

**Opioid administration practice patterns in patients with
acute respiratory failure who undergo invasive mechanical ventilation**

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Supplemental Table 1: Inclusion and exclusion criteria

| Variables | KPNC definition | eRI definition |
|--|--|--|
| Inclusion | | |
| Adult patients | Admission age 18+ | Admission age 18+ |
| Diagnosis of acute respiratory failure | n/a | Diagnoses from the diagnosis or admissiondx tables for respiratory failure or a related concept |
| Invasive mechanical ventilation for at least 24 hours | Algorithm using ventilator flow sheet start/stop times | Invasive mechanical ventilation defined using proprietary algorithm from Philips eRI that uses nurse bedside charting information, procedure information, and vital sign data |
| Exclusion | | |
| Surgery | Admitted under a primary surgical service | Diagnoses from the diagnosis or admissiondx tables including the word "surgery" or "Operative" |
| Trauma | Exclude if in principle, primary or secondary diagnosis position: HCUP CCS codes 207, 225, 226, 228, 229, 230, 231, 232, 233, 234, 235, 236 | Diagnoses from the diagnosis or admissiondx tables including the word "trauma" |
| Burns | Exclude if in principle, primary or secondary diagnosis position: HCUP CCS code 240 | Diagnoses from the diagnosis or admissiondx tables including the word "burns" |
| Drug overdose | Exclude if in principle, primary or secondary diagnosis position: HCUP CCS codes 241, 242, 243, 661, 662 | Diagnoses from the diagnosis or admissiondx tables including the word "drug overdose" or "Overdose" |
| Comfort measures only within 24 hours of invasive mechanical ventilation initiation | Timestamped orders for advanced directives "comfort care" | Presence of comfort measures only in the careplangeneral table that occurred within 24 hours of invasive mechanical ventilation initiation |
| Admitted to cardiac or neurologic ICU | Admitted to specialty ICU (not general medical ICU), which we defined as a cardiac or neurologic ICU | Not applicable |
| Neurologic-related diseases | Exclude if principle or primary diagnosis position_HCUP CCS codes 109, 110, 111, 112, 113, 227 | Diagnoses from the diagnosis or admissiondx tables including the word "neurologic" |
| Tracheostomy on ICU admission or within 72 hours of invasive mechanical ventilation initiation | Timestamped respiratory flowsheet for tracheostomy or operating room procedure for tracheostomy | Instances in the respiratorycare, physicaalexam, respiratorycharting, nursecare, or nursecharting tables for tracheostomy and that was present on admission or that occurred within 72 hours of invasive mechanical ventilation initiation |

ICU: intensive care unit. KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

Supplemental Table 2: Outcome and risk adjustment variable definitions

| Variables | KPNC definition or source of data | eRI definition |
|---|--|---|
| Outcome | | |
| Use of opioid infusions within the first 21 days of invasive mechanical ventilation | Medication administration record | Use of fentanyl, morphine, or hydromorphone infusion according to infusion medical administration record table. |
| Median dose of fentanyl continuous infusion equivalents within the first 21 days of invasive mechanical ventilation | Dose in medication administration record calculated as follows: (1) starting with the first hour of IMV sum the total dose of fentanyl equivalents given in each 24-hour period of IMV up to 21 days, and (2) take the median of summed fentanyl dose equivalents over all days of IMV Doses of hydromorphone and morphine were converted to fentanyl using the following equivalencies: 100 µg / hour of fentanyl = 1.5 milligrams (mg) / hour of hydromorphone = 10 mg / hour of morphine | Dose in opioid infusion medication administration record calculated as follows: (1) Calculate hourly fentanyl equivalent rate (100 mcg/hr fentanyl = 1.5 mg/hr hydromorphone = 10 mg/hr morphine). If a rate changes within a 1-hour period, set the following hour to the new rate (if there are multiple rate changes within one hour, set the following hour rate to the most recent new rate). (2) Exclude fentanyl equivalent hourly rates >2000 mcg/hr (unlikely to be accurately charted). (3) Use last observation carried forward for a 3-hr window after the last charted fentanyl rate, unless the last charted fentanyl rate is 0 (in this case, do not carry forward). (4) For each 24-hour period of MV, sum the hourly fentanyl equivalents. Then take the median of the summed fentanyl equivalents across the duration of mechanical ventilation for each patient. Opioid rates were including in outcome calculation through 21 days or until first occurrence of extubation, comfort care status, or tracheostomy. |
| Maximum hourly rate of fentanyl equivalents during the first 21 days of invasive mechanical ventilation | Maximum hourly dose administered in medication administration record | Maximum recorded hourly fentanyl equivalent per patient during the first 21 days of invasive mechanical ventilation |
| Cumulative dose of fentanyl equivalents during the first 21 days of invasive mechanical ventilation | Cumulative dose administered in medication administration record | Sum of recorded hourly fentanyl equivalents per patient during the first 21 days of invasive mechanical ventilation |
| Risk adjustment | | |
| Age at admission | Age variable | 'age' variable |
| Male Sex | Sex variable | 'Gender' variable |
| Race | Race and ethnicity variables | 'ethnicity' variable |

| Variables | KPNC definition or source of data | eRI definition |
|------------|---|--|
| Opioid Use | <p>ICD-9</p> <p>304 Opioid Type Dependence, Unspecified 304.01 Opioid Type Dependence, Continuous 304.02 Opioid Type Dependence, Episodic 304.03 Opioid Type Dependence, In Remission 304.7 Combinations Of Opioid Type Drug With Any Other Drug Dependence, Unspecified 304.71 Combinations Of Opioid Type Drug With Any Other Drug Dependence, Continuous 304.72 Combinations Of Opioid Type Drug With Any Other Drug Dependence, Episodic 304.73 Combinations Of Opioid Type Drug With Any Other Drug Dependence, In Remission 305.5 Opioid Abuse, Unspecified 305.51 Opioid Abuse, Continuous 305.52 Opioid Abuse, Episodic 305.53 Opioid Abuse, In Remission 965 Poisoning by opiates and related narcotics 965 Poisoning by opium, unspecified 965.01 Poisoning by heroin 965.02 Poisoning by methadone 965.09 Poisoning by other opiates and narcotics E850 Accidental poisoning by analgesics antipyretics and antirheumatics E850.0 Accidental poisoning by heroin E850.1 Accidental poisoning by methadone E850.2 Accidental poisoning by opiates and related narcotics E935.0 Heroin causing adverse effects in therapeutic use E935.1 Methadone causing adverse effects in therapeutic use E935.2 Other opiates and related narcotics causing adverse effects in therapeutic use</p> | Prescription for any prescription opioid on admission medication reconciliation list |
| | <p>ICD-10</p> <p>F11.10 Opioid Abuse, Uncomplicated F11.120 Opioid Abuse With Intoxication, Uncomplicated F11.121 Opioid Abuse With Intoxication Delirium F11.122 Opioid Abuse With Intoxication With Perceptual Disturbance F11.129 Opioid Abuse With Intoxication, Unspecified F11.14 Opioid Abuse With Opioid-Induced Mood Disorder F11.150 Opioid Abuse With Opioid-Induced Psychotic Disorder With Delusions F11.151 Opioid Abuse With Opioid-Induced Psychotic Disorder With Hallucinations F11.159 Opioid Abuse With Opioid-Induced Psychotic Disorder, Unspecified F11.181 Opioid Abuse With Opioid-Induced Sexual Dysfunction F11.182 Opioid Abuse With Opioid-Induced Sleep Disorder F11.188 Opioid Abuse With Other Opioid-Induced Disorder F11.19 Opioid Abuse With Unspecified Opioid-Induced Disorder F11.20 Opioid Dependence, Uncomplicated F11.21 Opioid Dependence, In Remission F11.220 Opioid Dependence With Intoxication, Uncomplicated F11.221 Opioid Dependence With Intoxication Delirium F11.222 Opioid Dependence With Intoxication With Perceptual Disturbance F11.229 Opioid Dependence With Intoxication, Unspecified F11.23 Opioid Dependence With Withdrawal F11.24 Opioid Dependence With Opioid-Induced Mood Disorder F11.250 Opioid Dependence With Opioid-Induced Psychotic Disorder With Delusions F11.251 Opioid Dependence With Opioid-Induced Psychotic Disorder With Hallucinations F11.259 Opioid Dependence With Opioid-Induced Psychotic Disorder, Unspecified F11.281 Opioid Dependence With Opioid-Induced Sexual Dysfunction F11.282 Opioid Dependence With Opioid-Induced Sleep Disorder F11.288 Opioid Dependence With Other Opioid-Induced Disorder F11.29 Opioid Dependence With Unspecified Opioid-Induced Disorder F11.90 Opioid Use, Unspecified, Uncomplicated F11.920 Opioid Use, Unspecified With Intoxication, Uncomplicated F11.921 Opioid Use, Unspecified With Intoxication Delirium F11.922 Opioid Use, Unspecified With Intoxication With Perceptual Disturbance</p> | |

