of stay (6.4 ± 7.8 days vs 5.0 ± 4.3 days, p=0.009) and higher hospital cost ($21,892 ± $11,540 vs $18,206 ± $10,864, p=0.002) compared to patients without respiratory depression. Patients at high risk for respiratory depression, determined using the PRODIGY risk prediction tool, who had ≥1 respiratory depression episode had higher hospital costs compared to high risk patients without respiratory depression ($21,948 ± $9,128 vs $18,474 ± $9,767, p=0.0495). Propensity weighted analysis identified 17% higher costs for patients with ≥1 respiratory depression episode (p=0.007). Length of stay significantly increased total cost, with cost increasing exponentially for patients with ≥1 respiratory depression episode as length of stay increased.

**Conclusions:** Respiratory depression on the general care floor is associated with a significantly longer length of stay and increased hospital costs. Early identification of patients at risk for respiratory depression may reduce the incidence of respiratory depression and its associated clinical and economic burden.

**Trial registration:** ClinicalTrials.gov, NCT02811302

**Background**

A large majority of all adverse events in hospitalized patients transpire before arrival in the intensive care unit (ICU), including 41% of in-hospital cardiac arrest events. When these events occur, about 40% of patients die before they leave the hospital [1]. Though perceived as a low-acuity environment, the hospital ward is actually a common venue for critical events during a period in which patients are especially prone to developing clinical deterioration and life-threatening complications [2, 3].

An episode of respiratory depression is very common on the general care floor, occurring in up to 46% of patients [4]. Respiratory depression, if defined by hypoxemia, occurs in up to a fifth of all continuously monitored patients for at least an hour of duration of recovery after non-cardiac surgery on the general...
care floor [5]. These are not benign occurrences, but may be associated with a series of adverse events [4, 6–12]. Opioid-induced respiratory depression is a common variant that is associated with significant morbidity and mortality [11–14]. Urman and colleagues examined 13,389 index hospitalizations where initially opioid-free patients underwent surgery. Of the 12,218 (91%) patients who received postoperative opioids, 1,111 (9.1%) were identified to have potential Opioid Related Adverse Drug Events (ORADEs), of which 52% were respiratory in nature. Furthermore, the presence of an ORADE was associated with 55% longer postoperative length of stay, 29% lower odds of discharge home, and 2.9 times the odds of death [15]. Similarly, Kessler and colleagues showed that from an initial cohort of 36,529 patients, 98.6% received opioids, and 13.6% patients with an ORADE had a 55% longer length of stay, 36% increased risk of 30-day readmission, and 3.4 times higher risk of inpatient mortality than did patients who did not experience an ORADE [14]. This extent of clinical burden is supported by other literature as well [11, 16–20]. In addition to being clinically burdensome, ORADEs are costly. Numerous studies report the additive (risk-adjusted) hospitalization cost burden of surgical patients with ORADEs to be between $4350–$8225, [14, 15, 17, 20] representing a 27%-47% increase in (risk-adjusted) admission costs. Importantly, a majority of these increases in healthcare utilization and cost were assessed for all ORADEs and did not delineate differences between respiratory vs non-respiratory ORADEs. Need for postoperative oxygen as a surrogate for opioid-induced respiratory depression in the post-anesthesia care unit is also associated with significant increases in day of surgery charges, respiratory charges, total charges, hospital length of stay, reintubation, and use of invasive or non-invasive ventilatory support [21].

Recently, the international PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial identified a 46% incidence of opioid-induced respiratory depression episodes [4]. These episodes were detected by continuous capnography and pulse oximetry monitoring using the Capnostream™ 20p or 35 portable bedside monitor (Medtronic, Boulder, CO), which collects and displays end-tidal carbon dioxide, respiratory rate, pulse oximetry, and pulse rate on a single monitor [22]. As an observational trial, the monitor alarms were silenced and the monitor screen turned off to blind healthcare providers to the monitoring data. Standard of care monitoring was performed per site protocol [4]. Adverse events requiring rescue action or prolonged hospitalization occurred more commonly in patients with $\geq 1$ opioid-induced respiratory depression episode. Mean hospital length of stay was 3 days longer as well, in these patients. Although the impact of general ORADEs on healthcare resource utilization and cost is well described, less is understood about the influence of respiratory ORADEs, including respiratory depression episodes, on length of stay and cost. Therefore, we performed a priori analyses to derive length of stay and cost comparisons in United States patients with and without opioid-induced respiratory depression in an analysis of the PRODIGY cohort.

