ORIGINAL RESEARCH

Trends in Infective Endocarditis Hospitalizations, Characteristics, and Valve Operations in Patients With Opioid Use Disorders in the United States: 2005–2014

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Background—To evaluate changes in patient characteristics and outcomes for infective endocarditis (IE) related to opioid use disorder (OUD), we used the National (Nationwide) Inpatient Sample (NIS) to characterize the trend in hospitalizations for patients with IE with and without OUD and those treated medically and surgically.

Methods and Results—Temporal trends in hospitalization characteristics for patients with IE with and without OUD and those treated medically and surgically were estimated via the NIS data in 2005–2014. Hospitalizations for OUD and IE increased from 119 to 202 and from 12 to 15 cases per 100 000 between 2005 and 2014, respectively. Hospitalizations with OUD among all IE hospitalizations increased from 6.3% in 2005 to 11.6% in 2014. Among all IE hospitalizations, patients being admitted for IE in the setting of OUD were younger compared with the cohort of IE without OUD (aged 37.6±0.21 years versus 60.9±0.16 years). Myocardial infarction, diabetes mellitus, chronic kidney disease, peripheral vascular disease, and heart failure were more common in patients without OUD. The OUD cohort more frequently had liver disease (46.0% versus 10.8%) and immunosuppressed status (4.3% versus 2.1%). Valve operations for IE accounted for 10.2% of all valve operations in 2005, and this increased to 12.7% in 2014. These proportions were similar between OUD (11.4%) and non-OUD (11.1%) cohorts. Operative mortality was lower in patients with OUD (4.3% versus 9.4%, $P<0.001$).

Conclusions—IE associated with OUD has a distinct phenotype and has become more prevalent. Surgical outcomes are favorable and operations were performed in similar proportions of patients who had IE with OUD compared with patients who had IE without OUD. **(*J Am Heart Assoc*. 2020;9:e012465. DOI: 10.1161/JAHA.119.012465.)**

Key Words: incidence • infective endocarditis • opioid use disorder • valve replacement

Infective endocarditis (IE) is a highly morbid disease of various causes and heterogeneous manifestations. A subgroup of patients requires an operation that is generally associated with high risk of mortality and morbidity.[1,2] The incidence of IE has increased in the past 2 decades,[3] with shifts in pathogenesis and manifestations.[4] The use of injection drugs is a risk factor for IE and of particular interest in the context of the recent opioid epidemic in the United States.[5] This rising patient group with endocarditis associated with opioid use disorder (OUD) has distinct phenotypes of being younger and having fewer cardiovascular comorbidities, although this is based on studies from a limited number of centers and at a state-level.[6,7] Inferred from this observation is the temporal change in characteristics of patients with IE. However, national-level trends in IE associated with OUD and patient characteristics are unknown. In addition, temporal trends of valve operations and outcomes in this population in the United States remain poorly elucidated. In this study, we used National (Nationwide) Inpatient Sample (NIS) data to evaluate the trend in hospitalizations for IE associated with OUD, predictors of undergoing valve operations, and its outcomes.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Healthcare Cost and Utilization Project at https://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp.

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012465

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Clinical Perspective

What Is New?

- This study demonstrated that patient characteristics differ significantly between patients with infective endocarditis with and without opioid use disorder, and that those with opioid use disorder tend to be younger with less cardiopulmonary comorbidity.
- This study also demonstrated that the proportions of patients with endocarditis undergoing valve operations were similar between those with and without opioid use disorder.

What Are the Clinical Implications?

- There is an increasing need to recognize the distinct phenotype in patients with endocarditis related to opioid use disorder, and adjust our perception of the operative risk, as the short-term outcome of patients with opioid use disorder is favorable compared with that of other forms of endocarditis traditionally occurring in older and more comorbid populations.

