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Epidemiology, Outcomes, and Trends of Patients with Sepsis and Opioid-Related Hospitalizations in US Hospitals

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Abstract

Objective: Widespread use and misuse of prescription and illicit opioids has exposed millions to health risks including serious infectious complications. Little is known, however, about the association between opioid use and sepsis.

Design: Retrospective cohort study.

Setting: 373 U.S. hospitals.

Patients: Adults hospitalized between January 2009-September 2015.

Interventions: None.

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Measurements: Sepsis was identified by clinical indicators of concurrent infection and organ dysfunction. Opioid-related hospitalizations were identified by ICD-9-CM codes and/or inpatient orders for buprenorphine. Clinical characteristics and outcomes were compared by sepsis and opioid-related hospitalization status. The association between opioid-related hospitalization and all-cause, in-hospital mortality in patients with sepsis was assessed using mixed-effects logistic models to adjust for baseline characteristics and severity of illness.

Results: The cohort included 6,715,286 hospitalizations; 375,479 (5.6%) had sepsis, 130,399 (1.9%) had opioid-related hospitalizations, and 8,764 (0.1%) had both. Compared to sepsis patients without opioid-related hospitalizations (n=366,715), sepsis patients with opioid-related hospitalizations (n=8,764) were younger (mean 52.3 vs 66.9 years), healthier (mean Elixhauser score 5.4 vs 10.5), had more bloodstream infections from gram-positive and fungal pathogens (68.9% vs 47.0% and 10.6% vs 6.4%, respectively), and had lower in-hospital mortality rates (10.6% vs 16.2%, adjusted OR 0.73, 95% CI 0.60–0.79; $p<0.001$ for all comparisons). Of 1,803 patients with opioid-related hospitalizations who died in-hospital, 928 (51.5%) had sepsis. Opioid-related hospitalizations accounted for 1.5% of all sepsis-associated deaths, including 5.7% of sepsis deaths amongst patients <50 years old. From 2009–2015, the proportion of sepsis hospitalizations that were opioid-related increased by 77% (95% CI 40.7%−123.5%).

Conclusions: Sepsis is an important cause of morbidity and mortality in patients with opioid-related hospitalizations, and opioid-related hospitalizations contribute disproportionately to sepsis-associated deaths among younger patients. In addition to ongoing efforts to combat the opioid crisis, public health agencies should focus on raising awareness about sepsis among patients who use opioids and their providers.

Keywords

sepsis; epidemiology; opioid-related disorder; opioid dependence; infections; electronic health records

INTRODUCTION

Overdose deaths involving prescription opioids, heroin, and synthetic opioids have increased almost six-fold in the United States since 1999 (1). In 2018 alone, opioid-related overdoses were responsible for 46,802 deaths and accounted for over two-thirds of all deaths from drug overdoses (2). The scope of the problem led to the declaration of a national public health emergency in 2017 (3, 4).

The mounting morbidity and mortality associated with opioid use disorder, however, extends beyond overdoses to include a rise in infectious complications (5). Injection drug use predisposes patients to bloodborne viruses, such as HIV and hepatitis B and C, as well as acute skin and soft tissue infections, bloodstream infections, and endocarditis (6–8). Prescription opioids have also been associated with increased risk of community-acquired pneumonia (9–11). In addition, opioids have immunomodulatory effects that may predispose patients to severe complications of infection including sepsis (11, 12).

Despite the risk of serious acute infections in patients who misuse prescription opioids or use illicit opioids, little is known about the epidemiology and outcomes of sepsis

in this population. Prior epidemiological studies of patients with opioid use and abuse/dependence have mainly focused on a narrow group of infections and relied exclusively on administrative data (7, 13, 14). A better understanding of the relationship between the use and misuse of prescribed and illicit opioids and the broad range of infections that cause sepsis could inform strategies to mitigate both problems (15, 16). Such strategies include raising awareness of sepsis in opioid users and their providers, implementing screening for opioid use disorders in high-risk patients presenting with sepsis, and improving recognition, treatment, and prognostication in opioid users presenting with sepsis.