**Methods**

**Patient population**

The observational PRODIGY trial (ClinicalTrials.gov: NCT02811302, 23/06/2016) enrolled 1,495 post-surgical or medical patients expected to receive parenteral opioids on the general care floor across 16 trial
sites in 7 countries (United States, Japan, Singapore, Germany, France, the Netherlands, and Spain) between April 2017 and May 2018 [4, 22]. Patients who did not receive parenteral opioids and/or did not undergo continuous capnography and pulse oximetry monitoring were excluded from the primary study analysis, resulting in an analysis cohort of 1,335 patients in 7 countries [4]. Clinical trial registration, institution approval (Institutional Review Board or Research Ethics Committee, depending on trial site) and written informed consent were completed before patients were enrolled and continuously monitored using blinded capnography and pulse oximetry monitoring (Capnostream™ 20p or 35 portable bedside monitor, Nellcor™ pulse oximetry, Medtronic, Boulder, CO) for up to 48 hr. This study was approved by the Institutional Review Board or Research Ethics Committee, depending on trial site. The study protocol was performed in accordance with the Declaration of Helsinki, laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan. Institutional Review Board and Research Ethics Committees that approved this research include the following: CPP Ile de France 2 (Hopital Foch); Ethik-Kommission Medizinische Fakultät (University Hospital Bonn); Rinshoushiken Shinsa Senmon Inkai (Okayama University Hospital); The Jikei Ethics Committee (Jikei University); METC MUMC+ (University Medical Center, Maastricht); National Healthcare Group (NHG) Domain Specific Review Board (DSRB) (National University of Singapore); Comité de Ética del Hospital Clinico Universitario de Valencia (Hospital Clinico Universitario de Valencia); Western Institutional Review Board (Beaumont Hospital, Emory University, Ohio State University Wexner Medical Center, and Providence Regional Medical Center); Partners Human Research Committee (Brigham and Women's Hospital); Cleveland Clinic Institutional Review Board (Cleveland Clinic); The MetroHealth System Institutional Review Board (MetroHealth Medical Center); University at Buffalo Institutional Review Board (University at Buffalo); Colorado Multiple Institutional Review Board (University at Colorado).

Of the 1,495 prospectively enrolled PRODIGY patients, 1,335 patients underwent continuous capnography and pulse oximetry monitoring and received opioids on the general care floor, including 769 patients in the United States. This sub-analysis of healthcare utilization data, which was prospectively collected during the trial, was performed using the 769 United States patients (N = 566 patients outside of the United States were excluded). Within the United States patient cohort (N = 769), retrospectively collected cost data was unavailable for 349 patients, resulting in a final patient cohort of 420 United States PRODIGY patients for analysis of cost differences between patients with and without ≥ 1 respiratory depression episode. Although provision of cost data was not a requirement for site participation in the trial, the cost data for the 420 patients was collected from five United States PRODIGY trial sites (Beaumont Hospital, Royal Oak, MI; Buffalo General Medical Center, Buffalo, NY; Emory University, Atlanta, GA; MetroHealth Medical Center, Cleveland OH; The Ohio State University Medical Center, Columbus, OH). Due to confounding factors, such as differences in healthcare policies that affect patient length of stay and readmission procedures between countries, differences in healthcare cost and reimbursement systems between countries, and limited sample sizes when considering PRODIGY results on a country-specific level (N = 28 to N = 213), we chose to focus this cost analysis solely on United States PRODIGY patients, who represent the largest cohort within the hospital cost dataset (N = 420).
Therefore, our healthcare utilization analysis included 769 United States patients, and our cost analysis included 420 United States patients.

A respiratory depression episode was defined as any of: respiratory rate $\leq 5$ bpm, oxygen saturation $\leq 85\%$, or end-tidal carbon dioxide $\leq 15$ or $\geq 60$ mmHg for $\geq 3$ minutes; apnea episode lasting $> 30$ seconds; or any respiratory opioid-related adverse event requiring intervention, including but not limited to: narcotic overdose, partial airway obstruction, respiratory insufficiency requiring non-invasive positive pressure, respiratory failure, upper airway obstruction, cardiopulmonary arrest, and death due to respiratory or pulmonary related complications [4, 22]. Patients’ PRODIGY score was retrospectively determined using the PRODIGY risk prediction tool, described by Khanna et al [4]. Briefly, patients were classified as low, intermediate, or high risk for respiratory depression using the risk prediction tool, which has an AUC of 0.74 [4].

**Objectives**

An *a priori* secondary objective of the PRODIGY trial was to compare patients with and without respiratory depression for healthcare utilization, including the following endpoints: hospital length of stay, readmission rates, post-discharge healthcare utilization, and healthcare costs [22]. Post-discharge healthcare utilization included clinic, urgent care, and emergency department visits, primary care or rehabilitation service, therapy-related clinic or urgent care visits, inpatient hospitalization, and outpatient care leading to hospitalization. Healthcare utilization data was collected for patients during a 30-day follow-up call, as designed in the trial protocol [22] and as is often conducted in respiratory- and ORADEFocused studies [14, 17, 19, 20]. The 30-day window for follow-up is a widely accepted timeframe for readmissions. For example, the Centers for Medicare and Medicaid (CMS) tracks complications within the 30 day window for its Hospital Readmission Reduction Program [23]. Due to variations in healthcare practices, policies, reimbursement systems, and costs between countries, these objectives were analyzed for the largest sub-cohort in PRODIGY, patients enrolled at United States trial sites.

