

RESEARCH ARTICLE

# Disparities in United States hospitalizations for serious infections in patients with and without opioid use disorder: A nationwide observational study

June-Ho Kim<sup>1,2,3\*</sup>, Danielle R. Fine<sup>2,4</sup>, Lily Li<sup>2,5</sup>, Simeon D. Kimmel<sup>6,7</sup>, Long H. Ngo<sup>2,8</sup>, Joji Suzuki<sup>2,9</sup>, Christin N. Price<sup>2,10</sup>, Matthew V. Ronan<sup>11</sup>, Shoshana J. Herzig<sup>2,8</sup>



**1** Division of General Internal Medicine and Primary Care, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, **2** Harvard Medical School, Boston, Massachusetts, United States of America, **3** Ariadne Labs, Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America, **4** Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **5** Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, **6** Section of Infectious Diseases, Department of Medicine, Boston Medical Center, Boston, Massachusetts, United States of America, **7** Section of General Internal Medicine, Department of Medicine, Boston Medical Center, Boston, Massachusetts, United States of America, **8** Division of General Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America, **9** Department of Psychiatry, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, **10** Brigham and Women's Physicians Organization, Brigham and Women's Hospital, Boston, Massachusetts, United States of America, **11** Department of Medicine, West Roxbury VA Medical Center, Veterans Affairs Boston Healthcare System, Boston, Massachusetts, United States of America

\* [jkim34@bwh.harvard.edu](mailto:jkim34@bwh.harvard.edu)

**OPEN ACCESS**

**Citation:** Kim J-H, Fine DR, Li L, Kimmel SD, Ngo LH, Suzuki J, et al. (2020) Disparities in United States hospitalizations for serious infections in patients with and without opioid use disorder: A nationwide observational study. *PLoS Med* 17(8): e1003247. <https://doi.org/10.1371/journal.pmed.1003247>

**Academic Editor:** Andrew D. Wiese, Vanderbilt University Medical Center, UNITED STATES

**Received:** January 14, 2020

**Accepted:** July 8, 2020

**Published:** August 7, 2020

**Copyright:** © 2020 Kim et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Data cannot be shared publicly because a Data Use Agreement is required before accessing the dataset. Data are available for purchase from the Healthcare Cost and Utilization Project ([hcup-us.ahrq.gov](https://hcup-us.ahrq.gov)) for researchers who meet the criteria for access to the database. Data from this study were from the 2016 National Inpatient Sample (NIS) database.

**Funding:** JK and DF were supported by a grant from the Health Resources and Services

## Abstract

### Background

Patients with opioid use disorder (OUD) who are hospitalized for serious infections requiring prolonged intravenous antibiotics may face barriers to discharge, which could prolong hospital length of stay (LOS) and increase financial burden. We investigated differences in LOS, discharge disposition, and charges between hospitalizations for serious infections in patients with and without OUD.

### Methods and findings

We utilized the 2016 National Inpatient Sample—a nationally representative database of all discharges from US acute care hospitals. The population of interest was all hospitalizations for infective endocarditis, epidural abscess, septic arthritis, or osteomyelitis. The exposure was OUD, and the primary outcome was LOS until discharge, assessed by using a competing risks analysis to estimate adjusted hazard ratios (aHRs). Adjusted odds ratio (aOR) of discharge disposition and adjusted differences in hospital charges were also reported. Of 95,470 estimated hospitalizations for serious infections (infective endocarditis, epidural abscess, septic arthritis, and osteomyelitis), the mean age was 49 years and 35% were

Administration ([hrsa.gov](https://www.hrsa.gov)) (National Research Service Award for Primary Care T32HP10251). SK was supported by grants from the Research in Addiction Medicine Scholars Program ([drugabuse.gov](https://www.drugabuse.gov)) (R25DA033211) and the Boston University Clinical HIV/AIDS Research Training Program ([niaid.nih.gov](https://www.niaid.nih.gov)) (5T32AI05207409). JS was supported by a grant from the National Institute on Drug Abuse ([drugabuse.gov](https://www.drugabuse.gov)) (K23DA042326). SH was supported by grants from the National Institute on Aging of the National Institutes of Health ([nia.nih.gov](https://www.nia.nih.gov)) (K23AG042459) and the Agency for Healthcare Research and Quality ([ahrq.gov](https://www.ahrq.gov)) (R01HS026215). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** I have read the journal's policy and the authors of this manuscript have the following competing interests: SK is a consultant for Abt Associates on a Massachusetts Department of Public Health funded project to provide technical assistance to skilled nursing facilities to improve addiction care. SH is funded by grant number K23AG042459 from the National Institute on Aging (NIH) and R01HS026215 from the Agency for Healthcare Research and Quality.

**Abbreviations:** aHR, adjusted hazard ratio; aOR, adjusted odds ratio; HCUP, Healthcare Cost and Utilization Project; ICD-10, International Classification of Diseases–10th Revision; IV, intravenous; LOS, length of stay; NIS, National Inpatient Sample; OPAT, outpatient parenteral antibiotic therapy; OUD, opioid use disorder; PAC, post-acute care.

female. 46% had Medicare (government-based insurance coverage for people age 65+ years), and 70% were non-Hispanic white. After adjustment for potential confounders, OUD was associated with a lower probability of discharge at any given LOS (aHR 0.61; 95% CI 0.59–0.63;  $p < 0.001$ ). OUD was also associated with lower odds of discharge to home (aOR 0.38; 95% CI 0.33–0.43;  $p < 0.001$ ) and higher odds of discharge to a post-acute care facility (aOR 1.85; 95% CI 1.57–2.17;  $p < 0.001$ ) or patient-directed discharge (also referred to as “discharge against medical advice”) (aOR 3.47; 95% CI 2.80–4.29;  $p < 0.001$ ). There was no significant difference in average total hospital charges, though daily hospital charges were significantly lower for patients with OUD. Limitations include the potential for unmeasured confounders and the use of billing codes to identify cohorts.

## Conclusions

Our findings suggest that among hospitalizations for some serious infections, those involving patients with OUD were associated with longer LOS, higher odds of discharge to post-acute care facilities or patient-directed discharge, and similar total hospital charges, despite lower daily charges. These findings highlight opportunities to improve care for patients with OUD hospitalized with serious infections, and to reduce the growing associated costs.

## Author summary

### Why was this study done?

- There has been an increase in hospitalizations in the United States for serious infections among patients with opioid use disorder.
- These infections typically require several weeks of intravenous antibiotics, which can eventually be administered at home or at facilities outside of the hospital if the patient has no other inpatient needs. However, patients with opioid use disorder are often kept in the hospital to finish their treatment, which could have significant financial costs, use hospital resources, and cause patient harm.
- We conducted this study in order to understand differences in length of hospital stay, type of hospital discharge, and related financial charges between patients with and without opioid use disorder in the US.

### What did the researchers do and find?

- We analyzed a cross-sectional dataset representative of all hospitalizations for serious infections in the US during 2016 and compared length of hospital stay, type of hospital discharge, and financial charges.
- From 95,470 estimated hospitalizations, patients with opioid use disorder stayed an average of 4 days longer in the hospital compared to those without the disorder, with a 39% lower likelihood of discharge from the hospital at any given length of stay.

- Patients with opioid use disorder were less likely to be discharged home and more likely to be sent to a post-acute care facility or to self-discharge. Although daily hospital charges were lower for patients with opioid use, charges for the total hospitalization were similar given the longer stays.

### What do these findings mean?

- These disparities in hospital stays and destinations after discharge suggest that people with opioid use disorder may lack post-discharge options such as skilled nursing facilities or home care for antibiotic infusions and thus remain in the hospital longer than their counterparts without opioid use disorder.
- Consideration should be given to expanding discharge options for people with opioid use disorder to reduce costly hospital stays and provide equitable care for serious infections.

## Introduction

One of the many downstream consequences of the opioid crisis has been a marked increase in the incidence and associated costs of hospitalizations for serious bacterial infections associated with injection drug use such as endocarditis, osteomyelitis, septic arthritis, and epidural abscesses [1–6]. Treatment of these infections usually requires a prolonged course of intravenous (IV) antibiotics, which can often be completed from home in patients without another indication for a rehabilitation stay [7–11]. However, because this treatment involves sustained IV access, clinicians may be reluctant to discharge patients with opioid use disorder (OUD) to home, and home infusion companies may be reluctant to provide home services [12,13]. In addition, people with OUD face barriers to accessing post-acute care (PAC) facilities [13]. Taken together, these factors may result in longer hospital length of stay (LOS) and increased utilization of PAC facilities among people with OUD-associated infections, with important financial implications for hospitals and payers [14,15].