Data Definitions and Variable Selections

The Healthcare Cost and Utilization Project (HCUP) NIS data set from 2005 to 2014 was used for this study. The NIS is a nationally representative administrative database provided by the Agency for Healthcare Research and Quality (AHRQ) that contains administrative and demographic data that represent approximately a 20% sample of all-payer inpatient hospitalization in the United States.[8]

The following discharge *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes were used to define IE: 421.0, 421.1, 421.9, 036.42, 098.84, 112.81, 115.04, 115.14, or 115.94, which had been validated against individual medical records in a prior study.[4] OUD was defined as that containing the following: 304.0, 304.7, 305.5, 965.0, E850.0–E850.2, or E935.0–E935.2. These codes did not specify the route of drug administration. Although nonopioid drugs play an important role in the epidemiology of endocarditis, we focused on OUD given the current epidemic. Valve operations, other concomitant cardiac operations, and comorbidities include the *ICD-9-CM* codes listed in Table S1. Because the NIS data set does not have a flag variable differentiating conditions that were present before the index admission and conditions that developed during hospitalizations, specific attention was paid to define comorbidities that were less likely to overlap with complications following cardiac surgery.

All investigators with access to the data have a signed Data User Agreement with HCUP. This study was approved as exempt from review by the Yale Human Investigations Committee.

Statistical Analysis

In 2012, the sampling of NIS was redesigned to improve the accuracy of national estimates. To account for this change, HCUP has provided Trend Weight files for years before 2012, which were used in our analysis. SAS software version 9.4 (SAS Institute) was used for all steps of the analysis. Incidences of defined cases were reported in the national estimate and incidences adjusted for the US population were based on US census.[8] To provide the accurate estimate of standard errors accounting for the stratified cluster sampling design, SURVEY procedures were used with a hospital-level clustering for descriptive analyses as recommended by the HCUP.[9] Bivariate analyses were performed using chi-square for categorical variables and Student *t* test for continuous variables. Temporal trend in the incidence and proportions of hospital admissions and operations were evaluated using bivariate Poisson regression, modeling for incidence as the independent variable and year as the dependent variable. Offset function was used to account for the changes in denominator values for those describing incidence rates or proportions, such as annual incidence rates of IE being adjusted by the offset of annual census population. Input data for Poisson regression were generated from the point estimate from the SURVEY procedure described above. Standard errors associated with the population estimate was propagated in Poisson model in an error term. Continuous variables are summarized by mean with SD and standard error, unless otherwise specified. Categorical variables are summarized by percentages with standard error in the tables. Statistical significance was set at $P<0.05$.

Results

Temporal trends of the population-adjusted incidence of hospital discharges related to OUD and IE are depicted in Figure 1. Hospitalizations for OUD significantly increased from 119.0 per 100 000 in 2005 to 202.5 per 100 000 in 2014, with an annual increase of 8.7 cases per 100 000 ($P<0.0001$ for trend). Similarly, hospitalizations related to IE also increased from 12.1 per 100 000 in 2005 to 15.0 per 100 000 in 2014, with an annual increase of 0.3 cases per 100 000 ($P<0.0001$ for trend). Percentage of hospitalizations related to OUD among all cases of IE almost doubled from 6.3% in 2005 to 11.6% in 2014 (Figure 2A) ($P<0.0001$ for trend). Concurrently, the proportion of cases of IE not related to OUD decreased over time. The percentage of patients with IE who underwent valve operations among all cases of IE showed a modest increase from 10.2% in 2005 to 12.7% in 2014 (Figure 2B) ($P<0.0001$ for trend). Incidence of IE with OUD across age differed between sex but it was similar between sex in IE without OUD (Figure 3).

