**Table E1. ICD-9-CM Codes Used to Identify Opioid-Related Hospitalizations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ICD9\_Code** | **Description** | **Any Opioid Poisoning** | **Poisoning from Analgesics** | **Any Opioid Poisoning, Adverse Effect, or Abuse/Dependence** |
| 965.00 | Poisoning - opium NOS | X |  | X |
| 965.01 | Poisoning - heroin | X |  | X |
| 965.02 | Poisoning - methadone | X | X | X |
| 965.09 | Poisoning - opiates NEC | X | X | X |
| 304.00 | Opioid type dependence, unspecified |  |  | X |
| 304.01 | Opioid type dependence, continuous |  |  | X |
| 304.02 | Opioid type dependence, episodic |  |  | X |
| 304.70 | Combinations of opioid type drug with any other drug dependence, unspecified |  |  | X |
| 304.71 | Combinations of opioid type drug with any other drug dependence, continuous |  |  | X |
| 304.72 | Combinations of opioid type drug with any other drug dependence, episodic |  |  | X |
| 305.50 | Opioid abuse, unspecified |  |  | X |
| 305.51 | Opioid abuse, continuous |  |  | X |
| 305.52 | Opioid abuse, episodic |  |  | X |
| E850.0 | Accidental poisoning by heroin | X |  | X |
| E850.1 | Accidental poisoning by methadone | X | X | X |
| E850.2 | Accidental poisoning by other opiates and related narcotics | X | X | X |
| E935.0 | Heroin causing adverse effects in therapeutic use |  |  | X |
| E935.1 | Methadone causing adverse effects in therapeutic use |  |  | X |
| E935.2 | Other opiates and related narcotics causing adverse effects in therapeutic use |  |  | X |

Abbreviations: NOS, not otherwise specified; NEC, not elsewhere classifiable.

**Table E2**. **Characteristics of Patients with Opioid-Related Hospitalizations by the Presence of Sepsis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Patients with Opioid-Related Hospitalizations (n=130,399)** | | |
| **No Sepsis**  **(n=121,635; 93.3%)** | **Sepsis**  **(n=8,764; 6.7%)** | **P-value** |
| **SOCIODEMOGRAPHICS** |  |  |  |
| **Age, (mean ± SD)** | 46.9 (17) | 52.3 (16.2) | <.001 |
| **Gender, Male (%)** | 58,100 (47.8) | 4,214 (48.1) | 0.568 |
| **Race (%)** |  |  | <.001 |
| **White** | 93,515 (77.6) | 6,916 (80) |  |
| **Asian** | 567 (0.5) | 62 (0.7) |  |
| **Black** | 15,158 (12.6) | 841 (9.7) |  |
| **Hispanic** | 7,266 (6) | 553 (6.4) |  |
| **Other** | 3,946 (3.3) | 271 (3.1) |  |
| **CLINICAL CHARACTERISTICS** |  |  |  |
| **Elixhauser Score (mean ± SD)** | -0.5 ± 7.2 | 5.4 ± 9 | <.001 |
| **ICU Admission (%)** | 17,385 (14.3) | 5,608 (64) | <.001 |
| **ICU LOS, days (mean ± SD)** | 2.9 (7.2) | 6.7 (11.3) | <.001 |
| **Hospital LOS, days (mean ± SD)** | 5.9 (6) | 13.4 (16.2) | <.001 |
| **Discharge Disposition (%)** |  |  | <.001 |
| **Death** | 875 (0.7) | 928 (10.6) |  |
| **Hospice** | 928 (0.8) | 280 (3.2) |  |
| **Hospital Transfer** | 1,882 (1.5) | 324 (3.7) |  |
| **Subacute Facility** | 11,374 (9.4) | 1,863 (21.3) |  |
| **Home** | 106,576 (87.6) | 5,369 (61.3) |  |
| **Discharge AMA (%)** | 7,718 (6.3) | 321 (3.7) | <.001 |
| **Positive Blood Culture (%)** | 1,660 (1.4) | 1,484 (16.9) | <.001 |
| **TYPE OF OPIOID USE *a*** |  |  |  |
| **Any Opioid Poisoning, Adverse Effect, or Abuse/Dependence** | 114,177 (93.9) | 8,513 (97.1) | <.001 |
| **Any Opioid Poisoning** | 14,600 (12) | 2,497 (28.5) | <.001 |
| **Poisoning from Analgesics** | 10,424 (8.6) | 1,717 (19.6) | <.001 |
| **Documentation of Inpatient Administrations of Buprenorphine** | 7,458 (6.1) | 251 (2.9) | <.001 |

