School of Nursing

The Epidemiology of Out of Hospital Cardiac Arrest in Western Australia: A Population-based linked Data Study

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This thesis is presented for the Degree of
Doctor of Philosophy
of
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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

This thesis includes five original manuscripts published in peer reviewed journals. Three are published in the Elsevier journal Resuscitation; One is published in the Elsevier journal Resuscitation Plus; and one is published in BMJ Open, a journal of the BMJ Publishing Group. Both Elsevier and the BMJ Publishing Group permit the author of a published article to include it within a thesis provided it is not published commercially.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014.The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number HR 128/2013.

My name was added to the list of investigators for HR 128/2013: "Western Australian Prehospital Care Record Linkage Project" to enable data access and analysis on the 17thJuly 2019.

Approval to access St John Western Australia Patient Care Records was gained from the St John Western Australia Research Advisory Group (now called the Research Governance Committee).

Signature: ………………………………………

21st April 2022
Date :………………………………………

Abstract

Background: Out-of-hospital cardiac arrest (OHCA) is a time critical medical emergency that carries substantial societal and economic costs. In Australia, approximately 25,000 individuals[1] die annually from OHCA, making it one of the leading causes of mortality in the country. Although global OHCA survival remains low, some regions have reported steady improvements over time. Improvements in OHCA survival have resulted from both coordinated initiatives to strengthen the 'OHCA chain of survival' and the establishment of OHCA registries to monitor and track the effectiveness of these initiatives. Importantly, population-based studies not only provide significant insight into the epidemiology of OHCA but can identify potential areas for improvement.

Despite the plethora of OHCA research, several gaps in the literature remain. Firstly, the 'Utstein resuscitation registry template' recommends reporting survival to hospital discharge (STHD) or alternatively 30-day survival as a core outcome - in effect implying a 'quasi-equivalence' between the two metrics. However, no research to date has investigated this equivalence nor the validity of comparing different survival measure across jurisdictions. Secondly, despite a growing trend in comorbidity globally, there appears to be little consensus in the literature on the effect pre-arrest comorbidity has on OHCA outcomes. Finally, with OHCA survival steadily increasing, more focus needs to be placed on the epidemiology of longer-term OHCA survival. This thesis aims to address these gaps.

Aim: The overall aim of this doctoral research is to investigate the prognostic determinants and long-term survival of OHCA through an exploration of the epidemiology of OHCA in the Perth metropolitan area.

Methods: This thesis is comprised of five discrete studies, all of which have been published in peer reviewed journals. The first three studies focus primarily on survival within the first 30 days of an arrest while the last two studies focus on longer-term survival (survival beyond 30 days). The WA OHCA database was used for all retrospective cohort studies. I have briefly outlined the methods and results for each of the five studies below.

Study 1. *Majewski D, Ball S, Bailey P, Bray J, Finn J. Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia. Resuscitation Plus. 2022;9:100201.*

In the first study I conducted a retrospective cohort study of all EMS attended OHCAs of presumed cardiac aetiology in the Perth metropolitan area between 2001 and 2018. This study aimed to describe the temporal trends of OHCA incidence, patient and arrest characteristics, and survival. Trends in patient and arrest characteristics were assessed using either logistic or ordinal regression (as appropriate). Trends in OHCA incidence were assessed using 'JoinPoint' regression, while trends in survival (ROSC and 30-day) were examined using multivariate logistic regression.

Results: I found no significant temporal trends in the incidence of OHCA (of presumed cardiac aetiology) between 2001 and 2018. Rates of bystander CPR and bystander AED defibrillation both increased over the study period, although there was a downward trend in the proportion of arrests presenting with shockable rhythms. With respect to OHCA survival, I found that 30-day survival significantly improved between 2001 and 2018, with the Utstein comparator group survival (bystander witnessed, initial ventricular fibrillation (VF)/ventricular tachycardia (VT) rhythm arrests) increasing by 12% (95% CI, 9.0% to 14.0%) per annum between 2001 and 2018.

Study 2. *Majewski D, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation. 2020;157:108-11.*

The second study was a retrospective cohort study of patients (≥16 years of age) who experienced an OHCA of medical aetiology in the Perth metropolitan area between 1998 and 2017 and survived at least 30-days following the arrest. In this study I aimed to describe the 10-year relative survival of OHCA patients (relative to their age- and sex-matched peers) and determine whether 10-year survival increased in-excess of any increases in the population life expectancy. Relative survival ratios were used to model survival and were calculated by dividing 'observed survival' of the study cohort by the 'expected survival' of an age- and sex-matched cohort estimated using the Australian Bureau of Statistics (ABS) WA life tables.

Results: Study 2 included a cohort of 871 initial 30-day OHCA survivors. I found that patients experienced only modest reductions in long-term survival, with 84% (95% CI, 78% to 90%) of the 10-year survival of the age- and sex-matched general population. Furthermore, there was a significant improvement in the relative 10-year survival of OHCA patients between 1998-2007 (76% relative survival) and 2008-2017 (92% relative survival), suggesting that long term OHCA survival has improved in-excess of any increases in population life expectancy.

Study 3. *Majewski D, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34.*

For the third study, I used the same patient cohort as Study 2 to explore whether pre-hospital factors such as initial presenting arrest rhythm continued to be associated with longer term survival in patients who already survived 30 days. Associations between 8-year OHCA survival and presenting initial arrest rhythm were assessed using a Multi-Resolution Hazard (MRH) estimator model and reported using 1-year intervals.

Results: I found that initial arrest rhythm was significantly associated with longer-term OHCA survival. Patients with non-shockable arrests (compared to those with shockable arrests) experienced significantly higher mortality in the first (Hazard ratio (HR) 3.33, 95% CI 2.12 to 5.32), second (HR 2.58, 95% CI 1.22 to 5.15), third (HR 2.21, 95% CI 1.02 to 4.42) and fourth (HR 2.21, 95% CI 1.02 to 4.42) year post arrest; however, after four years initial arrest rhythm ceased to be significantly associated with ongoing survival.

Study 4. *Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.*

In Study 4, I performed a systematic review of existing literature to investigate the association between pre-arrest comorbidity and OHCA outcome. The databases MEDLINE, Ovid Embase, Scopus, CINAHL, Cochrane Library and MedNar were searched, and papers were included if they: i) reported OHCA of medical aetiology, and (2) provided a quantitative comparison between pre-arrest comorbidity and OHCA outcome. The primary outcome was STHD and the secondary outcome was neurological status post arrest. A meta-analysis was to be performed if the clinical and statistical heterogeneity was low.

Results: A total of 29 observational studies were included in the systematic review investigating the association between pre-arrest comorbidity and OHCA outcomes. I found a high degree of clinical heterogeneity between the included studies with regards to patient recruitment, inclusion criteria, outcome measures and statistical methods meaning a meta-analysis of results was not appropriate. Overall, pre-arrest comorbidity appeared to be associated with both reduced 30-day survival and poorer neurological outcomes following OHCA, although individual results between studies varied greatly.

Study 5. *Majewski D, Ball S, Bailey P, McKenzie N, Bray J, Morgan A, Finn J. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. Resuscitation. 2021;166:43-8.*

In the fifth and final study, I conducted a retrospective cohort study of all EMS attended OHCAs in the Perth metropolitan area between 1999 and 2018 that had an attempted resuscitation (or bystander defibrillation) and were transported to the emergency department (ED). The specific aims of this study were to determine the concordance between the two survival outcomes, STHD and 30-day survival, and explore the characteristics of discordant cases. Concordance between the two survival outcomes were tested using McNemar's test. The findings of this study were used to inform selection of the 'most appropriate' survival metric for the other studies in this thesis.

Results: This study included a total of 7953 OHCA cases transported to ED. I found the reported outcomes for the variables STHD and 30-day survival to be concordant, with only 30 cases (0.38%) being discordant for survival outcome. Of the 30 discordant cases, 15 were reported to have survived to hospital discharge but not 30 days, and 15 were reported to have survived to 30 days but not to hospital discharge. There were no discernible patterns in the characteristics of discordant cases. The findings of this study suggest the two survival outcomes reported in the WA OHCA database could be considered 'equivalent', however this may not be true for other OHCA registries.

Conclusion: This research demonstrates that OHCA survival in Perth has improved over time, with longer-term survival increasing in-excess of any increases in population life expectancy. However, patients presenting with non-shockable initial arrest rhythms experience significant ongoing mortality (compared to those with shockable arrest rhythms). The findings of this thesis suggest that efforts in Perth aimed at strengthening the ‘chain of survival’ have resulted in tangible improvements across all OHCA survival measures, however continued reductions in the proportion of arrests presenting with shockable rhythms may prove a challenge in the future.

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List of Abbreviations

ABS	Australian Bureau of Statistics
AED	Automated External Defibrillator
ALS	Advanced Life Support
ANCOR	Australian and New Zealand Committee on Resuscitation
aOR	Adjusted Odds Ratio
APC	Annual Percentage Change
ARC	Australian Resuscitation Council
ASIR	Age standardised incidence rate
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPC	Cerebral Performance Category
CSP	Clinical Support Paramedic
CPGs	Clinical Practice Guidelines
ED	Emergency Department
EMS	Emergency Medical Services
FACEM	Fellowship of the Australian College for Emergency Medicine
FCICM	Fellowship of the College of Intensive Care Medicine
HR	Hazard Ratio
ICU	Intensive Care Unit
IHCA	In hospital cardiac arrests
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile Range
MI	Myocardial Infarction

MPDS	Medical Priority Dispatch System
MRH	Multi-Resolution hazard
NHMRC	National Health and Medical Research Council
OHCA	Out of Hospital Cardiac Arrest
OR	Odds Ratio
PCR	Patient Care Records
PEA	Pulseless Electrical Activity
PH	Proportional Hazards
PRECRU	The Prehospital Resuscitation and Emergency Care Research Unit
ROSC	Return of Spontaneous Circulation
SJ-WA	St John Western Australia
STHD	Survival to Hospital Discharge
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WA	Western Australia

Publications, Presentations and Scholarships

Publications

Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.

Majewski D, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation. 2020;157:108-11.

Majewski D, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34.

Majewski D, Ball S, Bailey P, McKenzie N, Bray J, Morgan A, et al. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. Resuscitation. 2021;166:43-8.

Majewski D, Ball S, Bailey P, Bray J, Finn J. Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia. Resuscitation Plus. 2022;9:100201.

Conference Presentations

Rapid fire presentation: 2020 New Investigator Symposium, hosted by the Australasian Resuscitation Outcomes Consortium, and the Australian and New Zealand Resuscitation Councils, virtual conference, Perth, Australia, 2020.

Has long-term OHCA survival really improved?

Other Presentations

Presentation for Candidacy, School of Nursing, Curtin University, Perth, Australia, 2017.

The Epidemiology of Out of Hospital Cardiac Arrests in Western Australia: A Population-based Linked Data Study.

Poster presentation at Mark Liveris Seminar, Faculty of Health Sciences, Curtin University, Perth, Australia 2018.

*Systematic review and meta-analysis of the relationship between comorbidities and out of hospital cardiac arrest outcomes (**Third Prize** for the Best Poster Display Award)*

Oral Presentation at Prehospital and Emergency Care Australia and New Zealand Face to Face Steering Committee meeting. Melbourne, Australia 2019.

Out-of-hospital cardiac arrest in Western Australia.

Milestone Three Presentation. School of Nursing, Curtin University, Perth, Australia, 2020.

Milestone Three. The Epidemiology of Out of Hospital Cardiac Arrests in Western Australia: A Population-based Linked Data Study.

Scholarships

- Australian Government Research Training Program (RTP) scholarship.
- Curtin University Postgraduate Scholarship (CUPS)
- Australian National Health and Medical Research Council (NHMRC) Prehospital Emergency Care Centre for Research Excellence (PEC-ANZ) (#1116453)

Statement of Author Contributions to Published Papers and Submitted Papers

Published Papers

1. **Majewski D**, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.

Author	Contribution	Signature
David Majewski	75%	
Dr Stephen Ball	15%	
Professor Judith Finn	10%	

I, David Majewski, was the primary author of this paper with my contribution amounting to 75%. I undertook the search of the literature and selected potentially relevant papers. Dr Stephen Ball independently screened these papers to identify relevant articles for inclusion and both Dr Stephen Ball and I independently performed the risk of bias assessments. I then performed the analyses and drafted the manuscript. All authors reviewed the manuscript prior to submission.

2. **Majewski D**, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation. 2020;157:108-11.

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Dr Stephen Ball	10%	
Associate Professor Paul Bailey	5%	
Associate Professor Janet Bray	5%	
Professor Judith Finn	10%	

I, David Majewski, was the primary author of this paper with my contribution amounting to 70%. The study was primarily conceived by myself and my supervisors Prof Judith Finn and Dr Stephen Ball. Data for the study was sourced from the St John Western Australia (SJ-WA) OHCA database by Dr Stephen Ball, the database manager, and provided to me as de-identified data. I conducted all data cleaning and analysis. I prepared the manuscript, which was reviewed in the first instance by my supervisors Professor Judith Finn and Dr Stephen Ball. Subsequent revisions involved all manuscript co-authors. All authors were involved in the critical review of the article for important intellectual content and final approval of the submitted manuscript.

3. **Majewski D**, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34.

Author	Contribution	Signature
David Majewski	70%	
Dr Stephen Ball	10%	
Associate Professor Paul Bailey	5%	
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Professor Judith Finn	10%	

I, David Majewski, was the primary author of this paper with my contribution amounting to 70%. The study was primarily conceived by myself and my supervisors Prof Judith Finn and Dr Stephen Ball. Data for the study was sourced from the SJ-WA OHCA database by Dr Stephen Ball, the database manager, and provided to me as de-identified data. I conducted all data cleaning and analysis. I prepared the manuscript, which was reviewed in the first instance by my supervisors Professor Judith Finn and Dr Stephen Ball. Subsequent revisions involved all manuscript co-authors. All authors were involved in the critical review of the article for important intellectual content and final approval of the submitted manuscript.

4. **Majewski D,** Ball S, Bailey P, McKenzie N, Bray J, Morgan A, et al. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. Resuscitation. 2021;166:43-8.

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Alani Morgan	5%	
Professor Judith Finn	15%	

I, David Majewski, was the primary author of this paper with my contribution amounting to 60%. The study was primarily conceived by Prof Judith Finn, with some input from myself and Stephen Ball. Data for the study was sourced from the SJ-WA OHCA database by Dr Stephen Ball, the database manager, and provided to me as de-identified data. I conducted all data cleaning and analysis. Date of hospital discharge is a routinely collected component of the WA OHCA database and is obtained by registered nurse Nicole McKenzie via manual review of patient hospital records. I prepared the manuscript, which was reviewed in the first instance by my supervisors Professor Judith Finn and Dr Stephen Ball. Subsequent revisions involved all manuscript co-authors. All authors were involved in the critical review of the article for important intellectual content and final approval of the submitted manuscript.

5. **Majewski D**, Ball S, Bailey P, Bray J, Finn J. Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia. Resuscitation Plus. 2022;9:100201.

Author	Contribution	Signature
David Majewski	70%	
Dr Stephen Ball	10%	
Associate Professor Paul Bailey	5%	
Associate Professor Janet Bray	5%	
Professor Judith Finn	10%	

I, David Majewski, was the primary author of this paper with my contribution amounting to 70%. The study was primarily conceived by myself and my supervisors Prof Judith Finn and Dr Stephen Ball. Data for the study was sourced from the SJ-WA OHCA database by Dr Stephen Ball, the database manager, and provided to me as de-identified data. I conducted all data cleaning and analysis. I prepared the manuscript, which was reviewed in the first instance by my supervisors Professor Judith Finn and Dr Stephen Ball. Subsequent revisions involved all manuscript co-authors. All authors were involved in the critical review of the article for important intellectual content and final approval of the submitted manuscript.

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Chapter 1 Introduction

1.1 Introduction

Globally, out of hospital cardiac arrest (OHCA) survival is low, with less than 10% of victims surviving to hospital discharge.[2] In the United States, OHCA is estimated to claim the equivalent of 4 million years of 'potential life' annually,[3] with an estimated 347,322 OHCA cases[4] per annum. In Australia, OHCA is responsible for almost $2 billion (AUD) in lost productivity annually; an amount comparable to that from all cancers combined.[5] Over the last three decades there has been a plethora of OHCA research,[6, 7] which has helped inform resuscitation science and practical initiatives to improve OHCA outcomes. However, despite these developments, OHCA continues to pose a substantial global health burden.[2, 8]

Despite the advancements in resuscitation science, important knowledge gaps remain. Firstly, there are few recent studies exploring the long-term temporal changes in OHCA incidence and outcomes. Without an understanding of how OHCA patient and arrest factors have evolved over time it is difficult to anticipate future demands on emergency medical services (EMS). Secondly, the association between pre-arrest patient comorbidity and OHCA outcomes is poorly understood, with previous studies reporting conflicting results. Some studies have reported pre-arrest comorbidity negatively impacts survival[9-11] while others have reported no association.[12, 13] Thirdly, although shorter-term OHCA survival outcomes (such as survival to 30 days) have been extensively reported,[2] relatively few studies have reported on the longer-term survival outcomes of patients. For example, it is unclear whether an OHCA results in any detrimental effects on the life expectancy of survivors. Likewise, it's not clear whether prehospital determinants of short-term survival remain prognostic determinants of longer-term survival. Importantly, with an increasing number of patients surviving OHCA,[14] more attention needs to be placed on examining the longer-term outcomes of OHCA. Finally, although substantial progress has been made to standardise the reporting of OHCA outcomes,[15] definitional variations continue to challenge epidemiological research.[8] This includes reporting OHCA survival.[15] A recent literature reveals that some studies[2, 16] report survival to hospital discharge (STHD) and 30-day survival separately, while others[17-19] combine the two survival outcomes. Concordance between the commonly reported OHCA outcomes, STHD and 30-day survival, has not been previously verified.

1.2 Research Aim and Objectives

1.2.1 Aim

The overall aim of this doctoral research is to investigate the prognostic determinants and long-term survival of OHCA through an exploration of the epidemiology of OHCA in the Perth metropolitan area.

1.2.2 Specific Research Objectives

The following research objectives were defined to address the specific research aim above.

1. **To describe the temporal trends of OHCA in Perth, Western Australia (WA).**
   Undertake a population-based cohort study of OHCA in Perth to:

   a) Explore the temporal trends in the incidence, patient- and arrest-characteristics, and 30-day survival of OHCA patients.

2. **To determine whether OHCA patients who survive at least 30-days following an arrest experience a reduction in subsequent survival compared to the age- and sex-matched general population.**
   Undertake a population-based cohort study of long-term OHCA survival to:

   b) Explore the long-term survival of initial (30-day) OHCA survivors relative to the age- and sex-matched general population; and
   c) Determine whether there have been any improvements over time in the long-term (10-year) survival of initial OHCA survivors, independent of any increases in population life expectancy.

3. **To determine whether longer term survival in initial 30-day OHCA survivors differs by initial arrest rhythm.**
   Undertake a population-based cohort study of long-term OHCA survival to:

   d) Explore the association of initial arrest rhythm on long-term survival in a cohort of 30-day survivors; and
   e) Determine whether any other prehospital patient and arrest factors have an association with the long-term survival of OHCA patients.

4. **Examine the effects of pre-arrest comorbidity on OHCA outcomes.**
   Undertake a systematic review and meta-analysis (if possible) of existing published literature to:

   f) Examine the association between pre-arrest comorbidity and OHCA survival and neurological outcome.

5. **To determine whether the commonly reported OHCA outcomes, survival to hospital discharge (STHD) and 30-day survival, can be considered equivalent survival outcomes.**
   Undertake a population-based cohort study to compare survival outcomes at 30 days and at hospital discharge to:

   g) Ascertain the concordance between STHD and 30-day survival; and

   h) Explore the characteristics of OHCA cases that are discordant for survival.

1.3 Thesis Approach

This thesis is structured using a 'thesis by compilation' approach and comprises eight chapters. Chapter One provides an overview of the aims of this thesis while Chapter Two provides a contextual overview of OHCA, with particular emphasis on the WA context. Chapters 3-7 are comprised of five individual studies which have been published in peer reviewed journals. Chapter Three consists of a population-based retrospective cohort study of the trends in OHCA incidence, prehospital characteristics, and 30-day survival in the Perth metropolitan area between 2001 and 2018. Chapter Four consists of a retrospective cohort study to explore the longer-term OHCA survival of patients who initially survived at least 30 days following their arrest. Specifically, I investigated the 10-year survival of OHCA patients relative to the age- and sex- matched general population. I further explored long-term survival in Chapter Five by conducting a retrospective cohort study to determine whether pre-hospital factors, such as initial presenting arrest rhythm, continued to be associated with longer term OHCA survival. In Chapter Six, I present a systematic review of the literature on the association between pre-arrest comorbidity and OHCA survival and neurological outcomes. Finally, in Chapter Seven I present a retrospective cohort study where I explore the equivalence of the two Utstein[15] recommended survival outcomes, 30-day OHCA survival and STHD. Chapter Eight provides a discussion of the key findings of my doctoral research, identifies potential limitations, and includes recommendations for future research. Table 1 below shows how the specific research objectives are addressed by each chapter in this thesis.

Table 1. Overview of thesis chapters.

Chapter	Description	Aim	Objective
1	***Introduction***		
2	***Background*** A brief contextual overview of OHCA and EMS in Perth, WA. This includes an overview of EMS data collection process and a description of the WA OHCA registry. An overview of the study methodology used in this thesis.		
3	***Temporal trends in OHCA*** Paper published: ***Majewski D****, Ball S, Bailey P, Bray J, Finn J. Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia. Resuscitation Plus. 2022;9:100201.*	(1)	a
4	***Long term OHCA survival*** Paper published: *Majewski D, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation. 2020;157:108-11.*	(2)	b,c
5	***Factors associated with long-term OHCA survival*** Paper published: *Majewski D, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34*	(3)	d,e
6	***Pre-arrest Comorbidity and OHCA Outcomes*** Paper published: ***Majewski D****, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655*	(4)	f
7	***Measuring OHCA Survival Outcomes*** Published paper: ***Majewski D****, Ball S, Bailey P, McKenzie N, Bray J, Morgan A, Finn J. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. Resuscitation. 2021;166:43-8.*	(5)	g,h
8	***Discussion, Recommendations and Concluding Remarks***		

Chapter 2 Background

The purpose of this chapter is to provide an overview of OHCA, with a focus on the Perth, WA context. Specifically, it provides an overview of the EMS in Perth and the OHCA data collection process relevant to this thesis.

2.1 Out-of-Hospital Cardiac Arrests

2.1.1 Definition

Commonly, the terms ‘cardiac arrest’ and ‘heart attack’ are used interchangeably; even though the two conditions are distinctly different.[20] A heart attack is where blood supply to one, or more of the coronary arteries is interrupted, resulting in ischemic damage to the heart muscle – however, crucially, the heart continues to pump blood.[21] On the other hand, a cardiac arrest is a time-critical medical emergency that occurs when the effective mechanical pumping activity of the heart ceases, and there is an absence of circulatory output;[22] resulting in a loss of consciousness. However, it is important to acknowledge that a heart attack itself may lead to a cardiac arrest.

Cardiac arrests are broadly categorised depending on the setting they occur. Arrests that occur in a hospital setting are termed ‘in hospital cardiac arrests’ (IHCA), while those occurring outside of a hospital setting are termed ‘out-of-hospital cardiac arrests.’ Distinguishing between the two categories of arrests is important, as they tend to vary by both the patient characteristics and outcome.[23]

2.1.2 Incidence and Survival

In a recent global study, the annual incidence of EMS-treated OHCA (i.e where EMS attempted resuscitative efforts) was reported to be between 30 and 97.1 persons per 100,000.[17] In Australia, the combined annual crude incidence of OHCA (of all aetiologies) in 2019 was reported to be 107.9 per 100,000 person-years; with 43.5% of OHCA cases being treated by EMS.[1] In WA, the crude OHCA incidence was reported to be 94.4 persons[19] per 100,000 population in 2015, and 103.8 persons[1] per 100,000 population in 2019.

A 2020 systematic review,[2] that included 141 studies, reported pooled OHCA survival rates (among adult patients who received CPR) for: 'return of spontaneous circulation' (ROSC) as 29.7%, STHD as 8.8%, and 1-year survival as 7.7%. Survival rates in the Oceania region tend to be higher,[2] with a recent Aus-ROC study reporting 30-day survival of 12.5% in 2019 among patients with an EMS attempted resuscitation.[1] However, this Aus-ROC study showed that OHCA survival varied between jurisdictions, from 9.9% in the state of WA to 14.4% in the state of Queensland.[1] Regional variations in OHCA outcomes have been previously reported, with a 2008 USA study[24] finding survival can vary as high as 7-fold between different jurisdictions. Some have suggested that the so-called 'Utstein factors' (e.g. arrest witness status, provision of bystander CPR, initial presenting arrest rhythm, EMS response time)[25] may be responsible for around half of this variation in OHCA survival.[26]

2.1.3 Management

Chain of Survival

The 'OHCA chain of survival' concept (Figure 1) has been adopted as the mainstay of OHCA management globally.[27] The chain of survival refers to a series of linked key actions that are part of an optimized resuscitative process known to improve survival, as follows: [1] early recognition and activation of emergency response, [2] early provision of CPR, [3] rapid defibrillation, [4] provision of advanced life support (ALS), [5] post cardiac arrest care and [6] finally the recovery period (which includes additional treatment, support or observation).[28] The 'chain of survival' stresses the importance of a *whole system* response to cardiac arrests to achieve the best outcomes – from bystanders (in the general public), to the EMS and finally to the hospitals.

Figure 1. The OHCA chain of survival[29]

2.2 OHCA Data

2.2.1 Research

In 1992, the International Liaison Committee on Resuscitation (ILCOR) was formed with representatives from various national resuscitation groups to provide a consensus summary of the scientific literature, and provide evidence-based resuscitation guidance.[30] Although ILCOR initially envisaged to provide resuscitation guidance to healthcare providers, since 2015[31] it has also expanded to provide consensus statements on first aid– again demonstrating the importance of involving the public to improve outcomes.

2.2.2 Utstein Definitions

In 1990, under the auspices of the group of resuscitation experts who would subsequently form the ILCOR, an inaugural meeting took place at the Utstein Abbey in Norway, to establish a consensus for the uniform reporting of OHCA outcomes.[32, 33] This became known as the 'Utstein Style',[33] first published in 1991,[32] with subsequent updates in 2004[34] and 2015.[15] The Utstein Style template is composed of both core and supplementary data elements. The core elements represent the minimum variables recommended to be collected for OHCA quality improvement purposes and which all OHCA registries should aim to capture and report.[15] In contrast, the supplementary elements are those variables which are desirable for reporting but not essential for quality improvement purposes.[15] For reporting longer term survival the Utstein Style recommends reporting either STHD or alternatively, 30-day survival.[25]

2.2.3 Prognostic Determinants of OHCA

Several of the Utstein reporting elements have been shown to be important determinants of OHCA survival.[22, 35] Each of these elements can be broadly categorised as either patient, arrest, or systems-of-care factors. A description of each of these is provided below.

Patient factors

A 2015 study[36] which recruited 101,968 OHCA patients from the CARES (Cardiac Arrest Registry to Enhance Survival) registry, found that advanced patient age was associated with a reduction in STHD. Similarly, a 2019 Japanese study[37] reported a detrimental association between advanced patient age and 30-day survival. A 2017 study from Melbourne[38] reported that increasing levels of pre-arrest patient comorbidity were independently associated with reduced odds of both STHD and survival with good neurological outcome. With respect to socioeconomic status, a 2020 systematic review[39] reported that low socioeconomic status (as opposed to a high socioeconomic status) was associated with reduced odds of STHD. Patient sex has also been associated with OHCA survival,[40] although there appears to be some uncertainty regarding the direction of this association, with two[41, 42] recent systematic reviews reporting significant, albeit, conflicting findings. One 2020 systematic review[41] ("*Sex differences in survival after out-of-hospital cardiac arrest: a meta-analysis"*) found that females had a substantially lower chance of survival in comparison to males. However the other 2021 systematic review[42] ("*Gender differences and survival after an out-of-hospital cardiac arrest: a systematic review and meta-analysis*") found that females actually had a significant survival advantage in comparison to males. Despite this discrepancy, both reviews commented that females were more likely to have unfavourable patient and arrest characteristics (i.e. older age and unwitnessed arrest) in comparison to males.[41, 42]

Arrest factors

Initial cardiac arrest rhythm is considered one of the most important predictors of OHCA survival, with shockable arresting rhythms associated with substantially higher odds of STHD then non-shockable ryhthms.[43, 44] In fact, a systematic review by Sassan et al found that OHCA patients who arrested with a shockable rhythm experienced survival odds that were between 3 to 20 fold higher then patients who arrested with non-shockable rhythms.[45] Other arrest characteristics associated with OHCA survival include the witness status of an arrest and arrest location.[40] More specifically, OHCAs that are witnessed[45] (either by EMS or a bystander) and/or occur in a public locations,[46, 47] are associated with a greater odds of STHD.

Systems of care factors

The chances of survival following an OHCA decrease by 7-10% for each minute without resuscitative efforts.[48] Given this, both early bystander recognition of an arrest and rapid activation of EMS are crucial elements in the chain of survival.[49, 50] Likewise, the provision of high quality[51] bystander CPR[52, 53] and early bystander AED defibrillation[53, 54] have been shown to result in substantially better odds of OHCA survival. The OHCA chain of survival also emphasises the early provision of advanced life support (ALS) to increase the chances of patient survival.[55] Indeed a 2018 study[56] that investigated the benefit of prehospital ALS patient care reported that patients who receive ALS care (as opposed to basic life support) from EMS had higher odds of survival (STHD). However, the authors of this study cautioned that the survival benefit was conditional on the ALS care being provided early in the resuscitation process. Unsurprisingly therefore, shorter EMS response times following an OHCA are associated with greater odds of STHD.[53] Lastly, the 'chain of survival' concepts also emphasises the delivery of in-hospital post-resuscitation care to improve survival outcomes.[50, 57] However recent studies[58, 59] appear to call into question the efficacy of some elements of post resuscitation care.

Several of the factors discussed above, such as bystander CPR,[52] bystander AED use,[54] post arrest care,[57] and patient age[60] also appear to be confounded to some extent by initial arrest rhythm. A 2020 study[60] that used machine learning techniques to identify the most important factors associated with 30-day OHCA survival in a cohort of 45,000 arrests, found that (in order of importance) initial arrest rhythm, patient age, time to CPR, EMS response time and the location of arrest were the most important factors associated with OHCA survival. Interestingly, this study found that Automated External Defibrillator (AED) use was not among the most important independent predictors of survival since it was highly associated with the initial arrest rhythm. Furthermore, this study also found that for non-shockable arrests, patient age was by far the most important predictor of survival.[60] A 2020 systematic review[39] also found that socioeconomic status was associated with OHCA outcome, with low socioeconomic status being associated with reduced OHCA survival. Furthermore, patient pre-arrest comorbidity has also been shown to be associated with reduced OHCA survival.[40, 61] Given the apparent dominance of the initial arresting rhythm amongst the prognostic factors, this thesis will place greater attention on this factor over others.

2.3 Context

2.3.1 Setting

Perth is both the capital and largest city of the state of Western Australia (WA). The greater Perth area occupies 6400 km^2 and stretches approximately 150 km along the south west coast of Australia.[62] The estimated population of the Perth metropolitan area in 2018 was 2.06 million with the population having grown 41% between 2001 and 2018.[63] In 2018, the median age of the Perth population was 36.4 years, with 19.4% of the population aged 60 years or over.[64]

2.3.2 St John WA

The exclusive provider of EMS in Perth is St John Western Australia (SJ-WA), a not-for-profit charitable organisation which first began EMS operations in Perth in 1922.[65] SJ-WA operates a single tiered advanced life support (ALS) EMS, with ambulances dispatched from 34 depots located across the Perth metropolitan area. In the 12 months to 30-Jun-2019, SJ-WA EMS responded to a total of 185,318 calls in the Perth metropolitan area.[66] In addition to EMS, SJ-WA also operates a non-emergency patient transport services, event health service and multiple urgent care centres offering general medicine, dental, allied health and radiology services. The SJ-WA State Operations Centre in Perth responds to all '000' (like '911' in the USA) medical emergency calls from the public and dispatches EMS using the Medical Priority Dispatch System (MPDS).[67] Emergency calls where the patient is suspected of being in cardiac arrest are assigned a 'Priority 1' (light and sirens response) code and two ambulances are immediately dispatched in addition to either a clinical support paramedic (CSP) or area manager who respond in a third vehicle.

2.3.3 Staffing

SJ-WA ambulances in metropolitan Perth are staffed either by two paramedics, or a paramedic and ambulance officer crew. Ambulance officers are student paramedics who complete a paramedic degree whilst concurrently working full time at SJ-WA under the guidance of a paramedic mentor. Since 2004, when the first paramedic degree was established in WA,[68] SJ-WA paramedics have become predominantly degree qualified with the paramedic profession gaining national registration in 2018.[69] SJ-WA paramedics are all ALS trained and have a scope of practice that includes endotracheal tube intubation, needle chest decompression, emergency surgical airways, manual defibrillation and both intravenous and intraosseous vascular access.[70] In contrast, the clinical skills and procedures that can be performed by ambulance officers generally depends on their stage of training and are clearly defined by the SJ-WA skills matrix.[71] In addition to ambulance officers and paramedics, SJ-WA also employs CSP and area managers in the metropolitan area who generally respond to more critical calls (such as OHCA) and provide leadership roles. SJ-WA also employs a small number of critical care paramedics[70] with additional training and expanded scope of practice who respond to calls by helicopter. However, they very seldom respond to calls within the Perth metropolitan area.

2.3.4 Clinical Practice Guidelines

The scope and standard of clinical care delivered by EMS staff in WA are defined by the SJ-WA clinical practice guidelines (CPGs).[72] The SJ-WA CPGs[70] for the prehospital management of OHCA are based on the Australian Resuscitation Council (ARC) ALS guidelines.[73] These CPGs also provide guidance on when paramedics may withhold or terminate resuscitative efforts, such as when resuscitative efforts are futile or when advanced directives are in place.[74]

2.3.5 Changes to St John WA OHCA Management

Over the years, there have been several important changes to SJ-WA clinical practice and policy in relation to OHCA. I will briefly mention the most important changes that have occurred during the study periods relevant to this thesis.

ALS medication

Prior to 2006 SJ-WA did not administer cardiac arrest drugs (such as adrenaline) during resuscitative efforts due to a lack of evidence for their efficacy. However, between August 2006 and November 2009 SJ-WA conducted a randomised double-blind placebo-controlled trial to investigate the efficacy of adrenaline use in OHCA.[75] The trial ultimately found that adrenaline increased ROSC but was under-powered to demonstrate a definite effect on STHD.[75] However, in light of international practice, SJ-WA subsequently introduced both adrenaline and the anti-arrhythmic drug amiodarone for the prehospital management of OHCA.

Increased emphasis on resuscitation attempts

In 2009 there was a large push by the ARC to increase OHCA resuscitation rates by promoting that "any attempt at resuscitation is better than no attempt".[76] This philosophy was strongly promoted to

SJ-WA EMS staff by the late Prof. Ian Jacobs, who was at the time both the Chair of the ARC and the Clinical Director at SJ-WA.

Mechanical chest compression

Between 2013-2014 SJ-WA implemented the use of the LUCAS (Lund University Cardiac Assist System)[77] device for OHCA in the Perth metropolitan area. The LUCAS device is a mechanical chest compression apparatus that ensures continuous chest compressions during patient movement and transport to hospital.[78] The LUCAS device is carried by SJ-WA area managers and CSP who respond to all OHCA, in addition to ambulance paramedic crews.

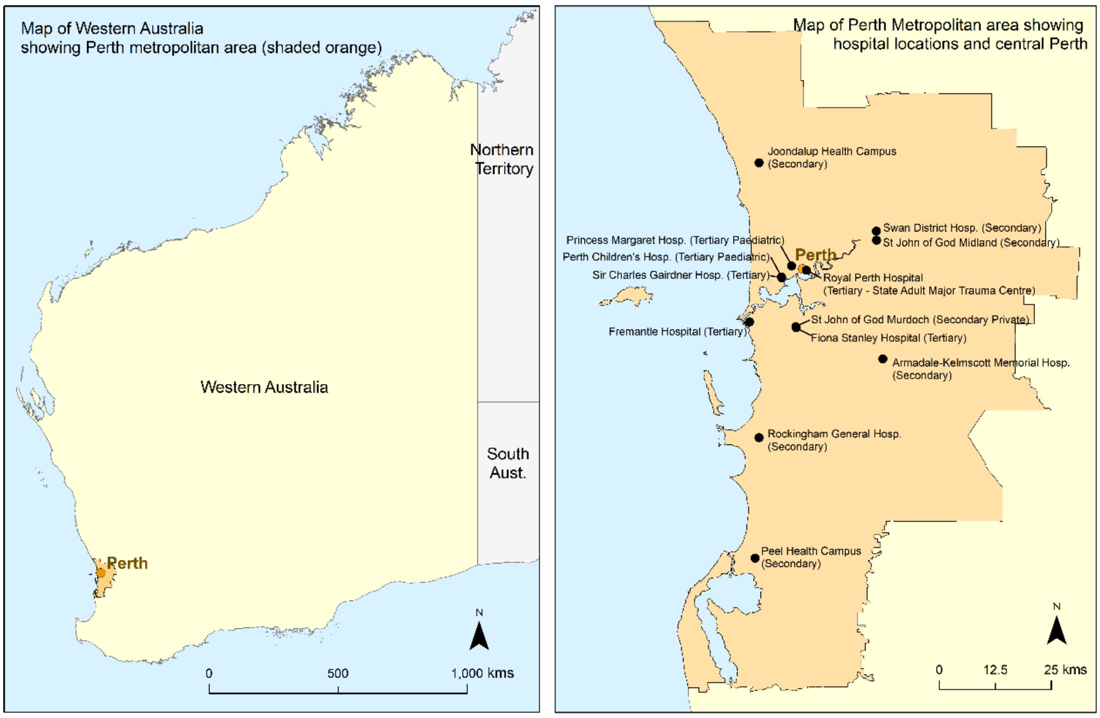
CPR

In 2005 ILCOR recommended[79] the compression-to-ventilation ratio provided in CPR be increased from 15:2 to the current ratio of 30:2. This recommendation was implemented in the 2006 SJ-WA CPGs. In addition to this, in July 2014 SJ-WA introduced CPR feedback devices into all ambulances in the Perth metropolitan area to monitor and improve CPR quality[80]; although use by paramedics was variable.[81]

2.3.6 Hospitals

Patients who experience an OHCA in the Perth metropolitan area, and who either achieve ROSC on scene, or receive ongoing CPR from paramedics, are transported to one of ten hospital ED located in the Perth metropolitan area (Figure 1).[82] All receiving hospitals are public except for St John of God Midland, which is privately run on behalf of the WA Health Department. Cardiac arrests of traumatic aetiology are transported to the closest hospital with available trauma services (with the state trauma unit located at Royal Perth Hospital being the preferred destination).

Overall, 69% of OHCA patients who are admitted to hospital are managed in the intensive care unit (ICU); with a median duration of ICU stay (for both survivors and non-survivors) of 2 days (Interquartile range (IQR); 1-5 days).[83, 84] Patients who are not admitted to ICU are admitted to other areas of the hospital (e.g. coronary care units and general wards). Post-resuscitation care provided by receiving hospitals is not standardised; however, the care provided is consistent with the Australian and New Zealand Committee on Resuscitation (ANCOR)[85] guidelines. Moreover, all of the EDs are staffed by Specialist Emergency Physicians with Fellowship of the Australasian College for Emergency Medicine (FACEM)[86] and ICU staffed by Specialist Intensive Care Physicians with Fellowship of the College of Intensive Care Medicine (FCICM).[87]



Source: Aust Bureau of Statistics 2016 shapefile for Great Capital City Statistical Areas

Figure 2. Location of hospitals in the Perth metropolitan area.

2.3.7 Data Sources

WA OHCA Registry

The WA OHCA Registry,[65] established in 1996 by the late Professor Ian Jacobs, is the oldest continuously operating OHCA registry in Australia and New Zealand. The registry is maintained by staff at the Prehospital Resuscitation and Emergency Care Research Unit (PRECRU) located at Curtin University, in WA. The registry records all OHCA cases attended by SJ-WA in the Perth metropolitan area, and since 2014, all OHCA in rural/remote WA. The registry contains detailed arrest information derived from SJ-WA ambulance patient care records (PCRs) and computer-aided dispatch data. The registry records all core variables recommended by the Utstein Resuscitation Registry Template for OHCA.[25]

New cases are routinely screened for inclusion in the WA OHCA registry from SJ-WA patient data. A set of sensitive but not specific criteria are applied by PRECRU (Curtin University) to select potential OHCA cases from SJ-WA's electronic patient care records (ePCR) and computer-aided dispatch (CAD) data. A research nurse at PRECRU then scrutinises the details of potential cases to identify those that satisfy the registry's formal inclusion criteria. Inclusions are where there is unequivocal evidence that the patient:

(1) Is unconscious, pulseless, and not breathing (or has 'agonal', gasping breaths) on arrival of SJ-WA; or

(2) Becomes unconscious, pulseless, and not breathing (or has 'agonal', gasping breaths) in the presence of SJ-WA (i.e. EMS-witnessed arrests); or

(3) Has a pulse on arrival of SJ-WA, having been successfully defibrillated by a bystander prior to the arrival of SJ-WA.

Excluded are:

(1) Any patients who suffer a cardiac arrest in a hospital facility where SJ-WA may be in attendance but where SJ-WA are not the primary care providers; or

(2) Any patients who suffer a cardiac arrest during an inter-hospital transfer where SJ-WA may be providing transport but where SJ-WA are not the primary care providers; or

(3) Any patients where the bystander or lay person suspected a cardiac arrest, but the patient was not in cardiac arrest on arrival of SJ-WA, and no defibrillation by bystanders has

occurred (thus, provision of bystander CPR on a patient is not itself treated as an inclusion criterion); and

(4) Any patients where there is a brief episode of pulselessness where SJ-WA did not provide CPR or defibrillation (and where there is no other evidence of the patient arresting).

The WA OHCA registry records both the core outcome variable of 'survived-to-hospital discharge' as well as the alternative outcome 30-day OHCA survival. All OHCA cases from the Perth metropolitan area transported to a hospital ED (as opposed to being pronounced deceased on scene or expired in transit to hospital) are followed up by a dedicated research nurse who performs a manual review of each patient's medical record (these reviews are done in-person at the relevant hospital; not from a hospital registry). Patient variables extracted from medical records include (but are not limited to); survival to ED discharge (yes/no), patient disposition from ED (transfer to another hospital, discharge to patient home/aged care/rehabilitation facility, admittance to hospital ward or hospital ICU), patient neurological status at hospital discharge,[88] total hospital length of stay and whether the patient survived to hospital discharge. Patient neurological status post arrest[88] is assessed using the cerebral performance category (CPC), which is a graded five-point scale of neurological function where: CPC 1 is indicative of a good cerebral performance; CPC 2 is indicative of a moderate cerebral disability; CPC 3 is indicative of severe cerebral disability; CPC 4 is indicative of a coma or vegetative state and finally CPC 5 is indicative of brain death.[89, 90] Importantly, all OHCA cases are scrutinised for consistency between the EMS PCR and the medical records.

The WA death registry (primary data source), together with the Perth Metropolitan Cemeteries Board database and EMS PCR forms (both secondary data sources) are used to determine 30-day survival of all OHCA patients. Specifically, 30-day survival status (yes/no) is determined by a dedicated PRECRU staff member who uses a combination of patient identifiers such as name, address, date of birth and date of arrest to identify a record in the WA death registry. If no match is found with the death registry, the Perth Metropolitan Cemeteries Board database is searched. If no match is found in the Cemeteries Board database, the ambulance PCR record is then scrutinized for any details that indicate the patient had not survived. Where a death date has been determined through these methods, the date of death is subtracted from the date of arrest, and an appropriate 30-day survival status is recorded; else 30-day survival is recorded as ‘yes’ where there is no evidence of the patient having died.

Other survival variables recorded in the WA OHCA registry include (1) ROSC at ED (also referred to as ‘Survived Event’) – i.e., return of spontaneous circulation at the time of transfer of care to medical staff at the receiving hospital; and (2) Any ROSC – i.e., return of spontaneous circulation at any time during the EMS resuscitation attempt. Both these variables are determined for each individual patient, by manual scrutiny of the electronic patient care records by PRECRU research staff.

Other OHCA variables

The WA OHCA registry also includes data on a range of variables, consistent with the Utstein guidelines. Below is a list of the variables used in this thesis:

- Patient characteristics
    - Age (in years; or unknown)
    - Sex (female; male; unspecified; unknown)
- Arrest characteristics
    - Aetiology (traumatic cause; poisoning/drug overdose; drowning; electrocution; asphyxia; malignancy/palliative; presumed cardiac)
    - Witnessed status (EMS-witnessed; bystander-witnessed; unwitnessed, unknown)
    - Arrest location (private residence; residential aged care facility; public location; other; unknown).
    - Initial arrest rhythm (Ventricular Fibrillation, VF; Ventricular Tachycardia, VT; Asystole; Pulseless Electrical Activity, PEA; AED non-shockable; AED-shockable; unknown)
- Pre-ambulance care
    - Bystander CPR provided before EMS arrival (yes; no; unknown)
    - Bystander AED pads applied (yes; no; unknown)
    - Bystander AED shock delivered (yes; no; unknown)
- Management of the patient by EMS
    - Response time (from call-answer by SJ-WA to arrival of first crew, in decimal minutes)
    - EMS resuscitation attempt provided [CPR provided by EMS and/or defibrillation by EMS] (yes; no; Do Not Resuscitate, DNR; unknown). NB: DNR in the WA OHCA

registry refers both to cases where (1) EMS did not start resuscitation due to a DNR order, and (2) EMS resuscitation was stopped prior to meeting clinical criteria due to a DNR order.

- Supplementary outcomes
  - Scene outcome (patient died on scene; was transported to hospital; unknown)

Where possible, data are automatically imported from the electronic patient care record (e.g., date-of-birth data is used to derive the patient's age at the time of the arrest). However, data coding for a large number of variables in the WA OHCA registry involves manual scrutiny by dedicated PRECRU research staff, of the electronic patient care records for each OHCA patient, including free-text Examination Text (case notes).

Personal identifiers are used as part of the WA OHCA registry, for matching OHCA records with hospital survival follow-up data, matching with the death registry, and for internal matching (e.g., to distinguish patients in ambulance incidents that have more than one patient). However, for this thesis (as with other research projects involving the WA OHCA registry), the unit data were supplied with personal identifiers removed (i.e., name, date-of-birth, address, location of arrest).

Several processes help provide quality assurance over the WA OHCA registry data. During the initial screening of potential cases, the research nurse will tentatively include (and flag for group review) any cases where there is ambiguity about inclusion. In addition, the research staff who undertake the subsequent coding of variables also flag for group review any cases with ambiguity about inclusion, as well as any ambiguities about the coding of variables. The broader PRECRU team who manage the WA OHCA registry then review flagged cases in monthly meetings, in reference to the inclusion and coding criteria, documenting the final coding reasons for each case under review.

Chapter 3 Temporal trends in OHCA

3.1 Overview

This chapter explores temporal trends in the incidence and outcomes of OHCA (of presumed cardiac aetiology) in the Perth metropolitan area over an 18-year period. The findings are reported in a manuscript published in the peer reviewed journal Resuscitation Plus. This manuscript is presented in section 3.4.

> ***Majewski D**, Ball S, Bailey P, Bray J, Finn J. Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia. Resuscitation Plus. 2022;9:100201.*

3.2 Background and Rationale

Prior to my thesis, there was only one existing study investigating the temporal trends of OHCA of presumed cardiac aetiology for the Perth metropolitan area, published in 2014.[91] That study looked at the trends in incidence, but not outcomes, to 2010. Therefore, the aim of this chapter is to provide an up-to-date, comprehensive description of the temporal trends in the incidence, patient and arrest characteristics, and 30-day survival of OHCA cases of presumed cardiac aetiology in metropolitan Perth from 2001 to 2018.

3.3 Methodology

<u>Study design</u>:

To address the aim of this chapter, I conducted a population-based retrospective cohort study of patients (of all ages) who experienced an OHCA in metropolitan Perth between 2001 and 2018. The study cohort was recruited from the WA OHCA registry. The three primary outcomes assessed were the temporal trends in OHCA: 1) incidence, 2) patient and arrest characteristics, and 3) survival. To be included in the study, patients had to have experienced an arrest of presumed cardiac aetiology (as defined by the 2004 Utstein guidelines)[34] and been attended by SJ-WA EMS.

I decided to focus on arrests of presumed cardiac aetiology since this aetiology makes up 70% of arrests in WA and they tend to have a more homogenous underlying pathology.[92]

Statistical analysis:

The annual OHCA incidence rates (OHCA cases per 100,000 person-years) were reported using crude incidence (to explore overall changes in incidence); age- and sex-specific incidence (to explore changes in incidence within specific demographic groups); and finally age standardised incidence rate (ASIR) (to explore changes in incidence while excluding demographic changes). Furthermore, given the importance of certain patient and arrest factors to OHCA survival, ASIRs were also determined specifically for cases of EMS-attempted resuscitation, and the Utstein comparator group (bystander-witnessed arrests with initial shockable arrest rhythm). Age and sex-specific incidence rates were calculated using annual estimates of the Perth resident population by age and sex, from the Australian Bureau of Statistics (ABS). Those same population reference data, in combination with the 2001 Australian (national) population standard[93] (also from the ABS), were used to generate ASIR values using the direct method of standardisation. Temporal trends in OHCA incidence rates were evaluated using Joinpoint regression[94] and reported as Annual Percentage Change (APC). Joinpoint regression was selected as it has several advantages over other statistical techniques. Firstly, Joinpoint regression allows for the analysis of multiple intra-period changes in trend.[95] This was an important consideration for this study as shifts in patient demographics, or advancements in medical care, over the study period could result in substantial intra-period variations in incidence. Secondly, unlike some other statistical methods for assessing trend, Joinpoint regression uses quantitative methods to identify statistically significant time points of changing trend.[95] Temporal trends in patient and arrest characteristics (of the study cohort) were assessed using either logistic regression (for dichotomous variables) or ordinal logistic regression (for any ordinal variables). The survival was assessed for two outcomes: ROSC (on arrival to the ED) and survival to 30 days. The annual survival rates were presented as a proportion of: 1) those that received an EMS-attempted resuscitation and 2) the Utstein comparator group (bystander witnessed arrests that presented with an initial shockable arrest rhythm). Temporal trends in annual survival rate were assessed using logistic regression.

3.4 Manuscript

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Clinical paper

Trends in out-of-hospital cardiac arrest incidence, patient characteristics and survival over 18 years in Perth, Western Australia

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Abstract

Objectives: To investigate trends in the incidence, characteristics, and survival of out-of-hospital cardiac arrests (OHCA) in the Perth metropolitan area between 2001 and 2018.

Methods: We calculated the crude incidence rate, age-standardised incidence rate (ASIR) and age- and sex-specific incidence rates (per 100,000 population) for OHCA of presumed cardiac aetiology. ASIRs were calculated using the direct method of standardisation using the 2001 Australian Population standard. Survival was assessed at return of spontaneous circulation at emergency department arrival and at 30 days. Temporal trends in patient and arrest characteristics were assessed with logistic regression, while trends in incidence were assessed using Joinpoint regression. Survival trends were assessed using binary logistic regression.

Results: A total of 18,417 OHCAs of presumed cardiac aetiology were attended by emergency medical services in Perth between 2001 and 2018. Overall, there were no significant changes in the crude or ASIR of OHCA over the study period, although OHCA incidence in 15–39 year-old males increased by 12.5% annually between 2011 and 2018. Both bystander cardiopulmonary resuscitation and bystander defibrillation increased over the study period, while the proportion of shockable arrests declined. Thirty-day OHCA survival improved significantly over time, with the odds of survival (in bystander-witnessed, initial shockable rhythm arrests) improving 12% (95% CI, 9.0% to 14.0%) annually, from 8.4% in 2001 to 44.0% in 2018.

Conclusion: Overall, there were no significant trends in OHCA incidence over the study period, although arrests in 15–39 year-old males increased significantly after 2011. There were significant improvements in 30-day survival between 2001 and 2018.

Keywords: Out-of-hospital cardiac arrest, Survival, Incidence, Trends

Introduction

Out-of-hospital cardiac arrest (OHCA) is a global health issue[1] that carries considerable societal and economic costs.[3] A recent study estimated that the annual economic loss to the Australian economy from sudden cardiac arrest was comparable to that from all cancers in Australia combined.[3] With an ageing population[4] it is likely these economic impacts will only be exacerbated in the future. Monitoring temporal trends in OHCA incidence enables the evaluation of the effectiveness of preventative public health strategies, while monitoring survival helps inform the clinical management of OHCAs. Importantly, understanding OHCA trends allows health authorities to better target future health spending.

Globally, temporal trends in OHCA incidence have shown considerable variation.[2,5,6] This variation is likely to be a result of regional differences in socioeconomic status[7] and underlying population health characteristics.[8] Encouragingly, recent international studies have generally reported increasing survival over time.[2,9–11] Our

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study aimed to investigate temporal trends in the incidence, patient and arrest characteristics, and 30-day survival of OHCA of presumed cardiac aetiology in the Perth metropolitan area over an 18-year period.

Methods

Study design

We conducted a population-based retrospective cohort study of patients (of all ages) who experienced an OHCA of presumed cardiac aetiology in the Perth metropolitan area and were attended by St John Western Australia (SJ-WA) emergency medical services (EMS) between 1st January 2001 and 31st December 2018. 'Presumed cardiac aetiology' was defined based on the exclusion of other obvious non-cardiac causes e.g., trauma, poisoning, drowning, drug overdose or asphyxia.[12] This study was approved by the Human Research Ethics Committee of Curtin University as a sub-study of the Western Australian Pre-hospital Care Record Linkage Project (HR128/2013).

Study setting

Perth is the capital, and largest city, in the state of WA, with a population of 1.39 million people in 2001[13] and 2.09 million in 2019.[14] The sole provider of road-based EMS in Perth is SJ-WA, which operates a single-tiered advanced life support service, staffed by nationally-registered paramedics. OHCA patients are currently transported to one of ten hospital emergency departments (ED) within the Perth area,[15] unless resuscitative efforts are ceased in the field by paramedics (or not commenced), due to futility or not-for-resuscitation orders.

Data sources

We sourced data from the SJ-WA OHCA Database[16] which contains details for all metropolitan OHCAs attended by SJ-WA EMS since 1996. The database is maintained by the Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU) at Curtin University, extracting data from patient care records (PCR) completed by SJ-WA paramedics, and linked to computer-aided dispatch data. The database contains data on patient demographics, arrest characteristics, EMS response intervals, pre-ambulance care by bystanders, and EMS interventions. The 'Utstein' prognostic variables[12] in the database include patient age and sex, witnessed status (bystander-witnessed; EMS-witnessed; unwitnessed), bystander cardiopulmonary resuscitation (CPR), EMS response time (call answer to arrival on scene), initial cardiac arrest rhythm (as recorded by paramedics), return of spontaneous circulation (ROSC) in the field, and ROSC on arrival at the Emergency Department (ED). Thirty-day survival following OHCA is determined by manual look-up in the WA Death Registry.[17] As a result of industrial action by SJ-WA paramedics in 2008, a number of OHCA cases for that year are thought to be missing/incomplete. We therefore excluded all cases from 2008.

Statistical analysis

Patient and arrest characteristics of the study cohort were summarised across 3-year time intervals (2001–2003, 2004–2006, 2007–2009 [excluding 2008], 2010–2012, 2013–2015, 2016–2018) as counts and percentages. Patient and arrest characteristics examined were patient age group (0–17, 18–39, 40–64, 65–79, and 80 + years), sex (male/female), arrest locations (public/other), EMS witnessed arrest (yes/no), bystander witnessed (yes/no), bystander CPR (yes/no), automated external defibrillator (AED) shock-given by bystander (yes/no), initial arrest rhythm (ventricular fibrillation/ pulseless ventricular tachycardia (VF/VT), Asystole/pulseless electrical activity (PEA), EMS-attempted resuscitation (yes/no), EMS response time (<10 mins, ≥10 mins), ROSC at ED (yes/no) and survived 30-days (yes/no). Annual crude, age- and sex-specific, and ASIR were calculated for the Perth metropolitan area and reported per 100,000 person-years. Additionally, ASIRs were determined for cases of EMS-attempted resuscitation, and the Utstein comparator group (bystander-witnessed arrests with initial shockable arrest rhythm).[12] Annual crude incidence rates were calculated as the number of OHCA events for each calendar year divided by the Perth population for that year (obtained from the Australian Bureau of Statistics (ABS)). Age- and sex-specific incidence rates were calculated by sex (male/female) and age group (0–14, 15–39, 40–64, 65–79, and 80 + years), using the number of OHCA cases for each group as the numerator and the Perth metropolitan population corresponding to each respective group as the denominator. ASIR were calculated using annual age-specific incidence rates across 5-year age groups, standardised using the direct method of standardisation to the 2001 Australian population standard.[18]

Temporal trends in patient and arrest characteristics were assessed using logistic regression for dichotomous variables (e.g. sex), and ordinal logistic regression [after confirmation of proportional odds assumption][19] for ordinal variables (e.g. patient age group). Temporal trends in OHCA incidence rates (e.g. crude, age- and sex-specific, and age-standardised) were examined using Joinpoint regression and reported as the Annual Percentage Change (APC) in incidence. Joinpoint regression applies a piecewise log-linear model using a permutation test to determine the optimal number of "joinpoints";[20] allowing it to identify overall trend as well as shorter intra-study period trends (where present). Temporal trends in survival outcome (ROSC at ED, 30-day survival) were assessed using unadjusted and adjusted logistic regression for two patient groups: i) those who received EMS-attempted resuscitation and ii) the Utstein comparator group.[12] Variables included in the adjusted models were: calendar-year of arrest [continuous], patient age (0–17, 18–39, 40–64, 65–79, and 80+ years), sex (female/male), arrest location (public/other), arrest witness status (unwitnessed/bystander witnessed/EMS witnessed), bystander CPR (no/yes), bystander AED shock (no/yes), initial arrest rhythm (Asystole/PEA, VF/VT) and EMS response time (in minutes, from call to scene). The logistic regression model for the Utstein comparator group excluded 'bystander status' and 'initial arrest rhythm' as these are specified in the definition of the sub-group. Analysis was performed using SPSS v26 (IBM Inc., Armonk, NY, USA) and Joinpoint regression version 4.9.0.0 (https://surveillance.cancer.gov/joinpoint/). Results were considered statistically significant for P values < 0.05.

Results

Between 2001 and 2018 EMS attended 25,561 OHCA cases in the Perth metropolitan area, of which 19,188 (75.1%) were of a presumed cardiac aetiology. After excluding cases from 2008 (n = 755) and those with missing key patient demographic data (n = 16), 18,417 cases were included in our final cohort (Fig. 1). Overall, 1677 (9.1%) patients from our cohort achieved ROSC at

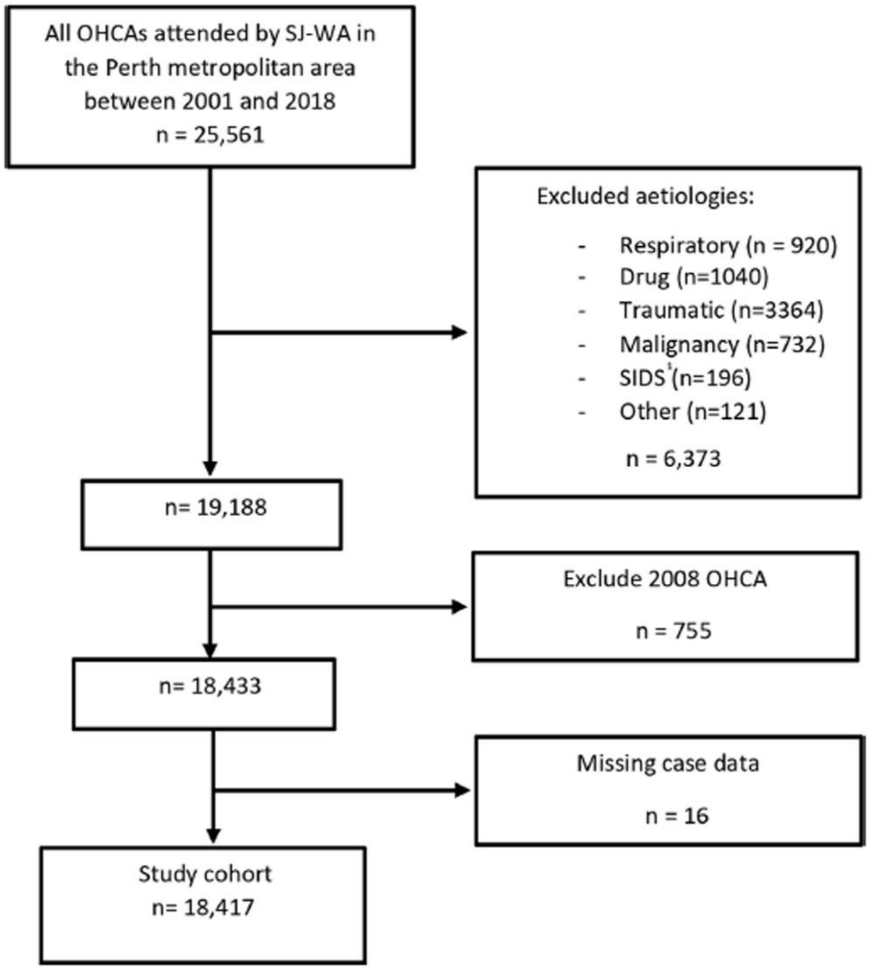

Fig. 1 – Flow diagram of study cohort.
1. Sudden Infant Death Syndrome.

ED and 920 (5.0%) survived to 30 days. Of the 8,340 (45.3%) cases who received a EMS-attempted resuscitation, 1599 (19.2%) attained ROSC at ED, and 841 (10.1%) survived to 30 days. Of the 1716 Utstein comparator group arrests (bystander-witnessed arrests with initial shockable rhythm), 585 (34.1%) achieved ROSC at ED and 435 (25.3%) survived to 30-days. Table 1 shows the characteristics of OHCA cases included over the study period, grouped by 3-year calendar intervals.

Trends in ROSC at ED

The overall proportion of OHCA patients with ROSC at ED increased over the study period, from 3.5% between 2001 and 2003 to 12.1% between 2016 and 2018 (Table 1). Fig. 2 shows the percentage of 30-day OHCA survivors by calendar year as a proportion of; i) all EMS-attempted resuscitations and ii) all Utstein comparator group resuscitations. In the EMS-attempted resuscitation group, the proportion of patients that attained ROSC at ED increased from 5.6% in 2001 to 26.5% in 2018 ($p < 0.001$), representing a crude improvement of 8.0% (OR 1.08; 95% CI, 1.07–1.10) per annum in the odds of ROSC at ED (Table 2a). In the Utstein comparator group, the proportion of patients that attained ROSC at ED increased from 9.5% in 2001 to 48.5% in 2018 ($p < 0.001$), representing a crude improvement of 12.0% (OR 1.12; 95% CI, 1.10–1.15) per annum in the odds of ROSC at ED. After adjustment for potential confounders (Table 2), the odds of ROSC at ED improved by 11.0% per annum for both the EMS-attempted resuscitation group (OR 1.11; 95% CI, 1.10–1.13) and the Utstein comparator group (OR 1.11; 95% CI, 1.09–1.14).

Trends in 30-day survival

There was a steady increase in 30-day survival over the study period, with overall 30-day survival in our study cohort increasing from 2.6% (between 2001 and 2003) to 6.7% (between 2016 and 2018). