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Clinical Outcomes of Infective Endocarditis in Injection Drug Users

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ABSTRACT

BACKGROUND Rising rates of hospitalization for infective endocarditis (IE) have been increasingly tied to rising injection drug use (IDU) associated with the opioid epidemic.

OBJECTIVES This study analyzed recent trends in IDU-IE hospitalization and characterized outcomes and readmissions for IDU-IE patients.

METHODS The authors evaluated the National Readmissions Database (NRD) for IE cases between January 2010 and September 2015. Patients were stratified by IDU status and surgical versus medical management. Primary outcome was 30-day readmission and cause, with secondary outcomes including mortality, length of stay (LOS), adjusted costs, and 180-day readmission. The Kruskal-Wallis and chi-square tests were used to analyze baseline differences by IDU status. Multivariable regressions were used to analyze mortality, readmissions, LOS, and adjusted costs.

RESULTS The survey-weighted sample contained 96,344 (77.8%) non-IDU-IE and 27,432 (22.2%) IDU-IE cases. IDU-IE increased from 15.3% to 29.1% of IE cases between 2010 and 2015 ($p < 0.001$). At index hospitalization, IDU-IE was associated with reduced mortality (6.8% vs. 9.6%; $p < 0.001$) but not 30-day readmission (23.8% vs. 22.9%; $p = 0.077$) relative to non-IDU-IE. Medically managed IDU-IE patients had higher LOS ($\beta = 1.36$ days; 95% confidence interval [CI]: 0.71 to 2.01), reduced costs ($\beta = -\$4,427$; 95% CI: −$7,093 to −$1,761), and increased readmission for endocarditis (18.1% vs. 5.6%; $p < 0.001$), septicemia (14.0% vs. 7.3%; $p < 0.001$), and drug abuse (4.3% vs. 0.7%; $p < 0.001$) compared with medically managed non-IDU-IE. Surgically managed IDU-IE patients had increased LOS ($\beta = 4.26$ days; 95% CI: 2.73 to 5.80) and readmission for septicemia (15.6% vs. 5.2%; $p < 0.001$) and drug abuse (7.3% vs. 0.9%; $p < 0.001$) compared with non−IDU-IE.

CONCLUSIONS The incidence of IDU-IE continues to rise nationally. Given the increased readmission for endocarditis, septicemia, and drug abuse, IDU-IE presents a serious challenge to current management of IE.
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Infective endocarditis (IE) carries a high morbidity and mortality and is increasing in incidence across the United States (1,2). Although congenital heart defects, rheumatic heart disease, and prosthetic valves can predispose patients to IE, injection drug use (IDU) remains a major cause, increasing the risk of IE 100-fold relative to the general population (2,3). IDU increases risk for IE through a number of mechanisms, including direct injury from injected particulate matter, poor injection hygiene, use of contaminated equipment, and drug-mediated physiological changes that yield vasospasm and cardiac injury (2,4-6). Given the particulate matter exposure, IDU-IE is more commonly right-sided, whereas non-IDU-IE is more commonly left-sided given increased oxygenation and turbulence-mediated endothelial injury (4,6-8).

The incidence of IE tracks closely with rates of IDU, whereby rises in IDU result in increasing incidence of IE (2,4,9,10). Despite this relationship, few have

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ABBREVIATIONS AND ACRONYMS

AMA = against medical advice

IDU = injection drug use

IE = infective endocarditis

LOS = length of stay

NRD = National Readmissions Database

examined outcomes in the IDU-IE population beyond acute hospitalization. Persistent endocarditis, subsequent valvular operations, and increased length of stay (LOS) may be more common in patients who inject drugs, but the rates and primary causes of readmissions following hospitalization for IDU-IE remain ill-defined (11,12). Whether outcomes differ by medical or surgical management of IDU-IE patients also remains unclear (13,14). Given the significant risks for persistent drug use and nonadherence in the IDU-IE population, elucidating the causes of readmission may underscore the magnitude of preventable readmissions and identify opportunities to improve care for IDU-IE patients while optimizing resource utilization.

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Therefore, the present study analyzed recent trends in mortality, resource utilization, and rehospitalization for IDU-IE in a national database based on medical or surgical treatment strategies. By analyzing mortality, LOS, adjusted costs, discharge location, and readmissions for the IDU-IE population, we aim to highlight possible approaches to improved management of this public health crisis.

METHODS

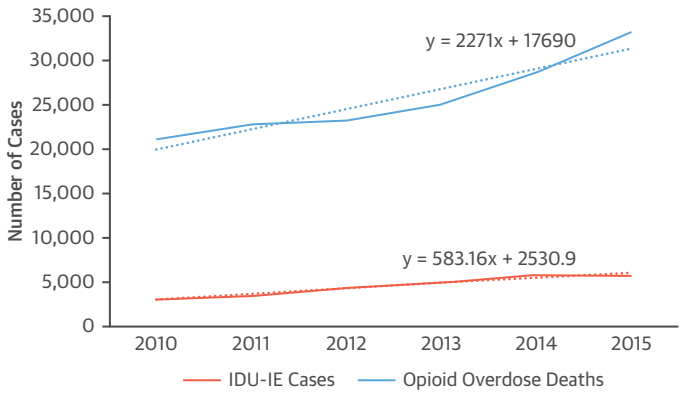
This was a retrospective study of all patients (age >15 years) presenting with IE in the National Readmissions Database (NRD) between January 2010 and September 2015. The NRD, maintained by the Healthcare Cost and Utilization Project, is a federal, state, and industry partnership that contains 17 million discharges encompassing 56% of U.S. hospitalizations. The NRD utilizes a 2-stage cluster design to post-stratify by hospital (census region, urban/rural location, teaching status, and bed size) and patient (sex and age) characteristics. The resulting individual discharge weights were utilized to generate national estimates for approximately 36 million hospital discharges.

We utilized previously published methods by Cooper et al. (9) and Wurcel et al. (4) to identify all patients with IDU-related IE. Patients classified with IDU-related IE met all 3 criteria: 1) a diagnosis of bacterial endocarditis or endocarditis not otherwise specified (encompassing International Classification of Diseases-Ninth Revision [ICD-9] codes 421.0, 421.1, 421.9, 424.90, 424.91, and 424.99); 2) a diagnosis or procedure code linked to an injected illicit drug, including cocaine, heroin, or methamphetamine; and 3) no documented congenital or rheumatic heart disease that would predispose to IE. Only patients age 15 to 64 years were included, as this range matched the age group divisions of national drug surveys and captures the majority of injection drug users while excluding seniors especially susceptible to IE (15). We included patients with cardiac procedures (including prosthetic valves, heart catheterization, and intracardiac balloons) because these conditions can both put patients at risk for endocarditis and result from endocarditis (4). Patients were classified as having non-IDU-related IE using the same ICD-9 diagnostic codes, with exclusions for documented congenital or rheumatic heart disease as well as any drug-related diagnoses or procedures.

