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MAJOR ARTICLE

Correlates of 90-Day Mortality Among People Who Do and Do Not Inject Drugs With Infective Endocarditis in Seattle, Washington

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Background. Infective endocarditis (IE) remains highly morbid, but few studies have evaluated factors associated with IE mortality. We examined correlates of 90-day mortality among people who inject drugs (PWID) and people who do not inject drugs (non-PWID).

Methods. We queried the electronic medical record for cases of IE among adults ≥18 years of age at 2 academic medical centers in Seattle, Washington, from 1 January 2014 to 31 July 2019. Cases were reviewed to confirm a diagnosis of IE and drug use status. Deaths were confirmed through the Washington State death index. Descriptive statistics were used to characterize IE in PWID and non-PWID. Kaplan-Meier log-rank tests and Cox proportional hazard models were used to assess correlates of 90-day mortality.

Results. We identified 507 patients with IE, 213 (42%) of whom were PWID. Sixteen percent of patients died within 90 days of admission, including 14% of PWID and 17% of non-PWID ($P = .50$). In a multivariable Cox proportional hazard model, injection drug use was associated with a higher mortality within the first 14 days of admission (adjusted hazard ratio [aHR], 2.33 [95% confidence interval {CI}, 1.16–4.65], $P = .02$); however, there was no association between injection drug use and mortality between 15 and 90 days of admission (aHR, 0.63 [95% CI, .31–1.30], $P = .21$).

Conclusions. Overall 90-day mortality did not differ between PWID and non-PWID with IE, although PWID experienced a higher risk of death within 14 days of admission. These findings suggest that early IE diagnosis and treatment among PWID is critical to improving outcomes.

Keywords. infective endocarditis; people who inject drugs; PWID; mortality.

Infective endocarditis (IE) remains a highly morbid condition with an estimated mortality of 15%–30%, even in high-resource settings with access to life-sustaining therapies [1–4]. Injection drug use is a major risk factor for IE, and over the past several decades, a documented rise in the incidence of IE in the United States has paralleled the rise in opioid and stimulant use disorders [5–9]. The management of IE in people who inject drugs (PWID) is complex given the high recurrence rates, social marginalization, stigma from healthcare providers, chronic viral infections (eg, hepatitis C virus [HCV], human immunodeficiency virus [HIV]), overdoses, and barriers to treatment adherence suffered by this group [10–12]. For these reasons, and in the setting of rising hospital admissions among PWID [13], healthcare systems need to better understand the unique needs and challenges faced by PWID, particularly in the management of highly morbid conditions such as IE [6, 14].

Updated IE treatment guidelines emphasize the need for cross-specialty collaboration [15] to provide PWID the supportive care necessary for prolonged antibiotic courses and possible operative management [16, 17]. However, contemporary data on clinical outcomes of IE are largely limited to small cohorts, and few have directly compared clinical features and mortality among PWID to those who do not inject drugs (non-PWID). To better assess the impact of injection drug use on outcomes among patients with IE, we performed a retrospective analysis evaluating differences in overall 90-day and 6-month mortality and explored the correlates of 90-day mortality in a large urban cohort of people with IE who do and do not inject drugs.

METHODS

Study Setting and Population

We completed a longitudinal cohort analysis of patients admitted to 2 academic medical centers in Seattle, Washington.

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The study population included persons ≥18 years of age who were admitted to either the University of Washington Medical Center–Montlake (UWMC-ML) or Harborview Medical Center (HMC) with a new diagnosis of IE between 1 January 2014 and 31 July 2019. Cases of IE were identified by applying a string-searching and pattern-matching text query for endocarditis in the diagnoses field of discharge summaries within the clinical data repository that comprises electronic health records from both hospitals. This method of case identification has been previously published, showing a sensitivity of 76%, a specificity of 98%, and positive predictive value of 85% for identifying cases of IE [18]. Using a standardized data collection form (REDCap) [19, 20], all cases were subsequently confirmed by review of the medical record, which was performed by a member of the study team. For patients with a clinical diagnosis of endocarditis but no evidence of vegetation on transthoracic or transesophageal echocardiogram, or in ambiguous cases, records were reviewed by 2 infectious diseases (ID) physicians and included in the cohort if they met the modified Duke criteria for definite IE [21, 22].