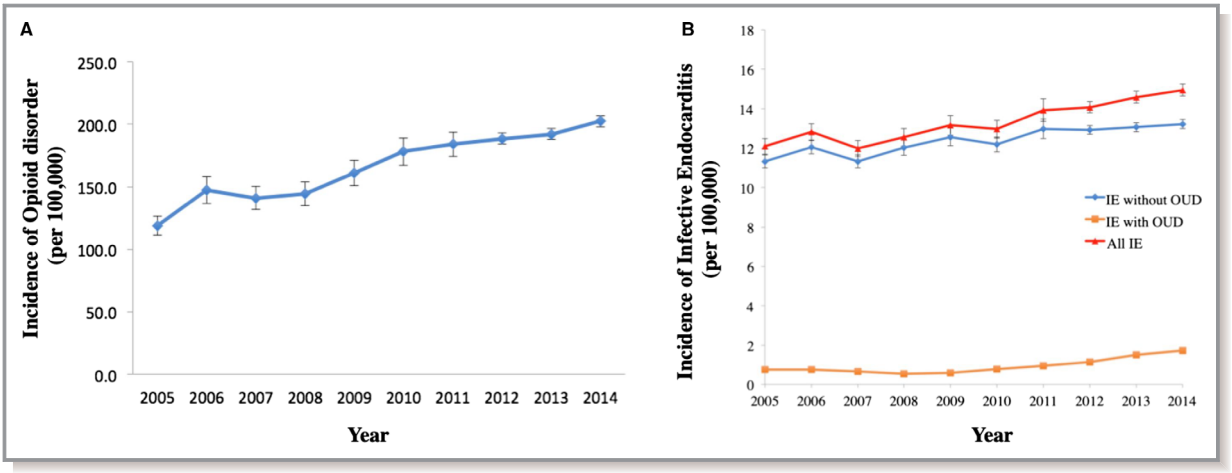

Figure 1. Trends in opioid use disorder (OUD) and infective endocarditis (IE) between 2005–2014. Figure depicts temporal trends in hospital discharge related to OUD (**A**) and IE (**B**). Incidences are adjusted for the US census population and expressed in per 100 000 unit. Error bar represents standard error associated with the population estimate.

Table 1 summarizes bivariate comparisons of characteristics of patients with IE with and without OUD. Mean age (± represents the standard error of estimate) of those with and without OUD was 37.6±0.21 and 60.9±0.16 years, respectively ($P<0.0001$). Cardiovascular comorbidity, including previous myocardial infarction, diabetes mellitus, previous