Prior research and clinical experience suggest that patients with OUD who are hospitalized with endocarditis or undergoing surgery for complications related to endocarditis have longer LOS and more patient-directed discharges (also referred to as “discharges against medical advice”) compared to those without OUD [2,16–19]. To our knowledge, there is no research to date assessing national differences in healthcare utilization of patients with and without OUD who are hospitalized for serious infections requiring prolonged IV access.

Using nationally representative data, we compared markers of healthcare utilization in hospitalizations of patients with a serious infection with and without OUD. We hypothesized that, even when accounting for differences in baseline characteristics, hospitalizations for serious infection among patients with OUD would have longer LOS, fewer discharges to home with services, and more patient-directed discharges and PAC discharges compared to those among patients without OUD. We also hypothesized that the charges related to inpatient hospitalization would be greater for patients with OUD, primarily driven by increased LOS.

## Methods

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline ([S1 STROBE Checklist](#)). A prospective analysis plan was developed in August 2018, with analysis conducted from August to December 2018. The supplementary propensity score analysis was done in January 2019 to confirm the primary results. Additional analyses in response to peer review in March 2020 included adding the hospital as a random intercept, which did not change the estimates, and assessing changes in the logistic regression models when adding and removing covariates, which showed that controlling for age and payor primarily account for changes in our estimates ([S1 Table](#)).

## Data

We used data from the 2016 National Inpatient Sample (NIS), the largest all-payer inpatient database in the United States (US). The NIS, sponsored by the Agency for Healthcare Research and Quality, was developed under the Healthcare Cost and Utilization Project (HCUP) to include data from 20% of all hospitalizations from participating hospitals nationwide. The database contains information on approximately 8 million hospitalizations each year, with sample weights provided by HCUP allowing for estimates to be representative of the 35 million hospitalizations in the US in 2016 [20].

We included all hospitalizations for serious infections from January 1 to December 31, 2016, for adult patients 18 years or older. Serious infections included endocarditis, epidural abscess, septic arthritis, and osteomyelitis, identified using the International Classification of Diseases–10th Revision (ICD-10) diagnosis codes in the primary diagnosis field ([S2 Table](#)). We identified ICD-10 codes from prior studies of serious infections and OUD, utilizing correlates of ICD-9 codes where necessary [1,2]. We limited the codes for infections to the primary diagnosis field to improve specificity in identifying relevant hospitalizations.

## Study variables

The main exposure of interest was OUD, which was defined as hospitalizations in which a non-primary diagnosis field contained an ICD-10 code for an opioid-related disorder ([S2 Table](#)). The key outcome of interest was hospital LOS until discharge, reported in days. Secondary outcomes were discharge disposition, total hospital charges, and hospital charges per day (calculated by dividing total hospital charges by LOS).

Because we were interested in differences in healthcare utilization, independent of differences in baseline characteristics, we controlled for several covariates in our models. Patient characteristics included age, sex, race/ethnicity, primary payer, quartile of median household income based on the patient's zip code of residence, Elixhauser Comorbidity Index (excluding drug use to avoid adjusting for our exposure of interest), and the type of serious infection. Hospital characteristics included size (based on number of beds), type of hospital (rural, urban non-teaching, or urban teaching), and US region (northeast, midwest, south, or west). Hospitalization characteristics included whether the admission was elective, whether it was on a weekend, and the number of major operating room procedures performed during the hospital stay.

## Statistical analysis

In bivariable analyses, characteristics and outcomes of hospitalizations for serious infections were compared between patients with and without OUD. Differences were examined using *t* tests for continuous variables and Rao–Scott chi-squared tests for categorical variables.

For the primary outcome of interest, LOS, we performed a competing risks survival analysis to compare time to hospital discharge between hospitalizations with and without OUD, treating death, patient-directed discharge, and transfer to another acute care hospital as competing risks. We modeled the cumulative incidence function for each cohort, using Gray's test to assess for differences, and performed a multivariable competing risks regression analysis using the Fine–Gray subdistribution hazard function to estimate adjusted hazard ratios (aHRs) for the probability of discharge at any given time [21,22]. Additional statistical information and model specifications are detailed in [S1 Text](#).

We fitted multivariable logistic regression models to estimate adjusted odds ratios (aORs) for each discharge disposition (home, home without health services, home with health services, PAC facility, patient-directed discharge, transfer to an acute care hospital, and death) versus the others (e.g., home versus not home). Finally, we calculated differences in hospital charges using multivariable linear regression.

All multivariable models were adjusted for the aforementioned patient, hospital, and hospitalization characteristics. The Fine–Gray model for competing risks was adjusted using the NIS survey weights; for all other models, we utilized survey analysis procedures to account for NIS survey weights, stratification, and clustering, to adjust for the complex sampling design and produce estimates representative of all US hospitalizations in 2016.

Analyses were performed using SAS 9.4 (SAS Institute). We report 95% confidence intervals for aHRs and aORs, using  $p < 0.05$  to indicate statistical significance for all comparisons. The Beth Israel Deaconess Medical Center Institutional Review Board deemed this study as not human subjects research.

## Sensitivity analyses

We assessed the robustness of our findings by applying propensity score matching using a greedy match algorithm to balance covariates between our 2 cohorts, which we confirmed using standardized mean differences, and recalculated hazard and odds ratios between our matched groups.

To examine the degree to which differences are driven by decisions around home IV antibiotic administration, we performed an analysis in which we compared our outcomes of interest between hospitalizations with and without OUD for conditions not usually requiring prolonged IV access (pneumonia, acute congestive heart failure, acute cholecystitis).

To explore whether disparities in receipt of surgery may drive any observed differences in LOS, we ran stratified competing risks analyses in hospitalizations with and without any major operating room procedures during admission.

We investigated the sensitivity of our cohort definitions by examining an analytic cohort of patients hospitalized with a serious infection in any diagnosis code position. We also performed a survival analysis excluding patients who were transferred in from another hospital to examine whether left truncation might affect our results. Lastly, we examined models that adjusted for homelessness, identified using ICD-10 codes in any of the secondary diagnosis code positions ([S2 Table](#)), as well as severity of illness, as defined using All Patient Refined Diagnosis Related Groups by HCUP.

## Results

### Characteristics of hospitalizations for serious infection with and without OUD

We identified 95,470 hospitalizations with serious infection as a primary diagnosis, of which 7,635 (8.0%) had a secondary diagnosis code for OUD (OUD group), and 87,835 (92.0%) did

not (non-ODU group) (Table 1). Endocarditis was the most frequent infection in the OUD group (38.4%), while osteomyelitis was most common in the non-ODU group (55.2%).

ODU hospitalizations involved patients who were younger (mean age 41.2 versus 59.3 years) and more likely to be female (44.0% versus 34.7%), be white (74.0% versus 69.4%), have Medicaid (58.7% versus 18.2%) or be uninsured (10.4% versus 5.5%), and be in the lowest quartile of median household income (37.6% versus 33.3%), compared to the non-ODU group. The OUD group had a mean of 2.7 comorbid conditions in the modified Elixhauser Comorbidity Index (excluding drug use) compared to 3.3 for the non-ODU group (see S3 Table for frequencies of the individual Elixhauser Comorbidity Index conditions as well as rates of hepatitis C infection and homelessness). The OUD group had an average of 0.7 major operating room procedures compared to 1.1 for the non-ODU group. Additionally, OUD hospitalizations were more likely to be at large, urban teaching hospitals in the northeast region. All differences were statistically significant.

### Differences in disposition

ODU hospitalizations were less likely to be discharged home (45.3% versus 63.1%), particularly with home health services (10.8% versus 27.8%), and more likely to have a patient-directed discharge (19.1% versus 2.6%) or be transferred to another acute care hospital (6.8% versus 4.5%, all  $p < 0.001$ ) compared to the non-ODU group (Table 2).

Multivariable models were adjusted for age, sex, race/ethnicity, primary payer, quartile of median household income based on the patient's zip code of residence, Elixhauser Comorbidity Index (excluding drug use to avoid adjusting for our exposure of interest), type of serious infection, hospital size (based on number of beds), type of hospital (rural, urban non-teaching, or urban teaching), hospital region (northeast, midwest, south, or west), elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures performed during the hospital stay. After adjusting for these covariates, ODU hospitalizations were less likely to be discharged to home with or without services (aOR 0.38; 95% CI 0.33–0.43;  $p < 0.001$ ) and more likely to be discharged to a PAC facility (aOR 1.85; 95% CI 1.57–2.17;  $p < 0.001$ ) or have a patient-directed discharge (aOR 3.47; 95% CI 2.80–4.29;  $p < 0.001$ ) compared to non-ODU hospitalizations. There were no significant differences in the odds of being transferred to another acute care hospital or in-hospital mortality.

