Investigating the Factors Influencing Survival After Out-of-Hospital Cardiac Arrest: Sex-Based Differences in Resuscitation and Outcomes

by

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Abstract

The objective of the studies in this dissertation was to examine the effects of sex on out-of-hospital cardiac arrest (OHCA) interventions and outcomes, including survival to hospital discharge, one-year survival, and survival with favourable neurological function. Data were obtained from the British Columbia (BC) Cardiac Arrest Registry, Population Data BC, and a multi-centre clinical trial carried out in the USA and Canada. Analysis methods comprised logistic regression, survival analysis, and multilevel analysis.

The first study was an analysis of a cohort of 7,398 adults with OHCA in BC and showed that in patients who did not achieve prehospital ROSC, males had 1.2-fold greater odds of being transported to hospital compared to females (95% CI 1.04, 1.37).

The second study was a retrospective analysis of 8,115 OHCA cases in BC and revealed that females had greater adjusted odds of ROSC (OR 1.29, 95% CI 1.15 – 1.42, p <0.001), but not survival to hospital discharge (OR 1.14, 95% CI 0.96 – 1.35, p = 0.129).

The third study was an analysis of linked data from various clinical databases in BC and revealed no significant difference in one-year survival by sex (HR males vs. females 1.14, 95% CI 0.72 – 1.81, p = 0.57).

The fourth study was a retrospective analysis of data (N=22,416) from the Resuscitation Outcomes Consortium multi-center randomized controlled trial. The study identified initial shockable rhythm and hypothermia management as the strongest predictors of favourable

neurological outcome. Further analysis showed that males derived significantly greater benefit from hypothermia management and initial shockable rhythms than females.

The fifth study was based on 23,725 cases from the trial mentioned above. The cohort was stratified into four groups by age and sex: younger females (i.e. premenopausal), older females, younger males, and older males. The study found no difference in neurological outcome between younger males and younger females (OR 0.95, 95% CI 0.69 – 1.32, $p = 0.75$). The result suggests premenopausal females had no advantage with respect to good brain function.

These findings highlight the independent effect of sex on short and long-term survival, and the interaction effect of age and sex on neurological outcome.

Lay summary

Sudden out-of-hospital cardiac arrest (OHCA) is a leading cause of death affecting 400,000 people in North America annually. We sought to investigate sex-based differences in OHCA resuscitation outcomes. We found that in OHCA victims who were not resuscitated on the scene, females were less likely to be transported to hospital than males. With regards to resuscitation outcomes, we found that females were more likely to be resuscitated but were less likely to survive to hospital discharge. Our study identified eight predictors that increased the likelihood of a good outcome: younger age, arrest occurring in a public location, shorter duration of EMS arrival to the scene, witnessed arrest, bystander CPR, therapy that lowers the temperature of the body, good CPR quality, and having a heart rhythm that responds to the use of a defibrillator (shockable rhythm). Finally, we found that young premenopausal women had no advantage with respect to survival.

Preface

This is to certify that the work presented in this dissertation was conducted and written by Emad Awad. All research studies of this dissertation were conducted after receipt of ethics approval from the University of British Columbia - Providence Health Care Research Institute (Certificate No.: H18-02188).

Chapters 2, 3, 4, 5 and 6 of this dissertation were conceived and written as stand-alone manuscripts. Chapters 2, 3, and 6 were published in peer-reviewed academic journals. The Resuscitation Outcomes Consortium (ROC) Publications Committee reviewed these three chapters and approved their submission for publication. Chapters 4 and 5 will be submitted to a peer-reviewed academic journal for publication.

Data used in Chapters 2 and 3 were prospectively collected by the British Columbia (BC) ROC. Data used in Chapter 4 were linked datasets from various administrative and clinical databases in BC, including the BC Cardiac Arrest Registry, BC Vital Statistics, Cardiac Services BC, the BC Discharge Abstracts Database (DAD), and the Cardiac Services BC. In Chapters 5 and 6, we analyzed the ROC Continuous Chest Compression (CCC) clinical trial data, which were obtained from the National Heart, Lung, and Blood Institute Biological Specimen and Data Repository BioLINCC data access program through a Research Materials Distribution Agreement (RMDA) (https://biolincc.nhlbi.nih.gov/about/).

In this dissertation research, I coordinated and completed all data access procedures. I conducted all statistical analyses, and I wrote the first and final drafts of all manuscripts. My contribution was more than 90% for each of the five manuscripts. My supervisor (Dr. Karin Humphries), co-supervisor (Dr. Jim Christenson), and supervisory committee members (Dr. Joel Ginger and Dr. Colleen Norris) made contributions to the studies' designs and reviewed each of the five manuscripts, provided editorial and supervision input, and approved the final versions for journal submission and publication.

Chapter 2: Sex differences in out-of-hospital cardiac arrest interventions in British Columbia, Canada.

A version of Chapter 2 was published as Awad E, Christenson J, Grunau B, Tallon J, Humphries K (2020) entitled "Sex differences in out-of-hospital cardiac arrest interventions within the province of British Columbia, Canada" in the Resuscitation Journal. DOI: 10.1016/j. resuscitation.2020.01.016. Resuscitation Journal is a high-quality, peer-reviewed journal publishing clinical studies in emergency medicine and cardiopulmonary resuscitation. I conceptualized and designed the study with help from Dr. Humphries, Dr. Christenson, and Dr. Singer. I managed all data acquisition, cleaning, and manipulation; conducted the data analysis in consultation with all co-authors, and wrote the first draft of the manuscript, which was edited by Dr. Humphries and Dr. Norris, and revised by all authors.

Chapter 3: Sex differences in short-term survival in patients with out-of- hospital cardiac arrest in British Columbia, Canada.

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Chapter: 4 Sex differences in one-year survival following out-of-hospital cardiac arrest.

I conceptualized and designed the study; managed all data acquisition, cleaning, and manipulation; conducted the data analysis in consultation with all co-authors. A version of Chapter 4 will be submitted as a manuscript to a peer-reviewed journal. The author list includes Awad, E., Humphries, K., Fordyce, C., Grunau, B., Helmer, H., and Christenson, J. I wrote the first draft of the manuscript, which was edited and revised by all authors.

Chapter 5: Prehospital predictors of favourable neurological function at hospital discharge.

I conceptualized and designed the study; managed all data acquisition, cleaning, and manipulation; conducted the data analysis in consultation with all co-authors. A version of Chapter 5 will be submitted as a manuscript to a peer-reviewed journal for publication. The author list includes Awad, E., Christenson, J., Norris, C, and Humphries, K. I wrote the first draft of the manuscript. This draft will be reviewed by Dr. Humphries, Dr. Christenson, and Dr. Norris. The manuscript will be revised according to the reviewers' comments before submission for publication.

Chapter 6: The impact of premenopausal age on neurological function at hospital discharge.

A version of Chapter 6 was published as Awad EM, Humphries KH, Grunau BE, Christenson JM (2021) entitled “Premenopausal-aged females have no neurological outcome advantage after out-of-hospital cardiac arrest: A multilevel analysis of North American populations” in the Resuscitation Journal.” DOI: 10.1016/j.resuscitation.2021.06.024. I conceptualized and designed the study with help from Dr. Humphries, Dr. Christenson, and Dr. I managed all data acquisition, cleaning, and manipulation; conducted the data analysis in consultation with all co-authors, and wrote the first draft of the manuscript, which was edited by Dr. Humphries Dr. Grunau, and Dr. Christenson and revised by all authors.

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List of Abbreviations

AED	Automatic External Defibrillator
AHA	American Heart Association
BLS	Basic Life Support
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCC	Continuous Chest Compression
CHF	Congestive Heart Failure
CI	Confidence Interval
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
DAD	Discharge Abstracts Database
DM	Diabetes Mellitus
EMS	Emergency Medical Services
GCS	Glasco Coma Scale
HCP	Health Care Provider
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile Range
LRT	Likelihood Ratio Tests
MCAR	Missing Completely at Random
MRS	Modified Rankin Scale
N	Number

NSTEMI	Non-ST Segment Elevation Myocardial Infarction
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PEA	Pulseless Electrical Activity
RCT	Randomized Controlled Trial
ROC	Resuscitation Outcomes Consortium
ROSC	Return of Spontaneous Circulation
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
STEMI	ST Segment Elevation Myocardial Infarction
TOR	Termination of Resuscitation
VF/VT	Ventricular Fibrillation/Ventricular Tachycardia
VIF	Variance Inflation Factor

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Chapter 1-3 were based on BC ROC data. Chapters 5 and 6 were based on ROC CCC trial research data obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. The contents of these chapters do not reflect the opinions of the ROC or the NHLBI.

Dedication

I would like to dedicate this work to my sister, Hala Awad, who always kept me reinforced and focused on my life goals. To my parents, my wife, my brothers, and my children, Mohammad, Omar, Yousef, Ryan, and Al-Amir who are my greatest blessings. Thank you for all your love and laughter – God bless you all.

Chapter 1: Introduction

1.1 Background

Sudden cessation of the beating of the human heart, referred to as "cardiac arrest," is one of the leading causes of death in the USA and other countries (1–4). Approximately 400,000 sudden, unexpected cardiac arrests occur in the USA and Canada yearly (3,5,6), of which approximately 85% occur outside of hospitals, referred to as out-of-hospital cardiac arrest (OHCA) (7). OHCA is a major health concern worldwide, with an adult incidence rate of 55 per 100,000 person-years (1) Sudden OHCA is a common critical medical emergency that requires immediate intervention (1–3). More than half (55%) of OHCA patients in North America receive EMS treatment (8,9). While the resuscitation outcomes vary from one region to another (9), the overall survival to hospital discharge rate is approximately 10.4 % (8,9).

The cessation of blood flow to the brain and vital organs during cardiac arrest results in an oxygen-poor state that subsequently results in tissue damage. Without immediate medical intervention (early cardiopulmonary resuscitation and defibrillation), victims of cardiac arrest die within a few minutes. The immediate goal of OHCA intervention is return of spontaneous circulation (ROSC). After ROSC, cardiac arrest victims have unstable circulatory status and are still at risk of poor neurological outcome including severe neurologic disability, coma, and neurologic death (10). Providing cardiac arrest victims with prompt and optimal out-of-hospital intervention as well as in-hospital post-resuscitation care is essential for short term survival and for survival with minimal or no neurological complications (survival with favourable neurological outcome).

Many prehospital factors pertaining to treatment characteristics of OHCA impact survival. In addition to treatment-related factors, patient-related factors, such as 'sex', may influence survival. The academic Emergency Medicine Consensus Conference (2014) identified sex and gender aspects of OHCA epidemiology and outcome as research priorities in cardiopulmonary resuscitation (11).

Sex is defined as the biological construct of males and females, and it has four main dimensions: anatomy, physiology, genes, and hormones. Gender refers to as the socially constructed characteristics of men and women, and it has four main dimensions: gender roles, gender relation, gender identity and institutional gender. Gender differences between men and women varies from one society to another. While sex and gender are inter-linked, they are two different concepts (12).

Sex-based analysis of cardiac arrest intervention and outcome is an important area of research because the results and recommendations of such research will increase health care providers' understanding of sex differences in treatment and outcome and identify necessary modifications to clinical practice. Chapter 2,3, 4, and 5 of the current dissertation research focused on sex-based resuscitation differences and outcomes. While these chapters are addressing sex, there are likely gender-related characteristics that we cannot explicitly account for.

Before preceding further and summarizing the evidence from literature on sex differences in interventions and outcomes, it is imperative to understand other variables that influence or correlate with survival, so we can adjust for their effects when we conduct sex-based analyses (examine the effect of sex on survival). Not adjusting for their effects may result is a spurious association between sex and outcome of interest. Additionally, understanding these factors and their impacts on survival is of intrinsic importance for informing clinical practice and therefore improving the rate of OHCA survival. The following sections describe the existing evidence on the most important factors influencing OHCA resuscitation outcomes as well as sex differences in OHCA intervention and outcomes.

1.2 Factors influencing survival after OHCA

Health care providers (HCP) and Emergency Medical Services (EMS) personnel use a systematic approach to assess and treat victims of cardiac arrest. This systematic approach involves implementation of five critical actions known as the "chain of survival" (13). These actions include 1) rapid activation of EMS, 2) rapid initiation of cardiopulmonary resuscitation (CPR), 3) early defibrillation, 4) early delivery of advanced cardiac life support (ACLS) by EMS providers, and 5) incorporation of post-resuscitative care. Implementation of these interventions is crucially important as they increase the chances of survival (13). Previous studies have explored many factors and treatment characteristics related to the chain of survival and how these factors influence the survival of OHCA. In several observational studies, researchers dealt with these factors as independent variables and dealt with resuscitation outcome as a dependent variable. The main independent variables found to be associated with resuscitation outcomes include time from arrest to resuscitation commencement; witnessed arrest; provision of bystander CPR; quality of CPR including chest compression rate, depth, and fraction; initial heart rhythm; and defibrillation (2,14,23,15–22).

1.2.1 Witnessed arrest and early CPR

Early recognition of cardiac arrest and early CPR are critically important for survival (13). CPR involves initiating chest compressions and often ventilation. Compressing the heart through the chest pushes some blood to the brain, preserving brain function until ROSC or advanced measures can be started. Delay in initiating CPR for even a few minutes may lead to permanent brain damage and death. Every minute that passes without CPR reduces the chance of survival by almost 10% (24). Previous studies consistently demonstrate strong statistical evidence supporting that witnessed arrest and early bystander CPR are two crucial factors for survival (2,15,22,23,25–28).

The majority of cardiac arrest cases occur outside the hospital, at home or in a public place (6,7). Provision of immediate CPR by a family member or a public layperson who witnesses a victim collapsing increases the chance of survival. If CPR is initiated by a trained health professional, outcomes are even better than CPR delivered by a layperson. Hostler et al. (29) used logistic regression analysis to estimate the odds of survival for EMS witnessed OHCA cases relative to bystander witnessed cases (with and without CPR provided). After controlling for covariates, the adjusted odds ratios of survival to hospital discharge were significantly lower in bystander witnessed with bystander CPR (OR= 0.41, 95% CI 0.36–0.46), and bystander witnessed without bystander CPR (OR= 0.37, 95% CI 0.33–0.43) compared to EMS witnessed with EMS CPR.
A plausible explanation for why witnessed arrest has a positive impact on OHCA survival is that the time interval for commencing resuscitation is likely shorter. Also, it is likely that witnessed arrest subsequently results in early activation of the emergency medical system and early

recognition of the initial heart rhythm and defibrillation if necessary. This would also have positive impacts on resuscitation outcomes.

1.2.2 Initial rhythm and defibrillation

Early recognition of the initial heart rhythm is an important component of the chain of survival (13,24). The initial heart rhythm of victims of cardiac arrest could be either a shockable or non-shockable rhythm. Ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) are shockable rhythms, whereas pulseless electrical activity (PEA) and asystole are non-shockable. An initial rhythm of VF or VT (shockable rhythms) is linked to a higher likelihood of survival (24,30–32). If the initial cardiac rhythm is VF or VT, delivering an electrical shock (defibrillation) is a key for restoring normal heart contractions, thus increasing the possibility of survival. Defibrillation of shockable rhythms should not be delayed. Any delay in defibrillation will significantly decrease the chance of survival (24,30).

When the arrest occurs in a public location, a public Automated External Defibrillator (AED) is useful and can be used for recognizing and defibrillating the shockable rhythm. Thus, availability and usage of AEDs prevent delays in delivering a shock when needed. The use of a public AED is associated with a high rate of survival after OHCA (31). In a recent study, Pollack et al. (33) reported that bystander AED use before EMS arrival in OHCA with a shockable rhythm is significantly associated with better survival to hospital discharge and survival with good functional outcomes. A multicenter randomized controlled trial (Public Access Defibrillation trial) examined survival after CPR-only versus CPR plus AED provided by CPR trained volunteers. The trial results showed that the number of survivors for CPR-plus-AED group was double that of the CPR-only group (31). Partially supporting these results, a study by the ROC team reported that victims of OHCA who received AED (with or without shock delivery) before EMS arrival were 1.75 times more likely to survive compared to those who had no AED applied before EMS arrival (34). Logically, the use of a public AED would probably be concurrent with the provision of bystander CPR. A meta-analysis including 37 articles concluded that bystander-initiated CPR and early defibrillation are significantly associated with survival to hospital discharge (32).

Several researchers have examined the effects of initial rhythm and early defibrillation in combination with other prehospital factors on resuscitation outcomes (2,22,27,35). An observational study that applied logistic regression to develop a predictive model for survival after VF/VT OHCA found that among many intervention-related variables, both early CPR and early defibrillation were the strongest predictors for survival to hospital discharge (23). This study emphasized the significance of both early CPR and early defibrillation together to improve survival of VF/VT OHCA. Boyce et al. (27) retrospectively analyzed data from a relatively small sample (n=242) and found that survival to hospital discharge is positively associated with witnessed cardiac arrest, arrest due to cardiac cause, initial arrest rhythm being a shockable rhythm, and Glasgow Coma Scale (GCS) ≥13. Using a similar methodological approach but with a larger sample size (n= 38,646), a Swedish study reported a significant increase in one-month survival among OHCA victims with shockable rhythms compared to non-shockable rhythms. Furthermore, one-month survival was significantly associated with witnessed arrest and bystander CPR (22). On a larger scale, two systematic reviews have summarized the factors associated with short-term survival after OHCA: witnessed arrest, early CPR, initial rhythm of VF, early defibrillation, short time to ambulance arrival, younger age, and male sex (2,36).

The above-mentioned studies provided evidence that witnessed arrest and early CPR, as well as an initial rhythm of VF/VT and early defibrillation are significantly associated with improved survival. Some researchers have hypothesized that providing VF cardiac arrest victims with a short duration of CPR before delivering a shock may result in better survival outcomes. Results from some studies are in support of this hypothesis. One study reported a 6% increase in survival and favourable neurological outcomes for cardiac arrest victims who received 90 seconds of CPR prior to defibrillation compared to those who received minimal or no CPR (37). In contrast, two clinical trials conducted in Australia failed to demonstrate improved survival with CPR prior to defibrillation. The first trial found that 90 seconds of CPR before defibrillation did not improve survival in patients with VF OHCA (38). The second trial found three minutes of CPR before the first defibrillation compared to immediate defibrillation for VF OHCA patients with EMS response time of longer than five minutes was not more effective in improving survival (ROSC, survival to hospital discharge, and neurological status at discharge) (39). In line with these results, an older study reported that longer pre-shock delay increases the likelihood of defibrillation failure (40).

Stiell et al. (41) conducted a cluster-randomized trial on adults with OHCA at 10 ROC sites in the United States and Canada. This clinical trial compared two groups: the first group (early-analysis group) received 30 to 60 seconds of EMS-provided CPR before initial rhythm analysis defibrillation; the second group (later-analysis group) received three minutes of CPR before the initial rhythm analysis and defibrillation. The main outcome was survival to hospital discharge with good functional condition. This trial found no difference in the survival with good functional status in the early analysis group (30 to 60 seconds), as compared to the later analysis group (three minutes) of EMS-provided CPR before the first attempt of cardiac rhythm analysis and defibrillation.

Whether to provide CPR before defibrillation or defibrillate immediately may depend on the EMS response time (the time EMS providers take to arrive on scene and initiate CPR). In a clinical trial, Wik et al. (42) found that providing CPR prior to defibrillation improves outcomes including ROSC, survival to hospital discharge, and one-year survival for VF/VT patients with EMS-response intervals longer than five minutes, but not for patients with EMS response times of five minutes or less.

In cardiac arrest, the golden rule is to follow the chain of survival, described above, and provide prompt intervention. While waiting for the EMS to arrive, bystander CPR is critically important and should be initiated. Early use of an AED, if available, to analyze the rhythm and deliver a shock is also critically important for survival. Thus, shorter time intervals to initiating the recommended interventions are extremely important for OHCA survival. In addition to the initial rhythms and time intervals, quality of CPR is another crucial aspect that needs to be taken into account to further improve the survival with good neurological outcome (13).

1.2.3 Quality of CPR

The American Heart Association (AHA) guidelines for management of cardiac arrest summarize high quality CPR as the following: 1) providing chest compression at a rate of at least 100 compressions per minute and at a depth of at least five cm, 2) minimizing interruption in chest compression, 3) allowing chest recoil after each compression, and 4) avoiding excessive ventilation (43,44). Thus chest compression depth, rate, and fraction are major components of quality CPR (13). EMS and HCP may not always adhere to the recommended resuscitation guideline and this would negatively impact the resuscitation outcome. In evaluating adherence of EMS to the recommended resuscitation guideline, a study of 176 adults who suffered OHCA reported that victims of cardiac arrest only receive chest compression 50% of the time available during resuscitation attempts, and in the remaining 50% of time during which compressions are given, patients receive compressions at a lower rate and shallower depth than what is recommended (on average 64 compressions per min and compression depth of 34 mm) (45). Another study demonstrated that compressing the chest during resuscitation at a depth less than 38 mm reduces the survival to discharge rate by 30% (61); if the chest compressions are too slow, return of ROSC after OHCA is reduced by 30% (46). Therefore, to increase survival from OHCA, optimizing the quality of CPR is essential.

Many other studies highlighted the role of CPR quality (chest compression rate and depth) on the survival after OHCA outcomes. A recent study suggested that providing cardiac arrest victims with compression depth of 2 inches (5 cm) improves survival. This study found that each 5mm increase in mean chest compression depth increases the odds of survival: OR 1.30 (95% CI 1.00 –1.70) (47). In a prospective cohort study, Stiell et al. (48) examined the association between

CPR chest compression depth and three measures of resuscitation outcomes in OHCA: ROSC, one-day survival, and hospital discharge. This study's results provided strong evidence that increased chest compression depth is associated with better outcomes for all three survival measures. However, the study did not find evidence to support or disprove the 2010 AHA's ACLS recommendations of a two-inch compression depth. The study concluded that the most effective compression depth is unknown (48). This seems logical as estimating a standardized compression depth for all patients is difficult because of the differences in body size, weight, and body mass index. Nevertheless, a recent study reported chest compressions depth exceeding 6 cm was found to be associated with potential injuries such as sternal fracture, pneumothorax and ruptures of the myocardium and upper gastrointestinal organs (49). Therefore, the 2015 AHA resuscitation guidelines determined the upper limit as not greater than 6 cm (43).

Chest compression rate is another component of CPR quality. AHA guidelines for management of cardiac arrest recommend a chest compression rate of at least 100 compressions per minute. In line with this recommendation, a clinical study reported a chest compression rate of 100 to 120 for OHCA is significantly associated with ROSC (50). In a recent study, Idris et al. (16) examined the relationship between compression rate and survival to hospital discharge based on secondary analysis of data from the multicenter Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis trial (41,51,52). Idris et al. (16) identified a compression rate of 100 to 119 as the rate associated with the greatest odds of survival to hospital discharge.

Linked to the compression rate, chest compression fraction, defined as “the proportion of time spent performing chest compressions during CPR” (53), is associated with survival. A study by Christenson et al. (53) evaluated the effect of increasing the chest compression fraction on survival to hospital discharge for VF/VT OHCA cases. Using logistic regression analysis of data from the ROC, Christenson et al. demonstrated that an increased chest compression fraction is associated with increased odds of survival in patients with a prehospital VF/VT arrest: “the estimated adjusted linear effect on odd ratio of survival for a 10% change in chest compression fraction was 1.11 (95% CI 1.01–1.21).” Using a similar methodological approach, Vaillancourt et al. (17) demonstrated that a 10% increase in chest compression fraction in non-VF arrest patients is associated with increased odds of ROSC (OR:1.05, 95% CI 0.99– 1.12).

Certainly, poor quality of CPR leads to decreased blood flow to the brain and vital organs, which is already impaired due to cessation of the heart. This consequently results in poor resuscitation outcomes. Remarkably, many of the factors that are associated with survival, including the quality of CPR, are modifiable. Optimizing treatments related to these modifiable factors should result in improved survival.

1.2.4 Advanced airway management

The goal of airway management in OHCA is to provide the victim with adequate oxygenation and to protect the victim’s airway from aspiration (54). This can be achieved by manual manipulation of the mandible and an oropharyngeal/nasopharyngeal airway (basic air way management), or by techniques via supraglottic airways (SGA) or endotracheal intubation (ETI) (advanced airway management).

A number of meta-analysis were conducted to evaluate the effect of advanced airway management on OHCA outcome. Fouche et al. (55) conducted a meta-analysis (included 17 studies 1998-2013) comparing advanced airway interventions with basic airway interventions. For those with non-traumatic cardiac arrest who were treated with endotracheal intubation. Fouche et al. found endotracheal intubation was associated with reduced odds of surviving to hospital discharge (OR 0.49, 95% CI 0.32–0.74). Another meta-analysis of 10 studies of advanced airway compared with basic airway in 84,905 patients (pooled sample size) reported advanced airway was associated with decreased odds of survival (OR 0.51, 0.29–0.90) compared with basic airway, and endotracheal intubation (56).

The studies described above summarized the prehospital event characteristics and intervention that are associated with improved survival from OHCA. The next section describes the existing evidence on sex differences in OHCA intervention and outcomes.