Primary stratification was based on documentation of IDU, while secondary categories were surgical versus nonsurgical management. The primary outcome of interest was readmission within 30 days of index discharge and the corresponding reason for rehospitalization. Secondary outcomes included mortality, LOS, total adjusted costs, and discharge location at index hospitalization, as well as readmission rates and causes within 30 to 180 days (defined as 180-day readmission). Surgical management was defined as an intracardiac procedure, encompassing a valvuloplasty or valve replacement, on the tricuspid, aortic, mitral, or pulmonic valves.

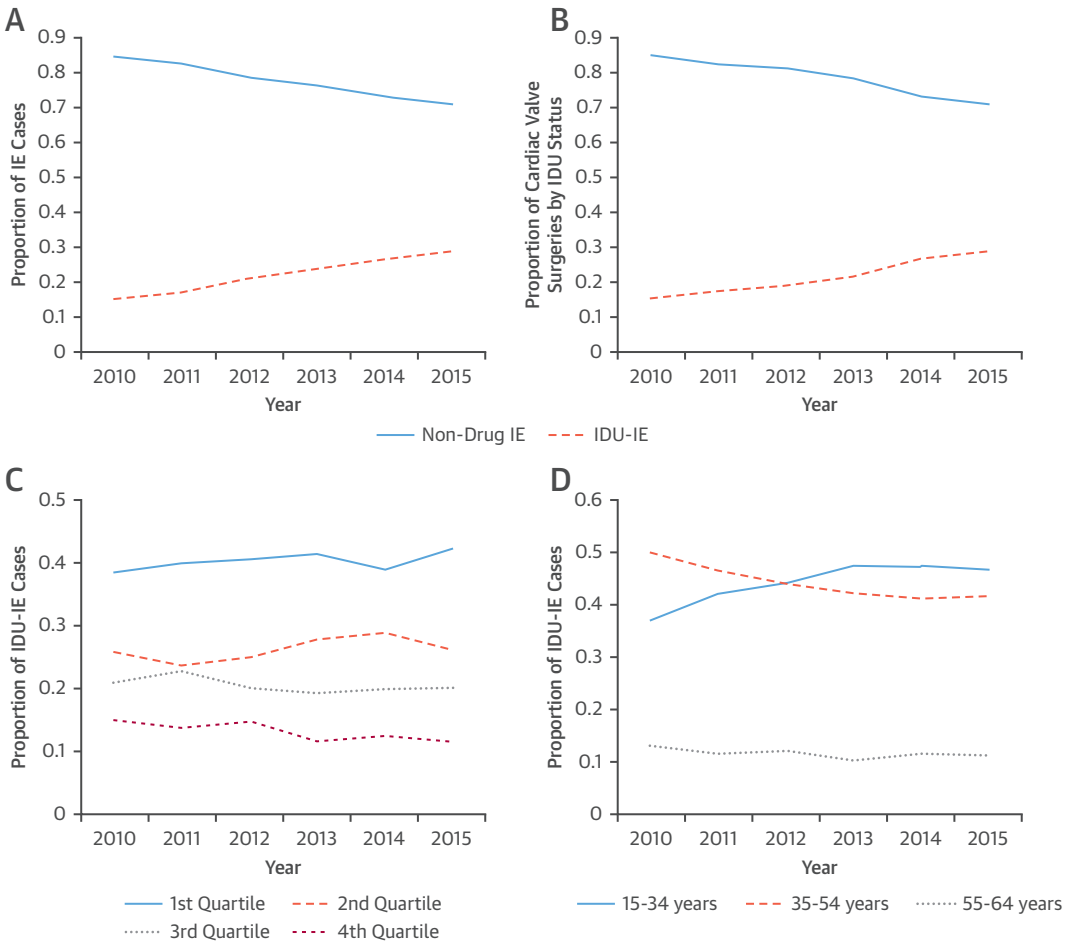
Patients were grouped by age into 3 categories in accordance with previous studies to allow for trend comparison: 15 to 34, 35 to 54, and 55 to 64 years (4,16). Insurance status was categorized into

FIGURE 1 Number of IDU-IE Cases Compared With Number of Opioid Overdose Deaths, 2010 to 2015



While the rate of opioid overdose deaths outpaced infective endocarditis with injection drug use (IDU-IE) cases, both experienced a positive upward trend since 2010 ($p < 0.001$).

FIGURE 2 Proportion of IE Cases by Demographic



(A) Proportion of infective endocarditis (IE) cases that are injection drug use (IDU)–related. **(B)** Proportion of cardiac valve surgeries for IDU-IE. **(C)** Proportion of IDU-IE cases by income quartile. **(D)** Proportion of IDU-IE cases by age group. For all figures, analysis of trend is significant at $p < 0.001$.

coverage by private insurance, Medicare, Medicaid, and other or unknown payer. The infecting organism was determined using ICD-9 codes for concurrent diagnosis of septicemia. The NRD's income quartile classification, which assigns an income quartile to patients based upon their income relative to the median household income in the patient's zip code, was used to ascertain socioeconomic status (17). Discharge locations were categorized as home with no assistance, home with health care assistance, skilled nursing facilities and intermediate care facilities, short-term inpatient hospitals, and discharge against medical advice (AMA).

Continuous variables were compared using the Kruskal-Wallis test, whereas chi-square analysis was performed to compare categorical variables. The nonparametric test for trend was utilized to evaluate changes in IDU-IE proportions and demographics over years. Multivariable logistic regression models were used to evaluate mortality and readmissions, and linear regressions were used to evaluate LOS and adjusted costs. All outcomes were adjusted for IDU, age categories, sex, insurance, income quartiles, Elixhauser Comorbidity Index, congestive heart failure, hypertension, chronic lung disease, pulmonary hypertension, peripheral vascular disease, coagulopathies, anemia, diabetes mellitus, liver disease, and renal failure. Kaplan-Meier survival analysis was used to display the risk of readmission for endocarditis, septicemia, and drug abuse by IDU-IE status. In all comparisons, $p < 0.05$ was considered statistically

TABLE 1 Demographics and Comorbidities for Non-Drug-Related IE Versus Drug-Related IE

	Non-Drug IE (n = 96,344)	IDU-IE (n = 27,432)	p Value
Age, yrs	50.4 ± 0.1	38.3 ± 0.1	<0.001
Female	39,609 (41.1)	12,421 (45.3)	<0.001
Emergent admission	85,966 (89.2)	26,189 (95.5)	<0.001
Insurance			
Private	33,867 (35.2)	3,450 (12.6)	<0.001
Medicare	29,750 (30.9)	3,336 (12.2)	<0.001
Medicaid	21,045 (21.8)	12,171 (44.4)	<0.001
Other	11,681 (12.1)	8,474 (30.9)	<0.001
Elixhauser comorbidity index	4.53 ± 0.02	4.65 ± 0.02	<0.001
Congestive heart failure	14,950 (15.5)	2,213 (8.1)	<0.001
Systemic hypertension	51,891 (53.9)	7,070 (25.8)	<0.001
Peripheral vascular disease	11,510 (11.9)	2,773 (10.1)	<0.001
Pulmonary hypertension	9,507 (9.9)	6,355 (23.2)	<0.001
COPD	17,760 (18.4)	4,554 (16.6)	<0.001
Diabetes mellitus	19,339 (20.1)	2,123 (7.7)	<0.001
Coagulopathy	18,438 (19.1)	6,115 (22.3)	<0.001
Anemia	32,746 (34.0)	10,422 (38.0)	<0.001
Liver disease	8,330 (8.6)	5,145 (18.8)	<0.001
Renal failure	27,412 (28.5)	2,286 (8.3)	<0.001
Neurological disorders	8,143 (8.5)	2,327 (8.5)	0.926
Alcohol abuse	5,913 (6.1)	3,682 (13.4)	<0.001
HIV/AIDS	515 (0.5)	150 (0.5)	0.892
Psychoses	5,174 (5.4)	3,706 (13.5)	<0.001

Values are mean ± SD or n (%).

