Recidivism Is the Leading Cause of Death Among Intravenous Drug Users Who Underwent Cardiac Surgery for Infective Endocarditis

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The proportional incidence of intravenous drug use (IVDU)-associated infective endocarditis (IE) cases requiring surgery has increased significantly, mirroring the national opioid crisis. Recidivism is common but its impact on postoperative outcomes is unclear. We aimed to evaluate short- and mid-term postoperative outcomes associated with recidivism in this population. We retrospectively reviewed 180 consecutive patients (54 IVDU and 126 non-IVDU) surgically treated for IE from 2011 to 2016. The institutional database was linked to the Connecticut Department of Public Health Death Index to capture statewide long-term mortality and causes of death. Regression models were fitted to evaluate the association between IVDU status and perioperative adverse events, mid-term survival, and causes of death. IVDU patients were younger and had fewer comorbidities. Diabetes, hypertension, peripheral vascular disease, and previous coronary artery bypass graft were less frequently present in IVDU patients compared to non-IVDU patients ($P < 0.05$ for all). The Society of Thoracic Surgeons mortality prediction score for IE was lower in IVDU patients (22.9 vs 33.6, $P < 0.001$). IVDU was associated with a significantly increased risk of perioperative adverse events (odds ratio 2.88, 95% confidence interval 1.02–8.12) and increased risk of mid-term mortality (hazard ratio 2.2, 95% confidence interval 1.04–4.78, $P = 0.04$). The leading cause of death in IVDU patients was related to recidivism whereas that of non-IVDU patients was related to chronic conditions. IVDU patients who underwent cardiac surgery for IE experienced higher risks of perioperative adverse events and inferior mid-term survival compared to non-IVDU, despite being younger and having less comorbidities. Deaths in IVDU cohort were predominantly due to recidivism. Efforts to improve long-term outcome of patients presenting with IVDU IE should include drug addiction intervention and other strategies to reduce recidivism.

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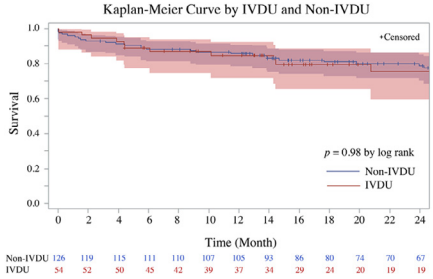
Keywords: Cardiac surgery, Endocarditis, Opioid epidemic, Recidivism



Postoperative mid-term survival for IVDU and non-IVDU.

Central Message

Patients undergoing surgery for IE due to IVDU are at higher risk of adverse events. Mid-term deaths in IVDU cohort were predominantly due to recidivism, highlighting importance of recidivism prevention.

Perspective Statement

Recidivism is common in patients with history of IVDU leading to cardiac surgery for IE, but its impact on surgical outcomes is unknown. This study identified that deaths in an IVDU cohort at mid-term was predominantly due to recidivism. The findings highlight the importance of resource allocations toward prevention of recidivism to improve the outcomes and survival of this complex patient population.

Abbreviations: IVDU, IV drug users; IE, infective endocarditis; STS, Society of Thoracic Surgeons

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INTRODUCTION

The United States have seen a sharp increase in heroin and other opioid drug use in recent years, leading to a public health crisis.[1,2] Concurrently, the number of hospitalization for infective endocarditis (IE) resulting from intravenous drug use (IVDU) has increased,[3,4] with the incidence rates of IE in the United States increasing from 11 to 15 per 100,000 between 2000 and 2011.[5,6] Surgical intervention plays an important role in the management of this complex patient population,[7] but the outcomes at short and long term are inferior compared to non-IVDU patients undergoing cardiac surgery for IE.[8,9] Recidivism

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is common among patients with history of IVDU,[10] but its impact on postoperative survival on patients who underwent cardiac surgery for IVDU-IE remains unknown. Provided that, in the absence of discrete guidelines, centers and surgeons have varying thresholds and policies to operate and reoperate on patients with IVDU-IE and prosthetic valve endocarditis (PVE) associated with IVDU, understanding the impact of recidivism on postoperative outcomes is pertinent. This study aimed to elucidate the differences in causes of death, mortality, and morbidity between IVDU patients and non-IVDU patients who underwent surgical intervention for IE.