### Length of stay

The mean LOS was 12.5 days for the OUD group compared to 8.1 days for the non-ODU group (difference 4.3 [95% CI 3.6–5.1]) (Table 3). When stratified by disposition location, the LOS for the OUD group was longer than for the non-ODU group for discharges to home without services (mean 15.5 versus 6.8 days; difference 8.7 [95% CI 7.2–10.2]), home with services (10.8 versus 7.6; difference 3.2 [95% CI 1.6–4.8]), and PAC facilities (13.8 versus 10.5; difference 3.3 [95% CI 2.3–4.4], all  $p < 0.001$ ). In a survival analysis, there were significant differences in LOS (time to hospital discharge) between hospitalizations with and without OUD for all infection types (Fig 1; S1 Fig).

Individuals in the OUD group had a 39% lower probability of discharge at any given LOS (aHR 0.61; 95% CI 0.59–0.63;  $p < 0.001$ ) compared to individuals in the non-ODU group (Fig 2) after adjusting for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures.

**Table 1. Baseline patient, hospitalization, and hospital characteristics of US hospitalizations for serious infections in patients with and without opioid use disorder in 2016.**

Characteristic	Opioid use disorder (N = 7,635)	No opioid use disorder (N = 87,835)	Total (N = 95,470)	p-Value
<b>Patient characteristics</b>				
Infection type, number (%)				
Infective endocarditis	2,935 (38.44)	10,195 (11.61)	13,130 (13.75)	<0.001
Epidural abscess	950 (12.44)	6,995 (7.96)	7,945 (8.32)	<0.001
Septic arthritis	1,690 (22.13)	22,135 (25.20)	23,825 (24.96)	<0.001
Osteomyelitis	2,060 (26.98)	48,510 (55.23)	50,570 (52.97)	<0.001
Age in years, mean (SE)	41.2 (0.39)	59.3 (0.15)	49.0 (0.19)	<0.001
Female, number (%)	3,355 (43.97)	30,420 (34.65)	33,775 (35.39)	<0.001
Primary payer, number (%)				
Medicare	1,230 (16.11)	42,655 (48.63)	43,885 (46.03)	<0.001
Medicaid	4,485 (58.74)	15,995 (18.24)	20,480 (21.48)	<0.001
Private	860 (11.26)	20,515 (23.39)	21,375 (22.42)	<0.001
Self-pay (uninsured)	790 (10.35)	4,810 (5.48)	5,600 (5.87)	<0.001
No charge	110 (1.44)	500 (0.57)	610 (0.64)	<0.001
Other	160 (2.10)	3,230 (3.68)	3,390 (3.56)	<0.001
Race/ethnicity, number (%)				
White	5,470 (74.02)	58,300 (69.35)	63,770 (69.73)	<0.001
Black	830 (11.23)	12,445 (14.80)	13,275 (14.52)	0.01
Hispanic	825 (11.16)	9,265 (11.02)	10,090 (11.03)	0.78
Asian or Pacific Islander	25 (0.34)	1,380 (1.64)	1,405 (1.54)	<0.001
Native American	110 (1.49)	870 (1.03)	980 (1.07)	0.13
Other	130 (1.76)	1,805 (2.15)	1,935 (2.12)	0.37
Median household income quartile, number (%)				
Quartile 1	2,780 (37.57)	28,590 (33.29)	31,370 (33.63)	0.004
Quartile 2	1,980 (26.76)	22,480 (26.17)	24,460 (26.22)	0.78
Quartile 3	1,595 (21.55)	19,360 (22.54)	20,955 (22.46)	0.31
Quartile 4	1,045 (14.12)	15,455 (17.99)	16,500 (17.69)	<0.001
Number of Elixhauser Comorbidity Index conditions, mean (SE)	2.65 (0.05)	3.34 (0.02)	3.29 (0.02)	<0.001
<b>Hospitalization characteristics</b>				
Number of major operating room procedures, mean (SE)	0.74 (0.04)	1.11 (0.01)	1.08 (0.01)	<0.001
Weekend admission, number (%)	1,780 (23.31)	15,645 (17.81)	17,425 (18.25)	<0.001
Elective admission, number (%)	505 (6.63)	14,525 (16.60)	15,030 (15.80)	<0.001
<b>Hospital characteristics</b>				
Size, number (%)				
Small	1,160 (15.19)	16,895 (19.23)	18,055 (18.91)	0.001
Medium	1,970 (25.80)	25,185 (28.67)	27,155 (28.44)	0.05
Large	4,505 (59.00)	45,755 (52.09)	50,260 (52.64)	<0.001
Urban/teaching status, number (%)				
Rural	360 (4.72)	8,190 (9.32)	8,550 (8.96)	<0.001
Urban, non-teaching	1,750 (22.92)	22,620 (25.75)	24,370 (25.53)	0.06
Urban, teaching	5,525 (72.36)	57,025 (64.92)	62,550 (65.52)	<0.001
Region, number (%)				
Northeast	2,130 (27.90)	15,510 (17.66)	17,640 (18.48)	<0.001
Midwest	1,305 (17.09)	19,305 (21.98)	20,610 (21.59)	0.002
South	2,465 (32.29)	35,180 (40.05)	37,645 (39.43)	<0.001

(Continued)

Table 1. (Continued)

Characteristic	Opioid use disorder (N = 7,635)	No opioid use disorder (N = 87,835)	Total (N = 95,470)	p-Value
West	1,735 (22.72)	17,840 (20.31)	19,575 (20.50)	0.08

National estimates were generated using discharge weights computed for the 20% sample from the 2016 National Inpatient Sample. The Rao–Scott chi-squared test was used for categorical variables. The *t* test was used for continuous variables. Additional characteristics not included as covariates in the primary statistical model are listed in S3 Table. Medicare is a US federal health insurance program for people age 65 years or older. Medicaid is a US federal and state program for low-income people. SE, standard error.

<https://doi.org/10.1371/journal.pmed.1003247.t001>

## Total and daily hospital charges

Using survey weights to calculate a nationally representative estimate, total charges for hospitalizations for serious infections in the US in 2016 were \$7.15 billion, with the OUD group accounting for \$739 million. The unadjusted average total charge for OUD hospitalizations was \$23,948.69 higher than for non-OUD hospitalizations. However, the average daily charge was \$1,016.17 less per hospital day for the OUD group compared to the non-OUD group. The largest difference in charges was seen in hospitalizations that ended in discharge home without services. For these, the OUD group had a mean total charge that was \$44,498.16 greater than that of the non-OUD group, yet the average daily charge for the OUD group was \$2,314.04 less per day than for the non-OUD group (Table 4).

When adjusted for covariates, there was no statistically significant difference in total hospital charges (difference \$2,189.04 [95% CI −\$4,145.54 to \$8,523.62],  $p = 0.50$ ), but average daily charges were significantly less for OUD hospitalizations (difference −\$1,637.77 [95% CI −\$2,003.47 to −\$1,272.07],  $p < 0.001$ ). Among discharges to home without services, OUD hospitalizations had higher average total charges (difference \$15,862.31 [95% CI \$6,558.96 to \$25,165.67],  $p < 0.001$ ) and lower average daily charges (difference −\$2,136.02 [95% CI −\$2,814.78 to −\$1,817.25],  $p < 0.001$ ). The covariates for the multivariable models were age, sex,

Table 2. Dispositions of hospitalizations for serious infections with and without opioid use disorder.

