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Article

Outcomes After Valvular Surgery for Infective Endocarditis in People Who Abuse Opioids

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Abstract

Background: A limited number of studies have analyzed outcomes following surgery for infective endocarditis (IE) in patients with opioid misuse. Therefore, this study aimed to assess post-surgery survival rates for IE in opioid users compared to those with community-acquired IE (CA-IE). The secondary outcomes included mortality, readmission, and reinfection rates during mid-term follow-up. **Methods**: Our retrospective study included 126 patients with IE who underwent surgical intervention from June 2007 to September 2024. Of the 126 patients, 75 were opioid abusers, while the remaining 51 were diagnosed with CA-IE. IE was diagnosed using the modified Duke criteria. To confirm malnutrition as a risk factor of mortality and morbidity MN after cardiac surgery, the patients were evaluated by an experienced dietitian preoperatively. Transthoracic echocardiography, with or without transesophageal echocardiography (TOE), was conducted to assess vegetation growth, valve dysfunction, and myocardial function. The key endpoint was mortality occurring within 30 days post-surgery. The secondary endpoints were the rates of IE recurrence, reoperation, and mortality during the follow-up period. Multivariable regression was employed to assess the relationship between mortality and opioid addiction over the follow-up period. **Results**: Over 65% of patients (n = 49) reported a history of intravenous heroin use, while 16 patients (21.3%) were identified as cocaine users, with various methods of admission recorded, including snorting and intravenous injection. Of the remaining 10 patients (13.3%), all had a history of using oral methamphetamine and dextroamphetamine, both of which are psychostimulant drugs, in combination with injected substances. The mean drug use duration was 9.4 years, with a standard deviation of 3.2 years, and a range of 3 to 11 years. In-hospital mortality rates were comparable between the two groups (three patients with opioid abuse (6.6%) vs. five patients with CA-IE (5.8%); $p = 0.685$). Isolated right-sided IE was more prevalent in individuals with opioid addiction compared to community-acquired IE (45.3% vs. 17.6%; $p = 0.012$), followed by mitral valve IE (14% vs. 21.5%; $p = 0.004$). The patients who abused opioids were significantly younger and exhibited fewer comorbidities. The mean intensive care unit duration for opioid-abusing IE patients was considerably greater than for non-abusing patients (3.9 days vs. 2.1 days; $p = 0.01$). The median duration of hospitalization was significantly longer for opioid users than for patients with CA-IE (49.9 $\pm$ 19.4 days vs. 27.1 $\pm$ 12.2 days; $p = 0.022$). Multivariate Cox regression analysis indicated that opioid abuse (hazard ratio (HR): 2.012, 95% confidence interval (CI): 1.96–4.56; $p = 0.002$), urgent surgery (HR: 1.96, 95% CI: 1.41–5.12; $p = 0.024$), congestive heart failure (HR: 2.58, 95% CI: 1.94–5.07; $p = 0.032$), and redo valvular surgery (HR: 1.78, 95% CI: 1.29–6.04; $p = 0.002$) were independent predictors of mortality. The median follow-up duration for individuals with opioid abuse and CA-IE was 60.7 $\pm$ 23.3 months and 59.4 $\pm$ 24.9 months, respectively. The incidence of readmission was more prevalent among patients who abused opioids than among those who did not. Nine opioid users with IE (12.8%) were readmitted due to a new episode of IE, whereas the readmission rate in the CA-IE group was 4% (n = 2 patients) due to recurrence of IE (odds ratio (OR): 3.96; $p = 0.004$). Reoperation rates in patients with a tendency to misuse opioids were considerably elevated compared to those with CA-IE (8.5% vs. 4%; OR: 4.12; $p = 0.01$). **Conclusion**: Mortality rates following surgery for IE were markedly elevated in patients with a history of opioid abuse throughout mid-term follow-up relative to those with CA-IE. Opioid users with IE had elevated readmission and reoperation rates compared to patients with community-acquired IE. Intravenous opioid administration, revision surgery, congestive heart failure, and emergency surgery were independent mortality risk factors. Prospective randomized studies are required to investigate risk factors for mortality, comorbidities, and readmission following a new episode of IE during the follow-up period.

Keywords: infective endocarditis; intravenous inject drug use; cardiac surgery; risk factors

1. Introduction

Infective endocarditis (IE), which affects the endocardium and cardiac valves, is an uncommon and life-threatening medical illness. In-hospital mortality following surgery varies between 8% and 35% [1,2]. More than 50% of IE patients require open heart surgery [3]. Patients who take opioids have a 50–100 times greater incidence of IE compared to those with community acquired IE [4,5]. Patients with community-acquired IE (CA-IE) endocarditis are older and exhibit greater comorbidities [6,7]. Significantly, the incidence of opioid misuse among IE patients undergoing heart surgery has risen in our nation.

The WHO report indicates that opioid addiction is associated with severe cardiac diseases, myocardial infarction, cerebrovascular incidents, and fatalities resulting from drug overdose, all of which are life-threatening clinical situations globally [1]. Although IE patients who misuse opioids are predominantly young and exhibit few comorbidities; numerous studies indicate a higher mortality rate compared to patients who do not misuse opioids [8,9].

In-hospital mortality among opioid-abusing patients was comparable to that of patients with CA-IE after surgery, as indicated by several previous studies [10–12]. Factors associated with in-hospital mortality following IE surgery included advance age, female gender, refractory sepsis accompanied by congestive heart failure, substantial vegetation mass, and history of heart failure, as indicated by multiple previous studies [6–10]. There are limited number of comparative studies on patients who abuse opioids that identify postoperative death, surgery related complications, and mortality in long-term period [7,8]. Ramadan *et al*. [9] revealed that patients with IE who abuse opioids experienced a greater incidence of pulmonary or cerebrovascular embolic events and exhibited significantly elevated mortality rates during an extended follow-up period compared to patients with CA-IE.