The goal of this study was to elucidate the epidemiology, outcomes, and trends of sepsis associated with opioid-related hospitalizations using detailed clinical and administrative data from a nationally representative set of hospitals.

MATERIALS AND METHODS

Study Design and Data Sources

This was a retrospective cohort study of all adult patients (20 years or older) admitted as inpatients from January 2009-September 2015 to 373 well-distributed U.S. academic and community hospitals. Patients' electronic health record (EHR) data was curated from 3 datasets: Cerner HealthFacts, Institute of Health Metrics, and HCA Healthcare, which have previously been described in detail (17). The study was approved by the institutional review boards at Harvard Pilgrim Health Care Institute (1301443).

Identifying Patients with Sepsis and Opioid-Related Hospitalizations

We identified hospitalizations with sepsis using the Centers for Disease Control and Prevention's (CDC's) Adult Sepsis Event definition, which requires clinical indicators of presumed serious infection (blood culture order and new antibiotics continued for ≥4 days or until ≤1 day prior to death, discharge to hospice, or transfer to another hospital) and concurrent organ dysfunction (initiation of vasopressors or mechanical ventilation, elevated lactate, increase in baseline creatinine or total bilirubin, or decrease in baseline platelets) (17). The Adult Sepsis Event is modeled after Sepsis-3 criteria but is optimized for automated implementation using routine EHR data. This validated definition has previously been shown to have higher sensitivity than explicit sepsis diagnosis codes for chart-review confirmed Sepsis-3 with comparable positive predictive value, higher positive predictive value than implicit sepsis codes (i.e., infection and organ dysfunction codes) with comparable sensitivity, and is less susceptible than administrative definitions to variable and changing diagnosis and coding practices over time (17, 18).

We identified patients with opioid-related (e.g., opioid use disorder and/or overdose) diagnoses using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes as per the Injury Surveillance Workgroup (ISW7) consensus document (Table E1, Supplemental Digital Content 1) (19). We used the broadest definition, *drug poisonings associated with opium, heroin, and opioid analgesics or opioid adverse effect, or abuse/dependence* to identify acute adverse events from opioid use or the presence of underlying opioid use disorder. Both principal and secondary diagnosis codes

were included to maximize sensitivity (20). We augmented diagnosis-based case-finding by including inpatient administrations of buprenorphine as an additional indicator of opioid-related hospitalizations. We did not include methadone due to the difficulty in distinguishing its use for treatment of chronic pain vs opioid dependence.

Descriptive and Statistical Analyses

We conducted descriptive analyses of patients with opioid-related hospitalizations, including demographics, comorbidities (using the Elixhauser method) (21), ICU admission, length-of-stay, and discharge disposition. Among patients with sepsis, we characterized types of sepsis-associated organ dysfunction (based on the Adult Sepsis Event "eSOFA" criteria) (22), source of infection (based on previously published ICD-9-CM algorithms) (23), and positive blood cultures (based on microbiology records, and excluding common skin contaminants). All bivariate group comparisons were conducted using chi-square test and student t-test for categorical and continuous variables, respectively.

We assessed the association between opioid-related hospitalization and all-cause, in-hospital mortality in patients with sepsis using mixed-effects logistic models to adjust for baseline characteristics and severity of illness. Covariates included 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) (24), 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. All covariates were included in the model as they were deemed a priori to be important potential confounders influencing the risk of sepsis-associated death. Missing laboratory data were assumed to be normal, as per commonly used calculations of severity-of-illness scores (25, 26). Hospitals were treated as random effects in the models. Regression analyses were run in each dataset separately and results were compiled using study-level meta-analysis (27). A sensitivity analysis was also conducted to evaluate in-hospital death or discharge to hospice as a combined outcome, and to evaluate the association between opioid-related hospitalization and in-hospital death stratified by specific ISW7 case definitions (all acute opioid poisonings, acute poisoning from analgesics, all acute and chronic poisonings, and buprenorphine).