AIDS = acquired immunodeficiency syndrome; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; IDU = injection drug use; IE = infective endocarditis.

TABLE 2 Univariate Analysis of Patient Outcomes for Non-Drug-Related IE Versus Drug-Related IE

	Non-Drug IE (n = 96,344)	IDU-IE (n = 27,432)	p Value
Index hospitalization			
Valve surgery	11,116 (11.5)	3,077 (11.2)	0.420
Tricuspid valve	860 (0.9)	771 (2.8)	<0.001
Mitral valve	5,766 (6.0)	1,349 (4.9)	<0.001
Aortic valve	6,652 (6.9)	1,490 (5.4)	<0.001
Pulmonic valve	114 (0.1)	41 (0.2)	0.424
Number of valves			0.356
1	8,980 (80.8)	2,528 (82.1)	
2	1,995 (17.9)	524 (17.0)	
3	141 (1.3)	26 (0.8)	
Infecting organism			
Staphylococcal			
MSSA	9,540 (9.9)	4,399 (16.0)	<0.001
MRSA	7,298 (7.6)	3,799 (13.8)	<0.001
Other staphylococcal	1,570 (1.6)	233 (0.8)	<0.001
Streptococcal	6,739 (7.0)	1,317 (4.8)	<0.001
Other	14,231 (14.8)	4,635 (16.9)	<0.001
Unspecified	56,966 (59.1)	13,049 (47.7)	<0.001
Outcomes			
Mortality	9,270 (9.6)	1,875 (6.8)	<0.001
LOS, days	14.4 ± 0.1	18.5 ± 0.2	<0.001
Adjusted cost (USD)	$39,296 ± $622	$39,107 ± $575	0.810
Discharge location			
Home	37,639 (39.1)	11,433 (41.7)	<0.001
Short-term inpatient	4,360 (4.5)	1,524 (5.6)	<0.001
SNF/ICF	18,341 (19.0)	5,434 (19.8)	0.147
Home with HHC	24,863 (25.8)	2,927 (10.7)	<0.001
AMA	1,720 (1.8)	4,178 (4.8)	<0.001
Died	9,270 (9.6)	1,875 (6.8)	<0.001
Other	152 (0.2)	61 (0.2)	0.141
Readmission within 30 days	20,576 (22.9)	6,091 (23.8)	0.077
Readmission within 30–180 days	11,803 (22.8)	3,086 (22.3)	0.487
30-day readmission			
Mortality	1,633 (7.9)	204 (3.4)	<0.001
LOS, days	9.0 ± 0.1	10.7 ± 0.3	<0.001
Adjusted cost (USD)	$23,002 ± $464	$20,382 ± $620	<0.001
Surgical management	$20,357 ± $1,262	$17,432 ± $1,565	0.159
Medical management	$23,311 ± $490	$20,690 ± $664	0.001
180-day readmission			
Mortality	452 (3.8)	124 (4.0)	0.723
LOS, days	7.6 ± 0.1	9.7 ± 0.4	<0.001
Adjusted cost (USD)	$20,876 ± $508	$20,238 ± $1,127	0.599
Surgical management	$19,293 ± $1,950	$19,273 ± $2,552	0.995
Medical management	$21,045 ± $522	$20,389 ± $1,220	0.616

Values are n (%) or mean ± SD.

AMA = discharge against medical advice; HHC = home health care; ICF = intermediate care facility; LOS = length of stay; MRSA = Methicillin-Resistant Staphylococcus Aureus; MSSA = Methicillin-Susceptible Staphylococcus Aureus; SNF = skilled nursing facility; USD = United States dollar; other abbreviations as in Table 1.

significant. All statistical analyses were performed using STATA 14.2 (StataCorp LP, College Station, Texas). The study was deemed exempt by the Institutional Review Board at the University of California, Los Angeles.

RESULTS

IE TRENDS AND DEMOGRAPHICS. In the survey-weighted sample of IE cases, there were 96,344 (77.8%) non-IDU-IE and 27,432 (22.2%) IDU-IE cases between 2010 and 2015. Figure 1 displays the number of IDU-IE cases relative to the number of opioid overdose deaths over time, as reported by the Centers for Disease Control and Prevention (15). While the rate of opioid overdose deaths outpaced IDU-IE cases, both have experienced a positive upward trend since 2010 ($p < 0.001$). Figures 2A to 2D illustrate demographic trends in IDU-IE between 2010 and 2015. The proportion of all IE cases that were IDU-related increased from 15.3% in 2010 to 29.1% in 2015 ($p < 0.001$). Those in the 15- to 34-year age group faced the greatest risk, as they accounted for 37.1% of IDU-IE cases in 2010 but 46.7% of all IDU-IE cases in 2015 ($p < 0.001$). Of all IDU-IE patients, 42.3% fell within the lowest income quartile in 2015 ($p < 0.001$).

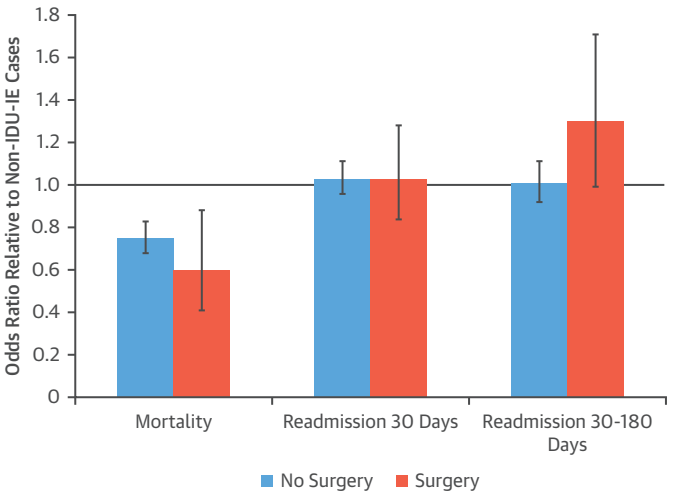
IDU-IE VERSUS NON-IDU-IE POPULATIONS. As presented in Table 1, patients with IDU-IE were significantly younger (38.3 years vs. 50.4 years; $p < 0.001$), more likely to be female (45.3% vs. 41.1%; $p < 0.001$), and more likely to be insured through Medicaid (44.4% vs. 21.8%; $p < 0.001$) relative to patients with non-IDU-IE. Patients with IDU-IE had lower rates of congestive heart failure (8.1% vs. 15.5%; $p < 0.001$), systemic hypertension (25.8% vs. 53.9%; $p < 0.001$), and renal failure (8.3% vs. 28.5%; $p < 0.001$) relative to patients with non-IDU-IE. However, patients using injection drugs had increased rates of pulmonary hypertension (23.2% vs. 9.9%; $p < 0.001$), coagulopathies (22.3% vs. 19.1%; $p < 0.001$), and liver disease (18.8% vs. 8.6%; $p < 0.001$).