**Statistical analysis**

Data analysis was performed using SAS v9.4 (SAS Institute Inc, Cary, North Carolina). Healthcare utilization and costs were evaluated using descriptive statistics for categorical variables (percentages and counts) and continuous variables (mean and standard deviation). Total hospital costs, reflecting the sum of fixed and variable costs incurred by the hospital, were extracted from the billing department and reported directly by United States trial sites, on a per-patient level. One trial site provided total hospital charges per enrolled patient, which we converted to cost using the current cost:charge ratio, as in the literature [24, 25]. The cost to charge ratio (CCR) of the facility was obtained from the Medicare hospital cost report. We multiplied the hospital charges to the CCR for the estimation of hospital cost. Hypothesis test of association was conducted using Wilcoxon rank-sum test for continuous variables. Depending on the sample size, Chi-square or Fishers exact test was used for categorical variables. Statistical significance was set at 0.05 for the two-sided p value.
Due to the retrospective nature of this analysis, no *a priori* power calculations were performed. To determine the impact of individual patients’ influence on average healthcare utilization and cost measures, outliers were identified using Cook’s Distance with a cutoff $> 4/(n-k-1)$, where $n$ is the number of observations and $k$ is the number of explanatory variables [26]. Length of stay and cost were evaluated with and without these patient outliers to determine whether a subset of patients strongly influenced observed trends in length of stay and costs in PRODIGY.

**Inverse probability of treatment weighting cost analysis**

Inverse probability of treatment weighting using the propensity score was generated to normalize demographic and clinical characteristics (age, sex, body mass index (BMI), race/ethnicity, smoking status, neck circumference, American Society of Anesthesiologists (ASA) physical status, length of surgery, opioid use, and complete history of medical conditions and diseases) between patients with and without $\geq 1$ respiratory depression episode [27]. An inverse probability of treatment weighting generalized linear model with log link function and gamma distribution was used to examine the impact of respiratory depression episode occurrence on healthcare cost. To test the effect between respiratory depression and length of stay, an interaction term of length of stay and respiratory depression was included in the generalized linear model of healthcare cost, alongside other patient demographic and clinical factors.

**Multiple regression analysis of length of stay**

To identify factors associated with patient length of stay, a multiple regression model was developed for patients with and without $\geq 1$ respiratory depression episode in the United States. The model was developed using stepwise selection with length of stay as the dependent variable and respiratory depression, baseline patient demographics, and clinical characteristics as independent variables. GLM with log link and Poisson distribution was used for the estimates.

**Missing data**

Patients with missing healthcare utilization data ($n = 1$) or with missing medical history data that prevented risk stratification by the PRODIGY score ($n = 10$) were excluded from the analysis.

**Results**

**Trial cohort**

Of the 1,335 patients enrolled in the PRODIGY trial who started continuous monitoring and received opioid therapy on the general care floor, healthcare utilization data was collected and analyzed for 769 patients in the United States (Fig. 1). The demographic and clinical characteristics of this cohort were described previously [4]. Thirty-seven percent ($N = 288/769$) of the patients in the United States experienced $\geq 1$ opioid-induced respiratory depression episode during continuous monitoring. After retrospectively assigning patients’ risk for respiratory depression using the PRODIGY score (S1 Table) [4],
259, 271, and 229 patients were classified as low, intermediate, and high risk for respiratory depression, respectively. Cost data was retrospectively collected and analyzed for 420 patients enrolled in the United States, including 138, 149, and 124 patients with low, intermediate, and high risk for respiratory depression (Fig. 1).

**Post-discharge healthcare utilization**

Overall, 13% of 769 United States patients with healthcare utilization data available (N = 100) reported post-discharge healthcare utilization within 30 days after hospital discharge (Table 1). The majority of this post-discharge healthcare utilization involved emergency department visits or inpatient hospitalization. Although post-discharge healthcare utilization was more common in patients with $\geq 1$ respiratory depression episode than in patients without respiratory depression episodes, this difference was not statistically significant. During the initial admission, a total of two patients (one with $\geq 1$ respiratory depression episode) required intubation, three patients (one with $\geq 1$ respiratory depression episode) experienced rapid response team activation, and three patients (two with $\geq 1$ respiratory depression episode) were transferred from the general care floor to the ICU. No code blue events occurred during the trial. While patients with respiratory depression had higher frequencies of hospital readmission 7-, 15-, and 30-days after discharge, the differences between patients with and without $\geq 1$ respiratory depression episode were not significant (Table 2).
Table 1
Post-discharge healthcare utilization across 769 patients enrolled in the United States with and without ≥ 1 respiratory depression episodes (%, n). Thirteen percent of United States patients with healthcare utilization data available (N = 100) used healthcare during the 30-days post-discharge.

| Healthcare Utilization          | ≥ 1 Respiratory Depression Episode | No Respiratory Depression Episodes |
|---------------------------------|-----------------------------------|-----------------------------------|
| Any Healthcare Utilization      | 14.6% (42)                        | 12.1% (58)                        |
| 95% CI                          | 10.5% − 18.7%                     | 9.2% − 15%                        |
| Clinic visit                    | 0.7% (2)                          | 1.5% (7)                          |
| Emergency department visit      | 7.6% (22)                         | 6.7% (32)                         |
| Inpatient hospitalization       | 5.9% (17)                         | 3.5% (17)                         |
| Urgent care                     | 0.7% (2)                          | 0.4% (2)                          |
| Primary care                    | 0% (0)                            | 0% (0)                            |
| Rehab center                    | 0% (0)                            | 0.2% (1)                          |
| Therapy-related care            | 0% (0)                            | 0.4% (2)                          |
| Other<sup>a</sup>               | 0.3% (1)                          | 0.2% (1)                          |
| No Healthcare Utilization       | 85.4% (246)                       | 87.9% (423)                       |

<sup>a</sup>Other includes telephone visit (n = 1) and outpatient surgery without overnight stay (n = 1).