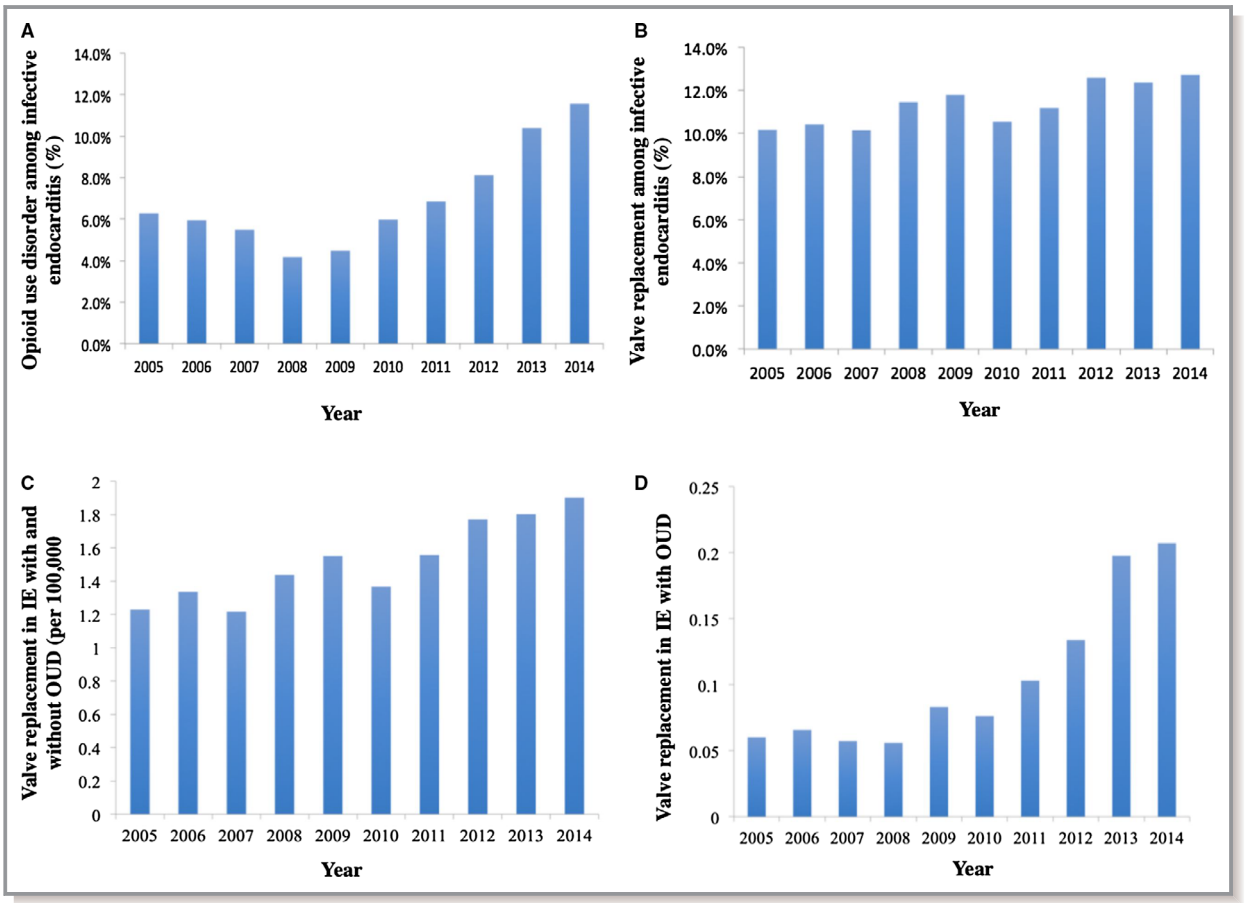

Figure 2. Percentages of opioid use disorder (OUD) and valve operations among patients with infective endocarditis (IE). Figure depicts temporal trends in (**A**) the percentages of OUD among all patients with IE, (**B**) percentage of valve operations among all patients with IE hospitalizations, (**C**) incidence of valve operations in all patients with IE, and (**D**) incidence of valve operations in patients who had IE with OUD, all showing increasing trends.

coronary artery bypass grafting, valve operation, peripheral vascular disease, and congestive heart failure, were more common in patients without OUD (all $P<0.0001$). Patients with OUD presented more commonly with liver disease (46.0% versus 10.8%, $P<0.0001$) and immunosuppressed status (4.3% versus 2.1%, $P<0.0001$), the majority of which was related to HIV in the IE with OUD cohort. Staphylococcus was the most common organism in both the opioid and nonopioid cohorts (55% and 35%, respectively). The percentage of patients with IE undergoing valve operations among those who had IE with and without OUD was similar between the 2 cohorts: 11.4% in IE without OUD and 11.1% in IE with OUD ($P=0.47$). The percentage of patients with IE undergoing valve operations increased in both the IE with OUD and the IE without OUD cohorts over time. The percentage of valve operations among patients who had IE with OUD increased from 7.9% in 2005 to 12.0% in 2014 ($P<0.0001$ for trend), and the percentage of valve operations among patients who had IE without OUD increased from 10.3% in 2005 to 12.8% in 2014 ($P<0.0001$ for trend).

Table 2 summarizes operative characteristics of those associated with valve operations. Mitral valve replacement and repair were more commonly performed in patients who had IE without OUD. Tricuspid valve operations were more commonly performed in patients who had IE with OUD (35.0% versus 10.4%, $P<0.0001$). Concomitant coronary artery bypass grafting and aortic operations were more commonly performed in patients who had IE without OUD. Unadjusted operative mortality was significantly lower in patients who had IE with OUD (4.3% versus 9.4%, $P<0.0001$).

Discussions

The most salient findings of this study are the following: (1) there was a significant temporal increase in IE and OUD, with increasing proportion of OUD among patients with IE; (2) patients with OUD had a distinct phenotype with a tendency to have fewer cardiovascular and pulmonary comorbidities while presenting more commonly with immunosuppressed state and liver disease; (3) operative characteristics of valve operation in patients with IE and OUD were distinct, with more common tricuspid valve operations and lower unadjusted mortality rate; and (4) per-population incidences of patients undergoing valve operations increased over time in both patients who had IE with and without OUD, and this increase was steeper in patients with OUD.