We aimed to evaluate our experiences with IE surgery in 126 patients, of whom 75 had a history of opiate misuse. Additionally, we analyzed the outcomes, mortality, rates of IE recurrence, reoperation, and mortality during the follow-up period in our cohort.

2. Material and Methods

From June 1, 2007, until September 1, 2024, our facility admitted 126 patients for IE surgery. The retrospective study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (No: 2924). All patients signed informed consent. No patients were lost to follow-up in our study. The follow-up data for our patients has been finalized, with no data omissions recorded. Seventy-five patients were opioid abusers (59.5%), while the remaining fifty-one patients had CA-IE (40.5%). Central venous cannulation, implantation of an intracardiac cardioverter defibrillator (ICD), pacemaker insertion, and prior heart valve replacement were the etiological factors for IE in 44 patients within the CA-IE cohort. The etiology of IE in the remaining seven patients in the CA-IE group was indeterminate. Patients with CA-IE exhibited a higher prevalence of comorbid illnesses, including hypertension (HT), diabetes mellitus (DM), peripheral artery disease (PAD), and chronic obstructive pulmonary disease (COPD), compared to those with IE who consume opiates ($p = 0.001$).

We computed the Nutritional Risk Score-2002 (NRS-2002), which effectively predicts malnutrition in the preoperative period immediately following hospitalization in patients requiring elective surgery. The mean body mass index in opioid-abusing patients was considerably lower than that of patients with CA-IE (19.6 kg/m^2 vs 22.4 kg/m^2, $p = 0.002$). Malnutrition was deemed acceptable if the patients' NRS-2002 score exceeded 4, as per the literature. Malnutrition was identified in 14.6% of patients who abuse opioids and in 7.8% of patients with CA-IE. The nutritional program was individually planned by a dietitian for both the preoperative and postoperative period. We initiated oral or intravenous nutritional supplementation based on the consultation with a dietitian until the patients were discharged from the hospital. We also recommended proper meals and nutritional support for these patients.

Echocardiographic analyses were conducted preoperatively. A thoracic CT was conducted due to suspicion of cerebrovascular or pulmonary embolic events prior to surgery. We assessed the New York Heart Association (NYHA) functional classification before the surgical procedure. The principal endpoint was mortality within 30 days post-surgery, whereas the secondary endpoints included overall mortality, recurrence of infective endocarditis, and reoperation during the follow-up period. The median follow-up duration post-hospital discharge for patients with opioid abuse and those with CA-IE was 60.7 $\pm$ 23.3 months and 59.4 $\pm$ 24.9 months, respectively.

We examined coagulation markers in patients experiencing pulmonary embolic episodes during the preoperative period. Thrombocyte counts, Protein C and S levels, Prothrombin time (PT), D-dimer, and international normalized ratio (INR) were assessed for clotting abnormalities before surgery.

2.1 Statistical Analyses

Statistical analysis was conducted utilizing SPSS software version 21 (IBM Corp., Armonk, NY, USA). The Student's *t*-test was employed to ascertain statistically significant differences between the means of two cohorts. Baseline characteristics and clinical outcomes among groups were compared utilizing χ^2 testing. Results were presented according to descriptive statistical criteria, including mean values and their standard deviations (SD), or median values. Continuous variables were expressed as medians, whereas categorical variables were represented as frequencies and percentages. Fisher's Exact tests were employed for com-

parisons between two groups. Univariate and multivariate analyses were employed to identify factors influencing mortality, readmission rates, and reoperation during mid-term follow-up. If the p-value is less than 0.05, it is considered significant. Kaplan-Meier survival curves were produced for mid-term follow-up based on mortality rates, utilizing log-rank test analysis. For all tests, a two-tailed $p < 0.05$ was deemed statistically significant.

2.2 Surgical Approach

Minimally invasive techniques, such as right anterior thoracotomy or mini-J sternotomy, were favored for patients with isolated right heart infective endocarditis classified as NYHA Class III and IV. This technical method allowed us to circumvent the negative effects of aortic cross-clamping, including cerebrovascular events and postoperative low output syndrome. In the other patients, we employed median sternotomy and aortic cross-clamping. We intended to do thorough debridement of all diseased tissues. We conducted the valve repair utilizing bioprosthetic material and employed either a biological or mechanical valve. In patients with severe degenerative valve disease or periannular abscess formation, we meticulously removed the valve leaflets together with nearby tissue and performed replacement using either biological or artificial heart valves. Following surgery, broad-spectrum antibiotics were provided for a duration of 4 to 6 weeks till hospital discharge.

3. Results

Table 1 summarizes the characteristics of patients, biochemical analyses, concomitant conditions, medications, and echocardiographic data. Patients with opioid addiction and IE were younger than those with CA-IE (38.9 $\pm$ 11.4 years vs 59.4 $\pm$ 16.9 years, $p = 0.001$). Comorbid disorders were more prevalent in patients with CA-IE compared to opioid-using patients with IE. Consultation with a psychiatrist revealed that our study indicated individuals who abuse opioids exhibited higher rates of depression (19.6% vs 9.3%, $p = 0.023$) and alcohol abuse (35.2% vs 18.6%, $p = 0.022$) compared to patients with CA-IE. The prevalence of Hepatitis C was significantly higher in individuals with opioid misuse compared to the CA-IE group (41.3% vs 6.6%) ($p < 0.0001$).