Disposition	Opioid use disorder (N = 7,610)	No opioid use disorder (N = 87,739)	Total (N = 95,349)	Unadjusted odds ratio (95% CI)	p-Value	Adjusted odds ratio (95% CI)	p-Value
Home							
All	3,450 (45.3)	55,390 (63.1)	58,840 (61.7)	0.49 (0.43, 0.54)	<0.001	0.38 (0.33, 0.43)	<0.001
Without services	2,625 (34.5)	31,010 (35.3)	33,635 (35.3)	0.98 (0.87, 1.10)	0.69	0.74 (0.64, 0.84)	<0.001
With services	825 (10.8)	24,380 (27.8)	25,205 (26.4)	0.31 (0.26, 0.37)	<0.001	0.37 (0.30, 0.45)	<0.001
Post-acute care facility (rehabilitation center, skilled nursing facility)	2,120 (27.9)	25,130 (28.6)	27,250 (28.6)	0.96 (0.84, 1.11)	0.61	1.85 (1.57, 2.17)	<0.001
Transferred to another acute care facility	520 (6.8)	3,935 (4.5)	4,455 (4.7)	1.62 (1.30, 2.02)	<0.001	0.90 (0.70, 1.16)	0.41
Patient-directed discharge	1,450 (19.1)	2,310 (2.6)	3,760 (3.9)	8.82 (7.43, 10.48)	<0.001	3.47 (2.80, 4.29)	<0.001
Died	70 (0.9)	974 (1.1)	1044 (1.1)	0.84 (0.48, 1.46)	0.53	0.97 (0.52, 1.80)	0.92

Data are given as number (%). Services for home discharges include a home IV provider or being under the care of an organized home health service organization. Post-acute care facilities include skilled nursing facilities, intermediate care facilities, inpatient rehabilitation facilities, hospice facilities, long-term care hospitals, and psychiatric hospitals. National estimates generated using discharge weights computed for the 20% sample from the 2016 National Inpatient Sample. Adjusted odds ratios, 95% confidence intervals, and *p*-values were calculated using multivariable logistic regression models to reflect the odds of each disposition compared with all other dispositions in patients with opioid use disorder versus no opioid use disorder. Multivariable models were adjusted for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures. Patient-directed discharge is coded as “against medical advice.”

<https://doi.org/10.1371/journal.pmed.1003247.t002>



**Table 3. Differences in LOS by disposition for US hospitalizations for serious infections in patients with and without opioid use disorder in 2016.**

Disposition	LOS, in days, mean (SE)		Difference in LOS, in days, mean (SE)	p-Value
	Opioid use disorder (N = 7,610)	No opioid use disorder (N = 87,739)		
All dispositions	12.48 (0.37)	8.14 (0.09)	4.34 (0.37)	<0.001
Home				
All	14.39 (0.63)	7.15 (0.10)	7.24 (0.62)	<0.001
Without services	15.52 (0.77)	6.79 (0.13)	8.73 (0.76)	<0.001
With services	10.79 (0.84)	7.60 (0.12)	3.19 (0.84)	<0.001
Post-acute care facility	13.81 (0.54)	10.48 (0.15)	3.34 (0.54)	<0.001
Transferred to another acute care facility	7.55 (0.84)	6.32 (0.28)	1.23 (0.89)	0.17
Patient-directed discharge	7.76 (0.57)	5.40 (0.39)	2.36 (0.71)	<0.001
Died	14.14 (5.06)	17.93 (2.24)	-3.79 (5.51)	0.49

Differences in LOS are not adjusted for differences in baseline characteristics. Services for home discharges include a home IV provider or being under the care of an organized home health service organization. Post-acute care facilities include skilled nursing facilities, intermediate care facilities, inpatient rehabilitation facilities, hospice facilities, long-term care hospitals, and psychiatric hospitals. LOS represents the number of midnights crossed during a hospitalization. Patient-directed discharge is coded as “against medical advice.” *p*-Values were calculated using the Student’s *t* test.

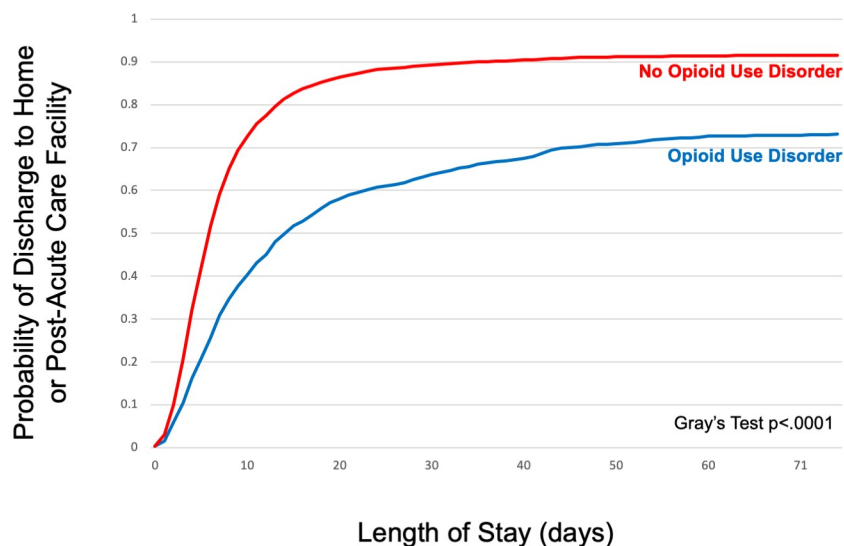
LOS, length of stay; SE, standard error.

<https://doi.org/10.1371/journal.pmed.1003247.t003>

race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures.

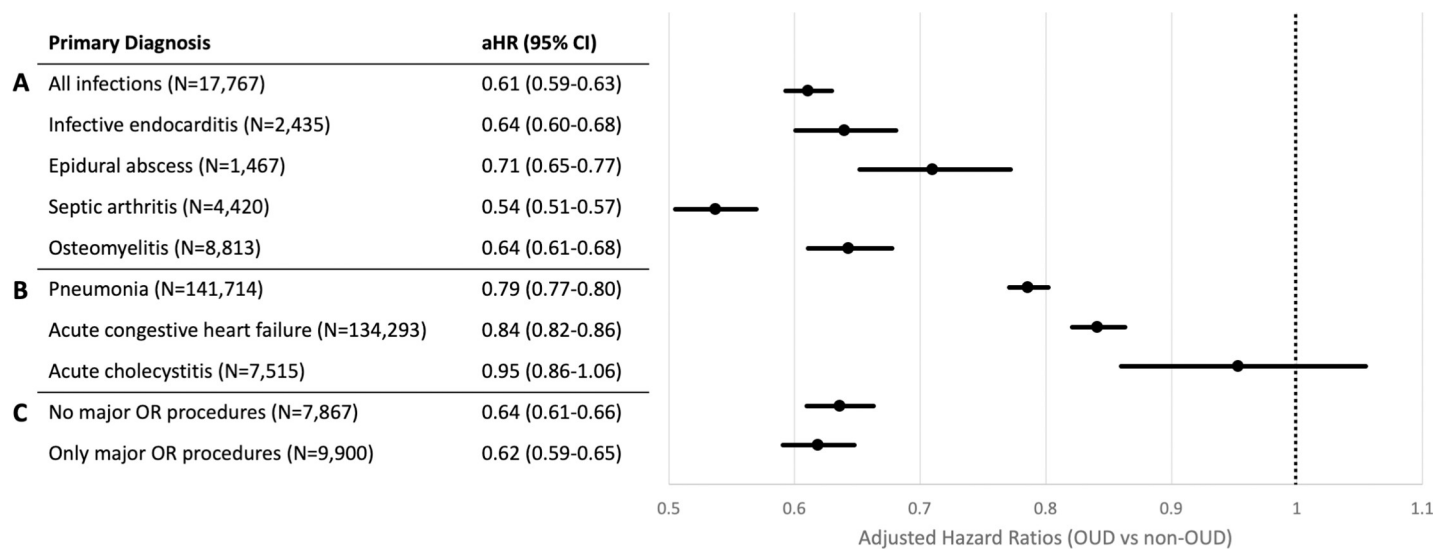
### Sensitivity analyses

In a propensity score matched analysis, both OUD and non-OUD hospitalizations had balanced frequencies of all measured baseline covariates (standardized mean difference < 0.1;



**Fig 1. Probability of discharge to home or a post-acute care facility at any given length of stay for US hospitalizations for serious infections in patients with and without opioid use disorder in 2016.** Cumulative incidence curves of length of stay to discharge estimated using a competing risks survival analysis model. The event of interest was defined as discharge to home or a post-acute care facility. Competing risks were defined as patient-directed discharge, transfer to another acute care hospital, or in-hospital death.