METHODS

Patient Population

We conducted a retrospective review of 180 (54 IVDU and 126 non-IVDU) consecutive patients who underwent cardiac surgery for IE from 2011 to 2016 at Yale-New Haven Hospital, a tertiary care hospital in the United States. The patients were defined as having endocarditis based on the Center for Disease control and Prevention surveillance definition.[11] This definition is adopted by the Society of Thoracic Surgeons (STS) adult cardiac surgery database and is similar to the Duke Criteria for IE. Intravenous drug use was defined as patients with a history of illicit drug use. Active IE was defined as receiving antibiotic therapy for IE at the time of operation or having histopathologic or microbiologic evidence of active IE of the valves that were removed or repaired at operation. IVDU was defined based on the STS adult cardiac surgery database specifications, indicating whether there was a documented history of illicit drug use. The study was approved by the Yale Institutional Review Board and individual patient consent was waived.

Data Sources and Outcomes

Data were collected through the local database and review of the electronic medical record linked with the Connecticut Department of Public Health Death Index to capture statewide long-term survival and causes of death. The STS data definitions (version 2.81 and 2.73) were used in all data fields. The causes of death were obtained via ICD9 code recorded in the Connecticut Department of Public Health Death Index and chart review. Those associated with recidivism were defined as related to recurrent endocarditis or death due to substance abuse. The evaluated outcomes were the causes of death, perioperative and mid-term mortality, and perioperative composite events: in-hospital death, dialysis, renal failure, pneumonia, prolonged ventilation, stroke, and sepsis. Short-term outcome was defined as those occurring within 30 days of index operation. Mid-term mortality was defined as mortality occurring up to the last date of follow-up. The median follow-up time in the entire cohort was 20.7 months, and therefore, the mid-term designation was elected for this duration.

Statistical Analysis

Differences in the patient characteristics were compared to 2-tailed *t*-test, chi-square test, or Fisher's exact test, where appropriate. Continuous variables are expressed in mean with standard deviation format unless otherwise specified. Endocarditis risk score, a point-based risk score system derived from the national STS database, was used to quantify preoperative risks.[12] A logistic regression model-related input variables consisting of variables outlined in Tables 1 and 2 and perioperative outcome measures: operative mortality and composite adverse events (death, prolonged intubation, stroke, renal failure, and sepsis). A multivariable step-wise Cox proportional hazard model was fitted to evaluate the association between IVDU status and mid-term survival. All multivariable models included IVDU status as a forced input covariate. Log-log curves were constructed to evaluate the proportionality assumption, and those variables violating the assumptions were stratified in the final Cox model. A *P* value <0.05 was used to define statistically significant differences and correlations. All analysis was conducted with SAS 9.4 (SAS Institute Inc, Cary, NC; Tables 3 and 4).

Table 1. Patient Characteristics

Variables	No IVDU ($n = 126$)	IVDU ($n = 54$)	*P* Value
Age (y)	62.8 ± 14.0	44.6 ± 13.7	**<0.0001**
Female	38 (30.2%)	7 (13.0%)	**0.015**
Race			
Caucasian	104 (83.2%)	38 (70.4%)	0.07
African-American	13 (10.4%)	6 (11.1%)	1.0
Other	—	—	
Body mass index (kg/m^2)	28.0 ± 6.3	24.8 ± 6.0	0.7
Baseline comorbidities			
Diabetes	38 (30.2%)	4 (7.4%)	**0.0009**
Dialysis	20 (15.9%)	4 (7.4%)	0.15
Hypertension	95 (75.4%)	19 (35.2%)	**<0.0001**
Preop creatinine (mg/dL)	1.53 ± 1.4	2.22 ± 2.5	**0.02**
Chronic lung disease	22 (17.5%)	5 (9.3%)	0.18
Liver disease	13 (10.3%)	23 (42.6%)	**<0.0001**
Immunosuppressed	15 (11.9%)	4 (7.4%)	0.44
Peripheral vascular disease	21 (16.7%)	2 (3.7%)	**0.015**
Stroke	37 (29.4%)	20 (37.0%)	0.4
Previous CABG	11 (8.8%)	0 (0%)	**0.035**
Previous valve surgery	40 (32.0%)	11 (20.4%)	0.15
Previous MI	23 (18.3%)	9 (16.7%)	1.0
Recent CHF	58 (46.0%)	17 (31.5%)	0.073
Cardiogenic shock	7 (5.6%)	2 (3.7%)	0.73
Arrhythmia	23 (18.3%)	6 (11.2%)	0.76
Pre-op EF (%)	58.3 ± 10.3	59.4 ± 9.2	0.47
Active endocarditis	98 (77.8%)	41 (75.9%)	0.85
Endocarditis risk score (points)	33.6 ± 13.3	22.9 ± 11.0	**<0.0001**

CABG, coronary artery bypass graft; CHF, congestive heart failure; EF, ejection fraction; IVDU, incidence of intravenous drug use; MI, myocardial infarction.
Bold values signify $P < 0.05$.

