The Impact of Preoperative Alcohol Use Screening on Postoperative Delirium in Cardiac Surgery Patients: A Retrospective Observational Study

by

Mudra G. Dave

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

In partial fulfilment of the requirement of the degree of

MASTER OF SCIENCE

Faculty of Kinesiology and Recreation Management

University of Manitoba

Winnipeg, Manitoba, Canada

Abstract

Background: As cardiac surgery patients continue to age and present with more complex health conditions, the occurrence of a challenging postoperative complication known as "delirium" is becoming increasingly common. Postoperative delirium (PoD) is a complex neuropsychological disorder characterized by symptoms such as inattention, drowsiness, and agitation, which has many long-term negative health impacts. A patient-associated risk factor of PoD is presumed to be a preoperative alcohol use disorder (AUD).

Objective: The primary purpose was to determine whether preoperative alcohol use, measured using the Alcohol Use Disorders Identification Test - Concise (AUDIT-C), is predictive of incident PoD in cardiac surgical patients. The secondary objective was to determine the risk factors associated with PoD available in the Manitoba Access Cardiac Surgery (MACS) database.

Hypothesis: Primary: Higher AUDIT-C scores are associated with the incidence of PoD in adults who underwent cardiac surgery. Secondary: risk factors identified from the MACS database are correlated with PoD in adults who underwent cardiac surgery.

Methods: This was a single-centre, retrospective observational cohort study. AUDIT-C score and PoD (as diagnosed using the Confusion Assessment Method (CAM) – ICU in the intensive care unit or CAM on the postoperative ward) were collected for all elective patients undergoing cardiac surgery between March 2015 – September 2020.

Results: The overall incidence of delirium in this study was 14.2%. There was an association between preoperative alcohol use measured by AUDIT-C and PoD (0.559 OR, 0.515-0.607 95% CI, $p = < 0.001$) before controlling for covariates. After controlling for age, procedure category, MoCA score, CFS, LVEF category, renal insufficiency, previous CVA/TIA, recreational drug use and CPB time, there was no significant association between alcohol use and PoD (0.376 OR,

0.070-2.011 95% CI, p = 0.253). Previously known risk factors, including age, frailty, MoCA scores, renal insufficiency, previous CVA/TIA and CPB time, were found to be significant.

Conclusion: Preoperative alcohol use measured by AUDIT-C is not a reliable predictor of PoD in cardiac surgery patients. Future research should explore the role of comprehensive measures of alcohol use on PoD.

Acknowledgements

I would like to express my sincere gratitude to my co-advisors, Drs. Todd Duhamel and Rakesh Arora, thank you for your invaluable mentorship, constant encouragement, and guidance during my graduate school process. Your expertise and commitment to scientific inquiry continue to profoundly shape my academic growth. To my committee members, Drs. Shaelyn Strachan and Asher Mendelson, a heartfelt thank you for your support and thoughtful advice. I would like to extend my gratitude to the lab members whose collaborative spirit and shared passion for research have motivated me through my MSc. journey.

To my parents, thank you for being my pillar of strength and for believing in me. Your sacrifices and support continue to fuel my determination to overcome challenges. To my grandparents, thank you for your boundless love and encouragement in pursuing higher education. To my Grade 8 teacher, thank you for the kindness and compassion you showcased during the challenging times of my life and for inspiring me to always strive for greatness. To my friends, thank you for being there to listen to my endless rants and for understanding the highs and lows of this academic endeavour.

I am also thankful to the Faculty of Graduate Studies for providing me with the University of Manitoba's Graduate Student Fellowship, Faculty of Kinesiology and Recreation Management for the Black, Indigenous and Person of Colour stipend, Graduate Service Award and a student stipend. I would also like to thank Research Manitoba for providing me with a Master's Studentship Award and Mitacs for providing me with the Accelerate internship. Lastly, I would like to express my gratitude to all those who, directly or indirectly, contributed to my graduate school experience. Thank you!

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List of Abbreviations

PoD: Postoperative Delirium

AUD: Alcohol Use Disorder

AUDIT-C: Alcohol Use Disorders Identification Test – Concise

CAD: Coronary Artery Disease

ICU: Intensive Care Unit

LOS: Length of Stay

HRQoL: Health-Related Quality of Life

15D: 15 Dimensional

IL-6: Interleukin-6

CRP: C-reactive protein

TNF-α: Tumor Necrosis Factor-alpha

IGF-1: Insulin-like Growth Factor 1

S-100B: calcium-binding protein B

IL-8: Interleukin-8

SAA: Serum amyloid A

APOE: Apolipoprotein E

IL-1: Interleukin-1

IL-2: Interleukin-2

ACh: Acetylcholine

NMDA: N-methyl-D-aspartate

MRI: Magnetic Resonance Imaging

NYHA: New York Heart Association

DSM – Diagnostic & Statistical Manual

APA: American Psychology Association

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

CAM: Confusion Assessment Method

CAM-ICU: Confusion Assessment Method – Intensive Care Unit

bCAM: Brief Confusion Assessment Method

CAM-ED: Confusion Assessment Method – Emergency Department

mCAM-ED: modified Confusion Assessment Method – Emergency Department

UB-CAM: Ultra-Brief Confusion Assessment Method

NH-CAM: Nursing Home Confusion Assessment Method

FAM-CAM: Family Confusion Assessment Method

3D-CAM: 3-Minute Diagnostic Interview for Confusion Assessment Method

CAM-S: Confusion Assessment Method-Severity

I-CAM: Intelligent Confusion Assessment Method

4AT: 4A's Test

ERAS-CS: Enhanced Recovery After Surgery – Cardiac Surgery

AUDIT: Alcohol Use Disorders Identification Test

AUDIT-5: Alcohol Use Disorders Identification Test-5

MAST: Michigan Alcohol Screening Test

MAST-G: Michigan Alcohol Screening Test-Geriatric

MMAST-G: Mini Michigan Alcohol Screening Test-Geriatric

SMAST-G: Short Michigan Alcohol Screening Test-Geriatric

CAGE: Cut-down, Annoyed, Guilty, Eye-opener

CARET: The Comorbidity-Alcohol Risk Assessment Tool

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test

ARPS: Alcohol-Related Problem Survey

BAC: Blood Alcohol Concentration

CDT: Carbohydrate-Deficient Transferrin

EtG: Ethyl Glucuronide

PEth: Phosphatidyl ethanol

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

SAGER: Sex and Gender Equity in Research

MACS: Manitoba's Access Cardiac Surgery

APPROACH: Alberta's Provincial Project for Outcome Assessment in Coronary Heart Disease

AVR: Aortic Valve Repair/Replacement

MVR: Mitral Valve Repair/Replacement

TVR: Tricuspid Valve Repair/Replacement

PHQ-9: Patient's Health Questionnaire-9

SPSS: Statistical Package for the Social Sciences

REB: Research Ethics Board

SAS: Statistical Analysis Software

VIF: Variance Inflation Factor

RCT: Randomized Controlled Trial

CFS: Clinical Frailty Scale

MoCA: Montreal Objective Cognitive Assessment

CPB: Cardiopulmonary Bypass

CVA: Cerebrovascular Accident

TIA: Transient Ischemic Attack

CABG: Coronary Artery Bypass Grafting

LVEF: Left Ventricular Ejection Fraction

ICDSC: Intensive Care Delirium Screening Checklist

OR: Odds Ratio

CI: Confidence Interval

ROC: Receiver Operating Curve

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Chapter 1: Literature Review

This literature review highlights the relationship between heart disease and postoperative delirium (PoD), delving into its underlying pathophysiology and screening tools available for detection. It will then discuss the impact of aging on PoD and its effects on peri-operative outcomes. Lastly, this literature review will discuss the various methods for assessing alcohol use and investigate the connection between alcohol use and PoD.

1.1 Heart Disease and Postoperative Delirium

Heart disease, the second leading cause of death in Canada, has been defined by the Heart and Stroke Foundation of Canada as "any condition that affects the structure or function of the heart" [1, 2]. Approximately one in every 12 Canadian adults over the age of 20 years are living with heart disease, and 14 of these adults are dying every hour [2]. The most common type of heart disease reported in Canada is Coronary Artery Disease (CAD), which is defined as "the buildup of plaque in the heart's arteries that could lead to heart attack, heart failure, or death" [1]. Though risk factors for the development of CAD are variable depending on country and ethnicity, common risk factors include smoking, hypertension, dyslipidemia and diabetes mellitus [3]. The presence of multiple risk factors often leads to the progression of CAD requiring surgical intervention [3, 4].

Another common heart disease is heart valve disease [1]. Anatomically, the human heart has four valves: mitral, tricuspid, aortic, and pulmonary valves [5]. When either of these valves fails to keep the blood flowing, it can potentially cause life-threatening circumstances [5]. This failure can be categorized into three main heart valve diseases: valvular stenosis, valvular insufficiency and valvular atresia [5]. Valvular stenosis refers to when the leaflets become stiff

due to calcium buildup reducing the blood flow [5]. Valvular insufficiency or regurgitation occurs when the valves leak blood in the backward direction [5] and valvular atresia refers to the incorrect formation of the valves before birth [5]. Treatment of all types of heart valve diseases varies from minimally invasive to open heart surgery [5, 6].

Heart diseases such as CAD and heart valve disease present various risks that remain difficult to mitigate fully. One such risk is the development of PoD after a cardiac surgery procedure [7]. Postoperative delirium is a prevalent yet intricate neuropsychiatric condition affecting approximately one in five (~20%) patients undergoing cardiac surgery [7] .Recognizing and diagnosing PoD is difficult due to its fluctuating nature [8]. This means that a patient may not display symptoms of PoD at 10:00 am but may at 10:45 am [8]. The clinical manifestation of PoD encompasses a range of psychomotor symptoms, including hypoactive, hyperactive, or a blend of both – a mixed state [9]. Hyperactive PoD presents with symptoms such as agitation, disorganized thoughts, disruptions in the sleep-wake cycle or hallucinations [9]. On the other hand, hypoactive PoD presents symptoms such as drowsiness and diminished responsiveness [9]. Mixed-state PoD entails a combination of hypoactive and hyperactive symptoms [9].

Postoperative delirium is associated with several adverse outcomes. First, cardiac surgery patients with PoD have a hospital length of stay that is twice as long as compared to patients without PoD [10]. Second, PoD is associated with a decline in health-related quality of life (HRQoL) measured using the 15 Dimensional (15D) – a standardized, self-administered tool that measures HRQoL based on mobility, vision, hearing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity [11]. Third, PoD is independently associated with functional decline (a decrease in an ability to complete instrumental activities of daily living) at one month and a greater association

at 12 months [12]. Fourth, PoD is associated with a decline in cognition, specifically in visuoconstruction (a neuropsychological domain that accounts for the ability to organize and manually manipulate spatial information to make a design) and processing speed (the ability to process information rapidly) [13]. Fifth, PoD significantly impacts the healthcare system. Though we have yet to determine the exact economic impact of PoD on healthcare utilization for cardiac surgery patients, a past study noted that an episode of PoD costs upwards of $8286 in healthcare utilization in Canada for patients undergoing hip replacement surgery [14]. It is likely that there is an equal burden in the cardiac surgery patient as another study by Gou et al. [15] looked at medicare costs of PoD in older patients undergoing elective surgery (including aortic aneurysm repair, lower extremity bypass, hip and knee replacement, etc.) and found that patients who developed PoD had significantly higher healthcare costs (mostly coming from rehospitalizations) than patients who did not experience PoD ($146358 vs. $94609). In addition, PoD is a significant predictor of mortality up to 10 years after a cardiac surgical procedure for patients who experience PoD [16]. As such, all of these negative outcomes can serve as barriers to a successful recovery post-cardiac surgery. To fully understand the clinical impact of PoD, it is important to look at the potential mechanisms and the pathophysiology of PoD.

1.2 The Pathophysiology of Postoperative Delirium

The proposed etiology of postoperative delirium is multifactorial, meaning that no single mechanism can fully explain its onset. Over the past decade, emerging literature has pointed towards a complex pathophysiology underlying PoD. This includes the role of oxidative stress [17], the involvement of various biomarkers and neurotransmitters [18] , and the impact on different brain structures [19]. Together, these factors contribute to the intricate and varied nature

of PoD. Making it a challenging complication to predict and manage in the patient undergoing cardiac surgery.