At index hospitalization, patients with IDU-IE received valve surgery at equivalent rates to patients with non-IDU-IE (11.5% vs. 11.2%; $p = 0.420$), as presented in Table 2. However, patients with IDU-IE were more likely to receive a tricuspid valve procedure (2.8% vs. 0.9%; $p < 0.001$) and less likely to receive a mitral (4.9% vs. 6.0%; $p < 0.001$) or aortic (5.4% vs. 6.9%; $p < 0.001$) valve procedure. Of patients with a documented infecting organism, those with IDU-IE were more likely to be infected with MSSA (16.0% vs. 9.9%; $p < 0.001$) and MRSA (13.8% vs. 7.6%; $p < 0.001$) than non-IDU-IE patients. In univariate analysis, IDU-IE was associated with reduced mortality (6.8% vs. 9.6%; $p < 0.001$) but no difference in readmission within 30 days (23.8% vs. 22.9%; $p = 0.077$) or 180 days (22.3% vs. 22.8%; $p = 0.487$). Patients with IDU-IE were less likely to be discharged to home with health care (10.7% vs. 25.8%; $p < 0.001$) but more likely to leave AMA (4.8% vs. 1.8%; $p < 0.001$).

After adjustment, both IDU-IE patients undergoing valve surgery (odds ratio [OR]: 0.60; 95% confidence interval [CI]: 0.41 to 0.88; $p = 0.009$) and those medically managed (OR: 0.75; 95% CI: 0.68 to 0.83; $p < 0.001$) experienced less mortality at index hospitalization compared with their non-IDU-IE counterparts (Figure 3). Furthermore, patients with IDU-IE who were surgically (OR: 1.03; 95% CI: 0.84 to 1.28; $p = 0.757$) and medically (OR: 1.03; 95% CI: 0.96 to 1.11; $p = 0.357$) managed were not at increased risk of 30- or 180-day readmission relative to their non-IDU-IE counterparts after adjustment (Figure 3).

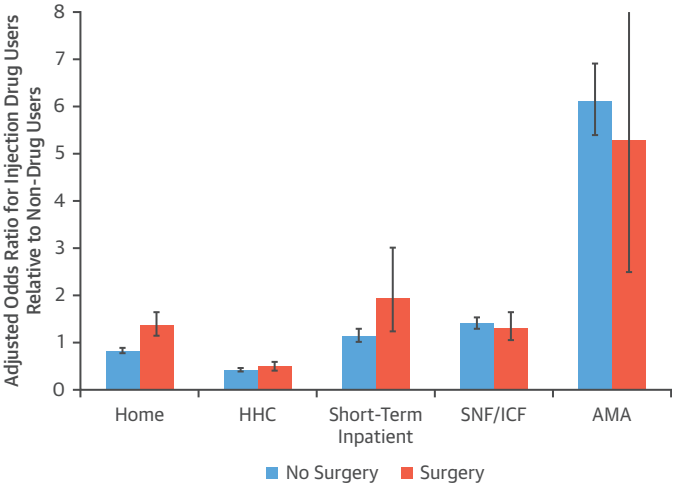
As shown in Figure 4, both categories of IDU-IE patients had higher adjusted rates of discharge AMA and lower discharge home with health care assistance. The adjusted coefficients in Table 3 demonstrate that medically managed IDU-IE patients had higher LOS ($\beta = 1.36$ days; 95% CI: 0.71 to 2.01;

FIGURE 3 Adjusted Odds Ratios for IDU-IE Relative to Non-IDU-IE Outcomes, by Surgical Versus Nonsurgical Management



Adjusted odds ratios accounted for injected drug use, age, sex, insurance, income, Elixhauser comorbidity score, congestive heart failure, hypertension, chronic lung disease, peripheral vascular disease, coagulopathies, anemia, pulmonary circulatory disorders, diabetes, liver disease, and renal failure. There was no significant increase in the risk of mortality, readmission at 30 days, or readmission at 30 to 180 days for IDU-IE cases relative to non-IDU-IE cases, regardless of surgical management. Abbreviations as in Figure 2.

FIGURE 4 Adjusted Odds Ratios for Discharge Location for IDU-IE Relative to Non-IDU-IE, By Surgical Versus Nonsurgical Management



Adjusted odds ratios accounted for injected drug use, age, sex, insurance, income, Elixhauser comorbidity score, congestive heart failure, hypertension, chronic lung disease, peripheral vascular disease, coagulopathies, anemia, pulmonary circulatory disorders, diabetes, liver disease, and renal failure. Patients with IDU-IE were significantly less like to be discharged home with or without health care, and significantly more likely to be discharged to a SNF/ICF, short-term inpatient center, or against medical advice. AMA = discharge against medical advice; HHC = home health care; ICF = intermediate care facility; SNF = skilled nursing facility; other abbreviations as in Figure 2.

TABLE 3 Adjusted* Predictive Value of IDU-IE on Length of Stay by Surgical Versus Nonsurgical Management

IDU-IE Treatment	Measure	Coefficient [95% CI]	p Value
No surgery	LOS, days	1.36 [0.71 to 2.01]	<0.001
	Adjusted cost (USD)	−$4,427 [−$7,093 to $1,761]	0.001
Surgery	LOS, days	4.26 [2.73 to 5.90]	<0.001
	Adjusted cost (USD)	−$824 [−$6,325 to $4,676]	0.769

*Adjusted for age, sex, insurance status, Elixhauser comorbidity index, income quartile, congestive heart failure, hypertension, peripheral vascular disorder, pulmonary circulatory disorders, chronic lung disease, diabetes mellitus, coagulopathy, anemia, liver disease, and renal failure.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

$p < 0.001$) but reduced costs ($\beta = -\$4,427$; 95% CI: −$7,093 to −$1,761; $p = 0.001$) at index hospitalization, whereas surgically managed IDU-IE patients had increased LOS ($\beta = 4.26$ days; 95% CI: 2.73 to 5.80; $p < 0.001$) but not increased costs ($\beta = -\$824$; 95% CI: −$6,325 to $4,676; $p = 0.769$) relative to non-IDU-IE patients.