*a* The categories are not mutually exclusive.

Abbreviations: LOS, length of stay; ICU: intensive care unit; AMA, against medical advice.

**Table E3. Risk-Adjusted Multivariable Model Results for In-Hospital Mortality in Sepsis Patients**

|  |  |  |
| --- | --- | --- |
| **Variable** | **OR (95% CI)** | **P-value** |
| Opioid-Related Hospitalization | 0.73 (0.67-0.79) | <.001 |
| **Sociodemographics** |  |  |
| Age | 1.02 (1.02-1.02) | <.001 |
| Male Gender | 0.92 (0.9-0.94) | <.001 |
| Race |  |  |
| White | Reference | **--** |
| Asian | 1.02 (0.96-1.1) | 0.493 |
| Black | 1.02 (0.99-1.06) | 0.22 |
| Hispanic | 1.05 (1-1.1) | 0.035 |
| Other | 1.03 (0.97-1.09) | 0.309 |
| **Severity-Of-Illness on Admission** |  |  |
| ICU Admission | 1.53 (1.49-1.57) | <.001 |
| CDC Organ Dysfunction – Ventilation | 2.64 (2.58-2.7) | <.001 |
| CDC Organ Dysfunction – Vasopressors | 2.56 (2.51-2.62) | <.001 |
| Peak Creatinine (mg/dL) | 1.03 (1.03-1.03) | <.001 |
| Peak Bilirubin (mg/dL) | 1.06 (1.05-1.06) | <.001 |
| Minimum Platelet (x 109/L) | 1.0 (1.0-1.0) | <.001 |
| Peak WBC (x 109/L) | 1.01 (1.01-1.01) | <.001 |
| Peak AST (units/L) | 1.0 (1.0-1.0) | <.001 |
| Minimum Hematocrit (%) | 1.0 (1.0-1.0) | 0.112 |
| Peak Anion Gap (mEq/L) | 1.04 (1.03-1.04) | <.001 |
| Minimum Albumin (mg/dL) | 0.63 (0.62-0.64) | <.001 |
| **Port/ Type of Infection** |  |  |
| Septicemia Bacteremia | 1.53 (1.5-1.57) | <.001 |
| Pulmonary | 1.09 (1.06-1.11) | <.001 |
| Genitourinary | 0.64 (0.62-0.65) | <.001 |
| Intra-Abdominal | 0.72 (0.7-0.74) | <.001 |
| Skin and Soft Tissue | 0.75 (0.72-0.78) | <.001 |
| Bone/ Joint | 0.72 (0.67-0.78) | <.001 |
| Obstetrics/ Gynecology | 0.53 (0.44-0.64) | <.001 |
| Central Nervous System | 1.24 (1.12-1.37) | <.001 |
| Other | 0.69 (0.67-0.71) | <.001 |
| Infection type (Hospital-onset) | 2.23 (2.17-2.3) | <.001 |
| **Comorbidities (Elixhauser)** |  |  |
| Chronic Heart Failure | 1.12 (1.09-1.15) | <.001 |
| Valvular Disease | 0.99 (0.95-1.03) | 0.617 |
| Pulmonary Circulation Disorders | 1.31 (1.26-1.36) | <.001 |
| Peripheral Vascular Disease | 1.21 (1.17-1.25) | <.001 |
| Hypertension | 0.81 (0.79-0.83) | <.001 |
| Paralysis | 0.99 (0.94-1.03) | 0.523 |
| Other Neurological Disorders | 1.09 (1.06-1.12) | <.001 |
| Chronic Pulmonary Disease | 0.93 (0.91-0.96) | <.001 |
| Diabetes without Chronic Complications | 0.91 (0.89-0.94) | <.001 |
| Diabetes with Chronic Complications | 0.87 (0.83-0.9) | <.001 |
| Hypothyroidism | 0.97 (0.94-1) | 0.061 |
| Renal Failure | 1.13 (1.1-1.16) | <.001 |
| Liver Disease | 1.31 (1.26-1.37) | <.001 |
| Peptic Ulcer Disease | 0.61 (0.39-0.96) | 0.034 |
| AIDS/HIV | 1.66 (1.47-1.87) | <.001 |
| Lymphoma | 1.42 (1.32-1.52) | <.001 |
| Metastatic Cancer | 2.05 (1.97-2.14) | <.001 |
| Solid Tumor without Metastasis | 1.34 (1.28-1.41) | <.001 |
| Rheumatoid Arthritis | 1.07 (1.01-1.13) | 0.029 |
| Coagulopathy | 1.17 (1.13-1.2) | <.001 |
| Obesity | 0.83 (0.81-0.86) | <.001 |
| Weight Loss | 0.93 (0.9-0.96) | <.001 |
| Fluid and Electrolyte Disorders | 1.1 (1.08-1.13) | <.001 |
| Blood Loss Anemia | 0.68 (0.63-0.75) | <.001 |
| Anemia Deficiency | 0.72 (0.71-0.74) | <.001 |
| Alcohol Abuse | 0.88 (0.84-0.92) | <.001 |
| Drug Abuse | 0.88 (0.82-0.94) | <.001 |
| Psychoses | 0.7 (0.67-0.74) | <.001 |
| Depression | 0.86 (0.83-0.89) | <.001 |
| Cardiac Arrhythmia | 1.19 (1.16-1.22) | <.001 |

Opioid-related hospitalization is the primary exposure of interest in the model and all reported estimates represents direct effects.

**Table E4. Regression Results for In-Hospital Mortality in Sepsis Patient by Different Injury Surveillance Workgroup (ISW7) Administrative Definitions.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Definition** | **Univariate Model** | | **Multivariate Model** | |
| **OR (95% CI)** | **P-value** | **OR a (95% CI)** | **P-value** |
| **Any Opioid Poisoning, Adverse Effect, or Abuse/Dependence** | 0.61 (0.57-0.65) | <.001 | 0.73 (0.67-0.80) | <.001 |
| **Any Opioid Poisoning** | 0.74 (0.65-0.83) | <.001 | 0.76 (0.66-0.87) | <.001 |
| **Poisoning from Analgesics** | 0.59 (0.51-0.70) | <.001 | 0.57 (0.48-0.68) | <.001 |
| **Documentation of Inpatient Administrations of Buprenorphine** | 0.34 (0.22-0.53) | <.001 | 0.42 (0.26-0.68) | <.001 |

a Adjusted for demographics (age, sex, and race), comorbidities, source of infection, hospital-onset sepsis (defined by the presence of all CDC criteria on hospital day 3 or later), and indicators of severity-of-illness within the first 2 days of hospitalization including admission to the ICU, vasopressors, mechanical ventilation, and patients’ worst values for creatinine, anion gap, bilirubin, liver function tests, platelet count, hematocrit, and albumin.

**Figure E1. Prevalence of Opioid-Related Hospitalization by Age Group**

1. All Hospitalized Patients (N=6,715,286)

**A screenshot of a cell phone

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Opioid-Related Hospitalization for Age ≤65: 2.8%

Opioid-Related Hospitalization for Age >65: 0.7%

1. Patients with Sepsis (n=375,479)

****

Opioid-Related Hospitalization for Age ≤65: 4.4%

Opioid-Related Hospitalization for Age >65: 0.9%