Characterizing Risk Factors Associated with the Recurrence of Infective Endocarditis and Mortality among People Who Inject Drugs

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics
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Abstract

**Background.** The incidence of infective endocarditis is progressively rising among people who inject drugs.

**Methods.** A retrospective cohort study was conducted using data from electronic medical records to characterize important predictors that contribute to the recurrence of infective endocarditis and evaluate the associations of survival time and predictors of interest in the presence of competing risks among people who inject drugs. Multivariate logistic and survival regression analyses were carried out to identify factors associated with infective endocarditis recurrence and death.

**Results.** We identified a significant association between PICC line misuse and infective endocarditis recurrence (OR=2.62, \(P=0.005\)). In addition, survival analyses showed that PICC line misuse increased both the rate of infective endocarditis recurrence (SHR=2.60, \(P=0.001\)) and mortality (HR=3.00, \(P=0.01\)).

**Conclusion.** PICC line misuse was associated with infective endocarditis recurrence and mortality. Preventative health interventions to target this high-risk group of patients need to be developed.

**Keywords**

Infective endocarditis; injection drug use; persons who inject drugs; recurrent endocarditis; competing risks
Summary for Lay Audience

Infective endocarditis is a potentially fatal infectious disease that damages the chambers and structural integrity of the heart. The use of injection drugs has become a significant contributing factor for the occurrence and recurrence of infective endocarditis. Previous studies have demonstrated that infective endocarditis is responsible for mortality rates of up to 40% and recurrence rates of up to 32% among the population of people who inject drugs (PWID). Treatment of infective endocarditis often involves cardiac surgery to replace damaged cardiac valves. However, this form of treatment is problematic among PWID due to high infective endocarditis recurrence rates and lethality of recurrent infection of prosthetic valves. Current knowledge is limited regarding the recurrence of infective endocarditis among PWID. Therefore, it is important to further the understanding of the risk factors associated with the recurrence of infective endocarditis to help guide informed decision-making regarding cardiac surgery among PWID. A challenge faced when assessing key factors that influence the recurrence of infective endocarditis is the presence of competing risks, which impede the recurrence of infective endocarditis and may lead to false inferences regarding the overall survival of PWID. This thesis used data from electronic medical records from St. Joseph's Hospital and London Health Sciences Center to characterize risk factors that are associated with the recurrence of infective endocarditis, assess the probability of infective endocarditis recurrence with consideration for death as a competing risk, and evaluate the association between survival time and important risk factors among PWID. Through analysis of endocarditis recurrence, this thesis identified peripherally inserted central catheter line misuse as an important risk factor for increased (1) odds of the development of recurrence of infective endocarditis, (2) rate of infective endocarditis recurrence, and (3) risk of mortality among PWID. Furthermore, this thesis identified admission to the intensive care unit and cardiac surgery as additional risk factors for increased risk of mortality among PWID. The results of this thesis will have a significant impact on public health efforts in the prevention of infective endocarditis recurrence and aid clinicians in targeting prevention strategies towards patients who have misused their peripherally inserted central catheter.
Dedication

To my parents, who push me to strive to be the best I can be.
Acknowledgments

First and foremost, I would like to express my sincere gratitude to my co-supervisors, Dr. Michael Silverman, and Dr. Tara Elton-Marshall, who have made my graduate experience one to remember. Thank you, not only for your guidance, time, and patience throughout these past two years, but for believing in me. I have learned so much from the both of you and am grateful for all that you taught me. You have helped me develop a unique and pivotal skillset that I will be able to draw on in my future endeavours. I would also like to thank my thesis advisory committee member, Dr. Yayuan Zhu for her time and invaluable biostatistical knowledge. I would like to extend my thanks to Dr. Esfandiar Shojaei for his constant support in data collection and cleaning. Lastly, I would like to thank my family and fellow graduate students who walked with me throughout my graduate journey.

This thesis would not have been possible without the help of all these people. I am eternally grateful for their support.
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIF</td>
<td>Cumulative hazards function</td>
</tr>
<tr>
<td>CSH</td>
<td>Cause-specific hazards function</td>
</tr>
<tr>
<td>HACEK</td>
<td><em>Haemophilus parainfluenza, Haemophilus aphrophilus, Actinobacillus (Haemophilus) actinomycetemcomitans, Cardiobacterium hominis</em>, the <em>Eikenella</em> species, and the <em>Kingella</em> species</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IDU</td>
<td>Injection drug use</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at random</td>
</tr>
<tr>
<td>MCAR</td>
<td>Missing completely at random</td>
</tr>
<tr>
<td>MNAR</td>
<td>Missing not at random</td>
</tr>
<tr>
<td>NEP</td>
<td>Needle exchange and recovery program</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PICC</td>
<td>Peripherally inserted central catheter</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Review and Meta-Analysis</td>
</tr>
<tr>
<td>PWID</td>
<td>People who inject drugs</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk/risk ratio</td>
</tr>
<tr>
<td>SH</td>
<td>Subdistribution hazard</td>
</tr>
<tr>
<td>SHR</td>
<td>Subdistribution hazard ratio</td>
</tr>
<tr>
<td>UI</td>
<td>Uncertainty interval</td>
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Chapter 1

1 Introduction

This chapter introduces the topic, objectives, and structure of the thesis. Section 1.1 provides an overview of the thesis topic. The objectives of the thesis are then outlined in Section 1.2. Section 1.3 discusses the role of the student. Lastly, Section 1.4 summarizes the structure of the thesis.

1.1 Overview of thesis topic

As a consequence of the rising opioid and stimulant epidemic, the incidence of infectious blood-borne diseases has significantly increased among the population of PWID. Common blood-borne diseases seen among PWID include human immunodeficiency virus (HIV), and hepatitis B and C viruses. Furthermore, the incidence of bacterial heart infections, such as infective endocarditis (henceforth referred to as endocarditis), have been gradually increasing among this marginalized, high-risk population.

Endocarditis is a type of heart inflammation that affects the endocardium (inner surface) of the heart valves and chambers. Endocarditis infection is separated into three types, left-sided, right-sided, and bilateral infection, each affecting their corresponding cardiac structures. Left-sided endocarditis is commonly found in the population of non-PWID (individuals who do not inject drugs), whereas right-sided infection is common in the population of PWID. Endocarditis is a considerable cause of morbidity and mortality in developed countries, with mortality rates of 25% among the general population and up to 40% among the population of PWID. Injection drug use (IDU) is considered a predominant risk factor for endocarditis due to the use of contaminated injection equipment and the injection of nonsterile substances.

Recurrence of endocarditis infection is defined in literature as a repeated episode that either occurs more than six months from the previous episode or is caused by a different causative organism. Among the general population, endocarditis recurrence has been found to be associated with increasing age, male sex, prior heart disease, presence
of prosthetic devices, and previous endocarditis episodes. Conversely, risk factors for recurrence of endocarditis differ among the population of PWID. Continued drug use, location of infection, bacteremia, and misuse of peripherally inserted central catheter (PICC) lines have been found to significantly increase the probability of endocarditis recurrence among the population of PWID.

1.2 Thesis objectives

There is limited literature on the recurrence of endocarditis among the population of PWID, specifically. To date, no study has assessed the probability of endocarditis recurrence specifically among the population of PWID with consideration for the effects of death as a competing risk. This thesis aimed to build on existing literature by addressing this knowledge gap. A retrospective cohort study using the world’s largest detailed population-based dataset of PWID and endocarditis was conducted to address the following research objectives:

**Research Objective 1.** Characterize important factors that contribute to the recurrence of endocarditis among PWID in London, Ontario

**Research Objective 2.** Assess the probability of disease recurrence in the presence of competing risks among PWID in London, Ontario

**Research Objective 3.** Evaluate the associations of survival time and predictor variables among PWID in London, Ontario

1.3 Role of the student

Data collection was conducted by Dr. Michael Silverman and St. Joseph's Health Care London and provided to the student for use in this thesis manuscript. The objectives and research questions were formulated by the student in conjunction with co-supervisors, Drs. Michael Silverman, and Tara Elton-Marshall. The thesis advisory committee, consisting of co-supervisors and Dr. Yayuan Zhu, provided input on thesis methodology. The student’s thesis committee provided regular consultation and guidance throughout the completion of the study.
1.4 Thesis structure

This thesis manuscript is comprised of five chapters and five appendices. Chapter 2 provides information on the current knowledge of endocarditis recurrence. Chapter 3 outlines the data source, study population and setting, measures and outcome variables, missing data and statistical methods used to address the study objectives and research questions. Chapter 4 presents the study findings for each defined objective. Finally, Chapter 5 discusses the implications of the study findings, strengths and limitations, and future directions.
Chapter 2

2 Literature review

There is limited literature that describes the recurrence of endocarditis among PWID. This chapter aims to outline current evidence regarding endocarditis and PWID to ascertain the plausibility of this thesis. Section 2.1 defines endocarditis, its pathophysiology, diagnosis and treatment, and associated risk factors. Section 2.2 provides the epidemiology of PWID worldwide, in Canada and in Ontario. Section 2.3 compares the clinical characteristics of endocarditis among PWID and non-PWID. Section 2.3 also defines recurrent endocarditis and provides evidence on the factors associated with its recurrence. Section 2.4 addresses current gaps in the literature and how this thesis will contribute to the field of knowledge. Section 2.5 briefly describes competing risks and Section 2.6 provides context of the current study, its setting, and population demographics.

2.1 Endocarditis

Endocarditis is a cardiovascular disease and a consequence of bacteremia.\textsuperscript{15} Endocarditis can be classified as either acute, subacute or chronic.\textsuperscript{16} Acute endocarditis is defined by rapid clinical presentation and life-threatening disease progression.\textsuperscript{16} Conversely, subacute and chronic infections are less dire and have indistinct clinical presentation.\textsuperscript{16} Endocarditis can result from numerous types of bacteria; common microorganisms include (1) streptococci: \textit{Viridans streptococci}, (2) staphylococci: \textit{Staphylococcus aureus} including methicillin resistant strains (MRSA), (3) enterococci, and (4) HACEK: \textit{Haemophilus parainfluenza, Haemophilus aphrophilus, Actinobacillus (Haemophilus) actinomycetemcomitans, Cardiobacterium hominis}, the \textit{Eikenella} species, and the \textit{Kingella} species (5) gram negative rods including pseudomonas, and (6) fungi.\textsuperscript{17} Streptococci and staphylococci are responsible for the majority of endocarditis cases; streptococci account for between 50\% and 80\% of all endocarditis cases in non-PWID and staphylococci account for 50\% of acute endocarditis cases, and 20\% and 30\% of subacute endocarditis cases.\textsuperscript{15,17} In PWID, staphylococci may account for 70\% or more cases and fungi are also more common.\textsuperscript{3}
Endocarditis occurs when the endocardial layer (endocardium) of the heart is damaged, resulting in inflammation and the release of thromboplastin, a blood coagulation tissue factor.\textsuperscript{18,19} The endocardium covers the heart’s inner lumen—chambers—and is composed of a layer of endothelial cells.\textsuperscript{20,21} Endocarditis consists of a multistage process called vegetation formation that occurs on the surface of the heart’s valve line of closure.\textsuperscript{18} This process begins when the bacteria spreading hematogenously bind to the damaged endocardium.\textsuperscript{19} Once attached, thromboplastin stimulates the accumulation of platelets and fibrin—cells and protein used in blood coagulating mechanisms, respectively—at the site of injury, which sheath the bacteria, forming a “vegetation”, illustrated in Figure 2.1. If left untreated, the vegetation can further damage the heart valves and result in congestive heart failure or the need for prosthetic valve replacement.\textsuperscript{19} Endocarditis can affect native valves, prosthetic valves or intracardiac devices.\textsuperscript{22}

![Figure 2.1 Infective endocarditis of the mitral valve](image)

**Figure 2.1 Infective endocarditis of the mitral valve**

Source: Mayo Foundation For Medical Education And Research – Endocarditis.\textsuperscript{23} Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved. (See Appendix A for letter of permission)
There are three types of native valve endocarditis: left-sided, right-sided and bilateral infection. Left-sided endocarditis is the most common type of infection and affects the mitral valve and the aortic valve.\textsuperscript{17} Conversely, right-sided endocarditis is common among PWID and patients with cardiac devices, and accounts for 5\% to 10\% of all endocarditis infections.\textsuperscript{24} Studies have demonstrated that patients with right-sided endocarditis tend to be younger and have less comorbidities.\textsuperscript{18} Vegetation formation of right-sided endocarditis affects the tricuspid valve with rare involvement of the pulmonary valve.\textsuperscript{17}

Prosthetic valve endocarditis is defined by infection of parts of a prosthetic heart valve.\textsuperscript{25} Prosthetic valve endocarditis is a complication of valve replacement; bacteria are introduced during surgical intervention or subsequently postoperatively via hematogenous dissemination in hospital (nosocomial) or in the community.\textsuperscript{25} The risk of nosocomial-acquired prosthetic valve endocarditis is estimated to be 5\% higher in patients who receive surgical intervention during an active case of endocarditis.\textsuperscript{25}

2.1.1 Diagnosis and treatment

Endocarditis is a complex disease with a variety of symptoms. Patients with endocarditis may experience the following conventional symptoms:

- **Constitutional symptoms**: fever, weight loss, anorexia, arthralgia, night sweats and/or rigors.\textsuperscript{17}
- **Cardiac phenomena**: development of heart murmur and/or worsening of current heart murmur.\textsuperscript{17}
- **Skin lesions**: Osler nodes on fingers or toes, Janeway lesions on palms of hand or soles of feet, embolic or vascular petechiae, and/or clubbing.
- **Eye hemorrhages**: Roth spots and/or conjunctival hemorrhages.\textsuperscript{17}
- **Spleenic phenomena**: splenic infarction.\textsuperscript{17}
- **Neurological phenomena**: cerebral emboli, acute confusion and/or mycotic aneurysms.\textsuperscript{17}
- **Renal phenomena**: renal infarction and/or glomerulonephritis.\textsuperscript{17}
Diagnosis of endocarditis can be difficult and requires a combination of signs, symptoms, clinical suspicion and diagnostic tests. The modified Duke Criteria were developed to provide healthcare professionals with a formal endocarditis diagnosis through a series of major and minor criteria, shown in Table 2.1. Suspected patients are stratified into three classifications based on the criteria they fulfill:

- **Definite endocarditis:** either (1) pathologically proven endocarditis, or (2) fulfillment of either (i) two major criteria, (ii) one major and three minor criteria, or (iii) five minor criteria.

- **Possible endocarditis:** fulfillment of either (i) one major and one minor criterion or (ii) three minor criteria.

- **Rejected:** either (1) firm alternative diagnosis, (2) resolution of endocarditis syndrome with antibiotic treatment for ≤ 4 days, or (3) no pathologic evidence of endocarditis at surgery or autopsy, with antibiotic treatment for ≤ 4 days.
Table 2.1 Duke Criteria for the Diagnosis of Endocarditis\textsuperscript{17,26}

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
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<tbody>
<tr>
<td>(1) Positive blood culture for endocarditis</td>
<td>(1) Predisposition: predisposing heart condition or intravenous drug use</td>
</tr>
<tr>
<td>A. Typical microorganism consistent with endocarditis from two separate blood cultures as noted below:</td>
<td>(2) Fever: temperature ≥ 38.0°C</td>
</tr>
<tr>
<td>i. viridans streptococci, Streptococcus bovis\textsuperscript{a}, or HACEK group; or</td>
<td>(3) Vascular phenomena: major arterial emboli, septic pulmonary infarct, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages and Janeway’s lesions</td>
</tr>
<tr>
<td>ii. community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus; or</td>
<td>(4) Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor</td>
</tr>
<tr>
<td>B. Microorganisms consistent with endocarditis from persistently positive blood cultures defined as:</td>
<td>(5) Microbiological evidence: positive blood culture but does not meet a major criterion as noted above\textsuperscript{b} or serological evidence of active infection with organism consistent with endocarditis</td>
</tr>
<tr>
<td>i. at least two positive cultures of blood samples drawn &gt; 12 hours apart or</td>
<td>(6) Echocardiographic findings: consistent with endocarditis but do not meet a major criterion as noted above</td>
</tr>
<tr>
<td>ii. all of three or a majority of four or more separate cultures of blood (with first and last sample drawn at least 1 hour apart).</td>
<td></td>
</tr>
<tr>
<td>(2) Evidence of endocardial involvement</td>
<td></td>
</tr>
<tr>
<td>A. Positive echocardiogram for endocarditis defined as:</td>
<td></td>
</tr>
<tr>
<td>i. oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or</td>
<td></td>
</tr>
<tr>
<td>ii. abscess, or</td>
<td></td>
</tr>
<tr>
<td>iii. new partial dehiscence of prosthetic valve</td>
<td></td>
</tr>
<tr>
<td>B. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HACEK, \textit{Haemophilus} species, \textit{Actinobacillus actinomycetemcomitans}, \textit{Cardiobacterium hominis}, \textit{Eikenella} species, and \textit{Kingella kingae}  
\textsuperscript{a} Includes nutritionally variant strains (\textit{Abiotrophia species})  
\textsuperscript{b} Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis
Treatment of endocarditis is dependent on the complexity of the disease. Antibiotic therapy is used for all cases, and is used alone when the structural integrity of the cardiac valves is maintained; approximately 50% of endocarditis cases are treated with antibiotic therapy alone.\textsuperscript{16,27} Conversely, surgical intervention is required if infection severely damages the integrity of the cardiac valves leading to heart failure, or if infection cannot be controlled with antibiotics alone or if recurrent emboli occur despite antibiotic therapy.\textsuperscript{27}

\subsection*{2.1.2 Risk factors}

Current literature demonstrates several factors that increase the risk of developing endocarditis. Cardiac structural abnormalities (rheumatic heart disease and congenital heart disease),\textsuperscript{15,16,28} prosthetic material (cardiac devices or prosthetic valves),\textsuperscript{15,28} invasive medical procedures,\textsuperscript{16} HIV and IDU\textsuperscript{16,28} have been identified in literature as primary risk factors for endocarditis and will be further explored in Section 2.3.1.