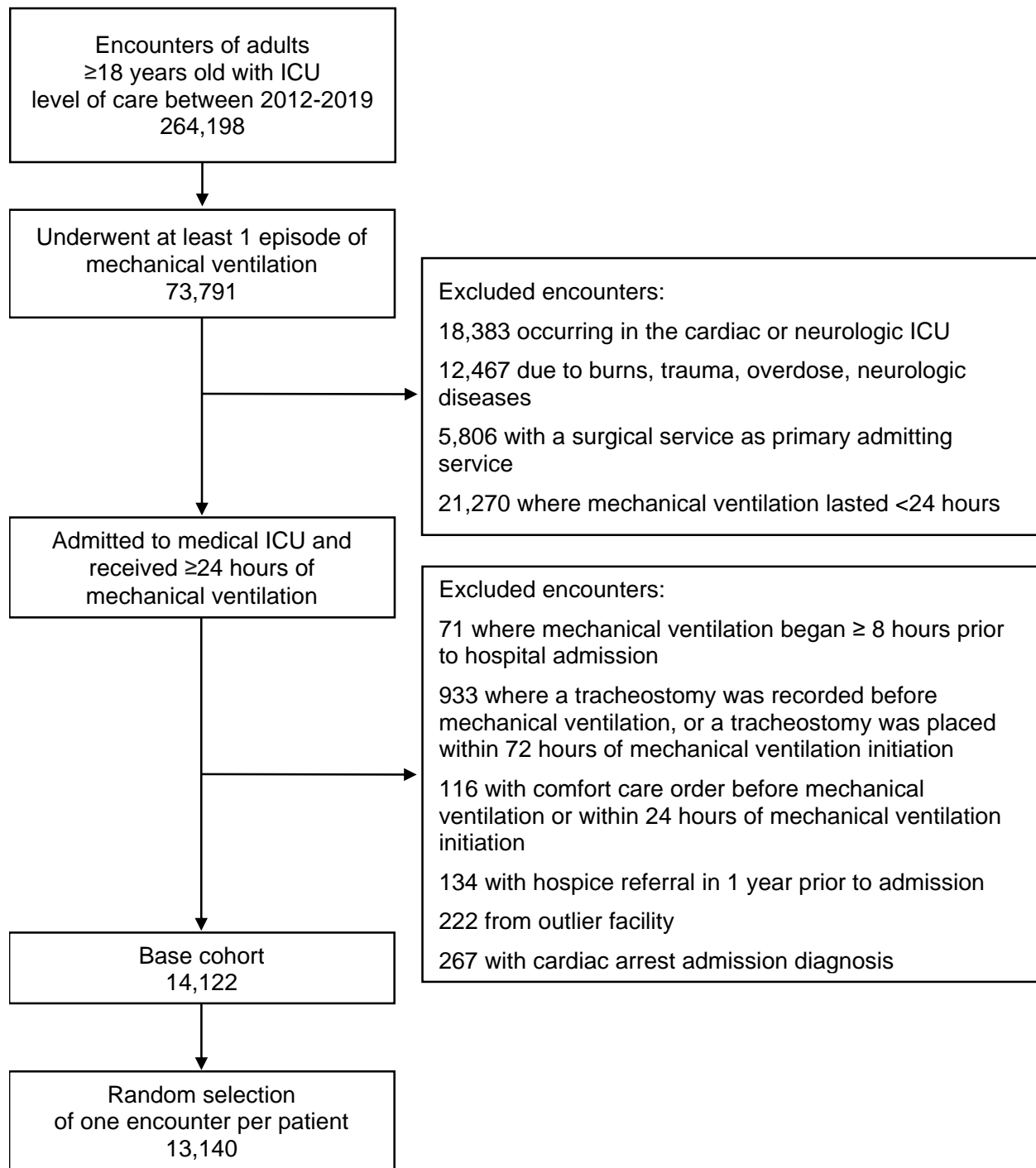
| Variables | KPNC definition or source of data | eRI definition |
|-----------|--|----------------|
| | F11.929 Opioid Use, Unspecified With Intoxication, Unspecified | |
| | F11.93 Opioid Use, Unspecified With Withdrawal | |
| | F11.94 Opioid Use, Unspecified With Opioid-Induced Mood Disorder | |
| | F11.950 Opioid Use, Unspecified With Opioid-Induced Psychotic Disorder With Delusions | |
| | F11.951 Opioid Use, Unspecified With Opioid-Induced Psychotic Disorder With Hallucinations | |
| | F11.959 Opioid Use, Unspecified With Opioid-Induced Psychotic Disorder, Unspecified | |
| | F11.981 Opioid Use, Unspecified With Opioid-Induced Sexual Dysfunction | |
| | F11.982 Opioid Use, Unspecified With Opioid-Induced Sleep Disorder | |
| | F11.988 Opioid Use, Unspecified With Other Opioid-Induced Disorder | |
| | F11.99 Opioid Use, Unspecified With Unspecified Opioid-Induced Disorder | |
| | T40.0 Poisoning by, adverse effect of and underdosing of opium | |
| | T40.OX Poisoning by, adverse effect of and underdosing of opium | |
| | T40.OX1 Poisoning by opium, accidental (unintentional) | |
| | T40.OX1A Poisoning by opium, accidental (unintentional), initial encounter | |
| | T40.OX1D Poisoning by opium, accidental (unintentional), subsequent encounter | |
| | T40.OX1S Poisoning by opium, accidental (unintentional), sequela | |
| | T40.OX2 Poisoning by opium, intentional self-harm | |
| | T40.OX2A Poisoning by opium, intentional self-harm, initial encounter | |
| | T40.OX2D Poisoning by opium, intentional self-harm, subsequent encounter | |
| | T40.OX2S Poisoning by opium, intentional self-harm, sequela | |
| | T40.OX3 Poisoning by opium, assault | |
| | T40.OX3A Poisoning by opium, assault, initial encounter | |
| | T40.OX3D Poisoning by opium, assault, subsequent encounter | |
| | T40.OX3S Poisoning by opium, assault, sequela | |
| | T40.OX4 Poisoning by opium, undetermined | |
| | T40.OX4A Poisoning by opium, undetermined, initial encounter | |
| | T40.OX4D Poisoning by opium, undetermined, subsequent encounter | |
| | T40.OX4S Poisoning by opium, undetermined, sequela | |
| | T40.1 Poisoning by and adverse effect of heroin | |
| | T40.1X Poisoning by and adverse effect of heroin | |
| | T40.1X1 Poisoning by heroin, accidental (unintentional) | |
| | T40.1X1A Poisoning by heroin, accidental (unintentional), initial encounter | |
| | T40.1X1D Poisoning by heroin, accidental (unintentional), subsequent encounter | |
| | T40.1X1S Poisoning by heroin, accidental (unintentional), sequela | |
| | T40.1X2 Poisoning by heroin, intentional self-harm | |
| | T40.1X2A Poisoning by heroin, intentional self-harm, initial encounter | |
| | T40.1X2D Poisoning by heroin, intentional self-harm, subsequent encounter | |
| | T40.1X2S Poisoning by heroin, intentional self-harm, sequela | |
| | T40.1X3A Poisoning by heroin, assault, initial encounter | |
| | T40.1X3D Poisoning by heroin, assault, subsequent encounter | |
| | T40.1X3S Poisoning by heroin, assault, sequela | |
| | T40.1X4A Poisoning by heroin, undetermined, initial encounter | |
| | T40.1X4D Poisoning by heroin, undetermined, subsequent encounter | |
| | T40.1X4S Poisoning by heroin, undetermined, sequela | |
| | T40.2 Poisoning by, adverse effect of and underdosing of other opioids | |
| | T40.2X Poisoning by, adverse effect of and underdosing of other opioids | |
| | T40.2X1 Poisoning by other opioids, accidental (unintentional) | |
| | T40.2X1A Poisoning by other opioids, accidental (unintentional), initial encounter | |
| | T40.2X1D Poisoning by other opioids, accidental (unintentional), subsequent encounter | |
| | T40.2X1S Poisoning by other opioids, accidental (unintentional), sequela | |
| | T40.2X2 Poisoning by other opioids, intentional self-harm | |
| | T40.2X2A Poisoning by other opioids, intentional self-harm, initial encounter | |
| | T40.2X2D Poisoning by other opioids, intentional self-harm, subsequent encounter | |
| | T40.2X2S Poisoning by other opioids, intentional self-harm, sequela | |
| | T40.2X3 Poisoning by other opioids, assault | |
| | T40.2X3A Poisoning by other opioids, assault, initial encounter | |
| | T40.2X3D Poisoning by other opioids, assault, subsequent encounter | |
| | T40.2X3S Poisoning by other opioids, assault, sequela | |
| | T40.2X4 Poisoning by other opioids, undetermined | |
| | T40.2X4A Poisoning by other opioids, undetermined, initial encounter | |
| | T40.2X4D Poisoning by other opioids, undetermined, subsequent encounter | |
| | T40.2X4S Poisoning by other opioids, undetermined, sequela | |
| | T40.3 Poisoning by, adverse effect of and underdosing of methadone | |

| Variables | KPNC definition or source of data | eRI definition |
|-----------|---|----------------|
| | <p>T40.3X Poisoning by, adverse effect of and underdosing of methadone</p> <p>T40.3X1 Poisoning by methadone, accidental (unintentional)</p> <p>T40.3X1A Poisoning by methadone, accidental (unintentional), initial encounter</p> <p>T40.3X1D Poisoning by methadone, accidental (unintentional), subsequent encounter</p> <p>T40.3X1S Poisoning by methadone, accidental (unintentional), sequela</p> <p>T40.3X2 Poisoning by methadone, intentional self-harm</p> <p>T40.3X2A Poisoning by methadone, intentional self-harm, initial encounter</p> <p>T40.3X2D Poisoning by methadone, intentional self-harm, subsequent encounter</p> <p>T40.3X2S Poisoning by methadone, intentional self-harm, sequela</p> <p>T40.3X3 Poisoning by methadone, assault</p> <p>T40.3X3A Poisoning by methadone, assault, initial encounter</p> <p>T40.3X3D Poisoning by methadone, assault, subsequent encounter</p> <p>T40.3X3S Poisoning by methadone, assault, sequela</p> <p>T40.3X4 Poisoning by methadone, undetermined</p> <p>T40.3X4A Poisoning by methadone, undetermined, initial encounter</p> <p>T40.3X4D Poisoning by methadone, undetermined, subsequent encounter</p> <p>T40.3X4S Poisoning by methadone, undetermined, sequela</p> <p>T40.4 Poisoning by, adverse effect of and underdosing of other synthetic narcotics</p> <p>T40.4X Poisoning by, adverse effect of and underdosing of other synthetic narcotics</p> <p>T40.4X1 Poisoning by other synthetic narcotics, accidental (unintentional)</p> <p>T40.4X1A Poisoning by other synthetic narcotics, accidental (unintentional), initial encounter</p> <p>T40.4X1D Poisoning by other synthetic narcotics, accidental (unintentional), subsequent encounter</p> <p>T40.4X1S Poisoning by other synthetic narcotics, accidental (unintentional), sequela</p> <p>T40.4X2 Poisoning by other synthetic narcotics, intentional self-harm</p> <p>T40.4X2A Poisoning by other synthetic narcotics, intentional self-harm, initial encounter</p> <p>T40.4X2D Poisoning by other synthetic narcotics, intentional self-harm, subsequent encounter</p> <p>T40.4X2S Poisoning by other synthetic narcotics, intentional self-harm, sequela</p> <p>T40.4X3 Poisoning by other synthetic narcotics, assault</p> <p>T40.4X3A Poisoning by other synthetic narcotics, assault, initial encounter</p> <p>T40.4X3D Poisoning by other synthetic narcotics, assault, subsequent encounter</p> <p>T40.4X3S Poisoning by other synthetic narcotics, assault, sequela</p> <p>T40.4X4 Poisoning by other synthetic narcotics, undetermined</p> <p>T40.4X4A Poisoning by other synthetic narcotics, undetermined, initial encounter</p> <p>T40.4X4D Poisoning by other synthetic narcotics, undetermined, subsequent encounter</p> <p>T40.4X4S Poisoning by other synthetic narcotics, undetermined, sequela</p> <p>T40.6 Poisoning by, adverse effect of and underdosing of other and unspecified narcotics</p> <p>T40.60 Poisoning by, adverse effect of and underdosing of unspecified narcotics</p> <p>T40.601 Poisoning by unspecified narcotics, accidental (unintentional)</p> <p>T40.601A Poisoning by unspecified narcotics, accidental (unintentional), initial encounter</p> <p>T40.601D Poisoning by unspecified narcotics, accidental (unintentional), subsequent encounter</p> <p>T40.601S Poisoning by unspecified narcotics, accidental (unintentional), sequela</p> <p>T40.602 Poisoning by unspecified narcotics, intentional self-harm</p> <p>T40.602A Poisoning by unspecified narcotics, intentional self-harm, initial encounter</p> <p>T40.602D Poisoning by unspecified narcotics, intentional self-harm, subsequent encounter</p> <p>T40.602S Poisoning by unspecified narcotics, intentional self-harm, sequela</p> <p>T40.603 Poisoning by unspecified narcotics, assault</p> <p>T40.603A Poisoning by unspecified narcotics, assault, initial encounter</p> <p>T40.603D Poisoning by unspecified narcotics, assault, subsequent encounter</p> <p>T40.603S Poisoning by unspecified narcotics, assault, sequela</p> <p>T40.604 Poisoning by unspecified narcotics, undetermined</p> <p>T40.604A Poisoning by unspecified narcotics, undetermined, initial encounter</p> <p>T40.604D Poisoning by unspecified narcotics, undetermined, subsequent encounter</p> <p>T40.604S Poisoning by unspecified narcotics, undetermined, sequela</p> <p>T40.69 Poisoning by, adverse effect of and underdosing of other narcotics</p> <p>T40.691 Poisoning by other narcotics, accidental (unintentional)</p> <p>T40.691A Poisoning by other narcotics, accidental (unintentional), initial encounter</p> <p>T40.691D Poisoning by other narcotics, accidental (unintentional), subsequent encounter</p> <p>T40.691S Poisoning by other narcotics, accidental (unintentional), sequela</p> <p>T40.692 Poisoning by other narcotics, intentional self-harm</p> | |