<https://doi.org/10.1371/journal.pmed.1003247.g001>



**Fig 2. Adjusted hazard ratios of length of stay until discharge for US hospitalizations for serious infections in patients with and without opioid use disorder in 2016.** Hazard ratios are from the Fine–Gray subdistribution hazard regression model, adjusted for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures. The model for serious infections also controlled for infection type. The event of interest was defined as discharge to home or a post-acute care facility. Competing risks were defined as patient-directed discharge, transfer to another acute care hospital, or in-hospital death. Hazard ratios were calculated for (A) the analysis of serious infections, (B) a sensitivity analysis of conditions not usually requiring prolonged intravenous access, and (C) a sensitivity analysis stratifying the primary model by hospitalizations with and without major operating room procedures. Unadjusted hazard ratios are found in [S4 Table](#). aHR, adjusted hazard ratio; OR, operating room; OUD, opioid use disorder.

<https://doi.org/10.1371/journal.pmed.1003247.g002>

[S5 Table](#)). A competing risks regression model using the matched cohorts showed that OUD hospitalizations had a 35% lower probability of discharge at any given LOS (aHR 0.65; 95% CI 0.63–0.68;  $p < 0.001$ ) compared to non-OUD hospitalizations—almost identical to the aHR in the main analysis ([S6 Table](#)).

Next, we evaluated hospitalizations for conditions not typically associated with a need for prolonged IV access (pneumonia, acute congestive heart failure, and acute cholecystitis) ([Fig 2](#)). The difference in the probability of discharge at any given LOS between OUD and non-OUD hospitalizations was attenuated among those hospitalized for conditions not typically associated with prolonged IV access (5%–21% difference) relative to hospitalizations for conditions associated with prolonged IV access (29%–46% difference) after adjusting for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures.

Results of our primary analysis did not differ by presence or absence of any major surgical procedures ([Fig 2](#)). For hospitalizations with no procedures, OUD hospitalizations had a 36% lower probability of discharge at any given LOS compared to non-OUD hospitalizations. For hospitalizations with procedures, OUD hospitalizations had a 38% lower probability of discharge at any given LOS than non-OUD hospitalizations.

Neither expanding the definition of serious infections to include an infection in any diagnosis code position nor excluding patients who were transferred in from another hospital meaningfully changed our primary results. Additionally, adding homelessness or severity of illness as covariates did not significantly alter our findings ([S1 Table](#)).

**Table 4. Unadjusted and adjusted total and daily hospital charges of hospitalizations for serious infections with and without opioid use disorder.**

Disposition	Hospital charges in US dollars, mean (SE)				Unadjusted difference in US dollars, mean (SE)				Adjusted difference in US dollars, mean (SE)			
	Opioid use disorder (N = 7,610)		No opioid use disorder (N = 87,739)		Total charges	p-Value	Per day charges	p-Value	Total charges	p-Value	Per day charges	p-Value
	Total	Per day	Total	Per day								
All dispositions	98,207.00 (3,707.52)	8,963.06 (223.24)	74,258.00 (1,282.46)	9,979.23 (120.08)	23,948.69 (2,902.83)	<0.001	-1,016.17 (175.26)	<0.001	2,189.04 (3,231.93)	0.5	-1,637.77 (186.50)	<0.001
Home												
All	100,540.00 (5,665.75)	7,989.47 (242.22)	62,973.00 (1,239.34)	9,934.25 (138.03)	37,566.83 (4,056.03)	<0.001	-1,944.78 (202.97)	<0.001	16,387.49 (3,867.36)	<0.001	-2,093.54 (229.06)	<0.001
Without services	101,429.00 (6,748.22)	7,482.96 (260.13)	56,931.00 (1,407.04)	9,797.00 (147.55)	44,498.16 (4,930.52)	<0.001	-2,314.04 (229.50)	<0.001	15,862.31 (4,744.60)	0.001	-2,136.02 (254.36)	<0.001
With services	97,683.00 (9,435.41)	9,613.47 (548.32)	70,686.00 (1,766.37)	10,108.00 (186.38)	26,996.94 (6,460.27)	<0.001	-494.94 (425.83)	0.25	19,190.07 (6,574.57)	0.004	-919.02 (460.03)	0.05
Post-acute care facility	123,936.00 (6,537.31)	9,199.30 (363.76)	99,510.00 (2,320.32)	9,685.69 (146.20)	24,425.09 (5,756.65)	<0.001	-486.39 (317.10)	0.13	-15,318.36 (7,911.10)	0.05	-1,358.36 (349.11)	<0.001
Transferred to another acute care facility	85,273.00 (11,299.00)	12,705.00 (1089.60)	57,785.00 (3,810.10)	10,975.00 (430.70)	27,487.48 (9,915.20)	0.006	1,730.06 (776.35)	0.03	13,460.67 (12,162.26)	0.27	-184.62 (922.69)	0.84
Patient-directed discharge	55,765.00 (4,242.05)	9,113.05 (455.69)	45,234.00 (2,957.42)	10,804.00 (482.19)	10,530.91 (4,786.69)	0.03	-1,691.26 (537.23)	0.002	9,712.80 (4,720.28)	0.04	-1,976.90 (830.41)	0.02
Died	202,731.00 (62,245.00)	21,382.00 (3,791.22)	198,936.00 (20,763.00)	14,902.00 (1,202.36)	3,794.65 (64,631.48)	0.95	6,480.22 (3,558.51)	0.07	-96,882.69 (77,906.76)	0.21	431.90 (3,931.55)	0.91

Charges represent the hospital billing for the hospital stay. Charges per hospitalization day were calculated by dividing total charges by length of stay. Adjusted mean charges, standard errors, and *p*-values were calculated using multivariable linear regression models. Multivariable models were adjusted for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures. Patient-directed discharge is coded as “against medical advice.” SE, standard error.

<https://doi.org/10.1371/journal.pmed.1003247.t004>

## Discussion

In this large, nationally representative study of inpatient hospitalizations from 2016, we found patients with OUD who were hospitalized for serious infections, compared to those without OUD, had longer LOS, were less likely to be discharged home, were more likely to be discharged to a PAC facility or have a patient-directed discharge, and had similar total hospital charges despite lower daily charges. Our results were robust to multiple analytic approaches and sensitivity analyses.

To our knowledge, this is the first national study to assess differences in hospital and PAC utilization between patients with and without OUD who are hospitalized for conditions requiring prolonged IV access. Our work is consistent with prior studies showing differential patterns of healthcare utilization and longer inpatient hospital stays for patients with OUD [2,3,5,18,19]. We build on these studies by exploring a variety of serious infections that disproportionately affect this population and demonstrating nationwide disparities in care even when accounting for several potential confounders. Thus, our study provides new insights into patterns of healthcare utilization for this costly downstream complication of the ongoing opioid crisis.

Our study suggests that patients with OUD were less likely to be discharged home, especially with home health services, and more likely to be discharged to a PAC facility, despite being younger, having fewer comorbidities, and undergoing fewer surgical procedures—characteristics usually not associated with longer hospital stays and discharges to PAC facilities [23–25]. This suggests healthcare providers and hospitals are discharging patients with OUD

to PAC facilities rather than home, independent of typical reasons for requiring rehabilitation or skilled nursing facilities. Inpatient providers' concerns about discharging patients with OUD to home with an IV line may contribute to these differences [12,13]. This hypothesis is bolstered by the finding that a significantly lower proportion of patients with OUD were discharged with home health services such as visiting nursing care or home IV services. Recent evidence has demonstrated the potential effectiveness and safety of outpatient parenteral antibiotic therapy (OPAT) among people who inject drugs [8,10,26–30]. Though additional evaluations are necessary, there may be opportunities to implement more OPAT in patients with OUD. There are also promising developments that could help narrow disparities in discharge dispositions, such as residential addiction treatment facilities that could be both safe and cost-saving, inpatient addiction medicine consultations that may improve antibiotic therapy completion rates and reduce readmissions, and, in select cases, the possibility that serious infections may be safely treated with partial oral antibiotic therapy [15,31–35].

Patients with OUD had significantly longer LOS than patients without OUD. There are several potential explanations for this. First, inpatient providers may keep patients with OUD in the hospital to complete their antibiotic course owing to concerns about discharging these patients with an IV line, as described above [12]. Second, these patients may have less access to PAC facilities or home IV services, thus limiting their potential discharge options [13]. Third, patients with OUD may have a higher severity of illness. This last hypothesis is less likely since patients with OUD were younger and had fewer comorbidities, fewer procedures, fewer average daily charges, and a lower proportion of inpatient mortality. Moreover, in our sensitivity analyses, we found that the disparity in LOS for OUD compared to non-OUD hospitalizations was attenuated when focusing on conditions that do not typically require prolonged IV access such as pneumonia or acute cholecystitis. This suggests that the need for ongoing IV access is a key driver of decisions around the appropriate setting of care for these patients and contributes to the observed disparities in LOS and disposition. The attenuated but still significant differences for pneumonia and acute congestive heart failure suggest that patients with OUD have prolonged hospital stays for other reasons as well. This could be due to inpatient complications with opioid withdrawal, higher severity of illness, or lack of access to necessary discharge options. Research on recent policy efforts to improve access to PAC facilities for OUD patients may provide valuable insights into the differences in healthcare utilization [36–39].