Table 2. Operative Variables

Variables	No IVDU ($n = 126$)	IVDU ($n = 54$)	*P* Value
Previous sternotomy	46 (36.5%)	10 (18.5%)	**0.022**
Status			
Urgent	94 (74.6%)	38 (70.4%)	0.54
Emergent	8 (6.4%)	2 (3.7%)	
Concomitant CABG	11 (8.7%)	3 (5.6%)	0.56
Single valve procedure	40 (31.8%)	34 (63.0%)	**0.0005**
Isolated aortic valve	23 (15.8%)	8 (19.1%)	0.64
Isolated mitral valve	27 (18.5%)	5 (11.9%)	0.36
Isolated tricuspid valve	13 (8.9%)	1 (2.4%)	0.20
Double valve procedure	72 (57.1%)	17 (31.5%)	–
Triple valve procedure	14 (11.1%)	3 (5.6%)	–
Cross clamp time (min)	102.7 ± 40.3	84.3 ± 38.8	**0.006**
IABP use	5 (3.4%)	1 (2.4%)	1.0
ECMO use	2 (1.4%)	0 (0%)	1.0

CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IVDU, incidence of intravenous drug use.
Bold values signify $P < 0.05$.

Table 3. Postoperative Outcomes

Variables	No IVDU ($n = 126$)	IVDU ($n = 54$)	*P* Value
Re-intubation	17 (13.5%)	3 (5.6%)	0.19
ICU LOS (hours)	161.6 ± 196	123.9 ± 168.6	0.19
Post-op LOS (day)	12.4 ± 12.1	12.4 ± 11.1	1.0
Reoperation for bleeding	5 (3.98%)	0 (0%)	0.32
Valve-related reoperation	1 (0.8%)	0 (0%)	1.0
Sternal wound infection	1 (0.8%)	0 (0%)	1.0
Sepsis	7 (5.6%)	1 (1.9%)	0.44
Stroke	4 (3.2%)	2 (3.7%)	1.0
Prolonged ventilation	40 (31.7%)	12 (22.2%)	0.21
Pneumonia	13 (10.3%)	2 (3.7%)	0.23
Renal failure	5 (3.9%)	3 (5.6%)	0.69
Dialysis need	20 (15.9%)	4 (7.4%)	0.15
Hospital death	5 (3.9%)	1 (1.85%)	0.67

ICU, intensive care unit; IVDU, intravenous drug use; LOS, length of stay.

RESULTS

Patient Characteristics

During the study period, 180 Patients received surgical intervention for IE, 54 of whom were classified as IVDU and 126 as non-IVDU. Table 1 outlines the baseline patient characteristics. Compared to Non-IVDU patients, IVDU patients were younger (44.6 ± 13.7 vs 62.8 ± 14.0 years, $P < 0.01$), less likely to have diabetes (4 [7.4%] vs 38 [30.2%], $P < 0.01$), hypertension (19 [35.2%] vs 95 [75.4%], $P < 0.01$), peripheral vascular disease (2 [3.7%] vs 21 [16.7%], $P = 0.02$), and previous coronary artery bypass graft (0% vs 11 [8.8%], $P = 0.04$). In addition, IVDU patients had higher levels of preoperative creatinine (1.5 ± 1.4 vs 2.2 ± 2.5 mg/dL, $P = 0.02$), and were more likely to have a history of liver disease (13 [10.3%] vs 23 [42.6%], $P < 0.01$). As a quantitative surrogate of patient risk profile, the endocarditis risk score was calculated and showed that non-IVDU patients had a higher STS endocarditis risk score of 33.6 ± 13.3 points compared to 22.9 ± 11.0 points for IVDU patients ($P < 0.0001$), indicating that IVDU cohort was of a lower preoperative risk profile.

Pathogens

Gram-positive bacteria accounted for the majority of pathogens among this patient population, specifically streptococcus, staphylococcus aureus, and coagulase negative staphylococcus. Fungi were more common among IVDU patients (non-IVDU 2.1% vs IVDU 9.5%). Conversely, staph aureus was more common among non-IVDU patients (non-IVDU 32.4% vs IVDU 23.8%). Additionally, Streptococci were more common among non-IVDU patients than IVDU patients (non-IVDU 33.8% vs IVDU 26.2%).