| Variables | KPNC definition or source of data | eRI definition |
|--|---|---|
| | T40.692A Poisoning by other narcotics, intentional self-harm, initial encounter T40.692D Poisoning by other narcotics, intentional self-harm, T40.692S Poisoning by other narcotics, intentional self-harm, sequela T40.693 Poisoning by other narcotics, assault T40.693A Poisoning by other narcotics, assault, initial encounter T40.693D Poisoning by other narcotics, assault, subsequent encounter T40.693S Poisoning by other narcotics, assault, sequela T40.694 Poisoning by other narcotics, undetermined T40.694A Poisoning by other narcotics, undetermined, initial encounter T40.694D Poisoning by other narcotics, undetermined, subsequent encounter T40.694S Poisoning by other narcotics, undetermined, sequela | |
| Admission body mass index | Body mass index at time of admission | Admissionweight variable in kg divided by admissionheight variable in meters squared |
| Central line during MV (up to 21 days) | "LDA" tab in EPIC | Presence of central line based on documentation in the note, nursecharting, intakeoutput, treatment vitalperiodic, or vitalaperiodic tables within the first 21 days of invasive mechanical ventilation |
| Arterial line during MV (up to 21 days) | "LDA" tab in EPIC | Presence of arterial line based on documentation in the nursecharting, intakeoutput, treatment, or vitalperiodic tables within the first 21 days of invasive mechanical ventilation |
| Chest tube during MV (up to 21 days) | "LDA" tab in EPIC | Presence of chest tube based on documentation in the physicalexam, intakeoutput, treatment, or respiratorycharting tables within the first 21 days of invasive mechanical ventilation |
| Mechanical ventilation duration | Timestamps from ventilator flow sheet | Duration of invasive mechanical ventilation according to proprietary algorithm from Philips eRI. Censored at 21 days, a change in goals of care towards less aggressive care, or tracheostomy |
| Number of Mechanical ventilation episodes during encounter | Timestamps from ventilator flow sheet | Number of invasive mechanical ventilation episodes according to proprietary algorithm from Philips eRI during ICU stay |
| Charlson score | Quan implementation; Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. <i>Med Care</i> . 2005; 43 :1130–9. doi: 10.1097/01.mlr.0000182534.19832.83. | Same as KPNC |
| SOFA | Using 24-hour windows of mechanical ventilation, we did a 24-hour look back period for input labs and vital signs without carry forward of values, taking the worst value in that time period; Walkey A, et al. Prognostic Accuracy of Presepsis and Intrasepsis Characteristics | Same as KPNC |

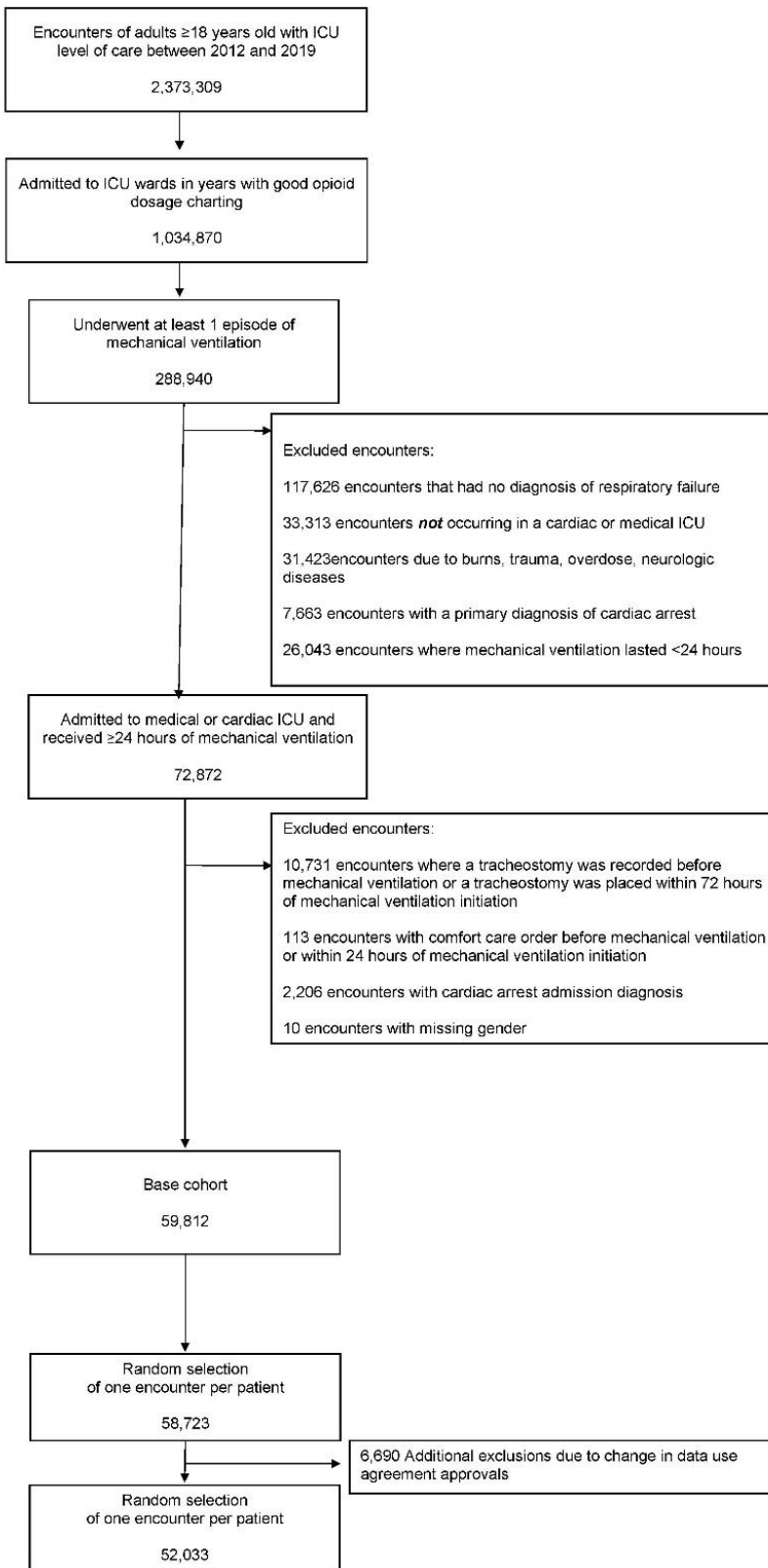
| Variables | KPNC definition or source of data | eRI definition |
|---|--|--|
| | for Prediction of Cardiovascular Events After a Sepsis Hospitalization. <i>Crit Care Explor.</i> 2022 Apr 8;4(4):e0674. doi: 10.1097/CCE.0000000000000674. eCollection 2022 Apr. | |
| PEEP | Ventilator flowsheet | PEEP values extracted from respiratorycharting (respchartvalue where respchartvalue label is "PEEP" or "PEEP/CPAP"), respiratorycare (peeplimit variable), and physicaalexam (physicaalexamtext variable where physicaalexamtext path was "notes/Progress Notes/Physical Exam/Physical Exam/Constitutional/Vital Sign and Physiological Data/PEEP/PEEP") tables. |
| Facility Location | 1 of 21 medical centers | Region variable |
| Hospital number of beds | Internal file | Numbedscategory variable |
| Teaching hospital status | Internal file | Teachingstatus variable |
| Code status at beginning of hospitalization | Care directive table | Careplangeneral table where cplgroup variable was "Care Limitation" |
| Principal discharge diagnoses group | Principal discharge diagnoses field | Diagnoses from diagnosis table |