No significant difference was observed between the two groups for the proportion of preoperative congestive heart failure or the median duration from the diagnosis of infective endocarditis to surgery. The overall in-hospital mortality rate was 6.3% for patients with IE who abuse opioids, compared to 5.8% for those with CA-IE ($p = 0.665$). Although there is no documented history of cardiovascular intervention in patients with IE who misuse opioids, seven patients (13.7%) in the CA-IE cohort had previously received heart valve replacement ($p = 0.001$). The Logistic Euro-Score-II (ES-2) was substantially higher in individuals with CA-IE compared to those who abuse opioids (3.2 $\pm$ 1.1 vs 1.9 $\pm$ 0.3) ($p = 0.022$).

We collected blood samples for culture results at least three times immediately after hospitalization in both groups to ensure proper antibiotic treatment. In all, blood culture yielded positive results in 82.5% of patients. Blood culture results indicated that Staphylococcus and Streptococcus species were the predominant causal agents in both groups (42.6% vs 37.2%) ($p = 0.66$). The causative bacteria and valvular involvement in both groups are detailed in Table 2.

Thoracic CT verified pulmonary embolic events in 6 patients with isolated right-sided IE among opioid abusers (8%), while 2 patients in the CA-IE group with right-sided IE exhibited pulmonary emboli (3.9%) ($p = 0.034$). Although thrombocyte counts, protein C and S levels, and PT values were within acceptable limits in individuals experiencing a pulmonary embolic event, D-dimer levels were markedly elevated in those with a pulmonary embolus. The mean D-Dimer and INR readings were 657 $\pm$ 119.8 ng/mL and 1.9 $\pm$ 0.8, respectively.

Isolated right-sided IE was substantially more prevalent in patients with opioid-related IE compared to CA-IE group ($p = 0.012$). Conversely, left cardiac involvement was more frequent in the CA-IE group than in opioid-abusing IE patients (odds ratio: 2.02, 95% confidence interval: 1.44–4.09, $p = 0.014$). Table 3 presents surgical procedures, perioperative features, and postoperative results.

The duration of ventilatory support was considerably prolonged in opioid-abusing patients compared to CA-IE (8.9 $\pm$ 1.4 hours vs 5.2 $\pm$ 1.2 hours, $p = 0.003$). The average ICU duration for patients who utilized opioids and CA-IE was 3.9 hours and 2.1 hours, respectively ($p = 0.01$). The median hospitalization duration for patients with IE who abuse opioids was 49.9 $\pm$ 19.4 days, but for patients with CA-IE, it was 27.1 $\pm$ 12.2 days ($p = 0.022$). In the CA-IE group, preoperative atrial fibrillation and the emergence of new arrhythmias were more prevalent compared to patients with opioid misuse (1.3% vs 9.8%, $p < 0.001$). Double valve replacement was markedly higher in opioid-abusing patients compared to the CA-IE group (10.6% vs 3.9%, $p = 0.006$). Moreover, tricuspid valve repair in conjunction with mitral valve replacement was a more prevalent surgical procedure among opioid-abusing patients compared to those with CA-IE (10.6% vs 5.8%, $p = 0.01$). The incidence of third-degree atrioventricular block necessitating pacemaker installation was markedly elevated in CA-IE patients (2.6% vs 3.9%, $p = 0.042$). A pretreatment elevated creatinine level was identified in 19 patients (15%). The prevalence of elevated creatinine levels in people abusing opioids was 15.3%, compared to 9.3% in patients with CA-IE ($p = 0.002$). No statistical difference was observed in the requirement for hemodialysis postoperatively between the two groups. No association was seen between elevated ES-2 levels and concomitant conditions regarding in-hospital

Table 1. Patient demographics in cases of infective endocarditis. Biochemical analyses, comorbid conditions, and echocardiographic results.

Basic characteristics	Total (n = 126)	PWAO (n = 75)	CA-IE (n = 51)	*p*
Age (years)	49.7 ± 5.4	38.9 ± 11.4	59.4 ± 16.9	0.001
Gender (male/female)	109/17	75/0	34/17	0.0001
Mean BMI (kg/m^2)	21.4	19.6	22.4	0.002
Hemoglobin (g/L, interquartile range)	12.1	11.5 (8.2–13.4)	13.8 (9.8–14.6)	0.002
Previous valve replacement (n; %)	7 (5.5)	-	7 (13.7)	0.001
Median white blood cell count (10^9/L)	18.4	17.4	19.8	NS
Mean creatinine level (g/dL)	142	174	82	0.006
Mean albumin (g/dL)	4.6	2.7	5.8	0.003
Medication				
β-blocker (n, %)	67 (53.1%)	49 (65%)	18 (35.9%)	0.07
Calcium channel blocker (n, %)	52 (41.2%)	33 (44%)	19 (37.2%)	NS
ARB or ACEI (n, %)	79 (62.6%)	47 (62%)	32 (62%)	1.0
Diuretics (n, %)	81 (64.2%)	58 (77.3%)	23 (30.6%)	NS
Comorbid disorders				
Smoking (n, %)	38 (30.1%)	29 (38.6%)	9 (17.6%)	0.011
High creatinine level (n, %)	19 (15%)	7 (9.3%)	12 (15.3%)	0.002
Rhythm disturbance (n, %)	17 (13.4%)	4 (5.3%)	13 (16.6%)	0.0001
Previous MACCE (n, %)	5 (3.9%)	1 (1.3%)	4 (7.8%)	0.001
Hypertension (n, %)	16 (12.6%)	3 (4%)	13 (25.4%)	0.001
Diabetes (n, %)	16 (12.6%)	2 (2.6%)	14 (27.4%)	0.001
COPD (n, %)	14 (11.1%)	3 (4%)	11 (21.5%)	0.001
NYHA-class				
I (n, %)	27 (21.4%)	16 (21.3%)	11 (21.5%)	NS
II (n, %)	42 (33.3%)	22 (42.6%)	20 (39.2%)	NS
III (n, %)	43 (34.2%)	29 (28%)	14 (27.4%)	NS
IV (n, %)	14 (11.1%)	8 (10.6%)	6 (11.7%)	NS
Euro-SCORE-II	2.6 ± 0.9	1.9 ± 0.3	3.2 ± 1.1	0.022
Echocardiography				
Mean LVEF (%)	56.1 ± 20.4	54.8 ± 18.1	58.5 ± 22.1	NS
LVEF <35 (n, %)	13 (10.3%)	9 (12%)	4 (7.8%)	0.033