1.3 Sex differences in OHCA interventions

Research has shown that that there are sex-based disparities in the management of and recovery from cardiovascular diseases (57–59). Correspondingly, clinical researchers hypothesize that sex differences in prehospital interventions for OHCA may exist (60,61). Studies have shown that females receive bystander-CPR less frequently than males (25,60,62–64), and shorter duration of resuscitation in emergency departments following OHCA (65). To better understand this sex disparity in management of OHCA, in 2016, Mumma and Umarov conducted a retrospective study of sex differences in prehospital treatment intervals, procedures, and medications among adults with OHCA (61). Applying multivariate regression analysis to secondary data from the

Resuscitation Outcome Consortium (ROC) registry (39,40), this study reported that the EMS response time to OHCA (from EMS dispatch to first rhythm capture and first EMS CPR) is significantly shorter for males than for females. This study also reported that females are less likely to receive successful intravenous or intraosseous access (OR 0.78, 95% CI 0.71–0.86, $p < 0.001$) and are less likely to receive resuscitation medications including adrenaline, lidocaine, and amiodarone during OHCA resuscitation (61). Further investigation is required to understand the reasons for the sex differences in the EMS response time and receiving medications.

In a recent study, Grunau and colleagues assessed the association between sex and the utilization of Automated External Defibrator (AED) during OHCA. Applying multivariable logistic regression to analyzed data on 61,473 cases of OHCA from the ROC registry (2011-2015), Grunau and colleagues found female sex was associated with a lower odds of AED application in OHCA occurring in public OHCA (OR 0.76, 95% CI 0.64–0.90) (66).

While the previous research answered important questions about sex differences in OHCA management, many other relevant questions remained unanswered. It is possible that other important resuscitation intervention measures for females differ from that of males. One of the most important resuscitation interventions not taken into consideration in the previous studies, despite being noted as significantly associated improved survival, is the quality of CPR, specifically the chest compression rate (16,50). Another intervention measure that was not examined is the decision to initiate hospital transportation in those with failed prehospital resuscitations. Chapter 2 of this dissertation filled this gap by comparing these OHCA intervention measures between males and females.

1.4 Sex differences in OHCA short term outcome

In addition to sex differences in OHCA interventions, several studies have examined the association between sex and OHCA survival outcomes. Most of the previous univariable analyses comparing OHCA characteristics between males and females reported that females had a lower proportion with an initial shockable rhythm, a lower proportion of arrest occurring in public locations, and were less likely to receive bystander CPR (25,60,62–64,67). However, after adjusting for these characteristics, previous observational studies conducted in different countries reported contradictory results. A multivariable retrospective analysis of data from the Japan National Registry revealed that males and females have similar likelihoods of one month survival (adjusted OR 1.06, CI 1.06 1.02–1.10) and neurological intact survival (adjusted OR 1.03, CI 1.06 0.97–1.09) (64). A retrospective observational study analyzing data from the New Zealand OHCA Registry (October 2013-September 2015) used multivariate logistic regression adjusting for known predictors of survival to assess sex differences in one-month survival. This study found no statistically significant difference by sex (adjusted OR 1.22, 95% CI 0.96–1.55), $p < 0.11$). (68). Another observational study in Australia reported survival to hospital arrival advantage in females but no difference in survival to hospital discharge (69). Using similar methodological approach and statistical analysis, a Swedish study reported survival to hospital admission and one-month survival advantages in females (OR 1.66, 95% CI 1.49–1.84) and (OR 1.27, 95% CI 1.03–1.56) respectively (70). In contrast, studies in the USA and Europe (62,71,72) showed higher survival at hospital discharge in males. A study in Ontario suggested that females have a lower survival to hospital discharge than males (1.7% vs. 3.2%; OR 0.55, 95% CI 0.41–0.72) (60).

It is unknown whether the discrepancies in the results are because of differences in treatment provided for both sexes during OHCA, differences in study populations, differences in follow-up time, or are due to the biological effect of sex on survival. To date no systematic review or meta-analysis assessing the heterogeneity of the results of previous studies were identified. The independent and joint effects of sex on resuscitation outcomes are thus unclear. Moreover, while many sex differences in OHCA survival have been explored in different regions, studies examined the effect of sex on survival in BC, Canada are still scant.

In summary, the results from the previous studies addressing the association between sex and survival are contradictory, and very little is known about sex differences in survival to hospital discharge after OHCA in BC. Chapter 3 of this dissertation addressed these issues by comparing the survival rate, including ROSC and survival to hospital discharge, between males and females and examining the independent effect of sex on ROSC and survival to hospital discharge in a cohort of patients with OHCA in BC, Canada.

1.5 Sex differences in OHCA long term outcome

As mentioned above, previous studies examined the association between sex and survival from OHCA reported significant imbalance in baseline characteristics predictive of OHCA outcome with females having a lower proportion with witnessed arrest, bystander CPR, and initial shockable rhythms (60,62,63,67). Other observational studies revealed significant differences in prehospital treatments, with females less likely to receive bystander CPR and defibrillation (73), resuscitation interventions and medications (61,74), and less likely to be transported to hospital prior to achieving ROSC, compared to males (67).

Many previous analyses have demonstrated that, after adjustment for baseline characteristics and prehospital interventions, females had equal or higher probability of short-term survival (survival to hospital discharge or 30 days survival) compared to males (25,62,68,70,75). Most previous studies of sex-based disparities in OHCA outcomes adjusted for only prehospital cardiac arrest characteristics and treatment variables while largely neglecting comorbid conditions, leaving a possibly large proportion of variation in outcomes unexplained. Furthermore, these studies investigated short term survival, specifically survival to hospital discharge (62,70,71) and one-month survival (25,68,70). However, sex differences in long-term survival and survival beyond hospital discharge have not been widely explored. Therefore, it is not known whether survival time is shorter in one sex compared to another.

In 2016, Chan et al. (76) performed an analysis of data from the Cardiac Arrest Registry to Enhance Survival in the USA to look at predictors of one-year survival. The study included only adults 65 years or older with OHCA who were discharged alive from hospital and applied multivariable Cox proportional hazard to assess one-year mortality. The analysis included the following variables: age, sex, race, initial cardiac rhythm, arrest location, witnessed status, initiation of bystander CPR, application of an AED by EMS, hospital disposition at discharge (home self-care, home health care, nursing facility, inpatient rehabilitation, hospice, and other), and discharge neurological status. The investigators found no difference in long-term mortality (one-year) by sex (HR 1.03, CI 0.82–1.31, $p = 0.79$). Despite providing useful information about predictors of long-term survival, this study has two limitations. First, the study included only older population in their analysis. Second, the investigators did not include comorbidity and in-hospital treatment variables in their analysis. Including these variables might have produced different results.

Similar to the earlier study, Andrew et al.(77) used Cox regression analysis to investigate factors influencing long-term survival outcomes and reported that sex has no significant association with one-year survival. However, the investigators of this study included only prehospital predictors of survival and did not include in-hospital treatment variables in their analysis.

In summary, many of the previous studies of sex differences in OHCA survival outcomes investigated short term survival, including ROSC (29,35,78,79), one day survival (48), survival to hospital discharge (16,19,23,26,29,48,53,79,80), and one-month survival (20,22,25,79). Sex differences in long-term survival and survival beyond hospital discharge have not been widely explored. Two observational studies examined sex differences in OHCA long-term outcome (76,77). However, these studies did not adjust for important clinical variables in their analysis, such as comorbidities and in-hospital interventions. Chapter 4 of this dissertation research was designated to fill these gaps. The primary objective of Chapter 4 was to investigate sex differences in one-year survival in a cohort of patients who survived OHCA and who were discharged from hospital alive considering all possible confounders, including OHCA characteristics, in-hospital interventions, and comorbidities.

1.6 Neurological function after OHCA

The cessation of blood flow to the brain during cardiac arrest results in an oxygen-poor state that subsequently results in brain tissue damage. Following resuscitation and return of spontaneous circulation (ROSC), cardiac arrest victims are still at risk of neurological complications, including seizure, coma, and death (10). Providing cardiac arrest victims with prompt and optimal out-of-hospital intervention improves the probability of survival with good neurological function (13,22,43).

As an outcome variable, neurological function is assessed using either Cerebral Performance Category (CPC) or more commonly modified Rankin Scale (mRS). The CPC is a scale ranging from one to five, where one means good cerebral performance and five means death. The mRS is a scale from zero to six, where a scale of zero represents no neurological deficit and a scale of six means death (81).

Many observational studies have examined the predictors of survival with good neurological outcomes. In their analyses, most of these studies dealt with the neurological function as binary outcome variable, where a mRS of >3 indicates unfavourable neurological function, and a mRS of ≤3 indicates favourable neurologic function (21,90–92). These studies identified the contributors to poor neurological outcome as: older age, longer time to ROSC, unwitnessed arrest, initial rhythm being a non-shockable rhythm, arrest due to non-cardiac etiology, low Glasgow Coma Scale (GCS) at admission (21,82–84), high ammonia and lactate levels at admission (84), elevated Central Venous Pressure during ICU stay (83), and lower pH level (82). Martinell et al. (82) used data from the TTM trial (85) to study unconscious patients who survived OHCA of presumed cardiac cause and were admitted to ICU. This study identified ten independent predictors of a poor cerebral performance at six months from OHCA (six variables related to pre-hospital factors, and four variables related to patient status on ICU admission).

These include older age, arrest occurred at home, initial rhythm other than VF, longer duration of arrest without CPR, longer duration to ROSC, and administration of epinephrine. The other four predictors of poor outcome were related to status on ICU admission; these include: bilateral absence of corneal and pupillary reflexes, low GCS (patient not responding to painful stimuli), lower pH level and a partial pressure of CO_2 in arterial blood lower than 4.5 kPa. Ruknuddeen et al. (86) studied a similar target population and identified three variables as independent predictors of unfavorable neurological outcome: “status myoclonus within 24 h, absence of brainstem reflexes and motor response worse than flexion on day 3.” While they provided useful results, these studies dealt with GCS, $PaCO_2$, brainstem reflexes, and motor response as independent variables in their analysis. Clinically, poor pre-hospital resuscitation, non-shockable rhythm, and longer duration of CPR would lead to poor neurological outcome, including low GCS, absence of brainstem reflexes, and poor motor response. In other words, these variables (low GCS, absence of brainstem reflexes, and poor motor response) are clinical signs of poor neurological function or in fact they mean bad neurological function. Adding them as independent variables to the predictive analysis model may have therefore made the results of these studies subject to overadjustment bias and imprecision.

1.7 Effect of epinephrine on neurological outcomes

One of the important prehospital treatments that may influence the neurological outcome is the administration of epinephrine. Epinephrine is given during OHCA because of its two interactions: an interaction with alpha receptors that results in constriction of the vessels, which increases blood flow and return to the heart (87), and an interaction with beta-1 receptors in the heart that increases heart rate and contractility (88). Nevertheless, studies of the effectiveness of epinephrine on survival with good neurological function yielded contradictory results (89–93).

A prospective cohort study (90) and a population-based study (91) reported that in resuscitation of OHCA, administration of epinephrine was associated with decreased odds of favourable neurological outcome. A systematic review of RCTS that compared standard dose epinephrine with 1) placebo, 2) high dose epinephrine, 3) epinephrine with vasopressin in adults with OHCA, and 4) vasopressin, demonstrated no survival benefit or neurological outcome advantages in any groups (94). Another systematic review and meta-analysis of 14 observational studies examining the effect of prehospital epinephrine reported that administration of epinephrine was significantly associated with unfavourable neurologic function at hospital discharge (OR, 0.51, 0.31–0.84, $p = 0.008$) (92).

A recently published RCT by Perkins et al. (93) designed to determine if administration of epinephrine during OHCA is safe and effective. The trial found no significant difference in the proportion of patients who survived with favorable neurologic function between the epinephrine group [(87/4007) 2.2%] and placebo group [(74/3994) 1.9%] (unadjusted OR, 1.18; 95% CI, 0.86–1.61). The trial also reported the proportion of survivors with severe neurologic damage was higher in the epinephrine group than in the placebo group (31.0% vs. 17.8%).

To sum up, studies that focused on the effect of prehospital factors on survival with favourable neurological outcome are still relatively scant, and studies examining the effect of epinephrine on survival with good neurological function provided mixed evidence. Chapter 4 of this dissertation examined the effect of prehospital predictors of survival, including administration of epinephrine, on neurological function at hospital discharge in patients with OHCA.

1.8 Effect of sex and age on neurological outcome

As mentioned earlier, several studies have shown that pre-hospital interventions, including shorter time to initiate resuscitation, bystander CPR, witnesses status, initial shockable initial rhythm, and rapid defibrillation, are associated with survival with favourable neurological fuction (19,21,24). In addition to these pre-hospital variables, sex and age were found to have associations with survival. Younger age is associated with better survival outcomes (82,95). Female sex is associated with more ROSC (69–71). However, previous studies examining the effect of sex on survival to hospital discharge and one-month survival reported contradictory results (25,60,79,80). While some reported no significant difference by sex (64,79,96), other studies reported one-month survival and survival to hospital discharge advantages in females (25,70). In contrast, many other studies (62,71,72) reported higher survival to hospital discharge in males.

There could be an age-sex interaction effect on neurological outcome. This interaction may explain the discrepancies in the results of the studies of sex effect on survival. Several studies examined the interaction effect of age and sex on resuscitation outcomes (63,71,97,98). Recent studies found that younger females, particularly of premenopausal age, have a higher probability of survival to hospital discharge than males in the same age group (63,71,97,98).

Morrison et al. applied logistic regression model on data from ROC to assess the association between age and sex and survival. Morrison et al. reported that premenopausal females (15-45 years old) had 1.66 times higher adjusted odds of survival to hospital discharge compared to age-matched males (OR 1.66, 95% CI 1.04, 2.64), but there was no difference in the older group (females vs. males >55 years old) (63). Johnson et al. reported similar results (71). These results suggested that female sex hormones seemingly play a protective role in survival, and this role might explain this survival advantage in premenopausal females. Of note, these previous studies focused on survival to hospital discharge but paid no attention to neurological function. Moreover, Morrison et al. analyzed nested data but did not account for nested data structure (clustering) effects on their analyses. Not accounting for the effect of nested data structure often leads to inaccurate estimates of standard error of the parameters and leads to excessive type 1 error (99).

Two other studies that examined the interaction effect of age and sex on OHCA neurological outcome (97,100) reported conflicting results. While a prospective, population-based observational study conducted in Japan reported that younger females (13-49 years) had better outcome after OHCA compared to males in the same age group and compared to older females (97), a multicenter, registry-based study conducted in Korea found that younger female has no association with neurological outcome (100).

The primary objective of chapter 5 of this dissertation was to investigate the potential impact of premenopausal age on neurological function at hospital discharge in patients with OHCA.

1.9 Summary of background literature

Substantial efforts have been made to identify the predictors of survival after OHCA. The main independent variables found to be associated with improved resuscitation outcomes include younger age, time from arrest to resuscitation commencement; witnessed arrest; provision of bystander CPR; quality of CPR including chest compression rate, depth, and fraction; initial heart rhythm of VF or VT; and early defibrillation.

Research has shown that that there are sex-based disparities in the management of OHCA. It has been shown that females receive bystander-CPR less frequently than males, and longer intervals of EMS response time (from EMS dispatch to first rhythm capture and first EMS CPR). Previous studies have also demonstrated that females are less likely to receive successful intravenous or intraosseous access and are less likely to receive resuscitation medications including epinephrine, lidocaine, and amiodarone during OHCA resuscitation. Whether there is sex -based differences in other interventions measures, such as chest compression rate and the decision to initiate hospital transportation in patients with failed prehospital resuscitations is unknown.

Considerable endeavors have been made to understand sex differences in OHCA outcomes. Previous studies on sex differences in OHCA reported significant imbalance in baseline characteristics predictive of OHCA outcome with females having a lower proportion with witnessed arrest, bystander CPR, and initial shockable rhythms. However, after adjusting for these characteristics, previous observational studies in different regions examining the effect of sex on survival to hospital discharge have yielded contradictory results. While some reported no difference in hospital-discharge survival by sex, others have increased survival in females, and in other studies higher survival in males. Moreover, no study assessing the effect of sex on survival was conducted in BC, Canada. Furthermore, most of the previous studies of sex differences in OHCA survival outcomes investigated short term survival, including survival to hospital discharge and one-month survival. Sex differences in survival beyond hospital discharge have not been widely explored.

Many studies have examined the predictors of survival with good neurological outcomes after OHCA. These studies identified the contributors to poor neurological outcome as: older age, longer time to ROSC, unwitnessed arrest, initial rhythm being a non-shockable rhythm, arrest due to non-cardiac etiology, low Glasgow Coma Scale (GCS) at admission, high ammonia and lactate levels at admission, elevated Central Venous Pressure during ICU stay, and lower pH level. While they provided useful results, these studies dealt with GCS, PaCO2, brainstem reflexes, and motor response as independent variables in their analysis. Clinically, low GCS, absence of brainstem reflexes, and poor motor response are clinical signs of poor neurological function. Including them as independent variables to the predictive analysis model may have therefore made the results of these studies subject to over-adjustment bias. Additionally, little is known about the effect of sex on survival with favourable neurological outcomes.

One of the common prehospital treatments that may influence the neurological outcome is the administration of epinephrine. Studies examining the effect of epinephrine on neurological outcome have produced contradictory results. Some observational studies reported epinephrine was associated with unfavourable neurological outcome. A systematic review of RCTS that compared epinephrine with other medication and placebo showed epinephrine has no neurological outcome advantages. Another meta-analysis of observational studies reported that administration of epinephrine was significantly associated with unfavourable neurologic function at hospital discharge. A recently published RCT found no significant difference in the proportion of patients who survived with favorable neurologic function between the epinephrine group and placebo group.

It has been shown that younger age is associated with better survival outcomes. It has also been shown that female sex is associated with more ROSC. Some studies found that younger females, particularly of premenopausal age, have a higher probability of survival to hospital discharge than males in the same age group. These results suggested that female sex hormones play a protective role in survival, and this role might explain this survival advantage in premenopausal females. However, these studies examined the effect of age and sex on survival to hospital discharge but paid no attention to neurological function. Two other studies that examined the interaction effect of age and sex on OHCA neurological outcome. However, they reported conflicting results.

The summary above provided information on the treatment-related factors that influence OHCA outcomes. Social factors such as, living conditions (e.g., live alone), and physical factors such as, Body Mass Index (BMI), could have an impact on survival. However, data on these factors were limited.

1.10 Study objectives

The purpose of this dissertation research was to explore the effects of sex on OHCA resuscitation intervention and outcomes, including ROSC, survival to hospital discharge, favourable neurological outcomes at hospital discharge, and one-year survival. This dissertation consists of six chapters. Each chapter fulfilled one specific objective. The specific objectives were to:

1- Provide an overview of current knowledge of the predictors of survival in adults suffering OHCA in addition to the current knowledge of the effect of sex on survival (Chapter 1-Literature review).
2- Quantify and evaluate sex differences in the OHCA interventions in BC, Canada, specifically examining the provision of bystander CPR, chest compression rate of professional rescuers, and the decision to initiate hospital transportation prior to achieving ROSC.
3- Quantify and evaluate sex differences in achieving ROSC and survival to hospital discharge in a cohort of patients with OHCA in the metropolitan regions of the province of BC, Canada.
4- Investigate sex differences in one-year survival in a cohort of patients who survived OHCA and who were discharged from hospital alive.
5- Identify the statistically significant prehospital predictors of survival with good neurological function at hospital discharge after OHCA and evaluate the effect of sex on neurological outcome.
6- Investigate the potential impact of premenopausal age on neurological function at hospital discharge in patients with OHCA.

Chapter 2: Sex differences in out-of-hospital cardiac arrest interventions in British Columbia, Canada

2.1 Summary

OHCA is common among females and males alike; however, previous studies reported differences in outcomes between sexes in different regions. To investigate possible explanations for this disparity, this study examined sex differences in resuscitation interventions in the province of BC. The study specifically examined sex differences in the provision of bystander CPR, chest compression rate of professional rescuers, and the decision to initiate hospital transportation prior to achieving ROSC.

This was an observational analysis of the BC Cardiac Arrest Registry (2011-16). Adults with non-traumatic and EMS-treated OHCA were included. Sex differences in bystander CPR, chest compression rate, and intra-arrest transport were examined using chi-square tests, student's t-test, multivariable linear and logistic regressions.

In total, 7398 patients were eligible for the bystander CPR analysis; 31% were female. More males received bystander CPR (54% vs. 50%); however, male sex was not associated with bystander CPR after adjustment for confounders (adjusted OR male vs. female: 1.07, 95% CI 0.96 – 1.18). There was no difference in the chest compression rate for males and females in unadjusted or adjusted analyses. Among subjects who did not achieve prehospital ROSC (n=5225, 32% females), 64 % were pronounced dead at the scene with the remaining transported to hospital. Males more often underwent intra-arrest transport than females (36.7% vs. 34.0%).

After adjustment, males had 1.2 greater odds of being transported to hospital than females (95% CI 1.04 – 1.37).

2.2 Introduction

Sudden Out of Hospital Cardiac Arrest (OHCA) is one of the leading causes of death in the USA, Canada, and other countries (1–4). Approximately 400,000 sudden, unexpected cardiac arrests occur in the USA and Canada yearly (3,5,6). OHCA patients need immediate medical interventions. The two optimal intervention outcomes for these patients are first, the return of spontaneous circulation (ROSC) and second, survival to hospital discharge with minimal or no neurological complications. To achieve these goals, the AHA recommends specific guidelines for OHCA interventions (101,102). These guidelines include early, quality cardiopulmonary resuscitation (CPR), airway and breathing management, and defibrillation. Research shows that factors related to these interventions, such as providing high quality CPR and early defibrillation, improve survival (2,16,31,53). There is also evidence to suggest that sex may influence the outcomes of patients with OHCA.

Many researchers have compared OHCA resuscitation outcomes between males and females, however, they reported contradicting results (25,60,80,103). One possible explanation for this variation in survival rates between males and females with OHCA is that they do not receive similar optimal treatment, or they may receive similar treatment in one region but their access to these treatments varies in different regions.

The main objective of this study was to quantify and evaluate sex differences in the OHCA interventions in the province of BC, Canada, specifically examining the provision of bystander CPR, chest compression rate of professional rescuers, and the decision to initiate hospital transportation prior to achieving ROSC. The study hypothesis was that in BC, males receive higher chest compression rates, more bystander CPR, and are more likely to be transported to hospital prior to ROSC.

2.3 Methods

2.3.1 Design and setting

We analyzed data from one center of the Resuscitation Outcomes Consortium (ROC) multicenter study. The ROC is a network of 11 regional clinical centers, with eight in the USA and three in Canada (Ottawa, Toronto, and BC), and a data coordinating center (104). The ROC conducts clinical trials and observational studies that focus on prehospital treatment of OHCA. The ROC Cardiac Arrest Epistry was designed as a population-based registry of data collected on all EMS-attended OHCA cases occurring in the 11 ROC geographical regions (105). The data used for this study was collected by the Resuscitation Outcomes Consortium (ROC) BC regional center (Core BC ROC). These data were prospectively collected between 2011 and 2016 on 8,328 EMS-attended OHCA patients in BC (105).

2.3.2 Study population

An analytic dataset was created from the Core BC ROC database. The analytic dataset included all adult males and females 18 years and older who suffered non-traumatic OHCA and were treated by EMS. Patients < 18 years, patients for whom sex was not recorded, patients with traumatic arrest, patients with “do not resuscitate” orders, and those pronounced dead on EMS arrival were excluded.

2.3.3 Key variables of interest and definitions

The key independent variable of interest was sex, recorded as male or female. The outcome variables of interest were provision of bystander CPR, chest compression rate, and the decision to initiate hospital transportation prior to ROSC. Data definitions are based on the literature and Utstein definitions (105,106). Specifically, bystander CPR is defined as CPR performed by a layperson before the EMS arrival. Chest compression rate is defined as the number of compressions performed per minute during CPR. Data on chest compression rate were obtained from the defibrillator pads, which monitor changes in thoracic impedance (50). Decision to initiate hospital transportation prior to ROSC applies for those EMS-treated OHCA patients who did not achieve ROSC in the field. Among those patients, if they were transported to hospital with ongoing CPR, this factor would be coded as ‘yes’, and those who never achieved ROSC and were not transported to hospital, but their resuscitation was terminated at the scene would be coded as ‘no’.

2.3.4 Statistical analysis

First, we calculated summary statistics for each baseline characteristic. We summarized continuous variables using mean and standard deviation or median and interquartile range, based on the distribution, and categorical variables using counts and percentages. Second, we performed bivariate analyses using Student’s t test for continuous variables and Chi square test for categorical variables to examine the association between baseline characteristics and sex.

Specifically, we used Chi-square tests to compare provision of bystander CPR and decision to initiate hospital transportation between males and females. We employed Student's t test to compare the chest compression rate between males and females. Both the Chi-square and t-test were assessed at 5% level of significance, using a two-sided test. Further, we calculated the proportion of patients who received CCR rates between 95 and 125 compressions/minute, (CCR recommended by the AHA) (44). For the variable missing more than 5% of data, CCR in particular, the Missing Completely at Random (MCAR) test was conducted to determine whether the data was missing at random. Third, we applied multivariable logistic regression (for binary outcome – provision of bystander CPR and decision to initiate hospital transportation) and ordinary least square regression analyses (for the continuous outcome variable – chest compression rate) with sex as the independent variable to further examine the relationship between sex and the outcomes of interest. Provision of bystander CPR analysis was conducted for all cohort and reconducted again for the subgroup of cohort who arrested in public location. All multivariable regression analyses controlled for all possible confounders including age, location of arrest, witness status, and initial cardiac rhythm. We tested two interaction terms (age X sex and witnessed status X bystander CPR) in all the regression models. The interaction was not included in the model if it was not statistically significant. We tested the models by inspecting the Normal Probability Plot of the Regression Standardized Residual and Residual Scatterplot ensured no violation of the regression assumptions of normality, linearity, and homoscedasticity (107). We also examined multicollinearity by calculating the Variance Inflation Factor (VIF) (108,109). All analyses were performed using IBM SPSS version 24, Armonk, NY.

2.3.5 Ethics approval

This study was approved by The University of British Columbia - Providence Health Care Research Ethics Board.

2.4 Results

2.4.1 Baseline and clinical characteristics for males and females

In total 8328 cases met the inclusion criteria. Of those, 213 (2.55%) were omitted (deleted list wise) due to missing data on one or more of the key variables (Figure 2.1). The analytic dataset included 8115 adult patients with non-traumatic OHCA (Figure 2.1). The mean age of the study cohort was 66.57 (17.17 SD). Of the total, 5566 (68.6%) were males and 1430 (17.6%) arrested in public locations. Table 2.1 shows the summary statistics for the study variables, overall and stratified by sex. When comparing the males to the females, the unadjusted analyses showed that males were significantly younger than females (mean age: 64.59 vs.67.75, $p < 0.001$). The males had a higher proportion of OHCA occurring in public locations (21.2% vs. 9.7%, $p < 0.001$), a higher proportion of bystander witnessed arrest (41% vs. 35.2%, $p < 0.001$), and a higher proportion of shockable rhythm as an initial cardiac arrest rhythm (29.2% vs. 14.5%, $p < 0.001$), compared to females. No significant differences were detected between the sexes regarding time interval from dispatch to EMS arrival (6 minutes or less) (45.9% vs. 47.6%, $p = 0.078$) and ROSC (38.9% vs. 38.3%, $p = 0.287$) in males and females respectively (Table 2.1).

2.4.2 Study outcome variables

2.4.2.1 Provision of bystander CPR

Of the 8115 adults with OHCA who were included in the analytic dataset, 717 OHCA cases were witnessed by EMS; thus, they were not eligible for bystander CPR and therefore they were excluded from the bystander analyses (Figure 2.1). Among the remaining 7398 patients included in the bystander CPR analysis 5126 were males (69.3%) and 2272 (30.7%) were females. Baseline characteristics for this group were very similar to the overall analytic data set. When comparing the males to the females, the unadjusted analysis showed that the males had a significantly higher proportion of bystander CPR than the females (54.5% vs. 49.8%, $p < 0.001$) (Table 2.2). The crude odds ratio for the provision of bystander CPR in males compared to females was (1.2, 95% CI 1.08 – 1.32)
Table 2.3).

Prior to conducting the logistic regression analysis, we examined multicollinearity by calculating the variance inflation factor (VIF). No VIF values exceeded 2.0 indicating no significant multicollinearity among independent variables (109). After controlling for all possible confounders, as detailed in Table 2.3, multivariable logistic regression analysis showed that the odds of receiving bystander CPR did not differ by sex, (adjusted OR male vs female: 1.07, 95% CI 0.96 – 1.18, $p = 0.21$).

We used forward variable selection technique to assess which variable attenuated the original difference. We entered sex at Step 1. We added age, bystander CPR, bystander witnessed, and public location one by one to the model. The final model included sex, age, bystander witnessed, and public location. The forward selection procedure showed that after adding the variable "public location of arrest" the association between sex and bystander CPR was no longer significant (Table 2.4). All the predictors in the final model, except sex, made a unique statistically significant contribution to the model. The strongest predictors of provision of bystander CPR were public location of arrest and bystander witnessed arrest, with ORs of 1.83 and 1.80 respectively.

We conducted multivariable logistic regression analysis again for the subgroup who arrested in a public location: N =1430, 1182 (82.6%) males vs. 248 (17.4%) females. Within this group, bystander CPR was performed in 68.3% of males and 65.8% of females. The analysis showed that sex was not associated with provision of bystander CPR for those who arrested in public locations (OR 1.09, 95% CI 0.80 - 1.48, p = 0.59), controlling for age and witness status.

2.4.2.2 Chest compression rate

Of the 8115 adults with OHCA who were included in the analytic dataset, 1154 (14.2%) patients had no data on chest compression rate. We ran The Missing Completely at Random *(*MCAR) test to determine whether the data was missing at random. The null hypothesis was that the data are missing completely at random. Based on the result, X^2 (2) = 0.291, p = 0.86, we failed to reject the null hypothesis and concluded that the data were missing completely at random.

Of the 6961 adult patients with OHCA and chest compression data (Figure 2.1), we explored sex differences in chest compression rates. Of those, 4807 (69.1%) were males and 2154 (30.9%) were females. Chest compression rates were approximately normally distributed for the entire cohort and for both males and female subgroups. Chest compression rates ranged from 36 to 157 compressions/min, with a mean of 110.69 and SD of 10.02. Of the total cohort, 90% received a compression rate between 95 and 125 compressions/minute (male vs. female 89.7% vs. 89.9%, $p = 0.4$). The variances were equal across the two sex groups (Levene's test, $p = 0.61$). When comparing the males to the females, the Student's t test result showed no significant differences in the chest compression rates for males (M = 110.865, SD = 9.98) and females (M = 110.689, SD = 10.0; $p = 0.98$) (Table 2.2). The crude *beta coefficient* for the chest compassions rate in males compared to females was (0.004, $p = 0.98$). This means that that the chest compression rate is predicted to be 0.004 compression per minute higher in males than in females, but this difference was not significant.

Prior to conducting multivariable analyses, we assessed variables to ensure no violation of the linear regression assumptions. We assessed multicollinearity by calculating VIF. No VIF values exceeded 1.08 indicating no significant multicollinearity among independent variables (22). Were checked for normality, linearity, and independence of residuals assumptions by inspecting the Normal Probability Plot of the Regression Standardized Residual and scatterplot. In the Normal P-P Plot, all points were in a reasonably straight diagonal line suggesting no major deviations from normality. In the Scatterplot of the standardised residuals, the residuals appeared roughly rectangular in distribution, with most of the scores concentrated in the centre suggesting no violation of the assumptions (107). In multivariable analyses, after adjusting for all variables known to influence chest compression rate, including age, public location, EMS witnessed status, dispatch to EMS time interval, and administration of epinephrine, there was no significant difference by sex (*beta coefficient* 'male vs female' = – 0.76, p = 0.77). This result suggests that the chest compression rates were similar in males and females.

2.4.2.3 Initiation of hospital transportation prior to ROSC

Of the 8115 adults with OHCA who were included in the analytic dataset, 2890 patients had successful resuscitation (achieved prehospital ROSC and were transported to hospital); thus, they were excluded from analyses that evaluated the initiation of hospital transport prior to ROSC. The remaining 5225 patients did not achieve ROSC prehospital (either they had resuscitation stopped and were pronounced dead at the scene or a decision was made to transport them to hospital with ongoing resuscitation).

We conducted a subgroup analysis on this sub-cohort (N= 5225) (Figure 2.1). Of those, 3558 (68.1%) were males and 1667 (31.9%) were females; 3353 (64.2%) were pronounced dead at the scene and 1872 (35.8%) were transported to hospital. The proportion of the males who were transferred to hospital prior to ROSC was significantly higher compared to the females (36.7% vs. 34.0%,) X^2 (1, N = 5225) = 3.506, p = 0.03 (Table 2.2). This result suggests that the decision to initiate hospital transport for those not achieving ROSC prehospital occurred more frequently in males than females. Prior to conducting the logistic regression analysis, we examined multicollinearity by calculating the VIF. The maximum VIF values were 3.2 indicating no significant multicollinearity among independent variables (109) . We used logistic regression analysis to estimate the adjusted odds of hospital transportation prior to ROSC for males relative to females. The results showed that, after adjustment, males had 1.19 times greater odds of being transported to hospital with ongoing resuscitation than females (adjusted OR 1.19, 95% CI 1.04 – 1.37, p = 0.01). A theory guided approach was used as a model building strategy (110). The model adjusted for all variables known to be associated with the outcome including age, public location, initial rhythm, and witnessed status.

2.5 Discussion

We examined approximately 8000 adults with non-traumatic OHCA from the BC cardiac arrest registry and investigated sex differences in three prehospital interventions: provision of bystander CPR, chest compression rate, and decision to initiate hospital transportation prior to ROSC. The results demonstrated that overall in BC there were no significant sex differences in bystander CPR or in mean chest compression rates by professional rescuers; However, among those who did not achieve prehospital ROSC, males had approximately 1.2 greater odds of being transported to hospital prior to ROSC compared to females.

Interestingly, while bystander CPR was more common in male sex in crude analysis, the forward variable selection procedure showed that only after adjustment for location type (public vs. private), sex was no longer significant. This suggests that the likelihood of bystander CPR may be less related to sex itself, but more related to differences in the locations at which male or female cases may have a cardiac arrest. Further research is required in this area.

Studies conducted in the USA, Europe, South Korea, and Australia reported a higher proportion of bystander CPR in males than females with OHCA; however, these results were not adjusted for other arrest characteristics (25,61,117,69,72,111–116). More recently, Blewer et al. (116) conducted a comparable study in multiple sites in the USA and reported that provision of bystander CPR in public is significantly higher in males compared to females (adjusted OR, 1.27; 95% CI, 1.05–1.53). Blewer et al. controlled for similar baseline characteristics as this BC study. One possible explanation for the difference in the results may be differences in the socioeconomic characteristics, which have been previously reported (118,119).

Regarding the CCR, our analyses did not demonstrate a difference in the mean chest compression rate or the proportion that had a compression rate in the recommended range when dichotomized by sex. The AHA guidelines for the management of cardiac arrest recommend providing chest compression at a rate of 100-120 compressions per minute (44). A CCR of 100 to 120 is associated with improved survival (16,50). Our descriptive and inferential statistics related to CCR suggest that EMS personnel in BC are closely adhering to the AHA guideline for OHCA CCR for both males and females.

In our investigation of hospital transport for those who remained in refractory arrest after on-scene efforts, we found that female cases were more likely to be declared dead at the scene of the arrest. After adjustment, male cases had almost 1.2-fold greater odds of being transported to the hospital with ongoing resuscitation. Whereas previous studies have identified criteria by which prehospital termination of resuscitation by EMS may be appropriate (120–122), these are not included in BC protocols (123).

Conversely, transport to hospital with ongoing resuscitative efforts is uncommon, with full resuscitations typically taking place at the scene of the arrest unless a reversible cause is identified that may be amenable to hospital-based care (123). It is unclear whether our findings represent gender-based inequities in the intensity of care provided. Alternatively, the characteristics of male cases (a higher percentage of males with witnessed arrest and shockable rhythms) may have been more likely to suggest an arrest etiology that was amendable to hospital-based treatment. Further, systematic differences in cardiac arrest location between sexes may have included males arresting in areas closer to a hospital, or in buildings with less difficult extrication processes, both of which may have made intra-arrest transport more feasible. Further research exploring the reasons for such a difference is required.

While sex differences in transportation to hospital before achieving ROSC remained significant after adjustment, the absolute difference was only 2.7% (male vs. female 36.7% vs. 34%). A prior study reported that survival to hospital discharge for patients who did not achieve prehospital ROSC is 3.6% (124). A recent study in BC reported the termination of resuscitation (TOR) guide applied at 6 minutes of resuscitation falsely recommended termination of resuscitation for 2.1% of patients (125). If we assume that the 2.7% additional females and 2.1% additional males and females, who could have been transported to hospital, had a similar 3.6% survival rate, the result would be approximately 1% additional survival. We consider this statistically and clinically important given that the overall OHCA survival to hospital discharge rate in BC is 14% (126). Our findings suggest that sex differences in decisions to initiate hospital transportation prior to ROSC should be further explored and the associations between transportation and survival should be further examined.

2.6 Limitations

This study has several limitations. First, the analyses were limited to data in the BC ROC dataset. The results may not be generalizable to other North American geographic areas. Second, the R^2 values for the models were low, suggesting that variability in outcomes is largely explained by other variables. Third, data on some variables, such as ethnicity and duration of resuscitation, were incomplete in the dataset and therefore not included in the analyses. If 'duration of resuscitation' in particular was adjusted for in the transportation to hospital prior to ROSC model, the results may have been different. Finally, the data set had limited information on the patient cohort. For example, pre-existing comorbid conditions which may have affected the results.

2.7 Conclusion

This study evaluated sex differences in the OHCA interventions in BC, Canada. Provision of bystander CPR, chest compression rate, and decision to initiate hospital transportation prior to ROSC were examined. The results showed that male and female patients with OHCA in BC receive the same chest compression rate and are equally likely to receive bystander CPR if they arrest in a public location. However, it is important to note the females are significantly less likely to arrest in a public location. In those who did not achieve prehospital ROSC (failed prehospital resuscitation), males are 1.2 greater odds of being transported to hospital prior to ROSC compared to females. The reason for this difference should be further explored. BC EMS professionals training should address the sex differences in the decision to initiate hospital transportation prior to prehospital ROSC.

Figure 2.1: Study flow diagram

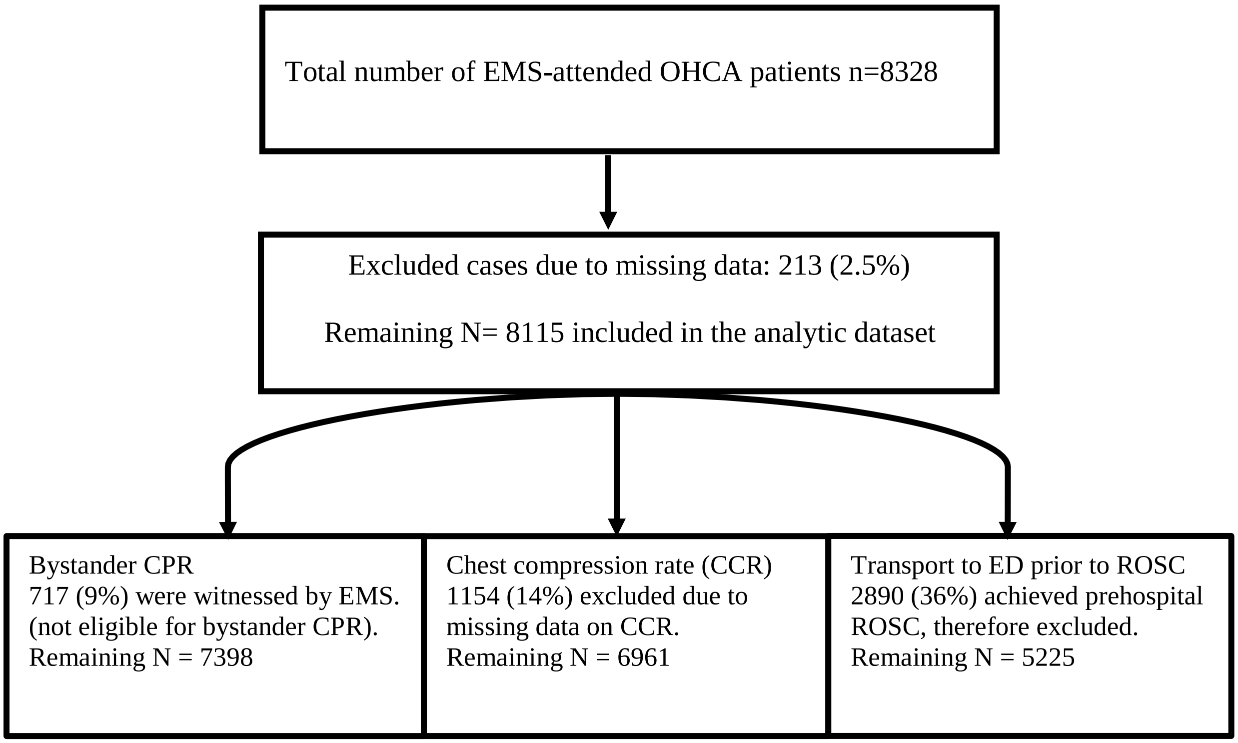

Table 2.1: Baseline characteristics stratified by sex

Variables	Total N=8115	Males n = 5566 (68.6)	Females n= 2549 (31.4%)	P value
Age (Mean ± SD)	66.57 ± 17.7	64.59 ± 17.3	67.75 ± 18.5	< 0.001
Location of arrest				
Nonpublic	6685 (82.4%)	4384 (78.7%)	2301 (90.3%)	< 0.001
Public	1430 (17.6%)	1182 (21.2%)	248 (9.7%)	
Dispatch to EMS arrival				
6 min or less	3769 (46.4%)	2555 (45.9%)	1214 (47.6%)	0.078
More than 6 min	4346 (53.6%)	3011 (54.1%)	1335 (52.4.%)	
Witness Status				
Unwitnessed	4108 (50.6%)	2761 (49.6%)	1374 (52.8%)	
Bystander witnessed	3179 (39.2%)	2281 (41.0%)	898 (35.2%)	< 0.001
EMS witnessed	828 (10.2%)	524 (9.4%)	304 (11.9%)	
Bystander CPR status				
No CPR	3456 (42.6%)	1132 (44.4%)	2324 (41.8%)	
Bystander CPR	3831 (47.2%)	1113 (43.7%)	2718 (48.8%)	< 0.001
EMS witnessed arrest	828 (10.2%)	304 (11.9%)	524 (9.4%)	
Initial rhythm				
Non-shockable	6117 (75.4%)	3938 (70.8%)	2179 (85.5%)	<0.001
Shockable	1998 (24.6%)	1628 (29.2.5%)	307 (14.5%)	
Administration of epinephrine	6097 (75.0%)	4257 (76.5%)	1840 (72.2%)	<0.001
Outcomes				
ROSC	3142 (38.7%)	2167 (38.9%)	975 (38.3%)	0.287
Alive at hospital discharge	1184 (14.6%)	899 (16.2%)	285 (11.2%)	<0.001

Table 2.2: Unadjusted comparisons of study outcomes between males and females

Study outcome variable	Total N	Males (n/mean)	Females (n/mean)	*P* value
Provision of bystander CPR	N=7398	5126 (69.3%)	2272 (30.7%)	
Bystander CPR	3912 (52.9%)	2781 (54.5%)	1131 (49.8%)	< 0.001
No Bystander CPR	3486 (47.1%)	2345 (45.7%)	1141 (50.2%)	
Chest compression rate/minute	N= 6961	4807 (69.1%)	2154 (30.9%)	0.98
	110.69 ± 10.02	110.87 ± 9.98	110.69 ± 10.0	
Failed prehospital resuscitation	N= 5225	3558 (68.1%)	1667 (31.9%)	
Decision to initiate transport	1872 (35.8%)	1305 (36.7%)	567 (34.0%)	0.03
Resuscitation stopped at scene	3353 (64.2%)	2253 (63.3%)	1100 (66.0%)	

Table 2.3: Effect of sex on the odds of bystander CPR (N=7398).

Variables	ß	OR	(95% CI)	*P* value
Unadjusted				
Male sex	1.80	1.20	1.08 – 1.32	< 0.001
Adjusted				
Male sex	0.06	1.07	0.96 – 1.18	0.21
Age (per year)	-0.01	0.99	0.98 – 0.99	< 0.001
Bystander witnessed	0.55	1.83	1.66 – 2.00	< 0.001
Public location	0.58	1.80	1.57 – 2.04	< 0.001

Odds ratio for age*sex interaction was not significant and did not improve the model, therefore, it was not included as a covariate in the model.

Table 2.4: Changes in the OR (male vs female) of bystander CPR after adding predictors to the model (N=7398)

Model	Variables in the model	OR (male vs female)	(95% CI)
Model 1	**Sex**	1.20	1.08 – 1.32
Model 2	**Sex and age**	1.17	1.06 – 1.30
Model 3	**Sex, age, bystander witness**	1.13	1.02 – 1.25
Model 4	**Sex, age, bystander witness, public location**	1.07	0.96 – 1.18

Table 2.5: Effect of sex on prehospital chest compression rate (N= 6961)

Variables	ß	SE	(95% CI)	*P* value
<u>Unadjusted</u>				
Male sex	0.004	0.26	-0.51 – 0.51	0.98
<u>Adjusted</u>				
Male sex	-0.76	0.26	-0.59 – 0.44	0.77
Age (per year)	-0.10	0.01	-0.27 – 0.001	0.06
Public location	1.07	0.33	0.62 – 1.92	< 0.001
EMS witnessed	-0.10	0.13	-0.35 – 0.15	0.44
Dispatch to EMS arrival	0.27	0.25	-0.21 – 0.75	0.26
Epinephrine administration	-1.60	0.30	-2.90 – -1.0	< 0.001

B coefficients for public location*bystander CPR and age*sex interactions were not significant and did not improve the model, therefore, they were not included in the model.

Table 2.6: Effect of sex on hospital transport prior to ROSC (N = 5225)

Variables	ß	OR	(95% CI)	*P* value
Male sex	0.18	1.19	1.04 – 1.37	0.01
Age (per year)	-0.12	0.99	0.98 – 0.99	< 0.001
Public location	0.96	2.61	2.19 – 3.11	< 0.001
Shockable initial rhythm	1.12	3.05	2.60 – 3.59	< 0.001
Bystander witnessed	1.04	2.84[1]	2.45 – 3.27[1]	< 0.001
EMS witnessed	2.28	9.77[2]	7.77 – 12.28[2]	< 0.001

[1]Estimated odds ratio of hospital transportation prior to ROSC with bystander witnessed arrest relative to unwitnessed arrest.
[2] Estimated odds ratio of hospital transportation prior to ROSC with EMS witnessed arrest relative to unwitnessed arrest.
Odds ratios for bystander CPR X sex and age X sex interaction were not significant and did not improve the model, therefore, they were not included in the model.

Chapter 3: Sex differences in short-term survival in patients with out-of-hospital cardiac arrest in British Columbia, Canada

3.1 Summary

Sudden OHCA is one of the leading causes of death in the USA and other countries. Providing cardiac arrest victims with prompt and optimal out-of-hospital resuscitation is essential for survival. OHCA is common among females and males; however, previous data showed differences in survival outcomes between sexes in different regions. The objective of this study was to quantify and evaluate sex differences in achieving ROSC and survival to hospital discharge in a cohort of patients with OHCA in the metropolitan regions of BC.

This was an observational, retrospective analysis of data that were prospectively collected by the Core BC ROC between 2011 and 2016 on OHCA patients. The study included all adult males and females 18 years and older who suffered non-traumatic OHCA and were treated by EMS in BC. Chi-square tests were used to compare survival to hospital discharge and ROSC between males and females. Multivariable logistic regression analyses were employed to further examine the association between sex and outcomes of interest (ROSC and survival to hospital discharge). The logistic regression analyses were adjusted for standard Utstein variables known to be associated with improved survival.

In total, 8115 patients were included in the analysis; 31.4% were females. Compared to males, females had a lower proportion of OHCA in public locations (9.7% vs. 21.2%, $p < 0.001$), bystander witnessed arrests (35.2% vs. 41%, $p < 0.001$), and with initial shockable rhythms

(14.5% vs. 29.2%, $p < 0.001$). Survival was 11.2% and 16.2% among females and males respectively ($p < 0.001$). Among those with return of spontaneous circulation (ROSC), females had a lower proportion of survival to hospital discharge (29% vs 41%, $p < 0.001$).

The crude odds of achieving ROSC was lower in females, but this difference was not significant (OR 0.98, 95% CI 0.89 – 1.08, $p = 0.65$). After adjustment for Utstein variables known to be associated with improved survival, the adjusted odds of achieving ROSC in females were 1.29 times greater than in males. Despite this advantage of ROSC in females, after adjustment, survival to hospital discharge was not significantly different by sex (adjusted OR 1.14, 95% CI 0.96 – 1.35, $p = 0.129$). Among all Utstein variables, 'initial shockable rhythm' was the variable most strongly associated with survival to discharge (OR 8.3, 95% CI 7.10 – 9.75, $p < 0.001$). The lower proportion of females with an initial shockable rhythm thus contributes to the lower crude survival to hospital discharge in females. Other reasons for the observed difference in the crude ROSC and survival to hospital discharge rates should be further explored.

3.2 Background

Sudden unexpected OHCA is one of the leading 'causes' of death in the USA and other countries (1,4). Providing cardiac arrest victims with prompt and optimal out-of-hospital intervention improves the probability of return of spontaneous circulation (ROSC) and survival with good neurological function (13,22,43). Several OHCA characteristics and interventions were found to be associated with outcomes including ROSC, survival to hospital discharge. These include smaller interval from arrest to commencement of CPR; witnessed arrest; provision of bystander CPR; quality of CPR; initial cardiac rhythm; and early defibrillation (2,15,18,22,43).

In addition to OHCA characteristics and treatment-related factors, patient-related factors, such as sex, may influence survival. Previous research has shown that there are sex-based disparities in the characteristics, intervention and outcome of OHCA (25,60,61,68,80). Most of the previous univariable analyses comparing OHCA characteristics between males and females reported that females are significantly older than males; had a lower proportion with an initial shockable rhythm, a lower proportion of arrest occurring in public location, and were less likely to receive bystander CPR (25,60,62–64). However, after adjusting for these characteristics, previous studies conducted in different countries reported contradictory results (25,60,80). Studies conducted in Japan and Switzerland reported that males and females have similar likelihoods of survival (64,96,103). A recent study in New Zealand reported no significant difference in one-month survival (68). Swedish studies reported one-month survival and survival at hospital discharge advantages in females (25,70). In contrast, studies in the USA and Europe (62,71,72) showed higher survival at hospital discharge in males.

The primary objective of this study was to evaluate and quantify sex differences in achieving ROSC and survival to hospital discharge in a cohort of patients with OHCA in the metropolitan regions of BC, Canada.

3.3 Methods

3.3.1 Design and setting

This study examined prospectively collected data from the BC site of the ROC BC Cardiac Arrest Epistry database (105). The data were collected between 2011 and 2016 in the metropolitan regions of BC, an area of approximately 2.5 million inhabitants (127). The database includes information on patient demographics, EMS scene arrival times, arrest location, bystander CPR, initial cardiac rhythm, EMS treatments, ROSC, and patients' status at hospital discharge (105).

Prehospital medical care for OHCA in BC is a coordinated effort between the provincial BC Emergency Health Services (BCEHS) and municipal fire departments. Fire department first responders are trained in basic cardiopulmonary life support, including automated external defibrillator application. BCEHS units have either advanced life support or basic life support designations. BCEHS provides medical care for the entire province of BC, with centralized leadership and guidelines (128).

3.3.2 Study population

We created an analytic dataset from the BC ROC registry. The analytic dataset included all adult males and females 18 years and older who suffered non-traumatic OHCA and were treated by EMS. Patients < 18 years, patients for whom sex was not recorded, patients with traumatic arrest, patients with "do not resuscitate" orders, and those pronounced dead on EMS arrival were excluded.

3.3.3 Key variables of interests and definitions

The independent variable of interest was sex (female and male). The primary and secondary outcomes of interest are survival to hospital discharge and ROSC, respectively. Based on the standardized Utstein definitions (106), ROSC is defined as the restoration of a spontaneous perfusing rhythm that results in a palpable pulse for any length of time. Survival to hospital discharge describes OHCA patients who were discharged from hospital alive. The level of measurement for the two outcomes of interest is binary (yes or no).

3.3.4 Statistical analysis

We calculated summary descriptive statistics for each baseline characteristic for the full cohort and stratified by sex. Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized using counts and percentages. We used Student's t-test (for continuous variables) and Chi-Square test (for categorical variables) to compare the baseline characteristics and outcomes by sex. We examined the full cohort and among those who achieved ROSC. We used Chi-square test to examine whether there are significant association between sex and each of the outcome measures. This was followed by multivariable stepwise logistic regression analyses using sex as an independent variable and the outcomes of interest (ROSC and survival to hospital discharge) as dependent variables. We entered "sex" in step 1, and then we used forward and backward variable selection techniques. We evaluated changes in R^2 and Hosmer-Lemeshow tests in each step. In the 'survival to hospital discharge,' we conducted the logistic regression analysis for the whole cohort and conducted the analysis again for the subgroup of the cohort who were transported to hospital (i.e., were not pronounced dead at the scene). The analyses included Utstein variables known to be associated with improved survival, including age, location of arrest, witness and bystander CPR, EMS call-to-arrival interval, and initial cardiac rhythm (129). Prior to multivariable analyses, we examined multicollinearity by calculating the variance inflation factor (VIF); we considered VIF under 2.0 as no evidence of multicollinearity (109). We tested an interaction term (age X sex) to include in the models if statistically significant. All analyses were performed using IBM SPSS version 26, Armonk, NY.

3.3.5 Ethics approval

This study was approved by The University of British Columbia - Providence Health Care Research Ethics Board.

3.4 Results

3.4.1 Baseline characteristics and univariate analysis

In total, 8328 cases met the inclusion criteria. Of those, 213 (2.6%) were excluded due to missing data on one or more of the key variables (Figure 3.1). The analytic dataset, therefore, included 8115 adult patients with OHCA. There were 2549 (31.4%) females and 5566 (68.6%) males. The summary statistics stratified by sex are shown in (Table 3.1). The mean age of females was significantly higher than the males (68 vs. 65 years, $p < 0.001$). Among females, there was a lower proportion of OHCA in public locations (9.7% vs. 21.2%, $p < 0.001$), a lower proportion of bystander witnessed arrest (35.2% vs. 41%, $p < 0.001$), and a lower proportion with an initial shockable rhythm (14.5% vs. 29.2%, $p < 0.001$). No significant differences were detected between the two groups regarding the time interval from EMS dispatch to scene arrival. With regards to the outcomes of interest, no significant difference was observed for ROSC (38.3% vs. 38.9%, $p = 0.29$); however, survival to hospital discharge was significantly lower in females (11.2% vs. 16.2%, $p < 0.001$). Among those successfully resuscitated (achieved ROSC), females had a significantly lower survival to hospital discharge (29% [285/975] vs. 41% [899/2167], $p < 0.001$).

3.4.2 Multivariable logistic regression analyses

3.4.2.1 ROSC

Overall, 3142 (38.7%) patients in the cohort (N 8115) achieved ROSC. The proportion of females who achieved ROSC compared to males was 38.3% vs. 38.9% ($p = 0.29$). The crude odds ratio for the ROSC in females compared to males was not significant (OR 0.98, 95% CI 0.89 – 1.08, $p = 0.65$). However, after adjustment, females had significantly greater odds of ROSC than males (OR 1.29, 95% CI 1.16 – 1.43, $p < 0.001$) (Table 3.2). No VIF exceeded 2.0, indicating the absence of multicollinearity assumption was met (109). The interaction term (age X sex) was not statistically significant and did not improve the model; therefore, it was not included in the model. All the predictors made an independent, statistically significant contribution to the model. The strongest predictor was the initial shockable rhythm, followed by EMS-witnessed arrest (Table 3.2).

3.4.3 Survival to hospital discharge

Overall, 1184 (14.6%) patients in the cohort (N 8115) survived to hospital discharge. The survival among female and male cases was 285/2549 (11.2%) and 899/5566 (16.2%), respectively ($p < 0.001$). The crude OR for the survival to hospital discharge in females compared to males, therefore, disadvantaged females (0.65, 95% CI 0.57 – 0.75, $p < 0.001$). However, after adjusting for all Utstein variables, multivariable logistic regression analysis showed that the difference in survival to hospital discharge was no longer significant (OR 1.14, 95% CI 0.96 – 1.35, $p = 0.129$) (Table 3.3). The final model included sex, age, public location, witnessed status, CPR status, shockable rhythm, and EMS arrival time. The chi-square value for the model's Hosmer-Lemeshow test was 5.53, with a significance level greater than 0.05 ($p =$

0.70), suggesting that the model fits the data well (130). No VIF exceeded 2.0, indicating the absence of multicollinearity assumption was met (109). The interaction term (age X sex) was not statistically significant and did not improve the model; therefore, it was not included in the model. All the predictors, except sex, made an independent, statistically significant contribution to the model. After full model adjustment, we did not detect an association of female sex with survival to hospital discharge (OR 1.14, 95% CI 0.96 – 1.35, $p = 0.129$). The two factors most strongly associated with survival to discharge were shockable rhythm and -witnessed arrest (Table 3.3).

Table 3.4 shows results of the stepwise variable selection procedure; age and public location contributed slightly to attenuating the original (crude) sex differences in survival to hospital discharge (crude OR Females vs. Males 0.65, 95% CI 0.57 – 0.75, $p < 0.001$). However, the association between sex and survival to hospital discharge remained statistically significant in all forward and backward variable selection steps until 'initial shockable rhythm' was added to the model. After adjusting for 'initial shockable rhythm,' the association was no longer significant.

3.4.4 Subgroup analysis survival to hospital discharge for the patients who arrived in hospital

Of the total cohort (N = 8115), 4083 (50%) were transported to hospital including 48% of the females and 51% of the males in the cohort (Table 3.1). Unadjusted analysis of this subgroup showed that female sex was associated with a lower probability of survival to hospital discharge (crude OR 0.65, 95% CI 0.54 – 0.77, $p < 0.001$). After adjustment, this association was no longer detected (OR 1.04, 95% CI 0.89 – 1.20, $p = 0.66$) (Table 3.5). Table 3.6 shows the results of the stepwise variable selection procedure, which demonstrated similar results to that of the overall cohort analysis.

3.5 Discussion

We examined EMS-treated OHCAs over six years from the metropolitan regions in BC treated by a single EMS system. We found that females and males had substantial differences in baseline characteristics predictive of OHCA outcomes. While crude survival was significantly lower in females, after adjustment of case characteristics, sex was no longer associated with survival. Of note, these results were based on an adjusted effect, and the effect of sex likely incorporates gender, which we could not explicitly measure. These results suggest that methods to improve modifiable characteristics of female OHCAs may have significant impacts on outcomes. Interestingly, while proportion with ROSC was nearly identical between males and females, females had worse outcomes at hospital discharge, demonstrating the higher mortality among women in the post-arrest management phase. Further research should investigate innovative methods to improve modifiable Utstein characteristics in females, and in investigating sex-specific post-arrest management strategies.

The baseline OHCA characteristics were not in favour of females. Females had a lower proportion of OHCA occurring in public locations, a lower proportion of bystander CPR, and a lower proportion with an initial shockable rhythm. As initial cardiac rhythm is associated with preceding no-flow duration (131), it is possible that the initial rhythms in females may be partially related to delays in CPR. It also may be related to differences in the etiology of cardiac arrest. Nonetheless, novel methods to identify female OHCAs in private locations (for example, personal wearable monitors) to alert bystanders and professional responders may confer substantial benefits.

Interestingly, despite the unfavourable baseline differences of females, our data demonstrated nearly identical proportions of ROSC between sexes. Further, after adjustment, female sex was associated with a higher probability of ROSC. Thus, among those resuscitated from OHCA, females had significantly more cases who died in the post-arrest treatment period. While this may be partially due to less favourable baseline characteristics, there are many care processes that may have contributed to these post-arrest deaths. Research into sex-specific management of post-cardiac arrest patients may reveal strategies to improve the outcomes of females with OHCA.

The reasons for the high proportion of females with ROSC are unclear. There must be another unmeasured (hidden) factor that improved odds of ROSC in females. The effect of this hidden variable appeared to disappear during the post-arrest course, leaving room for the survival predictors to tilt the balance again in favour of males (the adjusted odds of survival to hospital discharge was no longer significant). Put differently, the hidden variable appeared to assist females in achieving ROSC, but not effective in survival to hospital discharge.

One hypothesis to help explain the outcome discrepancy and potential hidden variable is the influence of sex hormones. Previous studies reported that female sex hormones may have a positive effect on resuscitation outcomes (63,71). Morrison et al. examined the association between premenopausal status and survival to hospital discharge and reported that when survival was adjusted for Utstein variables, premenopausal females (15-45 years old) had 1.66 higher odds of survival to hospital discharge compared to their age-matched males (OR 1.66, 95% CI 1.04 – 2.64), but no difference in in the older group (females vs. males >55 years old) (63). Johnson et al. reported similar results (71).

The reason for the higher rate of post-arrest deaths in women is unclear; however, sex-specific differences in post-ROSC interventions may play a role. These differences in care may be due to a perception of poor prognosis given the unfavourable baseline characteristics. This clinician prognostication may then contribute to poor post-ROSC outcomes (132). Previous study reported disparities in post-ROSC interventions between females and males (133). Bosson et al. found that females were less likely to receive post-ROSC coronary angiography compared to males (133). Such a sex-specific difference could explain why fewer females left hospital alive than males. The reasons for differences in post-arrest interventions could be gender-related reasons such as inequitable care. Yet, sex-specific reasons cannot be disregarded. Females may have different requirements concerning post-arrest coronary angioplasty. They may have different optimal hemodynamic targets to guide vasopressor treatment.

Consistent with our findings, a Korean study reported no statistical sex differences in adjusted survival to hospital discharge (134). Similarly, a study in Japan (64) reported no statistical sex differences in 30-day survival. However, this study included only patients with witnessed arrest and shockable rhythm. Very similar to the current BC study, a recent study in New Zealand found that male sex was associated with an increased probability of survival, however, when adjusted for baseline covariates, the association was no longer significant (OR 1.22, 95% CI 0.96

to 1.55, p=0.11) (68). Likewise, a large Japanese cohort reported higher crude survival in males; however, no significant association in the adjusted analysis (75).

Other studies comparing sex differences in OHCA survival reported results that are inconsistent with our study and other data. Swedish studies revealed that female sex is associated with better one-month survival (25) and survival to hospital discharge (70). Studies in the USA and Europe; however, (62,71,72) reported survival advantage in males.

It is unknown whether the discrepancies in the survival results among these studies are because of differences in study populations and baseline characteristics or differences in treatment provided for both sexes from region to another. With regards to the baseline characteristics, most of the previous studies (60,64,68,70,112) reported patients' characteristics that are similar to the current BC study; with females being older, having a lower proportion of public location arrests, and shockable rhythms.

One possible explanation for the variations in the survival results across different regions is that females and males do not receive similar resuscitation across countries. Perhaps the EMS care provided for OHCA patients is not the same in all regions. Our result suggests that the BC-EMS system provides OHCA resuscitation with no sex disparity in resuscitation efforts. A previous study in BC showed no difference in the provision of bystander CPR and chest compression rate by EMS rescuers when comparing males and females with OHCA (67).

3.6 Limitations

This study has several limitations. First, the analyses were limited to the BC data and may not be generalizable to other North American jurisdictions, or elsewhere in the world. Second, data on some variables, such as ethnicity, comorbidities were incomplete in the dataset, and therefore not included in the analyses. Third, we did not examine the effect of female sex hormones due to a lack of available data. Fourthly, the etiology of the arrest among women may be systematically different from men and may have significant effects on outcomes.

3.7 Conclusion

There are significant differences in OHCA characteristics between males and females. After adjusting females had 1.29 greater odds of ROSC compared to males; however, female sex was not associated with outcomes at hospital discharge. This suggests that females had a higher rate of death in the post-arrest period. Further innovative methods to improve modifiable baseline characteristics of female OHCA may have substantial impacts on survival. Further research into sex-specific differences in post-arrest care is needed.

Figure 3.1: Study flow diagram

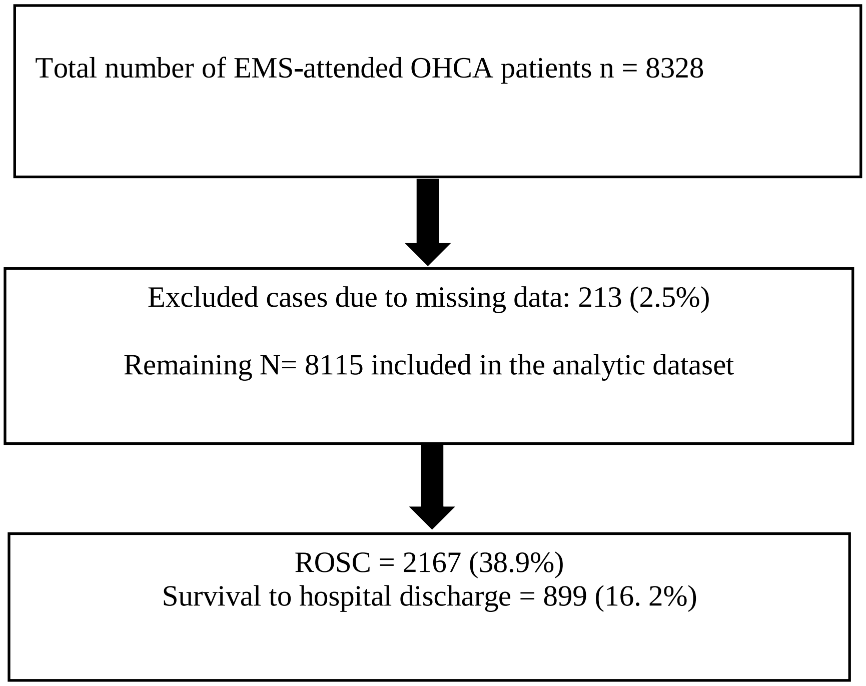

Table 3.1: Sex differences in baseline characteristics and survival

Variables	Total N=8115	Females n= 2549 (31.4%)	Males n = 5566 (68.6%)	*P* Value[1]
Age (Mean ± SD)	67± 17.7	67.75 ± 18.5	64.59 ± 17.3	< 0.001
Arrest in public location	1430 (17.6%)	248 (9.7%)	1182 (21.2%)	< 0.001
Dispatch to EMS arrival[2]				
(6 min or less)	3769 (46.4%)	1214 (47.6%)	2555 (54.1%)	0.078
Witness Status				
Bystander unwitnessed	4108 (50.6%)	1347 (52.8%)	2761 (49.6%)	
Bystander witnessed	3179 (39.2%)	898 (35.2%)	2281 (41.0%)	< 0.001
EMS witnessed arrest	828 (10.2%)	304 (11.9%)	524 (9.4%)	
Bystander CPR status				
No CPR[3]	3456 (42.6%)	1132 (44.4%)	2324 (41.8%)	
Bystander CPR	3831 (47.2%)	1113 (43.7%)	2718 (48.8%)	< 0.001
EMS witnessed arrest	828 (10.2%)	304 (11.9%)	524 (9.4%)	
Shockable initial rhythm	1998 (24.6%)	307 (14.5%)	1628 (29.2%)	<0.001
Administration of epinephrine	6097 (75.0%)	1840 (72.2%)	4257 (76.5%)	<0.001
Transported to hospital	4083 (50.3%)	1230 (48.2%)	2835 (51.3%)	0.050
Survival outcomes				
ROSC	3142 (38.7%)	975 (38.3%)	2167 (38.9%)	0.287
Alive at hospital discharge	1184 (14.6%)	285 (11.2%)	899 (16.2%)	<0.001

[1] *P* value <0.05 is significant: student's t-test for continuous variable and Chi-square test for categorical variables
[2] Time from 911 call to first EMS team arrives on the scene. Dichotomous variable (6 minutes or less vs. > 6 min).
[3] No immediate CPR provided by bystander or EMS personal.

Table 3.2: Effect of sex on ROSC-Logistic regression model (N=8115)

Variable	OR	(95% CI)	*P* value[1]
Female sex (Crude OR)	0.98	0.89 – 1.08	0.65
Adjusted Analysis			
Female sex	1.29	1.15 – 1.42	< 0.001
Age (per year)	0.99	0.99 – 0.99	< 0.001
Public location	1.58	1.39 – 1.80	< 0.001
Witness status			
Unwitnessed			
Bystander witnessed	2.59	2.33 – 2.90	< 0.001
EMS witnessed	3.31	2.77 – 3.95	< 0.001
CPR status			
No CPR			
Bystander CPR*	1.11	1.02 – 1.20	< 0.001
EMS CPR[2]	2.31	1.95 – 2.74	< 0.001
Initial shockable rhythm	3.32	2.96 – 3.73	< 0.001
EMS arrival < 6 min[3]	1.22	1.10 – 1.35	< 0.001

[1] *P* value <0.05 is significant.
[2] EMS-witnessed arrest, immediate CPR started by EMS.
[3] For EMS witnessed, we assumed the response time was zero (they fall under "less than 6 min" category).
P value of Hosmer Lemeshow goodness of fit test was 0.13. The model $R^2 = 0.19$.

Table 3.3: Effect of sex on survival to hospital discharge - Logistic regression (N=8115)

Variable	OR	(95% CI)	*P* value[1]
Female sex (Crude OR)	0.65	0.57 – 0.75	< 0.001
Adjusted analysis			
Female sex	1.14	0.96 – 1.35	0.129
Age	0.97	0.97 – 0.98	< 0.001
Public location	2.22	1.90 – 2.60	< 0.001
Witness status			
Unwitnessed			
Bystander witnessed	2.63	2.20– 3.14	< 0.001
EMS witnessed	5.65	4.45 – 7.20	< 0.001
CPR status			
No CPR			
Bystander CPR	1.20	1.02 – 1.41	< 0.001
EMS CPR	3.62	2.86 – 4.57	< 0.001
Initial shockable rhythm	8.32	7.10 – 9.75	< 0.001
EMS arrival < 6 min	1.54	1.31 – 1.81	< 0.001

[1] *P* value <0.05 is significant.
P value of Hosmer Lemeshow goodness of fit test was 0.29. The model $R^2 = 0.36$.

Table 3.4: Changes in the OR (female vs. male) of survival to hospital discharge after adding predictors

Model	Variables in the model (N= 8115).	OR (female vs. male)	(95% CI)
Model 1	Sex	0.65	0.57 – 0.75
Model 2	Sex and age	0.68	0.59 – 0.79
Model 3	Sex, age, public location	0.83	0.71 – 0.96
Model 4	Sex, age, public location, witness status	0.82	0.70 – 0.95
Model 5	Sex, age, public location, witness status, CPR status	0.81	0.69 – 0.94
Model 6	Sex, age, pub loc, witness status, CPR status, EMS arrival	0.82	0.70 – 0.95
Model 7	Sex, age, pub loc, witness, CPR stat, EMS arrival, initial shockable rhythm	1.14	0.96 – 1.35

Table 3.5: Outcomes of cases transported to hospital (n=4083)

Variable	OR	(95% CI)	*P* value+
Female sex (Crude OR)	0.65	0.54 – 0.77	< 0.001
Female sex (Adjusted OR)	1.04	0.89 – 1.20	0.662
Age	0.97	0.97 – 0.98	< 0.001
Public location	1.75	1.48 – 2.08	< 0.001
Witness status			
Unwitnessed			
Bystander witnessed	1.76	1.46 – 2.14	< 0.001
EMS witnessed	2.73	2.11 – 3.52	< 0.001
CPR status			
NO CPR			
Bystander CPR+	1.15	1.04 – 1.23	< 0.001
EMS CPR++	2.75	2.10 – 3.60	< 0.001
Initial shockable rhythm	6.13	5.18 – 7.25	< 0.001
EMS arrival < 6 min*	1.44	1.18 – 1.75	< 0.001

P value of Hosmer Lemeshow goodness = 0.20. The model R^2 = 0.34.

Table 3.6: Changes in the OR (female vs. male) of survival to hospital discharge for patients transferred to hospital (n=4083)

Model	Variables in the model (N= 8115).	OR (female vs male)	(95% CI)
Model 1	Sex	0.65	0.54 – 0.77
Model 2	Sex and age	0.69	0.58 – 0.82
Model 3	Sex, age, public location	0.81	0.68 – 0.97
Model 4	Sex, age, public location, witness status	0.80	0.65 – 0.95
Model 5	Sex, age, public location, witness status, CPR status	0.78	0.63 – 0.93
Model 6	Sex, age, pub loc, witness status /CPR status, EMS arrival	0.80	0.65 – 0.95
Model 7	Sex, age, pub loc, witness, CPR stat, EMS arrival, initial shockable rhythm	1.04	0.89 – 1.20

Chapter 4: Sex differences in one-year survival following out-of- hospital cardiac arrest

4.1 Summary

Several studies have investigated the association between sex and short-term survival, specifically survival to hospital discharge and one-month survival. However, sex differences in long-term survival and survival beyond hospital discharge have not been widely explored. The primary objective of this study was to investigate the association between sex and one-year survival in a cohort of patients who survived OHCA and who were discharged from hospital alive. We hypothesized that female sex is associated with higher one-year survival post hospital discharge.

This was a retrospective analysis of linked data (2011-2017) from various administrative and clinical databases in British Columbia (BC). We used Student's t-test or Mann–Whitney *U* test (as appropriate) for continuous variables and Chi-square test for categorical variables, to examine the association between baseline characteristics and sex. We used Kaplan–Meier curves, stratified by sex, to display survival, and the log-rank test to test for significant differences between males and females. This was followed by multivariable cox proportional hazards analysis to investigate the independent association between sex and one-year mortality.

We included 1278 hospital-discharge survivors, 284 (22.2%) were females. Females had relatively unfavourable prehospital OHCA characteristics and fewer hospital-based acute coronary diagnoses and interventions. Unadjusted analysis showed one-year survival in females

was lower than in males (males vs females 92.4% vs. 90.5%,); however, this difference was not statistically significant (log-rank p = 0.31). Unadjusted and adjusted analysis revealed no significant difference in one-year survival by sex (unadjusted HR males vs. females 0.80, 95% CI 0.51 – 1.24, p = 0.31) and (adjusted HR males vs. females 1.14, 95% CI 0.72 – 1.81, p = 0.57).

4.2 Background

OHCA is a major health concern worldwide, with an adult incidence rate of 55 per 100,000 person-years (1). Approximately 400,000 adults suffer OHCA each year in North America alone (135,136). Several prehospital factors are associated with an improved probability of survival, including early activation of emergency medical services, rapid commencement of cardiopulmonary resuscitation (CPR), witnessed arrest, bystander CPR, and initial shockable rhythm (2,15,18,22,41,43,50).

Another factor that may influence survival is ‘sex’. Previous studies on sex differences in OHCA reported significant imbalance in baseline characteristics predictive of OHCA outcome with females having a lower proportion with witnessed arrest, bystander CPR, and initial shockable rhythms (60,62,63,67). Reports from other studies demonstrated significant differences in prehospital treatments, with females less likely to receive bystander CPR and defibrillation (73), recommended resuscitation interventions and medications, (61,74) and less likely to be transported to hospital prior to achieving ROSC, compared to males (67). Many previous analyses have demonstrated that, after adjustment for baseline characteristics and prehospital interventions, females had equal or higher probability of short-term survival (survival to hospital discharge or 30 days survival) compared to males (25,62,68,70,75). Most previous studies of sex-based disparities in OHCA outcomes adjusted for only prehospital cardiac arrest characteristics and treatment variables while largely neglecting comorbid conditions, leaving a possibly large proportion of variation in outcomes unexplained. Furthermore, these studies investigated short term survival, specifically survival to hospital discharge (62,70,71) and one-month survival (25,68,70). However, sex differences in long-term survival and survival beyond hospital discharge have not been widely explored.

The primary objective of this study was to investigate sex differences in one-year survival in a cohort of patients who survived OHCA and who were discharged from hospital alive. We hypothesized that female sex is associated with higher one-year survival post hospital discharge, after adjustment for baseline differences.

4.3 Methods

4.3.1 Design and setting

First, we used the BC Cardiac Arrest Registry to identify patients who suffered OHCA (2011-2017). The BC Cardiac Arrest Registry contains information on OHCA characteristics, bystander interventions, treating EMS-units, time-stamped EMS treatments provided, including administration of drugs, advanced airway placement, and transport to hospital. Second, Population Data BC, a provincial administrative data steward, linked the BC Cardiac Arrest Registry data to administrative and clinical databases in BC including BC Vital Statistics, Cardiac Services BC, and the BC Discharge Abstracts Database (DAD). DAD includes detailed information on hospital date of admission, date of discharge, status at discharge (alive vs. dead), admission diagnoses, and comorbidities. The Cardiac Services BC HEART Information System provided data on cardiac interventions and outcomes. BC Vital Statistics provided information on all deaths, including date and location of death.

4.3.2 Study population

In the analytic dataset, we examined cases from the BC Cardiac Arrest Registry (which includes EMS-treated non-traumatic OHCA, defined as a case with EMS-provided chest compressions or a bystander-delivered AED shock), and included adult (age ≥ 18 years) EMS-treated OHCAs that survived to hospital discharge. We excluded cases who did not survive to hospital discharge and cases missing data on sex or other variables required for analysis.

4.3.3 Key variables of interests

The independent variable was sex (male and female). Sex data were obtained from hospital records. The primary outcome of interest was one-year mortality. One-year mortality was defined as death from any cause within one year from date of hospital discharge.

4.3.4 Statistical analysis

4.3.4.1 Univariate and bivariate analysis

We calculated summary statistics for each baseline characteristic. Continuous variables were presented as means and standard deviations (SD) or medians and interquartile ranges (IOQ) based on their distribution. Categorical variables were presented as counts and percentages. Bivariate analyses were performed using Student's t-test or Mann–Whitney *U* test (as appropriate) for continuous variables and Chi-square test for categorical variables, to examine the association between baseline characteristics and sex. One-year mortality was calculated and presented as crude rates, counts per 1000-person years, to account for differences in follow-up time. Kaplan–Meier curves, stratified by sex, was used to display survival, and the log-rank test was used to test for significant differences between males and females.

4.3.4.2 Multivariable analysis

We used Cox proportional hazards regression to investigate the independent association between sex and one-year mortality. For each subject in the study, entry into the study was considered to have begun on the date of hospital discharge and follow up was up to one year or until death or censoring. The primary endpoint was all-cause mortality.

We began the multivariable analysis by evaluating the effect of all possible explanatory variables including variables related to baseline characteristics, prehospital treatment, comorbidities, admission diagnoses, and in-hospital interventions, as follows: 1) OHCA characteristics and treatment variables: dispatch to EMS arrival time interval, location of arrest (public vs private), witness status (witnessed, vs. not witnessed), bystander CPR, initial cardiac rhythm (shockable vs non-shockable), administration of epinephrine; 2) Comorbidities: patients' medical history within three years prior to OHCA, including history of hypertension, diabetes mellitus (DM), congestive heart failure (CHF), coronary artery disease (CAD), chronic kidney disease (CKD), and cancer; 3) in-hospital most responsible diagnoses, ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and cardiogenic shock; 4) In-hospital interventions: percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), pacemaker implant, implantable cardioverter defibrillator (ICD). This was followed by a 5-step forward variable selection process. The clinically important variables known to be associated with survival with large effect size were entered first. In step 1, we examined the crude hazard ratio of sex by including sex only in the cox regression model. In step two, we included sex with variables related to OHCA characteristics. In step 3, we added comorbidities to the model. In step 4, we added medical diagnosis covariates, and in step 5, we added in-hospital interventions. We used theory guided approach to enter the variables in this order. Covariates were included in the models if they varied significantly by sex or had statistically significant effect on the outcome or they are known to be clinically important, based on evidence from the literature. Finally, we tested an interaction term (age X sex) to include in the models if statistically significant.

Prior to multivariable analyses, we examined the proportional hazard assumption by assessing whether the hazard ratio was constant over time. This was done by visualization of log minus log survival vs. log time graph, and by examining the interactions between all covariates with time (137). Kaplan–Meier survival analysis including plotting and graphing were performed using R version 4.0.3, Vienna, Austria. All other analyses were performed using IBM SPSS version 26, Armonk, NY.

4.3.5 Ethics approval

Ethics approval for this study was obtained from the affiliated University of British Columbia - Providence Health Care Research Ethics Board.

4.4 Results

4.4.1 Baseline characteristics and univariate analyses

Within our study time period, there were N=9982 EMS-treated OHCAs in the study footprint, of whom 8657 patients did not survive until hospital discharge. In total, 1325 OHCA patients met the inclusion criteria. Of those, 47 (3.5%) cases were excluded due to missing data on covariates required for the analysis (Figure 4.1). The analytic dataset, therefore, included a total of 1278 hospital-discharge survivors. Of those, 284 (22.2%) were females, 510 (40.0%) arrested in public locations, 933 (73.0%) had shockable initial rhythms, 677 (53.0%) had a history of hypertension, 322 (25.2%) had a history of DM, and 183 (14.3%) had a history of congestive heart failure (CHF). Table 4.1 shows the summary statistics for the baseline characteristics, OHCA treatment, and comorbidities, overall, and stratified by sex.

The females-males comparison showed that females had a lower proportion of OHCA occurring in public locations (25.7% vs. 44.0%, p <0.001) and a lower proportion with a shockable initial rhythm (57.7% vs. 77.4%, p <0.001). In comparing medical history, no significant differences were detected between males and females except that the proportion of females with prior CAD was lower than the proportion of males (29.6% vs. 56.6%, p <0.001). Furthermore, females had a lower proportion of acute STEMI on admission than males (18.3% vs. 34.0%, p <0.001), and the proportion of females who had in-hospital cardiac interventions, either PCI or CABG, was significantly lower than the proportion of males. Specifically, females had fewer PCIs and fewer CABG surgeries (26.1% vs. 39.6, p <0.001) and (1.8% vs. 12.3%, p <0.001), respectively. ICDs were implanted in 25% of patients; 22.2% of females and 25.7% of males, p = 0.22 (Table 4.1).

4.4.2 Survival analysis

Overall, the one-year survival rate was 91.9%. We did not find significant differences in survival rate by sex (males vs females 92.4% vs. 90.5%, $p = 0.31$). The calculated overall mortality rate was 81 per 1000-person years. The sex-specify mortality was higher in females (95 per 1000-person years) compared to males (76 per 1000-person years). Figure 4.2 shows Kaplan–Meier (KM) curve of survivors up to 12 months after hospital discharge. Survival in females was lower than in males, but the log-rank test showed that this difference was not statistically significant (log-rank $p = 0.31$).

4.4.3 Multivariable Model

Visual inspection of the covariates' log minus log survival curves showed the curves were parallel. There were no significant interactions between any covariates and time, indicating the proportional hazards assumption was not violated. Table 4.2 shows the unadjusted and adjusted cox regression analysis results. The unadjusted analysis showed no association between sex and risk of death (crude HR males vs. females 0.80, 95% CI 0.51 – 1.24 $p = 0.31$). After adjusting for OHCA characteristics, the analysis continued to show no association between sex and hazard of death (HR males vs. females 1.02, 95% CI 0.51 – 1.73, $p = 0.78$) (Model 2). The association between sex and one-year mortality remained insignificant after adding comorbidities and most responsible diagnoses to the model (Model 3 and 4). The final model which included covariates related to OHCA characteristics, comorbidities, most responsible diagnoses, and in-hospital interventions demonstrated no sex difference either (HR males vs. females 1.14, 95% CI 0.72 – 1.81, $p = 0.57$) (Model 5). We tested the interaction term (age X sex) in the final model. The age

X sex interaction was not statistically significant (HR 0.99, 95% CI 0.96 – 1.04, $p = 0.91$); therefore, it was not included in the model.

4.5 Discussion

In this cohort of EMS-treated OHCA subjects, who survived to hospital discharge, females tended to have relatively unfavourable prehospital characteristics and fewer hospital-based acute coronary diagnoses and interventions. However, unadjusted and adjusted analysis revealed no significant difference in one-year survival. This is the first study that examine the effect of sex on one-year survival adjusting for prehospital treatment, comorbidities, admission diagnoses, and in-hospital interventions. The results add to our knowledge of sex-based differences in long-term OHCA outcomes.

We were concerned that multiple clinical and demographics factors, besides sex, could affect mortality, and failure to account for these would lead to inaccurate results. To overcome this problem, we used a forward variable selection technique, adding one variable at a time, drawing from a comprehensive list of variables. We started by adding variables related to prehospital factors, followed by comorbidities, then diagnoses, and then in-hospital interventions. The crude hazard ratio was insignificant and adjusted hazard ratios remained insignificant, with the addition of additional variables, after each step. The variable forward selection technique made us able to observe a change in the HR from Crude HR of 0.80 to an adjusted HR of 1.14 (95% CI 0.72 – 1.81).

Previous analyses examining long-term survival have reported similar results. Andrew et al (77) was unable to detect an association between sex and one-year survival (male HR 1.17, 95% CI 0.97 to 1.40, p = 0.09). Chan et al. (76) also reported no difference in one-year mortality by sex (female HR 1.03, 95% CI 0.82–1.31, p = 0.79). In contrast to our study, Chan et al. and Andrew et al. did not include in-hospital treatment variables in their analysis. Nevertheless, all three studies found no association between sex and one-year survival. The consistency of these results, despite the variation in analytic techniques, supports the validity of our findings.

This study has a number of limitations. First, the results may not be generalizable to other regions where there are differences in prehospital EMS intervention and post arrest in-hospital care. However, we applied our study questions/hypothesis to a North American province where OHCA cases are served by a single, unified provincial EMS. Second, there could be some differences in the treatments provided for younger and older females group, we did not take into account these possible differences in our analysis. Third, the result may be not generalizable to all OHCA patients as we included OHCAs who were discharged from hospital alive. The rational for not including those with failed prehospital resuscitation and those who died in hospital in our analysis is that those patients had no chance to be exposed to some in-hospital treatments, such as PCI and CABG (or in-hospital treatments were nor indicated for them due to poor prognosis - for those who died in hospital). Including those patients in the analysis, which adjusted for in-hospital treatments variables, would produce inaccurate estimates of not only the significance but also the magnitude of the relationships between the explanatory and outcome variables.

4.6 Conclusion

Females have relatively unfavourable prehospital characteristics in OHCA and fewer hospital-based acute coronary diagnoses and interventions. However, we found no significant difference between males and females in one-year survival. This is the first study examining the effect of sex on post-discharge survival that adjusted for all possible confounders, including prehospital treatment, comorbidities, admission diagnoses, and in-hospital interventions. This study adds to our knowledge of sex-based differences in long-term OHCA outcomes.

Figure 4.1: Study flow diagram

Total number of EMS-attended OHCA patients
N =9982
Patients did not survive to hospital discharge = 8657

↓

Patients discharged from hospital alive n=1325

↓

Excluded cases due to missing data: 47 (3.5%)

Age: 11
Sex: 6
OHCA location: 6
Witness status: 9
EMS Arrival time: 9
Initial rhythm: 6
OHCA administration of epinephrine 2
Comorbidity: 0
Diagnosis: 0
Intervention: 0

↓

Remaining N= 1278 included in the study

Table 4.1: Sex differences in baseline characteristics, comorbidities and intervention

Variables	**Total** N=1278	**Females** n=284 (22.2%)	**Males** n =994 (77.8%)	***P* Value**[+]
Age (mean ± SD)	61.0± 15.3	66.0 ± 16.7	61.0 ± 14.9	0.22
OHCA characteristics				
Time to EMS arrival (median IQR)	8.1 (6.5-11.5%)	9.5 (7.1-13.2)	8.19 (6.4-11.0)	<0.001
Arrest in public location	510 (40.0%)	73 (25.7%)	437 (44.0%)	<0.001
Unwitnessed	233 (18.2%)	60 (21.1%)	173 (17.4%)	
Bystander witnessed	249 (19.5%)	78 (27.5%)	171 (17.2%)	<0.001
EMS witnessed arrest	796 (62.3%)	146 (51.4%)	650 (65.4%)	
No CPR	313 (24.5%)	71 (25.0%)	242 (24.3%)	
Bystander CPR	169 (13.2%)	130 (45.8%)	574 (57.7%)	<0.001
EMS CPR	796 (62.3%)	83 (29.2%)	178 (18.0%)	
Shockable initial rhythm	933 (73.0%)	164 (57.7%)	769 (77.4%)	<0.001
Administration of epinephrine	497 (38.9%)	92 (32.4%)	405 (40.7%)	0.01
Comorbidities				
Hypertension	677 (53.0%)	139 (48.9%)	538 (54.1%)	0.12
Diabetes mellitus	322 (25.2%)	71 (25.0%)	251 (25.3%)	0.93
CHF	183 (14.3%)	40 (14.1%)	143 (14.4%)	0.89
CAD	647 (50.6%)	84 (29.6%)	563 (56.6%)	<0.001
Chronic Kidney Disease	254 (19.9%)	47 (16.5%)	207 (20.8%)	0.11
Cancer	72 (5.6%)	12 (4.2%)	60 (6.0%)	0.24
Most responsible diagnosis				
Others (Non-MI)	818 (64.0%)	222 (78.2)	596 (60.0%)	
STEMI	390 (30.5%)	52 (18.3%)	338 (34.0%)	<0.001
NSTEMI	70 (5.5%)	10 (3.5%)	60 (6.0%)	
Cardiogenic shock	146 (11.4%)	29 (10.2%)	117 (11.8%)	0.47
In-hospital interventions				
Diagnostic angiography	886 (69.3%)	150 (52.8%)	736 (74.0%)	<0.001
No revascularization	683 (53.4%)	205 (72.2%)	478 (48.1%)	<0.001
PCI	468 (36.6%)	74 (26.1%)	394 (39.6%)	
CABG	127 (10.0%)	5 (1.8%)	122 (12.3%)	
Pacemaker implant	88 (6.9%)	20 (7.0%)	68 (6.8%)	0.90
ICD implant	319 (25.0%)	63 (22.2%)	256 (25.8%)	0.22
Survival outcomes				
One-year mortality	103 (8.1%)	27 (9.5%)	76 (7.6 %)	0.31

Figure 4.2: Kaplan-Meier survival estimates for females and males

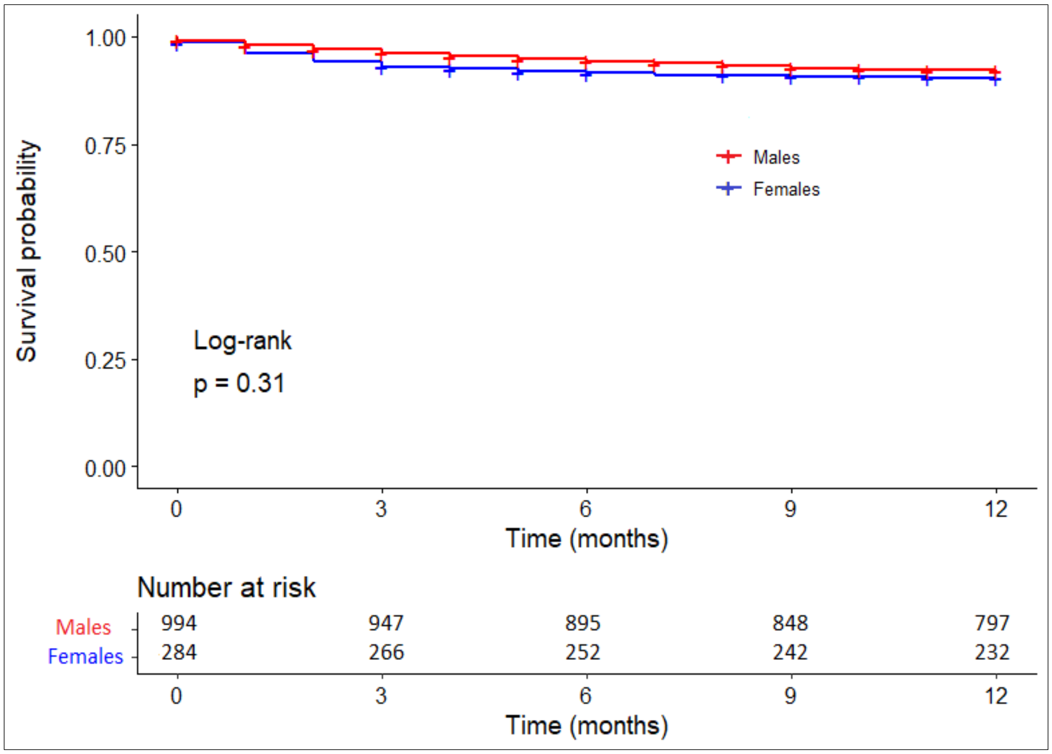

Table 4.2: Effect of sex on one-year mortality

Model	HR[1]	(95% CI)	*P* value[2]	Variable included
Model 1	0.80	0.51 – 1.24	0.31	Sex only
Model 2	1.02	0.57 – 1.72	0.78	Sex, age, and OHCA characteristics (arrest location, witnessed status, initial rhythm)
Model 3	1.09	0.67 – 1.73	0.70	Model 2 plus: comorbidities (CAD, CHF, CKD, and cancer)
Model 4	1.09	0.69 – 1.73	0.72	Model 3 plus: most responsible diagnosis (STEMI and NSTEMI).
Model 5	1.14	0.72 – 1.81	0.57	Model 4 plus: in-hospital interventions (ICD implant, PCI, and CABG)

Effect of sex on one-year mortality adjusting for OHCA characteristics, comorbidities, hospital diagnoses, and interventions.
[1] Hazard ratios (males vs females). [2] *P* value < 0.05 is significant.

Chapter 5: Prehospital predictors of survival with favourable neurological function

5.1 Summary

Many studies examined the predictors of survival after OHCA, including survival to hospital discharge and one-month survival. However, studies that identified the prehospital predictors of survival with favourable neurological outcome and the effect of sex on neurological function are still relatively scant. The primary objective of this study was to identify the statistically significant prehospital predictors of survival with good neurological function at hospital discharge after OHCA. The secondary objective was to assess whether sex as a biological variable has any association with favorable neurological function.

This was an observational study that analyzed data from the ROC multi-center randomized controlled trial (CCC trial) (June 2011 to May 2015). From the CCC database, we created an analytic dataset that included males and females 18 years and older, with non-traumatic, EMS-attended OHCA. We used multilevel logistic regression to identify the significant prehospital predictors of survival with favourable neurological outcomes (modified Rankin Scale ≤ 3), and to assess the effect of sex on neurological function.

In total, 22,416 patients were included. Of those, 8109 (36.2%) were females, 3,249 (14.5%) arrested in a public location, and 5,187 (23.1%) had an initial shockable rhythm. The multilevel logistic regression analysis identified that the following variables as significant predictors of favourable neurological outcome: younger age, shorter duration of EMS arrival to the scene,

arrest in public location, witnessed arrest, bystander CPR, chest compression rate (CCR) of 100-120 compressions per minute, induction of hypothermia, and initial shockable rhythm. The predictor with the largest effect size was the initial shockable rhythm (OR 6.53, 95% CI 5.47 – 7.80, $p < 0.001$). Two variables, insertion of an advanced airway and administration of epinephrine, were associated with poor neurological outcome. Our analysis also showed that males with OHCA have higher crude rates of survival with favourable neurological outcome. However, the adjusted rate was not statistically significant. While an initial shockable rhythm and hypothermia management contribute significantly to favourable neurological outcome, the lower proportion of females with an initial shockable rhythm and the lower proportion receiving hypothermia thus contribute to the lower rate of neurological intact survival in females. Other reasons for the observed difference should be further explored. Further analyses showed that hypothermia and initial rhythm had significantly greater effects on males than females, suggesting effect modifications of hypothermia and initial rhythm by sex. The reasons for the observed differences in the effect size by sex should be investigated.

5.2 Introduction

Sudden OHCA is a serious medical emergency affecting more than 350,000 North Americans yearly (135,138). Providing patients suffering from OHCA with optimal prehospital intervention improves the probability of return of spontaneous circulation (ROSC) and survival to hospital discharge (13,22,86). Even OHCA patients who receive prehospital resuscitation and achieve ROSC are at risk of developing anoxic brain complications, including coma and death (10).

Prehospital intervention is critical for survival. The prehospital predictors of OHCA outcomes, including ROSC and survival to hospital discharge, have been well investigated over the last 20 years. The interval between collapse and start of resuscitation (19), witnessed arrest, bystander CPR (19,22,25,29,39), quality of CPR (16,48,50,53), and initial cardiac rhythm and defibrillation (20,31,39) are associated with ROSC, including survival to hospital discharge (16,18,19,80,139) and one-month survival (17,20,22,25,53).

Many studies examined the predictors of survival with good neurological outcomes and identified the contributors to poor neurological outcome as: older age, longer time to ROSC, unwitnessed arrest, initial rhythm being a non-shockable rhythm, arrest due to non-cardiac etiology, low Glasgow Coma Scale (GCS) at admission (21,82–84), high ammonia and lactate levels at admission (84), elevated Central Venous Pressure (CVP) during ICU stay (83), and lower pH level (82). While they provided useful results, these studies dealt with GCS, $PaCO_2$, brainstem reflexes, and motor response as independent variables in their analysis. Clinically, poor pre-hospital resuscitation, non-shockable rhythm, and longer duration of CPR would lead to poor neurological outcomes, including low GCS, absence of brainstem reflexes, and poor motor response. In other words, these variables (low GCS, absence of brainstem reflexes, and poor motor response) are clinical signs of poor neurological function and in fact are markers of bad neurological function. Adding them as independent variables to the predictive analysis model, therefore, may have made the results subject to over adjustment bias and imprecision.

Studies that focused on the effect of prehospital factors on survival with favourable neurological outcome are still relatively scant. In addition to prehospital OHCA treatment-related predictors, there is evidence suggesting that sex may influence survival. Previous studies of the effect of sex on OHCA outcomes concentrated on survival to hospital discharge (62,70,71) and one-month survival (25,68,70). Few studies addressed the effect of sex on neurological function after OHCA.

The primary objective of this study was to identify the statistically significant prehospital predictors of survival with good neurological function at hospital discharge in a cohort of patients with OHCA in the USA and Canada. The secondary objective was to assess whether sex as a biological variable has any association with favorable neurological outcome after OHCA.

5.3 Methods

5.3.1 Design and Setting

We analyzed data from the Resuscitation Outcome Consortium (ROC) Continuous Chest Compression (CCC) trial (June 2011 to May 2015). (140). The ROC is a research network with 10 clinical regions (7 in the USA and 3 in Canada) conducting research in resuscitation science (104).

The ROC CCC trial was an unblinded, cluster-randomized, clinical trial, in which 114 emergency medical service (EMS) agencies across eight sites in the USA and Canada participated. The participating EMS agencies were grouped into 47 clusters. The CCC trial included adults with non-traumatic OHCA who received chest compressions provided by EMS or defibrillation by a bystander, and excluded OHCA witnessed by EMS, patients pronounced dead on EMS arrival, and those with “do not resuscitate” orders. The trial evaluated the effect of chest compressions provided continuously (CCC) versus chest compressions interrupted for ventilation, during resuscitation of OHCA patients, on the survival rate and neurological function (140). The CCC group received ventilation without pauses in compression (CCC at a rate of 100 compressions and ventilations recommended at 10 per minute). The control group received chest compressions interrupted for ventilation (compression-ventilation rate of 30:2). The trial results showed that there was no significant difference in survival or neurological function between the continuous versus interrupted chest compression groups. A detailed report of the CCC trial has been published (140).

5.3.2 Study population

From the CCC database, we created an analytic dataset that included males and females 18 years and older, with non-traumatic, EMS-attended OHCA. Patients <18 years old, cases with non-cardiac etiology of arrest, and cases missing data on any of the key variables were excluded.

5.3.3 Key variables of interest and measurements

The outcome variable of interest was neurological function at hospital discharge measured using a modified Rankin Scale (mRS): a scale from zero to six, where a scale of zero represents no neurological deficit and a scale of six means death (Table 5.1) (141). For this study, a mRS of >3 was coded as (0) and indicated unfavourable neurological function, and a mRS of ≤3 was coded as (1) and indicated favourable neurologic function.

A total of 11 independent variables known to be associated with short-term survival were screened as possible predictors for the neurological outcome. These included: age (per year), the interval from the 9-1-1 call to first to EMS arrival to the scene (per minute), sex (males vs.

female), location of arrest (public vs. private), bystander witnessed status (witnessed vs. unwitnessed), bystander cardiopulmonary resuscitation (CPR) (yes vs. no), chest compression rate (CCR), initial cardiac arrest rhythm (shockable vs. nonshockable), advanced airway placement (yes vs. no), administration of epinephrine (administered vs. not administered), and induction of hypothermia before or during hospitalization (yes vs. no).

5.3.4 Statistical analysis

We calculated descriptive statistics for baseline characteristics for the full cohort. Continuous variables were presented as medians and interquartile ranges, as they were not normally distributed. Categorical variables were presented as counts and percentages. To explore associations between the potential predictors with good neurological outcome, we performed bivariate analyses using Chi-Square test for the categorical variables, and point biserial correlation for the continuous variable. Bivariate relationships were assessed at a 5% level of significance.

To further examine and identify the significant prehospital predictors of favourable neurological outcome, we employed multilevel (hierarchical) logistic regression. Multilevel modeling was necessary to account for the nesting of patients within 47 clusters (99). We ran the hierarchal logistic regression analyses as follows: first, we built an intercept-only model (null model) and estimated the intercept ($\boldsymbol{\gamma 00}$) and variance ($\boldsymbol{\tau}^2$). $\boldsymbol{\gamma 00}$ represents the average log odds of survival with favourable neurological outcome across all clusters, and $\boldsymbol{\tau}^2$ represents the variance of clusters' average log odds of survival with favourable neurological outcome (142). Second, we calculated the intraclass correlation coefficient (ICC) and the design effect (DE). A DE value greater than two was considered an indication of the need for multilevel analysis (99). Third, using a forward and backward variable selection technique, we built a series of multivariable mixed models (random intercept models with patient-level predictors). This allowed us to account for the clustering effect (patients nested within clusters). In these models, we included patient-level variables known to be associated with survival (105). The patient-level variables were modelled as fixed effects, and the cluster was modeled as a random effect. The dependent variable was neurological function at hospital discharge (favourable vs. unfavourable). Fourth, to further examine the effect of sex, we stratified the sample by sex and ran the models in each of the sex subgroups. We then compared the predictors in each model for both the significance and effect sizes. Then we examined for possible interactions between sex and other variables. We used the Akaike information criterion (AIC) and the Likelihood Ratio Tests (LRT) to evaluate the overall fit of the models (143). All univariate statistical analyses were performed using IBM SPSS version 26, Armonk, NY, and multilevel analyses were performed using R version 4.0.1, Vienna, Austria.

5.3.5 Ethics approval

Ethics approval for this study was obtained from the affiliated University of British Columbia - Providence Health Care Research Ethics Board.

5.4 Results

5.4.1 Patients' characteristics and univariate analyses

A total of 23,711 OHCA cases were included in the CCC trial database. After excluding patients who did not meet the inclusion criteria and those with missing data on any of the key variables, 22,416 patients were eligible and included in the analysis (Figure 5.1). Of those, 8109 (36.2%) were females, 3,249 (14.5%) arrested in a public location, 10,403 (46.4%) received bystander

CPR, and 5,187 (23.1%) had an initial shockable rhythm. The summary statistics for the study variables and the bivariate analyses results (association between the potential predictors and good neurological outcome) are shown in (Table 5.2).

5.4.2 Multivariable logistic regression analyses

Null model

In the intercept-only model (null model), the estimated intercept $\boldsymbol{\gamma 00}$ was -2.645, while the estimated variance of the random effects $\boldsymbol{\tau^2}$ was 0.247 (95% CI 0.15 – 0.40, $p < 0.001$). This indicates that there was significant variability in the intercept among clusters. To allow further assessment for the clustering effect, we computed the ICC:

ICC = $\frac{\tau^2}{\tau^2 + \frac{\pi^2}{3}}$ where π = 3.14 (144)

ICC = $\frac{0.247}{0.247 + (3.14\ x\ 3.14)/3}$

ICC = $\frac{0.247}{0.247 + 3.28}$

ICC = 0.07

DE =1 + ICC (n - 1), n = the average number of patients per cluster.

DE = 1 + 0.07 (476 - 1)

DF =1 + 0.07 (475)

DE = 33.25

ICC and DE values suggested that multilevel analysis is needed.

Random intercept with level one predictors model

We began the modeling by including all potential predictors in one model, and then we used the backward and forward variable selection procedure and produced several models. In the full model that included all potential predictors, the analysis showed that all patient-level variables except sex significantly contributed to the model (Model 1) (Table 5.4).

In the series of models produced by the forward and backward variable selection procedure, sex remained statistically significant in favour of males. Only after adding two variables (hypothermia and/or initial rhythm), was sex no longer significant (OR 1.16, 95% CI 0.99 – 1.36, $p = 0.06$). Table 5.5 shows the changes in OR (male vs. female) for the neurological function when adding or removing variables.

To further examine the effect of sex, we stratified the sample by sex and ran the models in each of the sex subgroups. We then compared the predictors in each model for both the significance and effect sizes. The significance and effect sizes were very similar in the male and female models except in the effect of hypothermia and initial rhythm. Hypothermia and initial rhythm had larger effect sizes in male than females (Table 5.6). This suggests that the effect of hypothermia and initial rhythms depend on the levels of 'sex' variable (effects modification by sex). We thus ran three new models: 1- all predictors and the initial shockable rhythm by sex interaction **(**Table 5.7), 2- all predictors, the initial rhythm by sex interaction, and hypothermia management by sex interaction (Table 5.8), and 3- all predictors and the hypothermia management by sex interaction only (Table 5.9). To obtain meaningful and interpretable results of the interactions, prior to running these analyses, we recoded the variables of interest as follow:

sex (female = -1, male = 1), hypothermia (not received = -1, received = 1), initial rhythm (nonshockable = -1, shockable = 1). The results of these analyses showed that the initial shockable rhythm by sex interaction was significant in favour of males. I.e. initial shockable rhythm was significantly more effective in males than females, holding all other predictors constant **(**Table 5.7). However, after adding the hypothermia by sex interaction to the model, the initial rhythm by sex was no longer significant (Table 5.8). Moreover, after removing initial rhythm by sex and including "hypothermia by sex interaction" only, the hypothermia by sex remained significant. I.e. hypothermia management was significantly more effective in males than females, holding all other predictors constant (Table 5.9). The LR test and AIC showed that the last model (Table 5.9) was the best-fit model and therefore was accepted as the final model. In this final model, the following variables were found to have a statistically significant positive impact on good neurological outcome: younger age, shorter duration of EMS arrival to the scene, arrest in public location, witnessed arrest, bystander CPR, CCR of 100-120 compressions per minute, induction of hypothermia, and initial shockable rhythm. The predictor with the largest effect size was the initial shockable rhythm. The model indicated that patients with an initial shockable rhythm had 6.53 times greater odds of survival with good neurological function than those with unshockable rhythm, holding all other predictors constant (95% CI 5.47 – 7.80, $p < 0.001$). Two variables, insertion of an advanced airway and administration of epinephrine, were associated with poor neurological outcome. The model also revealed a significant interaction between sex and hypothermia. Males derived greater benefit from hypothermia management than females, holding all other predictors constant (difference in males vs. difference in females = 1.13, 95% CI 1.05 – 1.22, $p = 0.002$) (Table 5.9).

5.5 Discussion

We identified the significant predictors of survival with good neurological function at hospital discharge in a cohort of patients with OHCA from multiple regions in the USA and Canada. Our adjusted analysis revealed the following variables had a positive impact on favourable neurological function: younger age, shorter duration of EMS arrival to the scene, arrest in a public location, witnessed arrest, bystander CPR, quality of CPR represented by 100-120 chest compressions per minute, induction of hypothermia, and initial shockable rhythm. Two variables had negative impacts on neurological function, insertion of an advanced airway and administration of epinephrine. Our analyses also found two significant interaction effects: ‘hypothermia by sex’ and ‘initial rhythm by sex’. Our results revealed that males derived significantly greater benefit from hypothermia management and initial shockable rhythms than females.

With the exception of age, all of the significant predictive variables were event or treatment characteristics. Of note, many of these variables are modifiable, for example bystander CPR, induction of hypothermia, EMS arrival time, and insertion of an advanced airway. Initiatives and strategies that can improve treatment characteristics, such as strategies to shorten duration of EMS arrival to the scene and training more residents in basic life support bystander CPR, could improve survival with good neurological outcomes (22).

An initial shockable rhythm was the predictor with the largest effect size. The second largest effect size was hypothermia management. These findings are not inconsistent with the findings of previous studies that reported a strong positive association between an initial shockable rhythm and survival (143,144), and positive association between hypothermia and neurological outcome (145–147). Additionally, our analyses showed that advanced airway management and administration of epinephrine were associated with decreased odds of favourable neurological outcome. The insertion of an advanced airway may interrupt chest compressions, which results in decreased blood flow to the brain. This is a plausible explanation of the negative impact of advanced airway management on neurological outcome. In line with our results, a recently published RCT (92) compared an epinephrine group with a placebo group to determine if administration of epinephrine during OHCA is effective. The trial found that the proportion of survivors with severe neurologic damage was higher in the epinephrine group than in the placebo group (31.0% vs. 17.8%). A possible explanation of the negative impact of epinephrine is perhaps the peripheral vasoconstriction effect of epinephrine as reported in a previous animal study (148). However, other animal studies showed an increase of cerebral flow with bolus doses of epinephrine (149). Our dataset had limited data on epinephrine bolus doses. It is worth mentioning that advanced airway and epinephrine are indicated for patients with prolonged resuscitation; perhaps those with unshockable rhythms. Therefore, in our study, confounding by indication cannot be disregarded.

We also examined the effect of CPR quality, represented by CC rate, on neurological outcome. We found a CC rate between 100-120 compressions per minute is a significant predictor of favourable neurological function. Our analysis showed that the odds of good neurological function among those who received a CC rate between 100-120 compressions per minute is 1.6 times higher than that of patients who received 50-99 compressions per minutes, adjusting for all other predictors. Our finding is consistent with Idris et al. (16) who examined the relationship between compression rate and survival to hospital discharge based on secondary analysis of data from the ROC. Idris et al. (16) identified a compression rate of 100 to 119 as the rate associated with the greatest odds of survival to hospital discharge. Interestingly, our analysis showed that chest compressions delivered at a rate higher than 120 compressions per minutes was associated with poor neurological function. A plausible explanation for this is that compressions delivered too quickly (>120/min) may not allow the chest to recoil during CPR, resulting in poor blood flow to the brain.

With regards to the effect of sex, the bivariate analysis showed that males had a significantly higher rate of neurologically intact survival. However, this advantage disappeared after adjustment. In the series of models produced by the multivariable analyses, sex remained statistically significant until we added hypothermia and/or initial rhythm. Only in the models that included initial shockable rhythm and/or hypothermia was the variable ‘sex’ no longer statistically significant. This suggests that sex as a biological variable has no impact on neurological function, once initial shockable rhythm and hypothermia management are taken into account. Nevertheless, it is important to note survival with good neurological outcome was lower in females.

Further analysis demonstrated significant correlation between sex and initial rhythm. A similar correlation was shown in a recent North American study that reported females had a lower proportion of OHCA with an initial shockable rhythm compared to males (14.0% vs. 29.1%, $p < 0.001$) (19). An additional analysis also showed significant bivariate correlation between sex and hypothermia. Females had a lower proportion of receiving hypothermia management compared to males (13.4% vs. 17.0%, $p < 0.001$). While an initial shockable rhythm and hypothermia management contribute significantly to favourable neurological outcome, the lower proportion of females with an initial shockable rhythm and receiving hypothermia thus contribute to the lower crude rate of neurological intact survival in females.

As initial cardiac rhythm is associated with preceding no-flow duration (131), it is possible that the initial unshockable rhythms in females may be related to delays in CPR. It also may be related to differences in the etiology of cardiac arrest. Novel methods that lead to early identification of cardiac arrest in females and provision of immediate resuscitation may confer substantial benefits. The reason for sex differences in hypothermia management is not clear; it could be gender-related reasons, such as inequitable care, or sex-specific reasons, such as different requirements concerning hypothermia intervention.

To further examine the effect of sex on the outcome in relation to the baseline characteristics, we stratified the sample by sex and ran the analysis for each of the sex subgroups. We then compared the effect of predictors in each model. We found that hypothermia and initial rhythm had noticeably larger effect sizes in males than females, while the magnitude of the effects of the other predictors were similar. The marked difference in the effect size by sex, with much lower ORs in females than males, suggests possible interaction effects. Examination of possible interactions revealed that males derived significantly greater benefit from hypothermia management and initial shockable rhythms than females. These results suggest effect modifications of hypothermia and initial rhythm by sex. The reasons for the observed differences in the effect sizes of hypothermia and shockable rhythm should be investigated.

This study analyzed data from 47 clusters that participated in the ROC CCC trial. One strength of this study is that it applied multilevel analysis to account for clustering effect. Not accounting for clustering effect can produce inaccurate results, including incorrect estimates of the standard errors (SEs) for the level-one predictors, and increases in the odds of finding a relationship when one does not exist, i.e. inflated type 1 error (99).

Our study has several limitations. First, the study analyzed data from multiple North American regions and the results may not be generalizable elsewhere in the world. Second, our study is vulnerable to unmeasured confounders. Data on some variables, such as comorbidities, year, and time of the event were incomplete in the dataset and, therefore, not included in the analysis. Third, the study focused on prehospital interventions. Data on other in-hospital treatment variables, such as cardiac interventions and revascularization, were not available in the dataset, and therefore not included in the analyses. If they were included, they could have explained a larger proportion of the variance in the outcome.

5.6 Conclusion

We found 10 predictors of neurological function, eight predictors of favourable neurological outcome, and two predictors of poor neurological outcome, after OHCA. The predictors of favourable neurological function include younger age, shorter duration of EMS arrival to the scene, arrest occurring in a public location, witnessed arrest, bystander CPR, chest compression rate of 100-120 compressions per minute, induction of hypothermia, and initial shockable rhythm. The predictors of poor neurological outcome include insertion of an advanced airway and administration of epinephrine. The study focused mainly on the prehospital event characteristics and intervention. Further studies that examine the effect of both out-of-hospital and in-hospital interventions on neurological outcome are recommended.

Males with OHCA have higher crude rates of neurologically intact survival. However, the adjusted rate was not statistically significant. This suggests that sex as a biological variable has no independent effect on neurological function. Because an initial shockable rhythm and hypothermia management had the greatest impact on favourable neurological outcome, the lower proportion of females with an initial shockable rhythm and the lower proportion receiving hypothermia thus contribute to the lower crude rate of neurological intact survival in females. The magnitude of the effect of the hypothermia and initial shockable rhythm on neurological outcome were higher in males than females, suggesting effect modifications of hypothermia and initial rhythm by sex. Other reasons for the observed difference should be further explored.

Figure 5.1: Study flow diagram

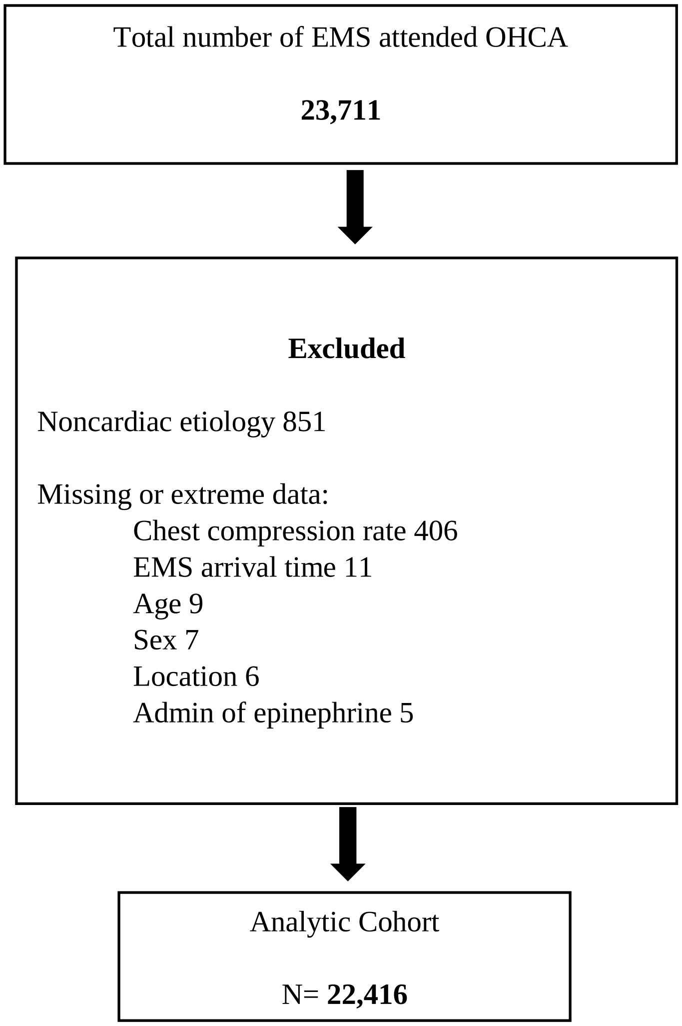

Table 5.3: Patients' characteristics and univariate associations with favourable neurological outcome

Study variable	N = 22,416	Favourable Neurological Outcome	*P* value
EMS arrival interval (min)	Median = 5.5 (4.2-6.9)	$r_{pb} = 0.05^1$	< 0.01
Age (years)	Median = 69 (57-81)	$r_{pb} = 0.13^2$	< 0.01
Sex			
Female	8109 (36.2%)	395 (4.9%)	< 0.001
Male	14307 (63.8%)	1234 (8.6%)	
Location of arrest			
Non-public	19167 (85.5%)	946 (4.9%)	< 0.001
Public	3249 (14.5%)	683 (21.0%)	
Bystander witnessed			
Unwitnessed	12845 (57.3%)	325 (2.5%)	< 0.001
Witnessed	9571 (42.7%)	1304 (13.6%)	
Bystander CPR			
No	12013 (53.6%)	568 (4.7%)	< 0.001
Yes	10403 (46.4%)	1061 (10.2%)	
Initial rhythm			
Nonshockable	17229 (76.9%)	328 (1.9%)	< 0.001
Shockable	5187 (23.1%)	1301 (25.1%)	
Chest compression rate per min			
50-99	3599 (16.1%)	196 (5.4%)	
100-120	17705 (78.9%)	1370 (7.7%)	< 0.001
>120	1112 (5.0%)	63 (5.7%)	
Advanced airway			
No	4958 (22.1%)	597 (36.6%)	< 0.001
Yes	17458 (77.9%)	1032 (5.9%)	
Admin of Epinephrine			
No	3950 (17.6%)	899 (22.8%)	< 0.001
Yes	18466 (82.4%)	730 (4.0%)	
Hypothermia management			
No	18906 (84.3%)	629 (3.3%)	< 0.001
Yes	3510 (15.7%)	1000 (28.5%)	

[1, 2] Point biserial correlation coefficient

Table 5.4: Model 1-Hierarchical multivariable regression model for favourable neurological outcome

	Full cohort N = 22,416		
Variable	**OR**	**(95% CI)**	***P* value**
EMS arrival interval (per min)	0.92	0.89 – 0.94	< 0.001
Age (per year)	0.97	0.96 – 0.97	< 0.001
Sex			
Female	ref		
Male	1.16	0.99 – 1.36	0.06
Location of arrest			
Not public	ref		
Public	1.77	1.53 – 2.06	< 0.001
Witness status			
Unwitnessed	ref		
Witnessed	3.02	2.76 – 3.55	< 0.001
CPR status			
No CPR	ref		
Bystander CPR	1.29	1.12 – 1.49	< 0.001
Chest compression rate			
50-99	ref		
100-120	1.59	1.31 – 1.95	< 0.001
>120	0.97	0.65 – 1.44	0.86
Initial cardiac rhythm			
Nonshockable	ref		
Shockable	6.48	5.40 – 7.75	< 0.001
Epinephrine			
No	ref		
Yes	0.10	0.08 – 0.12	< 0.001
Advanced airway			
No	ref		
Yes	0.59	0.49 – 0.69	< 0.001
Hypothermia management			
No	ref		
Yes	5.03	4.07 – 6.15	< 0.001

AIC 161979.14

Table 5.5: Changes in the OR (male vs female) for favourable neurological function

Model	OR[1] (M vs. F)	(95% CI)	*P* value[2]	Variable included
Model 1	1.16	0.99 – 1.36	0.06	Age, duration to EMS arrival, arrest in public location, witnessed status, bystander CPR, initial shockable rhythm, advanced airway, hypothermia, management, and administration of epinephrine
Model 2	1.17	1.02 – 1.35	0.005	Model 1 except hypothermia
Model 3	1.44	1.25 – 1.67	< 0.001	Model 1 except initial rhythm
Model 4	1.53	1.33 – 1.75	< 0.001	Model 1 excerpt hypothermia and initial rhythm

[1] Odds ratio (males vs females).
[2] *P* value < 0.05 is significant.

Table 5.6: Hierarchical multivariable logistic regression analysis stratified by sex

	Males model n = 14307 (63.8%)			Females model n = 8109 (36.2%)		
Variable	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**
EMS arrival (per min)	0.91	0.88 – 0.94	< 0.001	0.96	0.94 – 0.98	< 0.001
Age (per year)	0.97	0.96 – 0.98	< 0.001	0.98	0.97 – 0.99	< 0.001
Location of arrest						
Not public						
Public	1.70	1.35 – 2.26	< 0.001	1.74	1.34 – 2.25	< 0.001
Witness status						
Unwitnessed						
Bystander witnessed	2.90	2.40 – 3.51	< 0.001	2.04	1.76 – 2.35	< 0.001
CPR status						
No CPR						
Bystander CPR	1.35	1.15 – 1.60	< 0.001	1.24	1.03 – 1.49	0.006
Chest compression rate						
50-99						
100-120	1.72	1.35 – 2.18	< 0.001	1.42	1.05 – 1.88	< 0.001
>120	1.01	0.63 – 1.61	0.96	0.95	0.57 – 1.56	0.84
Initial rhythm						
Nonshockable						
Shockable	7.29	6.03 – 8.81	< 0.001	3.76	3.06 – 4.62	< 0.001
Epinephrine						
No						
Yes	0.09	0.08 – 0.11	< 0.001	0.27	0.21 – 0.33	< 0.001
Advanced airway						
No						
Yes	0.55	0.44 – 0.68	< 0.001	0.45	0.38 – 0.52	< 0.001
Hypothermia management						
No						
Yes	7.21	5.91 – 8.75	< 0.001	2.46	1.98 – 3.05	< 0.001

Table 5.7: Hierarchical multivariable regression model for favourable neurological outcome Included one interaction (Sex*Initial rhythm)

	Full cohort N = 22,416		
Variable	**OR**	**(95% CI)**	***P* value**
EMS arrival interval (per min)	0.92	0.90 – 0.94	< 0.001
Age (per year)	0.97	0.96 – 0.98	< 0.001
Sex			
Female	ref		
Male	1.02	0.98 – 1.10	0.07
Location of arrest			
Not public	ref		
Public	1.78	1.53 – 2.06	< 0.001
Witness status			
Unwitnessed	ref		
Witnessed	2.93	2.50 – 3.43	< 0.001
CPR status			
No CPR	ref		
Bystander CPR	1.27	1.17 – 1.48	< 0.001
Chest compression rate			
50-99	ref		
100-120	1.58	1.24 – 1.93	< 0.001
>120	0.97	0.65 – 1.44	0.86
Initial cardiac rhythm			
Nonshockable	ref		
Shockable	2.73	2.52 – 6.97	< 0.001
Epinephrine			
No	ref		
Yes	0.08	0.07 – 0.09	< 0.001
Advanced airway			
No	ref		
Yes	0.59	0.49 – 0.70	< 0.001
Hypothermia management			
No	ref		
Yes	5.06	4.10 – 6.17	< 0.001
Sex * Initial rhythm	1.44	1.35 – 1.54	0.001

AIC 161549.14

Table 5.8: Hierarchical multivariable regression model for favourable neurological outcome

Included 2 interaction terms: Sex*Initial rhythm and Sex*Hypothermia

	Full cohort N = 22,416		
Variable	**OR**	**(95% CI)**	***P* value**
EMS arrival interval (per min)	0.92	0.80 – 0.94	< 0.001
Age (per year)	0.97	0.96 – 0.97	< 0.001
Sex			
Female	ref		
Male	1.05	0.81 – 1.36	0.74
Location of arrest			
Not public	ref		
Public	1.79	1.54 – 2.08	< 0.001
Witness status			
Unwitnessed	ref		
Witnessed	3.03	2.58 – 3.56	< 0.001
CPR status			
No CPR	ref		
Bystander CPR	1.23	1.11 – 1.48	< 0.001
Chest compression rate			
50-99	ref		
100-120	1.58	1.30 – 1.94	< 0.001
>120	0.97	0.65 – 1.44	0.86
Initial cardiac rhythm			
Nonshockable	ref		
Shockable	6.48	5.40 – 7.75	< 0.001
Epinephrine			
No	ref		
Yes	0.10	0.08 – 0.12	< 0.001
Advanced airway			
No	ref		
Yes	0.59	0.49 – 0.70	< 0.001
Hypothermia management			
No	ref		
Yes	4.75	3.59 – 6.29	< 0.001
Sex * Initial rhythm	0.99	0.93 – 1.08	0.94
Sex * Hypothermia	1.28	1.10 – 1.48	0.001

AIC 161617.85

Table 5.9: Hierarchical multivariable regression model for favourable neurological outcome Included one interaction (Sex*Hypothermia)

	Full cohort N = 22,416		
Variable	**OR**	**(95% CI)**	***P* value**
EMS arrival interval (per min)	0.92	0.80 – 0.94	< 0.001
Age (per year)	0.97	0.96 – 0.97	< 0.001
Sex			
Female	ref		
Male	0.98	0.89 – 1.07	0.59
Location of arrest			
Not public	ref		
Public	1.77	1.53 – 2.07	< 0.001
Witness status			
Unwitnessed	ref		
Witnessed	3.01	2.57 – 3.54	< 0.001
CPR status			
No CPR	ref		
Bystander CPR	1.28	1.17 – 1.48	< 0.001
Chest compression rate			
50-99	ref		
100-120	1.58	1.30 – 1.94	< 0.001
>120	0.97	0.65 – 1.44	0.86
Initial cardiac rhythm			
Nonshockable	ref		
Shockable	6.53	5.47 – 7.80	< 0.001
Epinephrine			
No	ref		
Yes	0.10	0.08 – 0.12	< 0.001
Advanced airway			
No	ref		
Yes	0.59	0.49 – 0.70	< 0.001
Hypothermia management			
No	ref		
Yes	4.94	3.76 – 6.48	< 0.001
Sex * Hypothermia	1.13	1.05 – 1.22	0.002

AIC 160530.153

Table 5.10: Modified Rankin Scale

Scale	Description
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
3	Moderate disability: requiring some help, but able to walk without assistance.
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own needs without assistance.
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
6	Dead

Chapter 6: The impact of premenopausal age on neurological function at hospital discharge

6.1 Summary

We investigated the impact of premenopausal age on neurological function at hospital discharge in patients with OHCA. We hypothesized that premenopausal-aged females (18-47 years of age) with OHCA would have a higher probability of survival with favourable neurological function at hospital discharge compared with males of the same age group, older males, and older females (>53 years of age).

This study was a multilevel analysis of data from the Resuscitation Outcomes Consortium multi-center randomized controlled trial (June 2011 to May 2015). We included adults with non-traumatic OHCA treated by emergency medical service. We stratified the cohort into four groups by age and sex: premenopausal-aged females (18 to 47 years of age), older females (≥53 years old), younger males (18 to 47 years of age), and older males (18 to 47 years of age). We used multilevel logistic regression to examine the association between age-sex and favourable neurological outcomes (modified Rankin Scale ≤ 3).

In total, 23,725 patients were included: 1,050 (4.5%) premenopausal females; 1,930 (8.1%) younger males; 7,569 (31.9%) older females; and 13,176 (55.5%) older males. The multilevel analysis showed no difference in neurological outcome between younger males and younger females (OR 0.95, 95% CI 0.69 – 1.32, p = 0.75). Both older females (OR 0.36, 95% CI 0. 0.26 – 0.48, *p* < 0.001) and older males (OR 0.52, 95% CI 0.39 –0.69, *p* < 0.001) had a significantly

lower odds of favourable neurological outcome than younger females. Among all groups, older females had the worst outcomes. The results suggest females sex hormones do not impact OHCA outcomes.

6.2 Introduction

Sudden OHCA is a serious health concern in North America and worldwide (150). Providing cardiac arrest victims with prompt and optimal out-of-hospital intervention improves the probability of survival with good neurological function (13,19,22,24,43,73,151). Previous research demonstrated that younger age is associated with better survival (82,95). In addition to age, several studies showed that female sex is associated with a higher probability of ROSC (69–71). However, studies examining the effect of sex on survival to hospital discharge have reported contradictory results. While some reported no difference in hospital-discharge survival by sex (64,79,96), others have shown increased survival in females (25,70), and in other studies (62,71) higher survival in males.

Other researchers have delved deeper and examined the interaction effect of age and sex on resuscitation outcomes (63,71,97,98). Some studies reported that younger females, particularly of premenopausal age, had a higher probability of survival to hospital discharge than males in the same age group (63,71,97,98). Morrison et al. reported that 15-45 years old females had 1.66 times higher odds of survival to hospital discharge compared to age-matched males (63). Johnson et al. reported similar results (71). These results suggest that there may be a protective effects of female sex hormones to explain this survival advantage in premenopausal women. Of note, these previous studies focused on survival to hospital discharge but paid no or little attention to neurological function, whereas it is possible that sex hormones may affect the impact that cardiac arrest has on long-term neurological function. Two other studies that examined the interaction effect of age and sex on OHCA neurological outcome (97,100) reported conflicting results. While Kitamura et al. reported survival with good neurological advantage in females (97), Oh et al. found that female sex has no impact on neurological outcome (100).

The primary objective of this study was to investigate the potential impact of premenopausal age on neurological function at hospital discharge in patients with OHCA. We assumed that females 18 to 47 years old would have a higher concentration of female reproductive hormones, with the hypothesis that these hormones would result in higher probability of survival with favourable neurological outcomes compared to males of the same age, older males, and older females.

6.3 Methods

6.3.1 Design and setting

We analyzed data from the Resuscitation Outcome Consortium (ROC) Trial of Continuous or Interrupted Chest Compressions during CPR (the "CCC Trial") (140). The ROC a research network with 10 clinical centers in the USA and Canada conducting clinical research on OHCA resuscitation and outcomes (104). A detailed description of the regions and EMS agencies participated in the CCC trial has been published (140).

The ROC CCC Trial was an unblinded cluster randomized clinical trial including 114 emergency medical service (EMS) agencies in the USA and Canada, grouped into 47 clusters. Between June 2011 and May 2015, The CCC trial included non-traumatic EMS-treated OHCA $\geq$ 18 years and excluded patients who had arrest witnessed by EMS, "do not attempt resuscitate" order, and cardiac arrests due to asphyxia, uncontrolled bleeding, or known pregnancy. The trial evaluated the effect of chest compressions provided continuously versus chest compressions interrupted for ventilations on the survival and neurological function (140). The trial results demonstrated no significant outcome difference between the intervention group (chest compressions provided continuously) and control group (chest compressions interrupted for ventilation), suggesting a low risk of bias with post-hoc dataset analyses.

6.3.2 Study population

From the CCC data, we created an analytic dataset. We excluded cases with non-cardiac etiology of arrest, patients for whom age or sex was not recorded, and patients aged 48 to 52 years. Based on previous data (63,97,152), it is difficult to categorize individuals aged 48-52 into pre- or post-menopausal, as menopause is likely to happen during this time frame but with variability. Similar to previous studies (63,98), to reduce the risk of misclassification bias, we excluded these from our analysis.

6.3.3 Key variables of interest and measurements

The key independent variable was premenopausal status. Based on the estimation and assumptions from the literature (63,97,152), we classified 18 to 47 years old as premenopausal and ≥ 53 years old as postmenopausal (older females). Age and biological sex variables were combined into one variable named 'age-sex' and patients were stratified into four groups: premenopausal females, postmenopausal or older females, younger males (18 to 47 years of age), and older males (≥53 years old). The primary outcome was favourable neurological function at hospital discharge, defined as a modified Rankin Scale (mRS) score of ≤ 3 (Table 6.4) (141,153). The secondary outcome was survival to hospital discharge. This study assumes that females 18 to 47 years old would have a higher concentration of female reproductive hormones, with the hypothesis that these hormones would result in better survival with favourable neurological outcomes compared to males of the same age, older males, and older females.

6.3.4 Statistical analysis

We calculated descriptive statistics for baseline characteristics for the full cohort and stratified by age-sex groups. Continuous variables were presented as mean and SD, or median and interquartile range, as appropriate. Categorical variables were presented as counts and percentages. We compared baseline characteristics and outcomes by age-sex. We compared females to males within the same age groups using student's t-test (for continuous and normally distributed variables), Mann–Whitney *U* test (for continuous and not normally distributed variable), and Chi-Squared test (for categorical variables). All bivariate relationships were assessed at a 5% level of significance.

We employed multilevel (hierarchical) logistic regression analysis to examine the interaction effect of sex and age on neurological outcome. Multilevel modeling was necessary to account for the nesting of patients (level one) within 47 clusters (level two) (99). We ran the analyses as follows: first, we created a dummy variable (age-sex) with four categories, as mentioned above: young female, young male, old female, old male, and we specified the young females' group as the reference group. Secondly, we built a random intercept model and specified fixed regression coefficients of (age-sex). Thirdly, we added other predictors (one by one) to the model. Thereby, we built a series of multivariable mixed models (random intercept models with patient-level predictors). This allowed us to account for the clustering effect. In these models, we dealt with the dummy variable, (age-sex), as an independent variable, and controlled for the other patient-level covariates known to be associated with survival (129). All the patient-level variables were modelled as fixed effects, and the cluster was modeled as a random effect. The dependent variable was neurological function at hospital discharge (favourable vs. unfavourable neurological function). We used the Likelihood Ratio Tests (LRT) to evaluate the overall fit of the models and therefore choose the final model (143). Fourthly, to examine associations between outcomes and categories of age and sex among: (i) those who were transported to hospital (i.e. not pronounced dead in the prehospital setting); and, (ii) among those who survived to hospital discharge; we repeated the analysis within these two subgroups of the cohort. For the latter subgroup 2 analysis, we only examined the outcome of neurological function at hospital discharge, as all were hospital-discharge survivors. Whereas sex hormones may not have an impact among those who are declared dead early on the treatment pathway, we hypothesized that these hormones may have effects on neurological recovery, and thus more apparent in these subgroups. Finally, we conducted an analysis for the secondary outcomes (survival to hospital admission and discharge) for the cohort. All statistical analyses were performed using R version 4.0.1, Vienna, Austria.

6.3.5 Ethics approval

Ethics approval for this study was obtained from the affiliated University of British Columbia - Providence Health Care Research Ethics Board.

6.4 Results

6.4.1 Patients characteristics

A total of 26,148 patients with OHCA were included in the CCC trial from June 2011 to May 2015. After excluding those who did not meet the inclusion criteria, 23,725 patients were eligible for and included in the analysis (Figure 6.1). Of those, 1,050 (4.5%) were younger females, 1,930 (8.1%) were younger males, 7,569 (31.9%) were older females, and 13,176 (55.5%) were older males.

The summary statistics for the baseline characteristic, interventions, and outcomes, stratified by age-sex, are shown in (Table 6.1). When comparing the young males to the young females, the unadjusted analyses showed that young males had a higher proportion of OHCA in public locations (21.9% vs. 11.6%, $p < 0.001$), a higher proportion with an initial shockable rhythm (22.3% vs. 19.0%, $p < 0.001$), and a higher proportion received epinephrine (83.2% vs. 79.7%, $p = 0.02$), No significant differences were detected between the two groups regarding the other patient-level characteristics or outcomes (Table 6.1). When comparing the older males to the older females, we found among old males, there was a higher proportion of OHCA occurring in public locations (17.4% vs. 6.9%, $p < 0.001$), a higher proportion of bystander CPR (47.2% vs. 44.4, $p < 0.001$), and a higher proportion with an initial shockable rhythm (27.8% vs. 13.5%, $p < 0.001$). Older males were also more likely to receive epinephrine, advanced airway and hypothermia management. Favourable neurological outcome at hospital discharge was significantly higher in older males (8.2% vs. 3.7%, $p < 0.001$) (Table 6.1).

6.4.2 Multilevel logistic regression analyses

6.4.2.1 Random intercept model with level one predictors

Table 6.2 shows the final mixed multivariable model and the adjusted ORs with 95% confidence intervals for favourable neurological outcome. After adjusting for patient-level variables known to be associated with survival, we did not detect a significant difference in neurological outcome between younger males and younger (premenopausal) females (male OR 0.95, 95% CI 0.69 – 1.32, p = 0.75). Both older females (OR 0.36, 95% CI 0. 0.26 – 0.48, p < 0.001) and older males (OR 0.52, 95% CI 0.39 –0.69, p < 0.001) had a significantly lower odds of favourable neurological outcome than younger females. Older females were the least likely group to discharge with good neurological outcome (Table 6.2). All patient-level predictors made an independent, statistically significant contribution to the model. Initial shockable rhythm reported the largest effect size. Patients with an initial shockable rhythm had 7.58 times greater odds of survival with good neurological function compared to those with an unshockable rhythm, holding all other predictors constant (OR 7.58, 95% CI 6.53 – 8.83, p < 0.001).

With regards to the secondary outcome, the analyses showed no difference in survival to hospital admission between younger females and younger males (male OR 0.86, 95% CI 0.72 – 1.03, p = 0.09), and no difference in survival to hospital discharge either (male OR 0.91, 95% CI 0.67 – 1.23, p = 0.54), controlling for other variables known to be associated with survival (Table 6.3). Both older females and older males had a significantly lower odds of survival to hospital admission and hospital discharge. Among the four groups, older females had the lowest odds of survival to hospital admission and hospital discharge (Table 6.3).

6.4.3 Subgroup 1 analysis (patients transported to hospital)

Of the total cohort (N = 23725), 12718 (53.6%) were transported to hospital (including 55.3% [8355/15106] of the males in the cohort and 50.6% [4362/8619] of the females). Results of this subgroup analysis were similar to the full cohort. The adjusted multilevel analysis showed no significant difference in neurological outcome between younger males and females in the same age group (OR 0.95, 95% CI 0.70 – 1.31, $p = 0.76$) (Table 6.2). Males in the older age group had lower odds of favourable neurological outcome than younger (OR 0.58, 95% CI 0.45 –0.77, $p < 0.001$). Among all groups, older females had the lowest odds of favourable neurological outcome, controlling for other variables known to be associated with survival (OR 0.40, 95% CI 0.30 – 0.55, $p < 0.001$) (Table 6.2).

6.4.4 Subgroup 2 analysis (patients transported to hospital and discharged alive)

Of the total cohort (N = 23725), 2052 (8.6%) were discharged from hospital alive (including 10.2% [1536/15106] of the males in the cohort and 6.0% [516/8619] of the females). A total of 81.2% of those who survived to hospital discharge (1666/2052) had good neurological outcome. The multilevel analysis for this subgroup revealed no significant difference in neurological outcome between younger males and females in the same age group, controlling for other variables known to be associated with survival (OR 0.93, 95% CI 0.49 – 1.78, $p = 0.82$). Older males had a lower odds of favourable neurological outcome (OR 0.64, 95% CI 0.38 – 1.09, $p < 0.10$); however, this result was not statistically significant (Table 6.2). Older female had the lowest odds of favourable neurological outcome (OR 0.39, 95% CI 0.22 – 0.66, $p = 0.002$).

6.5 Discussion

We identified OHCAs from a large multicenter North American dataset and classified cases by age and sex. We found that there was no significant difference in neurological or survival outcomes between females of premenopausal age and males in the same age group. Moreover, the analyses revealed that there was no significant difference in survival to hospital admission and to hospital discharge between females of premenopausal age and their age-matched males. Our result suggests that premenopausal status, defined by age, does not confer protective outcomes effects among victims of OHCA.

Our data indicates that the incidence of OHCA in females was approximately half of males, both within the younger and the older comparison groups. This is consistent with previous research, demonstrating that regardless of any outcome differential between females or males who experienced OHCA, women are much less likely to experience an OHCA (154). When examining OHCA characteristics of males and females, we found that females were less likely to have an OHCA in a public location and have initial shockable rhythms. This was more prominent in the older age category however still apparent in the younger group. Similar to previous reports (21,139,155), initial shockable rhythm was the covariate with the strongest association with outcomes. While initial rhythm may indicate systematic differences in the etiology of the arrest, this may also be due to longer no-flow durations, suggested by fewer witnessed and public location arrests (131). Whatever the reason for the differences in OHCA location by sex, efforts to improve the outcomes of female OHCAs victims may focus on early identification of unwitnessed arrests in private locations. While females were more likely to have private location OHCAs, we did not see evidence of differences in care provided by prehospital or hospital-based clinicians. After adjusting for baseline differences, we found that there was no difference in neurological or survival outcomes between females of premenopausal age and males in the same age group. Moreover, the adjusted analyses revealed that both older females and older males had a lower odds of neurological outcome. We hypothesized that outcomes may differ between categories of age and sex among those who were transported to hospital and among those who survived to hospital discharge. Despite using a large sample size, we were unable to detect an association between age-sex categories and outcomes.

When we compared our findings with previously reported results, we found, in line with our study, a recent Korean study reporting females of child-bearing age have no advantage in neurological outcomes (100). Likewise, a study in Australia revealed the age-sex interaction was not significant for survival to hospital discharge (69). On the other hand, many other studies examining the effect of age and sex on OHCA outcomes reported survival to hospital discharge and survival with favourable neurological function advantages in premenopausal females. These studies suggested female sex hormones have positive impact of OHCA outcomes (63,71,97,98). Our findings of no survival advantage in premenopausal females, therefore, do not support these previous data postulating positive effects of female sex hormones on OHCA outcomes.

The discrepancies between our findings and other studies' findings could also be explained by issues related to inclusion, methodology, and analysis. Topjian et al. reported survival at hospital discharge advantage in premenopausal females. However, that study focused on in-hospital cardiac arrest only and excluded OHCA cases from their analyses (98). A study in Japan demonstrated survival with good neurological function advantage in females (97). However, EMS treatment protocols in Japan differ from those in North America. For example, “do not attempt resuscitation orders” and “termination of resuscitation efforts at the scene” are not applied in Japan (97). A North American study reported that premenopausal females had 1.66 higher odds of survival to hospital discharge compared to young males. However, this study used standard logistic regression to analyze nested data. Nested data violate the logistic regression assumption of interdependence of observations (26,34); therefore, applying multilevel analysis to account for clustering effect is the appropriate way to analyze this type of data. Not accounting for clustering effect can increase the odds of finding a relationship when it does not exist, i.e. inflated type 1 error (99).

It is worth noting that our results showed that the majority (81.2%) of those who survived to hospital discharge had good neurological outcome. Additionally, our analyses suggested that administration of epinephrine is associated with decreased odds of favourable neurological outcome. This is possibly due to the peripheral vasoconstriction effect of epinephrine as reported in an animal study (148). However, other animal studies showed an increase cerebral flow with continuous (156) and bolus doses of epinephrine (149). Our dataset had no data on continuous doses and limited data on bolus doses. Increased epinephrine is also associated with longer resuscitation and therefore no or low flow duration and subsequent increased ischemic insult (157).

Another important finding of our study was that, with adjustment for baseline characteristics, the older females’ group had the worst outcomes. They were the least likely group to survive to hospital discharge and survive with good neurological function. These disadvantages in older females were observed in the full cohort and in the subgroups' analyses. A recent North American study reported similar result (139). This disadvantage could be explained by the fact that the females in this age-group were older than their male counterparts (median age 76 vs. 71 years, $p < 0.001$).

Another possible explanation for the poor outcomes among older females is that they might have received less resuscitation and post resuscitation efforts during and after OHCA. Our bivariate analyses showed older females were less likely to receive epinephrine, advanced airway and hypothermia management compared to older males, but there was no significant difference in care delivery between younger females and males in the same age group. A previous study in Canada showed no sex-based differences in provision of bystander CPR and in chest compression rate by EMS rescuers, but without age stratification (67).

Our study has several limitations. First, though the study analyzed a large dataset from several North American regions and the results may be generalizable to North American jurisdictions, they may not be generalizable elsewhere in the world. Second, data on some variables, such as comorbidities, time of the event (OHCA), withdrawal of life sustaining therapies, do not resuscitate (DNR) status and other in-hospital interventions were incomplete in the dataset, and therefore they were not included in the analyses. If there were sex differences in these unmeasured variables and these differences disadvantaged younger females, controlling for these variables may have produced results in favour of females that may suggest a protective effect from sex hormones. Finally, the study used premenopausal age (18-47) as a surrogate of female sex hormones. We did not examine the actual effect of female sex hormones due to a lack of actual data on estrogen and progesterone levels.

6.6 Conclusion

In this large cohort of EMS-treated, OHCA in North America, we did not detect an association between premenopausal-age and survival with good neurological outcomes. The study results suggest that females sex hormones do not have a beneficial impact on OHCA outcomes. Our findings are not in line with results from other studies. Studies that prospectively define and evaluate menopausal status may be required to definitively assess the impact of female sex hormones on outcomes.

Note: A version of Chapter 6 was recently published in the Resuscitation Journal (158)

Figure 6.1: Study flow diagram

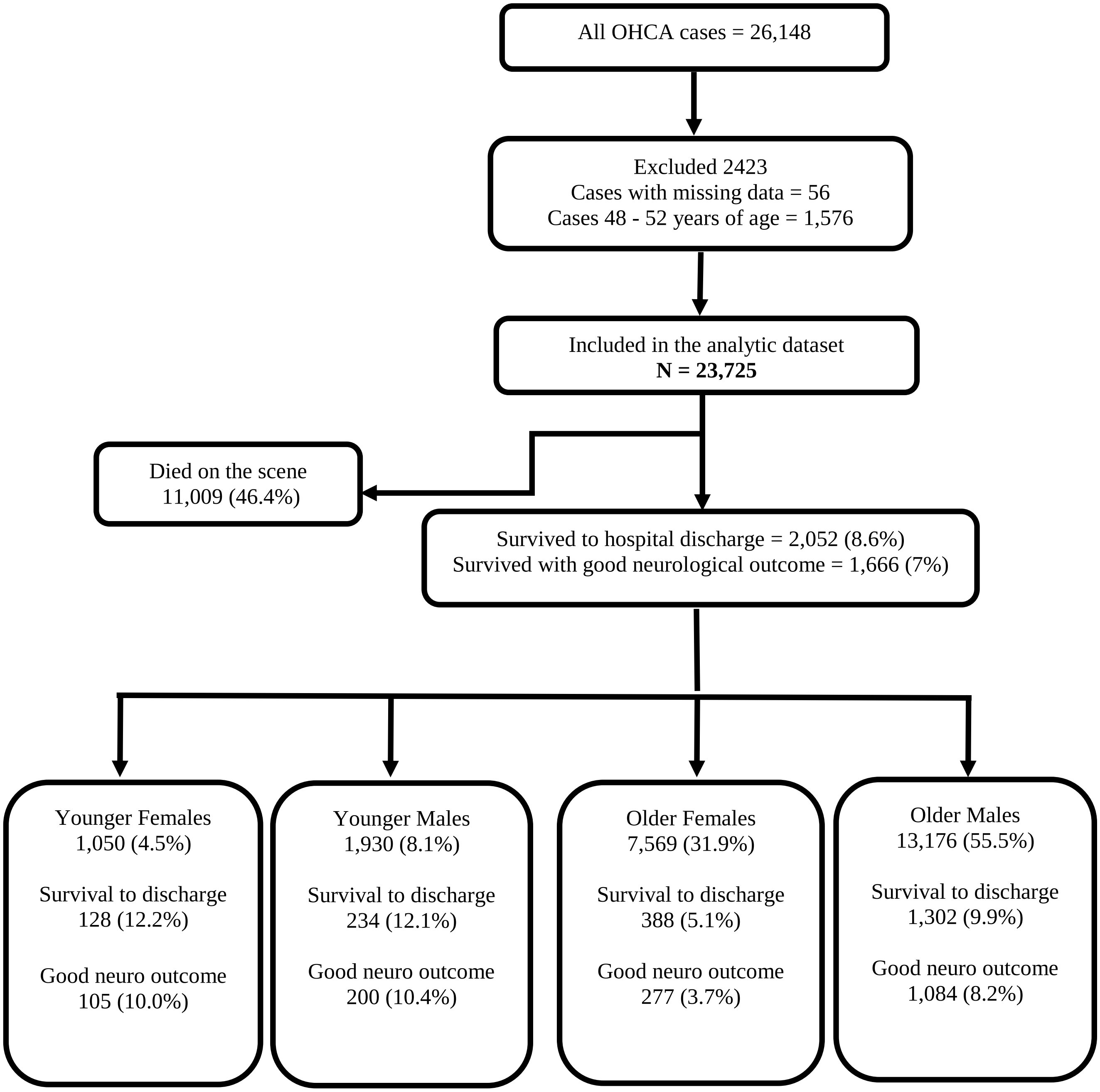

Table 6.1: Sex-Age group differences in baseline characteristic, interventions, and outcome

Patient-level variables*	Total 23,725	Young Females 1,050 (4.5%)	Young Males 1,930 (8.1%)	*P value*	Old Females 7,569 (31.9%)	Old Males 13,176 (55.5%)	*P value*
Age, median (IQR)	68 (56–81)	38 (30–44)	37(30–44)	0.93	76 (65–85)	71 (62–81)	<0.001
Arrest Location							
Nonpublic	20,367 (85.8%)	931 (88.7%)	1,504 (77.9%)	<0.001	7,048 (93.1%)	10,884 (82.6%)	<0.001
Public	2,292 (14.2%)	119 (11.3%)	426 (22.1%)		521 (6.9%)	2,292 (17.4%)	
EMS arrival time interval (mean±SD)	(5.7± 2.72)	(5.4± 2.5)	(5.6± 2.5)	0.09	(5.8± 2.8)	(5.8± 2.7)	0.21
Bystander witness							
Unwitnessed	13,611 (57.4%)	703 (67.0%)	1,255 (65.0%)	0.29	4,567 (60.3%)	7,086 (53.8%)	< 0.001
Witnessed	10,114 (42.6%)	347 (33.0%)	675 (35.0%)		3,002 (39.7%)	6,090 (46.2%)	
Bystander CPR							
No	12,761 (53.8%)	574 (54.7%)	1,026 (53.2%)	0.43	4,208 (55.6%)	6,953 (52.8%)	< 0.001
Yes	10,964 (46.2%)	476 (45.3%)	904 (46.8%)		3,361 (44.4%)	6,223 (47.2%)	
Initial rhythm							
Nonshockable	18,300 (77.2%)	833 (79.3%)	1,472 (76.3%)	0.01	6,526 (86.2%)	9,469 (71.8%)	< 0.001
Shockable	5348 (22.5%)	212 (20.2%)	454 (23.5%)		1,023 (13.5%)	3,659 (27.8%)	
Unknown	77 (0.3%)	5 (0.5%)	4 (0.2%)		20 (0.3%)	48(0.4%)	
Administration of epinephrine							
No	4,211 (17.8%)	213 (20.3%)	324 (16.8%)	0.02	1,440 (19.0%)	2,234 (17.0%)	< 0.001
Yes	19,514 (82.2%)	837 (79.7%)	1,606 (83.2%)		6,129 (81.0%)	10,942 (83.0%)	
Advanced airway							
No	5,295 (22.3%)	227 (21.6%)	425 (22.0%)	0.80	1,856 (24.5%)	2,787 (21.2%)	< 0.001
Yes	18,430 (77.7%)	823 (78.4%)	1,505 (78.0%)		5,713 (75.5%)	10,389 (78.8%)	
Targeted Temp Management							
No	20,061 (84.5%)	864 (82.3%)	1,599 (82.8%)	0.69	6,629 (87.6%)	10,969 (83.2)	< 0.001
Yes	3,664 (15.5%)	186 (17.7%)	331 (17.2%)		940 (12.4%)	2,207(16.8%)	
Survival outcomes							
ROSC							
No ROSC	11,019 (46.5%)	418 (39.8%)	775 (40.2%)		3,844 (50.8%)	5,982 (45.8%)	
Pre-hospital ROSC	5800 (24.4%)	271 (25.8%)	440 (22.8%)	0.13	1,798 (23.8%)	3,291 (25.0%)	< 0.001
Ongoing resuscitat [a]	6906 (29.1%)	361 (34.4%)	715 (37.0%)		1,927 (25.5%)	3,903 (29.6%)	
Hospital discharge							
Died	21,673 (91.3%)	922 (87.8%)	1,696 (87.9%)	0.96	7,181 (94.9%)	11,874 (90.1%)	
Survived	2,052 (8.7%)	128 (12.2%)	234 (12.1%)		388 (5.1%)	1,302 (9.9%)	< 0.001
Neuro outcomes							
Unfavourable	22,059 (93.0%)	945 (90.0%)	1,730 (89.6%)	0.80	7,292 (96.3%)	12,092 (91.8%)	< 0.001
Favourable	1,666 (7.0%)	105 (10.0%)	200 (10.4%)		277 (3.7%)	1,084 (8.2%)	

Table 6.2: Hierarchical multivariable logistic regression for favourable neurological outcome

	Full cohort N = 23,725			Subgroup 1 (Transported to hospital) n = 12,718			Sub-group 2 (Alive at hospital discharge) n = 2,052		
Variable	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**
Age-sex group									
Young female	ref			ref			ref		
Young male	0.95	0.69 – 1.32	0.752	0.95	0.70 – 1.31	0.760	0.93	0.49 – .78	0.821
Old female	0.36	0.26 – 0.48	< 0.001	0.40	0.30 – 0.55	< 0.001	0.39	0.22 – 0.66	0.002
Old male	0.52	0.39 –0.69	< 0.001	0.58	0.45 – 0.77	< 0.001	0.64	0.38 – 1.09	0.105
EMS arrival time interval	0.94	0.92 – 0.97	< 0.001	0.95	0.93 – 0.98	< 0.001	0.96	0.94 – 0.99	0.045
Public location	1.94	1.68 – 2.32	< 0.001	1.59	1.38 – 1.83	< 0.001	2.11	1.57 – 2.86	< 0.001
Byst witness	2.66	2.29 – 3.13	< 0.001	2.02	1.74 – 2.36	< 0.001	1.49	1.22 – 1.97	0.006
Bystander CPR	1.43	1.24 – 1.61	< 0.001	1.40	1.22 – 1.60	< 0.001	1.14	0.89 – 1.45	0.270
Shockable rhythm	7.58	6.53 – 8.83	< 0.001	5.41	4.66 – 6.27	< 0.001	3.05	2.31 – 4.05	< 0.001
Administration of epinephrine	0.08	0.07 – 0.09	< 0.001	0.08	0.07 – 0.09	< 0.001	0.24	0.17 – 0.31	< 0.001
Target temp management	6.8	5.91 – 7.8	< 0.001	4.09	3.57 – 4.70	< 0.001	1.01	0.77 – 1.33	0.840

Table 6.3: OHCA survival outcomes by age and sex (N= 23,725)

	Survival to hospital admission		Survival to hospital discharge		Favourable neurological outcome	
Age – sex group	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Young female **(Ref)**						
Young male	0.86 (0.72 – 1.03)	0.087	0.91 (0.67 – 1.23)	0.536	0.95 (0.69 – 1.32)	0.752
Old female	0.67 (0.59 – 0.79)	< 0.001	0.41 (0.31 – 0.51)	< 0.001	0.36 (0.26 – 0.48)	< 0.001
Old male	0.62 (0.54 – 0.72)	< 0.001	0.53 (0.41 – 0.68)	< 0.001	0.52 (0.39 –0.69)	< 0.001

Hierarchical multivariable logistic regression analyses were used.
ORs are adjusted for EMS arrival time interval, location of arrest, bystander witnessed status, bystander CPR, initial cardiac rhythm, administration of epinephrine, and target temperature management.

Table 6.4: Modified Rankin Scale

Scale	Description
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
3	Moderate disability: requiring some help, but able to walk without assistance.
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own needs without assistance.
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
6	Dead

Chapter 7: Conclusions

The predominant goal of this dissertation was to enhance our comprehensive understanding of out-of-hospital cardiac arrest (OHCA), particularly with respect to sex differences in OHCA characteristics, interventions, and outcomes. In addition, this research has provided a comprehensive review of the current evidence on the factors influencing resuscitation outcomes in adults with OHCA and has also highlighted the knowledge gaps in the literature (Chapter 1). The objectives of this dissertation refer to six areas of OHCA research, namely sex differences in OHCA interventions, survival to hospital discharge, one-year survival rates, prehospital predictors of survival, and the impact of premenopausal status on survival. To start off with objective 1 provided an overview of current knowledge of the predictors of survival in adults suffering OHCA in addition to the current knowledge of the effect of sex on survival (Chapter 1- Litrature review). Objective 2 quantified and evaluated sex differences in the OHCA interventions in the province of British Columbia (BC), Canada, specifically examining the provision of bystander cardiopulmonary resuscitation (CPR), chest compression rate of professional rescuers, and the decision to initiate hospital transportation in the absence of ROSC (Chapter 2). Objective 3: relates to quantification and evaluation of sex differences in achieving ROSC and survival to hospital discharge in a cohort of patients with OHCA in the metropolitan regions of BC, Canada (Chapter 3). Objective 4: deals with investigation of sex differences in one-year survival in a cohort of patients who survived OHCA and who were discharged from hospital alive (Chapter 4). Objective 5: has been to identify the statistically significant predictors of survival with good neurological function at hospital discharge after OHCA (Chapter 5). The 6th and final objective has been to investigate the potential impact of premenopausal age on neurological function at hospital discharge (Chapter 6).

7.1 Key Findings

7.1.1 Factors influencing survival

Chapter 1 provided an overview of current knowledge of the predictors of survival in adults suffering OHCA. Previous studies unanimously agreed that the main independent variables found to be associated with improved survival outcomes include younger age; shorter duration of EMS response; witnessed arrest; provision of bystander CPR; high quality of CPR, including chest compression rate, depth, and fraction; initial shockable rhythm; and early defibrillation. Many of these variables, such as early EMS response, bystander CPR, quality CPR, and early defibrillation, are intervention-related factors that are linked to the chain of survival described by the AHA. Adequately implementing the chain of survival is crucial to achieve the best chance of survival for patients suffering OHCA. In addition to treatment-related factors, some evidence suggests that sex as a biological factor may influence survival. Several studies examined the effect of sex on OHCA short term outcomes; however, they reported contradictory results.

7.1.2 Equal likelihood of females and males in BC to receive bystander CPR and chest compression rate

The findings from Chapter 2 demonstrated that, overall, in BC females and males with OHCA are equally likely to receive bystander CPR if they arrest in a public location. However, females are significantly less likely to arrest in a public location. Our analysis revealed that bystander CPR was more common for males in crude analysis. However, after adjustment for location type (public vs. private), sex was no longer significant. This suggests that the likelihood of bystander CPR may be less related to sex itself or gender, but more related to differences in the locations at which male or female cases may have a cardiac arrest. Further research would shed more light on this area.

Research conducted in other countries have consistently reported that females with OHCA receive less prehospital treatments, including bystander CPR. A recent multivariable analysis in the USA (113) reported that provision of bystander CPR in public locations is significantly higher in males compared to females. Interestingly, this does not seem to be the case in BC.

Regarding the quality of CPR, our analyses did not demonstrate a difference in the mean chest compression rate or the proportion that had a compression rate in the recommended range, when dichotomized by sex. The AHA guidelines for the management of cardiac arrest recommend providing chest compression at a rate of 100-120 compressions per minute (43). A CCR of 100 to 120 is associated with improved survival (15,49). Our descriptive and inferential statistics related to CCR suggest that EMS personnel in BC are closely adhering to the AHA guideline for OHCA CCR for both males and females.

7.1.3 Females with OHCA are less likely to be transported to hospital prior to ROSC

The results from Chapter 2 also demonstrated that in BC, female patients who did not achieve prehospital ROSC (failed prehospital resuscitation) are less likely to be transported to hospital with ongoing resuscitation compared to males. This finding suggests that for OHCA cases who remained in refractory arrest after on-scene resuscitation efforts, female cases are more likely to be declared dead at the scene of the arrest than males.

Importantly, transport to hospital with ongoing resuscitative efforts is uncommon, with full resuscitations typically taking place at the scene of the arrest unless a reversible cause is identified that may be amenable to hospital-based care (120). It is unclear whether our finding represents gender-based inequities in the intensity of care provided. Alternatively, the characteristics of male cases may have been more likely to suggest an arrest etiology that was amendable to hospital-based treatment. Furthermore, systematic differences in cardiac arrest location between the sexes may have included males arresting in public locations or areas closer to a hospital, both of which may have made intra-arrest transport more feasible for males. Further research exploring the reasons for such a difference is required.

Our multivariate analysis showed that, while the sex difference in transportation to hospital before achieving ROSC was significant, the absolute difference was only 2.7% (male vs. female 36.7% vs. 34%). A prior study reported that survival to hospital discharge for patients who did not achieve prehospital ROSC is 3.6% (121). A recent study in BC reported the termination of resuscitation (TOR) guide applied at 6 minutes of resuscitation falsely recommended termination of resuscitation for 2.1% of patients (122). If we assume that the 2.7% additional females and 2.1% additional males and females, who could have been transported to hospital, had a similar 3.6% survival rate, the result would be approximately 1% additional survival. This difference could be considered statistically and clinically important given that the overall OHCA survival to hospital discharge rate in BC is 10-14% (123). Our findings suggest that a more thorough examination is needed into sex differences concerning decisions to initiate hospital transportation prior to ROSC, as well as concerning the associations between transportation and survival.

7.1.4 Females with OHCA in BC have a greater rate of ROSC but not survival to hospital discharge

Numerous previous studies in different regions of BC compared OHCA short-term survival between males and females. However, the results of these studies show a great deal of variation. Possible explanations for the discrepancies in the survival results are because of differences in characteristics of the studies' populations or differences in treatment provided to both sexes from one region to another. Unfortunately, studies focusing on sex differences in survival after OHCA in the province of BC, Canada are limited. Chapter 3 filled this gap by evaluating sex differences in achieving ROSC and survival to hospital discharge in a cohort of patients with OHCA (2011-2016) in the metropolitan regions of BC.

The findings from Chapter 3 demonstrated that females and males had four substantial differences in baseline characteristics predictive of OHCA outcomes. Females were significantly older than males; had a lower proportion with an initial shockable rhythm; had a lower incidence of arrest occurring in public location; and also were less likely to receive bystander CPR. Despite the unfavourable baseline characteristics of female OHCA, our study demonstrated nearly identical proportions of ROSC between the sexes. Further, in the multivariable analysis (after adjustment for baseline differences), female sex was associated with a higher probability of ROSC, but not survival to hospital discharge. This suggests that among those resuscitated from OHCA, females had a higher incidence of death in the post-arrest treatment period. While this may be partially due to their less favourable baseline characteristics, there could be sex disparities in post-arrest interventions, such as coronary revascularizations, that may have contributed to these post-arrest deaths.

Given that baseline differences were relatively adverse for females, we expected to find significantly lower odds of ROSC in females. It is interesting, however, that our analysis showed otherwise. This implies that another unmeasured factor improved the odds of ROSC in females. The effect of this unmeasured, unknown variable might have tilted the unadjusted odds of ROSC in favour of females. Furthermore, the effect of this unmeasured variable was not evident during the post-arrest course, leaving room for the other survival predictors to tilt the balance again in favour of males (with the adjusted odds of survival to hospital discharge being no longer significant). In other words, the unmeasured variable appeared to be advantageous to females in achieving ROSC but did not prove to be effective in survival to hospital discharge.

One hypothesis to help explain the potential unmeasured variable is the influence of sex hormones. Previous studies reported that female sex hormones may have a positive effect on resuscitation outcomes (62,70). Such possible effects of estrogen and progesterone on ROSC and survival to hospital discharge clearly requires further research.

7.1.5 Effect of sex on one-year survival post hospital discharge

The majority of previous studies of sex-based disparities in OHCA outcomes have focused on short term survival (25,60–62,64,68,79,80,100,159). However, almost all of these research projects were limited in that they adjusted for only prehospital cardiac arrest characteristics and treatment, while largely neglecting in-hospital interventions and comorbid conditions. To address this knowledge gap, Chapter 4 presents a different research focus. It provides the first study, to our knowledge, that examines the effect of sex on one-year survival, adjusting for prehospital treatment, comorbidities, and in-hospital interventions. It concentrated on a cohort of OHCA patients who survived to hospital discharge and showed that after controlling for all possible confounders, including prehospital characteristics, comorbidities, and in-hospital interventions, sex had no significant association with one-year survival.

Two other analyses examining long-term survival have reported results that indicate no sex difference in one-year mortality (75,76). In contrast with our study, these studies did not include in-hospital treatment variables in their analysis. Nevertheless, all three studies suggest that sex is not associated with long-term survival.

Our finding, however, is not generalizable to all OHCA patients, because we focused on patients who have already survived to hospital discharge. Approximately 87% (8657/ 9982) of the total OHCAs in the study cohort did not survive to hospital discharge, and therefore they were excluded from the study. It could be claimed that due to exclusion of those who did not survive to hospital discharge, survivorship bias might have been introduced. However, as mentioned above, the focus of this study was OHCA who survived to hospital discharge; therefore, the findings are generalizable to OHCA survivors discharged from hospital alive, but not to all OHCA victims. The rationale for not including those with failed prehospital resuscitation and those who died in hospital in our analysis is that such patients had no chance to be exposed to some in-hospital treatments, such as PCI and CABG or in-hospital treatments were nor indicated for them due to poor prognosis. Including those patients in the analysis, which adjusted for in-hospital treatments variables, would produce inaccurate estimates of not only the significance, but also the magnitude, of the relationships between the independent variables of interest and the outcome.

7.1.6 Predictors of favourable neurological outcomes

The analysis of Chapter 5 identified eight significant predictors of favourable neurological outcome following OHCA. These include, younger age, shorter duration of EMS arrival to the scene, arrest in a public location, witnessed arrest, bystander CPR, CCR of 100-120 compressions per minute, induction of hypothermia, and initial shockable rhythm. The strongest predictor was the initial shockable rhythm. Our analysis showed that cases with an initial shockable rhythm have 6.53 times greater odds of survival with good neurological function than those with unshockable rhythm, holding all other predictors constant (95% CI 5.47 – 7.80, $p < 0.001$). Four of these variables are modifiable treatment-related factors; including EMS arrival time, bystander CPR, CCR, and hypothermia management. Initiatives and strategies that can improve treatment characteristics, such as strategies to shorten duration of EMS arrival to the scene and training more residents in basic life support bystander CPR, could improve survival with good neurological outcomes (22).

Chapter 5 analyses also identified two predictors of poor neurological function: advanced airway management and administration of epinephrine. It is worth mentioning that advanced airway and administration of epinephrine are indicated for patients with prolonged resuscitation; perhaps those with unshockable rhythms. Therefore, the possibility of confounding by indication cannot be eliminated.

We also examined the effect of CPR quality, represented by CC rate, on neurological outcome. We found a CC rate between 100-120 compressions per minute is a significant predictor of favourable neurological function. Our analysis showed that the odds of good neurological function among those who received a CC rate between 100-120 compressions per minute is 1.6 times higher than that of patients who received 50-99 compressions per minutes, adjusting for all other predictors. Our finding is consistent with Idris et al. (16) who identified a compression rate of 100 to 119 as the rate associated with the greatest odds of survival. Interestingly, our analysis showed that chest compressions delivered at a rate higher than 120 compressions per minutes are associated with poor neurological function. A plausible explanation for this is that compressions delivered too quickly (>120/min) may not allow the chest to recoil during CPR, resulting in poor blood flow to the brain.

7.1.7 Males have a higher crude survival with good neurological function than females

Another important finding of Chapter 5 is that males with OHCA have higher crude and adjusted rates of neurological intact survival. However, the adjusted rate was not statistically significant. Further analyses showed that a lower proportion of females with OHCA had an initial shockable rhythm or received hypothermia management compared to males (14.0% vs. 29.1%, $p < 0.001$) and (13.4% vs. 17.0%, $p < 0.001$), respectively. While an initial shockable rhythm and hypothermia management contribute significantly to favourable neurological outcome, the lower proportion of females with an initial shockable rhythm and the lower proportion receiving hypothermia thus contribute to the lower rate of neurologically intact survival in females.

7.1.8 Males derived greater benefit from hypothermia management and initial shockable rhythms than females

While both hypothermia management and initial shockable rhythms are significantly associated with favourable neurological outcome, the sex-stratified analysis (Chapter 5) revealed the magnitude of the effect of the hypothermia and initial shockable rhythms on favourable neurological outcome were lower in females than males. The marked difference in the effect size by sex suggests that the ‘sex’ variable acts as effect modifier. Examination of interaction terms (hypothermia by sex and initial shockable rhythm by sex) confirmed that males derive significantly greater benefit from hypothermia management and initial shockable rhythms than females. The reasons for the observed differences in the effect sizes of hypothermia and shockable rhythm should be investigated.

7.1.9 Premenopausal status does not have a beneficial impact on OHCA outcomes

Findings of Chapter 6 revealed that premenopausal age has no significant association with survival outcomes whether this refers to survival to hospital admission, survival to hospital discharge, or survival with favourable neurological function. These were the results of and analysis of the full cohort of OHCA. We hypothesized that outcomes may differ among those who were transported to hospital or among those who survived to hospital discharge. Despite the large sample size, we were unable to detect an association between premenopausal age and survival outcomes in this subgroup.

In line with our findings, a recent study found females of child-bearing age have no advantage in neurological outcomes (160). Likewise, a study in Australia revealed the age-sex interaction was not significant for survival to hospital discharge (69). In stark contrast, however, our results are not in line with three previous studies that reported survival advantages in premenopausal females. These studies suggested female sex hormones have a positive impact of OHCA outcomes (63,71,97,98). Our findings of no survival advantage in premenopausal females, therefore, do not corroborate these previous data postulating positive effects of female sex hormones on OHCA outcomes.

It is noteworthy that, none of the studies investigating the effect of premenopausal status, including our study, have examined the actual effect of female sex hormones due to a lack of actual data on estrogen and progesterone levels. Given the conflicting evidence on the role of female sex hormones on survival, there is certainly a need for studies that prospectively and accurately define and evaluate menopausal status to definitively assess the impact of female sex hormones on outcomes.

The findings of Chapter 6 also demonstrated that older females (>53 years of age) are less likely to have an OHCA in a public location and have initial shockable rhythms compared to younger females and males in all age groups. Another important finding of Chapter 6 is that the older females group have the worst outcomes. They are the least likely group to survive to hospital discharge and survive with favourable neurological function. A recent North American study reported similar results (33). While these disadvantages in older females could be explained by the unfavourable baseline characteristics in the older females, they could be due to differences in in-hospital interventions. Efforts to improve the outcome of older females may focus on early identification of OHCA, early recognition of initial rhythm, early defibrillation, and advanced in-hospital post resuscitation care. Further research addressing prehospital intervention and post resuscitation care provided for older females is required.

7.2 Strengths and limitations

The strength and limitations of each of the five studies in this dissertation are explained in detail in Chapters 2-6. Overall, there are numerous strengths to the present research. Firstly, the three studies were conducted in BC, Canada, using data from CanROC BC. The data were prospectively collected from 8115 OHCA cases in the metropolitan regions of BC, an area of approximately 2.5 million inhabitants. We included a large sample that is representative of the BC population. Both the quality of data and the sample size have reinforced that the results of these studies are generalizable to the BC population.

The last two studies used data from the ROC CCC Trial that included 114 EMS agencies in the USA and Canada grouped into 47 clusters. Communities and populations represented in the CCC trial data are substantial and cover large areas in North America. Additionally, the analyses used an advanced multilevel analysis to account for the clustering effect. The quality of the CCC trial data, sample size, and advanced statistical analysis employed have solidified both the internal and external validities.

The use of observational and nonexperimental studies in this dissertation presents some limitations. Despite being the most common type of clinical research, observational studies are more prone to confounding and bias compared to randomized clinical trials. However, we used several advanced statistical techniques to control for confounders and to reduce the bias. These include, stratification, multivariable regression with various variable selection strategies, multilevel analyses, and sensitivity analyses. One limitation was the lack of data on comorbid conditions which may have associations with the outcomes. However, in Chapter 4, we analyzed linked data that included comorbidity and adjusted for the effect of comorbid conditions in our analyses. In all of our multivariable analyses, the effects of variables known to be associated with survival, including EMS response time, bystander witness status, bystander CPR, and initial cardiac rhythm were consistent and expected in direction and magnitude. The consistency of these effects was observed in both the full cohorts and the subgroups analyses, and therefore, it provides validity to the methods employed in the studies.

7.3 Implications

This dissertation research has several implications for further research and clinical practice. The first three studies have BC specific implications. The most important implications are summarized below.

First, this research found that those females with OHCA in BC who did not achieve prehospital ROSC are less likely to be transported to hospital than males. The reason for this difference should be further explored. It is also recommended that BC EMS professionals training should address the sex differences in the decision to initiate hospital transportation prior to prehospital ROSC.

Second, we consistently found that in BC, females and males had substantial differences in baseline characteristics predictive of OHCA outcomes. Females are less likely to have an OHCA in a public location, to experience witnessed arrest, and to have initial shockable rhythms. Methods to improve modifiable characteristics of female OHCAs may have significant impacts on outcomes. Novel methods to identify female OHCAs in private locations, such as personal wearable monitors and emergency activation alarm, to alert bystanders and professional responders may confer substantial benefits.

Third, the findings of Chapter 3 indicate that female sex is associated with ROSC, but not survival to hospital discharge. Moreover, we found no significant difference between males and females in one-year post hospital discharge survival (Chapter 4). Since these were the first studies investigating sex differences in short- term and long-term survival in BC, they added to our knowledge of sex-based differences in short and long-term OHCA outcomes in BC. Further research should investigate sex-specific post-arrest in hospital management strategies in BC and other regions.

Fourth, in examining the effect of sex on neurological outcome (Chapter 5), the study revealed that males with OHCA have higher crude rates of neurologically intact survival than females. Further analysis showed that females had a lower proportion of OHCA with an initial shockable rhythm and a lower proportion received hypothermia management. Because initial shockable rhythm and hypothermia management contribute significantly to favourable neurological function, the lower proportion of females with these attributes likely contributes to the lower rate of neurologically intact survival in females. Further research should investigate other possible reasons for the observed difference. Furthermore, we found significant interaction effects (hypothermia by sex and initial shockable rhythm by sex) on neurological function. While hypothermia management and initial shockable rhythm are effective in both sexes, the magnitude of the effect of the hypothermia and initial shockable rhythms on favourable neurological outcome are lower in females than males. Two important research questions arising from these findings are: what is the association between sex and hypothermia management, and what are the reasons that can explain why females with OHCA derive lower benefits from the hypothermia management and shockable rhythms than males.

Fifth, in addition to determining the impact of sex on OHCA treatments and outcomes, this research identified predictors of survival with good neurological outcomes. The strongest predictor, that is, the predictor with the largest effect size was initial shockable rhythm. Research and advanced technology strategies to improve early identification of OHCA, early recognition of initial cardiac rhythm and early defibrillation would significantly improve survival. On the other hand, we found that administration of epinephrine has negative impacts on neurological outcomes. This negative effect was also reported by other studies. There is an increased possibility that the poor neurological function is not due to epinephrine but due to the severity of the cases (confounding by indication). Patients with unshockable rhythms require prolonged resuscitation and are more likely to receive epinephrine than those with VF or VT. Clinical trials on the effect of epinephrine have so far produced mixed evidence. A systematic review or meta-analysis of RCT would be desirable to determine the epinephrine effect or to identify the sub-group that benefit from epinephrine.

Sixth, despite using a large sample size, robust methodological approach, and advanced statistical analysis, we were unable to detect any association between premenopausal age and survival outcomes (Chapter 6). This suggests that premenopausal status does not confer protective outcomes among victims of OHCA. Interestingly, our findings along with findings of two other studies do not support previous data postulating positive effects of estrogen hormone on OHCA outcomes. Studies that prospectively define and evaluate premenopausal status are required to definitively assess the impact of female sex hormones on outcomes. While a randomized clinical trial examining the effect of sex hormones is not feasible, a meta-analysis that combines the results of the observational studies addressing the effect of female sex hormones on survival would be strongly recommended.

Seventh, when we examined the effect of age and sex on survival, we found that older females have the worst survival outcome compared to older males, younger females and younger males. The most important research questions arising from this finding are whether this survival disadvantage in older females is due to differences in baseline characteristics. Whether older females suffering OHCA receive the same prehospital and in-hospital quality care compared to older males, younger females, and younger males, and finally whether any systematic differences exist in the care provided for older females compared to others, should be explored.

The knowledge and insights gained from this research are expected to guide EMS and HCP in providing optimal care to these critically ill patients. Our findings in combination with findings of other research provide evidence to inform current clinical practice and are bound to help generate a standardized, evidence-based approach to the management of OHCA in both males and females. Such developments and improvements have the potential to save more lives.

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