Supplemental Figure 1. KPNC Cohort diagram



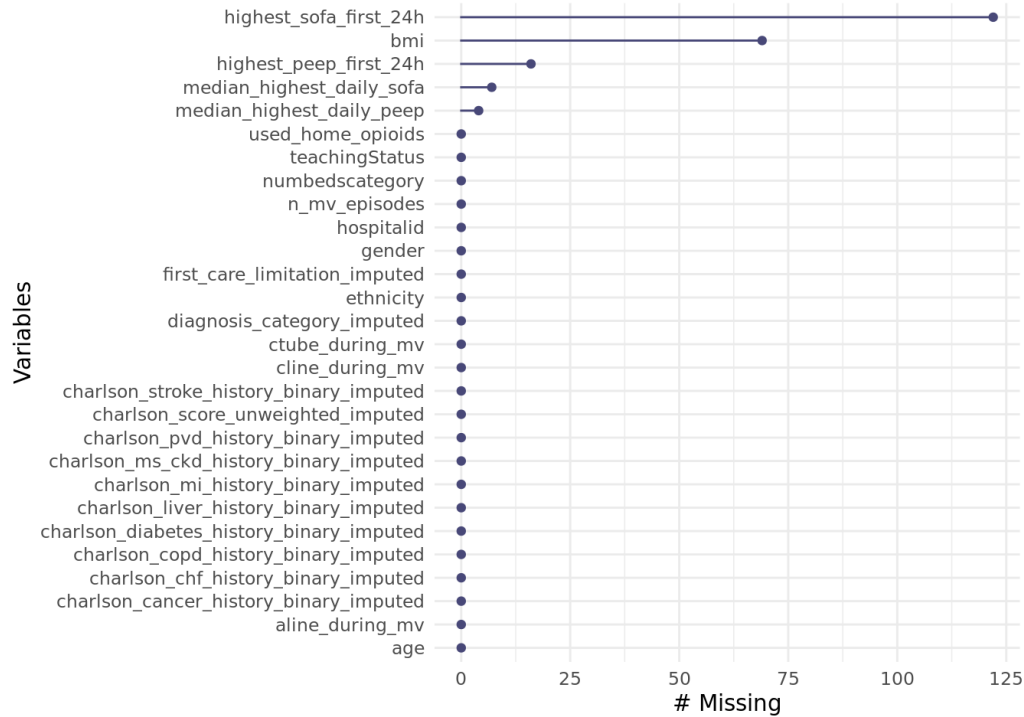
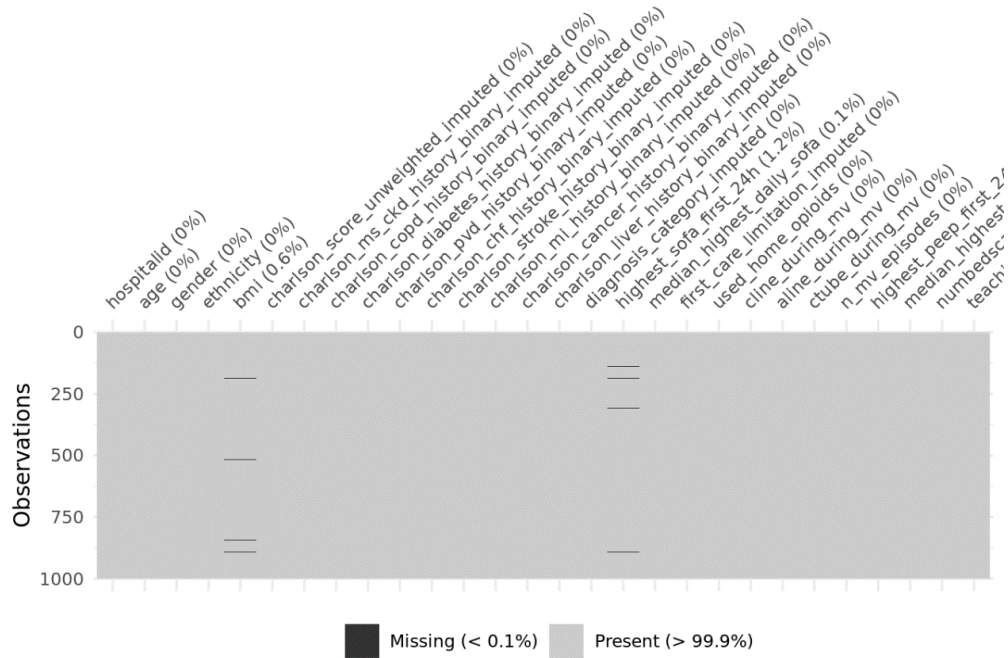
Abbreviations: ICU=intensive care unit

Supplemental Figure 2: eRI Cohort diagram

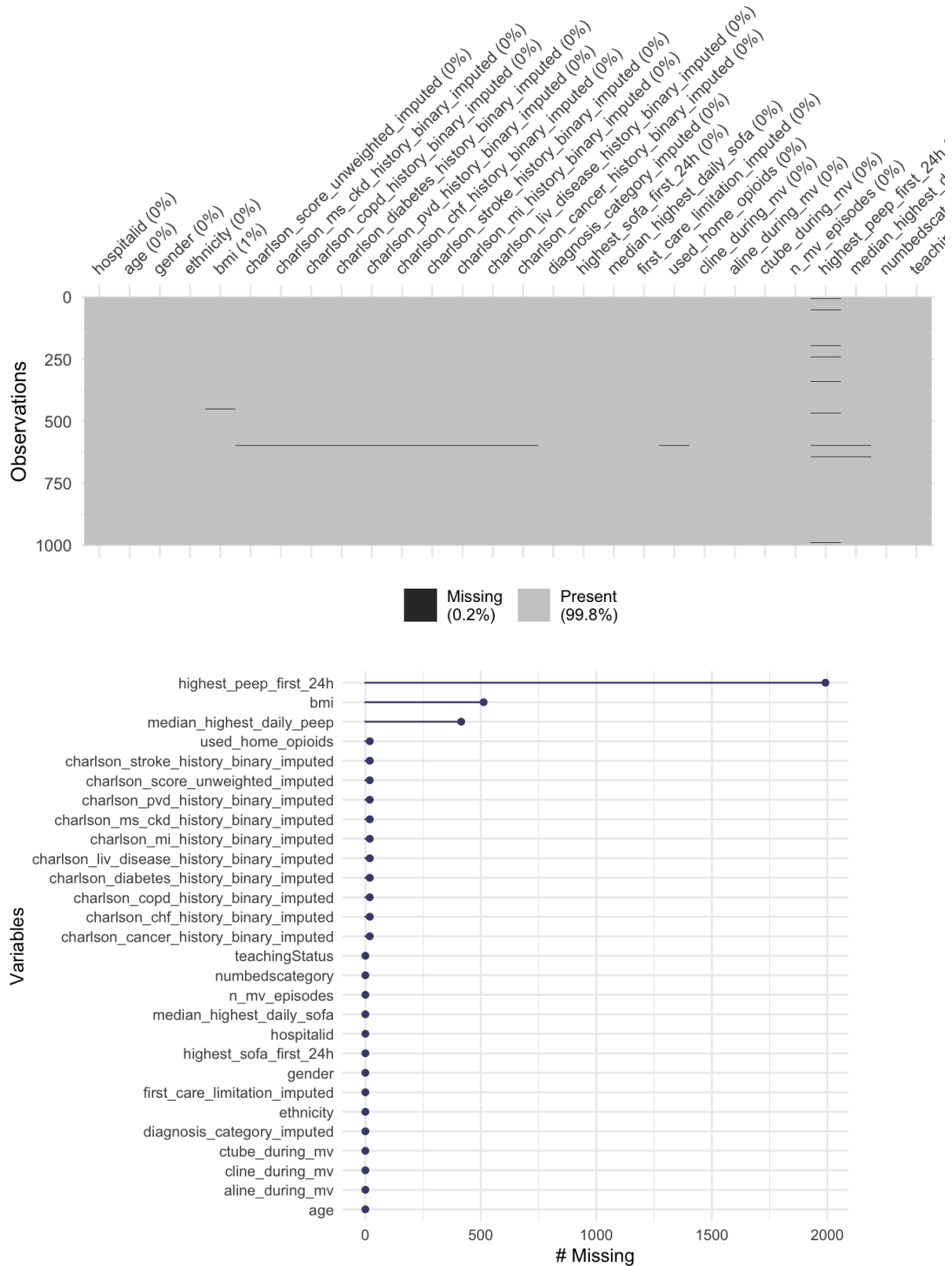


Abbreviations: ICU=intensive care unit

Supplemental Figure 3: KPNC Missing Data



Supplemental Figure 4: eRI Missing Data



Supplemental Table 3: Extended list of baseline characteristics

| Characteristic | KPNC N=13,140 | eRI N=52,033 |
|--|---------------|---------------|
| Chronic kidney disease, No. (%) | 4,664 (35.5) | 5,261 (10.1) |
| Chronic pulmonary disease, No. (%) | 5,124 (39.0%) | 11,789 (22.7) |
| Diabetes, No. (%) | 5,082 (38.7) | 16,161 (31.1) |
| Peripheral vascular disease, No. (%) | 6,713 (51.1) | 2,075 (4.0) |
| Chronic heart failure, No. (%) | 4,009 (30.5) | 10,563 (20.3) |
| Cerebrovascular disease, No. (%) | 2,649 (20.2) | 5,625 (10.8) |
| Myocardial infarction, No. (%) | 2,097 (16.0) | 5,037 (9.7) |
| Liver disease ¹ , No. (%) | 2,407 (18.3) | 3,031 (5.8) |
| Malignancy ² , No. (%) | 2,423 (18.4) | 7,635 (14.7) |
| Principal discharge diagnoses group, No. (%) | | |
| Pneumonia including aspiration | 464 (3.5) | 1,999 (3.8) |
| Myocardial infarction | 519 (3.9) | 552 (1.1) |
| Heart failure | 479 (3.6) | 2,103 (4.0) |
| Cardiac arrest or anoxic brain injury | 121 (0.9) | 0 |
| Arrhythmia | 327 (2.5) | 329 (0.6) |
| Deep vein thrombosis or pulmonary embolus | 90 (0.7) | 168 (0.3) |
| Bleeding (mainly gastrointestinal) | 296 (2.3) | 983 (1.9) |
| Seizure | 223 (1.7) | 773 (1.5) |
| Cirrhosis or liver failure | 215 (1.6) | 134 (0.3) |
| Obstructive lung disease | 181 (1.4) | 1,788 (3.4) |
| Other abdominal | 173 (1.3) | 142 (0.3) |
| Cancer | 158 (1.2) | 100 (0.2) |
| Kidney failure | 138 (1.1) | 299 (0.6) |
| Diabetes or electrolyte related | 134 (1.0) | 198 (0.4) |
| Neurologic | 115 (0.9) | 812 (1.6) |
| Pancreatitis | 96 (0.7) | 93 (0.2) |
| Alcohol-related | 82 (0.6) | 161 (0.3) |
| Altered mental status | 85 (0.6) | 908 (1.7) |
| Other | 909 (6.9) | 15,453 (29.7) |

Abbreviations: ICU: intensive care unit; IQR: interquartile range; MV: mechanical ventilation; PEEP: positive end expiratory pressure; SOFA: sequential organ failure assessment; KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