\subsection*{2.1.3 Epidemiology of endocarditis}

Endocarditis is life-threatening and a significant cause of morbidity and mortality in developed countries, resulting in a mortality rate of 25\%.\textsuperscript{3,5} Literature suggests that the general incidence of endocarditis is stable; incidence of endocarditis is estimated to be between 3 and 7.5 episodes per 100,000 person-years.\textsuperscript{3,29} Despite the overall stability of the incidence of endocarditis, it is steadily increasing among PWID, resulting in mortality rates of up to 40\%.\textsuperscript{3,4} As a result, IDU is considered a predominant risk factor for the disease.\textsuperscript{30} The incidence of endocarditis is considerably higher among PWID compared to those who do not use injection drugs.\textsuperscript{31}

The use of prescription opioids has become an important public health concern and contributes to the growing rates of substance use disorders in Canada.\textsuperscript{32} Non-medical use of prescription opioids can be administered through injection, swallowing or snorting.\textsuperscript{33} Opioid medication is often used to treat pain and can cause a sense of euphoria, making these types of medication highly addictive.\textsuperscript{34-36} Opioids are classified into three distinct categories: natural, semi-synthetic and synthetic.\textsuperscript{37} Natural opioids are directly derived
from the opium poppy and include codeine, morphine and thebaine. Semi-synthetic opioids, including hydromorphone, heroin and oxycodone, are chemically manufactured using natural opiates. Lastly, synthetic opioids are completely chemically manufactured and include methadone and fentanyl. The opioid crisis is attributable to increasing rates of opioid prescribing by healthcare professionals and the development of synthetic opioids.

Evidence suggests the non-medical use of prescription opioids is a contributing factor to the use of more potent injection opioids, such as heroin. Literature theorizes that the transition of prescription opioids to heroin is a multistep process, demonstrated in Figure 2.2. The first step in the theorized process is the ease of drug accessibility. Access to prescription opioids can result from one’s own prescription or a family member’s or friend’s prescription. Prolonged misuse of prescription opioids results in drug dependence. Drug dependence alters the function of neurons by decreasing their ability to release noradrenaline, a neurotransmitter responsible for stimulating alertness. Consequently, the neurons adapt to the presence of the opioid by increasing their activity, resulting in withdrawal symptoms such as anxiety, jitters and muscle cramps in the absence of the opioid. Although repeated use of the opioid suppresses these symptoms, it can also lead to opioid tolerance. Opioid tolerance occurs when the drug user no longer responds to the opioid stimulus. Thus, opioid drug users will either (1) need to increase the amount and frequency of the drug to obtain the desired effect or (2) transition to a more potent drug.

![Figure 2.2 Theory behind the transition from prescription-opioid use to injection drug use](image)
Lankenau et al.\textsuperscript{43} conducted an exploratory qualitative study to understand the patterns of prescription opioid misuse initiation among young PWID. Results from their study demonstrated 86\% of their study sample (43/50) misused prescription opioids prior to transitioning to heroin.\textsuperscript{43} Similar patterns of transition in Figure 2.2 were observed among sample participants who injected prescription opioids prior to heroin. Furthermore, the transition from prescription opioid misuse to injection opioid use can also be attributable to supply reduction efforts, which aim to address the opioid crisis.\textsuperscript{45} Electronic prescription drug monitoring programs are a type of supply reduction strategy that gather information on the proportion of prescriptions dispensed, limiting the availability of prescription opioids and therefore increasing their price.\textsuperscript{45,46} Consequently, drug users who are dependent on these drugs will need to either find more money to pay for the limited resources or find a less expensive option, such as heroin.\textsuperscript{45}

In addition to the opioid epidemic, the use of stimulants is an increasing public health concern among PWID.\textsuperscript{47} Non-medical use of prescription stimulants can be administered through injection of dissolved powder, smoking, snorting, or swallowing the drug in pill form.\textsuperscript{48} Prescription stimulants are often used to increase the levels of dopamine and norepinephrine in the brain which increases overall brain activity.\textsuperscript{48} Crystal methamphetamine, familiarly known as crystal meth, is an extremely powerful and addictive stimulant.\textsuperscript{49} Similar to prescription opioid misuse, prescription stimulant misuse has the potential to lead to serious substance use disorders.\textsuperscript{48,49} The transition from prescription stimulant use to crystal meth follows a similar multistep process as seen in Figure 2.2. Misuse of prescription stimulants can lead to drug dependence which prolongs the use of the stimulant. Furthermore, long-term drug misuse leads to drug tolerance, whereby stimulant drug users either (1) need to increase the amount and frequency of the drug to obtain the desired effect or (2) transition to a more potent drug, such as crystal meth.\textsuperscript{48}

The misuse of prescription opioids and stimulants is a global public health concern and is increasing among PWID. Furthermore, the use of injection opioids and stimulants increases the risk of transmission of blood-borne diseases, such as endocarditis, due to the use of contaminated injection paraphernalia.\textsuperscript{4,49,50} However, a systematic review by
Serhan and Silverman\textsuperscript{51} demonstrates that despite the rise in IDU-related endocarditis, current evidence does not suggest the type of drug injected has a significant impact on the development of endocarditis.

### 2.2 Injection drug use

IDU is a major public health concern that contributes significantly to worldwide mortality and morbidity.\textsuperscript{52} Moreover, IDU has high health, economic and social burdens. Harm reduction programs have been established to help reduce the burden of IDU.\textsuperscript{53} Literature demonstrates that needle exchange and recovery programs (NEP) are associated with a decrease in sharing needles and injection equipment, and risky behaviour.\textsuperscript{53–56} A study conducted by Bailey et al.\textsuperscript{55} found frequent users of NEPs ($\geq 7$ visits) were less likely to share their needles (odds ratio [OR] = 0.32, 95% confidence interval [CI] 0.19 to 0.54) or injection paraphernalia (OR = 0.51, 95% CI 0.30 to 0.85) with other users, or reuse their own equipment (OR = 0.25, 95% CI 0.13 to 0.45) than those who visited NEPs less often (1 to 6 visits), adjusting for age, gender, ethnicity, recruitment method, duration and frequency of injection use. Similarly, a study by Gibson et al.\textsuperscript{56} observed a significant decrease in the probability of reuse of unsterile needles (17% of NEP users versus 35% of non-NEP users, $P = 0.003$), needle sharing (27% of NEP users versus 50% of non-NEP users, $P = 0.001$) and high risk behaviour (12% of NEP users versus 24% of non-NEP users, $P = 0.03$) among NEP users compared to non-NEP users.

The World Health Organization\textsuperscript{57} assessed the evidence of the efficacy of NEPs in preventing blood-borne diseases, such as HIV. Evidence demonstrates a positive impact on injection practices among PWID.\textsuperscript{57} However, despite the strength of the evidence provided, the report draws attention to the limitations of the studies.\textsuperscript{57} From their review, the World Health Organization\textsuperscript{57} identified dichotomous classifications of NEP users and non-NEP users, which may confound and overestimate the probability of needle sharing and reuse among non-NEP users. Non-NEP users may only use sterile injection equipment that have been acquired from sources other than NEPs.\textsuperscript{57} Furthermore, these studies rely on self-reported data, which can be affected by a number biases that underestimate the protective effect of NEPs.\textsuperscript{57} In addition, a systematic review by Fernandes et al.\textsuperscript{58} found many studies assessing the effectiveness of NEPs were at
moderate to high risk of bias. The quality of evidence was assessed using the Risk of Bias In Systematic Reviews tool, which assesses risk of bias among eligibility criteria, selection of studies, data collection, appraisal, synthesis and findings. The results of this systematic review conclude that further high quality studies are required to adequately address the impact of NEPs on IDU.

PWID account for approximately 0.7% of the Canadian population, many of which face several barriers to care. IDU is heavily stigmatized, which significantly impacts the wellbeing and quality of life of PWID. As a result, PWID often face discrimination and may feel discouraged to access adequate healthcare or services aimed to reduce harm caused by IDU. Additionally, access to harm reduction services may be limited or inaccessible. Therefore, PWID tend to employ self-initiated harm reduction strategies; rubbing alcohol, soap or hand sanitizer may be used to clean injection equipment. However, these strategies are not always employed. Consequently, PWID are at a higher risk of developing blood-borne diseases, such as HIV, hepatitis C and endocarditis.

### 2.2.1 Epidemiology of injection drug use

In 2015, it was estimated that there was approximately 15.6 million PWID worldwide, which accounted for 0.33% (95% uncertainty interval [UI] 0.21 to 0.49) of individuals aged 15 to 64 years. A systematic review by Degenhardt et al. found Southeast Asia (4.0 million, 95% UI 3.0 to 5.0 million), eastern Europe (3.0 million, 95% UI 1.7 to 5.0 million) and North America (2.6 million, 95% UI 1.5 to 4.4 million) have the largest proportions of PWID. The prevalence of IDU varies across countries, resulting in prevalence rates ranging from 0.01% to 4.19%, illustrated in Figure 2.3. In addition, Degenhardt et al. found illicit injection drug use is more common among men than women (79.6% versus 20.4%, globally). In Canada, the prevalence of IDU ranges from 1.04% to 1.40%.
Figure 2.3 Estimated prevalence of injection drug use by country

Source: © 2017 Louisa Degenhardt, Amy Peacock, Samantha Colledge, et al. Published by Elsevier Ltd. DOI:https://doi.org/10.1016/S2214-109X(17)30375-3; Abbreviations: IDU, injecting drug use.

2.3 Endocarditis and injection drug use

Literature suggests approximately 5% to 20% of PWID will experience an episode of endocarditis. A study conducted by Wurcel et al. observed a substantial change in the overall proportion of IDU-related endocarditis hospitalizations in the United States between 2000 and 2013, resulting in an increase from 7% in 2000 to 12.1% in 2013.

2.3.1 Clinical characteristics of patients with endocarditis

2.3.1.1 Age, ethnicity and sex

Patient characteristics differ significantly among PWID and non-PWID with endocarditis. Demographic analyses regarding PWID and non-PWID show differences in sex, ethnicity and age. Among both non-PWID and PWID, endocarditis is more frequently observed among male patients than female patients, resulting in a 2:1 ratio. In addition, the majority of endocarditis patients are Caucasian. Among non-PWID, evidence suggests that the incidence of endocarditis increases with age. In the 1980s, the mean
The age of patients with endocarditis was observed to be between 44 and 46 years.\textsuperscript{22} However, as a consequence of medical advancement, the decreased incidence of rheumatic heart disease and increased incidence of degenerative valve heart diseases, the observed mean age of non-PVID with endocarditis rose dramatically and increased to greater than 70 years.\textsuperscript{22,69} Furthermore, literature suggests the risk of endocarditis among elderly patients (greater than 65 years of age) is 4.6 times higher than the general population.\textsuperscript{70} In contrast to the general population, PVID with endocarditis are younger. A study conducted by Rodger et al.\textsuperscript{3} reported a median (interquartile range [IQR]) age of 34 (28 to 42) years among PVID with endocarditis. Furthermore, studies conducted on the general population reported mean and median aged PVID between 20 and 40.8 years.\textsuperscript{4,11,14,30,66–68,71}

### 2.3.1.2 Cardiac structural abnormalities

Approximately 75\% of patients who suffer from endocarditis have accompanying heart diseases.\textsuperscript{16} Rheumatic heart disease and congenital heart disease cause lesions and scarring of the endothelial layer of the heart valves, which contributes to the onset of endocarditis.\textsuperscript{72} Prior to the development of antibiotics, rheumatic heart disease was the primary risk factor for development of endocarditis.\textsuperscript{22} However, as a consequence of medical advancement, the prevalence of rheumatic heart disease has decreased in developed countries, but remains a public health concern among patients in developing countries who have limited access to adequate healthcare services and consequently antibiotics.\textsuperscript{22,73} As a result, the significance of rheumatic heart disease as a risk factor for endocarditis in developed countries has decreased.\textsuperscript{69,72} However, congenital heart disease continues to be an important predisposing factor in the development of endocarditis.\textsuperscript{15,74} Studies have shown that predisposing heart diseases are more frequently associated with non-IDU related endocarditis compared to IDU-related endocarditis.\textsuperscript{30,75} Kadri et al.\textsuperscript{75} found that PVID were significantly less likely to have congenital heart disease compared to non-PVID (9.1\% versus 21.9\%, \( P < 0.001 \)). Similar results were found in a study by Rudasill et al.\textsuperscript{30} (8.1\% versus 15.5\%, \( P < 0.001 \)).
2.3.1.3 Invasive medical procedures

Bacteremia can also result from exposure to invasive medical and surgical procedures.\textsuperscript{76} As previously mentioned, bacteremia triggers endocarditis development. The increased risk of bacteremia from invasive medical and surgical procedures can also predispose patients to endocarditis. Approximately 25\% of endocarditis cases occur after medical exposure.\textsuperscript{76} A study conducted by Janszky et al.\textsuperscript{76} found invasive outpatient procedures, such as bone marrow puncture (relative risk/risk ratio [RR] = 4.33, 95\% CI 1.24 to 15.21), bronchoscopy (RR = 5.00, 95\% CI 1.10 to 22.82), dialysis (RR = 4.33, 95\% CI 2.10 to 8.95), coronary angiography (RR = 4.75, 95\% CI 1.61 to 13.96) and blood transfusions (RR = 5.50, 95\% CI 1.22 to 24.80) are associated with a four to 5.5-fold increase in the relative risk of endocarditis.

2.3.1.4 Prosthetic valves

Prosthetic devices, such as prosthetic heart valves, predispose patients to infection. Infection occurs when bacteria colonized on the surface of the skin enter the host when a prosthetic device is implanted.\textsuperscript{77} A challenge of treating prosthetic device infection is the presence of a biofilm on the surface of the device.\textsuperscript{77} A biofilm is composed of invasive bacteria and a matrix of adherent lipids, nucleic acids, polysaccharides and protein that protect the bacteria from the host’s immune response.\textsuperscript{77}

Surgery frequently occurs among patients infected by resistant and/or virulent microorganisms.\textsuperscript{78} Evidence demonstrates that surgical intervention has resulted in positive outcomes for non-PWID with endocarditis.\textsuperscript{3,79–84} However, clinicians are faced with difficulties when considering surgery for PWID as recurrent endocarditis and reoperation are frequent.\textsuperscript{3,85} As a result, prosthetic valve endocarditis is mostly observed among non-PWID. A study by Wang et al.\textsuperscript{86} found that compared to native valve endocarditis, prosthetic valve endocarditis was significantly associated with older age (65.0 versus 56.3 years, $P < 0.001$) and negatively associated with IDU (1.8\% prosthetic valve endocarditis versus 12.4\% native valve endocarditis, $P < 0.001$).
2.3.1.5 Human immunodeficiency virus

Globally, HIV affects approximately 2.8 million (95% UI 1.5 to 4.5 million) PWID, which accounts for 17.8% (95% UI 10.8% to 24.8%) of the PWID global population.\(^\text{63}\) Figure 2.4 demonstrates an estimated global prevalence of HIV among PWID. From their systematic review, Degenhardt et al.\(^\text{63}\) estimated large prevalence of HIV among PWID in eastern Europe (24.7%, 95% UI 15.6% to 33.9%) and Latin America (35.7%, 95% UI 15.0% to 56.6%), demonstrated in Figure 2.4. In comparison, estimates of prevalence rates of HIV among Canadian PWID were much lower (11.3%, 95% UI 8.5% to 14.2%) (Figure 2.4).\(^\text{64}\)

![Figure 2.4 Estimated HIV prevalence among people who inject drugs by country](image)

**Figure 2.4 Estimated HIV prevalence among people who inject drugs by country**

Source: © 2017 Louisa Degenhardt, Amy Peacock, Samantha Colledge, et al. Published by Elsevier Ltd. DOI:https://doi.org/10.1016/S2214-109X(17)30375-3; Abbreviations: IDU, injection drug use. No eligible report=evidence of IDU located, but no study of HIV prevalence among people who inject drugs that met our eligibility criteria was located.

Ontario had the highest proportion of HIV incident cases in Canada (39.2%) in 2018, followed by Quebec (29.9%).\(^\text{87}\) The majority of Canadians living with HIV were found to be between the ages 30 and 39 years (30.4%) with a diagnosis rate of 15.4 per 100,000 Canadians.\(^\text{87}\) The 20 to 29 and ≥ 50 age groups were found to have the second largest
proportion of Canadians living with HIV (22.5%). The diagnosis rate among the 20 to 29 year age group was the second highest, resulting in a rate of 11.5 cases per 100,000, which is similar to that of the 40 to 49 year age group. Of all reported HIV cases in 2018, male Canadians accounted for 70.7%. Among both male and female Canadians living with HIV, the highest proportion of cases belonged to the 30 to 39 year age group (28.9% versus 34.3%, respectively). IDU was documented as the third most frequently reported HIV exposure category in 2018. The incidence rate of HIV via IDU increased from 16.2% in 2017 to 18.3% in 2018. The risk of acquiring HIV was 22 times higher in PWID than the general population. HIV is common among PWID; the Centers for Disease Control and Prevention reports one in 10 injection drug users will acquire HIV.

Literature suggests patients living with HIV have a 40% to 75% increased risk of cardiovascular disease. Evidence shows HIV infection increases a patient’s relative risk of myocardial infarction and coronary heart disease by 1.5 to two-fold. Moreover, it is suggested that HIV infection is also associated with endothelial cell dysfunction, predisposing patients to endocarditis.

Coinfection of endocarditis and HIV occurs frequently in PWID. In a study comparing IDU-related and non-IDU related endocarditis, researchers observed that PWID were more likely to be affected by HIV (6% versus 1.2%, $P < 0.001$). Furthermore, the immunosuppression caused by HIV infection increases a patient’s risk of developing endocarditis. A study conducted by Gebo et al. found patients with lower CD4 counts (less than 50 cells/mm$^3$), indicating greater immunosuppression, were at higher risk of developing endocarditis compared to patients with higher CD4 counts. Multivariate analyses demonstrated a decrease in odds of developing endocarditis per increase in CD4 cell count. Similar results were found in a 1996 nested case-control study by Manoff and colleagues. In addition, Gebo et al. found no association between the use of highly active antiretroviral therapy and the development of endocarditis (OR = 0.71, 95% CI 0.38 to 1.37). Furthermore, the association between mortality due to endocarditis and HIV status was not statistically significant.
2.3.1.6 Causative organisms

There are many organisms that can cause endocarditis. Streptococci and staphylococci species account for 80% of endocarditis cases. The increase of healthcare acquired endocarditis has also increased the prevalence of *Staphylococcus aureus* and coagulase-negative staphylococci related endocarditis cases. In addition, the presence of enterococci has increased and has also been found to be associated with healthcare acquired endocarditis. The increase in staphylococci bacteremia in turn decreases the proportion of endocarditis cases attributable to viridans group streptococci. Causative organisms vary by region. In North America, *Staphylococcus aureus*, streptococci and enterococci are responsible for 43%, 17% and 13% of endocarditis cases, respectively. Conversely, these numbers differ dramatically in South America. Among endocarditis cases in South America, *Staphylococcus aureus*, streptococci and enterococci are responsible for 17%, 39% and 20% of endocarditis cases, respectively. Rheumatic heart disease resulting from untreated beta-haemolytic streptococcal throat infection is more predominant in South America than North America, resulting in a higher proportion of endocarditis cases caused by viridans streptococci.

Welton et al. observed that *Staphylococcus aureus* was the most prevalent causative organism for overall endocarditis cases (59%), followed by viridans group streptococci (16%) and *Enterococcus fæcalis* (9%). In addition, these causative organisms vary by IDU and non-IDU associated endocarditis. *Staphylococcus aureus* is a predominant causative organism found among both IDU- and non-IDU related endocarditis; however, its prevalence is greater among IDU-related endocarditis. Among PWID, the prevalence of *Staphylococcus aureus* has been observed to be between 30.6% and 77.8%. Conversely, among non-PWID, the prevalence of *Staphylococcus aureus* has been observed to be between 19.1% and 22.1%. Furthermore, streptococcus bacteremia has also been demonstrated to contribute to IDU and non-IDU related endocarditis; prevalence ranges from 4.4% to 13% among PWID and 7% and 15.8% in non-PWID.
2.3.1.7 Location of infection
As previously stated, left-sided endocarditis affects the mitral and aortic valves, right-sided endocarditis affects the tricuspid and pulmonic valves, and bilateral endocarditis affects structures on both the left- and right-side of the heart.\textsuperscript{7,17} Right-sided endocarditis is commonly observed among PWID,\textsuperscript{24} thus, the tricuspid valve is the primary location of vegetation. Rodger et al.\textsuperscript{3} found 58.4\% of IDU-related endocarditis cases had vegetation of the tricuspid valve, followed by the aortic (12.9\%) and mitral valves (11.9\%). In a subsequent study, Rodger et al.\textsuperscript{7} found similar vegetation trends; the tricuspid valve was affected in 62.7\% of IDU-related endocarditis cases, followed by the aortic and mitral valves (15.6\% each). Moreover, Ortiz-Bautista and colleagues\textsuperscript{24} also observed a large proportion of tricuspid valve vegetation (58\%) among PWID.

2.3.2 Recurrence of endocarditis

2.3.2.1 Search strategy and inclusion criteria
To gain better understanding of the current evidence of recurrent endocarditis among the population of PWID, specifically, a systematic review was conducted by searching MEDLINE (Ovid), EMBASE and Web of Science databases on July 27, 2020. For recurrent endocarditis, each database was searched using the following terms: repeat endocarditis OR repeat infective endocarditis OR repeat infectious endocarditis OR recurrent endocarditis OR recurrent infective endocarditis OR recurrent infectious endocarditis. Next, to find literature on injection drug use, each database was searched using the following terms: injection drug user* OR intravenous drug user* OR IDU* OR drug user* OR persons who inject drugs OR people who inject drugs OR PWID OR injector* OR drug injector* OR injecting drug user* OR injecting drug abuse* OR injection drug user* OR injection drug abuse* OR drug utilization or intravenous substance abuse* OR intravenous substance user*. Individual searches were conducted for recurrent endocarditis and injection drug use. Results were combined using the AND logical operator. A detailed outline of the search strategy can be found in Appendix C.

This search strategy returned 42 results which were exported into Mendeley. Of these results, 17 duplicates were removed. The title and abstract of the remaining 25 records
were screened and individual case reports and studies in which the primary focus was not recurrent endocarditis or PWID were removed. Full text screening of the remaining three articles was conducted; an editorial comment was excluded. This left two studies for analysis (n = 2), shown in Table 2.2. The review process is illustrated in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram\textsuperscript{98} in Figure 2.5.
### Table 2.2 Summary of literature regarding recurrent endocarditis among PWID

<table>
<thead>
<tr>
<th>Authors, date of publication</th>
<th>Setting</th>
<th>Patient population</th>
<th>Study sample size</th>
<th>Study objective(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang, Barnes &amp; Peacock 2018</td>
<td>Winston-Salem, North Carolina, United States</td>
<td>PWID ≥ 18 years diagnosed with endocarditis who were admitted to the Wake Forest Baptist Medical Center between January 2004 and January 2017.</td>
<td>94</td>
<td>• Report clinical and demographic characteristics, and outcomes of repeat endocarditis among PWID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Determine the clinical factors that predispose PWID to recurrent endocarditis</td>
</tr>
<tr>
<td>Rodger et al. 2019</td>
<td>London, Ontario, Canada</td>
<td>PWID ≥ 18 years diagnosed with definite endocarditis admitted to any of the three acute care centers in London, Ontario between February 2007 and March 2016</td>
<td>212</td>
<td>• Characterize recurrent endocarditis among PWID</td>
</tr>
</tbody>
</table>
Figure 2.5 PRISMA flow diagram
2.3.2.2 Defining recurrent endocarditis

Literature defines the recurrence of endocarditis as a repeated episode that either occurs more than six months from the previous episode or is caused by a different causative organism. It is estimated that repeated episodes of endocarditis occur in approximately 2% to 31% of patients. A study by Rodger et al. characterized recurrent endocarditis among PWID. From their study, Rodger et al. observed a recurrence rate of 32.1% among the PWID in their study sample, which is significantly greater than that of non-PWID (32.1% versus 6.2%, \( P < 0.001 \)). Rodger et al. also found the median time to recurrence (IQR) was 1.23 (0.33 to 2.86) years.

2.3.2.3 Risk factors for recurrent endocarditis among non-injection drug users

The risk factors for recurrent endocarditis among non-PWID and PWID differ significantly. Among the non-PWID population, recurrent endocarditis has been observed to be associated with several risk factors:

- **Increasing age.** Evidence demonstrates that the incidence of endocarditis increases with age. Mansur et al. determined that patients’ age significantly increased the risk of disease recurrence by 2% (RR = 1.02, \( P = 0.0003 \)).

- **Sex/gender.** Male sex was found to be significantly associated with increased risk of disease recurrence (RR = 1.61, \( P = 0.023 \)).

- **Heart disease.** Welton et al. found the proportion of prior heart disease (coronary heart disease, rheumatic heart disease, prosthesis, and murmurs) increased two-fold in patients with recurrent endocarditis episodes compared to those with single episodes (67% versus 38%, \( P < 0.05 \)). Similarly, in a literature review by Baddour, prior heart disease was commonly cited as a predisposing factor for recurrent episodes.

- **Prosthesis.** As previously stated, prosthetic devices predispose patients to infection due to the formation of a biofilm. Prosthetic valve endocarditis usually results from bacterial interaction during surgery. Mansur et al. observed a 105% increase in the risk of disease recurrence in the presence of prosthetic valves (RR = 2.05, \( P = 0.026 \)). Similarly,
Renzulli et al.\textsuperscript{12} determined prosthesis as a significant predisposing factor for recurrent endocarditis (30.2% versus 9.4%, $P = 0.001$).

2.3.2.4 Risk factors for recurrent endocarditis among injection drug users

IDU is a substantial predisposing factor for the development and recurrence of endocarditis.\textsuperscript{6,11,14,100} An early study examining predisposing factors for recurrence of endocarditis found PWID were at a significantly higher risk ($P < 0.005$) of developing recurrent endocarditis within 12 months after their initial episode.\textsuperscript{11} Studies have determined approximately 5.6% to 32.1% of PWID are likely to suffer from a recurrent episode of endocarditis.\textsuperscript{7,14} PWID have distinct risk factors that contribute to its recurrence:

Drug use. Recurrence of endocarditis is common among PWID primarily due to continued use of injection drugs.\textsuperscript{66,101} Welton et al.\textsuperscript{11} observed drug recidivism in 78% of patients with recurrent endocarditis episodes compared to patients with single episodes (78% versus 50%, $P < 0.05$). Furthermore, a study by Huang et al.\textsuperscript{14} found increased incidence of opioid injection drug use among patients who developed recurrent endocarditis episodes (95.4% versus 67.7%, $P = 0.01$).

Location of infection. Vegetation of the tricuspid valve is common among PWID with endocarditis and has been observed to be associated with disease recurrence (72.7% versus 35.3%, $P = 0.02$).\textsuperscript{14} Furthermore, the odds of developing recurrent endocarditis is increased nearly four-fold in the presence of echocardiographically visualized tricuspid valve vegetation (OR = 3.8, 95% CI 1.2 to 11.9).\textsuperscript{14}

Bacteremia. Rodger et al.\textsuperscript{7} found Staphylococcus aureus to be the leading causative organism among both first and second endocarditis episodes in PWID (77.8% versus 63.2%). However, fungal endocarditis (typically caused by Candida spp.) significantly increased among recurrent endocarditis episodes (7.4% versus 0.5%, $P = 0.0005$),\textsuperscript{7} which aligns with previous literature.\textsuperscript{6,14,102} The increased proportion of Candida in recurrent endocarditis episodes may be associated with preceding valvular damage.\textsuperscript{7} In addition, the presence of fungal causative organisms in repeated endocarditis episodes was
associated with a significant increase in the adjusted odds of mortality \( (\text{OR} = 16.49, 95\% \text{ CI} 1.12 \text{ to } 243.17, P = 0.04) \).\(^7\) Fungal endocarditis is frequently associated with IDU and immunocompromised patients.\(^{102}\)

**Surgical intervention.** Treatment of endocarditis among PWID is complex and clinicians are faced with numerous challenges. Firstly, antibiotic resistant bacteria are common among PWID, making it difficult to utilize antibiotic therapy, the primary treatment for endocarditis.\(^{78}\) However, evidence suggests that surgical intervention increases the odds of developing recurrent endocarditis five-fold \( (\text{OR} = 5.1, 95\% \text{ CI} 1.6 \text{ to } 16.3) \) among PWID.\(^{14}\) Moreover, PWID are at a higher risk of reinfection, resulting in increased risk of mortality should operation of a prosthetic valve occur.\(^{78}\)

**PICC line misuse.** PICC lines are used to administer intravenous treatments, such as drugs, fluids or blood transfusions.\(^{103}\) Misuse of PICC lines to inject drugs other than those used for treatment is a concern for patients identified as PWID.\(^{104}\) Rodger et al.\(^7\) observed a significant increase in the risk of recurrent endocarditis among PWID who misused their PICC line \( (\text{OR} = 1.97, 95\% \text{ CI} 1.01 \text{ to } 3.87, P = 0.04) \).

**Referral to addictions services.** It is posited that referring PWID to addiction services may decrease the probability of recurrence of endocarditis. Study results from Rodger et al.\(^7\) did not find a significant association between referral to addiction services and lower risk of endocarditis recurrence \( (\text{OR} = 0.54, 95\% \text{ CI} 0.26 \text{ to } 1.14, P = 0.11) \). However, this finding may be the result of low statistical power as a small proportion (20.8%) of patients were referred to addiction services during their first episode.\(^7\)

**Leaving against medical advice.** Leaving against medical advice occurs when patients decide to leave the hospital prior to finishing the recommended in-hospital treatment.\(^{105}\) This poses an increased risk in hospital readmission.\(^{105}\) The relationship between leaving against medical advice and endocarditis recurrence was explored by Rodger et al.\(^7\) Study findings suggest that leaving against medical advice was not significantly related to recurrent endocarditis \( (\text{OR} = 0.50, 95\% \text{ CI} 0.21 \text{ to } 1.20, P = 0.12) \).\(^7\) However, similar to the results assessing the relationship between referral to addictions services and endocarditis recurrence, this finding may be subjected to low statistical power as low
proportions of patients left against medical advice among first (16.5%) and second episodes (14.7%).

ICU admission. It is hypothesized that admission to the ICU will result in worse patient prognosis.

In addition, recurrent endocarditis is a consequence of the unique barriers to care that are faced by PWID. Harm reduction practices, such as the use of NEPs, are not often used especially in hospital and PWID are more likely to leave the hospital against medical advice.

2.4 Knowledge gaps

Review of the literature demonstrates limited knowledge regarding the recurrence of endocarditis among injection drug use populations. To date, two studies have been identified that focus on endocarditis specifically among injection drug users (Table 2.2).

Huang et al. conducted a retrospective cohort study on PWID aged ≥ 18 years from Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, United States of America (n = 94). Patients were admitted to the center between January 2004 to January 2017. Among this patient cohort, a small sub-cohort of patients was identified as having recurrent endocarditis cases within one year of the initial episode (n = 22). One-year survival was significantly lower among PWID with recurrent endocarditis compared to PWID with single-episode endocarditis (63.6% versus 95.4%, P < 0.01). In addition, compared to PWID who experienced single-episode endocarditis, those who experienced recurrent endocarditis frequently misused prescription opioids (95.5% versus 67.7%, P = 0.01), had increased visualization of tricuspid valve vegetations (72.7% versus 35.3%, P = 0.02) and surgical intervention (59.1% versus 24.6%, P < 0.01). Multivariate analyses demonstrated infection of tricuspid valves (OR = 3.8, 95% CI 1.2 to 11.9) and surgical intervention (OR = 5.1, 95% CI 1.6 to 16.3) were significantly associated with recurrent endocarditis.

Rodger et al. identified 68 PWID with recurrent endocarditis; 22/68 experienced a third episode and 5/22 experienced a fourth episode. A recurrence rate of 32.1% (68/212) was
determined among the PWID subjects, however, this rate does not consider competing risks. Conversely, the rate of endocarditis recurrence among non-PWID was much smaller (32.1% versus 6.2%, \( P < 0.001 \)). Similar clinical characteristics were observed for age, sex, HIV status, length of hospital stay, homelessness, site of infection, primary valve affected, substances used and surgical intervention among first and recurrent endocarditis episodes. Patients who experienced a second episode of endocarditis were more commonly infected by fungal endocarditis rather than bacterial endocarditis (\( P = 0.004 \)). In addition, Rodger et al. found that the odds of mortality were 16.49 (95% CI 1.12 to 243.17, \( P = 0.041 \)) times greater among PWID patients with fungal infection compared to those with other types of endocarditis infection, adjusting for surgical intervention, site of infection and prosthetic valves. Furthermore, among patients with second episodes of endocarditis, the mortality rate was determined to be 38.2% and the primary cause of death was observed to be sepsis (81%).

To date, no studies have been conducted that assess the probability of recurrence of endocarditis among PWID in the presence of competing risks, a concept that is imperative to survival analyses. This thesis aimed to bridge this knowledge gap by conducting a retrospective cohort study utilizing a population-based dataset of endocarditis and PWID that consists of city-wide data for London, Ontario. This thesis aimed to identify meaningful risk factors for disease recurrence among PWID and develop a predictive model with consideration of competing risks. A competing risks regression analysis was used to provide further context and assess the probability of disease recurrence in PWID.

### 2.5 Competing risks

Competing risks data refers to the phenomenon whereby multiple events can occur that impede the incidence of the outcome of interest. Competing risks are frequently disregarded in medical and epidemiological studies, which leads to biased estimates of the outcome’s cumulative incidence. Competing risk models will be further discussed in Chapter 3: Methods.
2.6 London, Ontario

Rates of infectious diseases that are frequently associated with IDU, such as HIV and hepatitis C, have increased among residents of Middlesex-London. The Infectious Disease Trends in Ontario tool provided by Public Health Ontario\(^\text{109}\) compares the trends of HIV (Figure 2.6) and hepatitis C (Figure 2.7) among Middlesex-London and Ontario. From 2014 to 2017, the rates of HIV in Middlesex-London drastically exceeded that of Ontario (Figure 2.6). 2016 was observed to have the highest rate of HIV in Middlesex-London, reaching a rate of 12.8 per 100,000 population.\(^\text{109}\) Further, rates of hepatitis C in Middlesex-London consistently exceeded that of Ontario from 2006 to 2018 (32.7 to 57.5 per 100,000 population [Middlesex-London] versus 31.3 to 36.4 per 100,000 population [Ontario]) (Figure 2.7).\(^\text{109}\)

![Figure 2.6 Yearly comparison of the rate of HIV in Middlesex-London and Ontario](image-url)

Figure 2.7 Yearly comparison of the rate of hepatitis C in Middlesex-London and Ontario


IDU is a predominant issue in London. The I-TRACK survey reported that compared to the national sample, the probability of injecting opioids was greater among sampled PWID in London. PWID in London were more likely to inject hydromorphone (75.5% in London versus 47.2% nationally) and morphine (75.5% in London versus 47.0% nationally). Moreover, PWID in London were more likely to lend (26.6% in London versus 15.5% nationally) and borrow (19.6% in London versus 15.5% nationally) used injection paraphernalia.

NEPs in London distribute high volumes of sterile needles to PWID. Each year, organizations, such as Middlesex-London Health Unit, Regional HIV/AIDS Connection
and My Sister’s Place, distribute over three million sterile needles in the Middlesex-London region to help reduce the incidence of blood-borne diseases.\textsuperscript{111}

In 2012, the seroprevalence of hepatitis C among PWID in London was recorded to be higher than the national average (79.1\% in London versus 68.0\% nationally).\textsuperscript{112} Further, a report from public health officials of Middlesex-London noted 70\% of HIV incident cases were attributable to IDU in 2016.\textsuperscript{113} Endocarditis has become an increasingly significant disease among PWID in Middlesex-London.\textsuperscript{113} Figure 2.8 illustrates the count of endocarditis cases among PWID in Middlesex-London from 2008 to 2015. From 2008, first-episode and recurrent episodes of IDU-related endocarditis have significantly increased in Middlesex-London.\textsuperscript{114} Moreover, case-fatality rates of endocarditis among Middlesex-London PWID range from 30 to 40\%.\textsuperscript{113}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{endocarditis_cases.png}
\caption{Number of endocarditis cases among PWID per year in Middlesex-London}
\end{figure}

\textit{Source: Dr. Michael Silverman, MD, FRCP, FACP, Chair/Chief Infectious Diseases LHSC and St. Joseph’s Hospital, Western University, London.}
Chapter 3

3 Methods

This chapter outlines the methods used in this study. Sections 3.1 and 3.2 describe the data source, its population and setting. Section 3.3 defines the concepts of recurrent endocarditis and location of infection. Section 3.4 introduces the measures and outcome variables and provides further information on their coding structure. Section 3.5 provides information on missing data and how it was handled in this study. Lastly, Section 3.6 outlines the statistical analyses that were conducted to address each of the three research objectives proposed in this study.

3.1 Data source

This study used a database provided by Dr. Michael Silverman and St. Joseph's Health Care London, a teaching hospital that encourages the development of education, healthcare and research. The endocarditis database provides demographic and clinical information on definite endocarditis cases in London, Ontario. Cases were reported using clinical data from electronic medical records at the London Health Sciences Centre. Data from the electronic medical records includes information on demographics, diagnostic imaging, microbiology, medication, and clinical notes. Data were reviewed by infectious disease physicians to ensure definite endocarditis criteria was fulfilled as outline by the Modified Duke Criteria. Ethics approval was obtained by Dr. Silverman and colleagues prior to data collection and retained throughout the current study.

3.2 Population and setting

The database consists of patients admitted to all three acute care hospitals in London, Ontario, Canada, between April 5, 2007 and March 15, 2018. The study population was composed of patients 18 years of age or older with definite cases of endocarditis (n = 564). Patients who were not identified as PWID were excluded from the study (n = 254). The final sample size used in this study was 310 PWID with definite endocarditis. Of the 310 PWID, 236 experienced only a single episode of endocarditis and 74 experienced two or more episodes. Figure 3.1 illustrates the inclusion/exclusion flowchart for the
study. Informed consent from participants was not required due to the de-identified and retrospective nature of the study.

Figure 3.1 Flowchart of study inclusion and exclusion criteria
Abbreviations: PWID, people who inject drugs.

3.3 Definitions
Definite endocarditis cases were classified as either single or repeat episodes.\textsuperscript{3} Repeated cases were defined using criteria proposed in the literature: recurrent episode that either occurs more than six months from the previous episode OR caused by a different causative organism.\textsuperscript{6-8} Microbial culture was used to assess the composition of vegetations to ensure patients readmitted to hospital for endocarditis less than six months from the previous episode met the criteria of repeat endocarditis. Each endocarditis episode may involve multiple admissions and patients may have multiple episodes. Infections affecting structures on the left side of the heart were defined as left-sided endocarditis, whereas infections affecting structures on the right side of the heart were
defined as right-sided endocarditis. In cases where structures on both sides of the heart were affected, endocarditis infection was defined as bilateral.

3.4 Measures and outcome variables

3.4.1 Demographic variables

Demographic characteristics used in this study include age at time of admission and sex. Age at time of admission was a continuous variable derived from subtracting the date of admission from date of birth. Sex was coded as a binary variable whereby 0 represented female patients and 1 represented male patients.

3.4.2 Exposure variables

Injection drug use. A variable for IDU was created to identify PWID. IDU was recoded into a binary variable in which 0 represented non-PWID and 1 represented PWID.

Echocardiography. Binary variables for tricuspid, pulmonic, aortic, mitral, right ventricle or atrium, and device or lead related vegetation were created in which 0 indicated the absence of valve vegetation and 1 indicated the presence of valve vegetation. Binary variables for right-sided, left-sided and bilateral endocarditis infection were then created. Right-sided endocarditis was defined using the presence of vegetation on the tricuspid valve, pulmonic valve, right ventricle or atrium, and right-sided implantable cardioverter-defibrillator and pacemaker leads. Left-sided endocarditis was defined using the presence of vegetation on the mitral valve, aortic valve, left-sided interventricular septum and left-sided implantable cardioverter-defibrillator leads. Bilateral endocarditis infection was defined by the presence of both right-sided and left-sided endocarditis infection. Subsequently, a categorical variable for the site of infection was then created; 1 indicated right-sided endocarditis infection only, 2 indicated left-sided endocarditis infection only and 3 indicated bilateral infection. In situations whereby the sample size is too small to adequately use the categorical variable, the binary variable for right-sided endocarditis will be used.

In-hospital treatment. Patient length of stay in days, was a continuous variable derived by subtracting the date of admission from date of discharge. PICC line misuse, ICU
admission, surgical intervention, leaving against medical advice and referral to addiction services were documented as binary variables with the outcomes 0 indicating no and 1 indicating yes.

**Drug misuse.** A binary variable for polysubstance misuse was created with the outcomes 0 representing mono-substance misuse of either opiates or stimulants, and 1 representing polysubstance misuse.

### 3.4.3 Outcome variables

**Recurrent endocarditis.** The primary outcome of interest for this thesis was the recurrence of endocarditis. De-identified patient personal identification numbers were used to identify the number of hospital admissions for definite endocarditis per patient. Hospital admission for recurrent cases of endocarditis was defined as any hospital readmissions that either occurred more than six months from the previous episode or whereby endocarditis infection was caused by a different causative organism. A binary variable for the presence of recurrent endocarditis was created using these criteria, whereby 0 represented patients who experienced only a single episode of endocarditis and 1 represented patients who experienced two or more episodes of endocarditis. A variable for the number of recurrent endocarditis episodes per patient was derived using the number of hospital admissions for definite endocarditis. Due to the small sample size of patients who went on to experience three episodes (32/74) and four episodes (5/32) of endocarditis, this variable could not be further broken down for analyses.

**Death.** Death was treated as a competing risk and recoded as a binary variable in which 0 indicated the patient was alive and 1 indicated patient death. In additional analyses, death was treated as a primary outcome.

### 3.4.4 Failure event variables

A categorical variable for survival status was derived to assess the probability of endocarditis recurrence in the presence of competing risks. Patients who experienced neither recurrent endocarditis nor death were coded as 0, indicating censoring. Patients who experienced recurrent endocarditis and either survived or died during the episode
were coded as 1, indicating observation of the outcome of interest. Patients who died and did not experience a recurrent episode of endocarditis were coded as 2, indicating the presence of a competing risk. The time-to-event variable was derived by subtracting the discharge date of the first admission from the date of either readmission, death, or last follow-up, corresponding to the survival status levels 1, 2 and 0, respectively.

A binary variable for mortality status was derived to measure the probability of mortality among PWID. Patients who did not experience death were coded as 0, indicating censoring. Patients who died were coded as 1, indicating observation of the outcome of interest. The time-to-death variable was derived by subtracting the discharge date of the first admission from the date of either death or last follow-up, corresponding to the survival status levels 1 and 0, respectively.

3.5 Missing data

Missing data is a common occurrence in epidemiological studies and requires careful consideration when conducting statistical analyses as inaccurate and biased results may be produced. There are three primary categories of missing data, (i) missing completely at random (MCAR), (ii) missing at random (MAR) and (iii) missing not at random (MNAR). Missing data is designated as MCAR when the missingness is not dependant on the observed or unobserved variables. Data is denoted MAR when the probability of missingness is not dependent on unobserved data. Conversely, when the probability of missingness is dependent on unobserved data, the data is said to be MNAR.

Of the three types of missingness, MCAR is the only one that can be assessed. MCAR can be evaluated by (1) assessing the distribution of the data using summary statistics and (2) assessing the relationship between the missingness and covariates using logistic regression. If the missing data are MCAR in nature, there will be no differences between observations with complete data and those with missing data. Therefore, binary missing data indicators will be generated for each variable with missing data and assessed using summary statistics and logistic regression. If the results determine that the missingness of the data is not MCAR, multiple imputation will be used. If the missing
data is determined to be MCAR, complete case analysis of observations with complete
data will be used.\textsuperscript{119}

Multiple imputation is a common method used for handling missing data and consists of
three stages: imputation, complete-data analysis and pooling.\textsuperscript{120} The imputation phase
replaces missing values with a random sample of probable imputation values generated
using observations with complete data; multiple datasets are created using this
technique.\textsuperscript{121} Next, statistical analyses are conducted for each dataset.\textsuperscript{121} Finally, the
results obtained for each dataset are combined to generate a multiple imputation result.\textsuperscript{121}
There are two primary approaches to multiple imputation, the multivariate normal
imputation and the fully conditional specification (FCS).\textsuperscript{122} In the multivariate normal
imputation approach, imputed values are obtained using a Bayesian technique, which
allows for the ascertainment of uncertainty levels in model parameter coefficients.\textsuperscript{122}
Furthermore, this model assumes each variable follows a multivariate normal
distribution.\textsuperscript{122} Conversely, the FCS approach is not dependent on the assumption of
normality, making this approach much more flexible.\textsuperscript{122} The FCS approach generates
regression models for each variable containing missing data that are conditional on the
variables in the desired imputation model.\textsuperscript{122} Estimates of each conditional regression
model using cases with complete data generates imputations and allows for ascertainment
of uncertainty levels in model parameter coefficients.\textsuperscript{122}

In the presence of binary and categorical variables, the assumption of multivariate
normality is not always reasonable, thus, use of multivariate normal imputation is not
plausible.\textsuperscript{122} Further, the FCS approach generates regression models for each variable,
allowing for flexibility in imputation.\textsuperscript{122} Since the dataset used in this study contains
continuous, binary and categorical variables, the FCS approach to imputation was used to
handle missing data.\textsuperscript{122}

3.6 Statistical analyses

Analyses of missing data were conducted using SAS 9.4\textsuperscript{®}.\textsuperscript{123} Survival plots were created
using SAS 9.4\textsuperscript{®}\textsuperscript{123} and R\textsuperscript{®}.\textsuperscript{124} All other analyses were conducted using Stata/IC 16.1.\textsuperscript{125}
The following sections discuss the statistical methods used to address the objectives and research questions proposed in the study.

3.6.1 Characterizing important factors that contribute to the recurrence of endocarditis among PWID in London, Ontario

To address objective 1 and the research question, “what are the key factors that contribute to the recurrence of endocarditis among PWID in London, Ontario?”, descriptive analyses were conducted comparing patient characteristics between PWID who only experienced a single episode of endocarditis and PWID who went on to experience recurrent (≥ two) endocarditis episodes. Pearson’s chi-squared and Wilcoxon rank sum tests were conducted for binary/categorical and continuous variables, respectively, to determine if the distribution of variables is equivalent across the two strata. Next, bivariate analyses of the primary outcome and exposure variables of interest were conducted to assess empirical relationships between recurrent endocarditis and independent demographic and exposure variables. Further, to assess the extent to which important factors contribute to the recurrence of endocarditis among PWID in London, Ontario, a complete case multivariate logistic regression analysis and FCS imputation logistic regression analysis were subsequently conducted. Multicollinearity was assessed between predictors of interest to ensure the variables were not linearly related. Model covariates were chosen based on subject matter knowledge. The model included age,9,10 sex,9 substance use,66,101,126 location of infection,126 and surgical intervention78,126 as covariates, as proposed by current literature. Further, this study aimed to assess the effects of length of hospital stay, PICC line misuse, addiction referral, leaving against medical advice and admission to the ICU. The model can be written as follows,

\[
P(x) = \frac{\exp(\beta_0 + \beta_1 \text{age} + \beta_2 \text{sex} + \beta_3 \text{LOS} + \beta_4 \text{location} + \beta_5 \text{surgery} + \beta_6 \text{PICC} + \beta_7 \text{addiction} + \beta_8 \text{AMA} + \beta_9 \text{substance} + \beta_{10} \text{ICU})}{1 + \exp(\beta_0 + \beta_1 \text{age} + \beta_2 \text{sex} + \beta_3 \text{LOS} + \beta_4 \text{location} + \beta_5 \text{surgery} + \beta_6 \text{PICC} + \beta_7 \text{addiction} + \beta_8 \text{AMA} + \beta_9 \text{substance} + \beta_{10} \text{ICU})}
\]

where \( P \) represents the probability that the event of interest will occur, \( x \) represents predictor variables, LOS represents length of hospital stay, PICC represents PICC line misuse and AMA represents leaving against medical advice. Coefficients were assessed for the direction and magnitude of effect of each independent predictor on the recurrence
of endocarditis. Significance was indicated using Wald test statistics, two-sided confidence intervals and $P$ values $< 0.05$.

### 3.6.2 Survival analysis

To assess the probability of endocarditis recurrence in the presence of competing risks among PWID in London, Ontario, survival analyses were conducted. Survival analysis is a division of statistics that consists of a set of methods for which the outcome of interest is the time until an event occurs, known as time-to-event data.\textsuperscript{127,128} Time-to-event endpoints often include death, time to relapse, time to disease progression or any outcome of interest that occurs within the patient population.\textsuperscript{128,129} An outcome of interest can be defined as either a success or failure.\textsuperscript{128,130} Events denoted failures, such as death or disease incidence, are often of greater clinical significance.\textsuperscript{128,130}

Survival analyses are comprised of two functions, the survivor function and the hazard function. The survivor function, denoted $S(t)$, describes the time in which a patient has survived over a follow-up period,\textsuperscript{128,129} and is given by

$$S(t) = \Pr(T > t)$$

where $T$ represents a patient’s survival time and $t$ represents a specific value of interest for $T$.\textsuperscript{128} The overall probability of survival among patients is estimated using event status and person follow-up time.\textsuperscript{131} A patient’s probability of survival is conditional on the patient surviving for a specified amount of time in which they are at risk of experiencing the outcome.\textsuperscript{131} Conversely, the hazard function represents the short-term event rate for patients who are still at risk (survived up to time $t$) of experiencing the outcome of interest\textsuperscript{107} and is given by

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

The hazard ratio (HR) is the measure of effect obtained from survival analyses.\textsuperscript{128} The hazard ratio is defined as the ratio of hazards between exposed and unexposed patients\textsuperscript{132} and is given by
\[ HR(t) = \frac{h_1(t)}{h_0(t)} \]

where \( h_1(t) \) is the hazard of the exposed patients and \( h_0(t) \) is the hazard of the unexposed patients.

The Cox proportional-hazards regression model is used to assess the association between multiple predictors and a time-to-event outcome.\(^\text{107}\) We assume a proportional hazards model as,\(^\text{107}\)

\[
h(t|\mathbf{x}) = h_0(t) \exp(\beta_1 \text{age} + \beta_2 \text{sex} + \beta_3 \text{LOS} + \beta_4 \text{location} + \beta_5 \text{surgery} + \beta_6 \text{PICC misuse}
+ \beta_7 \text{addiction} + \beta_8 \text{AMA} + \beta_9 \text{substance} + \beta_{10} \text{ICU})
\]

where \( \mathbf{x} \) represents predictor variables, \( h_0(t) \) represents the baseline hazard function, LOS represents length of hospital stay, PICC represents PICC line misuse and AMA represents leaving against medical advice.

A unique feature of survival analysis is its ability to allow for incompletely determined responses for some patients,\(^\text{127}\) which are often considered ‘censored data’. Censored data refers to the phenomenon whereby some information is known about the patient’s survival time, however, the exact survival time is unknown.\(^\text{128}\) Essentially, a patient’s data is censored when the outcome of interest has not been observed.\(^\text{133}\) Censoring of time-to-event data usually occurs when (i) the patient is lost to follow-up, (ii) the patient does not experience the event prior to the end of the study, or (iii) the patient dies or is withdrawn from the study.\(^\text{128}\) Right-censoring occurs when the true survival time at time \( t \) is greater than or equal to the survival time observed at time \( t \).\(^\text{107,128,133}\)

### 3.6.2.1 Competing risks

Competing risks data refers to the phenomenon whereby multiple events can occur that impede the occurrence of the outcome of interest.\(^\text{106,107}\) In terms of recurrence of endocarditis, death is considered a competing risk as it impedes a patient’s ability to be reinfected by the disease. The presence of competing risks hinders the use of traditional
survival analysis methods, such as Kaplan–Meier methods, as “event time is neither observed nor censored”.\textsuperscript{129}

Competing risks are common in practice and are often ignored. A survey by van Walraven and McAlister,\textsuperscript{134} observed 46\% (46/100) of studies were biased by competing risks, of which, 37.5\% produced estimates that were overestimated by $\geq 10\%$. These studies typically used traditional Kaplan–Meier methods, which censor competing risks.\textsuperscript{129,134}

In the presence of competing risks, the cumulative incidence function (CIF) and cause-specific hazard function (CSH)—analogs of the survivor and hazard functions, respectively—are used. The CIF describes the probability of experiencing an event ($j$) by time $t^{107,129}$ and is given by

$$ CIF_k(t) = P(T \leq t, \delta = j), \quad j = 1, \ldots, J. $$

Conversely, the CSH describes the short-term rate of occurrence of the $j$th event (denoted failure) in patients who are event free,\textsuperscript{106,107,129} and is given by,\textsuperscript{135}

$$ h(t) = \lambda_j^{cs}(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t, D = j | T \geq t)}{\Delta t}. $$

where $\lambda_j^{cs}$ represents the CSH for the $j$th event among subjects that are event-free and $D$ represents the type of event that occurred.\textsuperscript{106,136} The CSH describes the instantaneous rate of failure from each event type in patients who are event free up to time $t$.\textsuperscript{129} As a result, the risk set for the CSH includes patients who are currently event free.\textsuperscript{129}

An analog of the relationship between the survivor function and hazard function is defined by the subdistribution hazard (SH), proposed by Fine and Gray.\textsuperscript{137} The SH describes the instantaneous rate of an event given no other event, competing or otherwise, has occurred before time $t$.\textsuperscript{129} We assume a proportional hazards model for the SH function as,\textsuperscript{135}

$$ h(t) = \lambda_j^{sd}(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t, D = j | T \geq t \cup (T < t \cap D \neq j))}{\Delta t}. $$
where $\lambda_{jd}^j$ represents the SH for the $j$th event among subjects who have not experienced the event of type $j$ and $D$ represents the type of event that occurred.\textsuperscript{106,136} In contrast to CSH, the risk set of SH includes patients who are currently event free and patients who have experienced a competing risk.\textsuperscript{129}

Competing risk survival data can be modeled using either the cause-specific Cox regression model or the Fine–Gray model. Both models are adequate for assessing competing risk survival data, however, they differ in terms of their relationship with the CIF, interpretation, application of proportional-hazards model and proportional hazards assumptions.\textsuperscript{129} The choice of which model to use is often driven by the type of research question investigators wish to answer. Etiologic-based research questions, which aim to identify the effects of exposures on a disease, are answered using the cause-specific Cox regression model, whereas prognostic-based research questions, which aim to address disease progression or likelihood, are answered using the Fine–Gray model.\textsuperscript{129,138} This thesis aims to address the probability of endocarditis recurrence in the presence of death as a competing risk, therefore, the Fine–Gray model will be used.

### 3.6.3 Measuring the probability of endocarditis recurrence in the presence of competing risks among PWID in London, Ontario

To address Objective 2 and the research question, “what is the probability of the recurrence of endocarditis among PWID in London, Ontario, in the presence of competing risks?”, the CIF of endocarditis recurrence was assessed and graphed. Time at risk was defined as the time from hospital discharge from the first admission until either readmission for a second episode of endocarditis or death. While traditional Kaplan–Meier methods overestimate the probability of an event occurring in the presence of competing risks, this study conducted both Kaplan–Meier and Fine–Gray estimates to demonstrate the importance of accounting for competing risks.
3.6.4 Assessing the associations of survival time and predictor variables among PWID in London, Ontario

This study used the Fine–Gray model to develop a predictive model to address Objective 3 and the research question, “what is the association between survival time and predictor variables accounting for death as a competing risk?”. Competing risk survival analyses were conducted to investigate the association of recurrent endocarditis and predictors of interest. The model for recurrence among PWID included age, sex, length of stay, PICC line misuse, location of infection, surgical intervention, leaving against medical advice, admission to the ICU, referral to addiction services and type of substance misused. Time at risk was defined as the time from hospital discharge from the first admission until either readmission for a second episode of endocarditis or death. Significance was determined using Wald test statistics, two-sided confidence intervals and $P$ values < 0.05.

3.6.5 Evaluating the associations of mortality and predictor variables among PWID in London, Ontario

Since death is a definitive time-to-event endpoint, competing risks do not need to be considered. Therefore, it is feasible to conduct traditional Kaplan–Meier and Cox proportional hazards regression analyses to investigate the relationship between mortality and predictors of interest. The model for mortality included age, sex, length of stay, PICC line misuse, location of infection, surgical intervention, leaving against medical advice, admission to the ICU, referral to addiction services, type of substance misused and recurrent endocarditis. Time at risk was defined as the time from hospital discharge from the first admission until death. Significance was determined using Wald test statistics, two-sided confidence intervals and $P$ values < 0.05.

3.6.5.1 Immortal time bias

Immortal time bias is defined as a period of follow-up time of a cohort in which it is not plausible for the outcome of interest to have occurred.\textsuperscript{139} This type of bias is primarily observed in studies that evaluate the effect of a treatment on survival.\textsuperscript{140} A key aspect of immortal time bias is that the exposure classification requires individuals to survive until the date they receive treatment.\textsuperscript{140} Individuals who die prior to receiving treatment are
deemed unexposed, creating a false sense of survival advantage for exposed individuals. Analyses that fail to account for such bias underestimate the hazard ratio and provide false conclusions regarding treatment effectiveness. There are two main approaches that account for immortal time bias, (1) matching and (2) using time-dependent covariates. Matching occurs in the study design stage and consists of pairing individuals who share similar baseline characteristics but differ with respect to treatment status. In observational studies, pairs are matched based on covariate values or propensity score. In contrast, a time-dependent covariate is a predictor in a Cox model whose value may differ over time. Due to the retrospective nature of the current study, surgical intervention and recurrent endocarditis were treated as time-dependent covariates to account for immortal time bias.
Chapter 4

4 Results

This chapter presents the study’s findings. Section 4.1 highlights the results of the descriptive analyses of the baseline characteristics of single and recurrent endocarditis episodes among PWID. Missing data diagnostics are covered in Section 4.2. Section 4.3 presents the results of the bivariate and multivariate logistic regression analyses and addresses Objective 1 of the study, characterizing important factors that contribute to the recurrence of endocarditis among PWID in London, Ontario. Section 4.4 evaluates multicollinearity between predictor variables. The CIF of endocarditis recurrence with consideration for death as a competing risk is estimated and modeled in Section 4.5 and addresses Objective 2 of the study, estimating the probability of disease recurrence in the presence of competing risks among PWID in London, Ontario. Objective 3, assessing the associations of survival time and predictor variables among PWID in London, Ontario, is addressed in Sections 4.6 to 4.8. Section 4.6 assesses the associations between endocarditis recurrence and predictors of interest in the presence of competing risks. Section 4.7 models the Kaplan–Meier failure function for mortality among the PWID population. Finally, Section 4.8 presents the results of the bivariate and multivariate time-dependent Cox proportional-hazards regression analyses.

4.1 Descriptive analyses

Among the study population, 236 PWID experienced a single episode of endocarditis, whereas 74 experienced recurrent episodes of endocarditis. Consequently, the rate of recurrence among the study population was determined to be 23.9% (74/310).

To determine whether the mean and standard deviation or the median and IQR should be used to assess the continuous variables in the dataset, boxplots for the variables age and length of hospital stay were created to identify their distributions (Figure 4.1). The boxplots for age and length of hospital stay demonstrate right-skewedness, indicating the presence of outliers. As a result, the median and IQR were used to assess age and length of hospital stay.
Figure 4.1 Boxplots demonstrating the distribution of age and length of stay stratified by single and recurrent endocarditis episodes

Table 4.1 illustrates the baseline characteristics of patients stratified by endocarditis status (those who only experienced a single episode of endocarditis and those who went on to experience recurrent endocarditis episodes). The median age at time of admission was identical between patients who experienced a single episode of endocarditis and those who experienced recurrent episodes. Similarly, sex of the patients was evenly distributed across both strata. The median length of hospital stay was slightly higher among patients who would go on to experience recurrent episodes compared to patients who only experienced one episode ($P = 0.04$). Echocardiographic characteristics were similar among both single and recurrent episodes. The tricuspid valve was the primary cardiac structure affected among both single and recurrent episodes. However, infection of the tricuspid valve occurred more frequently among PWID who went on to experience recurrent episodes of endocarditis (66.2% versus 82.2%, $P = 0.01$). The distribution of location of infection differed significantly across strata ($P = 0.04$). Right-sided infection was the predominant type of endocarditis among both single and recurrent episodes but
observed to be more frequent among PWID who went on to experience recurrent episodes of endocarditis (61.4% versus 75.3%). Furthermore, the distribution of left-sided infection was found to be significantly different between patients who only experienced a single episode compared to those who would go on to experience recurrent episodes. Left-sided endocarditis infection was observed less frequently among PWID who went on to experience recurrent episodes of endocarditis (31.6% versus 16.4%). The distribution of PICC line misuse differed significantly between the two strata ($P < 0.001$). Among single episodes, PICC line misuse was relatively low (19.0%). Conversely, the proportion of patients who misused their PICC line increased among those who would go on to experience recurrent episodes (43.8%). Referral to addiction services was also higher among those who went on to experience a recurrent episode compared to those who experienced a single episode (45.9% versus 31.5%, $P = 0.02$). Polysubstance misuse of opiates and stimulants was found in higher proportions among single and recurrent episodes (64.7% and 65.3%, respectively) compared to substance misuse of either opiates or stimulants alone, however the difference in distribution across strata was not found to be statistically significant ($P = 0.93$). The proportion of patients who underwent cardiac surgery was low in both strata (single episode: 17.3% versus recurrent episodes: 17.6%). This slight difference in distribution was not statistically significant ($P = 0.97$). Patients who went on to experience recurrent episodes of endocarditis had a slightly lower proportion of ICU admissions than single episode cases (29.7% versus 36.0%), which was found to not be statistically significant ($P = 0.32$). A slightly higher proportion of patients who experienced recurrent episodes left against medical advice compared to patients who experienced a single episode (25.7% versus 20.3%, respectively), however, this difference was not statistically significant ($P = 0.33$).
Table 4.1 Baseline characteristics from initial hospitalization stratified by patients who only experienced a single episode of endocarditis and those who went on to experience recurrent endocarditis episodes among PWID

<table>
<thead>
<tr>
<th></th>
<th>Number of Episodes Experienced</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Episode (n = 236)</td>
<td>≥ Two Episodes (n = 74)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Age (years), median [IQR]</strong></td>
<td>34.0 [28.0–43.0]</td>
<td>34.0 [28.0–41.0]</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Female</td>
<td>113 (47.9)</td>
<td>38 (51.3)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>123 (52.1)</td>
<td>67 (48.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary valve infected, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid</td>
<td>151 (66.2)</td>
<td>60 (82.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulmonic</td>
<td>3 (1.32)</td>
<td>1 (1.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Mitral</td>
<td>53 (23.3)</td>
<td>10 (13.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Aortic</td>
<td>47 (20.6)</td>
<td>8 (11.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Right ventricle/atrium</td>
<td>6 (2.6)</td>
<td>2 (2.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Site of infection, n (%)</strong></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Right-sided</td>
<td>140 (61.4)</td>
<td>55 (75.3)</td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>72 (31.6)</td>
<td>12 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>16 (7.0)</td>
<td>6 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay, median [IQR]</strong></td>
<td>25.6 [12.8–45.0]</td>
<td>33.0 [16.0–57.0]</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>PICC misuse, n (%)</strong></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>187 (81.0)</td>
<td>41 (56.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (19.0)</td>
<td>32 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical intervention, n (%)</strong></td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>No</td>
<td>195 (82.6)</td>
<td>61 (82.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (17.4)</td>
<td>13 (17.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Admission to the ICU, n (%)</strong></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>No</td>
<td>151 (64.0)</td>
<td>52 (70.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85 (36.0)</td>
<td>22 (29.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Substance misuse, n (%)</strong></td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Opiate or stimulant only</td>
<td>73 (35.3)</td>
<td>25 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Polysubstance</td>
<td>134 (64.7)</td>
<td>47 (65.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>29</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Referral to addiction services, n (%)</strong></td>
<td>161 (68.5)</td>
<td>40 (54.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74 (31.5)</td>
<td>34 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Left AMA, n (%)</strong></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>No</td>
<td>188 (79.7)</td>
<td>55 (74.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48 (20.3)</td>
<td>19 (25.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.
4.2 Analysis of missing data

Missing data was assessed for the variables used in subsequent multivariate analyses (Table 4.2). Approximately 84.8% (263/310) of the observations were complete for all variables. Of the missing data, 14.2% (44/310) of observations were missing data for one variable and 0.96% (3/310) of observations were missing data for two variables.

Table 4.2 Missingness of variables used in analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>N Missing</th>
<th>% Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>310</td>
<td>47</td>
<td>15.2%</td>
</tr>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at admission</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Sex</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Exposure variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis Location</td>
<td>301</td>
<td>9</td>
<td>2.9%</td>
</tr>
<tr>
<td>PICC misuse</td>
<td>304</td>
<td>6</td>
<td>1.9%</td>
</tr>
<tr>
<td>Addiction services referral</td>
<td>309</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Left AMA</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Confirmed in-hospital drug use</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Substance misuse</td>
<td>279</td>
<td>31</td>
<td>10.0%</td>
</tr>
<tr>
<td>Outcome variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent endocarditis</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Survival status</td>
<td>310</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Time-to-event</td>
<td>307</td>
<td>3</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Abbreviations: PICC, peripherally inserted central catheter; AMA, against medical advice; ICU, intensive care unit.

Formal assessment of MCAR was conducted using summary statistics and Little’s test for MCAR.144,145 Due to the small proportion of missing data per variable in Table 4.2, it was not feasible to evaluate the relationship between the missingness and covariates using logistic regression. Table 4.3 illustrates the summary statistics for each missing data indicator and covariates.

The distribution of PICC line misuse was seen to vary across missing and observed values for location of endocarditis infection. Among patients missing information regarding the location of infection, approximately 11.1% misused their PICC line. Conversely, 25.4% of patients with information regarding the location of infection misused their PICC line. Similar divergences are seen for male sex (observed: 50.5%
versus missing: 77.8%), median length of hospital stay (observed: 29.0 days versus missing: 11.0 days), admission to the ICU (observed: 34.2% versus missing: 44.4%), surgical intervention (observed: 17.9% versus missing: 0.0%), disease recurrence (observed: 24.3% versus missing: 11.1%), percent of patients censored (observed: 52.8% versus missing: 66.7%) and median time-to-event (observed: 17.0 months versus missing: 44.0 months). In contrast, the distributions of addiction referral, substance type, age, and leaving against medical advice were similar across missing and observed values. These results suggest that the distribution of PICC line misuse, sex, length of hospital stay, admission to the ICU, surgical intervention, disease recurrence, survival status, and time-to-event varies across missing and observed values for location of infection and provide evidence against MCAR.

Similar distributions for median age, median length of hospital stay, and median time-to-event were observed for missing and observed values of PICC line misuse. The distributions of location of infection (observed: 65.1% versus missing: 50.0%), addiction referral (observed: 34.3% versus missing: 66.7%), substance type (observed: 64.2% versus missing: 100.0%), male sex (observed: 51.0% versus missing: 66.7%), admission to the ICU (observed: 34.9% versus missing: 16.7%), surgical intervention (observed: 17.1% versus missing: 33.3%), leaving against medical advice (observed: 21.4% versus missing: 33.3%), disease recurrence (observed: 24.0% versus missing: 16.7%) and percent of patients censored (observed: 52.6% versus missing: 83.3%) varied across missing and observed values of PICC line misuse.