Survival and Adverse Event

Kaplan-Meier analysis, shown in Figure 1, showed that unadjusted mid-term survival was not significantly different between the IVUD and non-IVDU cohort ($P = 0.98$ by log-rank). A multivariable logistic regression model for composite postoperative event demonstrated that there was no statistically significant difference in the risk of composite event between IVDU and non-IVDU patients (odds ratio [OR] 1.85, 95% confidence interval [CI] 0.74–4.62, $P = 0.19$). Factors that were associated with higher risk of composite events were nonelective case (OR 4.17, 95% CI 1.72–10.11, $P = 0.016$), history of hypertension (OR 3.55, 95% CI 1.40–9.03, $P = 0.008$), history of preoperative dialysis (OR 2.94, 95% CI 1.06–8.17, $P = 0.039$), number of valves operated on (OR 2.47, 95% CI 1.35–4.52, $P = 0.003$, and history of pneumonia (OR 2.05, 95% CI 1.30–3.23, $P = 0.002$).

Mid-Term Survival and Causes of Death

A Cox proportional hazard analysis adjusting for potential confounders demonstrated that IVDU status was associated with

Table 4. Cause of Death During the Follow-Up Period

Cause of death	No IVDU ($n = 35$)	IVDU ($n = 13$)	*P* Value
IVDU-related or endocarditis	11 (31.4%)	9 (69.2%)	0.1
COPD, CKD, CAD, Cardiomyopathy, malignancy	12 (34.3%)	1 (7.7%)	
Other	6 (17.1%)	1 (7.7%)	
Unknown	6 (17.1%)	2 (15.4%)	

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IVDU, intravenous drug use.

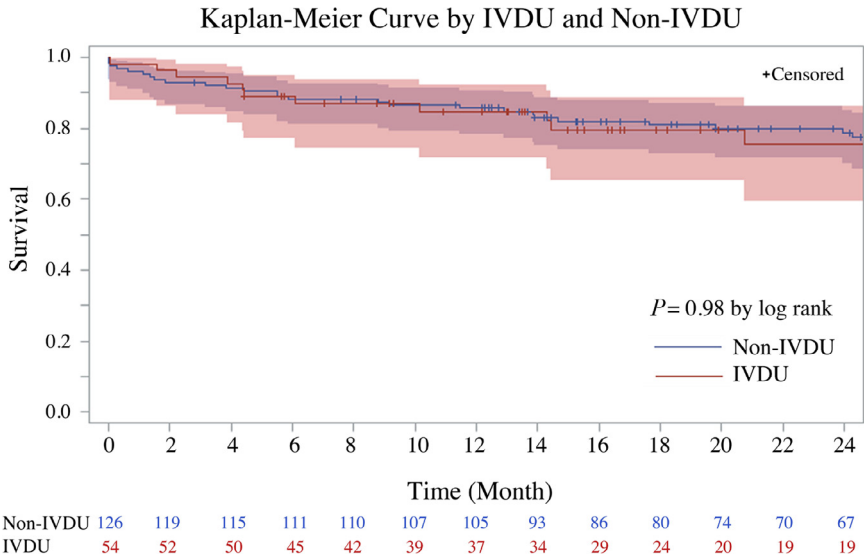

Figure 1. Kaplan-Meier curve of long-term mortality comparing IVDU and Non-IVDU patients. IVDU, incidence of intravenous drug use.

increased risk of long-term mortality (hazard ratio 2.2, 95% CI 1−4.8, P = 0.04). The leading cause of postoperative death among IVDU patients was recidivism (69.2%), of which one-third was due to overdosing, as defined as deaths attributable to substance overdose and recurrent IE. In contrast, the leading cause of death in non-IVDU patients was chronic cardiopulmonary disease, kidney disease, and malignancy (34.3%).

DISCUSSION

Several notable findings of this study are the following: (1) the IVDU cohorts at baseline were younger and had fewer comorbidities as evidenced by the lower endocarditis risk score, (2) adjusted mid-term risk of mortality was higher in IVDU cohort, and (3) the leading cause of death in IVDU cohort at mid-term was recidivism, while that of non-IVDU patients was chronic conditions.

The observation that our IVDU cohort is younger and harbors less chronic conditions is in line with the one made in a report from Cleveland Clinic, which demonstrated that unadjusted survival at long-term was similar between IVDU and non-IVDU cohort, with 6-month survival >80%, but the risk-adjusted probability of long-term survival free of reoperation was lower in IVDU patients compared to non-IVDU patients.[9] Our unadjusted mid-term survival rate is comparable, and in line with our time-dependent risk-adjusted model suggesting inferior outcomes in the IVDU cohort.