Abbreviation: 95% CI = 95% confidence interval
Table 2

Healthcare utilization and cost of healthcare in United States patients with and without \( \geq 1 \) respiratory depression episode. Outliers were identified using Cook's Distance, resulting in exclusion of 10 patients with \( \geq 1 \) respiratory depression episode and 13 patients without a respiratory depression episode from the cohort of 769 United States patients with healthcare utilization data. Within the sub-cohort of 420 patients with cost data, 5 patients with \( \geq 1 \) respiratory depression episode and 6 patients without a respiratory depression episode were identified as outliers and excluded.

| Healthcare Utilization | All Patients (N = 768)\(^a\) | Patient Cohort Excluding Outliers (N = 745) |
|------------------------|-------------------------------|------------------------------------------|
|                        | Patients with \( \geq 1 \) Respiratory Depression Episode | Patients without Respiratory Depression Episode | p-value | Patients with \( \geq 1 \) Respiratory Depression Episode | Patients without Respiratory Depression Episode | p-value |
| Length of Stay, All Patients \( \text{(Average } \pm \text{ SD (N))} \) | 7.1 ± 9.6 \( \text{(287)} \) | 5.7 ± 6.5 \( \text{(481)} \) | .032 | 6.4 ± 7.8 \( \text{(277)} \) | 5.0 ± 4.3 \( \text{(468)} \) | .009 |
| Length of Stay, PRODIGY Risk Score \( \text{(Average } \pm \text{ SD (N))} \) | 6.8 ± 9.4 \( \text{(53)} \) | 5.2 ± 6.4 \( \text{(206)} \) | .266 | 5.6 ± 3.8 \( \text{(52)} \) | 4.6 ± 4.0 \( \text{(201)} \) | .126 |
| Low                    | 6.8 ± 10.7 \( \text{(92)} \) | 6 ± 6.1 \( \text{(178)} \) | .497 | 6.5 ± 10.6 \( \text{(90)} \) | 5.5 ± 4.8 \( \text{(173)} \) | .365 |
| Intermediate           | 7.5 ± 9.1 \( \text{(137)} \) | 6.4 ± 7.8 \( \text{(92)} \) | .322 | 6.7 ± 6.8 \( \text{(130)} \) | 5.3 ± 3.8 \( \text{(89)} \) | .053 |
| High                   | 7, 2.4% \( \text{(12)} \) | 11, 2.3% \( \text{(13)} \) | 1.000 | 7, 2.5% \( \text{(12)} \) | 11, 2.4% \( \text{(13)} \) | .879 |
| 7-day readmission \( \text{(N,%)} \) | 12, 4.2% \( \text{(13)} \) | 13, 2.7% \( \text{(13)} \) | .297 | 12, 4.3% \( \text{(12)} \) | 13, 2.8% \( \text{(13)} \) | .255 |
| 15-day readmission \( \text{(N,%)} \) | 16, 5.6% \( \text{(16)} \) | 17, 3.5% \( \text{(17)} \) | .200 | 16, 5.8% \( \text{(16)} \) | 17, 3.6% \( \text{(17)} \) | .169 |

\(^a\)Within the United States cohort (N = 769), 1 patient was excluded from length of stay analysis due to missing data.

Abbreviations: 95% CI = 95% confidence interval; N = number of patients; PRODIGY = PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY; SD = standard deviation; USD = United States Dollars
| Healthcare Utilization | All Patients (N = 768)a | Patient Cohort Excluding Outliers (N = 745) |
|------------------------|-------------------------|---------------------------------------------|
|                        | Patients with ≥ 1 Respiratory Depression Episode | Patients without Respiratory Depression Episode | **p-value** | Patients with ≥ 1 Respiratory Depression Episode | Patients without Respiratory Depression Episode | **p-value** |
| **Healthcare Costs**   | All Patients (N = 420) | Patient Cohort Excluding Outliers (N = 409) |
| Total Cost (USD), All Patients (Average ± SD (N)) | $23,619 ± $16,868 | $19,193 ± $13,517 | .006 | $21,892 ± $11,540 | $18,206 ± $10,864 | .002 |
| Total Cost (USD), PRODIGY Risk Score (Average ± SD (N)) | $22,316 ± $13,679 | $18,633 ± $14,050 | .222 | $22,316 ± $13,679 | $17,705 ± $11,818 | .081 |
| Low                    | $22,272 ± $14,661 | $20,331 ± $14,594 | .447 | $21,665 ± $13,300 | $18,858 ± $10,423 | .258 |
| Intermediate           | $25,057 ± $19,490 | $18,608 ± $9,714 | .017 | $21,948 ± $9,128 | $18,474 ± $9,767 | .0495 |
| High                   | $23,294 ± $15,088 | $20,057 ± $13,555 | .013 | $22,171 ± $12,727 | $18,971 ± $10,725 | .007 |

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*aWithin the United States cohort (N = 769), 1 patient was excluded from length of stay analysis due to missing data.*

Abbreviations: 95% CI = 95% confidence interval; N = number of patients; PRODIGY = PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY; SD = standard deviation; USD = United States Dollars
### Healthcare Utilization

| Health Care Utilization | All Patients (N = 768)\(^a\) | Patient Cohort Excluding Outliers (N = 745) |
|------------------------|-------------------------------|--------------------------------------------|
|                       | Patients with ≥ 1 Respiratory Depression Episode | Patients without Respiratory Depression Episode | p-value | Patients with ≥ 1 Respiratory Depression Episode | Patients without Respiratory Depression Episode | p-value |
| Exponentiated Estimates from Generalized Linear Model (95% CI) | 1.16 (1.03–1.31) | 1.17 (1.04–1.31) |

\(^a\)Within the United States cohort (N = 769), 1 patient was excluded from length of stay analysis due to missing data.