Finally, we calculated trends in the annual proportion of cases associated with opioid-related hospitalization among sepsis patients and their in-hospital mortality rates, and for all hospitalizations from 2009–2015 (data from 2015 were limited to January-September). Different hospitals contributed data in different years; therefore, temporal trends were modeled using Poisson regression models, adjusting for hospital characteristics (institution, region, teaching status, bed count, and annual admissions) and case mix (median age of hospitalized patients, sex and race/ethnicity distributions, and proportion of ICU versus total admissions) (17). Generalized estimating equations were used to account for hospital-level clustering and correlations in the data over time. Adjusted rates were generated by creating binary indicators for each year in the model, with 2009 as the reference year. Percentages were presented as relative annual changes.

All analyses were conducted in R version 3.6 (r-project.org). For all analyses, $p<0.05$ was considered statistically significant and two-tail tests were used.

RESULTS

Baseline Characteristics and Outcomes of Patients with Opioid-Related Hospitalizations by Presence of Sepsis

The study cohort consisted of 6,715,286 hospitalized adults, of whom 375,479 (5.6%) had sepsis, 130,399 (1.9%) had opioid-related hospitalization, and 8,764 (0.1%) had both sepsis and an opioid-related hospitalization (Figure E1, Supplemental Digital Content 1). Compared to patients with opioid-related hospitalization without sepsis (n=121,635/130,399; 93.3%), those with opioid-related hospitalization and sepsis (n=8,764; 7.2%) were older (mean 52.3 years vs 46.9 years), had more comorbidities (mean Elixhauser score 5.4 vs −0.5), higher rates of ICU admission (64.0% vs 14.3%), longer length of stay in the ICU (mean 6.7 vs 2.9 days) and hospital (mean 13.4 vs 5.9 days), and higher in-hospital mortality rates (10.6% vs 0.7%; $p<0.001$ for all comparisons) (Table E2, Supplemental Digital Content 1). Patients with sepsis met the opioid-related hospitalization case definition more frequently from any poisonings (28.5% vs 12%) and poisoning from analgesics (19.6% vs 8.6%), but less frequently from inpatient buprenorphine prescription (2.9% vs 6.1%) compared to opioid-related hospitalization patients without sepsis ($p<0.001$ for all comparisons).

Overall, amongst the 1,803 hospitalized patients with opioid-related hospitalization who died in-hospital, 928 (51.5%) had sepsis. This was higher than the prevalence of sepsis in patients without opioid-related hospitalization who died (n=59,433/163,278, 36.4%, $p<.001$).

Baseline Characteristics, Organ Dysfunction, Infections, and Outcomes of Patients with Sepsis by Presence of Opioid-Related Hospitalization Status

Compared to sepsis patients without opioid-related hospitalization (n=366,715/375,479, 97.7%), sepsis patients with opioid-related hospitalization (n=8,764, 2.3%) were younger (mean age 52.3 vs 66.9 years), more likely to be white (80% vs 70.7%), and had fewer comorbidities (mean Elixhauser score 5.4 vs 10.5) ($p<0.001$ for all comparisons) (Table 1). The distribution of dysfunctional organs at sepsis onset was similar, except that mechanical ventilation and acute kidney injury were more common in sepsis patients with opioid-related hospitalization (35.9% vs 24.0% and 56.4% vs 46.8%, respectively).

Sepsis patients with opioid-related hospitalization had higher rates of pulmonary infections (54.2% vs 47.8%), skin and soft tissue infections (13.5% vs 10.1%), bone/joint infections (4% vs 2.8%), and endocarditis (4.7% vs 0.8%), but less frequently had genitourinary infections (23.5% vs 32.4%) and intra-abdominal infections (9.5% vs 14%) compared to sepsis patients without opioid-related hospitalization. Positive blood cultures were present in 1,484 patients with sepsis and opioid-related hospitalization (16.9%). The most common pathogens isolated were *Staphylococcus aureus* (45.6%), *Streptococcus* species (20.9%), and yeast species (9.8%); this distribution was different from sepsis patients without opioid-

related hospitalization, in whom Escherichia species (23.8%) were most common, followed by *Staphylococcus aureus* (21.8%) and *Streptococcus* species (19.1%) (Table 2). Overall, percentages of gram-positive bloodstream infections and fungal infections were higher for sepsis patients with opioid-related hospitalization (68.9% vs 47.0% and 10.6% vs 6.4%, respectively), while gram-negative organisms were less common (28.3% vs 49.3%).

Sepsis patients with opioid-related hospitalization had higher rates of ICU admission (64.0% vs 51.7%) and longer hospital length of stay (13.4 vs 11.9 days) compared to those without OUD/overdose. However, they were more often discharged home (61.3% vs 43.7%) and more likely to leave against medical advice (3.7% vs 0.6%). Conversely, they were less often discharged to subacute facilities (21.3% vs 30.9%) or hospice (3.2% vs 6.4%) and had lower in-hospital mortality rates (10.6% vs 16.2%, crude odds ratio [OR] 0.60, 95% confidence interval [CI] 0.56–0.65). After adjusting for baseline characteristics and severity of illness, opioid-related hospitalizations remained associated with a lower risk of in-hospital mortality in patients with sepsis (adjusted OR 0.73, 95% CI: 0.60–0.79) (Table E3, Supplemental Digital Content 1). Results were similar when using a combined outcome of in-hospital death or discharge to hospice (adjusted OR 0.81, 95% CI: 0.75–0.85), and across the different ISW7 administrative definitions (Table E4, Supplemental Digital Content 1).

The overall prevalence of opioid-related hospitalization among patients with sepsis who died was low (n=928/60,361, 1.5%). However, the prevalence of opioid-related hospitalization was relatively high in sepsis patients under age 50 years who died (5.7% vs 1.0% in patients under vs over 50 years, p<.001).

Trends from 2009–2015

From 2009–2015, the proportion of all hospitalizations associated with opioid-related hospitalization increased from 1.7% to 2.4% (relative increase 41.4%, 95% CI: 6.1% −88.4%, p=.02). Increases were also seen using a case-finding definition based only on diagnosis codes (without requiring inpatient administrations of buprenorphine) for acute opioid poisoning and both acute and chronic poisonings from illicit opioids and opioid analgesics (Figure 1A). The proportion of sepsis hospitalizations associated with opioid-related hospitalization using the primary case-finding definition also increased from 1.9% to 3.3% (77.3% relative increase, 95% CI 40.7%−123.5%, p<.001). Increases were also seen using case-finding definitions of opioid-related hospitalization based only on diagnosis codes (Figure 1B). Figure 1A and 1B also demonstrate that only a fraction of opioid-related hospitalizations were associated with buprenorphine use and that this fraction did not increase over time. Adjusted in-hospital mortality in sepsis associated with opioid-related hospitalizations decreased from 14.1% to 12.9%, but this relative decrease was not statistically significant (8.5%, 95% CI −38.8–36.8%, p=.67).

DISCUSSION

Sepsis and opioid-related hospitalizations are two prevalent and substantial public health threats (4, 28), but the extent and consequences of their association have not previously been well described. Using detailed clinical data from 373 U.S. hospitals, we found that sepsis was present in 7% of patients with opioid-related hospitalizations and in over

half of all patients with opioid-related hospitalization who died in hospital. Only 2% of sepsis hospitalizations were opioid-related, but this proportion increased over time. The overall number of sepsis-associated deaths that were also opioid-related hospitalizations was low, and opioid-related hospitalizations accounted for a disproportionate fraction of sepsis-associated deaths in patients younger than 50. Patients with sepsis and opioid-related hospitalizations tended to have pyogenic infectious complications and bloodstream infections from gram-positive and fungal infections. Despite higher rates of mechanical ventilation and ICU admission, opioid-related hospitalization among patients with sepsis was associated with lower mortality rates before and after risk-adjustment.

In a systematic review, Larney et al. reported that skin and soft tissue infections, endocarditis, and bone and joint infections commonly complicated injection drug use (29). Using a national administrative database, Ronan et al. demonstrated a nearly two-fold increase from 2002–2012 in hospitalizations with opioid abuse/dependence codes and serious infections, including endocarditis, osteomyelitis, septic arthritis, and epidural abscess (7). McCarthy et al. similarly found that rates of serious infections among persons with substance use disorders increased from 2012–2017, particularly infective endocarditis in younger persons (8). Our study builds on this literature but gives greater insight specifically into the important link between sepsis and opioid-related hospitalizations. Furthermore, using consistent and objective clinical criteria for sepsis adds confidence to our estimates since CDC's Adult Sepsis Event definition has greater sensitivity than sepsis diagnosis codes with comparable positive predictive value, while also being less susceptible to changing and variable diagnosis and coding practices (17, 30–32).

The high rate of pyogenic complications in patients with opioid-related hospitalizations presenting with sepsis suggests clinicians should consider early diagnostic imaging and source control. *Staphylococcus aureus* and fungal pathogens in bloodstream infections were also more common in sepsis patients with versus without opioid-related hospitalization. Prior studies have also reported that injection drug use is a risk factor for invasive methicillin-resistant *Staphylococcus aureus* infections and candidiasis (33–36). While anti-Staphylococcal therapy is commonly included in empiric sepsis treatment regimens, our findings suggest that clinicians should have a low threshold for empiric antifungal therapy in patients with opioid-related hospitalizations presenting with sepsis.

The types of organ dysfunction among sepsis patients with and without opioid-related hospitalizations were similar, with the notable exception of higher rates of respiratory failure requiring mechanical ventilation in the opioid-related hospitalization group. Respiratory failure is a known source of morbidity and mortality associated with opioid overdose, typically due to direct respiratory suppression, aspiration, acute lung injury, and/or septic emboli (37, 38).

Despite higher rates of mechanical ventilation and ICU admission, crude and risk-adjusted mortality rates were lower in sepsis patients with opioid-related hospitalizations compared to those without. Other investigators have found that opioid administration in hospitalized patients with sepsis is associated with worse outcomes, potentially as a consequence of immunosuppressive effects, impairment of gut barrier integrity, and modulation of the

gut microbiota (12, 39–41). The favorable outcomes in sepsis patients with opioid-related hospitalizations in our cohort may reflect some degree of residual confounding, likely mediated by younger age and the presence of fewer chronic conditions. Prior studies have demonstrated that sepsis-associated mortality is highly influenced by age and severe comorbidities (21, 42, 43). Regardless of the exact mechanism, our observations suggest that aggressive care may be warranted even when patients with opioid-related hospitalization present with severe illness.

Only a small fraction of individuals with opioid-related hospitalizations in our cohort received buprenorphine. Furthermore, the low prevalence of inpatient buprenorphine administration among individuals with opioid-related hospitalizations did not increase over the course of the study, whereas there has been a marked contemporaneous increase in total outpatient buprenorphine prescriptions in the United States (44).This suboptimal use of addiction treatment in hospitalized patients is consistent with previous studies (45) and suggests an urgent need to better integrate infectious disease and opioid use disorder care to improve substance use and infectious outcomes (46–48).

Our study has several strengths, including the use of objective clinical criteria to identify sepsis, the addition of medication data to augment diagnosis-based case finding definitions for opioid-related hospitalizations, and the use of detailed clinical data for descriptive analyses and risk adjustment. Our study also has important limitations. First, our study sample was drawn from a convenience sample of hospitals, potentially limiting generalizability. However, our hospital cohort was geographically diverse and covered a broad spectrum of U.S. hospitals (17). Second, our primary method for identifying patients with opioid-related hospitalizations relied on hospital discharge diagnosis codes, but prior work suggests that illicit drug use may often go unrecorded in coded discharge data (49). Third, we also relied on hospital discharge diagnosis codes to identify infectious syndromes, which may have variable accuracy across hospitals. Fourth, our datasets did not include vital signs, mental status, or other physiologic variables necessary to calculate established scores like APACHE or SOFA for mortality risk-adjustment. Fifth, not all hospitals contributed data each year for our analysis of trends. For this reason, we used regression models to adjust for hospital-level differences. Sixth, our data are limited to trends through 2015; a similar analysis using more recent data would increase the current relevance of findings. However, we believe the link between sepsis and opioid-related hospitalizations that we observed is unlikely to have substantially changed given that other studies have demonstrated ongoing high sepsis incidence and opioid overdose in recent years (2, 50). Lastly, our opioid-related hospitalization case definition included chronic poisonings from all opioid analgesics and did not distinguish between specific opioids; other studies, however, suggest that opioids vary in their immunosuppressive properties (40).