1.2.1 Role of Oxidative Stress

Oxidative stress is commonly defined as an increase in the reactive oxygen species, dangerous compounds in our cells that can potentially initiate cell death [17, 20]. This increase in oxidative stress is also observed during surgical procedures, particularly those requiring anesthesia [17]. Notably, cardiac surgery can amplify the magnitude of inflammatory markers by up to 100 times compared to baseline levels [21, 22]. Consequently, the literature provides sufficient evidence that individuals undergoing surgery are at a higher risk of experiencing PoD due to elevated oxidative stress and inflammation [17, 20].

1.2.2 Biomarkers and Neurotransmitters

The term “biomarkers” is short for “biological markers,” defined as a measurable biological substance that indicates disease presence and severity [18]. Though current evidence does not point towards a singular biomarker responsible for PoD, much research in the last decade has focused on identifying these biomarkers to aid in the prevention, diagnosis and treatment of PoD. A recent systematic review by Dunne et al. [18] looked at 73 relevant papers published between January 2000 and June 2019, identifying 14 biomarkers. The 14 biomarkers are as follows: Interleukin-6 (IL-6), C-reactive protein (CRP), calcium-binding protein B (S-100B), Insulin-like Growth Factor 1 (IGF-1), amino acids, Tumor Necrosis Factor-alpha (TNF-α), Interleukin-8 (IL-8), Serum amyloid A (SAA), Apolipoprotein E (APOE), Interleukin-1 (IL-1), Interleukin-2 (IL-2), Melatonin and Estradiol [18]. Of the 14 biomarkers, the most commonly

studied biomarkers were identified to be IL-6, CRP, cortisol, S-100B, IGF-1 and TNF-α [18]. These six biomarkers all had a positive association with PoD, meaning that elevated levels of these biomarkers were associated with the occurrence of PoD [18]. The authors caution readers towards a lack of consensus between associations of these biomarkers with PoD as all studies included in this systematic review were observational studies and no rigorous study designs (e.g., randomized controlled trials) have been used in the current literature [18].

Similar to current research with biomarkers and PoD, identifying the role of the different neurotransmitters needs more rigorous inquiry. However, several studies point towards acetylcholine (ACh) – a neurotransmitter associated with arousal, attention, learning, memory, regulation of sleep-wake cycles, muscle contraction, digestion and other important processes in the human body [23]. Past studies have found an association between a low level of ACh found in plasma and cerebrospinal fluid, which is common in patients who experience PoD [24]. Another study points towards the role of dopamine in the occurrence of PoD [25]. Specifically, an elevation of dopamine levels has been observed to cause many PoD-associated symptoms [25]. In a study by Bokesch et al. [26], they found the role of glutamate (an excitatory neurotransmitter) caused activation of N-methyl-D-aspartate (NMDA) in cardiac surgery patients to be associated with neurological events like PoD and transient ischemic attacks. A review by Maldonado [23] revealed that neurotransmitter levels vary in the different subtypes of PoD. For instance, ACh will likely decrease in hypo, hyper, and mixed-type PoD [23]. In comparison, glutamate is seen in increased levels in all types of PoD [23]. Additionally, dopamine is seen to increase in hypoactive PoD with no data on hyper and mixed-type PoD [23]. Serotonin is a unique neurotransmitter as increased levels were observed in hypoactive PoD patients but decreased levels in hyperactive patients with

no data on the mixed-type PoD [23]. Understanding the role of neurotransmitters and biomarkers can potentially lead to the development of effective treatments for PoD.

1.2.3 Involvement of Different Brain Structures

Another prominent area of pathophysiological discovery in PoD has been the goal of understanding which anatomical brain structures are triggered. This work started in the late 1900s and has not progressed with definite answers. For example, researchers hypothesized that the brain stem, cerebral cortical and subcortical areas, the frontal right hemisphere and the thalamus are responsive structures in PoD [27]. However, this hypothesis has yet to be proven in human studies. As research in this area progressed, a new and emerging technique to study these structural changes started being described as neuroimaging [28]. This simple technique does not require brain surgery and is similar to magnetic resonance imaging (MRI) to take detailed brain images in humans [28]. In an integrative review of 11 publications, it was learnt that the commonly noted brain irregularities in PoD were white matter hyperintensity (defined as an increased observation of activity on MRI, brain atrophy (defined as loss or shrinkage of brain tissues), ischemic lesions (defined as an area of damage or injury in the brain) with most located in the frontal and parietal lobes, cerebral edema (defined as an accumulation of fluid in the brain tissue) and inflammation within the brain [19]. This knowledge of the role of different brain structures in PoD deepens our understanding of the complex neurobiology underlying delirium.

1.3 Independent Factors Associated with Postoperative Delirium in Cardiac Surgical Patients

Postoperative delirium is complex as there can be many independent risk factors putting a patient at high risk. Table 1 below summarizes two systematic reviews [29, 30] and two meta-analyses [31, 32] conducted in the last 13 years that identify the risk factors for postoperative delirium. As seen in Table 1, there are three common re-occurring pre-operative risk factors: age, pre-existing cognitive impairment and depression. There are several reasons why understanding the independent risk factors for PoD is crucial [31]. First, it allows clinicians to identify patients at risk of PoD preoperatively [32]. It can enable the healthcare team to address modifiable risk factors and optimize patient care, reducing the likelihood of the occurrence of PoD for the patient. Secondly, the knowledge of the independent risk factors for PoD can contribute to developing evidence-based guidelines and protocols for PoD prevention and management [33].

Table 1. Risk factors associated with postoperative delirium.

Study	Study Design	Number of Studies Included	Population of Study	Total sample of participants	Postoperative delirium Screening Tools	Independent Risk Factors
Koster et al. [29]	Systematic review	10	Cardiac surgery patients	18,828	DSM-IV, APA guidelines, DSM-III-R, CAM	Atrial fibrillation, cognitive impairment, depression, history of stroke, older age, peripheral vascular disease, red blood cell transfusion, abnormal albumin level, low cardiac output, use of intra-aortic balloon pump, inotropic medication.
Lin, Chen & Wang [31]	Meta-analysis	25	Cardiac surgery patients	5,121	DSM-IV, DSM-IV-TR, ICD-10, CAM, CAM-ICU, ICDSC	Age, depression, and history of stroke, cognitive impairment, diabetes mellitus, and atrial fibrillation, duration of surgery, prolonged intubation, surgery type, red blood cell transfusion, elevation of inflammatory markers and plasma cortisol level, and postoperative complications
Gosselt et al. [30]	Systematic Review	34	Cardiac surgery patients with cardiopulmonary bypass	Included studies had a sample size between 36 – 4,079.	CAM, CAM-ICU	Age, previous psychiatric conditions, cerebrovascular disease, pre-existent cognitive impairment, type of surgery, peri-operative blood product transfusion, administration of risperidone, postoperative atrial fibrillation and mechanical ventilation time.
Chen et al. [32]	Meta-analysis	14	Cardiac surgery patients	13,286	DSM-IV, DSM-V, CAM, CAM-ICU, ICDSC	Aging, diabetes, preoperative depression, mild cognitive impairment, carotid artery stenosis, NYHA functional class III or IV, time of mechanical ventilation, length of intensive care unit stay.

NYHA – New York Heart Association. DSM – Diagnostic & Statistical Manual . APA – American Psychology Association. CAM – Confusion Assessment Method. ICDSC - Intensive Care Postoperative delirium Screening Checklist .

1.4 Postoperative Delirium Screening Tools

The advancement in the body of literature elucidating the complex pathophysiology of PoD has led to the development of various PoD screening tools. However, the gold standard of PoD detection is the criteria set by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [34]. The DSM-IV's guidelines for delirium detection are as follows [34]:

- Disturbance of consciousness with reduced ability to focus, sustain or shift attention.
- A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
- The disturbance develops over a short period of time and tends to fluctuate during the course of the day.
- The history, physical examination, or laboratory findings show that the disturbance is caused by the direct physiological consequences of a general medical condition.

Though these gold standard criteria for delirium detection exist, it is primarily used by trained mental health professionals to form a diagnosis [34]. Further, PoD presentation can vary widely (e.g., hypoactive to hyperactive symptoms) amongst different patients, so healthcare professionals may encounter challenges in detecting PoD accurately solely based on the DSM-IV criteria. This limitation also decreases the likelihood of early detection in clinical centres with limited resources (i.e., the number of psychiatrists present). This also presented an opportunity for interdisciplinary collaboration amongst different healthcare professionals in the patient's care team to detect PoD early. Using a standardized PoD detection tool can ensure that all team members are on the same page when it comes to recognizing PoD. Further, DSM-IV criteria are broad and can be used in various clinical settings. Though this may be seen as a positive, a PoD detection tool can be

specialized for a certain patient population. Overall, PoD detection tools can help expedite PoD recognition and thereby identify effective management strategies in a timely manner.

One such rapid review compared the current PoD detection tools in acute care, identifying 75 PoD detection tools [35]. Amongst these 75 tools, there were 12 different versions of the original Confusion Assessment Method (CAM), including the Brief Confusion Assessment Method (bCAM), CAM long form, the CAM-Severity (CAM-S) long form, CAM-S short form, CAM – Emergency Department (CAM-ED), modified CAM for the emergency department (mCAM-ED), Ultra-brief-CAM (UB-CAM), Intelligent CAM (I-CAM), Nursing Home CAM (NH-CAM), CAM – Intensive Care Unit (CAM-ICU), Family-CAM (FAM-CAM), and the 3-Minute Diagnostic Interview for CAM-defined Postoperative delirium (3D-CAM) [35]. The other 62 tools have been identified in this rapid review by Brefka et al. [35]. Of these tools, the most valid tools for detecting PoD in the adult intensive care unit are the ICDSC and CAM-ICU [35].

The CAM-ICU assesses acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairments, perceptual disturbances, psychomotor agitation and retardation and altered sleep-wake cycle with a 68% sensitivity and 90% specificity in patients undergoing cardiac surgery [36]. A high sensitivity means that the tool is good at identifying positive cases and high specificity means that the tool is good at identifying negative cases. Clinically, a higher sensitivity is the goal as it allows us to predict the patients who will experience PoD. This is because a false positive can only lead to more precautions by the healthcare team to ensure no PoD occurs. The CAM-ICU incorporates the Richmond Agitation-Sedation Scale (RASS) as part of its PoD screening process. The prevalence rate of PoD in this patient population has been noted to be 31% in a recent study published by Krewulak et al. [9]. The ICDSC assess for altered level of consciousness, inattention,

hallucinations/delusions/psychosis, psychomotor agitation/retardation, inappropriate speech/mood, sleep-wake cycle disturbance and symptom fluctuation with a specificity of 91% and sensitivity of 94% amongst the cardiac surgery patients [37]. When comparing the CAM-ICU and ICDSC, the CAM-ICU was found to be more sensitive in a multidisciplinary ICU (i.e., ICU patients are not just cardiac surgery patients) [38].

An emerging tool for assessing PoD in cardiac surgery patients is the 4 A's T test (4AT). It assesses alertness, AMT4 (which asks for patient age, date of birth, place, and current year), attention, and acute change with a measured 85% sensitivity and 90% specificity in cardiac surgery patients [39]. The prevalence rate of PoD using the 4AT postoperatively is observed to be 24% [40].

1.4.1 Impact of Aging On Postoperative Delirium

Individuals over the age of 65 years are at a higher risk of experiencing PoD, especially the ones who require medical attention [41]. As part of the aging process, older adults experience loss of muscle mass, reduced energy and an overall decrease in the physiological reserve, which is known as frailty [42]. Adverse outcomes such as a prolonged intensive care unit stay, increased risk of mortality and morbidity have been mainly correlated to frailty and older age, especially in the cardiac surgery patient population [43]. Further, patients who are screened to be frail through measures such as the short performance battery test or the clinical frailty scale have been 50% more likely to experience PoD [44]. Additionally, as seen in Table 1, older age is a common independent risk factor for experiencing PoD amongst cardiac surgery patients.

1.4.2 Impact of Aging On Peri-operative Outcomes

Older age is a significant predictor of not just PoD but several peri-operative outcomes of the cardiac surgery patient [45]. For example, older adults undergoing cardiac surgery often present with multiple comorbidities such as hypertension, diabetes, frailty, previous stroke, etc., which increase the complexity of their surgical recovery [46]. A 2016 study by Cooper et al. [47] found older adults had a higher likelihood of 30-day and one-year mortality than compared to their younger counterparts. Similarly, Alexander et al. [48] also found that older adults had significantly higher in-hospital mortality after a cardiac surgical procedure than their younger counterparts. Additionally, they also found that older adults had twice the likelihood of experiencing postoperative stroke and renal failure [48]. In light of the substantial impact of older age on perioperative outcomes for cardiac surgery patients, it becomes imperative to explore strategies to optimize patient outcomes.

Though it is important to understand the pathophysiology of PoD, including the role of biomarkers, oxidative stress, and involvement of brain structures, there remains a gap in knowledge on how to optimize patients best preoperatively to decrease the likelihood of PoD. Consequently, it is critical to reflect on the associated risk factors such as age and others identified in Table 1, including but not limited to depression, cognitive impairment, previous stroke, atrial fibrillation, etc. None of these risk factors are modifiable during the cardiac surgery patient's waiting period. As such, preoperative optimization should identify risk factors that can potentially be intervened on. One such risk factor is alcohol use [29, 49]. The following sections will define alcohol use and its impact on health, then highlight the different screening tools and biomarker tests for identifying alcohol use and describe the current evidence on the role of alcohol use on PoD in the cardiac surgery patient population.

1.5 Alcohol Use

The Canadian Centre on Substance Use and Addiction released the public health guideline on alcohol consumption, which states the following:

a) Zero drinks per week is considered no risk;

b) One to two standard drinks per week are regarded as low-risk;

c) Three to six standard drinks per week are considered moderate-risk and

d) Seven or more standard drinks per week are considered increasingly high risk.

The term "standard drink" refers to one of the following: 341 ml of beer (5% alcohol) or 341 ml (5% alcohol) cooler, cider, ready-to-drink or 142 ml (12% alcohol) wine or 43 ml (40% alcohol) spirits including whisky, vodka, gin etc [50].

Despite the guidelines, research has shown that alcohol use has both beneficial and harmful effects on overall health; however, it is classified as a depressant [51]. In the late 1900s and early 2000s, researchers published their findings on alcohol use. Work by Ashley et al. [52] and Puddey et al. [53] stated the potential benefits of light to moderate doses of alcohol in protecting against ischemic heart disease and other ischemic diseases such as ischemic stroke. Another study found a 24.7% decrease in the risk of coronary heart disease due to the increased concentration of high-density lipoprotein through moderate alcohol use (30 g of alcohol per day – equivalent to 720 ml of beer or 300 ml of wine) [54]. Furthermore, a study found moderate alcohol use to be protective for type 2 diabetes in both men and women [55], while another study found that moderate alcohol users had a reduced risk of developing dementia [56].

On the other hand, several studies have pointed towards the harmful effects of alcohol use. In a metanalysis published in 2015, a dose-response relationship was found between high alcohol

use and stomach, liver, gallbladder, pancreas and lung cancer [57]. Additionally, in a narrative literature review and meta-analysis from 2011, a causal linkage between alcohol use disorders and major depression was noted [58]. Further, excessive alcohol use has been known to cause alcoholic hepatitis (inflammation of the liver), cirrhosis (scarring of the liver) [59], hypertension [60], cardiomyopathy [61], neurodegenerative diseases such as Parkinson's disease [62] and Wernicke-Korsakoff Syndrome (memory disorder due to lower levels of thiamine potentially caused due to chronic alcohol use) [63].

The current alcohol use guidelines for cardiac surgery patients come from the Enhanced Recovery After Surgery – Cardiac Surgery (ERAS-CS). It recommends that hazardous alcohol use and smoking should be stopped four weeks before elective surgery [33]. Alcohol use also impacts the human brain in several different ways. Alcohol impairs cognitive function, including memory and learning, by inhibiting the action of the glutamate receptor, NMDA [64]. Consequently, chronic alcohol use has been associated with brain shrinkage, particularly impacting the frontal lobe responsible for executive functioning such as decision-making, problem-solving, attention and concentration [65]. Some of these symptoms are common symptoms of PoD (e.g., inattention).

Further, chronic alcohol use has also been associated with worse mental health outcomes such as depression and anxiety [66]. In addition to these effects, alcohol use may increase the risk of delirium, especially in the context of major stressors such as cardiac surgery. Chronic alcohol use disrupts the body's stress systems, including the hypothalamic-adrenal axis [67]. This, combined with the potential for alcohol withdrawal during the postoperative period, may increase the likelihood of PoD [68].

In addition to these health impacts, alcohol use may influence PoD through its effects on biomarkers related to neuroinflammation and cognitive function. Alcohol use, even in moderate

amounts, can alter biomarkers such as CRP, IL-6, and cortisol, all of which have been associated with the development of PoD [18]. Older adults, in particular, may be more vulnerable to these changes due to age-related declines in brain plasticity [69] and cognitive reserve [70]. While some studies have suggested that moderate alcohol consumption can reduce the risk of dementia [56], the impact of PoD, particularly in the context of surgery and potential alcohol withdrawal, remains unclear. Accurately assessing alcohol consumption becomes increasingly important, especially for vulnerable patients undergoing cardiac surgery, to help identify patients at higher risk for postoperative complications such as PoD [71].

1.5.1 Screening Tools for Alcohol Use

In the past thirty years, due to the complexity of measuring alcohol use, there have been different tools developed to measure alcohol use. These are divided into screening tools (i.e., questionnaires) or clinical biomarker tests. Several screening tools measure alcohol use. Many of these have modified versions, such as shorter and translated forms. These include:

1. AUDIT (Alcohol Use Disorders Identification Test) – a ten-item questionnaire developed by the World Health Organization to identify patients with hazardous patterns of alcohol use. The sensitivity and specificity are 67% and 95%, respectively [72].
2. AUDIT-C (Alcohol Use Disorders Identification Test – Concise) – a shorter, three-questions version of the AUDIT. The sensitivity and specificity are 100% and 81%, respectively [72].

3. AUDIT-5 (Alcohol Use Disorders Identification Test – 5) – a shorter, five questions version of the AUDIT specifically for older adults . The sensitivity and specificity are 87% and 86%, respectively [73].
4. MAST (Michigan Alcohol Screening Test) – a 22-item questionnaire developed at the University of Michigan Medical School in 1971 to identify alcohol abuse and dependence. The sensitivity and specificity are 36% and 36-96%, respectively [74].
5. MAST-G (Michigan Alcohol Screening Test – Geriatric) – a 24-item questionnaire developed version of the MAST for the geriatric patient population. The sensitivity and specificity are 86% and 47%, respectively [75].
6. MMAST-G (Mini Michigan Alcohol Screening Test – Geriatric) – a two-item questionnaire version of the MAST-G developed for the geriatric patient population. The sensitivity and specificity are 78% and 76%, respectively [75].
7. SMAST-G (Short Michigan Alcohol Screening Test – Geriatric) – a shorter, ten-item questionnaire version of the MAST specifically for the older adults. The sensitivity and specificity are 75% and 69%, respectively [75].
8. CAGE (Cut-down, Annoyed, Guilty, Eye-opener) Questionnaire – a four-questions screening tool to identify alcohol abuse. The sensitivity and specificity are 77% and 94%, respectively [76].
9. CARET (The Comorbidity - Alcohol Risk Assessment Tool) – a three questions tool assessing the quantity and frequency of alcohol use, existing co-morbidities and symptoms of medical and psychiatric disorders, and use of medications. The sensitivity and specificity are 86% and 78%, respectively [77].

10. ASSIST (Alcohol, Smoking and Substance Involvement Screening Test) – an eight questions screening tool to identify substance and alcohol abuse. The sensitivity and specificity are 50-96% and 54-97%, respectively [78].
11. ARPS (Alcohol-Related Problems Survey) – a 60-item survey screening tool designed for community-dwelling older adults to identify alcohol use. The sensitivity and specificity are 80% and 50%, respectively [79].

1.5.2 Clinical Biomarker Tests for Alcohol Use

Various types of clinical biomarkers indicate alcohol use some achieved through a blood test while some through a urine test. These are:

1. BAC (Blood Alcohol Concentration) – measures the amount of alcohol present in an individual's bloodstream at the time of measurement [80].
2. CDT (Carbohydrate-Deficient Transferrin)—This blood test measures CDT (a blood protein) that can be influenced by alcohol usage in the past four weeks [81].
3. EtG (Ethyl Glucuronide) – this urine test measures EtG (an ethanol metabolite that remains in the body for up to 80 hours) [82].
4. Phosphatidyl ethanol (PEth)—This blood test measures PEth (a phospholipid only formed in the presence of ethanol) and detects alcohol use over the past two weeks [83].

1.6 Alcohol Use and Postoperative Delirium

Alcohol use may increase the risk of delirium through a combination of physiological mechanisms (e.g., brain damage). Understanding these potential harmful impacts and some

benefits of controlled alcohol consumption, the role of clinically measured alcohol use on PoD remains unclear. Therefore, to identify the current knowledge and knowledge gaps in the literature about this relationship between PoD and alcohol use, PubMed was searched using MeSH terms "alcohol use" AND "postoperative delirium," which yielded 195 publications. These publications were screened for relevance by titles and summaries. Titles and summaries were screened based on whether they consisted of "alcohol" and "postoperative delirium" terms. Based on the titles and summary, 35 studies were selected for further screening. A total of 10 of the 35 studies were excluded, as four were not in the English language and six were case reports. Abstracts of the remaining 25 studies were read for relevance and context (i.e., alcohol must have been measured preoperatively and delirium postoperatively). Of the 25 remaining studies, 15 were deemed relevant. Four of those 15 studies were conducted in a cardiac surgery patient population and are summarized in Table 3. The other 11 were in the non-cardiac surgery patient population and, therefore, not summarized.

Table 2. Current knowledge on the relationship between alcohol use and postoperative delirium.

Study	Study design	Study Sample	Setting	Postoperative delirium assessment tool	Alcohol use assessment technique	Findings
Humphreys et al. [84]	Prospective	180; cardiac-surgery patients	Australia	Delirium Symptom Interview	National Health and Medical Research Guidelines (Australia)	Harmful levels of alcohol (≥ 3 standard drinks/day) was associated with quality of life but not with PoD.
Nguyen et al. [7]	Prospective	197; cardiac-surgery patients	Canada	CAM-ICU	AUDIT-C	Patients who were delirious did not experience self-reported problems with alcohol consumption.
Jarvela et al. [85]	Prospective	1036; cardiac-surgery patients	Finland	ICDSC	AUDIT-C	There is no significant difference between the incidence of PoD and high AUDIT-C scores.
Spiropoulou et al. [49]	Prospective	86; cardiac-surgery patients	Greece	CAM-ICU	Medical history form	Occasional alcohol use is positively correlated with PoD.

CAM-ICU – Confusion Assessment Method – Intensive Care Unit. ICDSC – Intensive Care Postoperative Delirium Screening Checklist.

As seen in Table 3, the four studies yielded mixed findings on the association between preoperative alcohol use and PoD in cardiac surgery patients [86, 84, 85, 49]. Three of the four studies (i.e., Humphreys et al. [84]; Nguyen et al. [7]; Jarvela et al. [85]) reported no association between preoperative alcohol use and PoD; while one study (i.e., Spiropoulou et al. [49]) identified a positive correlation between occasional preoperative alcohol use and PoD (in other words, patients who consumed alcohol occasionally had a higher likelihood of experiencing delirium). There are a few limitations in these studies to consider.

First, three of the four studies (i.e., Humphreys et al. [84], Jarvela et al. [85], Spiropoulou et al. [49]) were conducted in a different country than Canada (i.e., Australia, Finland, Greece). Their findings may be influenced by regional, cultural or public health guidelines related to alcohol use which may not be applicable to the Canadian population. For example, in Canada, the guidelines recommended no alcohol use as being the safest followed by a low-risk drinking of two standard drinks per week. However, Australia suggests a limit of no more than four standard drinks in a day [87]. This difference in guidelines speaks to the potential discrepancy that may be present in the patient population between these geographic regions. Second, two of the four studies (i.e., Nguyen et al. [7]; Jarvela et al. [85]) used a valid and comprehensive tool to measure alcohol use; the remaining two relied on either the public health guideline specific to their country (i.e., Humphreys et al. [84]) or an approach which has yet to be validated (a question asked by physicians and collected on the medical history form; Spiropoulou et al. [49]). Third, Humphreys et al. [84] examined alcohol use as a potential covariate of PoD through univariate analysis only. Meaning, no covariates were considered in the relationship between preoperative alcohol use and PoD. Fourth, Nguyen et al. [7] used alcohol use as a covariate in their regression model to determine the association between PoD and mood six months post cardiac surgery. Similar to

Humphreys et al. [84], Nguyen et al. [7] did not delineate the association between preoperative alcohol use and PoD with other possible covariates. The same holds true for the study by Jarvela et al. [85]. In this study, they also noted their limitation of missing AUDIT-C scores data which may have influenced their finding of no association between preoperative alcohol use and PoD. Finally, as noted above, the study by Spiropoulou et al. [49] did find a positive correlation between preoperative alcohol use and PoD but this study did not utilize a validated tool to measure alcohol use. This may concern the generalizability and reliability of their findings about alcohol use. These limitations underscore the current gap in knowledge, highlighting the need for a rigorous study with a larger sample size to be able to better control for covariates and more accurately determine this unclear relationship between preoperative alcohol use and PoD in cardiac surgery patients. This may be one of the reasons why previously published systematic reviews and meta-analyses on independent risk factors of PoD [Table 1] do not consider preoperative alcohol use as one of the risk factors.

Chapter 2: Methods

2.1 Statement of Problem

In Canada, 22.7 million individuals report consuming alcohol, with 15% of adults over the age of 25 years (i.e., 2.7 million individuals) engaging in binge drinking, defined as seven or more drinks per week [88]. While this data reflects alcohol use amongst the general adult population [88], its relevance becomes more pronounced when considering the growing number of older adults requiring healthcare interventions. Currently, 90% of individuals aged 60 and older have at least one chronic ailment, such as cardiovascular disease, which demands healthcare support [89]. By 2031, the Canadian population is anticipated to include an estimated 9.5 million people aged 60 years and above [90].

As this demographic continues to expand, there will be an increasing trend towards performing cardiac surgeries on older patients who bear a substantial load of concurrent health issues. This shift is anticipated to result in a higher likelihood of perioperative complications, including PoD, necessitating perioperative intervention [91]. Patients who developed PoD experience an increased likelihood of long-term cognitive deficits, higher odds of post-traumatic stress disorder [92], later-life dementia [93], morbidity and mortality [94]. The current medical landscape lacks a precise treatment plan for PoD once it has been diagnosed. As such, dedicated efforts are being made by research scientists and healthcare professionals to develop clinical pathways to identify patients at risk of PoD in their preoperative phase of care. Screening patients for preoperative alcohol use may help identify patients with an elevated PoD risk. However, as discussed in section *1.6 Alcohol Use and Postoperative Delirium*, the current gap in knowledge stems from the absence of a thorough examination of the relationship between preoperative alcohol use and PoD. Therefore, my thesis aims to thoroughly examine whether preoperative alcohol use

correlates with PoD in cardiac surgery patients and identify risk factors from the MACS database that are associated with PoD.

2.2 Hypothesis

The primary hypothesis is that higher AUDIT-C scores (indicating higher alcohol consumption) are associated with the incidence of PoD in adults who underwent cardiac surgery. The secondary hypothesis is that risk factors identified from the MACS database are correlated with PoD in adults who underwent cardiac surgery.

2.3 Study Design

This study was a single-centre, retrospective observational study. It was designed according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [Appendix A] and the SAGER (Sex and Gender Equity in Research) guidelines [95, 96]. An observational study is the best-fit for the study because it allows for information collection in its natural form. This means that an observational study design does not have any artificial manipulation of study variables compared to a given experimental study. There are two types of observational studies, exploratory and descriptive [97]. Exploratory refers to observational studies that systematically investigate the relationship between two or more variables, which is the design that this study is utilizing [97]. In contrast, this study cannot be labelled as a descriptive observational study because it has not been designed to merely describe the characteristics and conditions of patients undergoing cardiac surgery without testing relationships between variables [97].

2.4 Setting

This study was conducted at the St. Boniface Hospital in Winnipeg, Manitoba. More specifically, Manitoba's Access Cardiac Surgery (MACS) database and Manitoba's adopted software of the Alberta's Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) database were used to obtain research data. The MACS database contains data on all open-heart cardiac surgeries at the St. Boniface Hospital. Data collected include admission type (e.g., emergent patient, outpatient (elective)), health history, medications, cardiac diagnosis, type of procedure and postoperative complications. Registered nurses conduct a chart review of all these patients upon their discharge. Similarly, Manitoba's adopted software of APPROACH, is a registry of all patients who are undergoing a cardiac intervention (not necessarily heart surgery). The comorbidities and any missed fields are later completed by a chart review conducted by registered nurses upon the patient's discharge from the hospital after their cardiac intervention. Comparing the two databases, the APPROACH database had more detailed information available (e.g., intraoperative data like CPB time) than the MACS database. However, the MACS database had collected the independent variable, "AUDIT-C" scores along with other questionnaires which was the reason behind using both databases for data extraction.

2.5 Participants

This study received ethics approval from the University of Manitoba's Research Ethics Board (HS24656 (H2021:064)) and St. Boniface Hospital's Research Review Committee (RRC/2021/1955). This study included all adults (18 years of age and older) undergoing non-emergent cardiac surgical procedures (e.g., Coronary Artery Bypass Grafting (CABG), Aortic

Valve Repair/ Replacement (AVR), Mitral Valve Repair/ Replacement (MVR), Tricuspid Valve Repair/Replacement (TVR) or any combinations of these procedures). This decision to include all adults 18 years of age and older was made because adults of all ages may experience PoD [98], even though it is recognized that older adults are more susceptible to PoD due to age-related changes and vulnerabilities in their health. The decision to only include AVR, MVR, TVR, CABG or a combination of these procedures was made because most of the published cardiac surgery literature focuses on these well-established and standardized surgeries, simplifying the comparison outcomes across the patient populations. Patients who underwent cardiac surgery due to an emergency (i.e., patients who came in through the emergency department and were not scheduled for an elective outpatient procedure) were excluded. This is because the emergent patients have not been through the pre-operative assessment clinic appointment, which is where patients complete the alcohol use screening.

2.6 Variables, Data Measurement & Collection

The outcome variable, or dependent variable, in this study, is PoD, measured using the CAM-ICU and CAM conducted three times a day by a registered nurse or once every nursing shift until the patient is discharged from the hospital. This data is recorded on a paper called a "flowsheet" in the ICU and is attached to the patient's physical chart and on the flowsheet tab of the electronic personal record for the CAM. After which, nurses responsible for the MACS and APPROACH databases gather the patient's chart and enter the data. Postoperative delirium on the MACS database does not capture the time of CAM-ICU nor CAM assessment; it merely states whether the assessment was conducted during the day, evening or night. Postoperative delirium was recorded as a binary variable (i.e., 0 = no PoD, 1 = yes PoD), allowing for a straightforward

classification of its presence or absence. Postoperative delirium was treated as a binary variable because it is easy to communicate with potential stakeholders including clinicians and policymakers. It also allows for clear decision-making in clinical settings as interventions and escalation of care are primarily based on knowing whether PoD is present or not present. Further, when dealing with a larger dataset, collecting PoD as a binary outcome allows researchers to have a complete dataset, minimizing missing values. Despite this, there are limitations in treating PoD as a binary variable. For example, such an approach risks the loss of granular data, where collapsing all PoD screens into a binary variable will not allow for the study of severity, intensity or duration of PoD.

The predictor variable, or independent variable, in this study, was the preoperative alcohol use, measured using the validated AUDIT-C tool [Appendix B] [72] conducted by a nurse during the patient's preoperative assessment clinic appointment (this is a three-hour appointment, which approximately occurs seven-14 days before their scheduled surgery day). The AUDIT-C is composed of three questions: (1) how often did you have a drink containing alcohol in the past year? (2) how many drinks containing alcohol did you have on a typical day when you were drinking in the past year?, and (3) how often did you have six or more drinks on one occasion in the past year? [72]. A patient can score between zero through 12. A score of zero means no alcohol use, with increasing scores indicating higher alcohol use [72].

2.6.1 Covariates

This study considered several covariates established in previous investigations to be associated with PoD. Covariates include age, sex, procedure category, Montreal objective Cognitive Assessment (MoCA), Patient's Health Questionnaire-9 (PHQ-9), Clinical Frailty Scale (CFS), LVEF category, previous cerebrovascular accident (CVA) (i.e., stroke)/ transient ischemic

attack (TIA), renal insufficiency, preoperative creatinine, recreational drug use, diabetes and cardiopulmonary bypass time (CPB).

Age, MoCA score, PHQ-9 score, preoperative creatinine and CPB time were identified as continuous variables. Each of the variables collected will be described in the following paragraph. The categorical variables included as covariates are procedure category (1 = valve; 2 = CABG; 3 = COMBO), CFS (1 = fit (CFS < 3); 2 = pre-frail (CFS = 3); 3 = frail (CFS ≥ 4)) and LVEF category (1 = hyperdynamic (EF > 70%); 2 = normal (EF 50% - 70%); 3 = mild dysfunction (EF 40% - 49%); 4 = moderate dysfunction (EF 30% - 39%); 5 = severe dysfunction (EF < 30%)). The categorical, binary variables included: sex (0 = males; 1 = females), previous CVA/TIA (0 = no CVA/TIA; 1 = yes CVA/TIA), renal insufficiency (0 = no renal insufficiency; 1 = yes renal insufficiency), recreational drug use (0 = no drug use; 1 = yes drug use), and diabetes (0 = no diabetes; 1 = yes diabetes).

As noted in Table 1, the most common preoperative independent risk factors of PoD were age, preexisting cognitive impairment (in my thesis, cognitive impairment was measured using the available and validated MoCA scores – a tool that assesses seven cognitive domains: naming, attention and calculation, language abstraction, recall, orientation and visuospatial and executive function with a possible score out of 30 points [99]), depression (in my thesis, an alternative and validated questionnaire commonly used as a first step of screening for depression – the PHQ-9: a tool made up of nine questions with a possible score out of 27 [100]) and previous stroke. I considered each of these variables as covariates. Similar to the independent variable (AUDIT-C), MoCA, PHQ-9, the collection of previous health history (including recreational drug use, LVEF, CFS, renal insufficiency, and previous stroke) and preoperative blood test (which identifies the value for creatinine amongst other biomarkers) was conducted by a nurse at the preoperative

assessment clinic appointment. LVEF [101], CFS [44], renal insufficiency [102] and preoperative creatinine [103] have all been established in the literature to have an association with PoD. On the other hand, the association between recreational drug use and PoD is quite sparse; there is, however, evidence of an association between cannabis users being associated with higher AUDIT-C scores [104]. Additionally, an intraoperative covariate is associated with PoD is CPB time [105]. It has been shown that longer CPB times have been associated with an increased likelihood of experiencing PoD [105] , which was included as a covariate in this study. This data was entered into the MACS and/or the APPROACH database from the patient's physical chart once the patients were discharged from the hospital after their cardiac surgery procedure by nurses.

A biostatistician within the Cardiac Sciences Program who had technical access to the backend of the two databases helped with data extraction. Considering the nature of retrospective studies, data extraction may lead to missing values in data fields (e.g., may be missed to input into the database during the initial stages by clinicians/nurses or the code written to extract such data may have minor errors that were missed by the biostatistician). Should this occur, to ensure the missing fields are truly missing in the databases, a thorough front-end (i.e., the front user interface) one-by-one search for the missing variable was conducted. To do this, I logged into the databases. I found each patient using their unique medical record number and navigated the database to find if the missing values were truly missing or were available in the database but not captured in the data extraction. The majority of the missing values (for >100 patients) were in the following variables: CPB time, LVEF category and preoperative creatinine, If I was unable to locate the data point for a variable, it was considered to be a missing field.

2.7 Bias

This study may be prone to confounding bias or information bias. Confounding bias refers to the inability to account for a variable associated with both the outcome and predictor variables. This may occur as the current knowledge on PoD and alcohol use is limited (i.e., Table 3) and the multifactorial nature of PoD (i.e., Table 2). To mitigate this, the study's research team constantly reviewed literature and incorporated new information to ensure all relevant variables available to us were accounted for. On the other hand, information bias refers to the potential errors in data extraction due to missing data. This may occur, given the nature of a retrospective study. To mitigate this, MD ensured that missing data was looked for thoroughly one by one for each patient in the two databases.

2.8 Sample size

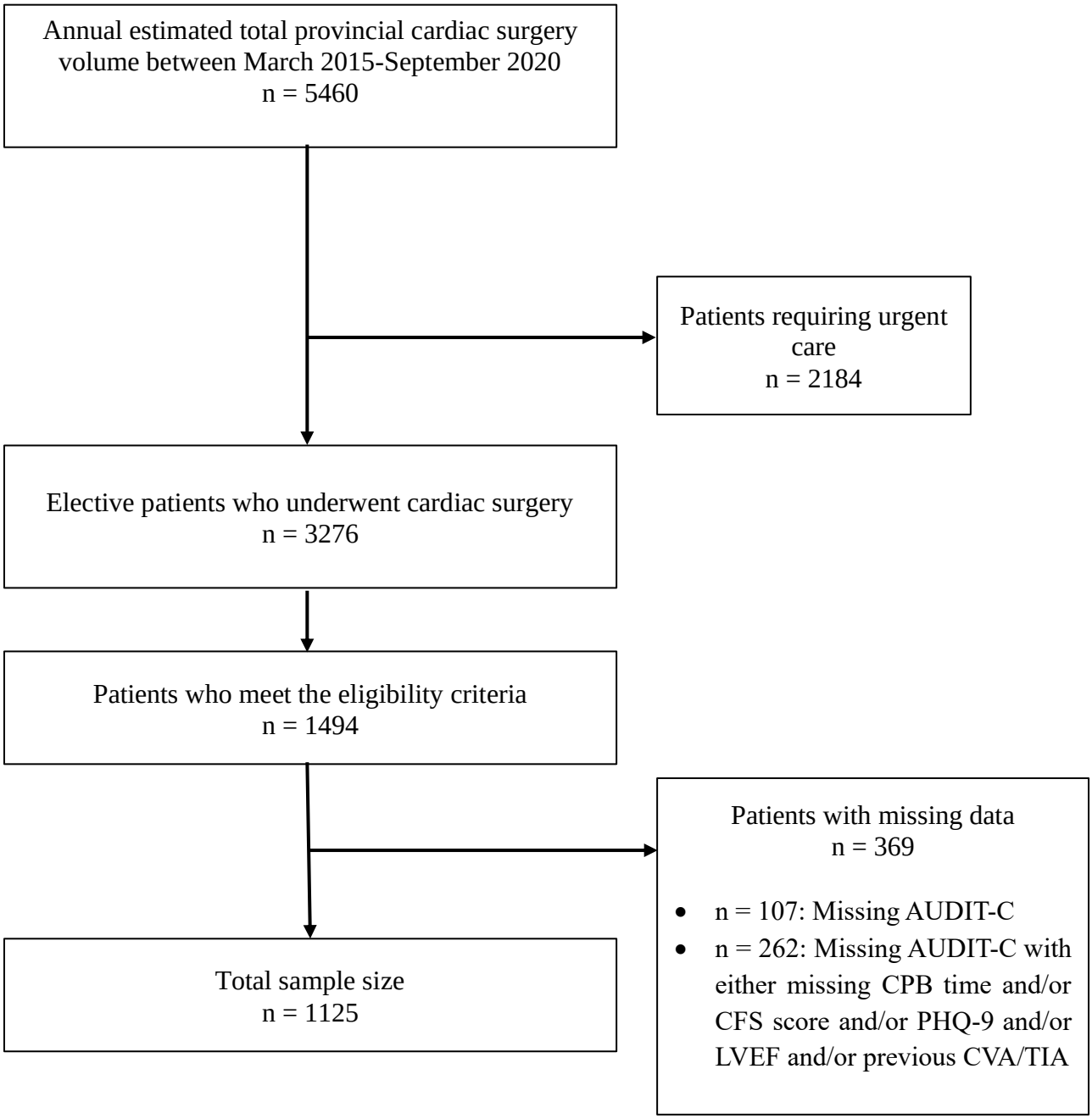
The annual estimated total provincial cardiac surgery volume is 1092 patients (including outpatients and in-patients) undergoing an invasive cardiac surgery procedure every year (Figure 1). During the study's time frame (March 2015-September 2020), approximately five years, an estimated 5460 patients will have undergone cardiac surgery at the St. Boniface Hospital. As the AUDIT-C is primarily only completed for outpatients, approximately 40% of the patients requiring in-patient urgent surgeries were excluded. Of the remaining 3276 patients, 1494 underwent an AVR, MVR, TVR, CABG or a combination of these surgical procedures and met the inclusion criteria. Though retrospective studies rely on the data availability more than the required sample size, it is still important to calculate a sample size to achieve adequate power.

The estimated sample size calculation for this study was done using the following formula [106]:

$$sample\ size = \frac{10 \cdot k}{P}$$

Where k is the number of predictors and covariates (i.e., 1 predictor (AUDIT-C) + 13 covariates = 14) and P is the proportion of the dependent variable, PoD (i.e., 0.21 signifies a 21% incidence of PoD among local cardiac surgery patients [44]. A minimum sample size of 666 patients is sufficient to detect meaningful differences and associations in this study. Further, we have 1494 patients with missing values and 1125 with a complete dataset. As calculated above, the sample is sufficiently powered with a sample size of 1125. Missing data was handled using the list-wise deletion method. Accounting for missing data using advanced statistical techniques such as multiple imputations [107] was not implemented because the sample size with complete data of 1125 was beyond the required sample size of 666 patients to detect a meaningful difference. The use of multiple imputations was deemed beyond the scope of this MSc. thesis by my thesis advisory committee.

Figure 1. Flowchart of Eligible Patients



2.10 Statistical Analysis

When appropriate for continuous variables, descriptive characteristics will be summarized using the mean and standard deviation or median and interquartile range. Categorical variables will be summarized using counts and percentages. The outcome variable/dependent variable is PoD. Overall postoperative delirium screening will be reported as a binary outcome (1, if the patient has tested PoD positive, or 0 if the patient has tested postoperative delirium negative during the entirety of the hospital stay). The independent variable will be alcohol use, which will be collected as a continuous variable.

A bivariate analysis was conducted to learn the relationship between PoD and each confounding variable of age, sex, procedure category, MoCA, CFS, AUDIT-C, PHQ-9, LVEF category, preoperative creatinine, renal insufficiency, previous CVA/TIA, diabetes, recreational drug use and CPB time. If the variables meet the significance level of p-value ≤ 0.25, it was included in building a multivariable logistic regression model to test the relationship between alcohol use and PoD. We tested for assumptions of logistic regression including, linearity of the logit, independence, and multicollinearity amongst all variables. When assumptions were not met, for example, linearity of the logit for age and CPB time, a transformation was applied to the variable. Our study carefully considered the potential implication of type I error using p-value ≤ 0.05 for our analysis. Given the exploratory nature of certain aspects of this study and the desire to identify potential associations that warrant further investigation, we have used a conventional alpha level of p-value ≤ 0.05. This decision is supported by the rationale that overly conservative adjustments may obscure potentially important findings and hinder the advancement of knowledge in the field [108].

Nonetheless, it is acknowledged the possibility of chance findings and emphasizing the need for replication in future studies.. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version, 29.0.2.0 (20).

2.11 My contributions to the project

During my time working as a research assistant with Dr. Rakesh Arora's (MSc co-advisor) group, I learned how to collect data by screening physical patient charts. At the beginning of 2021 in January, I noticed that elective cardiac surgery patients are asked about their alcohol consumption as part of their delirium risk screening. After observing several patients in other ongoing studies who would be screened as high-risk for postoperative delirium based merely on their high AUDIT-C score would not experience delirium. This was intriguing to me and I wanted to learn why.

Upon conducting a literature search, I realized that the AUDIT-C tool used to measure alcohol use has not commonly been used with cardiac surgery patients nor has the relationship between alcohol use measured using that tool and PoD extensively been studied. I proposed this idea to Dr. Arora, who supported this study. During this time, I was successful at obtaining ethics approval from the University of Manitoba's REB and St. Boniface's Research Review Committee. An experienced biostatistician for the cardiac sciences program, Mr. Brett Hiebert pulled the data for the study. Unfortunately, the data pulled had a few issues (i.e., elective surgery patients were defined differently in the database than the waitlist office defines). Additionally, this dataset was incomplete. Over the last two years, I worked to decrease the missing data of the variables included in the dataset by going through each database for each patient with missing data. Once the data was complete, I cleaned the data to make it ready for analysis. I then developed a statistical plan

and consulted a biostatistician for guidance. Once the plan was approved, I conducted the analysis in SPSS and the biostatistician performed the analysis independently using SAS (Statistical Analysis Software). We then confirmed whether the generated results were accurate to be able to complete this thesis.

Chapter 3: Results

3.1 Descriptive statistics

A total of 1125 patients met the eligibility criteria and were included in this study. Of these, 160 patients experienced delirium at some point during their hospital stay, resulting in a delirium rate of 14.2%. The median age of patients who experienced delirium was 71 years, with 70% being male. In contrast, the median age of non-delirious patients' was 67 years, with 73% being male. The most common surgical procedure amongst patients who experienced delirium was CABG (46%) followed by valve repairs/replacement (31%) and combination procedure (24%). Table 3 presents the descriptive statistics of all covariates included in the study, segregated by delirium and no delirium.

Table 3. Descriptive statistics

Variables	**Delirium** n = 160	**No Delirium** n = 965
Age; median (Q1-Q3)	71 (62-77)	67 (59-73)
Sex		
Male; count (%)	112 (70%)	701 (73%)
Female; count (%)	48 (30%)	264 (27%)
Procedure Category		
Valve	49 (31%)	411 (43%)
CABG	73 (46%)	397 (41%)
Combo	38 (24%)	157 (16%)
AUDIT-C score; median (Q1-Q3)	1 (0-3)	1 (0-4)
MoCA score; mean (SD)	24 (4.2)	26 (3.14)
CFS		
Fit (CFS < 3); count (%)	17 (11%)	197 (20%)
Pre-frail (CFS = 3); count (%)	50 (31%)	317 (33%)
Frail (CFS ≥ 4); count (%)	93 (58%)	451 (47%)
PHQ-9 score; median (Q1-Q3)	3 (1-6)	3 (1-6)
LVEF Category		
Hyperdynamic (EF >70%); count (%)	5 (3.1%)	21 (2.2%)
Normal (EF 50%-70%); count (%)	112 (70%)	725 (75%)
Mild dysfunction (EF 40%-49%); count (%)	4 (2.5%)	35 (36%)
Moderate dysfunction (EF 30%-39%); count (%)	32 (20%)	131 (14%)
Severe dysfunction (EF < 30%); count (%)	7 (4.4%)	53 (5.5%)
Preoperative creatinine; median (Q1-Q3)	85 (70-112)	79 (68-92)
Renal insufficiency; count (%)	45 (28%)	116 (12%)
Diabetes; count (%)	67 (42%)	324 (34%)
Previous CVA/TIA; count (%)	17 (11%)	48 (5%)
Recreational drug use; count (%)	8 (5.0%)	31 (3.2%)
CPB time; median (Q1-Q3)	139 (100-175)	123 (97-160)

CABG – Coronary Artery Bypass Grafting; AUDIT-C – Alcohol Use Disorders Identification Test-Concise; MoCA – Montreal objective Cognitive Assessment; CFS – Clinical Frailty Scale; PHQ-9 – Patient's Health Questionnaire -9; LVEF – Left Ventricular Ejection Fraction; CVA/TIA – Cerebrovascular Accident/Transient Ischemic Attack; CPB – Cardiopulmonary Bypass.

3.2 Bivariate analysis

Table 5 presents the bivariate analysis results with respective odds ratio, 95% Confidence Intervals and *p*-value for each covariate conducted separately with the dependent variable. As seen in Table 5, covariates including age, procedure category, CFS, MoCA score, preoperative creatinine, renal insufficiency, diabetes, previous CVA/TIA, and CPB time were significant in this step of the analysis, meeting the cut-off p-value ≤ 0.25. An example of the interpretation is as follows: for each additional year in age, the odds of experiencing delirium decreased by 3.3% (1-OR = 0.033) with 95% confidence that the actual decrease in odds lies between 1.6% and 5.1% (95% CI: 1.016-1.051). The association between age and delirium is statistically significant ($p < 0.001$).

Understanding that these covariates were statistically significant in the bivariate analysis does not indicate including all covariates in the final model [109]. It is important to check whether each covariate remains significant in the presence of other covariates, also considering if there is clinical relevance in including variables [109]. Upon conducting this, it was found that preoperative creatinine (1.000 OR, 0.998-1.002 95% CI, $p = 0.766$) and diabetes (1.076 OR, 0.736-1.574 95% CI, $p = 0.706$) did not meet the p-value ≤ 0.25, therefore, they were excluded from further analysis [Table 6].

Table 4. Bivariate analysis with individual covariate.

Variables	OR	95% CI	*p*-Value
Age	1.033	1.016-1.051	<0.001*
Sex			
Male	reference category		
Female	1.138	0.789-1.642	0.489
Procedure Category			
Valve	reference category		
CABG	1.542	1.047-2.272	0.028*
Combo	2.030	1.279-3.222	0.003*
AUDIT-C score	0.912	0.840-0.990	0.028*
MoCA score	0.900	0.860-0.941	<0.001*
CFS			
Fit (CFS < 3)	reference category		
Pre-frail (CFS = 3)	1.828	1.025-3.259	0.041*
Frail (CFS ≥ 4)	2.390	1.388-4.115	0.002*
PHQ-9 score	1.021	0.985-1.059	0.253
LVEF Category			
Hyperdynamic (EF >70%)	reference category		
Normal (EF 50%-70%)	0.649	0.240-1.756	0.394
Mild dysfunction (EF 40%-49%)	0.480	0.116-1.989	0.312
Moderate dysfunction (EF 30%-39%)	1.026	0.359-2.929	0.962
Severe dysfunction (EF < 30%)	0.555	0.158-1.944	0.357
Preoperative creatinine	1.002	1.000-1.004	0.010*
Renal insufficiency	2.864	1.928-4.253	<0.001*
Diabetes	1.425	1.013-2.005	0.042*
Previous CVA/TIA	2.271	1.271-4.059	0.006*
Recreational drug use	1.586	0.715-3.515	0.256
CPB time	1.004	1.002-1.007	<0.001*

*Statistically significant ($p \leq 0.25$). CABG – Coronary Artery Bypass Grafting; AUDIT-C – Alcohol Use Disorders Identification Test-Concise; MoCA – Montreal objective Cognitive Assessment; CFS – Clinical Frailty Scale; PHQ-9 – Patient's Health Questionnaire -9; LVEF – Left Ventricular Ejection Fraction; CVA/TIA – Cerebrovascular Accident/Transient Ischemic Attack; CPB – Cardiopulmonary Bypass.

Table 5. Preliminary multivariable logistic regression analysis with all significant covariates.

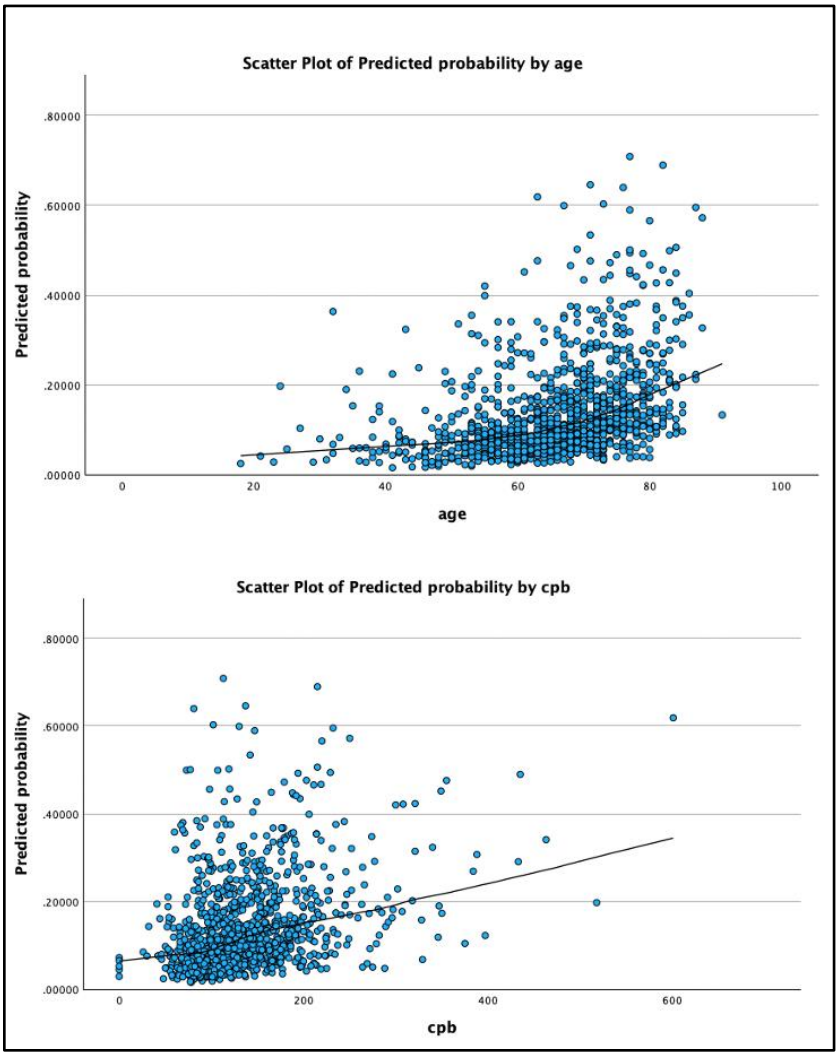
Variables	OR	95% CI	*p*-Value
Age	1.022	1.003-1.040	0.022*
Procedure Category			
Valve	reference category		
CABG	1.488	0.968-2.287	0.070*
Combo	1.100	0.658-1.839	0.715
AUDIT-C score	0.955	0.878-1.039	0.286
MoCA score	0.924	0.880-0.971	0.002*
CFS			
Fit (CFS < 3)	reference category		
Pre-frail (CFS = 3)	1.563	0.860-2.840	0.143*
Frail (CFS ≥ 4)	1.873	1.064-3.297	0.030*
Preoperative creatinine	1.000	0.998-1.002	0.766
Renal insufficiency	2.503	1.533-4.088	<0.001*
Diabetes	1.076	0.736-1.574	0.706
Previous CVA/TIA	1.894	1.027-3.495	0.041*
CPB time	1.005	1.003-1.008	<0.001*

*Statistically significant ($p \leq 0.25$). CABG – Coronary Artery Bypass Grafting; AUDIT-C – Alcohol Use Disorders Identification Test-Concise; MoCA – Montreal objective Cognitive Assessment; CFS – Clinical Frailty Scale; CVA/TIA – Cerebrovascular Accident/Transient Ischemic Attack; CPB – Cardiopulmonary Bypass.

3.3 Assumptions testing

Four assumptions were tested before conducting the final multivariable logistic regression. These include: linearity of the logit, independence, presence of interactions and absence of multicollinearity [109]. The linearity of the logit was tested for all continuous variables through smoothened scatter plots [110]. Two continuous variables: age and CPB time did not meet the linearity assumption [Figure 2]. Therefore, the transformation was applied using the following formula to achieve linearity: $y = 2x + x^2$ [111, 112]. All other continuous variables met the linearity assumption. Independence was assumed as this study did not use any variables measured at different timepoints. Interactions testing was conducted for all possible interactions of all covariates. The interactions test [Appendix C] demonstrated that there were no statistically significant interactions present. Multicollinearity was tested using the Variance Inflation Factor (VIF) [113]. As SPSS does not allow for multicollinearity testing to occur for logistic regression, a linear regression with all covariates was conducted to infer about multicollinearity. The VIF values equalled to one, meaning the assumption of an absence of multicollinearity was met.

Figure 2. Smoothened scatter plots of covariates violating linearity



3.4 Multivariable Logistic Regression

The multivariable logistic regression model controlled for transformed age, transformed CPB time, procedure category, MoCA score, CFS, renal insufficiency and previous CVA/TIA. Transformed age (1.000173 OR, 1.000036-1.000309 95% CI, p = 0.013), MoCA score (0.927 OR, 0.883-0.974 95% CI, p = 0.002), CFS frail (1.872 OR, 1.064-3.292 95% CI, p = 0.030), renal insufficiency (2.407 OR, 1.590-3.644 95% CI, p = <0.001), previous CVA/TIA (1.906 OR, 1.036-

3.506 95% CI, p = 0.038) and transformed CPB (1.000010 OR, 1.000003-1.000015 95% CI, p = 0.002) were statistically significant predictors of PoD. AUDIT-C score was not statistically significant (0.954 OR, 0.877-1.038 95% CI, p = 0.275) [Table 7].

Table 6. Final multivariable logistic regression model

Variables	**OR**	**95% CI**	***p*-Value**
Transformed Age	1.000173	1.000036-1.000309	0.013*
Procedure Category			
Valve	reference category		
CABG	1.473	0.977-2.223	0.064
Combo	1.207	0.729-1.998	0.465
AUDIT-C score	0.954	0.877-1.038	0.275
MoCA score	0.927	0.883-0.974	0.002*
CFS			
Fit (CFS < 3)	reference category		
Pre-frail (CFS = 3)	1.563	0.861-2.835	0.142
Frail (CFS ≥ 4)	1.872	1.064-3.292	0.030*
Renal insufficiency	2.407	1.590-3.644	<0.001*
Previous CVA/TIA	1.906	1.036-3.506	0.038*
Transformed CPB time	1.000010	1.000003-1.000015	0.002*

*Statistical significance (p-Value ≤ 0.05). CABG – Coronary Artery Bypass Grafting; AUDIT-C – Alcohol Use Disorders Identification Test-Concise; MoCA – Montreal objective Cognitive Assessment; CFS – Clinical Frailty Scale; CVA/TIA – Cerebrovascular Accident/Transient Ischemic Attack; CPB – Cardiopulmonary Bypass.

3.5 Model Performance Test

Model performance test was conducted only for the final multivariable logistic regression model. This is because the preliminary multivariable logistic regression model was a step in building the final model. Table 8 presents the model summary statistics including the Cox & Snell R Square and Nagelkerke R Square values to understand the overall fit and explanatory power of the model [114]. This model demonstrates low-moderate explanatory power, with a Cox & Snell R Square of 0.064 and a Nagelkerke R Square of 0.115, indicating that the Model explains approximately 6.4% (Cox & Snell derived) and 11.5% (Nagelkerke R Square derived) of the variance in the outcome variable (i.e., delirium).

The Hosmer and Lemeshow test to assess the goodness-of-fit indicates that this model ($p = 0.384$) fits the data adequately [Table 9] [114]. The area under the Receiver Operating Characteristic (ROC) is used to summarize the performance of the Model [110, 115]. The model has an AUC (area under the curve) value of 0.694 [Figure 3]. Any AUC value between 0.6 and 0.7 indicates poor performance [110, 115].

Table 7. Model Summary

Model	Cox & Snell R Square	Nagelkerke R Square
1	0.064	0.115

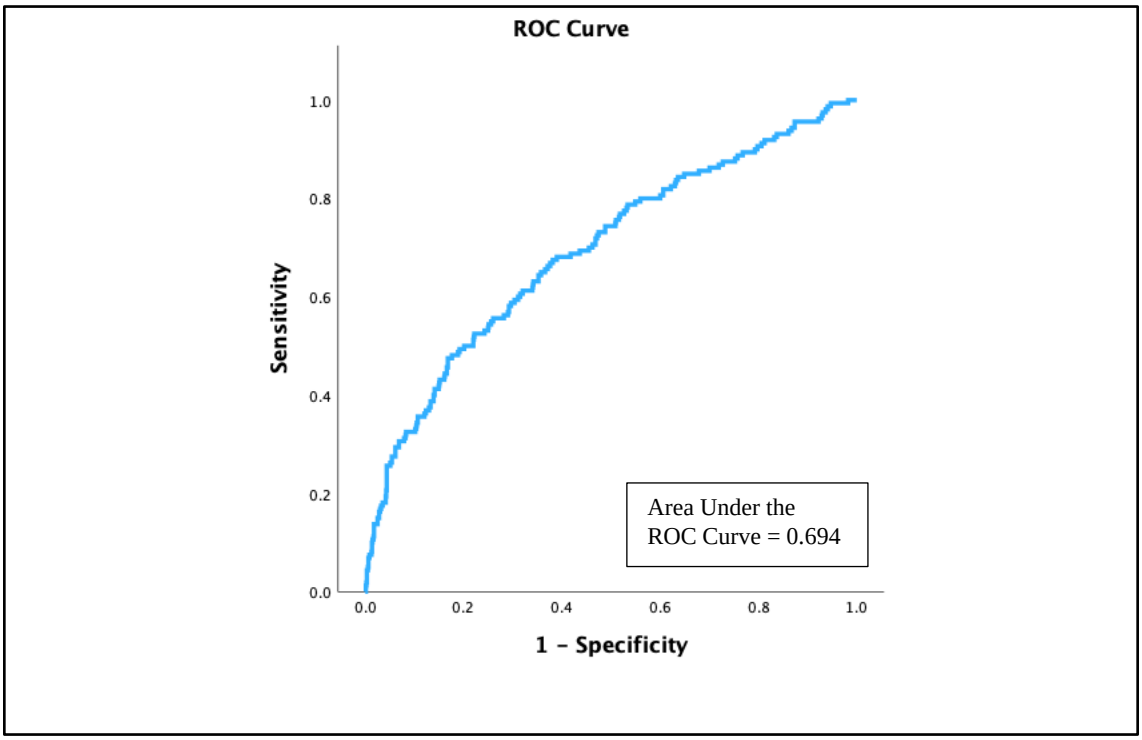
Model 1 – transformed age, procedure category, AUDIT-C score, MoCA score, CFS, renal insufficiency, previous CVA/TIA, transformed CPB time

Table 8. Hosmer and Lemeshow Test

Model	Chi-square	df	*p*-Value
1	8.523	8	0.384

Model 1 – transformed age, procedure category, AUDIT-C score, MoCA score, CFS, renal insufficiency, previous CVA/TIA, transformed CPB time

Figure 3. ROC curve for the model



Chapter 4: Discussion

This study investigated the association between preoperative alcohol use measured using the AUDIT-C and PoD in cardiac surgery patients. The AUDIT-C tool is a self-report tool with a sensitivity and specificity of 100% and 81%, respectively for diagnosing alcohol use disorder. The bivariate analysis (i.e., a simple correlation) identified a significant association between higher AUDIT-C scores (continuous variable) and PoD (binary variable) (0.912 OR, 0.840-0.941 95% CI, p = 0.028). This finding contradicts the findings by Jarvela et al. [85] and Nguyen et al. [7] that use the AUDIT-C as the alcohol use screening tool. However, after controlling for important covariates, the analysis demonstrated that higher AUDIT-C scores were not associated with PoD. This analysis did not support the hypothesis that higher AUDIT-C scores are associated with PoD. In other words, preoperative alcohol use screening with the AUDIT-C is not a reliable predictor of PoD in the cardiac surgery patient population. This finding is consistent with three of the four studies reviewed in Table 3 (Humphreys et al. [84], Nguyen et al. [7], Jarvela et al. [85]), which also reported no significant association between preoperative alcohol use and PoD among cardiac surgery patients.

As the findings of this study suggest that alcohol use as measured by the AUDIT-C is not predictive of PoD, it could potentially be attributed to St. Boniface Hospital's preoperative guidelines, which are in line with the American College of Cardiology/American Heart Association's 2014 guidelines and the ERAS-CS recommendations, advising patients to abstain from alcohol use and smoking for at least four weeks before surgery [116, 33]. However, this is speculative and assumes high patient compliance with the guidelines. Future research should investigate the compliance rate with preoperative alcohol cessation to better understand its impact on the development of PoD. To our knowledge, this is one of the first studies to examine the

relationship between alcohol use and PoD in the presence of important covariates using the AUDIT-C as the alcohol use screening tool and the CAM-ICU and CAM as the PoD diagnostic tool. Consequently, this study identified several risk factors associated with PoD in the multivariable logistic regression model: transformed age, MoCA scores, CFS, renal insufficiency, previous CVA/TIA, and transformed CPB time.

The incidence of PoD was 14.2% in the cohort. This was lower than reported in a previous study conducted at the St. Boniface Hospital published by Jung et al. [44], which reported a PoD incidence of 21% in patients undergoing cardiac surgery. However, the observed incidence of PoD was still in line with a systematic review by Koster et al. [29], which highlights that the incidence of delirium varies from 13.5% to 41.7%. This variance in the incidence of delirium may have occurred due to a change in perioperative management practices over the span of 2015 – 2020 at the St. Boniface Hospital. During this time frame, Winnipeg Regional Health Authority's Cardiac Surgery Department at the St. Boniface Hospital introduced and implemented the non-pharmacological interventions protocol for elective cardiac surgery patients based on their preoperative risk score of PoD [117]. For instance, if a patient was identified as high-risk for PoD based on age, procedure category, AUDIT-C score, etc., the protocol would be set to ensure no sudden room changes or staff changes occurred, and early mobility would be encouraged [117].

In this study, MoCA scores measuring cognitive function were inversely associated with PoD, wherein the odds of PoD decreased by approximately 7% (0.927 OR, 0.883-0.974 95% CI, $p = 0.002$) for each unit increase in MoCA score. Therefore, MoCA scores were associated with PoD, where patients with higher MoCA scores (better cognitive function) experience lower risk of PoD. This finding was supported by the findings of Sadlonova et al. [118] , who reported that better cognitive function reduces the risk of PoD. Sadlonova et al. [118] observed a statistical

difference between the MoCA scores of patients who experienced PoD and those who did not experience PoD (delirious: 22.3 ± 4.1 vs. non-delirious: 24.3 ± 3.4, *p*-value = <0.001). In contrast, Nguyen et al. [7] reported no statistical difference between the MoCA scores of patients who experienced PoD and those who did not experience PoD (delirious: 24.5 (20.0-27.0) vs. non-delirious: 25.0 (23.0-28.0), *p*-value = 0.07). The findings of this thesis study strengthen the literature reporting an association exists between MoCA scores and PoD in the cardiac surgery patient population.

Frailty assessed using the CFS was also a significant predictor of PoD.In my thesis study, frail patients (CFS ≥ 4) had an 87.2% increase in odds of developing PoD compared to fit patients (1.872 OR, 1.064-3.292 95% CI, $p = 0.030$). In contrast, pre-frail patients did not show a difference in odds compared to fit patients (1.563 OR, 0.861-2.835 95% CI, $p = 0.142$). Unlike this thesis study, findings by Sillner et al. [119] demonstrated that both pre-frailty (20.9%) and frailty (29.3%) are associated with PoD in hospitalized adults. However, the diagnostic tools they utilized differed from this thesis study. For example, they used the frailty index and clinician interview for frailty and delirium, respectively [119]. Though both diagnostic tools have been validated, the difference in our findings may result from the variance in the diagnostic tools with those used by Sillner et al. [119]. Furthermore, a local study by Jung et al. [44] determined that frailty (measured using the Modified Fried Criteria) causes a three to eight-fold increase in PoD risk post cardiac surgery. Though this association has been established in the cardiac surgery literature, it may be worthwhile to investigate the role of alcohol use on frailty.

Renal insufficiency emerged as another significant predictor of PoD in this study. Patients with renal insufficiency had more than double the odds of developing PoD (2.407 OR, 1.590-3.644 95% CI, $p = <0.001$), translating to a 140.7% increase in odds compared to patients without renal

insufficiency. Previous studies by Gosselt et al. [30] and Mangusan et al. [102] have also reported that patients with renal insufficiency are at a higher likelihood of experiencing PoD. Furthermore, a recent study by Guan et al. [120] found that higher perioperative creatinine value is associated with PoD in older adults, further corroborating the findings of this study. However, it is important to note that their findings were in the non-cardiac surgery patient population, pointing towards a generalizable finding of the role of renal insufficiency amongst patients requiring varying surgical specialties.

The non-linearity of CPB time is clinically expected as any minute over the 173-minute mark has been associated with worse postoperative outcomes such as an increased mortality rate and a longer hospital stay requiring increased postoperative support in the ICU [121]. Specifically, this study by Hu et al. [121] found that longer CPB times (≥173 minutes) increased the odds of mortality by 767%, with a 170% higher risk of in-hospital mortality. As seen in Figure 2, the majority of the data points are clustered around the 100-minute mark for CPB time, well below the 173-minute threshold used by Hu et al. [121]. Findings of this thesis study indicated that the transformed CPB time was another risk factor of PoD. The multivariable logistic regression model revealed that each additional minute squared of CPB time is associated with an increased likelihood of developing PoD (1.000010 OR, 1.000003-1.000015 95% CI, $p = 0.002$). Though the odds ratio is 1.000010, indicating that the effect size per squared minute of transformed CPB time is very small, the statistically significant *p*-value indicates that even a minor increase in transformed CPB time can significantly impact the likelihood of PoD. The findings of this study are difficult to compare to previous studies because the previous research did transform their CPB time in their analysis. However, looking at the overall consensus, the findings of this research are consistent with previous literature by O'Neal et al. [105] and Andrasi et al. [122]. In their

retrospective study, O'Neal et al. [105] found that a CPB duration of 142 minutes was significantly associated with PoD compared to a duration of 54 minutes in patients undergoing CABG surgery. The 142 minutes encompasses a combination type procedure or, in some cases, a complex procedure, whereas the 54 minutes may be observed in a less complex CABG procedure [105]. Though this is not a direct comparison to this thesis study's findings, it points towards a significant association between CPB time and PoD. Further, Andrasi et al. [122], looking at risk factors of PoD after cardiac surgery procedures with cardioplegic arrest (a process used in cardiac surgery to intentionally stop the heart to allow for surgical intervention to occur), found that every additional minute of CPB time increases the odds of experiencing PoD by 10.1%. The difference in odds found by Andrasi et al. [122] and that of this thesis study could be a result of the transformation applied to the CPB time or due to the different inclusion criteria of procedure types (i.e., this thesis study only included CABG, Valve or a Valve + CABG whereas, Andrasi et al. [122] included CABG, Valve, CABG + Valve, Aortic Surgery + CABG). Though the odds of experiencing PoD found by Andrasi et al. [122] are higher than that of this thesis study, the findings of this thesis study do indicate an association between CPB time and PoD exists.

Transformed age and previous CVA/TIA were also identified as significant predictors of PoD. The non-linearity of age can be biologically reasoned as patients who often require cardiac surgery are frequently older than 60 years of age, which is reflected in the smoothened scatter plot of Figure 2. The findings indicate that the transformed age variable was found to have an odds ratio of 1.000173 (95% CI: 1.000036-1.000309, $p = 0.013$), indicating that the effect size per squared year of transformed age is minimal, the statistically significant *p*-value suggests that even a minor increase in transformed age can significantly impact the likelihood of PoD. This finding of transformed age as a covariate of PoD is difficult to compare due to the nature of the

transformation directly. However, overarchingly, it aligns with previous literature findings, including but not limited to Koster et al. [29] and Lin et al. [31]. The systematic review by Koster et al. [29] identified two studies that found age to be a covariate and provided the odds ratio. The study by Banach et al. [123] Kazmierski et al. [124] found that older age increases the odds of experiencing PoD by 300% (4.0 OR, 1.5-10.4 95% CI) and Norkiene et al. [125] found that older age increases the odds of developing PoD by 282% (3.82 OR, 1.44-10.1 95% CI). The meta-analysis by Lin et al. [31] included four articles which found that age increases odds of experiencing PoD by 8% [11, 126, 127, 128]. They also included three articles [123, 129, 130] , which found that an age over 65 years is associated with a three-fold increased risk of developing PoD and two studies [131, 132] looked at an increase in age by 10 years and found no association with PoD. Although the precise impact of age varies across studies, each increase in year of age increased the odds of developing PoD, which speaks to the overall finding of this research.

Patients with a history of CVA/TIA in this study had nearly double the odds of developing PoD (OR = 1.906, 95% CI: 1.036-3.506, p = 0.038). This means that patients with a history of CVA/TIA had a 90.6% increase in odds of developing PoD. This association is supported by several published studies, including Shadvar et al. [133] and Katznelson et al. [134]. The findings of Shadvar et al. [133] suggest that a history of CVA/TIA was higher in the patients who developed PoD in cardiac surgery patients (17% in patients with PoD vs. 5.8% in patients without PoD). Katznelson et al. [134] found that a history of CVA/TIA increased the odds by 16.4% of developing PoD post-vascular surgery. Similar to the impact of age on PoD, history of CVA/TIA have varying impacts across studies and types of surgeries, but the finding of this research does stay consistent with previous literature that a history of CVA/TIA has an impact on PoD.

4.1 Limitations

This study has a few limitations to consider. One such limitation of this study is its retrospective observational design, which inherently cannot establish causality between AUDIT-C and PoD. While associations can be identified, we could not conclude that the identified associations directly cause PoD. Another limitation is the potential for residual confounding. Although we adjusted for various known risk factors in the multivariable logistic regression model, other unmeasured variables may influence the risk of PoD. Examples of these risk factors are identified in Table 1, including red blood cell transfusion, albumin level, cardiac output, duration of surgery and length of time in ICU. These variables have been collected in the MACS and APPROACH database and the exploration of them as risk factors for PoD may have added value to this thesis study by testing a more robust multivariable logistic regression model. Perhaps conducting a mortality-curve statistical analysis for rates of PoD based on hospital and ICU length of stay could have given us a more in-depth perspective of the impact of alcohol use on the cardiac surgery patient. Additionally, comparing the findings while including transformed variables with a model without including these variables could have been beneficial to our understanding of the multivariable logistic regression model and aided in creating a stronger, more robust model. However, the thesis advisory committee deemed that such an analysis was beyond the requirement of this Master's level project. Other potential risk factors to consider in exploring alcohol use and PoD may be the role of perioperative medications, including but not limited to anti-anxiety medications, anti-depressants, opioids and benzodiazepines [135].

The generalizability of our findings may be limited by the specific population studied. Our cohort consisted of valve, CABG or combination surgery patients from a single institution, which may not represent a broader patient population or other surgical specialties. Differences in patient

demographics or healthcare settings could influence the incidence and risk factors for PoD, limiting the applicability of our results to other contexts. Additionally, the alcohol use guidelines by public health bodies may vary by country. Multi-center studies with diverse patient populations are needed to validate our findings and ensure generalizability.

Moreover, the study's reliance on AUDIT-C scores to assess preoperative alcohol use poses some challenges. The AUDIT-C is a screening tool designed to identify hazardous drinking behaviours, but it may not capture all relevant aspects of alcohol consumption, such as chronicity, binge drinking patterns, or the impact of alcohol on overall health. Additionally, self-reported measures, including the AUDIT-C, are subject to social desirability bias, where patients may underreport their alcohol consumption due to stigma or fear of judgment. To mitigate social desirability bias, a few different approaches could be considered, such as providing patietns with the opportunity to answer the questions instead of a nurse practitioner asking the questions [136] or using indirect questioning [137]. Both approaches may reduce social desirability bias.

While this study provides valuable insights into the role of alcohol use and PoD in cardiac surgery patients, its observational nature, potential for residual confounding, limited generalizability and reliance on self-reported alcohol use measures are important limitations to consider. Addressing these limitations in future research will enhance our understanding of the role of preoperative alcohol use screening on PoD and improve patient care outcomes.

4.2 Future Directions

Given the findings of this study, several avenues for future research emerge to further elucidate the relationship between preoperative alcohol use and PoD in cardiac surgery patients. First, considering the limitations of using self-reported AUDIT-C as a sole measure of preoperative

alcohol consumption, future studies could incorporate more comprehensive assessments of alcohol use, such as the collection of a combination of quantitative and qualitative measures. For example, biomarkers for alcohol use and in-depth interviews could be used, or researchers could consider testing different alcohol use screening tools.

Moreover, the study's retrospective observational design highlights the need for prospective studies to determine if there is any causality. A randomized controlled trial (RCT) could be conducted where people who report high alcohol use are randomized to different periods of reduced drinking to determine if that has a positive health impact. Differently said, the RCTs could explore whether targeted preoperative interventions for at-risk patients, such as alcohol cessation programs or enhanced monitoring, could reduce the incidence of PoD in the cardiac surgery patient population. However, it is critical to consider whether a RCT is an appropriate next step. This is because the findings of this study were in line with three of the four studies identified in Table 2 that alcohol use is not predictive of PoD in the cardiac surgery patient population. More importantly, it would be essential to measure whether a preoperative intervention of alcohol cessation for a wait-time period that may be less than two weeks is of benefit to the postoperative outcomes and risk of PoD. Despite this, a feasibility trial could enhance our understanding of PoD in relation to preoperative alcohol use. This feasibility trial should explore not only the role of alcohol use but also the impact of alcohol withdrawal which may have a stronger influence on PoD. Using both qualitative and quantitative measures such as self-reported alcohol use, biomarker tests, and clinical assessments would provide a more comprehensive picture of alcohol-related factors in PoD risk. To enhance the generalizability, this feasibility trial should be conducted across multiple centres with diverse patient populations covering a broad range of cardiac procedures and healthcare settings (e.g., larger centres with adequate resources). By addressing

these future research directions, we can build on the findings of this thesis study to enhance our understanding of preoperative alcohol use screening on PoD, improve risk stratification, and ultimately improve patient outcomes and enhance recovery post-cardiac surgery.

4.3 Conclusion

This study investigated the association between preoperative alcohol use, measured using the AUDIT-C, and PoD in cardiac surgery patients. The initial bivariate correlation analysis identified a significant association between AUDIT-C scores and PoD. However, after controlling for covariates identified in previous investigations, the multivariable logistic regression analysis demonstrated that AUDIT-C scores were not associated with PoD. This suggests that alcohol consumption, as measured by the AUDIT-C screening tool, may not be a reliable predictor of PoD. However, this study did identify several other significant predictors of PoD. Lower MoCA scores, indicating greater cognitive impairment, were associated with an increased likelihood of PoD and frailty as assessed by the CFS. Renal insufficiency emerged as a critical predictor, with affected patients showing a 133.9% increase in odds of developing PoD. Additionally, longer CPB times, transformed age and history of CVA/TIA were associated with PoD. The two main limitations of the study include its retrospective design and reliance on a self-reported tool for screening alcohol use. Future research should focus on prospective, multi-centre studies to enhance the prediction and prevention of PoD in the cardiac surgery patient population.

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Appendix A – STROBE Guidelines

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

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Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix B – Alcohol Use Disorders Identification Test – Concise

AUDIT-C

MRN:_____ **Date:_____**

1. **How often did you have a drink containing alcohol in the past year?**
   a. Never 0
   b. Less than monthly 1
   c. Monthly 2
   d. Weekly 3
   e. Daily or almost daily 4

2. **How many standard drinks containing alcohol did you have on a typical day in the last year?**
   a. Never 0
   b. Less than monthly 1
   c. Monthly 2
   d. Weekly 3
   e. Daily or almost daily 4

3. **How often did you have six or more standard drinks on one occasion in the past year?**
   a. Never 0
   b. Less than monthly 1
   c. Monthly 2
   d. Weekly 3
   e. Daily or almost daily 4

Reference:
World Health Organization. (2001). The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care.

*AUDIT-C is available for public use.

Appendix C – Interactions Assumption Test

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	age_transformed	.000	.001	.168	1	.682	1.000	.999	1.002
	procedure_categ			.115	2	.944			
	procedure_categ(1)	.109	2.082	.003	1	.958	1.115	.019	65.995
	procedure_categ(2)	.918	2.778	.109	1	.741	2.505	.011	580.341
	audit_c	.128	.469	.075	1	.785	1.137	.454	2.848
	moca	.050	.161	.097	1	.755	1.052	.766	1.443
	cfs			3.451	2	.178			
	cfs(1)	2.518	3.589	.492	1	.483	12.405	.011	14074.100
	cfs(2)	5.104	3.380	2.280	1	.131	164.673	.218	124146.554
	renal_insuff(1)	.154	2.302	.004	1	.947	1.166	.013	106.326
	prev_cvatia(1)	-2.111	4.057	.271	1	.603	.121	.000	344.248
	cpb_transformed	.000	.000	2.232	1	.135	1.000	1.000	1.000
	age_transformed * procedure_categ			.525	2	.769			
	age_transformed by procedure_categ(1)	.000	.000	.222	1	.637	1.000	1.000	1.000
	age_transformed by procedure_categ(2)	.000	.000	.456	1	.499	1.000	1.000	1.001
	age_transformed by moca	.000	.000	.229	1	.632	1.000	1.000	1.000
	age_transformed * cfs			4.154	2	.125			
	age_transformed by cfs(1)	.000	.000	2.103	1	.147	1.000	1.000	1.001
	age_transformed by cfs(2)	.000	.000	.030	1	.863	1.000	1.000	1.001
	age_transformed by renal_insuff(1)	.000	.000	.011	1	.916	1.000	1.000	1.000

	age_transformed by prev_cvatia(1)	.000	.000	1.013	1	.314	1.000	1.000	1.001
	age_transformed by cpb_transformed	.000	.000	.240	1	.624	1.000	1.000	1.000
	moca * procedure_categ			.461	2	.794			
	moca by procedure_categ(1)	.004	.062	.004	1	.947	1.004	.889	1.135
	moca by procedure_categ(2)	-.047	.081	.343	1	.558	.954	.815	1.117
	cfs * procedure_categ			1.091	4	.896			
	cfs(1) by procedure_categ(1)	.017	.801	.000	1	.983	1.017	.212	4.893
	cfs(1) by procedure_categ(2)	-.654	1.061	.379	1	.538	.520	.065	4.165
	cfs(2) by procedure_categ(1)	-.342	.763	.201	1	.654	.710	.159	3.165
	cfs(2) by procedure_categ(2)	-.641	.983	.426	1	.514	.527	.077	3.618
	procedure_categ * renal_insuff			3.317	2	.190			
	procedure_categ(1) by renal_insuff(1)	.391	.573	.464	1	.496	1.478	.480	4.547
	procedure_categ(2) by renal_insuff(1)	-.821	.684	1.443	1	.230	.440	.115	1.680
	prev_cvatia * procedure_categ			.064	2	.969			
	prev_cvatia(1) by procedure_categ(1)	.112	1.019	.012	1	.912	1.119	.152	8.238
	prev_cvatia(1) by procedure_categ(2)	-.131	1.172	.013	1	.911	.877	.088	8.721
	cpb_transformed * procedure_categ			.708	2	.702			
	cpb_transformed by procedure_categ(1)	.000	.000	.227	1	.634	1.000	1.000	1.000

cpb_transformed by procedure_categ(2)	.000	.000	.254	1	.614	1.000	1.000	1.000
cfs * moca			1.909	2	.385			
cfs(1) by moca	-.129	.118	1.185	1	.276	.879	.697	1.109
cfs(2) by moca	-.153	.112	1.882	1	.170	.858	.689	1.068
age_transformed by audit_c	.000	.000	1.785	1	.182	1.000	1.000	1.000
audit_c * procedure_categ			.335	2	.846			
audit_c by procedure_categ(1)	-.019	.108	.032	1	.859	.981	.794	1.212
audit_c by procedure_categ(2)	.059	.137	.183	1	.669	1.060	.810	1.388
audit_c by moca	.008	.015	.263	1	.608	1.008	.978	1.038
moca by renal_insuff(1)	.002	.066	.001	1	.981	1.002	.880	1.139
moca by prev_cvatia(1)	.059	.112	.282	1	.595	1.061	.852	1.321
cpb_transformed by moca	.000	.000	3.151	1	.076	1.000	1.000	1.000
cfs * renal_insuff			1.516	2	.469			
cfs(1) by renal_insuff(1)	.993	.876	1.283	1	.257	2.699	.484	15.037
cfs(2) by renal_insuff(1)	.582	.864	.453	1	.501	1.789	.329	9.736
cfs * prev_cvatia			2.031	2	.362			
cfs(1) by prev_cvatia(1)	-.429	1.534	.078	1	.780	.651	.032	13.169
cfs(2) by prev_cvatia(1)	-1.486	1.532	.941	1	.332	.226	.011	4.555
cfs * cpb_transformed			3.592	2	.166			
cfs(1) by cpb_transformed	.000	.000	.176	1	.675	1.000	1.000	1.000
cfs(2) by cpb_transformed	.000	.000	.733	1	.392	1.000	1.000	1.000
audit_c * cfs			3.303	2	.192			
audit_c by cfs(1)	-.171	.140	1.498	1	.221	.843	.641	1.108

	audit_c by cfs(2)	-.244	.134	3.299	1	.069	.784	.602	1.019
	prev_cvatia(1) by renal_insuff(1)	-.093	.874	.011	1	.915	.911	.164	5.054
	cpb_transformed by renal_insuff(1)	.000	.000	1.023	1	.312	1.000	1.000	1.000
	audit_c by renal_insuff(1)	.007	.112	.004	1	.947	1.008	.808	1.256
	cpb_transformed by prev_cvatia(1)	.000	.000	.381	1	.537	1.000	1.000	1.000
	audit_c by prev_cvatia(1)	.061	.151	.162	1	.687	1.063	.790	1.429
	audit_c by cpb_transformed	.000	.000	.009	1	.923	1.000	1.000	1.000
	Constant	-4.887	4.678	1.091	1	.296	.008		

a. Variable(s) entered on step 1: age_transformed, procedure_categ, audit_c, moca, cfs, renal_insuff, prev_cvatia, cpb_transformed, age_transformed * procedure_categ , age_transformed * moca , age_transformed * cfs , age_transformed * renal_insuff , age_transformed * prev_cvatia , age_transformed * cpb_transformed , moca * procedure_categ , cfs * procedure_categ , procedure_categ * renal_insuff , prev_cvatia * procedure_categ , cpb_transformed * procedure_categ , cfs * moca , age_transformed * audit_c , audit_c * procedure_categ , audit_c * moca , moca * renal_insuff , moca * prev_cvatia , cpb_transformed * moca , cfs * renal_insuff , cfs * prev_cvatia , cfs * cpb_transformed , audit_c * cfs , prev_cvatia * renal_insuff , cpb_transformed * renal_insuff , audit_c * renal_insuff , cpb_transformed * prev_cvatia , audit_c * prev_cvatia , audit_c * cpb_transformed .