This study demonstrated that population-adjusted hospital admissions with the diagnosis of IE increased between 2005 and 2014. This is in line with the findings of a previous analysis using the NIS from 2000 through 2011,[3] although this prior study did not report on IE related to OUD. Prior analysis of the Medicare claims database reported that between 1999 and 2010, population-adjusted hospitalization rate for endocarditis declined over the decade.[10] The seeming discrepancy may be the result of the fact that the majority of Medicare beneficiaries are 65 years and older, which may not have captured the rising population of younger patients with endocarditis associated with OUD. Indeed, our analysis indicates that the proportion of OUD among hospitalizations related to IE has increased over the decade, while IE without OUD decreased in proportion, which, to our knowledge, has

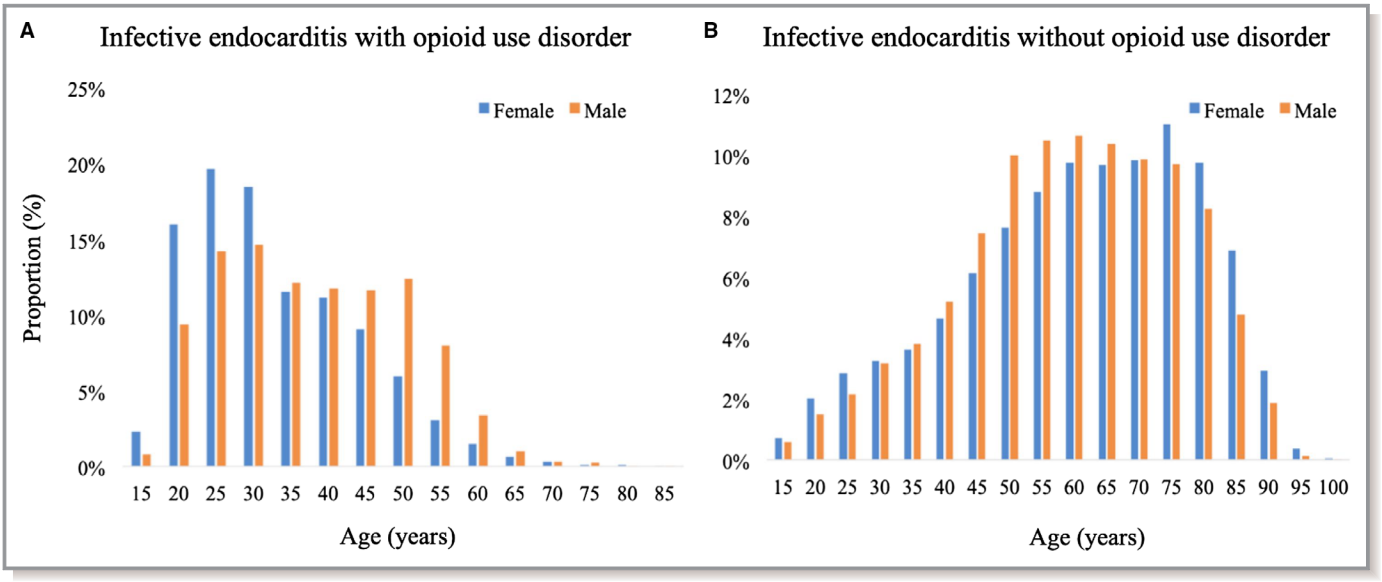

Figure 3. Incidence of infective endocarditis (IE) with and without opioid use disorder (OUD). Histograms depict proportional sex-stratified incidence of (**A**) patients who had IE with OUD and (**B**) patients who had IE without OUD, showing different age and sex interactions on the incidence between ID with and without OUD.