Abbreviations: 95% CI = 95% confidence interval; N = number of patients; PRODIGY = PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY; SD = standard deviation; USD = United States Dollars

### Hospital Length of Stay

In the United States, the average length of stay for patients with ≥ 1 respiratory depression episode was significantly higher compared to patients without respiratory depression episodes (7.1 ± 9.6 vs 5.7 ± 6.5 days, p = 0.032) (Table 2). Average length of stay was also significantly different between patients with and without ≥ 1 respiratory depression episode when outliers identified by Cook’s Distance were excluded from the analysis (6.4 ± 7.8 vs 5.0 ± 4.3 days, p = 0.009, respectively) (Table 2).

### Hospital Costs

The average total hospital cost for patients in the United States who experienced ≥ 1 respiratory depression episode was $4,426 higher (($23,619 ± $16,868 vs $19,193 ± $13,517, p = 0.006), compared to patients who did not experience a respiratory depression episode (Table 2). Excluding outliers, the average total hospital cost was $3,686 higher for patients with ≥ 1 respiratory depression episode ($21,892 ± $11,540 vs $18,206 ± $10,864 for patients without respiratory depression, p = 0.002). For patients at high risk for respiratory depression (i.e. those with high PRODIGY score) who experienced ≥ 1 respiratory depression episode, the average total cost was $6,648 higher ($25,057 ± $19,490 vs $18,608 ± $9,714, p = 0.017) than high risk patients who did not experience a respiratory depression episode. Analysis excluding patient outliers also identified a significant difference between high risk patients with and without ≥ 1 respiratory depression episode ($21,948 ± $9,128 vs $18,474 ± $9,767, p = 0.0495), respectively (Table 2).

Propensity weighted analysis of United States patients identified a $3,237 (16%) higher healthcare cost for patients with ≥ 1 respiratory depression episode ($23,294 ± $15,088 vs $20,057 ± $13,555 for patients without respiratory depression, p = 0.013), respectively (Table 2, S2 Table). Comparable results
were observed upon exclusion of patient outliers, where patients with ≥1 respiratory depression episode had healthcare costs $3,200 (17%) higher than patients without respiratory depression ($22,171 ± $12,727 vs $18,971 ± $10,725, respectively, p = 0.007) (S3 Table).

**Significant contributors to hospital costs**

A generalized linear model of healthcare costs in patients in the United States, excluding outliers, with and without ≥1 respiratory depression episode, identified several variables that significantly increase healthcare costs, including length of stay (1.03, 95% CI 1.02–1.05; p < 0.0001), longer length of surgery (1.34, 95% CI 1.24–1.46 for surgery ≥ 2 - <4hrs and 1.89, 95% CI 1.69–2.12 for surgery ≥ 4 hr, vs reference group, surgery < 2 hr; p < 0.0001), and procedure type (nervous system 1.62, 95% CI 1.26–2.09, vs reference group, therapeutic procedures and supportive care; p < 0.0001) (Table 3, S4 Table). Compared to a normal BMI (20 - <25), BMI < 20 was associated with reduced healthcare costs (0.77, 95% CI 0.58–1.02; p = 0.001). Similar results were observed in a generalized linear model for all patients, including outliers, where length of stay (1.06, 95% CI 1.05–1.07; p < 0.0001), length of stay and occurrence of ≥1 respiratory depression episode (1.04, 95% CI 1.01–1.06; p = 0.002), longer length of surgery (1.28, 95% CI 1.17–1.41 and 1.71, 95% CI 1.51–1.93 for surgery ≥ 2 - <4 or ≥ 4 hr, respectively; p < 0.0001), and procedure type (bone and joint 1.42, 95% CI 1.06–1.92, nervous system 1.81, 95% CI 1.35–2.41, and renal and urinary tract 2.07, 95% CI 0.93–4.58; p < 0.0001) significantly increased healthcare costs (S5 Table). In both analyses, the observed interaction between length of stay and occurrence of ≥1 respiratory depression episode indicates that in patients with ≥1 respiratory depression episode, as length of stay increases, healthcare costs increase exponentially, whereas in patients without respiratory depression episodes, length of stay increases healthcare costs linearly (Fig. 2A-B).
Table 3
Generalized linear model of healthcare costs in United States patients (excluding outliers).

| Clinical Characteristic                  | Exponentiated estimate | 95% CI               | p value |
|----------------------------------------|------------------------|----------------------|---------|
| Intercept                              | 5,908.22               | 2,704.85–12,905.39   | < .0001 |
| Length of stay                         | 1.03                   | 1.02–1.05            | < .0001 |
| Respiratory depression                 | 1.05                   | 0.91–1.21            | .505    |
| Length of stay* Respiratory depression | 1.01                   | 0.99–1.04            | .239    |
| Open Surgery (vs laparoscopic)         | 0.88                   | 0.77–1.01            | .067    |
| Length of surgery (hr)                 |                        |                      | < .0001 |
| ≥ 2 - <4 vs. <2                       | 1.34                   | 1.24–1.46            |         |
| >4 vs. <2                             | 1.89                   | 1.69–2.12            |         |
| BMI                                    |                        |                      | .0011   |
| <20                                    | 0.77                   | 0.58–1.02            |         |
| ≥ 20 - <25                            | ---                    | ---                  | ---     |
| ≥ 25 - <30                            | 0.90                   | 0.80–1.00            |         |
| ≥ 30 - <35                            | 1.01                   | 0.90–1.14            |         |
| ≥ 35                                   | 1.12                   | 0.98–1.27            |         |
| Procedure                              |                        |                      | < .0001 |
| Bone and joint                         | 1.22                   | 0.94–1.59            |         |
| Gastrointestinal                       | 1.01                   | 0.78–1.31            |         |
| Hepatobiliary                          | 1.30                   | 0.94–1.80            |         |
| Nervous system, skull and spine        | 1.62                   | 1.26–2.09            |         |
| Obstetric and gynecological            | 1.06                   | 0.80–1.41            |         |
| Renal and urinary tract                | 1.93                   | 0.97–3.87            |         |
| Respiratory tract                      | 0.98                   | 0.47–2.02            |         |
| Therapeutic procedures and supportive care | ---                  | ---                  | ---     |
| Other                                  | 1.36                   | 0.89–2.09            |         |

*Effect of medical procedure was estimated in a separate model due to the multicollinearity between length of surgery and medical patients.
| Clinical Characteristic | Exponentiated estimate | 95% CI     | p value |
|------------------------|------------------------|------------|---------|
| Medical\textsuperscript{a} | 0.42                   | 0.33–0.54  | < .001  |

\textsuperscript{a}Effect of medical procedure was estimated in a separate model due to the multicollinearity between length of surgery and medical patients.

Scaled Deviance/Degree of Freedom (DF): 1.16

Scaled Pearson/DF: 1.25.

Abbreviations: 95% CI = 95% confidence interval; BMI = body mass index

**Significant contributors to hospital length of stay**

A multi regression model of patients enrolled in the United States, excluding outliers, identified multiple significant contributors to increased hospital length of stay, including use of > 1- <4 or ≥ 4 opioids (p < 0.0001), surgery ≥ 2-<4 h or ≥ 4 h (p < 0.001), high risk surgery (defined using the revised European Society of Cardiology/European Society of Anaesthesiology guidelines on non-cardiac surgery) or open surgery (p = 0.0005 and p = 0.003, respectively), respiratory depression (p = 0.024), hypertension (p = 0.011), chronic heart failure (p = 0.008), and sepsis (p < 0.0001) (Table 4). After adjusting for patient baseline characteristics, the regression model found that patients with ≥ 1 respiratory depression episode had a hospital length of stay 9% (95% CI: 1.1%-17%) longer than patients without respiratory depression (p = 0.024). Similar results were observed upon analysis of all patients enrolled in the United States, including outliers (S6 Table), where the regression model identified a hospital length of stay 20% (95% CI: 6%-35%) longer in patients with ≥ 1 respiratory depression episode (p < 0.005).
Table 4
Multiple regression model of hospital length of stay for patients in the United States (excluding outliers).

| Clinical Characteristic                  | Estimate | Standard Error | Wald 95% Confidence Limits | Wald Chi-Square | Pr > Chi Square |
|-----------------------------------------|----------|----------------|---------------------------|----------------|----------------|
| BMI                                     |          |                |                           |                |                |
| ≥ 20 - <25                              | 0.0151   | 0.1060         | -0.1926 - 0.2228          | 0.0202         | .887           |
| ≥ 25 - <30                              | -0.0419  | 0.1039         | -0.2455 - 0.1617          | 0.1624         | .687           |
| ≥ 30 - <35                              | -0.0808  | 0.1076         | -0.2917 - 0.1301          | 0.564          | .453           |
| ≥ 35                                    | -0.2070  | 0.1053         | -0.4134 - 0.0007          | 3.8658         | .049           |
| Number of Opioids                       |          |                |                           |                |                |
| >1 - <4                                 | -0.2885  | 0.0672         | -0.4202 - 0.1568          | 18.4243        | < .0001        |
| ≥ 4                                     | -0.3768  | 0.0715         | -0.5171 - 0.2366          | 27.7411        | < .0001        |
| High risk surgery                       | 0.2468   | 0.0706         | 0.1084 - 0.3851           | 12.223         | .0005          |
| Open surgery                            | 0.1921   | 0.0643         | 0.0661 - 0.3181           | 8.9292         | .003           |
| Length of surgery (hr)                  |          |                |                           |                |                |
| ≥ 2 - <4                                | 0.1932   | 0.0468         | 0.1016 - 0.2849           | 17.0719        | < .0001        |
| ≥ 4                                     | 0.5523   | 0.0491         | 0.4562 - 0.6485           | 126.7597       | < .0001        |
| ≥ 1 Respiratory Depression Episode      | 0.0846   | 0.0374         | 0.0112 - 0.1579           | 5.1058         | .024           |
| Hypertension                            | -0.0964  | 0.0379         | -0.1707 - 0.0221          | 6.4728         | .011           |
| Chronic Heart Failure                   | 0.2964   | 0.1116         | 0.0777 - 0.5152           | 7.0546         | .008           |
| Sepsis                                  | 0.5316   | 0.1083         | 0.3193 - 0.744            | 24.0798        | < .0001        |

Abbreviations: BMI = body mass index

Discussion

This study evaluated the impact of respiratory depression on length of stay and hospital costs, which unlike the impact of general ORADEs on these outcomes, are not well described in the literature [11, 15–20]. United States patients who had ≥ 1 respiratory depression episode had a significantly longer length of stay and a higher cost of hospitalization, compared to patients without opioid-induced respiratory depression. Patients at high risk for respiratory depression (PRODIGY score) with ≥ 1 confirmed respiratory depression episode also had significantly higher hospital costs. In-depth propensity weighted
analysis found that patients with \( \geq 1 \) respiratory depression episode in the United States cohort had a
16% higher healthcare cost compared to patients without respiratory depression and a 17% higher
healthcare cost excluding patient outliers. Total healthcare costs, which included the sum of fixed and
variable costs incurred by the hospital, were significantly increased by patient length of stay, length of
stay complicated by occurrence of respiratory depression, longer length of surgery, and procedure type.
Importantly, respiratory depression identified by continuous capnography and pulse oximetry monitoring
was critical, since patients with respiratory depression experienced exponentially increased healthcare
costs as length of stay increased. In contrast, in the absence of respiratory depression episodes,
increased length of stay was associated with increased healthcare cost, but this association was linear.

The hospital general care unit or ward remains the site for an alarmingly high number of acute
cardiorespiratory compromise events [28]. About 290,000 in hospital cardiac arrests occur in the United
States each year of which 40% have a respiratory insufficiency etiology. These events are usually
preceded by a period of 6–8 hours of a gradual change in vital signs, which are not detected with
traditional ‘spot-check’ based monitoring as is in place today [29, 30]. A majority of opioid-induced
perioperative respiratory complications therefore occur in the under-monitored hospital ward and are
associated with serious patient outcomes, including anoxic brain injury and mortality, as well as legal
claims with significant financial burdens [13, 31]. Universal adoption of continuous monitoring systems is
an attractive option, however the initial resource expenditure, challenges of alarm fatigue and lack of
interventions based on alarm data remain at large. Here the PRODIGY trial allowed early identification of
and stratification of patients at risk for respiratory impairment and is a first crucial step to improving
patient outcomes and reducing healthcare cost. Other risk scores have been developed to identify
patients at risk for ORADEs [19] however PRODIGY is a novel score to identify patients at risk specifically
for opioid-induced respiratory depression [4]. Similar to our work, other trials have reported that ORADEs,
a majority of which are respiratory, are associated with increased healthcare utilization, longer hospital
length of stay, higher 30-day readmission, and increased healthcare costs [14, 15, 19–21, 31]. Studies
have also demonstrated the utility of continuous pulse oximetry on the ward, where up to 90% of
postoperative hypoxemia episodes go undetected by intermittent spot-check monitoring [5]. In one study,
continuous pulse oximetry on the ward reduced rescue events and ICU transfers, and hence decreased
healthcare costs [32]. Similarly, after implementing continuous capnography to monitor patients receiving
intravenous patient controlled analgesia opioids on the hospital ward, Stites and colleagues reported a
50% reduction in the incidence of opioid-induced respiratory depression rescue using rapid response
teams, and a 79% decrease in transfers to higher levels of care, both of which are costly endeavors [33].
The PRODIGY trial confirmed a 46% incidence of opioid-induced respiratory depression using continuous
pulse oximetry and capnography, which has been shown to detect respiratory depression better than
pulse oximetry alone [4, 5, 8, 34]. Given the high frequency of respiratory depression and our findings that
it increases healthcare utilization and cost, reducing the incidence of respiratory depression by utilizing
continuous oximetry and capnography and allowing for early detection of respiratory depression
episodes has the potential to improve patient outcomes and decrease healthcare utilization.
The additive cost burden of respiratory depression of $3,237 (16%) increase (with outliers) and $3,200 (17%) increase (without outliers) in hospitalization costs per PRODIGY trial analysis, is somewhat less than the $4350-$8225 [14, 15, 17, 20] (27–47%) range, reported in the literature. The more conservative cost burden estimate, as found by PRODIGY trial, may be explained by PRODIGY being a prospective trial that used continuous capnography and oximetry monitoring to identify opioid-induced respiratory depression, and strict adherence to inclusion and exclusion criteria, vs. literature studies [14, 15, 17, 20] which were retrospective in nature, relying on claims analyses, and coded instances of ORADEs, likely missing milder (and less costly) cases of ORADE.

Although other studies have reported differences in cost and healthcare outcomes for ORADEs, the factors contributing to these outcomes are not well described [14, 15, 19–21, 31]. Our analysis identified patient characteristics that significantly impacted length of stay and cost. Use of multiple opioids, longer, high risk, or open surgery, respiratory depression, and medical conditions including chronic heart failure, hypertension, and sepsis, all contributed to increased length of stay. Interestingly, the PRODIGY score accounts for chronic heart failure and opioid naivety when determining patient risk for respiratory depression [4]. Importantly, respiratory depression contributed to both length of stay and cost, highlighting its importance in determining patient outcomes. The findings of this trial may be of particular interest to payers (e.g., CMS), organizations related to quality measurement and reporting (e.g., National Quality Forum), and hospital administration, highlighting the unmet need in the quality of care for post-surgical patients on opioids, and the potential need to institute quality metrics to improve outcomes and reduce costs in this patient population. Finally, our analysis excluded outlier patients who had very high costs or an extended length of stay, and confirmed that inclusion or exclusion of these patients did not alter our main findings. Therefore, the increases in length of stay and cost for patients with respiratory depression are not due to a subset of patients requiring extended care or costly interventions but reflect differences between typical ward patients with and without respiratory depression.

Our work is limited by the fact that we included a portion of United States hospitals from our trial cohort, though PRODIGY also enrolled in Asia and Europe. While this may limit the generalizability of our data, we included a substantial number of United States patients and hospitals of various types and sizes. Our analysis evaluated the actual hospital cost incurred, including both fixed and variable costs, and did not rely on diagnosis related group payment data. However, this analysis was limited to the total hospital cost per patient, preventing identification of specific factors that may have contributed to increased hospital cost for patients with respiratory depression. Determination of opportunity cost and productivity loss associated with increased length of stay was out of the scope of this analysis but would be a valuable addition to future studies. Furthermore, an actual calculation of the ‘break-even’ cost of the institution of monitoring versus the cost of respiratory depression events is out of the scope of this work, but a planned future analysis.

Conclusions
The improvement of surveillance monitoring on the general care hospital floor has the potential to reduce postoperative complications and lower hospital costs [32, 33, 35, 36]. Patients with opioid-induced respiratory depression episodes detected by continuous capnography and oximetry experienced a longer hospital length of stay and exponentially higher hospital costs. Early institution of these monitoring measures in combination, with early proactive intervention, such as readjustment of analgesia, optimal fluid balance, aggressive incentive spirometry and additional bronchodilation, could mitigate the occurrence of respiratory depression and decrease hospital costs associated with such episodes.

**Abbreviations**

ASA: American Society of Anesthesiologists; BMI: Body Mass Index; CI: Confidence Interval; CNS: Central Nervous System; ICU: Intensive Care Unit; ORADE: Opioid Related Adverse Drug Event; PRODIGY: PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY; SD: Standard Deviation; USD: United States Dollars

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board or Research Ethics Committee, depending on trial site. Institutional Review Board and Research Ethics Committees that approved this research include the following: CPP Ile de France 2 (Hopital Foch); Ethik-Kommission Medizinische Fakultät (University Hospital Bonn); Rinshoushiken Shinsa Senmon Inkai (Okayama University Hospital); The Jikei Ethics Committee (Jikei University); METC MUMC+ (University Medical Center, Maastricht); National Healthcare Group (NHG) Domain Specific Review Board (DSRB) (National University of Singapore); Comité de Ética del Hospital Clínico Universitario de Valencia (Hospital Clínico Universitario de Valencia); Western Institutional Review Board (Beaumont Hospital, Emory University, Ohio State University Wexner Medical Center, and Providence Regional Medical Center); Partners Human Research Committee (Brigham and Women’s Hospital); Cleveland Clinic Institutional Review Board (Cleveland Clinic); The MetroHealth System Institutional Review Board (MetroHealth Medical Center); University at Buffalo Institutional Review Board (University at Buffalo); Colorado Multiple Institutional Review Board (University at Colorado). Written informed consent was obtained from all participants.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article (and its additional files).
Competing interests

All authors (or their institutions) received research support from Medtronic to conduct this trial. In addition, AK reports consulting fees from Medtronic, Edwards Lifesciences, and Philips North America, AK is supported by an NIH/NCATS Wake Forest CTSI award for a randomized trial of continuous postoperative hemodynamic and respiratory monitoring; LS reports a grant from Merck & Co. Inc. and consultant fees from Merck & Co. Inc, The 37 Company, and Ferrer International; CRJ reports participation in the Medtronic Nurse Advisory Group; SU reports speaker honorarium from Edwards Lifescience, LTD; WJ reports receiving a salary from Medtronic; WB reports grants from the European Union and Interreg Consortium, and personal fees from European Society of Anaesthesiology studies (PHOENICS and TETHYS) supported by B Braun Medical and Fresenius Medical Care, and from Medtronic.

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Authors' contributions

AKK helped acquire and interpret data, and draft and revise the manuscript. LS helped analyze and interpret data, and draft and revise the manuscript. SB helped acquire and interpret data and revise the manuscript. CJ helped acquire and interpret data and revise the manuscript. HM helped acquire and interpret data and revise the manuscript. SU helped acquire and interpret data and revise the manuscript. LKT helped acquire and interpret data and revise the manuscript. RS helped acquire and interpret data and revise the manuscript. WJ helped analyze data and draft and revise the manuscript. WB helped acquire and interpret data and revise the manuscript.

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**Figures**
Figure 1

Flow chart of PRODIGY trial patients included in healthcare utilization and cost analysis.
Figure 2

Effect of length of stay and occurrence of ≥1 respiratory depression episode on overall cost. (A) Overall cost, including all enrolled patients and (B) Overall cost, excluding outliers identified by Cook’s Distance. USD = United States Dollars.

Supplementary Files

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