Another important finding is the significantly higher incidence of patient-directed discharges (or “discharges against medical advice”) in the OUD group than the non-OUD group. Patient-directed discharges are a critical issue, especially due to their association with higher costs, readmission rates, and mortality [40]. Inpatient withdrawal management, substance use treatment, and social support are associated with lower likelihood of patient-directed discharge in patients with drug use [35,41,42]. These interventions are underutilized, but several successful models of inpatient withdrawal management and linkage to outpatient addiction treatment are emerging and may help to address the problem of patient-directed discharges in this patient population [43–49].

Lastly, we found that total adjusted hospital charges were similar between OUD and non-OUD hospitalizations, despite significantly lower average daily charges. The lower daily charges despite similar total charges for patients with OUD (or higher total charges for specific dispositions such as discharge home) suggest that LOS is an important driver of cost in OUD hospitalizations and reinforce the notion that patients with OUD have lower acuity and receive fewer hospital services but have comparable or more expensive hospital stays due to longer LOS. Given the disproportionate burden of these hospitalizations among patients on Medicaid and uninsured patients, there are serious and potentially preventable costs for patients, governments, insurance companies, and health systems.

Our study had some notable strengths and limitations. First, this was a cross-sectional observational analysis, so it could not demonstrate causal relationships or account for potential sources of unmeasured confounding. However, our results were robust to multiple sensitivity analyses. Additionally, the NIS allowed for the most comprehensive, high-quality, and validated national survey of inpatient hospitalizations. Second, the need to use ICD-10 codes in NIS likely led to measurement bias and underestimated cases of serious infections and OUD, as demonstrated in a recent study using the related HCUP State Inpatient Databases [50]. Though this had the disadvantage of lowering our population estimates of the various conditions, it also likely biased our results towards the null, which further highlights our significant findings. There is also the possibility of differential misclassification of potential confounders, which may have biased our results. Third, there has been a recent rise, particularly from 2017 onwards, in stimulant use, with a related rise in morbidity and mortality, which may affect decisions around hospitalizations and discharges. We did not account for stimulant use as our data focused on 2016, likely preceding this “fourth wave.” Lastly, homelessness is a major problem among patients with OUD, which could affect discharge decisions and access to PAC facilities and could lengthen hospital stays [51–53]. We sought to adjust for this by running a sensitivity analysis using homelessness as a covariate as described above, which did not significantly affect our results.

Given our findings of longer LOS for patients with OUD, differential disposition, and associated hospital charges, an important next step would be a mixed-methods study to understand the reasons for prolonged hospital stays for these patients. Additionally, more research is needed to assess the potential impact of OPAT, partial oral antibiotic therapy, and residential addiction treatment facilities in reducing hospital stays, lowering costs, and maintaining or improving outcomes of serious infections. Meanwhile, all hospitals caring for patients with substance use disorder should implement inpatient addiction medicine consultations, withdrawal management, substance use treatment, and linkage to outpatient addiction treatment, which may improve antibiotic therapy completion rates and reduce patient-directed discharges and readmissions. Additionally, recent policy efforts to improve access to PAC facilities for OUD patients should be evaluated. Policymakers can seek to lift barriers for OUD patients in accessing PAC facilities while providing more funding for PAC facilities to support and care for patients with OUD. Beyond that, hospitals and policymakers should work together to expand the number of discharge options for patients requiring prolonged IV therapy, including housing for patients with housing instability. In this way, the US health system can provide equitable care to patients with serious infections so that they can avoid costly and lengthy hospitalizations that increase their risk of nosocomial infections, deconditioning, and inpatient complications.

In conclusion, we found significant disparities between patients with and without OUD who were hospitalized for serious infections. Patients with OUD stayed in the hospital longer than those without OUD, and they had a higher odds of going to a PAC facility or choosing a patient-directed discharge, despite there being no known evidence that a shorter hospital stay and outpatient IV antibiotic therapy would lead to worse outcomes. Further studies elucidating the source of these disparities, and health systems and policy interventions to address them, may reduce hospital stays, lower costs, and improve the equity of care for patients affected by the opioid crisis.

## Supporting information

**S1 STROBE Checklist. Checklist of items that should be included in reports of observational studies.**

(DOCX)

**S1 Fig. Cumulative incidence curves of length of stay to discharge by infection type.** Cumulative incidence curves of length of stay to discharge estimated using a competing risks survival analysis model. The event of interest was defined as discharge to home or a post-acute care facility. Competing risks were defined as discharge against medical advice, transfer to another acute care hospital, or in-hospital death. Gray's test was used to assess for statistically significant differences in cumulative incidence between the 2 cohorts. Shaded regions indicate 95% confidence bounds. (DOCX)

**S1 Table. Additional models with hospital as a random intercept, model covariates, severity of illness, and homelessness.** Covariates for all adjusted models (unless otherwise specified) were age, sex, race/ethnicity, primary payer, quartile of median household income based on the patient's zip code of residence, Elixhauser Comorbidity Index (excluding drug use to avoid adjusting for our exposure of interest), type of serious infection, hospital size (based on number of beds), type of hospital (rural, urban non-teaching, or urban teaching), hospital region (northeast, midwest, south, west), elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures performed during the hospital stay. SE, standard error. (DOCX)

**S2 Table. ICD-10 codes for diagnoses. ICD-10 codes from the Centers for Disease Control and Prevention ICD-10-CM browser tool, available at <https://icd10cmtool.cdc.gov/>.** The ICD-10 codes for serious infection (endocarditis, epidural abscess, septic arthritis, and osteomyelitis) were identified in the primary diagnosis code position (first out of 30 possible codes) for the main analysis. Opioid use disorder was defined as having a corresponding ICD-10 code as a secondary diagnosis code (any of diagnosis code positions 2 to 30). Pneumonia, acute congestive heart failure, and acute cholecystitis were identified in the primary diagnosis code position, for a sensitivity analysis. Lastly, homelessness, used as a covariate in a sensitivity analysis, was defined using secondary diagnosis codes. (DOCX)

**S3 Table. Baseline characteristics of hospitalizations for serious infections with and without opioid use disorder—individual Elixhauser Comorbidity Index conditions, hepatitis C virus infection, and homelessness.** National estimates were generated using discharge weights computed for the 20% sample from the 2016 National Inpatient Sample. The Rao-Scott chi-squared test was used to compare differences between the 2 cohorts. (DOCX)

**S4 Table. Unadjusted hazard ratios of length of stay until discharge for US hospitalizations for serious infections in patients with and without opioid use disorder in 2016.** Hazard ratios are from the Fine-Gray subdistribution hazard regression model. The event of interest was defined as discharge to home or a post-acute care facility. Competing risks were defined as patient-directed discharge, transfer to another acute care hospital, or in-hospital death. (DOCX)

**S5 Table. Baseline characteristics for propensity score matched cohorts.** Propensity scores for having opioid use disorder were generated using survey-weighted logistic regression, adjusting for all patient, hospitalization, and hospital characteristics listed in the table. The 2 cohorts were then matched using a greedy match algorithm to produce balanced cohorts of 6,605 weighted hospitalizations each. Standardized mean differences were then calculated across the cohorts by the baseline characteristics, with an absolute difference of less than 0.1 as a threshold for balance between the 2 cohorts. (DOCX)

**S6 Table. Hazard ratio for the probability of discharge at any given length of stay and odds ratios for dispositions after propensity score matching.** Propensity scores for having opioid use disorder were generated using survey-weighted logistic regression, adjusting for age, sex, race/ethnicity, primary payer, median household income, Elixhauser Comorbidity Index, infection type, hospital size, hospital type, hospital region, elective versus non-elective admission, weekday versus weekend admission, and the number of major operating room procedures. The 2 cohorts were then matched using a greedy match algorithm to produce balanced cohorts of 6,605 weighted hospitalizations each. Adjusted odds ratios, 95% confidence intervals, and *p*-values were calculated using multivariable logistic regression models to reflect the odds of each disposition compared with all other dispositions in patients with opioid use disorder versus no opioid use disorder. Hazard ratios were calculated from the Fine–Gray subdistribution hazard regression model. The event of interest was defined as discharge to home or a post-acute care facility. Competing risks were defined as discharge against medical advice, transfer to another acute care hospital, or in-hospital death.