Table 1. Patient Characteristics of IE With and Without History of OUD

Variables	Nonopioid IE (n=380 834)		Opioid IE (n=29 156)		*P* Value
	No. or Mean	% or SE	No. or Mean	% or SE	
Age, y	60.91	0.16	37.57	0.21	<0.0001
Women	153 228	40.2%	13 489	46.3%	
Race					
White	231 370	70.1%	18 720	71.5%	<0.0001
Black	53 579	16.2%	3729	14.2%	
Hispanic	26 464	8.0%	2785	10.6%	
Other	18 486	5.6%	962	3.7%	
Comorbidity					
MI	46 128	12.1%	1520	5.2%	<0.0001
DM	106 029	27.8%	2334	8.0%	<0.0001
PCI	11 496	3.0%	116	0.4%	<0.0001
Previous CABG	25 228	6.6%	179	0.6%	<0.0001
Previous valve operation	24 815	6.5%	1291	4.4%	<0.0001
PVD	23 517	6.2%	344	1.2%	<0.0001
CHF	135 803	35.7%	4232	14.5%	<0.0001
COPD	54 182	14.2%	1843	6.3%	<0.0001
CKD (no dialysis)	100 605	26.4%	2199	7.5%	<0.0001
CKD (dialysis)	24 087	6.3%	466	1.6%	<0.0001
Liver disease	41 220	10.8%	13 412	46.0%	<0.0001
Morbid obesity	13 025	3.4%	309	1.1%	<0.0001
Immunosuppressed	7887	2.1%	1240	4.3%	<0.0001
HIV*	5160	65.2%	1205	97.2%	<0.0001
Organisms					
Streptococcus	94 435	24.8%	3694	12.7%	<0.0001
Staphylococcus	132 461	34.8%	16 114	55.3%	
Gram negative	27 123	7.1%	2064	7.1%	
Fungal	4611	1.2%	441	1.5%	
Other/unknown	122 203	32.1%	6844	23.5%	
Valve operation	43 577	11.4%	3234	11.1%	0.47
In-hospital mortality	33 894	8.9%	87	0.3%	<0.0001

CABG indicates coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IE, infective endocarditis; MI, myocardial infarction; OUD, opioid use disorder; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SE, standard error.
*HIV percentage is among immunosuppressed patients.

not been previously demonstrated. This study did not evaluate the causal relationship between OUD and IE, and the temporal relationship warrants interrogation of causality.

Our study also identified the shifting demographic in hospitalizations for IE, with the rise of patients with OUD. The opioid epidemic has preferentially affected a younger population,[5,11] which is reflected in our finding of more younger patients being hospitalized for IE related to OUD compared with those for IE without OUD. These shifting demographics also imply that hospitals and clinicians treating patients with IE must develop and be familiar with multidisciplinary management of addiction disorder in order to optimize outcomes for this patient population.[12] Additionally, the emergence of an OUD-related IE cohort of predominantly younger patients with a distinct comorbidity profile likely warrants recalibration of conventional risk assessment for surgically managed IE.[13] Of note, recent population-based studies in Europe reported the opposite trend, in which the incidence of IE increased in the older population and those related to intravenous drug use decreased.[14,15] Such

Table 2. Operative Characteristics of Patients With IE Undergoing Valve Operations

Variables	Nonopioid IE (n=43 577)		Opioid IE (n=3234)		*P* Value
	No. or Mean	% or SE	No. or Mean	% or SE	
AVR	25 151	57.7%	1492	46.1%	<0.0001
MV replacement	17 631	40.5%	967	29.9%	<0.0001
MV repair	5214	12.0%	269	8.3%	0.005
TVR	4522	10.4%	1133	35.0%	<0.0001
PVR	579	1.3%	40.2	1.2%	0.79
Valves, No.	1.22	0.01	1.21	0.02	
Concomitant CABG	6931	15.9%	129	4.0%	<0.0001
Concomitant aortic operation	2494	5.7%	124	3.8%	0.038
In-hospital mortality	4111	9.4%	139	4.3%	<0.0001

AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; IE, infective endocarditis; MV, mitral valve; PVR, pulmonic valve replacement; SE, standard error; TVR, tricuspid valve replacement or repair.

differences highlight the importance of interpreting epidemiological data within geographic contexts.

Although patients with IE related to OUD were younger and had fewer cardiovascular comorbidities compared with patients who had IE without OUD, the unadjusted proportions undergoing operative management were similar between the 2 groups. Comparing temporal trends of the annual incidences of valve replacement in patients with and without OUD revealed that the increase in incidence over time was sharper in those with OUD. A possible explanation may be that operative indications for right-sided endocarditis is much less rigorously defined compared with those of left-sided endocarditis,[16] and that the threshold to operate on this population may have lowered over the course of years, leading to more operations. Traditionally, those with intravenous drug use present more commonly with right-sided endocarditis, and our analysis also confirmed this finding (Table 2).