CONCLUSIONS

Sepsis is an important cause of morbidity and mortality in patients with opioid-related hospitalizations, and opioid use disorders and overdose contribute disproportionately to sepsis hospitalizations and sepsis-associated deaths among younger patients. In addition to ongoing efforts to combat the opioid crisis, future public health interventions should focus

on bolstering awareness of sepsis among patients who use opioids and their providers. Screening for opioid use disorder during hospital care episodes for young and healthy patients whose clinical course includes sepsis may also enable identification and referral of patients who can benefit from medications for opioid use disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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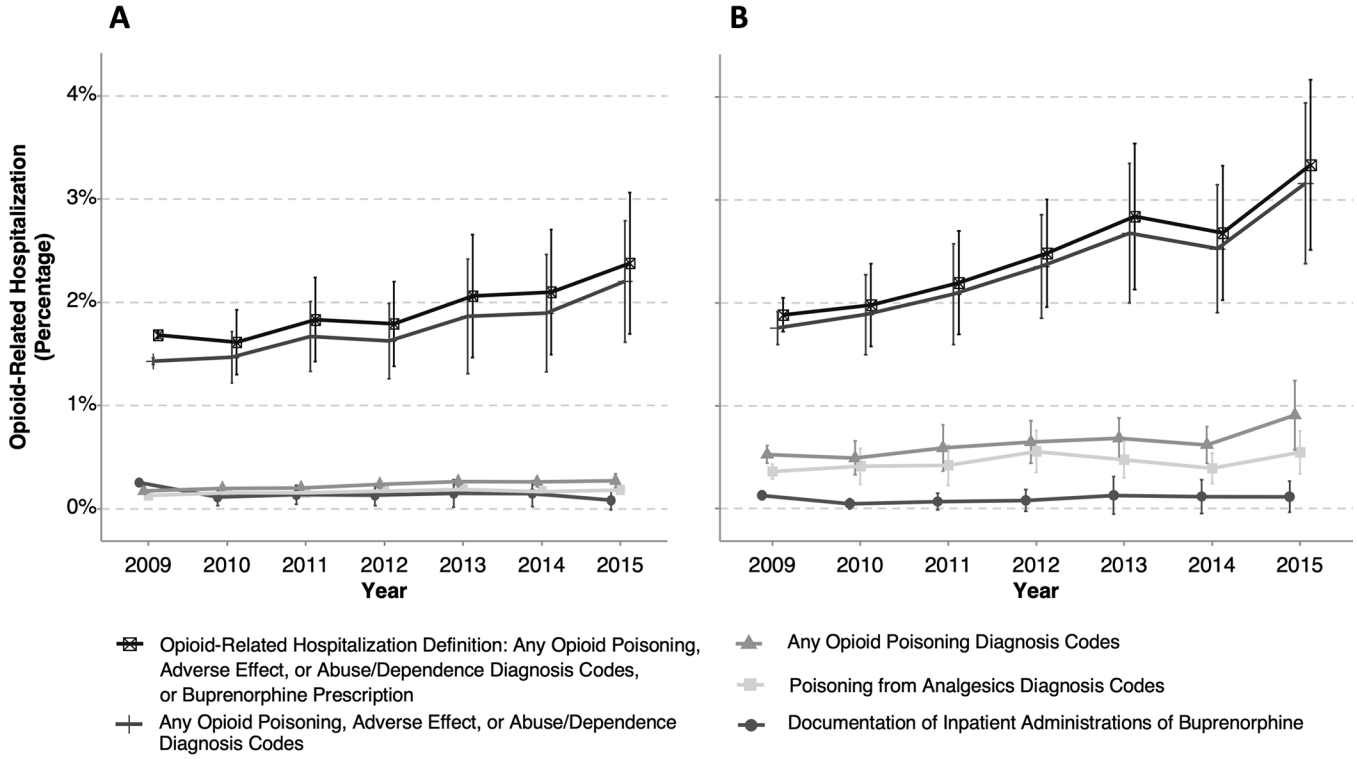

Figure 1.

Trends for the prevalence of opioid-related hospitalization between 2009–2015: all hospitalizations (N=6,715,286) (**A**); and sepsis hospitalizations (n=375,479) (**B**).

Table 1.

Characteristics of Patients with Sepsis by Opioid-Related Hospitalization Status

Variable	Patients with Sepsis (n=375,479)		
	Not Opioid-Related Hospitalization (n=366,715; 97.7%)	Opioid-Related Hospitalization (n=8,764; 2.3%)	P-value
SOCIODEMOGRAPHICS			
Age, (mean ± SD)	66.9 ± 16.5	52.3 ± 16.2	<.001
Gender, Male (%)	180,172 (49.1)	4,214 (48.1)	0.052
Race (%)			<.001
White	256,085 (70.7)	6,916 (80)	
Asian	9,499 (2.6)	62 (0.7)	
Black	52,273 (14.4)	841 (9.7)	
Hispanic	32,667 (9)	553 (6.4)	
Other	11,686 (3.2)	271 (3.1)	
CLINICAL OUTCOMES			
Elixhauser Score (mean ± SD)	10.5 ± 9.5	5.4 ± 9	<.001
ICU Admission (%)	189,551 (51.7)	5,608 (64)	<.001
ICU LOS, days (mean ± SD)	7 ± 13.6)	6.7 ± 11.3	0.052
Hospital LOS, days (mean ± SD)	11.9 ± 12.4	13.4 ± 16.2	<.001
Discharge Disposition (%)			<.001
Death	59,433 (16.2)	928 (10.6)	
Hospice	23,478 (6.4)	280 (3.2)	
Hospital Transfer	10,318 (2.8)	324 (3.7)	
Subacute Facility	113,164 (30.9)	1,863 (21.3)	
Home	160,322 (43.7)	5,369 (61.3)	
Discharge AMA (%)	2,150 (0.6)	321 (3.7)	<.001
Positive Blood Culture (%)	58,987 (16.1)	1,484 (16.9)	<.001
ORGAN DYSFUNCTION			
Ventilation (%)	87,878 (24)	3,144 (35.9)	<.001
Vasopressors (%)	102,942 (28.1)	2,576 (29.4)	0.007
Lactate (%)	162,620 (44.3)	3,718 (42.4)	<.001
Creatinine (%)	171,726 (46.8)	4,947 (56.4)	<.001
Bilirubin (%)	31,315 (8.5)	715 (8.2)	0.207
Platelets (%)	38,378 (10.5)	1,058 (12.1)	<.001

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

Table 2.

Positive Blood Culture Pathogens for Patients with Sepsis by Opioid-Related Hospitalization Status

	Sepsis and Positive Blood Cultures (n=60,471)		
	Not Opioid-Related Hospitalization (n= 58,987; 97.5%)	**Opioid-Related Hospitalization (n=1,484; 2.5%)**	**P-value**
PATHOGEN [a]			
Staphylococcus aureus	12,861 (21.8)	677 (45.6)	<.001
Streptococcus	11,286 (19.1)	310 (20.9)	0.09
Yeast	3,551 (6.0)	145 (9.8)	<.001
Escherichia	14,011 (23.8)	133 (9.0)	<.001
Enterococcus	5,046 (8.6)	112 (7.5)	0.17
Klebsiella	5,745 (9.7)	89 (6)	<.001
Pseudomonas	2,776 (4.7)	62 (4.2)	0.342
Enterobacter	1,656 (2.8)	38 (2.6)	0.569
Acinetobacter	806 (1.4)	27 (1.8)	0.139
Haemophilus	671 (1.1)	24 (1.6)	0.087
PATHOGEN TYPE			
Gram positive (%)	27,743 (47.0)	1,022 (68.9)	<.001
Gram negative (%)	29,056 (49.3)	420 (28.3)	<.001
Fungus (%)	3,774 (6.4)	157 (10.6)	<.001
Anaerobe (%)	3,340 (5.7)	67 (4.5)	0.058
Polymicrobial (%)	4,528 (7.7)	155 (10.4)	<.001

[a]Patient can have multiple pathogens; pathogens are sorted by decreasing prevalence in the opioid-related hospitalization group.