(DOCX)

**S1 Text. Statistical analysis and model specification.**

(DOCX)

## Author Contributions

**Conceptualization:** June-Ho Kim, Danielle R. Fine, Lily Li, Simeon D. Kimmel, Joji Suzuki, Christin N. Price, Matthew V. Ronan, Shoshana J. Herzig.

**Data curation:** June-Ho Kim, Danielle R. Fine, Lily Li, Simeon D. Kimmel, Shoshana J. Herzig.

**Formal analysis:** June-Ho Kim, Long H. Ngo, Shoshana J. Herzig.

**Funding acquisition:** Shoshana J. Herzig.

**Investigation:** June-Ho Kim, Danielle R. Fine, Lily Li, Simeon D. Kimmel, Shoshana J. Herzig.

**Methodology:** June-Ho Kim, Long H. Ngo, Shoshana J. Herzig.

**Project administration:** June-Ho Kim, Shoshana J. Herzig.

**Resources:** Shoshana J. Herzig.

**Software:** Shoshana J. Herzig.

**Supervision:** Long H. Ngo, Shoshana J. Herzig.

**Validation:** June-Ho Kim, Long H. Ngo, Joji Suzuki, Christin N. Price, Matthew V. Ronan, Shoshana J. Herzig.

**Visualization:** June-Ho Kim.

**Writing – original draft:** June-Ho Kim.

**Writing – review & editing:** June-Ho Kim, Danielle R. Fine, Lily Li, Simeon D. Kimmel, Long H. Ngo, Joji Suzuki, Christin N. Price, Matthew V. Ronan, Shoshana J. Herzig.

## References

1. Ronan MV, Herzig SJ. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002–12. *Health Aff (Millwood)*. 2016; 35(5):832–7.

2. Schranz AJ, Fleischauer A, Chu VH, Wu L-T, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med.* 2019; 170(1):31–40. <https://doi.org/10.7326/M18-2124> PMID: 30508432
3. Hartman L, Barnes E, Bachmann L, Schafer K, Lovato J, Files DC. Opiate injection-associated infective endocarditis in the southeastern United States. *Am J Med Sci.* 2016; 352(6):603–8. <https://doi.org/10.1016/j.amjms.2016.08.010> PMID: 27916215
4. Gray ME, Rogawski McQuade ET, Scheld WM, Dillingham RA. Rising rates of injection drug use associated infective endocarditis in Virginia with missed opportunities for addiction treatment referral: a retrospective cohort study. *BMC Infect Dis.* 2018; 18(1):532. <https://doi.org/10.1186/s12879-018-3408-y> PMID: 30355291
5. Salehi Omran S, Chatterjee A, Chen ML, Lerario MP, Merkler AE, Kamel H. National trends in hospitalizations for stroke associated with infective endocarditis and opioid use between 1993 and 2015. *Stroke.* 2019; 50(3):577–82. <https://doi.org/10.1161/STROKEAHA.118.024436> PMID: 30699043
6. Wurcel AG, Anderson JE, Chui KKH, Skinner S, Knox TA, Snyderman DR, et al. Increasing infectious endocarditis admissions among young people who inject drugs. *Open Forum Infect Dis.* 2016; 3(3): ofw157. <https://doi.org/10.1093/ofid/ofw157> PMID: 27800528
7. D’Couto HT, Robbins GK, Ard KL, Wakeman SE, Alves J, Nelson SB. Outcomes according to discharge location for persons who inject drugs receiving outpatient parenteral antimicrobial therapy. *Open Forum Infect Dis.* 2018; 5(5):ofy056. <https://doi.org/10.1093/ofid/ofy056> PMID: 29766017
8. Pericàs JM, Llopis J, González-Ramallo V, Goenaga MÁ, Muñoz P, García-Leoni ME, et al. Outpatient parenteral antibiotic treatment (OPAT) for infective endocarditis: a prospective cohort study from the GAMES cohort. *Clin Infect Dis.* 2019; 69(10):1690–700. <https://doi.org/10.1093/cid/ciz030> PMID: 30649282
9. Mansour O, Heslin J, Townsend JL. Impact of the implementation of a nurse-managed outpatient parenteral antibiotic therapy (OPAT) system in Baltimore: a case study demonstrating cost savings and reduction in re-admission rates. *J Antimicrob Chemother.* 2018; 73(11):3181–8. <https://doi.org/10.1093/jac/dky294> PMID: 30085088
10. Suzuki J, Johnson J, Montgomery M, Hayden M, Price C. Outpatient parenteral antimicrobial therapy among people who inject drugs: a review of the literature. *Open Forum Infect Dis.* 2018; 5(9):ofy194. <https://doi.org/10.1093/ofid/ofy194> PMID: 30211247
11. Vazirian M, Jerry JM, Shrestha NK, Gordon SM. Outcomes of outpatient parenteral antimicrobial therapy in patients with injection drug use. *Psychosomatics.* 2018; 59(5):490–5. <https://doi.org/10.1016/j.psych.2018.02.005> PMID: 29685397
12. Rapoport AB, Fischer LS, Santibanez S, Beekmann SE, Polgreen PM, Rowley CF. Infectious diseases physicians’ perspectives regarding injection drug use and related infections, United States, 2017. *Open Forum Infect Dis.* 2018; 5(7):ofy132. <https://doi.org/10.1093/ofid/ofy132> PMID: 30018999
13. Wakeman SE, Rich JD. Barriers to post-acute care for patients on opioid agonist therapy; an example of systematic stigmatization of addiction. *J Gen Intern Med.* 2017; 32(1):17–9. <https://doi.org/10.1007/s11606-016-3799-7> PMID: 27393486
14. Psaltikidis EM, Silva END, Moretti ML, Trabasso P, Stucchi RSB, Aoki FH, et al. Cost-utility analysis of outpatient parenteral antimicrobial therapy (OPAT) in the Brazilian national health system. *Expert Rev Pharmacoecon Outcomes Res.* 2018; 19(3):341–52. <https://doi.org/10.1080/14737167.2019.1541404> PMID: 30362845
15. Jewell C, Weaver M, Sgroi C, Anderson K, Sayeed Z. Residential addiction treatment for injection drug users requiring intravenous antibiotics: a cost-reduction strategy. *J Addict Med.* 2013; 7(4):271–6. <https://doi.org/10.1097/ADM.0b013e318294b1eb> PMID: 23648642
16. Dewan KC, Dewan KS, Idrees JJ, Navale SM, Rosinski BF, Svensson LG, et al. Trends and outcomes of cardiovascular surgery in patients with opioid use disorders. *JAMA Surg.* 2019; 154(3):232–40. <https://doi.org/10.1001/jamasurg.2018.4608> PMID: 30516807
17. Wurcel AG. Drug-associated infective endocarditis trends: what’s all the buzz about? *Ann Intern Med.* 2019; 170(1):68–9. <https://doi.org/10.7326/M18-3026> PMID: 30508422
18. Tank A, Hobbs J, Ramos E, Rubin DS. Opioid dependence and prolonged length of stay in lumbar fusion: a retrospective study utilizing the National Inpatient Sample 2003–2014. *Spine (Phila Pa 1976).* 2018; 43(24):1739–45.
19. Rudasill SE, Sanaiha Y, Mardock AL, Khoury H, Xing H, Antonios JW, et al. Clinical outcomes of infective endocarditis in injection drug users. *J Am Coll Cardiol.* 2019; 73(5):559–70. <https://doi.org/10.1016/j.jacc.2018.10.082> PMID: 30732709
20. Freeman WJ, Weiss AJ, Heslin KC. Overview of U.S. hospital stays in 2016: variation by geographic region. *Healthcare Cost and Utilization Project Statistical Brief #246.* Rockville (MD): Agency for Healthcare Research and Quality; 2006.



21. Fine JP, Gray RJ. A Proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999; 94(446):496–509.
22. Gray RJ. A class of  $K \times K$ -sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988; 16(3):1141–54.
23. Pakzad H, Thevendran G, Penner MJ, Qian H, Younger A. Factors associated with longer length of hospital stay after primary elective ankle surgery for end-stage ankle arthritis. *J Bone Joint Surg Am.* 2014; 96(1):32–9. <https://doi.org/10.2106/JBJS.K.00834> PMID: 24382722
24. Wang Y, Stavem K, Dahl FA, Humerfelt S, Haugen T. Factors associated with a prolonged length of stay after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). *Int J Chron Obstruct Pulmon Dis.* 2014; 9:99–105. <https://doi.org/10.2147/COPD.S51467> PMID: 24477272
25. Bowles KH, Holmes JH, Ratcliffe SJ, Liberatore M, Nydick R, Naylor MD. Factors identified by experts to support decision making for post acute referral. *Nurs Res.* 2009; 58(2):115–22. <https://doi.org/10.1097/NNR.0b013e318199b52a> PMID: 19289932
26. Ho J, Archuleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. *J Antimicrob Chemother.* 2010; 65(12):2641–4. <https://doi.org/10.1093/jac/dkq355> PMID: 20864497
27. Allison GM, Muldoon EG, Kent DM, Paulus JK, Ruthazer R, Ren A, et al. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. *Clin Infect Dis.* 2014; 58(6):812–9. <https://doi.org/10.1093/cid/cit920> PMID: 24357220
28. Beielor A, Magaret A, Zhou Y, Schleyer A, Wald A, Dhanireddy S. Outpatient parenteral antimicrobial therapy in vulnerable populations—people who inject drugs and the homeless. *J Hosp Med.* 2019; 14(2):105–9. <https://doi.org/10.12788/jhm.3138> PMID: 30785418
29. Buehrle DJ, Shields RK, Shah N, Shoff C, Sheridan K. Risk factors associated with outpatient parenteral antibiotic therapy program failure among intravenous drug users. *Open Forum Infect Dis.* 2017; 4(3):ofx102. <https://doi.org/10.1093/ofid/ofx102> PMID: 28680904
30. Tattevin P, Revest M. Outpatient parenteral antibiotic treatment (OPAT) for infective endocarditis: insights from the real life. *Clin Infect Dis.* 2019; 69(10):1701–2. <https://doi.org/10.1093/cid/ciz027> PMID: 30649207
31. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med.* 2019; 380(5):415–24. <https://doi.org/10.1056/NEJMoa1808312> PMID: 30152252
32. Boucher HW. Partial oral therapy for osteomyelitis and endocarditis—is it time? *N Engl J Med.* 2019; 380(5):487–9. <https://doi.org/10.1056/NEJMe1817264> PMID: 30699312
33. Li H-K, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med.* 2019; 380(5):425–36. <https://doi.org/10.1056/NEJMoa1710926> PMID: 30699315
34. Englander H, Wilson T, Collins D, Phoutrides E, Weimer M, Korhuis PT, et al. Lessons learned from the implementation of a medically enhanced residential treatment (MERT) model integrating intravenous antibiotics and residential addiction treatment. *Subst Abus.* 2018; 39(2):225–32. <https://doi.org/10.1080/08897077.2018.1452326> PMID: 29595367
35. Marks LR, Munigala S, Warren DK, Liang SY, Schwarz ES, Durkin MJ. Addiction medicine consultations reduce readmission rates for patients with serious infections from opioid use disorder. *Clin Infect Dis.* 2018; 68(11):1935–7.
36. Department of Health and Human Services. Nondiscrimination and opioid use disorder. Washington (DC): Department of Health and Human Services; 2018 [cited 2019 Mar 29]. Available from: <https://www.hhs.gov/sites/default/files/fact-sheet-nondiscrimination-and-opioid-use.pdf>.
37. US Department of Justice. U.S. Attorney's Office settles disability discrimination allegations at skilled nursing facility. Washington (DC): US Department of Justice; 2018 [cited 2019 Mar 29]. Available from: <https://www.justice.gov/usao-ma/pr/us-attorney-s-office-settles-disability-discrimination-allegations-skilled-nursing>.
38. Legal Action Center. DOJ settlement with skilled nursing facility: excluding people on addiction medication violates the ADA. New York: Legal Action Center; 2018 [cited 2020 Jul 15]. Available from: <https://www.lac.org/news/doj-settlement-with-skilled-nursing-facility-excluding-people-on-addiction-medication-violates-the-ada>.
39. Mass.gov. Circular letter: DHCQ 16-11-662—Admission of residents on medication assisted treatment for opioid use disorder. Mass.gov; 2016 [cited 2019 Mar 29]. Available from: <https://www.mass.gov/circular-letter/circular-letter-dhcq-16-11-662-admission-of-residents-on-medication-assisted>.

40. Glasgow JM, Vaughn-Sarrazin M, Kaboli PJ. Leaving against medical advice (AMA): risk of 30-day mortality and hospital readmission. *J Gen Intern Med*. 2010; 25(9):926–9. <https://doi.org/10.1007/s11606-010-1371-4> PMID: 20425146
41. Chan ACH, Palepu A, Guh DP, Sun H, Schechter MT, O'Shaughnessy MV, et al. HIV-positive injection drug users who leave the hospital against medical advice: the mitigating role of methadone and social support. *J Acquir Immune Defic Syndr*. 2004; 35(1):56–9. <https://doi.org/10.1097/00126334-200401010-00008> PMID: 14707793
42. Ti L, Milloy MJ, Buxton J, McNeil R, Dobrer S, Hayashi K, et al. Factors associated with leaving hospital against medical advice among people who use illicit drugs in Vancouver, Canada. *PLoS ONE*. 2015; 10(10):e0141594. <https://doi.org/10.1371/journal.pone.0141594> PMID: 26509447
43. Rosenthal ES, Karchmer AW, Theisen-Toupal J, Castillo RA, Rowley CF. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med*. 2016; 129(5):481–5. <https://doi.org/10.1016/j.amjmed.2015.09.024> PMID: 26597670
44. Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med*. 2018; 169(3):137–45. <https://doi.org/10.7326/M17-3107> PMID: 29913516
45. Suzuki J. Medication-assisted treatment for hospitalized patients with intravenous-drug-use related infective endocarditis. *Am J Addict*. 2016; 25(3):191–4. <https://doi.org/10.1111/ajad.12349> PMID: 26991660
46. Trowbridge P, Weinstein ZM, Kerensky T, Roy P, Regan D, Samet JH, et al. Addiction consultation services—linking hospitalized patients to outpatient addiction treatment. *J Subst Abuse Treat*. 2017; 79:1–5. <https://doi.org/10.1016/j.jsat.2017.05.007> PMID: 28673521
47. Wakeman SE, Metlay JP, Chang Y, Herman GE, Rigotti NA. Inpatient addiction consultation for hospitalized patients increases post-discharge abstinence and reduces addiction severity. *J Gen Intern Med*. 2017; 32(8):909–16. <https://doi.org/10.1007/s11606-017-4077-z> PMID: 28526932
48. Englander H, Mahoney S, Brandt K, Brown J, Dorfman C, Nydahl A, et al. Tools to support hospital-based addiction care: core components, values, and activities of the improving addiction care team. *J Addict Med*. 2019; 13(2):85–9. <https://doi.org/10.1097/ADM.0000000000000487> PMID: 30608265
49. Peterson C, Xu L, Mikosz CA, Florence C, Mack KA. US hospital discharges documenting patient opioid use disorder without opioid overdose or treatment services, 2011–2015. *J Subst Abuse Treat*. 2018; 92:35–9. <https://doi.org/10.1016/j.jsat.2018.06.008> PMID: 30032942
50. Miller AC, Polgreen PM. Many opportunities to record, diagnose, or treat injection drug-related infections are missed: a population-based cohort study of inpatient and emergency department settings. *Clin Infect Dis*. 2018; 68(7):1166–75.
51. Baggett TP, Hwang SW, O'Connell JJ, Porneala BC, Stringfellow EJ, Orav EJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. *JAMA Intern Med*. 2013; 173(3):189–95. <https://doi.org/10.1001/jamainternmed.2013.1604> PMID: 23318302
52. Tsai J, KasproW WJ, Rosenheck RA. Latent homeless risk profiles of a national sample of homeless veterans and their relation to program referral and admission patterns. *Am J Public Health*. 2013; 103(Suppl 2):S239–47.
53. Bachhuber MA, Roberts CB, Metraux S, Montgomery AE. Screening for homelessness among individuals initiating medication-assisted treatment for opioid use disorder in the Veterans Health Administration. *J Opioid Manag*. 2015; 11(6):459–62. <https://doi.org/10.5055/jom.2015.0298> PMID: 26728642