The distributions of location of infection (observed: 68.6% versus missing: 30.0%), PICC line misuse (observed: 27.7% versus missing: 0.0%), addiction referral (observed: 38.1% versus missing: 6.5%), male sex (observed: 48.8% versus missing: 74.2%), median length of hospital stay (observed: 31.0 days versus missing: 15.0 days), admission to the ICU (observed: 31.2% versus missing: 64.5%), surgical intervention (observed: 15.4% versus missing: 35.5%), leaving against medical advice (observed: 23.3% versus missing: 6.5%) and disease recurrence (observed: 25.8% versus missing: 6.5%) varied across missing and observed values of substance type. In contrast, median age, survival status and
median time-to-event had similar distributions for missing and observed values of substance type.

The distributions of addiction referral, median age, and admission to the ICU were similar across missing and observed values for time-to-event. In contrast, the distributions of location of infection (observed: 65.1% versus missing: 33.3%), PICC line misuse (observed: 24.5% versus missing: 100.0%), substance type (observed: 64.5% versus missing: 100.0%), male sex (observed: 51.1% versus missing: 66.7%), median length of hospital stay (observed: 29.0 days versus missing: 39.0 days), surgical intervention (observed: 17.3% versus missing: 33.3%), leaving against medical advice (observed: 21.2% versus missing: 66.7%), disease recurrence (observed: 24.1% versus missing: 0.0%) and percent of patients censored (observed: 52.7% versus missing: 100.0%) varied across missing and observed values of time-to-event.

Since there was only a single missing value for addiction referral, it was not reasonable to determine if the MCAR assumption was violated.

To further assess whether the missing data is MCAR, Little’s test of MCAR was conducted. The results of Little’s test gave a $P$-value < 0.001. This provides evidence that the variables, location of infection, PICC line misuse, referral to addiction services, substance type misused and TTE are not MCAR under a 0.05 significance level.\footnote{145}

From the results, it can be determined that the missing indicators for location of infection, PICC line misuse, substance type and time-to-event do not comply with the MCAR assumption that there are no differences between observations with complete data and those with missing data. Therefore, FCS imputation analysis will be conducted jointly with the multivariate logistic regression and survival analyses.
Table 4.3 Summary statistics of levels of missing indicators for variables location, PICC line misuse, addiction referral, substance type and time-to-event

<table>
<thead>
<tr>
<th>Missingness Indicator</th>
<th>Location (% RSIE)</th>
<th>% PICC misuse</th>
<th>% Addiction referral</th>
<th>% Polysubstance</th>
<th>Age (median)</th>
<th>% Male</th>
<th>% ICU</th>
<th>% Surgery</th>
<th>% Left AMA</th>
<th>% Recurrent episode</th>
<th>% Censored</th>
<th>TTE (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Observed</td>
<td>25.4%</td>
<td>35.0%</td>
<td>64.9%</td>
<td>34.0</td>
<td>50.5%</td>
<td>29.0</td>
<td>34.2%</td>
<td>17.9%</td>
<td>21.6%</td>
<td>24.3%</td>
<td>52.8%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>11.1%*</td>
<td>33.3%</td>
<td>62.5%</td>
<td>35.0</td>
<td>77.8%*</td>
<td>11.0*</td>
<td>44.4%*</td>
<td>0.0%*</td>
<td>22.2%</td>
<td>11.1%*</td>
<td>66.7%*</td>
</tr>
<tr>
<td><strong>PICC misuse</strong></td>
<td>Observed</td>
<td>65.1%</td>
<td>34.3%</td>
<td>64.2%</td>
<td>34.0</td>
<td>51.0%</td>
<td>29.0</td>
<td>34.9%</td>
<td>17.1%</td>
<td>21.4%</td>
<td>24.0%</td>
<td>52.6%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>50.0%*</td>
<td>-</td>
<td>66.7%*</td>
<td>100.0%*</td>
<td>34.5</td>
<td>24.5</td>
<td>16.7%*</td>
<td>33.3%*</td>
<td>33.3%*</td>
<td>16.7%*</td>
<td>83.3%*</td>
</tr>
<tr>
<td><strong>Addiction referral†</strong></td>
<td>Observed</td>
<td>64.7%</td>
<td>25.1%</td>
<td>-</td>
<td>64.8%</td>
<td>51.1%</td>
<td>29.0</td>
<td>34.6%</td>
<td>17.5%</td>
<td>21.7%</td>
<td>24.0%</td>
<td>53.1%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>100.0%*</td>
<td>0.0%*</td>
<td>-</td>
<td>100.0%*</td>
<td>50.0</td>
<td>15.3</td>
<td>0.0%*</td>
<td>0.0%*</td>
<td>0.0%*</td>
<td>100.0%</td>
<td>129.0*</td>
</tr>
<tr>
<td><strong>Substance type</strong></td>
<td>Observed</td>
<td>68.6%</td>
<td>27.7%</td>
<td>38.1%</td>
<td>34.0</td>
<td>48.8%</td>
<td>31.0</td>
<td>31.2%</td>
<td>15.4%</td>
<td>23.3%</td>
<td>25.8%</td>
<td>53.8%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>30.0%*</td>
<td>0.0%*</td>
<td>6.5%*</td>
<td>-</td>
<td>32.0</td>
<td>74.2%*</td>
<td>15.0%</td>
<td>64.5%*</td>
<td>35.5%*</td>
<td>6.5%*</td>
<td>48.4%</td>
</tr>
<tr>
<td><strong>TTE</strong></td>
<td>Observed</td>
<td>65.1%</td>
<td>24.5%</td>
<td>35.0%</td>
<td>64.5%</td>
<td>51.1%</td>
<td>29.0</td>
<td>34.5%</td>
<td>17.3%</td>
<td>21.2%</td>
<td>24.1%</td>
<td>52.7%</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>33.3%*</td>
<td>100.0%</td>
<td>33.3%</td>
<td>100.0%</td>
<td>37.0</td>
<td>66.7%*</td>
<td>39.0%</td>
<td>33.3%*</td>
<td>33.3%*</td>
<td>66.7%*</td>
<td>0.0%*</td>
</tr>
</tbody>
</table>

Abbreviations: RSIE, right-sided endocarditis infection; PICC, peripherally inserted central catheter; ICU, admission to the ICU; AMA, against medical advice; TTE, time-to-event.

* indicates varying distributions for values of missing indicators.

† there is only one missing value for addiction referral, therefore, MCAR cannot be determined.
4.3 Logistic regression analyses

4.3.1 Bivariate logistic regression analyses

Bivariate analyses of the empirical association between the predictors of interest and recurrent endocarditis among PWID is shown in Table 4.4. Study results demonstrate that for each day increase in the length of hospital stay, a patient’s odds of developing recurrent endocarditis significantly increased by 1% (OR = 1.01, 95% CI 1.00 to 1.02, \( P = 0.002 \)). Similarly, for patients that misused their PICC line, the odds of developing recurrent endocarditis were found to be 3.32 (95% CI 1.88 to 5.85, \( P < 0.001 \)) times higher compared to patients who did not misuse their PICC line. Moreover, the odds of developing recurrent endocarditis were found to significantly increase almost 2-fold (OR = 1.85 95% CI 1.09 to 3.15, \( P = 0.02 \)) for patients who were referred to addiction services compared to those who were not referred to addiction services. Left-sided infection was the only variable found to significantly decrease the odds of developing recurrent endocarditis (\( P = 0.01 \)). The odds of developing recurrent endocarditis were found to significantly decrease in patients with left-sided infection (OR = 0.42, 95% CI 0.21 to 0.84) compared to patients with right-sided infection. Age, sex, bilateral infection, surgical intervention, admission to the ICU, polysubstance misuse and leaving against medical advice were not found to be statistically associated with the odds of developing a recurrent episode of endocarditis among the study population.

4.3.2 Multivariate logistic regression analyses

Results of the CCA and FCS imputation of the multivariate logistic analysis of the association between the predictors of interest and recurrent endocarditis among PWID is shown in Table 4.4. Similar results were obtained for both CCA and FCS analyses. Multivariate analysis demonstrated PICC line misuse to be statistically associated with the odds of developing recurrent endocarditis (CCA: \( P = 0.005 \), FCS: \( P = 0.006 \)). PICC line misuse was found to be associated with a 2.54 to 2.62 increase in adjusted odds of developing recurrent endocarditis (CCA: OR = 2.62, 95% CI 1.34 to 5.14; FCS: OR = 2.54, 95% CI 1.30 to 4.94) compared to patients who did not misuse their PICC line.
Table 4.4 Bivariate and multivariate logistic regression for recurrent infective endocarditis in PWID

<table>
<thead>
<tr>
<th></th>
<th>Bivariate Analysis</th>
<th>CCA Multivariate Analysis</th>
<th>FCS Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.96</td>
<td>1.01</td>
</tr>
<tr>
<td>Sex (ref=female)</td>
<td>0.87</td>
<td>0.52</td>
<td>1.47</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.00</td>
<td>1.02</td>
</tr>
<tr>
<td>Location of infection (ref = right-sided IE)</td>
<td><strong>0.01</strong></td>
<td>0.21</td>
<td>0.84</td>
</tr>
<tr>
<td>Left-sided</td>
<td>0.96</td>
<td>0.34</td>
<td>2.57</td>
</tr>
<tr>
<td>PICC line misuse (ref = no misuse)</td>
<td>3.32</td>
<td>1.88</td>
<td>5.85</td>
</tr>
<tr>
<td>Referral to addiction services (ref = not referred)</td>
<td>1.85</td>
<td>1.09</td>
<td>3.15</td>
</tr>
<tr>
<td>Surgical intervention (ref = no surgery)</td>
<td>1.01</td>
<td>0.51</td>
<td>2.02</td>
</tr>
<tr>
<td>Admission to the ICU (ref = not admitted)</td>
<td>0.75</td>
<td>0.43</td>
<td>1.32</td>
</tr>
<tr>
<td>Misuse of Opiates and Stimulants (ref = opiate or stimulant use only)</td>
<td>1.02</td>
<td>0.58</td>
<td>1.80</td>
</tr>
<tr>
<td>Left AMA (ref = did not leave AMA)</td>
<td>1.35</td>
<td>0.74</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance (\(P < 0.05\)).

Abbreviations: CCA, complete case analysis; FCS, fully conditional specification; OR, odds ratio; CI, confidence interval; PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.

*Adjusted ORs were generated from multivariable logistic regression models. The CCA and FCS models were adjusted for age, sex, length of hospital stay, location of infection, PICC line misuse, referral to addiction services, surgical intervention, ICU admission, substance misused and leaving AMA.*
4.4 Multicollinearity

Multicollinearity was assessed among variables to ensure redundancy of information was excluded. Diagnostic results of multicollinearity are displayed in Table 4.5. The variance inflation factor (VIF) determines the amount of multicollinearity among variables, whereas tolerance (1/VIF) refers to the degree of multicollinearity among variables. As a general rule, VIFs over 10 and tolerances lower than 0.1 imply the need for further investigation. Table 4.5 demonstrates adequate VIF and tolerance values, indicating the lack of multicollinearity among the chosen predictors.

Table 4.5 Multicollinearity diagnostics

<table>
<thead>
<tr>
<th></th>
<th>VIF</th>
<th>√VIF</th>
<th>Tolerance</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.26</td>
<td>1.12</td>
<td>0.80</td>
<td>0.20</td>
</tr>
<tr>
<td>Sex</td>
<td>1.16</td>
<td>1.08</td>
<td>0.86</td>
<td>0.14</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.20</td>
<td>1.10</td>
<td>0.83</td>
<td>0.17</td>
</tr>
<tr>
<td>Location of infection</td>
<td>1.17</td>
<td>1.08</td>
<td>0.85</td>
<td>0.15</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.21</td>
<td>1.10</td>
<td>0.83</td>
<td>0.17</td>
</tr>
<tr>
<td>PICC misuse</td>
<td>1.30</td>
<td>1.14</td>
<td>0.77</td>
<td>0.23</td>
</tr>
<tr>
<td>Substance misuse</td>
<td>1.14</td>
<td>1.07</td>
<td>0.88</td>
<td>0.12</td>
</tr>
<tr>
<td>Addiction services</td>
<td>1.12</td>
<td>1.06</td>
<td>0.90</td>
<td>0.10</td>
</tr>
<tr>
<td>Left AMA</td>
<td>1.19</td>
<td>1.09</td>
<td>0.84</td>
<td>0.16</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>1.17</td>
<td>1.08</td>
<td>0.86</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Mean VIF 1.19

Abbreviations: VIF, variance inflation factor; R², coefficient of determination; PICC, peripherally inserted central catheter; AMA, against medical advice; ICU, intensive care unit.

4.5 Cumulative incidence function for endocarditis recurrence in the presence of death

The Fine–Gray model for competing risks was used to estimate the CIF for recurrent endocarditis and death. Of the 310 patients, 53.2% (165/310) were censored, 23.9% (74/310) experienced a recurrent episode of endocarditis and 22.9% (71/310) died without experiencing a recurrent episode of endocarditis. Figure 4.2 illustrates the CIF estimate for recurrent endocarditis episodes in the presence of death as a competing risk for PWID. At 93 months, the CIF of endocarditis recurrence among PWID was estimated to be 0.38 (95% CI 0.29 to 0.47).
Figure 4.2 Estimate of the cumulative incidence function for recurrent endocarditis with consideration for death as a competing risk

4.5.1 Comparing the Fine–Gray and Kaplan–Meier methods

As previously mentioned in Chapter 3: Methods, the Kaplan–Meier failure function fails to account for competing risks and produces results that overestimate the incidence of the event of interest. When accounting for the competing risk of death, the cumulative incidence of endocarditis recurrence among PWID was estimated to be 0.38 (95% CI 0.29 to 0.47) at 93 months. However, when using the Kaplan–Meier failure function, which censors competing risks, the failure probability at 93 months was estimated to be 0.41 (95% CI 0.31 to 0.52) (Figure 4.3). Consequently, censoring death rather than taking it into account resulted in an absolute difference of 3.0%.
Figure 4.3 Kaplan–Meier failure estimator for recurrent endocarditis

4.6 Fine–Gray subdistribution hazard regression analyses

4.6.1 Bivariate Fine–Gray subdistribution hazard regression analysis for recurrent endocarditis

Bivariate Fine–Gray subdistribution hazard regression analyses were used to describe the association between recurrent endocarditis and predictors of interest. Results of the regression analysis are displayed in Table 4.6. Length of hospital stay was found to be significantly associated with the subdistribution hazard ratio (SHR) of endocarditis recurrence (SHR = 1.01, 95% CI 1.00 to 1.01, \( P < 0.001 \)) at the bivariate level. Additionally, PICC line misuse was also found to be significantly associated with the SHR of endocarditis recurrence (SHR = 2.61, 95% CI 1.62 to 4.18, \( P < 0.001 \)) at the bivariate level.
4.6.2 Multivariate Fine–Gray subdistribution hazard regression analyses for recurrent endocarditis

Results of the multivariate regression analyses are displayed in Table 4.6. PICC line misuse was found to be significantly associated with the adjusted SHR (CCA: $P = 0.001$, FCS: $P = 0.002$). That is, PICC line misuse was associated with an increase of 2.5 to 2.6 (CCA: SHR = 2.60, 95% CI 1.47 to 4.58; FCS: SHR = 2.50, 95% CI 1.41 to 4.43) in the rate of recurrent endocarditis in patients who are either event-free or have experienced a competing event. Moreover, PICC line misuse was associated with an increase in incidence of recurrent endocarditis.
### Table 4.6 Bivariate and multivariate Fine–Gray subdistribution hazard regression for recurrent infective endocarditis in PWID with consideration for death as a competing risk

<table>
<thead>
<tr>
<th></th>
<th>Bivariate Analysis</th>
<th>CCA Multivariate Analysis</th>
<th>FCS Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.97</td>
<td>1.02</td>
</tr>
<tr>
<td>Sex (ref = female)</td>
<td>1.02</td>
<td>0.65</td>
<td>1.60</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.01</td>
<td>1.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Location of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ref = right-sided IE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>0.65</td>
<td>0.35</td>
<td>1.20</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1.39</td>
<td>0.58</td>
<td>3.33</td>
</tr>
<tr>
<td>PICC line misuse (ref = no misuse)</td>
<td>2.61</td>
<td>1.62</td>
<td>4.18</td>
</tr>
<tr>
<td>Referral to addiction services (ref = not referred)</td>
<td>1.55</td>
<td>0.99</td>
<td>2.45</td>
</tr>
<tr>
<td>Surgical intervention (ref = no surgery)</td>
<td>0.86</td>
<td>0.47</td>
<td>1.58</td>
</tr>
<tr>
<td>Admission to the ICU (ref = not admitted)</td>
<td>1.26</td>
<td>0.78</td>
<td>2.04</td>
</tr>
<tr>
<td>Misuse of Opiates and Stimulants (ref = opiate or stimulant use only)</td>
<td>0.89</td>
<td>0.55</td>
<td>1.44</td>
</tr>
<tr>
<td>Left AMA (ref = did not leave AMA)</td>
<td>1.15</td>
<td>0.67</td>
<td>1.97</td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance (P < 0.05).

Abbreviations: CCA, complete case analysis; FCS, fully conditional specification; SHR, subdistribution hazard ratio; CI, confidence interval; PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.

<sup>a</sup>Adjusted SHRs were generated from multivariable Fine–Gray regression models. The CCA and FCS models were adjusted for age, sex, length of hospital stay, location of infection, PICC line misuse, referral to addiction services, surgical intervention, ICU admission, substance misused and leaving AMA.
To further investigate the association between PICC line misuse and endocarditis recurrence, the cumulative incidence function stratified by PICC line misuse status was plotted (Figure 4.4). The plot demonstrates a substantial difference in cumulative incidence of recurrent endocarditis among patients who misused their PICC line and those who did not. From the plot, it can be seen that the incidence of disease recurrence was substantially higher in patients who misused their PICC line (0.63 versus 0.32).

![Cumulative incidence plot](image)

**Figure 4.4** Cumulative incidence plot of recurrence stratified by PICC line misuse status among PWID, with consideration for death as a competing risk

### 4.7 Kaplan–Meier failure function for mortality

Since recurrent endocarditis is not a terminal event and does not impede the observation of death as an outcome of interest, traditional Kaplan–Meier methods were used for estimating the probability of mortality among PWID with endocarditis. Of the 310 patients in the study, 99.4% (308/310) had complete data for mortality or long-term patient follow-up. Of the 308 patients, 66.2% (204/308) were censored and 33.8% (104/308) died. Figure 4.5 illustrates the Kaplan–Meier failure function estimate for
death among PWID. The results shown in Figure 4.5 demonstrate an estimated cumulative incidence for death among PWID of 0.26 (95% CI 0.16 to 0.39) at 139 months.

![Image of Kaplan-Meier curve](image_url)

**Figure 4.5 Estimated Kaplan–Meier curve of the cumulative failure function for death**

### 4.8 Time-dependent Cox proportional-hazards analysis for death

#### 4.8.1 Bivariate time-dependent Cox proportional-hazards analysis for death

The overall mortality rate among the study population was observed to be 33.7% (104/308). Of the patients who died, 41.3% (43/104) experienced a recurrent episode of endocarditis. Results of the bivariate analyses assessing the relationships between mortality and predictors of interest are demonstrated in Table 4.7. At the bivariate level, age at time of admission was found to be significantly associated with mortality among PWID with endocarditis (HR = 1.04, 95% CI 1.00 to 1.07, \(P = 0.03\)). That is, the hazard
of mortality is 4% greater per year increase in a patient’s age at the time they are admitted to the acute care hospital. In addition, misuse of polysubstances was found to be significantly associated with the hazard of mortality (HR = 0.51, 95% CI 0.25 to 1.01, P = 0.05). Furthermore, the hazard of mortality was found to be significantly higher among PWID who were admitted to the ICU compared to PWID who were not admitted (HR = 2.04, 95% CI 1.03 to 4.06, P = 0.04). Moreover, surgical intervention was found to significantly increase the hazard of mortality among PWID (HR = 2.85, 95% CI 1.28 to 6.31, P = 0.01).

4.8.2 Multivariate time-dependent Cox proportional-hazards analyses for death

An adjusted time-dependent Cox proportional-hazards model was used to evaluate the association between death and covariates of interest. Results of the multivariate time-dependent Cox proportional-hazards regression analyses are displayed in Table 4.7. To avoid immortal time bias, surgical intervention and recurrent endocarditis were treated as time-dependent covariates. Furthermore, results of the Schoenfeld test of proportional-hazards assumption found that all other covariates used in the model satisfy the proportional-hazards assumption (Appendix E).

The results in Table 4.7 demonstrate strong evidence for the association between death and PICC line misuse (CCA: P = 0.01, FCS: P = 0.007). This result suggests that the risk of mortality among patients who misused their PICC line was 3.00 to 3.21 (CCA: HR = 3.00, 95% CI 1.29 to 7.00; FCS: HR = 3.21, 95% CI 1.37 to 7.53) times higher than patients who did not misuse their PICC lines. Additionally, the results demonstrate a 2.15 to 2.33 increase in the risk of mortality (CCA: HR = 2.33, 95% CI 1.05 to 5.19, P = 0.04, FCS: HR = 2.15, 95% CI 1.00 to 4.63, P = 0.05) among patients who were admitted to the ICU compared to those who were not. Moreover, the CCA model suggests that surgical intervention was not significantly associated with the risk of mortality among PWID (P = 0.19) while the FCS model demonstrates a significant association between surgical intervention and mortality (P = 0.05).
### Table 4.7 Bivariate and multivariate time-dependent Cox proportional-hazards regression for long-term mortality in PWID

<table>
<thead>
<tr>
<th></th>
<th>Bivariate Analysis</th>
<th>CCA Multivariate Analysis</th>
<th>FCS Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00</td>
<td>1.07</td>
</tr>
<tr>
<td>Sex (ref = female)</td>
<td>1.42</td>
<td>0.73</td>
<td>2.78</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.01</td>
<td>1.00</td>
<td>1.02</td>
</tr>
<tr>
<td>Right-sided infection (ref = Yes)</td>
<td>1.46</td>
<td>0.72</td>
<td>2.94</td>
</tr>
<tr>
<td>PICC line misuse (ref = no misuse)</td>
<td>1.87</td>
<td>0.95</td>
<td>3.67</td>
</tr>
<tr>
<td>Referral to addiction services (ref = not referred)</td>
<td>1.23</td>
<td>0.62</td>
<td>2.45</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2.85</td>
<td>1.28</td>
<td>6.31</td>
</tr>
<tr>
<td>Recurrent endocarditis</td>
<td>1.18</td>
<td>0.27</td>
<td>5.24</td>
</tr>
<tr>
<td>Admission to the ICU (ref = not admitted)</td>
<td>2.04</td>
<td>1.03</td>
<td>4.06</td>
</tr>
<tr>
<td>Misuse of Opiates and Stimulants (ref = opiate or stimulant use only)</td>
<td>0.51</td>
<td>0.25</td>
<td>1.01</td>
</tr>
<tr>
<td>Left AMA (ref = did not leave AMA)</td>
<td>0.52</td>
<td>0.20</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance ($P < 0.05$).

**Abbreviations:** CCA, complete case analysis; FCS, fully conditional specification; HR, hazard ratio; CI, confidence interval; PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.

*Adjusted HRs were generated from time-dependent multivariable Cox proportional hazards regression models. The CCA and FCS models were adjusted for age, sex, length of hospital stay, right-sided infection, PICC line misuse, referral to addiction services, surgical intervention, ICU admission, substance misused and leaving AMA.
The Kaplan–Meier failure function for death was stratified by PICC line misuse status to explore the relationship between mortality and PICC line misuse among PWID (Figure 4.6). The Kaplan–Meier survival plot illustrates a considerable decrease in the probability of survival among patients who misused their PICC line compared to those who did not; 0.61 versus 0.85, respectively, from 65 months onwards.

Figure 4.6 Kaplan–Meier plot of the cumulative survival stratified by PICC line misuse status among PWID

Similarly, the Kaplan–Meier failure function for death was stratified by ICU admission status to explore the relationship between mortality and ICU admission among PWID (Figure 4.7). The Kaplan–Meier survival plot illustrates a considerable decrease in the probability of survival among patients who were admitted to the ICU compared to those who did not; 0.63 versus 0.82, respectively, from 65 months onwards.
Figure 4.7 Kaplan–Meier plot of the cumulative survival stratified by ICU admission status among PWID
Chapter 5

5 Discussion

This chapter discusses the study findings, their implications and conclusions made. Section 5.1 discusses the key findings presented in the study and their implications. The strengths and limitations of the study are evaluated in Sections 5.2 and 5.3, respectively. Finally, study conclusions and future directions are discussed in Section 5.4.

5.1 Overview and interpretation of study findings

This is the first study, to our knowledge, that assesses the probability of recurrent endocarditis among PWID while accounting for competing risks. Additionally, to our knowledge, this is the first study that evaluates the effects of predictors on mortality specifically among PWID with endocarditis. The three main objectives of this study were to (1) characterize important factors that contribute to the recurrence of endocarditis among PWID in London, Ontario, (2) assess the probability of disease recurrence in the presence of competing risks among PWID in London, Ontario, and (3) evaluate the associations of survival time and predictor variables among PWID in London, Ontario. The following sections outline the key findings of the study and how they relate to current knowledge.

5.1.1 PICC line misuse

PICC line misuse was observed to be the primary factor significantly associated with the odds and hazard of developing recurrent endocarditis as well as the hazard of mortality among PWID. Significant differences in the distribution of PICC line misuse were observed across strata of PWID who only experienced a single episode of endocarditis and PWID who went on to experience ≥ two episodes of endocarditis. Among the PWID in this study, PICC line misuse was observed at a higher frequency among PWID who went on to experience ≥ two episodes of endocarditis. Study results demonstrated significant associations between PICC line misuse and the odds of developing recurrent endocarditis at the bivariate and multivariate levels. The results of the bivariate logistic analysis of PICC line misuse and recurrent endocarditis in this study differs from current
literature; a study conducted by Rodger et al.\textsuperscript{7} did not find a significant association between PICC line misuse and recurrent endocarditis at the bivariate level. However, when accounting for other variables in their multivariate analysis, Rodger et al.\textsuperscript{7} observed a significant increase in odds of developing recurrent endocarditis among patients who misused their PICC line, which aligns with the results found in the current study.

In their previous study, Rodger et al.\textsuperscript{7} did not account for the effects of survival time and competing risks on the development of recurrent endocarditis. A novel aspect of this study is (1) the use of the Fine–Gray model to assess the impact of survival time and death as a competing risk on the rate of endocarditis recurrence, and (2) using a time-dependent Cox proportional-hazards model to assess the impact of survival time on the rate of mortality. When assessing the rate of endocarditis recurrence, PICC line misuse was observed to be significantly associated with an increase in rate of endocarditis recurrence with consideration for death as a competing risk at both the bivariate and multivariate levels. Conversely, when assessing the relationship between PICC line misuse and the rate of mortality among PWID, PICC line misuse was not observed to be significantly associated with an increased rate of mortality. However, when adjusting for the other variables in the model, PICC line misuse was observed to significantly increase the rate of mortality among PWID.

5.1.2 Length of hospital stay

The distribution of length of hospital stay was observed to significantly differ between PWID who only experienced a single episode of endocarditis and PWID who went on to experience ≥ two episodes of endocarditis. This finding is not consistent with current literature. A single study by Huang et al.\textsuperscript{14} assessed the distribution of length of hospital stay between patients who experienced a single endocarditis episode and patients who went on to experience recurrent endocarditis episodes. From their study, Huang et al.\textsuperscript{14} found no significant difference between the distribution of length of hospital stay between the two strata. However, due to the smaller sample size in the study by Huang et al.\textsuperscript{14}, the model may not have had sufficient power to detect differences.
Current literature has not modelled the relationship between the length of patient hospital stay and recurrent endocarditis among PWID. Despite looking at the distribution of length of hospital stay, Huang et al.,\textsuperscript{14} did not model the relationship. Thus, a novel aspect of this study is the inclusion of length of hospital stay in the regression model. Bivariate analysis of the relationship between length of hospital stay and recurrent endocarditis illustrated a significant positive association, however, when accounting for other variables in the model, this association was no longer observed. This may be due to the fact that, in some instances, hospital stay may have been prolonged due to factors that may make the patient more likely to relapse, such as unstable behaviour, unstable housing, and mental health issues.

A similar association was observed when assessing the relationship between length of hospital stay and the rate of endocarditis recurrence. Furthermore, when assessing the relationship between the length of hospital stay and the hazard of mortality, no association was observed.

5.1.3 Echocardiography

The distribution of tricuspid valve vegetation differed significantly between PWID who only experienced a single episode of endocarditis and PWID who went on to experience \( \geq \) two episodes of endocarditis. This result aligns with that found by Huang et al.\textsuperscript{14}, who observed a significant difference in vegetation of the tricuspid valve among first and second episodes of endocarditis. In addition, this study found significant differences in the distribution of left-sided infection across strata of PWID who only experienced a single episode of endocarditis and PWID who went on to experience \( \geq \) two episodes of endocarditis. Results of this study demonstrated PWID with left-sided infection had a significant decrease in the odds of developing recurrent endocarditis compared to PWID with right-sided endocarditis infection in bivariate analyses. However, this association was no longer significant after accounting for the other variables in the model. The result of the bivariate analysis differs from that seen in the literature. Rodger et al.\textsuperscript{7} found no significant association between the odds of developing recurrent endocarditis and left-sided infection at the bivariate level.
Moreover, the results of the current study did not observe a significant difference in the distribution of bilateral infection across strata. Furthermore, the results failed to demonstrate an association between bilateral infection and the odds of developing recurrent endocarditis at both the bivariate and multivariate levels. These results align with that seen in the literature. Rodger et al.\textsuperscript{7} found no significant association between the odds of developing recurrent endocarditis and bilateral infection at the bivariate and multivariate levels.

When assessing the association between the location of infection (left-sided and bilateral infection) and the hazards of recurrent endocarditis and mortality, no association was observed.

5.1.4 Referral to addiction services

This study observed a significant positive association between referral to addiction services and recurrent endocarditis at the bivariate level. The findings of the current study could suggest that PWID who went on to experience ≥ two episodes of endocarditis could be on the higher end of the addiction spectrum than PWID who only experienced a single episode of endocarditis. Moreover, this finding implies that addiction treatment alone is not sufficient for decreasing the odds of experiencing recurrent endocarditis. Results of the bivariate analysis of the current study differs from that seen in the study by Rodger et al.,\textsuperscript{7} who observed an insignificant association between addiction services and recurrent endocarditis. This finding may be the result of low statistical power as a small proportion of patients were referred to addiction services during their first episode.\textsuperscript{7} When controlling for other variables in the model, the current study failed to observe a significant association between referral to addiction services and recurrent endocarditis, which is consistent with existing literature. When assessing the association between referral to addiction services and the hazards of recurrent endocarditis and long-term mortality, no association was observed. Data on patient follow-up with addiction service attendance within a community setting was unavailable. Therefore, it is plausible that the lack of follow-up may have negatively affected the long-term impact of addiction services on the development of recurrent endocarditis and mortality. In addition, in-
patient counselling was not randomly assigned, therefore, patients with more severe addiction may have been referred.

5.1.5 Surgical intervention

The distribution of surgical intervention did not significantly differ between PWID who only experienced a single episode of endocarditis and PWID who went on to experience \( \geq \) two episodes of endocarditis. In contrast, Huang et al.\textsuperscript{14} observed a significantly larger proportion of patients who went on to experience a recurrent episode had undergone surgical intervention. In comparison to the current study, a larger proportion of PWID who went on to experience a recurrent episode of endocarditis in the study by Huang et al.\textsuperscript{14} underwent surgical intervention (59.1\% versus 17.6\%), which may explain the discrepancy seen between the two studies. Results of the current study found no association between surgical intervention and the odds of developing recurrent endocarditis at the bivariate or multivariate levels. Furthermore, the study failed to observe an association between surgical intervention and the hazard of developing recurrent endocarditis. However, when assessing the association between surgical intervention and mortality, the current study observed PWID who underwent surgical intervention were found to have a significantly increased risk of mortality than those who did not undergo surgical intervention, under FCS model assumptions. This discrepancy implies that the missing data reduced statistical power and led to biased results by excluding valuable information that was provided by incomplete observations. When assessing the association between surgical intervention and the hazards of recurrent endocarditis and mortality, no association was observed. Although deemed statistically insignificant, the positive associations between PWID who underwent surgical intervention and the odds of developing recurrent endocarditis and hazard of mortality observed in the current study are clinically significant and align with current knowledge; surgical intervention is not recommended to PWID as they are more susceptible to disease recurrence and death.\textsuperscript{7} In contrast, the findings by Rodger et al.\textsuperscript{7} do not align with current knowledge as they observed a decrease in adjusted odds of recurrent endocarditis among PWID who underwent surgical intervention compared to those who did not undergo surgical intervention.
5.1.6  Admission to the ICU

A novel aspect of this study was the evaluation of ICU admittance on recurrent endocarditis and mortality. The distribution of ICU admittance was not significantly different between PWID who only experienced a single episode of endocarditis and PWID who went on to experience \( \geq \) two episodes of endocarditis. Similar distribution results were observed by Huang et al.\(^{14}\) Furthermore, this study did not observe significant associations between admission to the ICU and the odds of developing recurrent endocarditis on the bivariate and multivariate levels. Moreover, admission to the ICU was not observed to be significantly associated with the hazard of developing recurrent endocarditis. However, admission to the ICU was observed to be significantly associated with the hazard of mortality, which aligns with the hypothesis that admission to the ICU will result in worse patient prognosis.