Careful and thorough decision-making should take place in patients with IE and OUD because of the high likelihood of recurrent postoperative drug use, which may render the operation futile in the absence of multidisciplinary addiction treatment.[17] Indeed, analyses of surgical registries have demonstrated that patients with a history of substance use undergoing cardiac operation for IE are at higher risk of long-term valve-related complications,[6] and that the leading cause of late death may be caused by recidivism among this population.[12] The decision to offer operations in this population is complex, as it is not solely based on the probability of short-term survival, but is based on comprehensive assessment of social situations, likelihood of abstinence, and providers' practice beliefs. Additionally, a large multicenter registry of patients undergoing valve operations for IE with a history of substance use showed that repeat valve operation significantly increases the risk of short-term mortality.[18] The current rise of this new population warrants better understanding of how to best address this disease. Various interventions, including the use of long-acting opioid analogue[19] and hospitalization,[20] have been shown to facilitate abstinence. A multidisciplinary approach is necessary, as the disease is strongly social in nature, and either medical or surgical therapy alone is likely not adequate.

Limitations

The stratified sampled design of NIS poses limitations with regard to the precision of estimates. Additionally, diagnosis coding based on *ICD* codes alone limits the assessment of granular data, including the microbiologic pathogenesis of IE, which was coded to be "unknown" or "other" in ≈30% of the cohort. Similarly, the location of valves involved could not be identified for the medically managed cohort, as the only codes available to identify this were procedure codes indicating which valves were operated on. The NIS discharge records do not allow for delineation of the acuity of diagnoses directly, and, hence, IE assessed in this study includes endocarditis both in active and treated phases. This inclusion of a treated IE cohort may have yielded the operative mortality rate that was lower than those previously reported. Finally, although a temporal relationship between the incidence of OUD and OUD with IE was observed, causal inference was not evaluated in this study and may warrant further interrogation.

Conclusions

Between 2005 and 2014, hospitalizations associated with OUD and IE increased. Patients with IE associated with OUD had a distinct phenotype with a tendency to be younger, infrequently having cardiovascular and renal comorbidity, and more frequently having immunosuppressed status and liver diseases. This may explain the lower operative mortality from valve operation in patients with OUD. Recognition of the rise in this distinct patient population is important in facilitating management tailored to the needs specific to these patients with OUD.

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Disclosures

None.

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Supplemental Material

Table S1. ICD-9 codes used to define diagnosis, comorbidity, and operations.

Variables	Class	ICD codes (diagnosis code, unless specified)
Age	Continuous	NA
Race	White, black, Hispanic, others	NA
Female	Male, female	NA
Admission status	Elective, non-elective	NA
History of PCI	yes/no	V458.2
Peripheral vascular disease	yes/no	440, 443, 447.1
Diabetes mellitus	yes/no	249, 250
Myocardial infarction	yes/no	410, 411, 412, 429.7
Previous CABG	yes/no	V458.1
Previous valve replacement	yes/no	V433
CHF	yes/no	428, 398.91
Infective endocarditis	yes/no	421, 424.9, 112.81, 074.22
Chronic lung disease	yes/no	491, 492, 494, 496
CKD	Without dialysis	403, 404, 582, 585, 588
	With dialysis	5856, V56
Liver disease	yes/no	070, 571, 572, 573
Immunosuppressed	yes/no	V42.0, V42.1, V42.6, V42.7, 042
Morbid obesity	yes/no	278.01
Operation		
TVR	yes/no	Procedure code: 35.14 (repair), 35.27 (replace), 35.28 (replace)
Aortic operation	yes/no	Procedure code: 38.34, 38.35, 38.44, 38.45
CABG	yes/no	Procedure code: 36.10 - 36.17, 36.19
AVR	yes/no	Procedure code: 35.21, 35.22
MVR	yes/no	Procedure code: 35.23 and 35.24
MV repair	yes/no	Procedure code: 35.14, 35.27, 35.28