¹Combines mild and moderate-to-severe liver disease categories

²Combines metastatic and localized malignancy categories

Supplemental Table 4: Associations between fixed effects and opioid infusion use

| Characteristic | KPNC | | | eRI | | |
|---|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| (Intercept) | 0.34 | 0.15 | 0.79 | 0.56 | 0.20 | 1.55 |
| Age at admission (per 1-year increase) | 0.99 | 0.98 | 0.99 | 0.98 | 0.98 | 0.98 |
| Male sex (female reference) | 1.11 | 1.02 | 1.2 | 1.06 | 1.02 | 1.11 |
| Race | | | | | | |
| Black race (Asian reference) | 0.97 | 0.83 | 1.13 | 0.85 | 0.66 | 1.08 |
| Hispanic (Asian reference) | 0.95 | 0.83 | 1.11 | 0.82 | 0.63 | 1.07 |
| Other/unknown/missing race (Asian reference) | 0.98 | 0.81 | 1.19 | 0.96 | 0.75 | 1.24 |
| White race (Asian reference) | 1.07 | 0.95 | 1.21 | 1.03 | 0.81 | 1.30 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 1 | 1 | 1.01 | 1.00 | 1.00 | 1.00 |
| Charlson score (unweighted) per 1 point increase | 0.92 | 0.87 | 0.99 | 0.98 | 0.93 | 1.03 |
| Chronic kidney disease | 0.96 | 0.84 | 1.08 | 1.06 | 0.96 | 1.18 |
| Chronic pulmonary disease | 1.36 | 1.22 | 1.52 | 1.22 | 1.13 | 1.31 |
| Diabetes | 1.03 | 0.9 | 1.19 | 0.88 | 0.81 | 0.94 |
| Peripheral vascular disease | 1.07 | 0.94 | 1.21 | 0.99 | 0.88 | 1.12 |
| Congestive heart failure | 0.85 | 0.76 | 0.96 | 0.89 | 0.82 | 0.96 |
| Cerebrovascular disease | 0.83 | 0.72 | 0.94 | 0.83 | 0.76 | 0.91 |
| Myocardial infarction | 1.11 | 0.96 | 1.26 | 1.09 | 0.99 | 1.20 |
| Cancer | 1.36 | 1.17 | 1.58 | 1.25 | 1.16 | 1.36 |
| Liver disease | 1.03 | 0.9 | 1.19 | 0.77 | 0.68 | 0.87 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | 1.32 | 0.68 | 2.59 | 0.72 | 0.45 | 1.15 |
| Cardiac arrest or anoxic brain injury | 0.96 | 0.51 | 1.79 | NA* | NA* | NA* |
| Arrhythmia | 3.06 | 1.79 | 5.31 | 1.37 | 0.82 | 2.27 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| Other abdominal | 2.27 | 1.27 | 4.1 | 1.12 | 0.62 | 2.02 |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | 2.44 | 1.42 | 4.18 | 0.96 | 0.60 | 1.53 |
| Cancer | 1.9 | 1.05 | 3.46 | 1.76 | 0.93 | 3.35 |
| Congestive heart failure | 2.27 | 1.35 | 3.82 | 0.96 | 0.62 | 1.50 |
| Obstructive lung disease | 2.18 | 1.22 | 3.9 | 1.46 | 0.93 | 2.27 |
| Diabetes or electrolyte related | 1.38 | 0.76 | 2.53 | 1.01 | 0.58 | 1.77 |
| Deep vein thrombosis or pulmonary embolus | 2.01 | 1.04 | 3.9 | 1.16 | 0.65 | 2.03 |
| Cirrhosis or liver failure | 1.12 | 0.63 | 1.97 | 0.60 | 0.32 | 1.12 |
| Myocardial infarction | 2.8 | 1.65 | 4.71 | 1.01 | 0.63 | 1.64 |
| Neurologic | 1.8 | 0.97 | 3.35 | 0.65 | 0.40 | 1.05 |
| Other | 1.77 | 1.07 | 2.92 | 1.09 | 0.71 | 1.68 |
| Pancreatitis | 5.05 | 2.41 | 10.49 | 2.68 | 1.31 | 5.54 |
| Pneumonia including aspiration | 2.03 | 1.2 | 3.42 | 1.33 | 0.85 | 2.06 |
| Kidney failure | 1.68 | 0.91 | 3.06 | 1.06 | 0.63 | 1.80 |
| Respiratory failure | 1.8 | 1.11 | 2.97 | 1.19 | 0.77 | 1.83 |
| Seizure | 0.74 | 0.42 | 1.32 | 0.54 | 0.33 | 0.86 |
| Sepsis | 1.72 | 1.06 | 2.8 | 1.25 | 0.81 | 1.93 |
| SOFA in first 24 hours of MV (per 1-point increase) | 0.99 | 0.96 | 1.01 | 1.01 | 0.99 | 1.02 |
| Median of patients daily SOFA during MV (up to 21 days) | 1.05 | 1.03 | 1.08 | 1.02 | 1.00 | 1.03 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 1.04 | 0.85 | 1.27 | 0.92 | 0.83 | 1.02 |
| Partial code vs DNR | 1.02 | 0.76 | 1.38 | 0.40 | 0.17 | 0.98 |
| History of opioid use 1-year prior to admission | 1.03 | 0.8 | 1.32 | 1.34 | 1.14 | 1.58 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| Central line during MV (up to 21 days) | 1.49 | 1.35 | 1.65 | 1.65 | 1.55 | 1.74 |
| Arterial line during MV (up to 21 days) | 1.7 | 1.55 | 1.88 | 1.65 | 1.55 | 1.74 |
| Chest tube during MV (up to 21 days) | 1.22 | 1.02 | 1.48 | 1.31 | 1.13 | 1.52 |
| Number of mechanical ventilation episodes during encounter | 0.95 | 0.86 | 1.04 | 1.15 | 1.05 | 1.26 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 1.04 | 1.02 | 1.06 | 1.03 | 1.02 | 1.04 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 1.11 | 1.07 | 1.13 | 1.09 | 1.08 | 1.11 |
| Hospital number of beds 100-500 (versus <100) | 0.96 | 0.49 | 1.86 | 0.46 | 0.17 | 1.23 |
| Hospital number of beds >500 (versus <100) | NA | NA | NA | 0.54 | 0.16 | 1.77 |
| Teaching hospital | 0.86 | 0.41 | 1.79 | 0.73 | 0.22 | 2.40 |

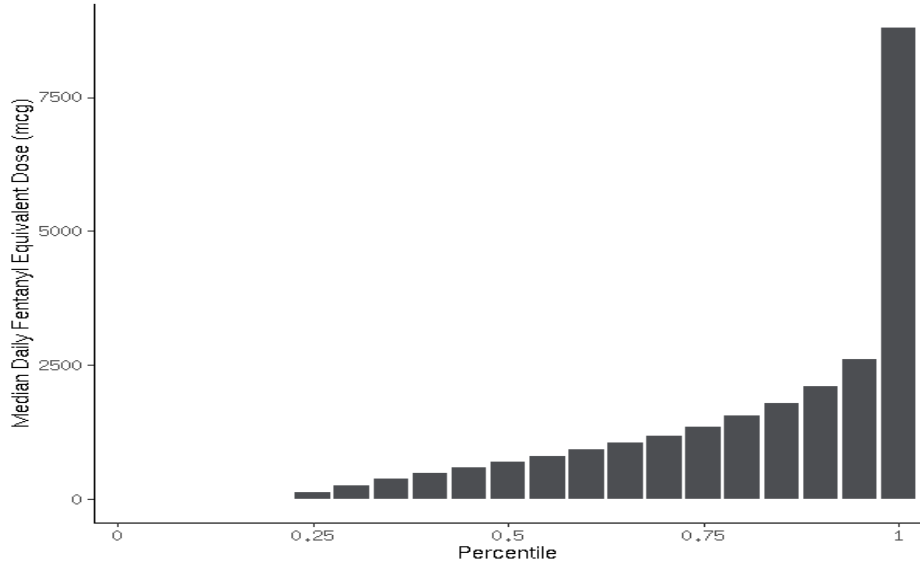
KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

NA: not applicable

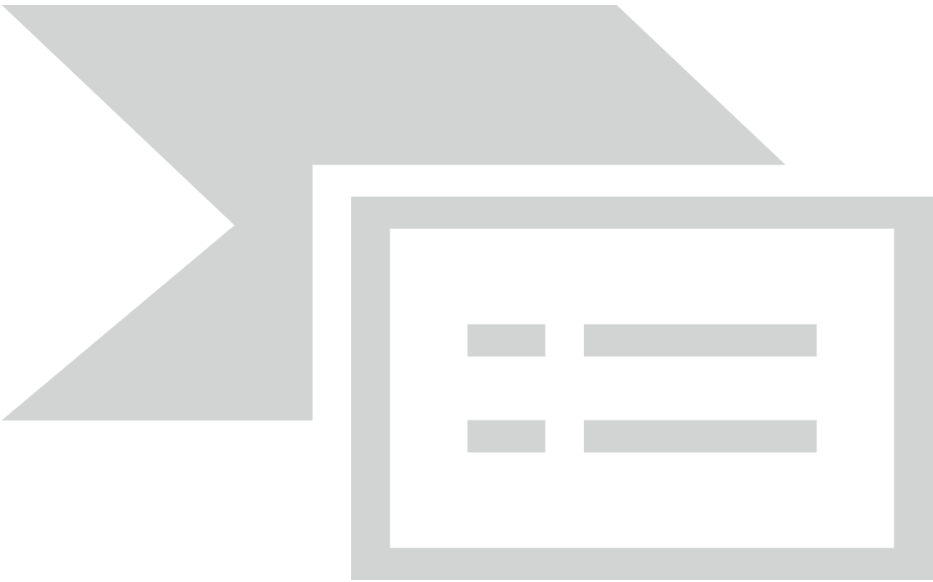
*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Figure 5: Distribution of median daily fentanyl equivalent among those who received opioid infusion

KPNC



ERI



Supplemental Table 5: Associations between fixed effects and median daily fentanyl equivalent dose