5.1.7  Age at time of admission

Current literature states that PWID with endocarditis tend to be younger, with a mean and median age between 20 and 40.8 years.\(^{3,4,7,11,14,30,66–68,71}\) The results found in the current study align with the current literature with a median age falling in the aforementioned range. The distribution of age at time of admission was similar between PWID who only experienced a single episode of endocarditis and PWID who went on to experience \( \geq \) two episodes of endocarditis. Similar results for age distribution across strata was observed by Huang et al.\(^{14}\) Current literature has not assessed the associations between age at time of admission, recurrent endocarditis, and mortality among PWID with endocarditis. The current study failed to find associations between age at time of admission and the odds of developing recurrent endocarditis at the bivariate and multivariate levels. Furthermore, age at time of admission was also not observed to be significantly associated with the hazards of recurrent endocarditis and mortality.

5.1.8  Sex

Endocarditis is observed more frequently in literature among male patients than female patients among both non-PWID and PWID, resulting in a 2:1 ratio.\(^{6,9,16,65–67}\) The results of the current study found the distribution of endocarditis to be similar among male and
female PWID, rather than a 2:1 ratio. Furthermore, the distribution of sex was not significantly different between PWID who only experienced a single episode of endocarditis and PWID who went on to experience ≥ two episodes of endocarditis. Similar results for the distribution of sex was observed in the study by Huang et al.\textsuperscript{14} Current literature has not assessed the associations of sex on recurrent endocarditis and mortality among PWID with endocarditis. The findings of the current study failed to observe a significant association between sex and the odds of developing recurrent endocarditis on the bivariate and multivariate levels. Furthermore, sex was also found to not be associated with the hazards of developing recurrent endocarditis and mortality.

### 5.1.9 Substance misuse

The distribution of substance type misused was similar between PWID who only experienced a single episode of endocarditis and PWID who went on to experience ≥ two episodes of endocarditis. The current study failed to find associations between substance type misused and the odds of developing recurrent endocarditis at the bivariate and multivariate levels. Current literature has not assessed the associations between substance type misused and the hazard of developing recurrent endocarditis and mortality among PWID with endocarditis. The current study failed to observe a significant association between substance type misused and the hazards of recurrent endocarditis and mortality. Conversely, a study by Kimmel et al.\textsuperscript{147} observed reduced mortality in PWID patients with IDU-related endocarditis who received medication for opioid use disorder. However, this association was only observed within the month the medication was received,\textsuperscript{147} which was likely due to poor retention. Further studies need to be conducted to ascertain this relationship.

### 5.1.10 Leaving against medical advice

The distribution of PWID who left against medical advice did not significantly differ between PWID who only experienced a single episode of endocarditis and PWID who went on to experience ≥ two episodes of endocarditis. The current study failed to observe significant associations between leaving against medical advice and the odds of developing recurrent endocarditis at the bivariate and multivariate level. Similar results
were observed by Rodger et al.\textsuperscript{7} However, the findings of the two studies may be the result of low statistical power as a low proportion of patients left against medical advice among first episodes. Current literature has not assessed the associations between leaving against medical advice and the hazard of recurrent endocarditis and mortality among PWID with endocarditis. The current study found leaving against medical advice was not significantly associated with the hazard of developing recurrent endocarditis and mortality.

### 5.2 Study strengths

This study has many strengths, including:

- **Case definition.** This study used data on definite endocarditis cases that were reviewed by several Infectious Disease Specialists and determined using the prescribed Modified Duke Criteria.\textsuperscript{17,26}

- **Sample size.** This study has the largest study sample of unique PWID (n = 310) compared to the two other identified studies by Rodger et al.\textsuperscript{7} (n = 212) and Huang et al.\textsuperscript{14} (n = 22)

- **Missing data.** Another strength of this study is the methods used to remediate missing data. This study conducted analyses using both the CCA and FCS imputation methods to ensure missing data does not heavily affect the results.

- **Accounting for immortal time bias.** Since the time at risk for the Cox proportional-hazards regression analyses was from hospital discharge from first admission to death, surgery and hospital readmission for recurrent endocarditis cases varied with time. Therefore, this study accounted for immortal time bias in the Cox proportional-hazards regression analyses by incorporating surgery and recurrent endocarditis as time-dependent covariates.

- **Innovation.** This is the first study, to our knowledge, to assess the probability of endocarditis recurrence among the IDU population with consideration for death as a competing risk. The study used the Fine–Gray model to assess the probability of
endocarditis recurrence. In comparison to the traditional Kaplan–Meier model, the Fine–Gray method is a more sophisticated approach to evaluating patient survival by considering the possibilities of competing risks. By using the Fine–Gray model, this study found survival estimates that were not overestimated. In addition, this study is the first, to our knowledge, to evaluate the effects of covariates on mortality among PWID with endocarditis.

5.3 Study limitations

The study was subjected to several limitations, such as:

Consistency of data collection. One limitation is the use of hospital data and the need to rely on the consistency of data collection and documentation. Hospital datasets do not always collect data systematically. The collection of hospital data is often done by several individuals, which may result in discrepancies of data collection. For example, data on the type of substance misused was collected using either self-report, which can be subjected to recall bias, or via urine toxicology assays. Consequently, there may be some variability in the accuracy of responses as some data rely on self report and others rely on urine toxicology. In addition, patient misuse of PICC lines may have been underestimated as healthcare professionals may not always be aware of the misuse or may not always document it.

Study entry. The database used for this study did not have access to information regarding the date of antibiotic therapy completion. Therefore, patient time at risk was defined from discharge from first admission to the occurrence of an event in an attempt to ensure bias did not arise due to immortal time. However, a better point of study entry would be date of admission.

Negative echocardiography. Patients with endocarditis infection may not have abnormal echocardiography. In this study, several observations for location of infection were coded as missing data. However, it is expected that these missing data consist of patients with a negative (normal) echocardiogram.
Left truncation. Left truncation is a form of censoring in survival analysis whereby the period between time origin and entry into the cohort is not observed. In this study, left truncation occurred when patients who died prior to discharge from the first admission were excluded from the study as they were ineligible for reinfection, which may have produced selection bias and reduced the precision and accuracy of the study.

Limited demographic variables. Demographic variables used in this study consisted of age and sex. Information on patient ethnicity are not captured in medical charts in Canada, therefore, it was not feasible to include ethnicity as a covariate.

Magnitude of covariates on overall incidence. One limitation of the Fine–Gray subdistribution hazard regression model is that the magnitude of effect of the predictors of interest on the overall incidence of endocarditis recurrence can not be directly quantified from the model. Therefore, although one can assume that if PICC line misuse increases the SHR it also increases the cumulative incidence of endocarditis recurrence, it can not be concluded that the effect size of PICC line misuse on the SHR is the same as the effect size of PICC line misuse on the incidence of endocarditis recurrence.

Time-dependent covariates in Fine–Gray analyses. Another limitation to this study was the lack of consideration for potential time-dependent covariates in the Fine–Gray analyses. Statistical software such as SAS, Stata and R have the ability to include time-dependent covariates in the Fine–Gray subdistribution hazard model. However, inclusion of time-dependent covariates restricts the interpretation of the relationship between the model covariates and the CIF. Consequently, future studies that consider time-dependent covariates using the Fine–Gray subdistribution hazard model should be conducted with caution.

5.4 Implications for policy and practice

The results of this study demonstrate that PICC line misuse is significantly associated with endocarditis recurrence and mortality and may be an indicator of severe addiction. While PICC line misuse may be remediated by continuous monitoring of PWID, this
solution is neither feasible nor practical. Therefore, public health prevention efforts should aim to address the underlying issue of PICC line misuse—addiction and stigma.

IDU is highly stigmatized, which negatively impacts PWID and often results in poorer health outcomes compared to non-PWID. Stigma and discrimination towards IDU can occur in several ways: (1) internally, whereby PWID apply negative messages and connotations to themselves, (2) socially, whereby negative connotations regarding IDU is applied through media and the community, and (3) structurally, whereby negative stereotypes regarding IDU are applied by healthcare providers and public service workers. Internal stigma and discrimination may affect PWID’s health-seeking and injection behaviours. Socially, stigma regarding IDU consists of the negative stereotype whereby PWID are viewed as having control over their addiction and blamed for their actions. Social stigma negatively impacts a PWID’s ability to access adequate medical and social supports and use of safe injection practices. Structural stigma may include negative attitudes of healthcare providers, which results in poor communication and reduced therapeutic relationship between healthcare providers and PWID, which may significantly contribute to disease recurrence.

Public health strategies to improve the barriers produced by stigma and discrimination, such as education and training, need to be implemented. Internal stigma may be mitigated by better informing PWID about their right to access services. At the social level, education can address the problematic language used to describe addiction and IDU, and create a person-first narrative. Currently, limited education is given to healthcare providers regarding the prevention and treatment of infectious diseases among PWID. Furthermore, there are inadequate strategies to decrease stigma at the structural level. To remediate the issues seen at the structural level, education programs for healthcare providers should focus on the prevention of diseases among PWID and the intricacy of substance use disorders as a whole. Furthermore, appropriate guidelines for treatment of serious infectious diseases among PWID need to be developed. The use of PICC lines in PWID is an enduring issue; some healthcare providers adhere to the moral imperative to provide all patients with standard care despite being identified as PWID, whereas other healthcare providers view the use of PICC lines as medically negligent due to the risks
Consequently, treatment of PWID with infectious diseases should be person-centred. In contrast to patient-centred treatment, which is focused on a patient’s medical condition, person-centred care focuses on a patient’s issues with consideration for their multimorbidity.\textsuperscript{155,156}

5.5 Conclusions

This study identifies PICC line misuse as a leading risk factor for recurrent endocarditis and mortality among PWID. Furthermore, this study identified admission to the ICU and surgical intervention as additional risk factors for mortality among PWID with endocarditis. Treatment of endocarditis among PWID is more difficult than among non-PWID as the recommended treatment guidelines are not always appropriate for this marginalized population. By identifying PICC line misuse as a leading predictor for recurrent endocarditis among PWID, clinicians are able to target prevention strategies towards patients who are more likely to misuse their PICC line. Furthermore, due to the high recurrence and mortality rates associated with prosthetic valve endocarditis, these prevention efforts can also aid surgeons and patients in informed decision-making regarding valve replacement surgery. Further research should be conducted to explore suitable treatments for endocarditis among PWID.
References


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Appendices

Appendix A Permission to use published images from Mayo Clinic

June 23, 2020

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Sincerely,

Rosemary Perry, Copyright Agent
Mayo Foundation for Medical Education and Research
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Many thanks!

Permissions Helpdesk  
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## Appendix C Literature search strategy

<table>
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<th>Database</th>
<th>Endocarditis terms</th>
<th>Injection drug terms</th>
<th>Results</th>
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</thead>
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<td>(repeat endocarditis or repeat infective endocarditis or repeat infectious endocarditis or recurrent infective endocarditis or recurrent infective endocarditis or recurrent infectious endocarditis).ti,ab.</td>
<td>(injection drug user* or intravenous drug user* or IUD* or drug user* or persons who inject drugs or people who inject drugs or PWID or injector* or drug injector* or injecting drug user* or injecting drug abuse* or injection drug user* or injection drug abuse* or drug utilization or intravenous substance abuse* or intravenous substance user*).ti.</td>
<td>9</td>
</tr>
<tr>
<td>Embase</td>
<td>(repeat endocarditis or repeat infective endocarditis or repeat infectious endocarditis or recurrent endocarditis or recurrent infective endocarditis or recurrent infectious endocarditis).ti,ab.</td>
<td>(injection drug user* or intravenous drug user* or IUD* or drug user* or persons who inject drugs or people who inject drugs or PWID or injector* or drug injector* or injecting drug user* or injecting drug abuse* or injection drug user* or injection drug abuse* or drug utilization or intravenous substance abuse* or intravenous substance user*).ti.</td>
<td>15</td>
</tr>
<tr>
<td>Web of Science</td>
<td>TI=((repeat endocarditis) or (repeat infective endocarditis) or (repeat infectious endocarditis) or (recurrent endocarditis)) or AB=((repeat endocarditis) or (repeat infective endocarditis) or (repeat infectious endocarditis) or (recurrent endocarditis))</td>
<td>TI=((injection drug user*) or (intravenous drug user*) or IUD* or (drug user*) or (persons who inject drugs) or (people who inject drugs) or (PWID or injector*) or (drug injector*) or (injecting drug user*) or (injecting drug abuse*) or (injection drug user*) or (injection drug abuse*) or (drug utilization) or (intravenous substance abuse*) or (intravenous substance user*))</td>
<td>18</td>
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</table>
Appendix D Assessing violations of the proportional hazards assumption for the outcome recurrent endocarditis

The proportional hazards assumption assumes that the effect of each covariate on the hazard ratio does not vary with time.\textsuperscript{157} The following Cox model is assumed for assessing the association between the risk of recurrent endocarditis and exposure variables. The assumption of proportional hazards is discussed and tested subsequently.

\[
\log[h(t|x)] = \log[h_0(t)] + \beta_1 \text{age} + \beta_2 \text{sex} + \beta_3 \text{LOS} + \beta_4 \text{location} + \beta_5 \text{surgery} + \beta_6 \text{PICC} \\
+ \beta_7 \text{addiction} + \beta_9 \text{AMA} + \beta_8 \text{substance} + \beta_{10} \text{ICU}
\]

Of the 310 patients used in the study, under the assumption of the Cox proportional-hazards model, 76.1\% (236/310) were censored and 23.9\% (74/310) experienced a recurrent episode (second episode) of endocarditis. Supplementary Table 1 shows the results of the Schoenfeld tests of proportional hazards assumption.

### Supplementary Table 1 Schoenfeld tests of proportional hazards assumption

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<tr>
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<th>(\chi^2)</th>
<th>df</th>
<th>(P)-value</th>
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<td></td>
<td></td>
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<td>-</td>
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</tr>
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<td>Location of infection</td>
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</tr>
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<tr>
<td>Addiction services referral</td>
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<td>Reference</td>
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<td>0.02</td>
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<td>Reference</td>
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The results of the Schoenfeld Residuals test demonstrate strong evidence of a declining relationship between the log-hazard ratio and PICC line misuse (rho = –0.28, P = 0.016). To evaluate the extent of assumption violation, scaled Schoenfeld residuals for PICC line misuse against time were plotted (Supplementary Figure 1).

**Supplementary Figure 1 Smoothed estimate of log-hazard ratio for PICC line misuse**

From Supplementary Figure 1, it was determined that there are few estimates past 30 months (few patients went 30 months without having experienced recurrent endocarditis). Limited information is available after 30 months, making it difficult to assess model assumptions and could also result in large variance of the resulting estimates. Therefore, patients who experienced an event after 30 months were artificially censored to relax model assumption and improve estimation efficiency. Supplementary Table 2 illustrates...
the results of the Schoenfeld tests of proportional hazards assumption where time-to-event > 30 months was artificially censored.

**Supplementary Table 2 Schoenfeld tests of proportional hazards assumption where time-to-event > 30 months is artificially censored**

<table>
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<tr>
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</tbody>
</table>

Abbreviations: PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.

The results in Supplementary Table 2 show that PICC line misuse no longer violates the proportional hazards assumption. To further investigate, scaled Schoenfeld residuals for PICC line misuse against time with artificial censoring were plotted (Supplementary Figure 2).
Supplementary Figure 2 Smoothed estimate of log-hazard ratio for PICC line misuse with artificial censoring of time-to-event >30 months

The results in Supplementary Table 2 and Supplementary Figure 2 do not demonstrate strong evidence that PICC line misuse violates the assumption of proportional hazards. Therefore, we conducted the survival analyses for evaluating the risk of recurrent endocarditis based on the Cox model defined previously.
Appendix E Assessing violations of the proportional hazards assumption for the outcome death

Of the 308 patients with complete data for death status and long-term follow-up, under the assumption of the Cox proportional-hazards model, 66.2% (204/308) were censored and 33.8% (104/308) died. Supplementary Table 3 shows the results of the Schoenfeld tests of proportional hazards assumption. The results of the Schoenfeld Residuals test fail to demonstrate strong evidence of a significant violation of the proportional hazards assumption.

Supplementary Table 3 Schoenfeld tests of proportional hazards assumption

<table>
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Global Test 10.63 12.00 0.62

Abbreviations: PICC, peripherally inserted central catheter; ICU, intensive care unit; AMA, against medical advice.
# Curriculum Vitae

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<tr>
<th>Name</th>
<th>Janica Adams</th>
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</table>
| **Post-secondary Education and Degrees** | The University of Western Ontario  
London, Ontario, Canada  
2019–2021 M.Sc. Epidemiology and Biostatistics  
The G. Raymond Chang School of Continuing Education, Ryerson University  
Toronto, Ontario, Canada  
2018–2019 Certificate in Occupational Health and Safety  
Ryerson University  
Toronto, Ontario, Canada  
2013–2018 B.Sc. (Honours) Biomedical Science |
| **Honours and Awards** | Western Graduate Research Scholarship (WGRS)  
2019–2021 |
|                | Dean’s list  
2017–2018 |
| **Related Work Experience** | Health Analyst  
Informatics  
Public Health Ontario  
March 2021–Present |
|                | R Workshop Co-Instructor  
Department of Epidemiology and Biostatistics  
Western University  
2020–2021 |
|                | Research Assistant  
Department of Epidemiology and Biostatistics  
Western University  
2019–Present |
Differences in mental health service use among white and non-white immigrants to Canada. Poster presented at: Joint Mental Health Research and Innovation Day 2020 |