Continuous variables were expressed as mean ± standard deviation when normally distributed, or as median (interquartile range) in other cases. Categorical variables were provided as absolute values (percentages). BMI, body mass index; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; MACCE, major adverse cardiac and cerebrovascular event; LVEF, left ventricular ejection fraction; PWAO, patients who misuse opioids; Statistically significant if $p < 0.05$.

mortality (HR: 1.03, 95% CI: 0.78–1.24), $p = 0.470$. Furthermore, multivalvular surgery (HR: 0.88, 95% CI: 0.67–0.98, $p = 0.419$), prolonged ECC (HR: 0.76, 95% CI: 0.58–0.91, $p = 0.492$), and pulmonary embolic events were not associated with postoperative mortality (HR: 0.61, 95% CI: 0.49–0.74, $p = 0.543$).

Follow-Up Period

No patients were lost during the follow-up period in either group. The median follow-up duration for patients who abuse opioids-IE and CA-IE was 60.7 ± 23.3 months (maximum 77 months) and 59.4 ± 24.9 months (maximum 69 months), respectively. The survival rates in both groups are summarized in Table 4. In patients who abuse opioids, the 1-year and 3-year survival rates were 89.6% and 88%, respectively, while the 1-year and 3-year survival rates in the CA-IE group were 96% and 94% (P1 = 0.89, P2 = 0.94). The four-year survival rates for IE patients who abuse opioids and the CA-IE group were comparable (81.5% vs 82.4%) ($p = 0.660$). At the conclusion of the follow-up period, the overall survival rate was markedly lower in patients who abused opioids compared to those with CA-IE (64.3% vs 76%, $p = 0.031$).

Table 5 summarizes univariate and multivariate logistic regression models for predicting all-cause mortality. Opioid usage was an independent predictor of mortality risk (HR: 2.012, 95% CI: 1.96–4.56, $p = 0.02$). Urgent surgery (HR: 1.96; 95% CI: 1.41–5.12, $p = 0.024$), preoperative

Table 2. Etiological microorganisms associated with infective endocarditis and valvular involvement.

Etiologic agents	Total: 126	PWAO (n = 75)	CA-IE (n = 51)	*p*
S. aureus (n, %)	55 (42.6)	36 (48)	19 (37.2)	0.66
Streptococci (n, %)	33	20 (28)	13 (25.1)	0.449
Enterococcus (n, %)	10	5 (5.3)	5 (15.6)	0.026
Fungal (n, %)	6	3 (4)	3 (3.9)	0.89
Actinobacillus (n, %)	1 (0.8)	1 (1.3)	-	
Cardiobacterium (n, %)	1 (0.8)	-	1 (1.9)	0.79
Pseudomonas aereginosa (n, %)	3 (2.3)	2 (2.6)	1 (1.9)	
Total (n, %)	109 (86.5)	67 (89.3%)	42 (82.3%)	0.78
Culture negative (n, %)	17 (13.4)	12 (16)	5 (9.8)	
Single valve IE				
Tricuspid valve (n, %)	43	34 (45.3)	9 (17.6)	0.012
Mitral valve (n, %)	22	11 (14.6)	11 (21.5)	0.004
Aortic (n, %)	18	6 (8)	12 (23.5)	0.021
Prosthetic valve (n, %)	7	-	7 (13.7)	0.001
Total (n, %)	90 (71.4)	53 (70.6)	32 (62.7)	0.036
Multivalvular involvement IE				
Tricuspid + mitral valves (n, %)	18 (14.2)	14 (18.6)	4 (7.8)	0.013
Mitral + aortic valves (n, %)	18 (14.2)	8 (10.6)	10 (19.6)	0.036
Total (n, %)	36 (28.4)	22 (29.3)	19 (37.2)	0.044

Table 3. Surgical prcedures, operative characteristics, and postoperative outcomes.

	Total (126)	PWAO (75)	CA-IE (51)	*p*
Surgical procedures				
TVRep. (n, %)	35	28 (37.3)	7 (13.7)	0.0001
TVR (n, %)	8	6 (8)	2 (3.9)	0.026
MVR (n, %)	8	4 (5.3)	4 (7.8)	0.023
MVRep. (n, %)	15	7 (9.3)	8 (15.6)	0.655
AVR (n, %)	18	6 (8)	12 (23.5)	0.003
Surgical approach for multivalvular involvement				
TVrep.+MVR (n, %)	11	8 (10.6)	3 (5.8)	0.01
TVR+MVrep. (n, %)	10	6 (8)	4 (7.8)	0.890
AVR+MVR (n, %)	10	8 (10.6)	2 (3.9)	0.006
Mean ECC (min.)	121 ± 34.5	109 ± 14.2	144 ± 22.8	0.378
Mean ACC (min.)	76 ± 12.8	81 ± 13.9	94 ± 18.1	0.556
Inotropic use (%)	73	66.3	59.8	0.590
Mean intubation time (hours)	6.3 ± 2.8	8.9 ± 1.4	5.2 ± 1.2	0.003
Wound infection (n, %)	7 (5.5)	4 (2.6)	3 (5.8)	0.654
NOAF (n, %)	6	1 (1.3)	5 (9.8)	<0.001
A-V block (n, %)	4	2 (2.6)	2 (3.9)	0.042
Dialyses (n, %)	6	4 (5.3)	2 (3.9)	0.534
Stroke (n, %)	4 (3.1)	3 (4)	1 (1.9)	0.430
Mean postoperative Hgb (g/dL)	10.8 ± 4.8	9.3 ± 4.3	12.7 ± 5.8	0.046
Transfusion [Unite]	2.4 ± 9.8	2.6	2.2	0.955
Mean LOS in ICU (days)	3.4 ± 2.2	3.9 ± 1.2	2.1 ± 0.8	0.01
Mean hospitalization (days)	39.2 ± 12.7	49.0 ± 19.0	27.1 ± 12.2	0.022
Revision after surgery (n, %)	3 (2.3)	2 (2.6)	1 (1.9)	0.439
In-hospital mortality (n, %)	8 (6.3)	5 (6.6)	3 (5.8)	0.685