Only index hospitalizations for IE were included in the study. For patients with multiple hospitalizations for IE during the study period, only the earliest hospitalization was counted. Patients <18 years of age, those with a history of IE but no active infection, and those who were transferred to either UWMC-ML or HMC following completion of antibiotic therapy were excluded from the cohort. Patients with intracardiac device infections were similarly excluded unless they had concurrent valvular involvement.

Variables and Measures

We extracted demographic information, including age, sex, race, and health insurance status from the data repository. Information on death was obtained from discharge summaries and from the Washington State death index, which links to our data repository. Comorbid conditions were identified from *International Classification of Diseases, Ninth Revision* or *Tenth Revision* codes, admitting diagnoses, diagnoses associated with a procedure, discharge diagnoses, and encounter diagnoses. Clinical variables, including the date of admission, admission to the intensive care unit (ICU), valve surgery within 90 days of admission, date of discharge, length of stay, and readmission within 30 days, as well as microbiologic and valvular data, when noted in the discharge summary, were also extracted. Chart review was performed to fill in missing clinical variables and to verify housing status at the time of admission and injection drug use status, both of which were obtained from the social history section of admission notes and initial ID consult notes or from social work notes. Patients were classified as PWID if there was documentation of active injection drug use at the time of admission, or if clinical notes indicated they had injected drugs within the prior 3 months. If information on housing status and/or injection drug use was missing from the medical record, the individual was classified as housed and/or non-PWID. Interrater reliability for determining PWID status was assessed for a random 12% of cases, comparing initial classification of PWID status with that obtained by the review of an ID physician, blinded to the original ascertainment. This review demonstrated excellent concordance with 98% agreement in assessments of PWID status and a κ statistic of 0.96 (95% confidence interval [CI], .89–1.03).

Left-sided endocarditis was defined as involvement of the mitral or aortic valve, while right-sided endocarditis was defined as involvement of the tricuspid or pulmonic valve. In the setting of no valvular involvement on echocardiography but evidence of septic pulmonary emboli, participants were classified as having right-sided endocarditis.

Statistical Analysis

We tabulated descriptive statistics for baseline characteristics, including frequencies and proportions for categorical variables and medians and ranges for continuous variables. χ^2, Fisher exact, and *t* tests were used, as appropriate, to assess and determine differences between IE patients based on injection drug use status.

The χ^2 test was used to compare the proportion of PWID and non-PWID who died within 90 days and 6 months of admission. Kaplan-Meier log-rank tests and multivariable Cox proportional hazard models were used to assess for correlates of 90-day mortality. We identified factors a priori that were previously reported or suspected to be associated with mortality, which included age, sex, left-sided endocarditis, *Staphylococcus aureus* endocarditis, and current injection drug use. In accordance with prior studies [6, 23, 24], and because the risk of death due to IE is unlikely to be constant with increasing age, we chose to evaluate age using categorical groups. To satisfy the proportional hazards assumption, the correlation between 90-day mortality and injection drug use was evaluated using time-dependent variables. The Kaplan-Meier curves suggested a drop in mortality rate after 2 weeks, so separate hazard ratios were calculated for mortality between the date of admission (day 0) and 14 days postadmission and between 15 and 90 days postadmission. All statistical analyses were performed in R software, version 4.0. This study was approved by the Institutional Review Board at the University of Washington (STUDY00003291).

RESULTS

We identified 507 patients with IE hospitalized between 1 January 2014 and 31 July 2019, 213 (42%) of whom had injected drugs in the past 3 months. The median age of the cohort was 45 years (interquartile range, 32–60 years), 76% were White and non-Hispanic, 92% had health insurance,

and 23% were living unhoused (Table 1). Nearly half (49%) were admitted to the ICU at some point during their hospitalization, and 24% underwent cardiac valve surgery within 90 days of admission. The most common microbiologic etiologies for IE were methicillin-sensitive *S aureus* (MSSA) (27%), *Streptococcus* species (23%), and methicillin-resistant *S aureus* (MRSA) (22%). The tricuspid (38%) and aortic (38%) valves were most commonly affected.

When comparing PWID to non-PWID, PWID were younger (median age, 33 vs 56 years, $P < .001$), more likely to be female (46% vs 29%, $P < .001$), more likely to be living unhoused (43% vs 8%, $P < .001$), and less likely to have underlying

Table 1. Demographic Characteristics of People Who Do and Do Not Inject Drugs With Infective Endocarditis at 2 Seattle Hospitals, 2014–2019

Characteristic	Entire Cohort (n = 507)	PWID (n = 213)	Non-PWID (n = 294)	*P* Value[a,b]
Median age, y (IQR)	45 (32–60)	33 (28–43)	56 (42–67)	<.001[c]
Female sex	183 (36)	99 (46)	84 (29)	<.001
Race/ethnicity[d]				.24[e]
American Indian/Alaska Native	31 (6)	20 (9)	11 (4)	
Asian/Pacific Islander	24 (5)	1 (0)	23 (8)	
Black, non-Hispanic	48 (9)	17 (8)	31 (11)	
Latinx/Hispanic	23 (5)	7 (3)	16 (5)	
White, non-Hispanic	383 (76)	167 (78)	216 (73)	
Other	14 (3)	7 (3)	7 (2)	
Comorbidities				
Malignancy, any	38 (7)	11 (5)	27 (9)	.13
Cerebrovascular disease	94 (19)	24 (11)	70 (24)	<.001
Chronic pulmonary disease	47 (9)	14 (7)	33 (11)	.10
Congestive heart failure	121 (24)	33 (15)	88 (30)	<.001
Liver disease	13 (3)	2 (1)	11 (4)	.08[f]
Myocardial infarction	14 (3)	2 (1)	12 (4)	.05[f]
Peripheral vascular disease	60 (12)	14 (7)	46 (16)	.003
Renal disease	67 (13)	17 (8)	50 (17)	.005
Health insurance	464 (92)	199 (93)	265 (90)	.25
Homeless	115 (23)	91 (43)	24 (8)	<.001
Admitted to ICU	247 (49)	98 (46)	149 (51)	.34
Cardiac valve surgery within 90 d	122 (24)	42 (20)	80 (27)	.07
Microbiology of IE[d]				<.001[g]
MRSA	111 (22)	75 (35)	36 (12)	
MSSA	137 (27)	77 (36)	60 (20)	
MRSA and/or MSSA	248 (49)	152 (71)	96 (33)	
Streptococcus spp	117 (23)	36 (17)	81 (28)	
Enterococcus spp	59 (12)	26 (12)	33 (11)	
CoNS	20 (4)	2 (1)	18 (6)	
Candida spp	16 (3)	5 (2)	11 (4)	
Other	84 (17)	19 (9)	65 (22)	
Cardiac valve involved[d]				<.001[h]
Aortic	195 (38)	55 (26)	140 (48)	
Mitral	177 (35)	61 (29)	116 (39)	
Tricuspid	191 (38)	134 (63)	57 (19)	
Pulmonic	21 (4)	8 (4)	13 (4)	
Prosthetic valve endocarditis	106 (21)	20 (9)	86 (29)	<.001

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CoNS, coagulase-negative staphylococci; ICU, intensive care unit; IE, infective endocarditis; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PWID, people who inject drugs.

[a] *P* value compares PWID and non-PWID.

[b] χ^2 test unless otherwise specified.

[c] *t* test used to calculate *P* value.

[d] Groups not mutually exclusive; percentages can sum to >100%.

[e] *P* value compares patients identified as White, non-Hispanic to those not identified as White, non-Hispanic.

[f] Fisher exact test used to calculate *P* value.

[g] *P* value compares patients with MSSA and/or MRSA infection to those without.

[h] *P* value compares patients with left-sided IE (aortic and/or mitral valve) to those without left-sided IE.