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| (Intercept) | 1127.29 | 743.64 | 1510.94 | 1037.60 | 510.80 | 1564.41 |
| Age at admission (per 1-year increase) | -11.22 | -12.73 | -9.71 | -12.83 | -14.34 | -11.33 |
| Male sex (female reference) | 65.12 | 25.65 | 104.59 | 85.17 | 48.49 | 121.84 |
| Race | | | | | | |
| Black race (Asian reference) | -37.94 | -117.38 | 41.49 | -80.20 | -265.61 | 105.20 |
| Hispanic (Asian reference) | 120.34 | 46.65 | 194.03 | 266.86 | 69.05 | 464.66 |
| Other/unknown/missing race (Asian reference) | 45.96 | -52.85 | 144.78 | -86.82 | -276.07 | 102.44 |
| White race (Asian reference) | 98.79 | 37.26 | 160.32 | -16.15 | -194.89 | 162.60 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 3.68 | 1.13 | 6.24 | 3.37 | 1.52 | 5.21 |
| Charlson score (unweighted) per 1 point increase | -41.67 | -78.87 | -4.46 | -41.73 | -78.15 | -5.31 |
| Chronic kidney disease | 36.71 | -29.94 | 103.36 | 15.49 | -67.26 | 98.23 |
| Chronic pulmonary disease | 87.41 | 29.91 | 144.91 | 133.15 | 74.51 | 191.79 |
| Diabetes | -11.44 | -84.76 | 61.87 | -17.07 | -74.75 | 40.62 |
| Peripheral vascular disease | 92.44 | 28.1 | 156.78 | -13.00 | -113.76 | 87.77 |
| Congestive heart failure | 1.01 | -63.71 | 65.73 | -26.78 | -90.22 | 36.66 |
| Cerebrovascular disease | -26.68 | -98.14 | 44.78 | -51.07 | -126.85 | 24.72 |
| Myocardial infarction | 6.7 | -63.7 | 77.11 | 91.75 | 16.56 | 166.93 |
| Cancer | 123.3 | 48.29 | 198.31 | 124.13 | 59.90 | 188.35 |
| Liver disease | 51.68 | -21.5 | 124.86 | -127.37 | -224.61 | -30.13 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | -40.94 | -438.87 | 356.98 | -174.39 | -523.22 | 174.44 |
| Cardiac arrest or anoxic brain injury | -635.89 | -1005.79 | -265.99 | NA* | NA* | NA* |
| Arrhythmia | -97.93 | -403.87 | 208 | -95.82 | -464.01 | 272.38 |
| Other abdominal | 178.42 | -147.26 | 504.1 | -153.68 | -596.79 | 289.43 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | -15.93 | -324.95 | 293.08 | -237.41 | -583.80 | 108.98 |
| Cancer | 35.32 | -294.59 | 365.24 | -122.88 | -576.97 | 331.21 |
| Congestive heart failure | -45.06 | -347.92 | 257.8 | -49.74 | -378.39 | 278.92 |
| Obstructive lung disease | 86.08 | -241.2 | 413.37 | 43.21 | -284.64 | 371.07 |
| Diabetes or electrolyte related | -260.32 | -612.13 | 91.48 | -493.02 | -903.69 | -82.36 |
| Deep vein thrombosis or pulmonary embolus | -185.15 | -543.5 | 173.2 | -123.68 | -557.19 | 309.84 |
| Cirrhosis or liver failure | -339.08 | -665.21 | -12.95 | -562.87 | -1031.90 | -93.84 |
| Myocardial infarction | -33.61 | -333.72 | 266.5 | 15.47 | -340.19 | 371.12 |
| Neurologic | -402.61 | -759.22 | -46 | -236.48 | -600.78 | 127.83 |
| Other | 1.8 | -291.88 | 295.47 | -35.12 | -353.08 | 282.84 |
| Pancreatitis | 504.13 | 167.11 | 841.14 | 75.45 | -353.96 | 504.87 |
| Pneumonia including aspiration | 50.41 | -252.39 | 353.22 | -32.94 | -357.25 | 291.38 |
| Kidney failure | -194.75 | -536.95 | 147.45 | -116.06 | -504.99 | 272.87 |
| Respiratory failure | -75.38 | -365.15 | 214.4 | -35.48 | -352.94 | 281.98 |
| Seizure | -378.2 | -729.82 | -26.59 | -233.14 | -592.83 | 126.55 |
| Sepsis | 1.44 | -285.13 | 288.01 | -100.68 | -419.50 | 218.14 |
| SOFA in first 24 hours of MV (per 1-point increase) | -36.28 | -46.58 | -25.98 | -1.97 | -14.94 | 10.99 |
| Median of patients daily SOFA during MV (up to 21 days) | 15.43 | 4.77 | 26.09 | -8.40 | -22.22 | 5.42 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 18.2 | -92.69 | 129.09 | -15.98 | -93.82 | 61.85 |
| Partial code vs DNR | -78.04 | -244.99 | 88.92 | -286.75 | -1058.79 | 485.29 |
| History of opioid use 1-year prior to admission | 35.38 | -87.14 | 157.89 | 386.60 | 287.75 | 485.45 |
| Central line during MV (up to 21 days) | 96.66 | 40.61 | 152.7 | 120.34 | 76.37 | 164.32 |
| Arterial line during MV (up to 21 days) | 137.31 | 91.08 | 183.53 | 98.85 | 54.96 | 142.74 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Chest tube during MV (up to 21 days) | 99.14 | 15.73 | 182.55 | 190.56 | 87.94 | 293.18 |
| Number of mechanical ventilation episodes during encounter | 22.51 | -26.37 | 71.39 | 28.34 | -37.67 | 94.35 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 7.58 | -1.05 | 16.21 | 4.54 | -2.09 | 11.16 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 40.05 | 29.62 | 50.47 | 62.87 | 54.54 | 71.20 |
| Hospital number of beds 100-500 (versus <100) | -3.11 | -210.51 | 204.29 | -169.53 | -555.11 | 216.05 |
| Hospital number of beds >500 (versus <100) | NA | NA | NA | -227.26 | -678.06 | 223.53 |
| Teaching hospital | 98.64 | -127.74 | 325.02 | -290.63 | -737.39 | 156.13 |

KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Table 6: Associations between fixed effects and maximal hourly fentanyl equivalent rate

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| (Intercept) | 98.67 | 71.67 | 125.68 | 113.29 | 16.77 | 209.82 |
| Age at admission (per 1-year increase) | -0.56 | -0.67 | -0.46 | -0.87 | -1.17 | -0.57 |
| Male sex (female reference) | 5.50 | 2.68 | 8.33 | 7.51 | 0.18 | 14.84 |
| Race | | | | | | |
| Black race (Asian reference) | -1.88 | -7.57 | 3.81 | -19.07 | -56.09 | 17.95 |
| Hispanic (Asian reference) | 3.54 | -1.74 | 8.82 | -2.22 | -41.71 | 37.27 |
| Other/unknown/missing race (Asian reference) | -2.39 | -9.47 | 4.69 | -27.15 | -64.93 | 10.64 |
| White race (Asian reference) | 2.87 | -1.53 | 7.28 | -17.87 | -53.55 | 17.82 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 0.30 | 0.12 | 0.49 | 0.78 | 0.41 | 1.14 |
| Charlson score (unweighted) per 1 point increase | -0.72 | -3.38 | 1.95 | -0.51 | -7.79 | 6.77 |
| Chronic kidney disease | -1.67 | -6.44 | 3.11 | 5.15 | -11.37 | 21.67 |
| Chronic pulmonary disease | 4.37 | 0.25 | 8.49 | 2.02 | -9.69 | 13.74 |
| Diabetes | -3.25 | -8.50 | 2.00 | -8.81 | -20.34 | 2.71 |
| Peripheral vascular disease | 1.94 | -2.67 | 6.55 | -0.41 | -20.55 | 19.73 |
| Congestive heart failure | -2.27 | -6.91 | 2.36 | -7.12 | -19.80 | 5.56 |
| Cerebrovascular disease | -4.23 | -9.35 | 0.89 | -16.01 | -31.15 | -0.86 |
| Myocardial infarction | 3.20 | -1.84 | 8.25 | 6.69 | -8.33 | 21.72 |
| Cancer | 5.32 | -0.05 | 10.70 | -1.92 | -14.75 | 10.92 |
| Liver disease | 0.64 | -4.61 | 5.88 | -9.20 | -28.63 | 10.24 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | -18.10 | -46.61 | 10.41 | -8.33 | -78.06 | 61.40 |
| Cardiac arrest or anoxic brain injury | -42.58 | -69.08 | -16.08 | NA* | NA* | NA* |
| Arrhythmia | -15.46 | -37.38 | 6.46 | 10.55 | -63.05 | 84.15 |
| Other abdominal | 6.54 | -16.79 | 29.88 | -5.47 | -94.04 | 83.11 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | -2.40 | -24.54 | 19.74 | 12.41 | -56.83 | 81.65 |
| Cancer | 1.43 | -22.21 | 25.06 | 20.78 | -69.99 | 111.54 |
| Congestive heart failure | -11.62 | -33.32 | 10.08 | 16.98 | -48.71 | 82.68 |
| Obstructive lung disease | 0.85 | -22.60 | 24.30 | 19.98 | -45.56 | 85.51 |
| Diabetes or electrolyte related | -25.23 | -50.44 | -0.02 | -28.54 | -110.63 | 53.55 |
| Deep vein thrombosis or pulmonary embolus | -17.22 | -42.89 | 8.46 | -26.65 | -113.31 | 60.01 |
| Cirrhosis or liver failure | -13.39 | -36.75 | 9.98 | 26.12 | -67.64 | 119.87 |
| Myocardial infarction | -11.59 | -33.09 | 9.91 | 12.50 | -58.59 | 83.59 |
| Neurologic | -18.22 | -43.77 | 7.33 | 30.41 | -42.41 | 103.23 |
| Other | -4.31 | -25.35 | 16.73 | 18.58 | -44.98 | 82.13 |
| Pancreatitis | 19.82 | -4.33 | 43.97 | 54.72 | -31.11 | 140.56 |
| Pneumonia including aspiration | -11.23 | -32.92 | 10.47 | 34.47 | -30.35 | 99.30 |
| Kidney failure | -16.08 | -40.60 | 8.44 | -9.43 | -87.17 | 68.31 |
| Respiratory failure | -11.33 | -32.09 | 9.43 | 22.41 | -41.04 | 85.87 |
| Seizure | -23.24 | -48.44 | 1.95 | 4.09 | -67.81 | 75.98 |
| Sepsis | -7.52 | -28.06 | 13.01 | 17.31 | -46.42 | 81.03 |
| SOFA in first 24 hours of MV (per 1-point increase) | -1.88 | -2.63 | -1.14 | 2.44 | -0.15 | 5.03 |
| Median of patients daily SOFA during MV (up to 21 days) | 1.08 | 0.32 | 1.85 | -2.63 | -5.39 | 0.13 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 9.66 | 1.72 | 17.61 | 5.02 | -10.53 | 20.57 |
| Partial code vs DNR | 0.84 | -11.12 | 12.80 | -20.90 | -175.20 | 133.41 |
| History of opioid use 1-year prior to admission | 5.22 | -3.56 | 14.00 | 27.06 | 7.31 | 46.81 |
| Central line during MV (up to 21 days) | 7.27 | 3.25 | 11.28 | 18.85 | 10.08 | 27.63 |
| Arterial line during MV (up to 21 days) | 7.99 | 4.68 | 11.30 | 11.99 | 3.23 | 20.76 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Chest tube during MV (up to 21 days) | 10.18 | 4.20 | 16.16 | 22.92 | 2.42 | 43.43 |
| Number of mechanical ventilation episodes during encounter | 2.37 | -1.13 | 5.87 | 1.61 | -11.58 | 14.80 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 1.14 | 0.52 | 1.76 | -0.18 | -1.52 | 1.16 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 1.07 | 0.32 | 1.82 | 4.28 | 2.61 | 5.95 |
| Hospital number of beds 100-500 (versus <100) | 6.20 | -7.47 | 19.87 | 23.54 | -37.53 | 84.61 |
| Hospital number of beds >500 (versus <100) | | | | -2.52 | -73.18 | 68.14 |
| Teaching hospital | 5.49 | -9.36 | 20.34 | -42.54 | -112.46 | 27.37 |

KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Table 7: Associations between fixed effects and cumulative fentanyl equivalent dose

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| (Intercept) | 1657.92 | -1334.52 | 4650.37 | 2444.64 | -2446.75 | 7336.03 |
| Age at admission (per 1-year increase) | -73.20 | -85.49 | -60.91 | -100.21 | -114.03 | -86.39 |
| Male sex (female reference) | 242.72 | -78.19 | 563.62 | 644.12 | 307.85 | 980.39 |
| Race | | | | | | |
| Black race (Asian reference) | -617.53 | -1262.74 | 27.68 | -1088.34 | -2787.45 | 610.76 |
| Hispanic (Asian reference) | 554.84 | -44.13 | 1153.81 | 2727.17 | 914.36 | 4539.99 |
| Other/unknown/missing race (Asian reference) | 72.44 | -731.16 | 876.04 | -992.11 | -2726.59 | 742.37 |
| White race (Asian reference) | 313.59 | -186.57 | 813.75 | -188.49 | -1826.78 | 1449.8 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 28.18 | 7.40 | 48.96 | 35.73 | 19.02 | 52.45 |
| Charlson score (unweighted) per 1 point increase | -352.10 | -654.63 | -49.58 | -312.09 | -645.81 | 21.64 |
| Chronic kidney disease | 257.94 | -284.10 | 799.97 | -127.25 | -885.56 | 631.06 |
| Chronic pulmonary disease | 469.54 | 2.00 | 937.08 | 977.86 | 440.5 | 1515.23 |
| Diabetes | 147.66 | -448.42 | 743.75 | -316.65 | -845.07 | 211.78 |
| Peripheral vascular disease | 593.89 | 70.73 | 1117.05 | 107.27 | -816.09 | 1030.63 |
| Congestive heart failure | -138.41 | -664.66 | 387.83 | -286.79 | -868.03 | 294.46 |
| Cerebrovascular disease | -79.24 | -660.17 | 501.69 | -791.46 | -1485.89 | -97.02 |
| Myocardial infarction | 211.30 | -361.26 | 783.85 | 842.52 | 153.56 | 1531.48 |
| Cancer | 1006.04 | 396.21 | 1615.87 | 843.67 | 255.11 | 1432.23 |
| Liver disease | 419.14 | -175.82 | 1014.11 | -948.75 | -1839.81 | -57.69 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | 784.34 | -2450.59 | 4019.27 | -298.17 | -3495.12 | 2898.78 |
| Cardiac arrest or anoxic brain injury | -2570.25 | -5577.56 | 437.05 | NA* | NA* | NA* |
| Arrhythmia | -475.78 | -2962.99 | 2011.43 | 880.56 | -2494.55 | 4255.67 |
| Other abdominal | 822.40 | -1825.95 | 3470.75 | -1013.56 | -5074.22 | 3047.1 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | 547.11 | -1965.37 | 3059.59 | -95.99 | -3271.01 | 3079.02 |
| Cancer | 393.12 | -2289.06 | 3075.29 | -2725.22 | -6886.28 | 1435.85 |
| Congestive heart failure | 190.15 | -2272.26 | 2652.56 | 371.18 | -2641.46 | 3383.82 |
| Obstructive lung disease | 887.65 | -1772.98 | 3548.29 | 1317.3 | -1687.84 | 4322.45 |
| Diabetes or electrolyte related | -678.62 | -3538.64 | 2181.41 | -2582.21 | -6347.23 | 1182.81 |
| Deep vein thrombosis or pulmonary embolus | -835.79 | -3749.74 | 2078.15 | 478.09 | -3494.5 | 4450.69 |
| Cirrhosis or liver failure | -1270.59 | -3921.76 | 1380.58 | -3180.2 | -7478.45 | 1118.05 |
| Myocardial infarction | -28.04 | -2467.79 | 2411.71 | 505.3 | -2754.9 | 3765.5 |
| Neurologic | -3108.72 | -6010.07 | -207.38 | -1146.07 | -4484.28 | 2192.15 |
| Other | 307.25 | -2080.09 | 2694.58 | 624.06 | -2289.96 | 3538.08 |
| Pancreatitis | 4770.79 | 2030.89 | 7510.70 | 2442.59 | -1492.2 | 6377.39 |
| Pneumonia including aspiration | 1680.43 | -781.08 | 4141.93 | 287.29 | -2684.55 | 3259.14 |
| Kidney failure | -376.25 | -3158.45 | 2405.95 | 1426.46 | -2137.94 | 4990.87 |
| Respiratory failure | 291.47 | -2064.23 | 2647.18 | 523.66 | -2385.68 | 3433 |
| Seizure | -1308.14 | -4166.66 | 1550.37 | -1034.66 | -4331.43 | 2262.1 |
| Sepsis | 1180.99 | -1148.62 | 3510.60 | -209.23 | -3131.16 | 2712.7 |
| SOFA in first 24 hours of MV (per 1-point increase) | -196.30 | -279.90 | -112.70 | 99.06 | -19.78 | 217.9 |
| Median of patients daily SOFA during MV (up to 21 days) | 143.72 | 57.15 | 230.29 | -196.46 | -323.24 | -69.68 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 48.58 | -852.86 | 950.02 | -142.42 | -855.63 | 570.79 |
| Partial code vs DNR | -412.22 | -1769.51 | 945.07 | -804.47 | -7879.01 | 6270.07 |
| History of opioid use 1-year prior to admission | 930.55 | -65.45 | 1926.54 | 2514.26 | 1608.33 | 3420.2 |
| Central line during MV (up to 21 days) | 899.09 | 438.92 | 1359.25 | 709.84 | 303.4 | 1116.29 |
| Arterial line during MV (up to 21 days) | 1062.21 | 685.96 | 1438.46 | 724.29 | 320.95 | 1127.62 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Chest tube during MV (up to 21 days) | 1584.97 | 904.04 | 2265.91 | 904.55 | -39.47 | 1848.57 |
| Number of mechanical ventilation episodes during encounter | 85.88 | -312.13 | 483.90 | 264.67 | -340.22 | 869.56 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 135.41 | 64.50 | 206.32 | 12.57 | -48.89 | 74.02 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 271.53 | 186.43 | 356.63 | 526.33 | 449.8 | 602.87 |
| Hospital number of beds 100-500 (versus <100) | 194.97 | -1164.03 | 1553.96 | -544.08 | -4179.77 | 3091.6 |
| Hospital number of beds >500 (versus <100) | NA | NA | NA | -1535.11 | -5790.57 | 2720.35 |
| Teaching hospital | 738.34 | -723.86 | 2200.54 | -3185.18 | -7402.7 | 1032.34 |
| Length of MV1 (hours) | 21.48 | 20.46 | 22.49 | 32.24 | 31.08 | 33.4 |

KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Table 8: Associations between fixed effects and opioid infusion use in complete cases

| Characteristic | KPNC | | | eRI | | |
|---|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| (Intercept) | 0.35 | 0.15 | 0.80 | 0.56 | 0.20 | 1.53 |
| Age at admission (per 1-year increase) | 0.99 | 0.98 | 0.99 | 0.98 | 0.98 | 0.98 |
| Male sex (female reference) | 1.11 | 1.02 | 1.20 | 1.07 | 1.02 | 1.12 |
| Race | | | | | | |
| Black race (Asian reference) | 0.97 | 0.83 | 1.13 | 0.89 | 0.69 | 1.14 |
| Hispanic (Asian reference) | 0.95 | 0.82 | 1.10 | 0.86 | 0.65 | 1.12 |
| Other/unknown/missing race (Asian reference) | 0.97 | 0.81 | 1.18 | 1 | 0.77 | 1.30 |
| White race (Asian reference) | 1.07 | 0.95 | 1.20 | 1.06 | 0.83 | 1.36 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 1.00 | 1.00 | 1.01 | 1.00 | 1.00 | 1.00 |
| Charlson score (unweighted) per 1 point increase | 0.93 | 0.87 | 1.00 | 0.97 | 0.92 | 1.02 |
| Chronic kidney disease | 0.96 | 0.85 | 1.09 | 1.07 | 0.96 | 1.19 |
| Chronic pulmonary disease | 1.34 | 1.20 | 1.50 | 1.26 | 1.16 | 1.35 |
| Diabetes | 1.03 | 0.89 | 1.18 | 0.88 | 0.82 | 0.95 |
| Peripheral vascular disease | 1.06 | 0.94 | 1.21 | 1.00 | 0.88 | 1.14 |
| Congestive heart failure | 0.85 | 0.76 | 0.96 | 0.90 | 0.83 | 0.97 |
| Cerebrovascular disease | 0.81 | 0.71 | 0.93 | 0.84 | 0.76 | 0.92 |
| Myocardial infarction | 1.10 | 0.96 | 1.26 | 1.09 | 0.99 | 1.20 |
| Cancer | 1.35 | 1.16 | 1.56 | 1.27 | 1.17 | 1.38 |
| Liver disease | 1.03 | 0.89 | 1.19 | 0.78 | 0.69 | 0.89 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | 1.32 | 0.67 | 2.58 | 0.69 | 0.43 | 1.09 |
| Cardiac arrest or anoxic brain injury | 0.93 | 0.50 | 1.74 | NA* | NA* | NA* |
| Arrhythmia | 3.02 | 1.75 | 5.20 | 1.38 | 0.83 | 2.30 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| Other abdominal | 2.12 | 1.18 | 3.81 | 1.23 | 0.68 | 2.22 |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | 2.50 | 1.45 | 4.32 | 0.96 | 0.60 | 1.53 |
| Cancer | 1.90 | 1.05 | 3.45 | 1.62 | 0.85 | 3.09 |
| Congestive heart failure | 2.21 | 1.31 | 3.73 | 0.95 | 0.61 | 1.48 |
| Obstructive lung disease | 2.14 | 1.20 | 3.82 | 1.44 | 0.92 | 2.24 |
| Diabetes or electrolyte related | 1.39 | 0.76 | 2.56 | 1.00 | 0.57 | 1.76 |
| Deep vein thrombosis or pulmonary embolus | 1.97 | 1.02 | 3.83 | 1.13 | 0.63 | 2.01 |
| Cirrhosis or liver failure | 1.05 | 0.60 | 1.86 | 0.57 | 0.30 | 1.08 |
| Myocardial infarction | 2.73 | 1.62 | 4.60 | 1.01 | 0.63 | 1.63 |
| Neurologic | 1.78 | 0.96 | 3.32 | 0.63 | 0.39 | 1.01 |
| Other | 1.74 | 1.05 | 2.87 | 1.06 | 0.69 | 1.64 |
| Pancreatitis | 4.88 | 2.35 | 10.17 | 2.70 | 1.32 | 5.55 |
| Pneumonia including aspiration | 1.98 | 1.17 | 3.34 | 1.27 | 0.82 | 1.98 |
| Kidney failure | 1.64 | 0.90 | 3.00 | 1.01 | 0.60 | 1.71 |
| Respiratory failure | 1.77 | 1.08 | 2.89 | 1.15 | 0.75 | 1.77 |
| Seizure | 0.72 | 0.40 | 1.28 | 0.51 | 0.32 | 0.82 |
| Sepsis | 1.68 | 1.04 | 2.73 | 1.22 | 0.79 | 1.88 |
| SOFA in first 24 hours of MV (per 1-point increase) | 0.99 | 0.97 | 1.01 | 1.01 | 1.00 | 1.03 |
| Median of patients daily SOFA during MV (up to 21 days) | 1.05 | 1.03 | 1.08 | 1.01 | 0.99 | 1.03 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 1.03 | 0.84 | 1.26 | 0.90 | 0.81 | 1.00 |
| Partial code vs DNR | 1.03 | 0.76 | 1.40 | 0.28 | 0.11 | 0.74 |
| History of opioid use 1-year prior to admission | 1.04 | 0.81 | 1.34 | 1.32 | 1.12 | 1.55 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------------|----------|----------|---------------------|----------|----------|
| | Adjusted odds ratio | Lower CI | Upper CI | Adjusted odds ratio | Lower CI | Upper CI |
| Central line during MV (up to 21 days) | 1.51 | 1.37 | 1.67 | 1.63 | 1.54 | 1.73 |
| Arterial line during MV (up to 21 days) | 1.69 | 1.53 | 1.87 | 1.63 | 1.53 | 1.73 |
| Chest tube during MV (up to 21 days) | 1.24 | 1.03 | 1.49 | 1.31 | 1.13 | 1.52 |
| Number of mechanical ventilation episodes during encounter | 0.95 | 0.86 | 1.04 | 1.16 | 1.06 | 1.27 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 1.04 | 1.02 | 1.06 | 1.03 | 1.02 | 1.04 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 1.11 | 1.08 | 1.14 | 1.10 | 1.08 | 1.11 |
| Hospital number of beds 100-500 (versus <100) | 0.96 | 0.49 | 1.86 | 0.48 | 0.18 | 1.25 |
| Hospital number of beds >500 (versus <100) | | | | 0.51 | 0.16 | 1.67 |
| Teaching hospital | 0.86 | 0.41 | 1.80 | 0.63 | 0.19 | 2.11 |

KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

NA: not applicable

*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Table 9: Associations between fixed effects and median daily fentanyl equivalent dose in complete cases

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| (Intercept) | 1105.27 | 647.33 | 1516.81 | 1025.75 | 498.12 | 1553.38 |
| Age at admission (per 1-year increase) | -10.98 | -12.37 | -9.26 | -12.92 | -14.43 | -11.41 |
| Male sex (female reference) | 67.43 | 23.41 | 102.67 | 81.90 | 45.17 | 118.63 |
| Race | | | | | | |
| Black race (Asian reference) | -28.08 | -117.03 | 49.4 | -97.38 | -287.08 | 92.31 |
| Hispanic (Asian reference) | 122.63 | 50.97 | 195.99 | 230.84 | 28.85 | 432.82 |
| Other/unknown/missing race (Asian reference) | 57.26 | -46.36 | 146.26 | -98.55 | -292.03 | 94.93 |
| White race (Asian reference) | 104.53 | 33.9 | 166.36 | -33.75 | -217.00 | 149.50 |
| Admission Body Mass Index in kg/m ² per 1 point increase | 3.87 | 1.86 | 6.24 | 3.35 | 1.53 | 5.17 |
| Charlson score (unweighted) per 1 point increase | -44.58 | -79.33 | -8.18 | -36.63 | -73.13 | -0.12 |
| Chronic kidney disease | 37.05 | -35.27 | 89.9 | 10.49 | -72.19 | 93.17 |
| Chronic pulmonary disease | 88.91 | 24.77 | 137.64 | 133.82 | 75.15 | 192.50 |
| Diabetes | -6.19 | -85.49 | 59.53 | -23.07 | -80.87 | 34.74 |
| Peripheral vascular disease | 93.98 | 35.68 | 153.94 | -29.29 | -130.52 | 71.94 |
| Congestive heart failure | 1.69 | -47.14 | 72.72 | -29.87 | -93.35 | 33.60 |
| Cerebrovascular disease | -23.02 | -90.38 | 42.03 | -57.03 | -133.06 | 19.01 |
| Myocardial infarction | 13.57 | -85.23 | 77.91 | 103.73 | 28.10 | 179.36 |
| Cancer | 118.94 | 45.11 | 181.07 | 109.64 | 45.01 | 174.28 |
| Liver disease | 60.88 | -27.08 | 133.9 | -138.03 | -235.30 | -40.77 |
| Principal discharge diagnoses (reference is alcohol-related) | | | | | | |
| Altered mental status | -39.83 | -426.37 | 272.88 | -140.20 | -489.43 | 209.04 |
| Cardiac arrest or anoxic brain injury | -639.16 | -1028.88 | -335.68 | NA* | NA* | NA* |
| Arrhythmia | -100.22 | -415.49 | 213.42 | -61.44 | -429.72 | 306.83 |
| Other abdominal | 165.39 | -187.19 | 423.68 | -120.30 | -560.59 | 319.98 |

| Characteristic | KPNC | | | eRI | | |
|--|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Principal discharge diagnoses continued (reference is alcohol-related) | | | | | | |
| Bleeding (mainly gastrointestinal) | -23.22 | -331.06 | 266.21 | -213.62 | -559.98 | 132.74 |
| Cancer | 37.19 | -343.2 | 324.23 | -117.83 | -576.07 | 340.40 |
| Congestive heart failure | -44.18 | -352.62 | 249.31 | -71.75 | -400.86 | 257.36 |
| Obstructive lung disease | 86.12 | -252.55 | 357.24 | 68.27 | -260.14 | 396.68 |
| Diabetes or electrolyte related | -261.68 | -691.01 | 37.55 | -520.06 | -930.94 | -109.18 |
| Deep vein thrombosis or pulmonary embolus | -185.65 | -554.04 | 105.73 | -98.86 | -531.38 | 333.65 |
| Cirrhosis or liver failure | -338.62 | -633.43 | -110.02 | -526.83 | -998.30 | -55.37 |
| Myocardial infarction | -28.53 | -353.11 | 224.82 | 42.96 | -312.73 | 398.66 |
| Neurologic | -392.73 | -766.73 | -180.75 | -218.16 | -582.43 | 146.12 |
| Other | -9.37 | -312.27 | 233.72 | -4.56 | -323.26 | 314.14 |
| Pancreatitis | 489.4 | 154.05 | 812.57 | 113.90 | -314.53 | 542.33 |
| Pneumonia including aspiration | 53.11 | -247.22 | 309.79 | -9.77 | -334.78 | 315.24 |
| Kidney failure | -190.77 | -546.36 | 124.89 | -85.73 | -475.00 | 303.54 |
| Respiratory failure | -78.94 | -414.99 | 151.57 | -8.16 | -326.39 | 310.06 |
| Seizure | -368.64 | -636.49 | -72.07 | -195.36 | -555.55 | 164.83 |
| Sepsis | 0.87 | -311.63 | 239.92 | -70.53 | -390.04 | 248.99 |
| SOFA in first 24 hours of MV (per 1-point increase) | -37.29 | -49.69 | -29.39 | -6.66 | -20.17 | 6.86 |
| Median of patients daily SOFA during MV (up to 21 days) | 16.27 | 6.11 | 28.36 | -4.99 | -19.23 | 9.25 |
| Code status at beginning of hospitalization | | | | | | |
| Full code vs DNR | 18.19 | -107.72 | 144.3 | -20.66 | -98.05 | 56.72 |
| Partial code vs DNR | -77.59 | -262.02 | 104.26 | -362.76 | -1222.42 | 496.90 |
| History of opioid use 1-year prior to admission | 35.04 | -116.63 | 202.05 | 389.94 | 291.78 | 488.10 |
| Central line during MV (up to 21 days) | 97.4 | 36.75 | 172.36 | 115.84 | 71.71 | 159.96 |
| Arterial line during MV (up to 21 days) | 136.55 | 89.23 | 190.59 | 108.87 | 64.92 | 152.82 |

| Characteristic | KPNC | | | eRI | | |
|---|---------------|----------|----------|---------------|----------|----------|
| | Adjusted Beta | Lower CI | Upper CI | Adjusted Beta | Lower CI | Upper CI |
| Chest tube during MV (up to 21 days) | 105.45 | 50.55 | 177.2 | 201.17 | 98.28 | 304.07 |
| Number of mechanical ventilation episodes during encounter | 20.63 | -25.45 | 63.04 | 33.04 | -33.12 | 99.20 |
| Highest PEEP in first 24 hours of MV in cmH ₂ O | 7.28 | -1.44 | 17.99 | 3.53 | -3.07 | 10.12 |
| Median highest daily PEEP during MV (up to 21 days) in cmH ₂ O | 40.53 | 26.59 | 50.95 | 66.22 | 57.90 | 74.54 |
| Hospital number of beds 100-500 (versus <100) | -1.76 | -219.42 | 175.91 | -168.27 | -553.14 | 216.60 |
| Hospital number of beds >500 (versus <100) | | | | -243.51 | -694.50 | 207.49 |
| Teaching hospital | 101.02 | -146.3 | 375.91 | -399.61 | -862.49 | 63.27 |

KPNC: Kaiser Permanente Northern California; eRI: Philips eICU Research Institute.

*Patients with cardiac arrest excluded from the eRI cohort.

Supplemental Figure 6: Correlation matrix between median daily fentanyl equivalent dose and other sedation and analgesia medications