congestive heart failure (HR: 2.58; 95% CI: 1.94–5.07, $p = 0.032$), and redo valve surgery (HR: 1.78; 95% CI: 1.29–6.04, $p = 0.002$) were further predictors of mortality.

The Kaplan–Meier survival curve analyses for patients who abuse opioids-IE shown in Fig. 1.

The follow-up period indicated that the reoperation rate among patients who abuse opioids was substantially

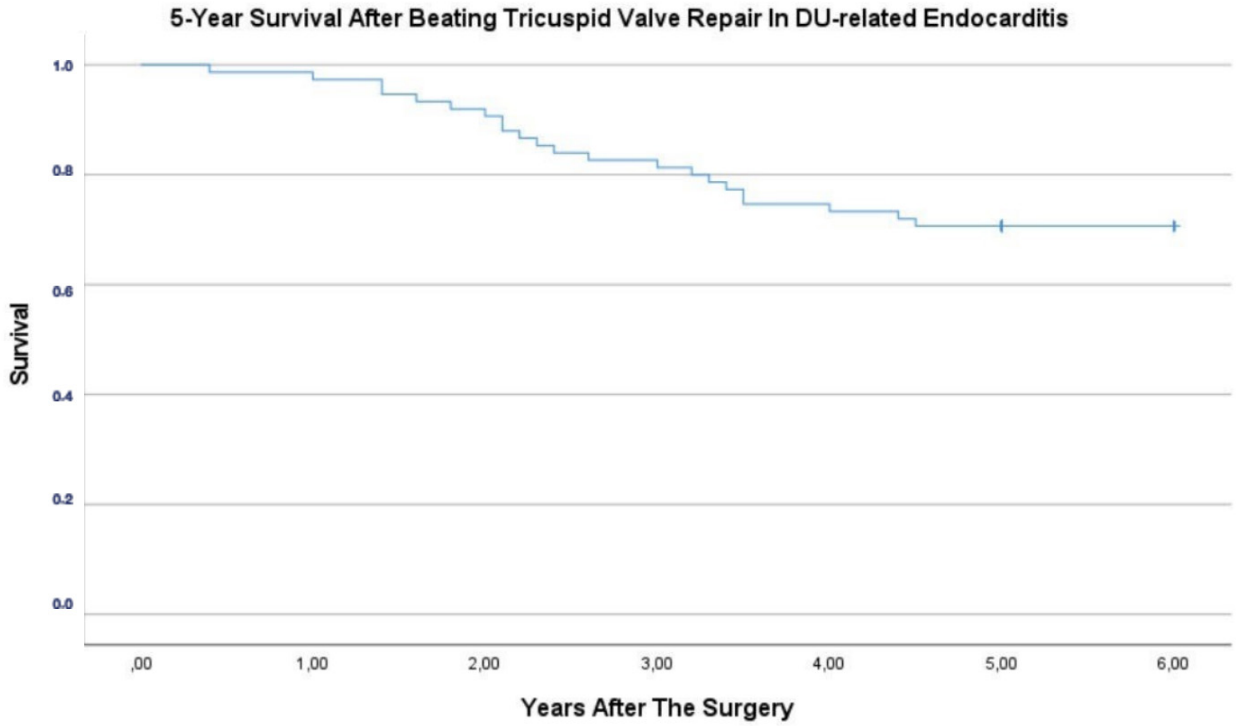

Fig. 1. Kaplan-Meier survival curve analyses shows abuse of opioids with endocarditis. Follow-up Time is given in years.

Table 4. Mortality during follow-up period.

	PWAO-IE (70)	CA-IE (50)	*p*
1-year mortality (n, %)	6 (8.5)	4 (8.3)	0.89
3-year mortality (n, %)	8 (11.4)	6 (12)	0.94
5-year mortality (n, %)	11 (15.7)	2 (4)	0.042
Overall mortality (n, %)	25 (35.7)	12 (24)	0.031

Continuous variables are presented as mean ± standard deviation if normally distributed, or as median (IQR) otherwise. Categorical variables are characterized by absolute values (percentages). IE, infective endocarditis. Patients who misuse opioids are individuals who administer medicines via injection. PWAO: individuals who misuse opioids, CA-IE, community-acquired infective endocarditis. Statistically significant if $p < 0.05$.

higher than that of CA-IE (8.5% vs 4%) (OR: 4.12; $p = 0.01$).

The cumulative incidence of readmission was considerably greater in patients who abuse opioids compared to those who do not. Nine opioid users (12.8%) were readmitted due to a new episode of IE during the follow-up period, while the recurrence incidence of IE was 4% among patients with community-acquired IE (n = 2 patients) (OR: 3.96; $p = 0.004$). It has been reported that 7 of the 9 IE patients who were readmitted to the hospital did recur to opiate use. All patients in both groups exhibited significant valvular damage with a new episode of infective endocarditis. The mean delay from the initial surgery to reoperation was 26.4 ± 11.4 months (range: 7–39 months) in the CA-IE group, whereas the mean interval from hospital discharge to reoperation was 24.1 ± 10.2 months (range: 8–26 months) in patients with opioid misuse.

Despite the use of antibiotics alongside extensive medical treatment for IE recurrence over a period of four weeks, six opioid users necessitated reoperative valve surgery. The remaining three patients with a fresh episode of infective endocarditis in the opioid addiction group were discharged with medical therapy alone. Medical treatment was unsuccessful in two patients within the CA-IE group. Consequently, we executed valve replacement and discharged the patient from the hospital in a stable clinical condition.

4. Discussion

We reported the clinical results of our population-based retrospective observational analysis, which included 126 patients with infective endocarditis, of whom 75 had a history of opiate misuse, conducted between June 1, 2007, and September 1, 2024. Data from patients were obtained from the hospital database and their medical records. No difference was observed when comparing preoperative NYHA functional class and preoperative mean LVEF between the two groups; however, LVEF was below 35% in 12% of patients with opioid misuse and 7.8% in CA-IE ($p = 0.033$). Comorbidities were more prevalent in the CA-IE group. The Logistic ES-2 score was considerably elevated in CA-IE compared to patients who abuse opioids (64% vs 13%, HR: 1.23, $p = 0.001$). The majority of individuals who

Table 5. Cox's regression analysis for all-cause mortality.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Opioid use	2.026 (1.304–6.09)	0.01	2.012 (1.96–4.56)	0.002
Urgent surgery	1.67 (1.24–3.64)	0.001	1.96 (1.41–5.12)	0.024
Redo valvular operation	1.23 (2.20–6.26)	0.01	1.78 (1.29–6.04)	0.002
Congestive heart failure	2.88 (1.122–4.329)	0.002	2.58 (1.94–5.07)	0.032

CI, confidence interval; HR, hazard ratio. Significant if $p < 0.05$.

misuse opioids have a history of heroin and cocaine use. Oral methamphetamine and dextroamphetamine were the other stimulant agents utilized. No substantial difference was observed in comparison to the causative bacteria. Table 2 indicates that blood cultures were negative in 13.4% of patients overall. Patients who misuse opioids and had CA-IE were primarily infected with Staphylococcus and Streptococcus species (OR: 0.67, 95% CI: 0.44–1.02, $p = 0.39$). In our cohort, depression and alcohol addiction were more prevalent among patients who abused opioids compared to the CA-IE group. Consistent with prior research, the prevalence of Hepatitis C was significantly higher in opioid users compared to the CA-IE group (41.3% vs 6.6%) ($p < 0.001$).

No significant difference was found when compared to in-hospital mortality in both groups. In previous studies, the authors reported some contradictory results regarding mortality after IE surgery in opioids users [7–9]. In addition, our results of lenght of stay in ICU, and hospitalization were similar compared to previous studies [9–12]. No significant difference in mortality has been observed between opioid users and individuals with CA-IE in prior studies, nevertheless, other data suggests greater death rates among opioid users [10–12]. However, in accordance with our findings, the authors found elevated rates of reoperation and a new episode of infective endocarditis in drug users compared to non-users [13–15].

Previous investigations indicated varying frequencies of isolated right heart, isolated left heart, or biventricular involvement in patients with infective endocarditis. Consistent with prior data, isolated right-sided IE was more prevalent and associated with a higher incidence of pulmonary embolic events in individuals with opioid addiction compared to those with community-acquired IE. We conducted valvular repair in over 50% of opioid users, while valvular repair was appropriate for approximately 25% of patients with CA-IE. The necessity for valve replacement was comparable in both groups (50% vs 52.9%). Multivalvular surgery necessitated by biventricular involvement was markedly more prevalent in opioid-abusing patients compared to those with CA-IE (32% vs 17.6%).

As anticipated, patients with substance addiction issues were much younger and exhibited fewer comorbidities compared to those with CA-IE. Nonetheless, the length of stay in the ICU and the duration of hospitalization were more likely extended in patients who abuse opioids compared to the CA-IE group. Significantly, all opioid-using patients with injection drug use were male, which may reflect local epidemiological trends. Consequently, our study exhibited no selection bias.

The characteristics of patients and their preoperative clinical status for IE surgery are crucial determinants of mortality and the recurrence of new infective endocarditis post-surgery. The rates of independence from recurrence of IE were 90%, 75%, and 64% among opioid users, and 95%, 92%, and 90% among patients with CA-IE, respectively. The incidence of valve reoperation was elevated in opioid users compared to non-users in the multivariable logistic analysis (HR: 2.94; 95% CI: 1.98–5.62, $p < 0.001$). Our analysis indicated that advanced age, female sex, severe congestive heart failure, vegetation size, and urgent surgical procedures were associated with increased mortality risk factors. Other authors demonstrated that intravenous drug usage with bi-ventricular involvement was a determinant for mortality.

To achieve favorable outcomes following IE surgery, several treatment modalities and surgical scheduling have been proposed, particularly for patients with opioid dependence. The authors examined the results of individuals with infective endocarditis who underwent just medical treatment against those who got surgery followed by medical treatment [12–14]. Østergaard *et al.* [12] demonstrated that there was no significant difference in mortality rates among their patients with infective endocarditis when comparing conservative treatment alone to surgical intervention. Although the mortality rate was comparable between drug users with IE and CA-IE following medical treatment alone, the recurrence of IE and endocarditis-related cardiovascular events, such as MACCE, was considerably elevated in patients who underwent only conservative treatment over the follow-up period. Ternhag *et al.* [13] and Delahaye *et al.* [14] reported similar mortality rate in their series who underwent surgery or medical treatment only. Shrestha *et al.* [15] revealed that conservative treatment alone could facilitate recovery in over 50% of patients with infective endocarditis. In addition, Rodger *et al.* [16] reported clinical results after medically treatment alone and surgery in their IE patients. They proposed that surgery for IE was associated with lower mortality as was referral to addiction treatment.