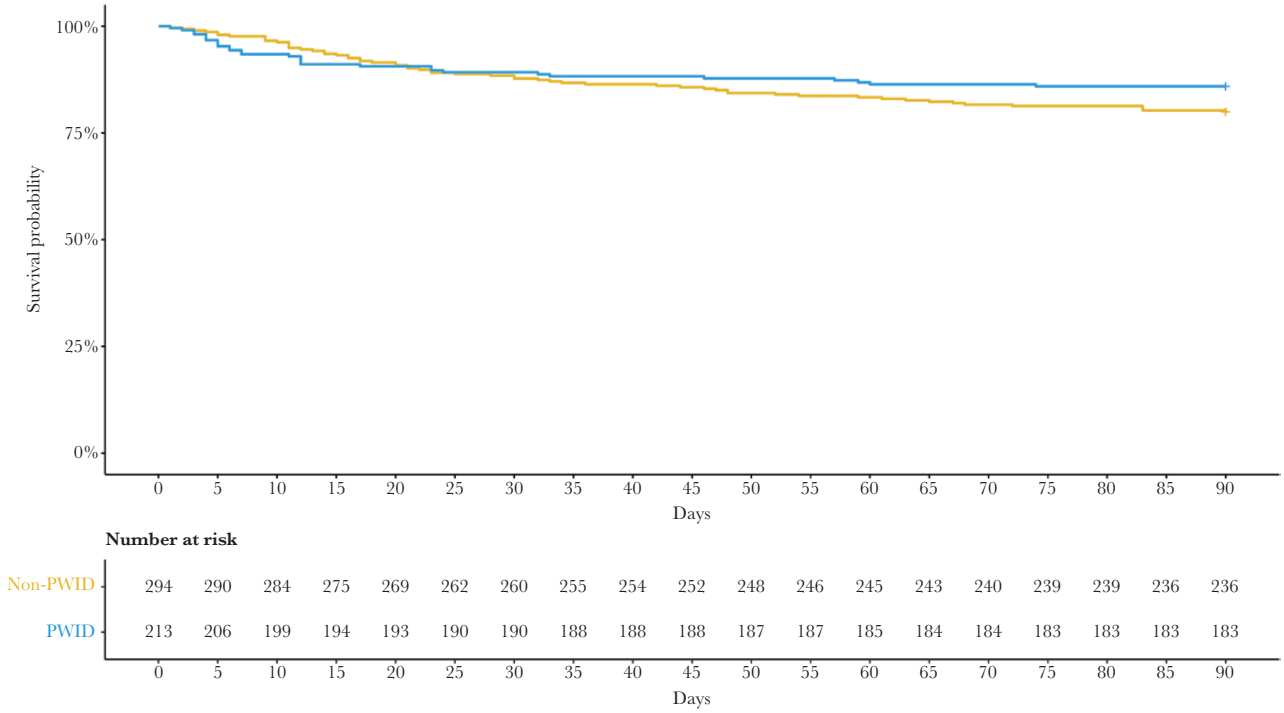

Figure 1. Kaplan-Meier curve showing probability of survival at 0 to 90 days among people who inject drugs and who do not inject drugs with infective endocarditis.

comorbidities. PWID were similarly more likely to have *S aureus* endocarditis (MRSA: 35% vs 12%, MSSA: 36% vs 20%, $P < .001$) and more likely to have right-sided endocarditis (tricuspid valve and/or pulmonic valve in 67% vs 23%, $P < .001$), when compared to non-PWID. There were no significant differences in race and ethnicity, the proportion admitted to the ICU, the proportion with health insurance, or the proportion who underwent cardiac valve surgery within 90 days of admission, when comparing PWID and non-PWID.

Overall, 79 (16%) individuals in the cohort died by 90 days and 88 (17%) by 6 months. When comparing PWID to non-PWID, there was not a significant difference in the proportion who died within 90 days of admission (n = 30 [14%] vs n = 49 [17%], $P = .50$) or within 6 months after admission (n = 34 [16%] vs n = 54 [18%], $P = .56$). Similarly, among the subset of patients who underwent surgical management for IE, there was no significant difference in the proportion of PWID vs non-PWID who died within 90 days (n = 6 [14%] vs n = 6 [8%], $P = .38$) and 6 months (n = 7 [17%] vs n = 6 [8%], $P = .21$) of admission.

In a multivariable Cox proportional hazard model that included age, sex, left-sided IE, and *S aureus* IE, PWID status was associated with a higher mortality within the first 14 days following admission (adjusted hazard ratio [aHR], 2.33 [95% CI, 1.16–4.65], $P = .02$); however, there was not a significant association between PWID status and mortality between 15 and 90 days following admission (aHR, 0.63 [95% CI, .31–1.30], $P = .21$) (Figure 1). When compared to right-sided IE, left-sided IE was associated with a higher 90-day (aHR, 3.18 [95% CI, 1.69–5.98], $P < .001$) mortality (Figure 2). Additionally, being >50 years of age was associated with a higher 90-day mortality when compared to those <35 years of age (aHR, 2.38 [95% CI, 1.24–4.55], $P = .01$). Neither sex nor infection due to *Staphylococcus aureus* were independently associated with 90-day mortality (Table 2).

On review of patients who died within 14 days of admission (PWID = 20, non-PWID = 19), most PWID deaths occurred in the setting of MRSA or MSSA IE (n = 16 [80%]), and cases were often complicated by central nervous system emboli and/or multisystem organ failure. Conversely, for non-PWID many of the deaths within 14 days of admission occurred in patients ≥65 years of age and/or among those with multiple underlying comorbidities (n = 14 [74%]).

DISCUSSION

Although there have been several other large cohorts describing clinical characteristics and outcomes among patients with IE [2, 6, 25–27], to the best of our knowledge this large contemporary cohort is one of the few to investigate the impact of injection drug use on mortality from IE and the only to show an increased risk for early mortality among PWID when compared to non-PWID. These data suggest that early diagnosis and treatment of IE among PWID is critical to improve survival.