SURGICAL VERSUS MEDICAL MANAGEMENT IN IDU-IE. The univariate analysis of the differences between surgically and medically managed IDU-IE patients is presented in Table 4. IDU-IE patients who received cardiac valve surgery were of similar age (38.5 years vs. 38.3 years; $p = 0.615$) but were less likely to be female (35.1% vs. 46.6%; $p < 0.001$). Medicaid was the largest insurer among IDU-IE patients, but there was no difference in Medicaid coverage between surgical and medical IDU-IE patients (45.9% vs. 44.2%; $p = 0.264$). IDU-IE patients receiving surgery also tended to have more comorbidities (Elixhauser score) (5.6 vs. 4.5; $p < 0.001$), including higher rates of congestive heart failure (15.0% vs. 7.2%; $p < 0.001$), peripheral vascular disease (26.6% vs. 8.0%; $p < 0.001$), and coagulopathies (35.0% vs. 20.7%; $p < 0.001$), yet they experienced less mortality at index hospitalization (4.7% vs. 7.1%; $p = 0.007$). Surgically managed patients had higher adjusted costs ($99,298 vs. $31,529; $p < 0.001$) and increased length of stay (32.8 days vs. 16.7 days; $p < 0.001$), and they were less likely to be discharged AMA (4.2% vs. 16.6%; $p < 0.001$) relative to those medically managed.

CAUSES OF READMISSION. At readmission within 30 days, endocarditis, septicemia, circulatory disorders necessitating cardiac catheterization, cardiac valve surgery, and drug abuse were the top 5 reasons for readmission among medically managed IDU-IE patients (Figure 5A). Medically managed IDU-IE patients were more likely to be readmitted for endocarditis (18.1% vs. 5.6%; $p < 0.001$), septicemia (14.0% vs. 7.3%; $p < 0.001$), and drug abuse (4.3% vs. 0.7%; $p < 0.001$) but less likely to receive a subsequent cardiac valve surgery (5.3% vs. 8.1%; $p < 0.001$) relative to medically managed patients with non-IDU-IE. Of surgically managed IDU-IE patients, endocarditis, cardiac catheterization for circulatory disorders, and septicemia represented the top 3 reasons for 30-day readmission (Figure 5B). Relative to

TABLE 4 Demographics, Comorbidities, and Outcomes for IDU-IE Patients Receiving Medical Versus Surgical Management at Index Hospitalization

	IDU-IE No Surgery (n = 24,314)	IDU-IE Surgery (n = 3,073)	p Value
Demographics and Comorbidities			
Age, yrs	38.3 ± 0.1	38.5 ± 0.4	0.615
Female	11,339 (46.6)	1,081 (35.1)	<0.001
Emergent admission	23,297 (95.7)	2,892 (94.0)	0.016
Insurance			0.031
Private	3,012 (12.4)	438 (14.2)	0.064
Medicare	3,034 (12.5)	302 (9.8)	0.019
Medicaid	10,757 (44.2)	1,414 (45.9)	0.264
Other	7,550 (31.0)	924 (30.0)	0.416
Elixhauser comorbidity index	4.54 ± 0.02	5.56 ± 0.06	<0.001
Congestive heart failure	1,750 (7.2)	462 (15.0)	<0.001
Hypertension	6,288 (25.8)	782 (25.4)	0.782
Peripheral vascular disease	1,953 (8.0)	820 (26.6)	<0.001
Pulmonary hypertension	5,783 (23.7)	572 (18.6)	0.002
COPD	4,000 (16.4)	554 (18.0)	0.170
Diabetes mellitus	1,868 (7.7)	255 (8.3)	0.473
Coagulopathy	5,039 (20.7)	1,076 (35.0)	<0.001
Anemia	9,000 (37.0)	1,422 (46.2)	<0.001
Liver disease	4,543 (18.7)	603 (19.6)	0.734
Renal failure	2,008 (8.2)	279 (9.1)	0.410
Alcohol abuse	3,233 (13.3)	448 (14.6)	0.253
HIV/AIDS	139 (0.6)	11 (0.4)	0.348
Outcomes			
Died	1,730 (7.1)	145 (4.7)	0.007
Adjusted cost	$31,529 ± $464	$99,298 ± $2,026	<0.001
LOS	16.7 + 0.2	32.8 + 0.6	<0.001
Readmission within 30 days	5,507 (24.2)	584 (20.4)	0.007
Readmission within 180 days	2,681 (21.8)	405 (25.8)	0.044
Discharge location			
Home	10,219 (42.0)	1,214 (39.5)	0.124
Short-term inpatient	1,411 (5.8)	113 (3.7)	0.006
SNF/ICF	4,575 (18.8)	859 (27.9)	<0.001
Home with HHC	2,315 (9.5)	611 (19.9)	<0.001
AMA	4,048 (16.6)	131 (4.2)	<0.001
Died	1,730 (7.1)	145 (4.7)	0.007
Other	57 (0.2)	4 (0.1)	0.459

Values are mean ± SD or n (%).

Abbreviations as in Tables 1 and 2.

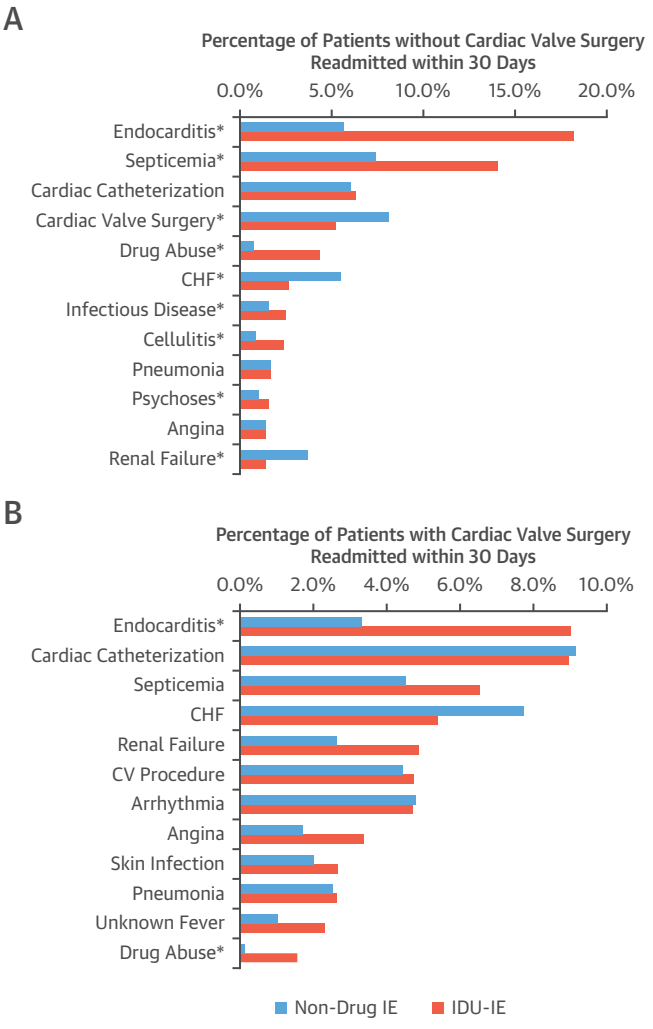
surgically managed patients with non-IDU-IE, surgically managed patients with IDU-IE were readmitted more frequently for endocarditis (9.0% vs. 3.3%; p = 0.002) and drug abuse (1.6% vs. 0.1%; p = 0.002).

Causes for readmission within 30 to 180 days are reported in Figure 6A. Medically managed patients with IDU-IE were more often readmitted for septicemia (12.5% vs. 6.9%; p < 0.001), drug abuse (8.8% vs. 1.2%; p < 0.001), and endocarditis (7.3% vs. 1.4%; p < 0.001). For surgically managed IDU-IE patients, the most common reasons for 180-day readmission included septicemia, circulatory disorders necessitating catheterization, and drug abuse. Septicemia (15.6% vs. 5.2%; p < 0.001) and drug abuse (7.3% vs. 0.9%; p<0.001) were significantly more frequent in IDU-IE patients relative to the non-IDU-IE population (Figure 6B).

Kaplan-Meier survival analysis demonstrated significantly increased readmission for drug abuse in patients with IDU-IE relative to patients with non-IDU-IE (Figure 7) (log rank p < 0.001). After adjustment in a Cox proportional hazards model, IDU-IE remained the strongest predictor of 180-day readmission for drug abuse (hazard ratio [HR]: 4.91; 95% CI: 2.88 to 8.39). Patients with IDU-IE were also significantly more likely to be readmitted for septicemia, a difference that manifests early and remains a significant predictor (HR: 1.83; 95% CI: 1.54 to 2.16; p < 0.001) after adjustment (Figure 8) (log rank p < 0.001). Finally, there is an early and sustained increase in the risk of readmission for endocarditis in patients with IDU-IE relative to those with non-IDU-IE (Figure 9) (log rank p < 0.001), which persists after adjustment (HR: 2.42; 95% CI: 1.99 to 2.93; p < 0.001).

PREVENTABLE READMISSIONS AND COSTS. The estimated number of preventable readmissions and the associated costs are displayed in Table 5. Across all IDU-IE patients readmitted within 180 days, 329 were readmitted for drug abuse and thus represent the conservative estimate of the number of preventable readmissions. Patients with continued drug use may have also presented with readmission for septicemia or persistent/recurrent endocarditis. Therefore, a high estimate for the number of preventable readmissions includes the additional 1,209 IDU-IE patients readmitted for septicemia and 1,261 patients readmitted for IE. Using the average costs listed in Table 2, the estimated additional expenditure on unnecessary readmissions for IDU-IE may lie between $6.7 and $57 million from 2010 to 2015.

FIGURE 5 Reasons for Readmission Within 30 days by IDU Status and Surgical Management

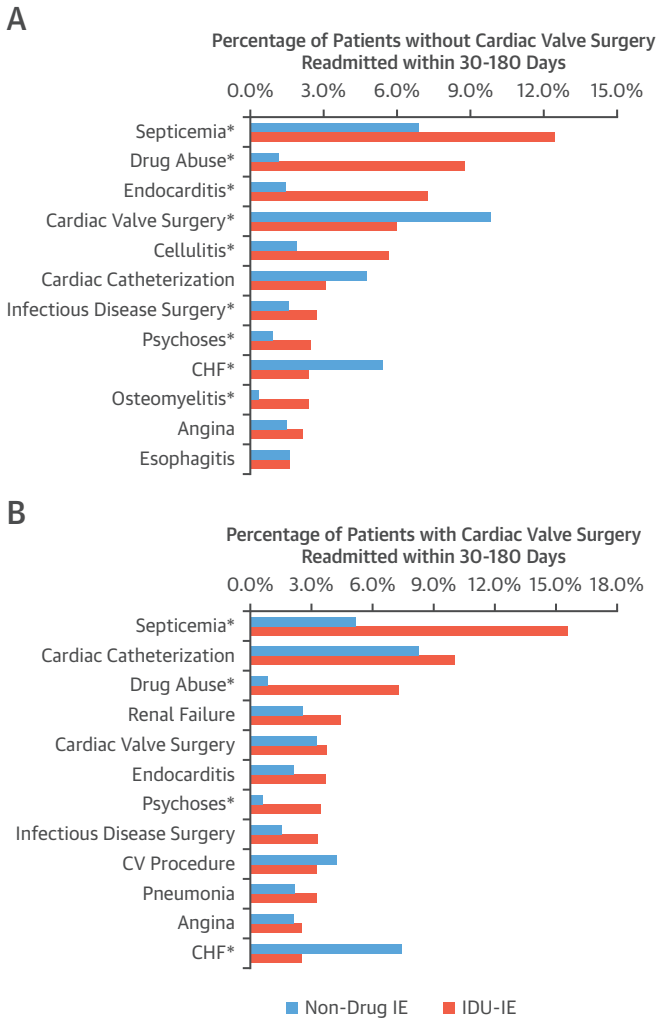


(A) Readmissions for nonsurgical cases of IDU-IE compared with non-drug IE. **(B)** Readmissions for surgical cases of IDU-IE compared with non-drug IE. *Significant difference at p < 0.05. CHF = congestive heart failure; CV = cardiovascular; other abbreviations as in Figure 2.

DISCUSSION

Hospitalizations for IE have increased in parallel with the opioid epidemic and its rising rates of IDU (7,18,19). Although the demographics of IDU-IE patients have been well characterized, the readmissions, mortality, LOS, and costs of IDU-IE patients—with particular attention to those receiving medical versus surgical management—remain unclear. This study of the National Readmissions Database found that the proportion of IDU-IE cases

FIGURE 6 Reasons for Readmission Within 30 to 180 Days by IDU Status and Management



(A) Readmissions for nonsurgical cases of IDU-IE compared with non-drug IE. **(B)** Readmissions for surgical cases of IDU-IE compared with non-drug IE. *Significant difference at $p < 0.05$. Abbreviations as in Figures 2 and 5.

nationwide has continued to rise between 2010 and 2015. When compared to those with non-IDU-IE, patients with IDU-IE have reduced mortality and no increased risk in the overall rate of 30- or 180-day readmissions (**Central Illustration**). However, they are significantly more likely to be readmitted for subsequent episodes of endocarditis, septicemia, and drug abuse, many of which may represent readmissions preventable with more aggressive care for substance abuse at the index hospitalization. The study provides several insights that deserve further discussion.

PERSISTENT IDU-IE TRENDS. Our findings indicate that IDU-IE remains a persistent and growing public health burden, as the proportion of IDU-IE cases recorded in the NRD increased by 90.2% between 2010 and 2015. Our work demonstrates the recent amplification of drug-related morbidity and extends the findings of Wurcel et al. (4) (2016), who showed a 72% increase in IDU-IE nationally between 2000 and 2013. Although past IE hospitalizations were tied to methamphetamine use, recent hospitalizations have been linked to opioids, as nearly 6% of U.S. residents age 15 to 64 years reported opioid abuse in 2015 (18,19). Given the tripling of heroin overdose deaths between 2010 and 2015, our finding corroborates the persistent, dramatic rise in the proportion of IDU-IE cases in tandem with the opioid epidemic (20–22). We report that the 2015 national proportion of IDU-IE was 29.1%, which remains below the 37.8% rate reported by a single institution in North Carolina perhaps due to regional trends of opioid abuse (11,23). However, we confirm that the risk of IDU-IE remains highest in patients age 15 to 34 years, and we find that it continues to grow, indicating that initiatives to reduce IDU have not been efficacious (4,11,13). Of patients with a documented infecting organism, MSSA and MRSA were significantly more common in IDU-IE patients relative to non-IDU-IE patients, which aligns with previous epidemiological findings (24).