Clinical results were comparable in both groups. To achieve favorable results, we recommend surgical intervention involving the extensive excision of all contaminated tissues in patients with infective endocarditis who exhibit significant valve dysfunction, with or without recurrent pulmonary embolism, and who have congestive heart failure. The length of stay in intensive care and duration of hospitalization were short in patients who received minimally invasive surgery in our group. Consequently, for chosen patients with isolated right-sided infective endocarditis, we recommend a right anterior mini-thoracotomy utilizing a beating heart approach. However, randomized clinical trials are necessary to examine the benefits of minimally invasive procedures utilizing a beating heart in specific individuals.

Kocabaş *et al*. [17] documented the surgical results of 210 individuals with CA-IE over a span exceeding 15 years. Seventeen Recovery was achieved in 24% of patients following solely medicinal treatment; nevertheless, surgery was necessitated for their 110 patients with IE. The death rate in Kocabaş's study [17] was superior to that of our series (19.5% compared to 5.8%). In contrast to our series, they did not report the outcomes of their surviving patients over the follow-up period. Wurcel *et al*. [18] reported the outcomes of 228 patients with infective endocarditis, of whom 79 were opioid abusers. Consistent with our study findings, the disparity in short-term mortality was not substantial in either group. They demonstrated that opioid use-related IE was linked to a higher death rate compared to CA-IE over the follow-up period (53% vs 31%).

The median follow-up in our study was 60.7 $\pm$ 23.3 months for the overall cohort, and 59.4 $\pm$ 24.9 months for patients with opioid abuse and the CA-IE group, respectively. Although results were comparable in both groups over four years (excluding recurrence of infective endocarditis and reoperation), the mortality rate was considerably elevated in patients with opioid misuse compared to those with community-acquired infective endocarditis (34% vs 14%, $p = 0.003$) at the conclusion of the follow-up period. Our study findings indicate that opioid misuse, urgent surgery, congestive heart failure, and redo valve surgery are independent predictors of mortality in patients with infective endocarditis throughout the follow-up period.

Surgery for TVIE (replacement or repair) and mitral valve repair were the predominant surgical interventions in IE patients with opioid misuse compared to those without in our cohort. Ramadan *et al*. [9] have found similar results. They demonstrated that the tricuspid valve was the most damaged valve in patients who abuse opioids, presenting with a higher incidence of pulmonary embolic events. Other major findings in our study included that the duration of ventilatory support, length of stay in the ICU, and overall hospitalization time were markedly greater in patients with opioid misuse compared to those with CA-IE.

Complications, in-hospital mortality, and long-term mortality following IE surgery remain divergent and contentious. Consistent with our study, the 30-day mortality following IE surgery among drug users was comparable to that observed in CA-IE in several prior investigations [3–5]. Although mortality and morbidity factors for long-term outcomes in IE patients were consistent across numerous studies, there are conflicting data on mortality determinants, survival rates, readmission, and reoperation rates [6,9]. According to our investigation, numerous publications demonstrated that prognosis was markedly unfavorable in opioid users following IE surgery during the follow-up period [5–9]. We hypothesise that relapse to drug use, poor hygiene, the heterogeneity of characteristics of patients, and severity of cardiovascular disorders are responsible for different outcomes after IE surgery. While older age, female gender, and congestive heart failure were reported as mortality factors [1,2], vegetation size [7], embolic events [7,8], and time-dependent covariates [9] were reported as mortality factors. Pericàs *et al*. [6] showed that left heart involvement and intracardiac complications associated with infective endocarditis were factors contributing to mortality. Martín-Dávila *et al*. [7] showed that fungus as a cause of IE with septic shock was associated with higher mortality rates. Smith and colleagues [8] established that significant renal impairment, respiratory problems, and the utilization of an intraaortic balloon pump were determinants of mortality. In contrast to prior studies, our study findings indicated that vegetation size, pathogenic microorganisms, and intracardiac problems were not factors influencing mortality. Our study findings indicated that patients with right heart infective endocarditis and substantial vegetation size were at increased risk for pulmonary embolic events. Consequently, to verify preoperative pulmonary impairment and ensure suitable postoperative care, we recommend thoracic CT for patients with right-sided infective endocarditis exhibiting significant vegetation size prior to surgery.

Numerous scientific research indicate that the prevalence of opioid-addicted individuals undergoing IE surgery ranges from 8% to 29%. Beapark *et al*. [10] documented 510 patients with infective endocarditis, of which 11% had a history of opioid misuse. In contrast to previous studies, the proportion of intravenous drug users among infective endocarditis patients in our cohort was substantially higher than that of culture-negative infective endocarditis patients (59.5% vs 40.5%). Although the survival rates were comparable both postoperatively and during the lengthy follow-up period (19.9% vs 20.3%), patients who abused opioids exhibited a 1.5-fold increased risk of mortality in the mid-term follow-up. The chances of readmission and reoperation were thrice higher in patients who abuse opioids compared to those with CA-IE. Although postoperative survival rates were comparable between both groups, patients who abused opioids exhibited significantly greater mortality, readmission, and reoperation rates throughout the follow-up period

compared to patients with CA-IE. Our findings aligned with Beapark's research [10].