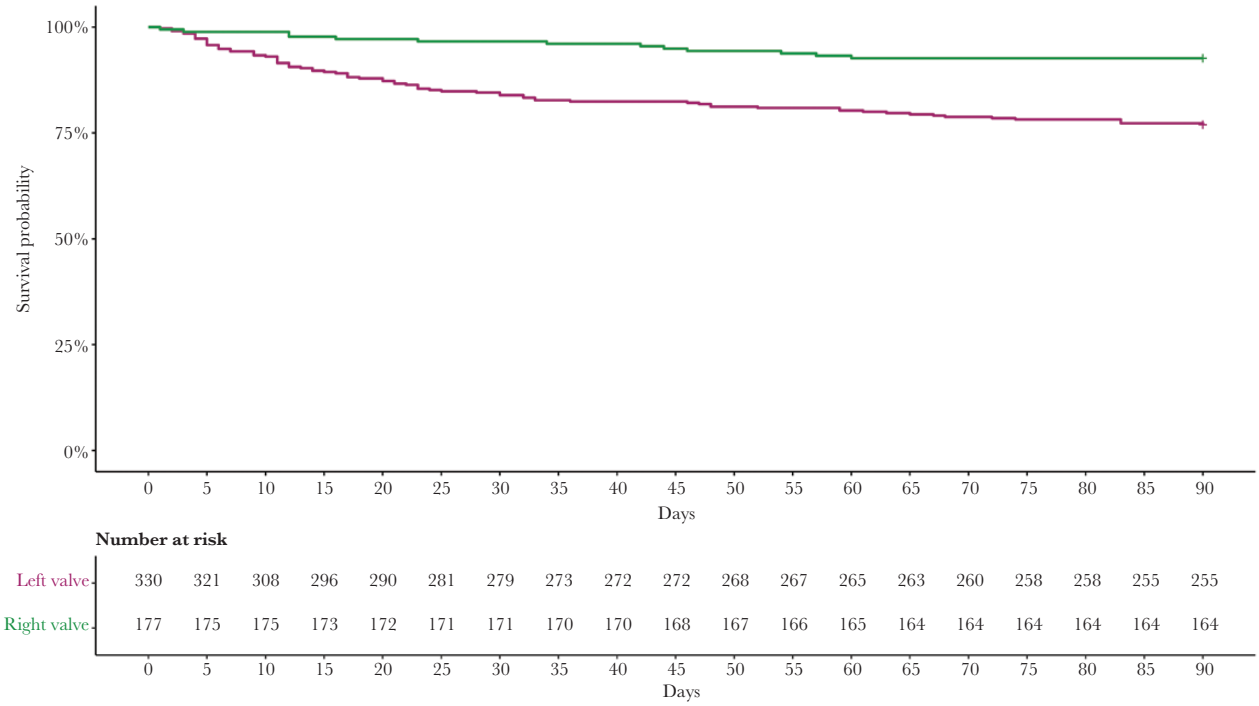

Figure 2. Kaplan-Meier curve showing probability of survival at 0 to 90 days among patients with with left-sided (aortic and/or mitral valve) and right-sided (tricuspid and/or pulmonic valve) infective endocarditis.

Consistent with other recent studies, PWID in our cohort were younger, more likely to be homeless, more likely to have *S aureus* endocarditis, and more likely to have right-sided disease, when compared to non-PWIDs [28–32]. PWID in our study were similarly more likely to be female, likely reflective of the lower rates of IE among women in the noninjecting drug population and rising numbers of women who inject drugs in the wake of the ongoing opioid epidemic [33–38]. In a recent study by Shah et al [39], female sex was also found to be a risk factor for IE among PWID, a finding authors hypothesize was related to differences in injection practices, with women being more likely to engage in receptive syringe sharing, sharing of injection works, and more likely to have had a male sexual partner initiate them into injection drug use [39].

It is notable that 90-day mortality was similar among PWID and non-PWID in our study, despite PWID being younger, having fewer comorbidities, and having more right-sided endocarditis—factors that have consistently been associated with lower mortality in previous studies [32, 34, 40–42]. This finding is consistent with a prior study by Leahey et al, which showed comparable 1-year all-cause mortality among a cohort of PWID and non-PWID with IE, despite younger age and lower rates of comorbidities among the PWID group [3, 6]. Nevertheless, we similarly found when adjusted for age, sex, left- vs right-sided endocarditis, and *S aureus* IE, PWID experienced a higher risk of mortality in the 2 weeks following admission when compared to non-PWID. This finding stands in contrast to prior studies, which have shown similar or lower rates of hospital mortality

Table 2. Multivariable Cox Proportional Hazard Ratios for 90-Day Mortality Among Patients With Infective Endocarditis at 2 Seattle Hospitals, 2014–2019

Characteristic	Unadjusted HR, 90-d Mortality (95% CI)	*P* Value	Adjusted HR, 90-d Mortality (95% CI)	*P* Value
IDU[a], days 0–14	1.41 (.75–2.67)	.29	2.33 (1.16–4.65)	.02
IDU[a], days 15–90	0.37 (.19–.72)	.003	0.63 (.31–1.30)	.21
Left-sided IE	3.45 (1.91–6.21)	<.001	3.18 (1.69–5.98)	<.001
Staphylococcus aureus IE	0.95 (.62–1.43)	.80	1.31 (.84–2.05)	.23
Age <35 y	Ref		Ref	
Ag 35–50 y	1.92 (1.00–3.71)	.05	1.84 (.94–3.60)	.07
Age >50 y	2.77 (1.56–4.91)	<.001	2.38 (1.24–4.55)	.01
Female sex	1.09 (.71–1.68)	.69	1.38 (.89–2.14)	.15

Abbreviations: CI, confidence interval; HR, hazard ratio; IDU, injection drug use; IE, infective endocarditis.

[a]Defined as active IDU at the time of admission or within the 3 months prior to admission.

among PWID with IE when compared to non-PWID with IE [6, 43]. In a recent study by Rudasill et al, authors used a national database to estimate rates of readmission and mortality among a large cohort of PWID and non-PWID with IE. In this study, authors found that at index IE hospitalization, PWID status was in fact associated with reduced mortality when compared to non-PWID status (6.8% vs 9.6%, $P < .001$), a finding authors hypothesized was related to younger age and increased right-sided valve replacement among PWID [6]. The discrepancy between our results and those of Rudasill et al may be related to differences in the cohorts and/or to the challenge of accurately capturing PWID status using diagnostic and administrative data, an obstacle that was significantly minimized via our method for chart adjudication in the present study.