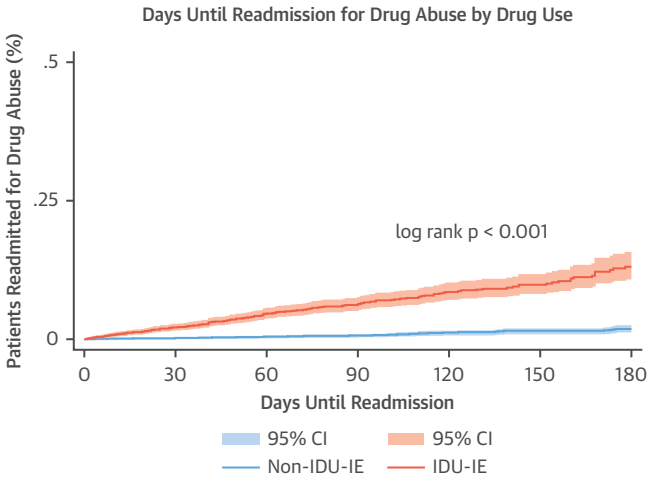
IDU-IE OUTCOMES. Outcomes for IDU-IE patients at index hospitalization were remarkably similar to, and even better than, those for non-IDU-IE patients. Although a previous institutional study found no difference in mortality between IDU-IE and non-IDU-IE patients, our study shows reduced mortality for IDU-IE patients, independent of comorbidities (11). The reduced mortality may be related to increased right-sided valve replacement and younger age among IDU-IE patients, which have been associated with lower mortality, and persists despite increased infection with *Staphylococcus aureus,* which is associated with a more severe clinical presentation (25–27). Most critically, the proportions of IDU-IE patients readmitted within 30 and 180 days were not different even after adjustment. Previous institutional work has demonstrated readmission rates as high as 49.0% in the IDU-IE population but has not characterized readmission relative to non-IDU-IE patients (14). The equivalent rates of readmission are unjustifiable given that IDU-IE patients are younger and largely healthier, with significantly fewer chronic conditions like congestive heart failure, diabetes, and renal failure relative to their non-IDU-IE counterparts.

IDU-IE READMISSIONS. Although readmission rates do not differ by IDU status, the reasons for readmission within 30 and 180 days diverge substantially. For medically managed IDU-IE patients, 30-day readmission is most frequently for endocarditis (18.1%) and septicemia (14.0%), possibly indicating persistent drug use. Although we cannot distinguish between new and recurrent infections, the fact that over 25% of medically managed IDU-IE patients were ultimately readmitted with endocarditis indicates a fundamental challenge to the present management of IDU-IE. Even in surgically managed IDU-IE patients, readmitted within 30 days, endocarditis remains 1 of the top 3 causes of readmission, along with high rates of septicemia. The overall readmission for persistent drug abuse among IDU-IE patients in our study was 13% within 6 months, a finding supported by previous reports of continued drug use between 5% and 52% (13,14,28). However, our actual rate of persistent drug use is likely much higher, as this statistic only reflects patients explicitly readmitted for drug abuse and does not capture probable indicators of continued IDU like septicemia and ongoing or recurrent endocarditis.

Despite recognition of the importance of drug rehabilitation for IDU-IE patients receiving surgery, relapse and drug abuse remain persistent issues for this population, accounting for 7.3% of readmissions within 30 to 180 days of surgery. Because persistent drug use is a significant risk factor for recurrent IE, repeat operations, and mortality, these readmission statistics identify a critical gap in the care of IDU-IE patients (5,13). Appropriate management of IDU-IE likely necessitates attention to drug rehabilitation to optimize patient outcomes. Failure to aggressively coordinate addiction counseling resulted in 329 excess readmissions for drug abuse alone. Another 2,470 patients readmitted for endocarditis or septicemia may also have persistent drug use, which has been reported as high as 70% among IDU-IE patients receiving valvular surgery (13). Thus, our failure to deliver comprehensive care to the IDU-IE population has potentially harmed thousands of patients while costing the health care system as much as $57 million. The human and economic costs threaten to persist and even grow if the opioid epidemic is not addressed (23).

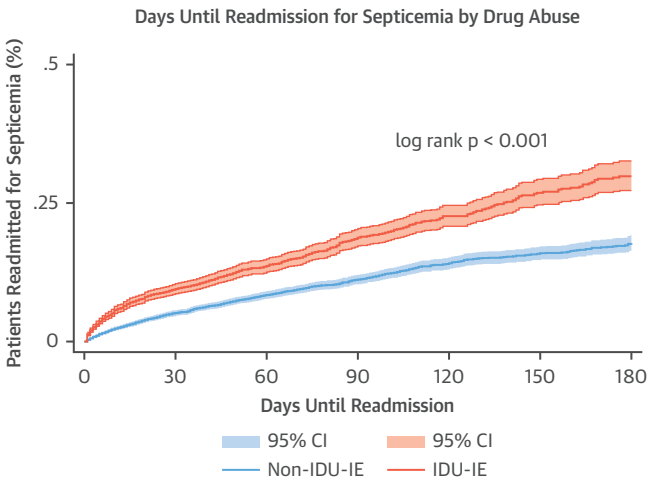
IDU-IE LENGTHS OF STAY. Our finding of increased LOS for IDU-IE patients further supports the notion of suboptimal care for the IDU-IE population, as it may reflect the absence of a transitional care plan (11). Concerns that discharging injection drug users with a central access line may lead to early drug relapse may also be driving this increased LOS (29,30). Despite such fears, studies suggest that outpatient antibiotic therapy, in conjunction with tamper-proof technology, substance abuse treatment, and social support, can improve outcomes (31). Discharge remains a persistent challenge for

FIGURE 7 Kaplan-Meier Survival Estimate of Readmission for Drug Abuse by Diagnosis of IDU-IE



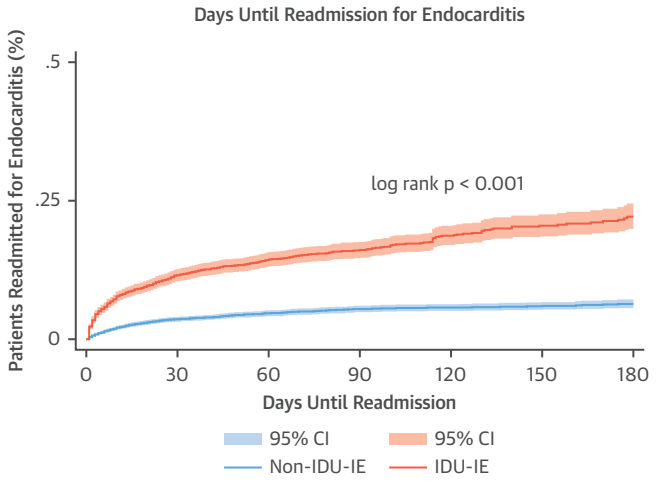
Patients diagnosed with IDU-IE are at greater risk of readmission for drug abuse within 180 days than patients diagnosed with non-IDU-IE (log rank $p < 0.001$). After adjustment in a Cox proportional hazards model, IDU-IE remains the strongest predictor of readmission for drug abuse within 180 days (hazard ratio: 4.91; 95% confidence interval [CI]: 2.88 to 8.39; $p < 0.001$). Abbreviations as in Figure 2.

FIGURE 8 Kaplan-Meier Survival Estimate of Readmission for Septicemia by Diagnosis of IDU-IE



Patients diagnosed with IDU-IE are at greater risk of readmission for septicemia within 180 days than patients diagnosed with non-IDU-IE (log rank $p<0.001$). After adjustment in a Cox proportional hazards model, IDU-IE remains a significant predictor of readmission for septicemia (hazard ratio: 1.83; 95% confidence interval [CI]: 1.54 to 2.16; $p < 0.001$).

FIGURE 9 Kaplan-Meier Survival Estimate of Readmission for Endocarditis by Diagnosis of IDU-IE



Patients diagnosed with IDU-IE are at greater risk of readmission for endocarditis within 180 days than patients diagnosed with non–IDU-IE (log rank $p < 0.001$). After adjustment in a Cox proportional hazards model, IDU-IE remains a significant predictor of readmission for endocarditis (HR: 2.42; 95% confidence interval [CI]: 1.99 to 2.93; $p < 0.001$).

IDU-IE patients, because although a majority of IDU-IE patients receive a social work consultation, only a minority receive addiction or psychiatry consultations, and <10% receive a plan for medication-assisted addiction treatment (14). Additional evidence suggests that clean injection strategies like needle exchange may be beneficial in preventing incidence and recurrence of IE (2). In light of our findings of increased readmissions for drug-related conditions, interventions for drug addiction appear suboptimal and may be a promising opportunity for reducing recurrent endocarditis and drug abuse relapse in IDU-IE patients (14,31).

STUDY LIMITATIONS. The present study has several important limitations inherent to its retrospective nature. We are limited by the accuracy of data and potential coding errors within the NRD database. The NRD does not provide detailed data on race, geographic region, or other demographics that could be valuable in pinpointing the changing demographics of IDU-IE. Furthermore, the NRD cannot track patients across years, so we are limited to readmissions within the calendar year of index hospitalization. While we suspect, based upon previous studies, that IDU-IE patients have greater rates of right-sided endocarditis, a more benign condition, the ICD-9 diagnosis codes in the NRD do not specify right or left sided endocarditis for medically managed patients (25,26). Furthermore, the use of bacteremia to identify the disease-causing pathogen was poorly coded, resulting in a majority of unspecified infections. Future studies should explore whether aggressive coordination of addiction counseling can lower the rates of readmission for persistent drug use.

CONCLUSIONS

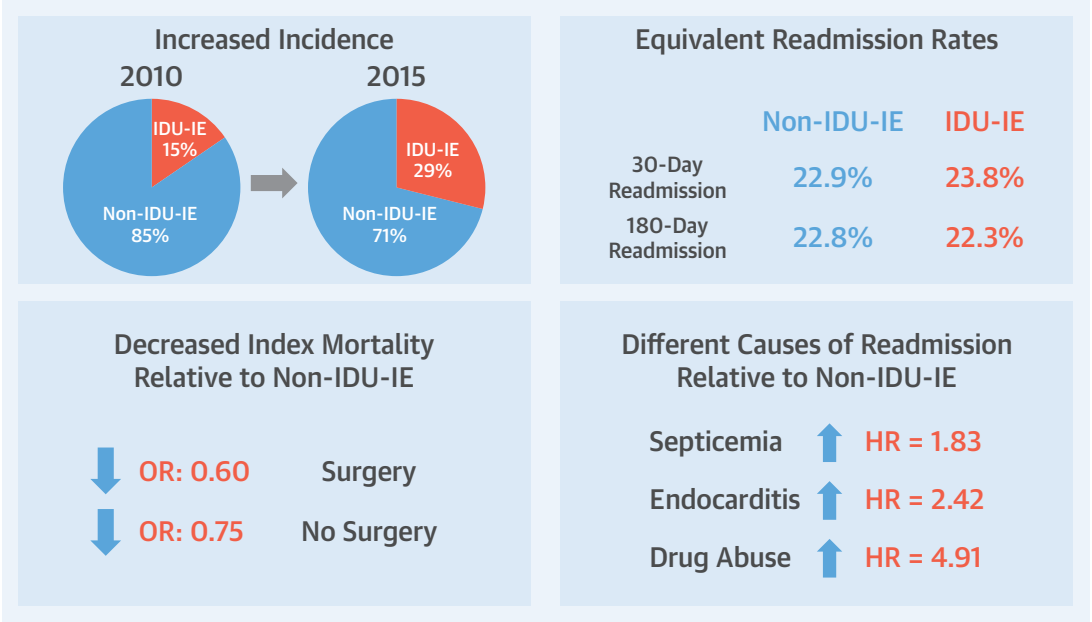
The opiate epidemic continues to affect the U.S. population. Our study and others have shown that the incidence of IDU-IE is increasing nationally, particularly among younger, low-income patients. Patients with IDU-IE are not at increased risk of readmissions within 30 or 180 days, but both medically and surgically managed patients are more likely to be readmitted with endocarditis, septicemia, and drug abuse. Our investigation has thus identified a significant opportunity to improve the care of IDU-IE by addressing the frequent readmissions likely tied to

TABLE 5 Estimated Preventable Readmissions and Cost of Readmissions in IDU-IE Patients

Time for Readmit	Index Management	Reason for Readmission			Estimated Number of Preventable Readmissions		Estimated Excess Costs (USD)	
		Drug Abuse	Septicemia	IE	Low	High	Low	High
30 days	Medical	148	773	999	148	1,920	$3,062,120	$39,724,800
	Surgical	9	38	52	9	99	$156,888	$1,725,768
	Overall	157	811	1,051	157	2,019	$3,219,008	$41,450,568
30–180 days	Medical	158	335	195	158	688	$3,221,462	$14,027,632
	Surgical	14	63	15	14	92	$269,822	$1,773,116
	Overall	172	398	210	172	780	$3,491,284	$15,800,748
Total	Medical	306	1,108	1,194	306	2,608	$6,283,582	$53,752,432
	Surgical	23	101	67	23	191	$426,710	$3,498,884
Total		329	1,209	1,261	329	2,799	$6,710,292	$57,251,316

IE = infective endocarditis.

CENTRAL ILLUSTRATION **Infective Endocarditis in Injection Drug Users**



Rudasill, S.E. et al. J Am Coll Cardiol. 2019;73(5):559-70.

Infective endocarditis in injection drug users is increasing in incidence and is associated with decreased index mortality, equivalent rates of 30- and 180-day readmission, and increased risk of readmission for septicemia, endocarditis, and drug abuse.

persistent drug use. Increased focus on addiction treatment and social support following hospital discharge has the potential to mitigate both the human and economic impacts of IDU-IE.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: The proportion of IE cases that are related to IDU continues to rise in tandem with the opioid epidemic.

TRANSLATIONAL OUTLOOK: Future studies should explore the impact of coordinated addiction counseling on rates of readmission and clinical outcomes after treatment of IE in patients with IDU.

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