Østerdal *et al*. [11] reported a cohort of 29 intravenous opioid users who had IE required heart valve surgery between 2001 and 2013. Their data demonstrated a 5-year mortality rate of 41%. In this study, 70% of intravenous drug users relapse upon hospital release. New episodes of IE were the primary cause of mortality among opioid users, occurring in 54% of patients. In our series, the incidence of new IE episodes and mortality during the same follow-up period among patients who abuse opioids was lower than that reported in Østerdal's series (25% vs 54%) [11]. This could be attributed to the features of the patients. Beapark and colleagues [10] have demonstrated analogous findings about the reinstated drug use and elevated death rate over the follow-up period. Beapark's study [10] showed that 76% of drug users died or readmitted to hospital due to reinfections. They assessed that 49 patients experienced a recurrence in drug usage. Among the 15 patients who underwent reoperation in the study, 13 had relapsed into drug usage necessitating the reoperation [10]. The rates of freedom from reinfection in their study were 62%, 42%, and 12% at 1 year, 3 years, and 6 years, respectively. Our study findings indicate that 7 out of 9 patients with opioid misuse and IE recurrence necessitated re-operation within our cohort. However, due to the absence of accurate data regarding the prevalence of opioid reuse following hospital discharge, we were unable to present the rate of relapse to opioid recidivism in our study.

Currently, there is no established agreement or strategy on superior treatment methods for infective endocarditis, particularly in opioid-dependent individuals. Shrestha *et al*. [15] found that mortality following IE surgery or reoperation due to a new episode of IE was more than tenfold greater in patients with opioid addiction compared to those with community-acquired IE. Straw *et al*. [19] reported that the death rate following IE surgery in opioid abusers was approximately 50% at the five-year mark. The survival rate throughout the 5-year follow-up period in both Beapark's [10] and Straw's studies [19] was much lower than that of our IE patients who take opioids. This may be attributed to an increased incidence of infective endocarditis and subsequent reoperations resulting from relapse into substance usage following hospital release in these prior studies.

The interdisciplinary consensus study released by The Association of Turkish Thoracic and Cardiovascular Surgery addresses diagnostic procedures for infective endocarditis, therapeutic options, preventative measures, risk score calculations, and optimal surgical time [20]. The study indicates that the incidence of IE among opioid abusers is 1.125 per 100,000 population. The survey indicates that opioid drug usage has risen among the youth in our country over the past two decades. Comparable reports have been disseminated by The European Cardiovascular Surgery, focusing on the enhancement of treatment protocols post-surgery in patients with infective endocarditis [21]. Opioid usage has reportedly risen over the past decade in the United States and European countries. Investigations indicate a rise in endocarditis associated with opioid usage [20,21].

Previous study results indicated no difference in mortality rates between opioid users and non-users, while other studies suggested an elevated mortality rate among individuals who abuse opioids. Numerous investigations have demonstrated elevated rates of reoperation and reinfection in individuals who abuse opioids compared to those with AC-IE. The recurrence of IE is prevalent and significantly contributes to post-discharge mortality; therefore, regular examinations following the treatment of IE patients are crucial. The causes of the new episode of IE have been examined by several authors [22,23]. Effects of relapse to drug use has been found as a reason of reinfection, reoperation, and mortality by Song and co-workers [19], and Rosenthal *et al*. [23]. They found that higher rate of in-hospital mortality due to recurrent IE episode even though in-hospital mortality rate was similar in their both groups.

5. Limitation

Our study was a single-center retrospective observational analysis with a somewhat limited sample size of patients who misuse opioids. The response rate for our survey was 100%, allowing for the estimation of the cumulative incidence of reoperation post-discharge. Nonetheless, both univariate and multivariate Cox regression models yielded solid results, illustrating the significant impact of opioid misuse on mortality rates during the mid-term follow-up period. The absence of data regarding relapse status and socioeconomic factors constituted an additional drawback of our study. Furthermore, there was a lack of reliable data regarding opioid addiction therapy in other hospitals. For the majority of patients who misuse opioids, there is insufficient data concerning continued drug use beyond hospital release. We could provide little data regarding their operation in another facility during the lengthy follow-up period. We attempted to conduct regression analysis to account for clinical factors. Nonetheless, it is statistically challenging to account for the disparities within our group. We were unable to obtain information regarding the duration of antibiotic therapy and if the surviving patients underwent drug rehabilitation at a drug addiction center.

6. Conclusion

Our study indicates that opiate addiction has led to a rise in incidence of IE in our country over the years. One of the significant elements of our study may contribute to the creation of a national database for opioid-related incidents of injury and exposure. Our findings indicate that mid-term outcomes following surgery for endocarditis in patients with a history of opioid misuse were adversely affected by elevated death rates, readmissions, re-operations,

and occurrences of new infective endocarditis episodes. Furthermore, patients who misuse opioids were younger than those reported in other research conducted in Europe and the United States. We provided nutritional support to undernourished patients with IE throughout the preoperative phase for the first time. It is essential to consider that the rising admission of young patients with IE who are opioid users presents challenges for care due to their systemic inflammation, inadequate hygiene, compromised nutritional status, and microangiopathy resulting from the use of contaminated materials. To address IE recurrence, we recommend valve repair utilizing biological material accompanied by vigorous debridement rather than valve replacement. Previous research indicates that drug recidivism significantly contributes to the recurrence of IE and mortality; therefore, doctors should consider referring patients to drug addiction treatment centers post-discharge. We require additional prospective trials in a substantial case series involving individuals with infective endocarditis who misuse opioids to establish a consensus on the treatment of this specific patient population.

Availability of Data and Materials

Data may be made available upon reasonable request to corresponding author.

Author Contributions

Study Design: OFD and AÇ, Data collection and processing: AÇ and OFD, Preoperative evaluation of malnutrition; DD, Review of Data analyses and interpretation: AÇ, DD; Writing of Article; OFD, AÇ. All authors contributed to critical revision of the manuscript, and read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The retrospective study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (No: 2924). All patients signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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