Although the underlying drivers of early mortality among PWID in our study are likely complex, several factors may have contributed to this finding including perceived and experienced stigma among PWID leading to a delayed presentation to care, a reluctance within the medical system to surgically manage IE among PWID, and other sociostructural factors related to addiction and homelessness. Indeed, several studies have shown that PWID present to care later for other ID, including HIV, and are less likely to engage in care for injection-related infections such as HCV [44–49]. Prior studies suggest that stigma and poor experiences with the healthcare system drive much of the reluctance among PWID to seek care, making it more likely that they present later in the course of illnesses, when standard interventions and management are often less effective [49–51]. Furthermore, when PWID do present to care, there can be reluctance within the medical system to provide evidence-based treatment for addiction (eg, medications for opioid use disorder [MOUD]) and other life-saving interventions, such as cardiac surgery, given the high rates of medical noncompliance and injection drug relapses among PWID [52, 53]. We did not collect data on treatments used for IE (eg, type of antibiotic, intravenous vs oral), indications for surgical intervention, time to surgery, drugs used or drug of choice for PWID, or use of MOUD as part of this study, and additional studies are needed to investigate how clinical factors, including the provision of MOUD, delayed presentation, time to cardiac surgery, contradictions to immediate anticoagulation following cardiac surgery (eg, cerebral emboli), and other patient-level characteristics may impact overall survival in PWID.

Our study has several limitations. First, it is a retrospective cohort study limited to 2 hospitals within a single academic institution, and results may not be generalizable. Although the specificity of our string-searching and pattern-matching algorithm was high, and cases were further adjudicated by a member of the study team, the sensitivity of our algorithm was only 76%, and it is likely we missed cases where IE was not included in the list of discharge diagnoses, was misspelled, or when the discharge summary was formatted in a nonconventional way. Nevertheless, a prior analysis from our group suggested that these aberrations were sporadic in nature and unlikely to be associated with significant selection bias [18]. In this study, PWID status was collected via chart review only, and therefore may be subject to misclassification, particularly in the absence of clinical documentation. Although active and recent injection drug use is well documented within ID consult notes per standard practice at UWMC-ML and HMC, and ID consultation for IE is nearly universal in our healthcare system, it is challenging to pinpoint the duration of early sobriety, and as such, it is possible that persons with a history of injection drug use, who had been sober for >3 months, may have been misclassified as PWID. Nevertheless, as highlighted in the Methods, concordance between initial and ID physician adjudication of PWID status was high. Additionally, we did not collect data on cause of death as part of this analysis or have a control group of hospitalized PWID and non-PWID without IE. It is possible that the increased risk of death seen among PWID in the first 14 days was not entirely attributable to IE. Nevertheless, while PWID are certainly at higher risk of death via overdose or via other infectious complications of injection drug use, we would not necessarily expect them to have a higher risk of non-IE-related death in the 14 days following hospitalization, when compared to non-PWID who were generally older and had more underlying medical comorbidities. Related to death ascertainment, if patients died outside of Washington State following discharge, it is possible that their death may not have been counted in our analysis.

CONCLUSIONS

In this contemporary urban cohort of 507 inpatients with IE, overall 90-day mortality did not differ when comparing PWID and non-PWID with IE; however, PWID had a higher mortality in the first 14 days following admission, despite being younger and having a higher frequency of right-sided endocarditis. These data suggest that early diagnosis and aggressive treatment of IE among PWID may be especially important, particularly as cases of IE continue to rise in the wake of the ongoing opioid epidemic.

Notes

Author contributions. M. A. C.: Conceptualization, methodology, data curation, writing—original draft. J. S.: Conceptualization, methodology, data curation, writing—review & editing. K. L.: Methodology, formal analysis, data curation, writing—review & editing, visualization. A. G.: Methodology, data curation, writing—review & editing. S. N. G.: Writing—review & editing, supervision. C. S., K. J. K., and R. D. H.: Conceptualization, writing—review & editing. E. G.: Conceptualization, data curation, writing—review & editing. S. D.: Conceptualization, methodology, data curation, writing—review & editing, supervision. H. N. K.: Conceptualization, methodology, formal analysis, data curation, writing—review & editing, supervision.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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