The observation that IVDU patients tend to be younger and harbor less comorbidities than their non-IVDU counterparts yet experiences higher hazard of adverse events at mid- and long-term associated with recidivism highlights the importance of postdischarge protocols to prevent return to injecting drugs.[9] A retrospective review of patients hospitalized with IVDU-IE showed that IVDU patients with IE have a high rate of readmission, recurrence of IE and death, yet the level of addiction intervention is suboptimal, measured in terms of social work consultation, addiction service involvement, and proper discharge planning.[10] According to a recent study, long-term causes of death in patients who undergo either medical or surgical treatment for IE are dominated by cardiovascular disease, notably being the cause of death in 55.2% of the surgically treatment patients, with a 10-year mortality of 41.6%.[13] Our finding of recidivism as the leading cause of death among IVDU-IE patients who underwent cardiac surgery highlights the importance of perioperative intervention to minimize recidivism. Such intervention may include implementing a protocol of screening, treatment initiation, and referral (STIR)[14] for all IE patients with a history of drug use disorder. Intervention may include but not be limited social work and psychiatric consults for assessment of patient's barriers for cessation, initiation of buprenorphine with primary care follow-up, combine with referral for cognitive behavioral therapy. A trial using the STIR approach by initiating buprenorphine for opioid-dependent individuals resulted in greater engaged treatment at 30 days and greater self-reported abstinence. In addition, the STIR patients were less likely to be enrolled in addiction in-patient services at 30 days.[15,16]

A prospective study of 2 separate institutional databases comprising of 436 patients (78 IVDU) showed that with the increasing proportion of surgically treated IVDU patients, they have lower operative mortality but similar overall mortality to that of non-IVDU patients, yet had a higher risk of valve-related complications attributed to reinfection.[17,18] Our study's findings corroborates this finding in that reinfection, return to injecting drugs, and drug overdose contribute to long-term mortality among IVDU patients. A retrospective cohort study done in the United States in 1979 comparing

IVDU and non-IVDU patients showed similar findings[19]: presumed continued was the leading cause of death among IVDU patients who underwent surgery for endocarditis. In this Cohort of 15 IVDU and 15 Non-IVDU patients, all IVDU patients returned to using drugs after their surgery.

Continued drug use is a consequence of addiction, and inherently increases the risk of reinfection. Addiction is a chronic neurobiological disorder, characterized in part by craving and withdrawal. Management of IVDU-IE should thus shift toward multidisciplinary teams involving psychiatry, infectious disease, cardiology and cardiac surgery, as well as social workers.[20] Such interventions and structured programs including patient navigator programs have been shown to reduce improve outcomes and reduce readmission rates and improve outcomes for at-risk patients in other areas of the medical field.[21] In a report of an intervention to transfer 205 IVDU patients requiring prolonged IV antibiotic treatment to residential addiction treatment program, this intervention was associated with a cost saving of $2.43 million over the course of 6 years by reducing hospital length of stay with a structured discharge planning.[22] Not only do such interventions have the potential of improving outcomes and reducing mortality, they also contribute to reducing costs for the healthcare system in the long term.

Long-term residential addiction treatment may not be a feasible option for many patients because of socioeconomic factors such as insurance coverage. Institutionalizing addiction consultation services and making use of them show that initiation of addiction treatment inpatient leads to outpatient clinic follow-up, with room for improvement.[23] While protocolization may result in efficiency, it must be noted that the treatment of this complex patient population must be individualized.

With regards to the recurrence of IE, the operative risk of patients with PVE has traditionally been high at 15.7−25.5%.[18] Our center's operative experience and outcomes in PVE have been favorable, with operative mortality rate comparable to that of native valve endocarditis.[24] With careful patient selection and infrastructures equipped to handle complex postoperative course, surgery for PVE may be advocated. However, interventions to recidivism and PVE in the first place are of utmost importance.

Limitations

The study harbors limitations inherent to a single-center retrospective design. Complete data on reoperation and recurrent endocarditis were not captured, as some patients underwent previous operation at outside institutions and the State registry used only records ICD code. The type of injection drugs used or the pattern/timing of their drug use prior to and after the operation were not captured. The sample size of the IVDU cohort is relatively small, although it is comparable to existing single-center studies.

CONCLUSIONS

IVDU patients who underwent cardiac surgery for IE were younger and had less comorbidities compared to non-IVDU patients but experienced higher risks of perioperative adverse events and inferior mid-term risk-adjusted survival. Deaths in IVDU cohort at mid-term were predominantly due to recidivism. These findings highlight the importance of resource allocations toward prevention of recidivism in the overall effort to improve the longer term outcomes and survival of this complex patient population.

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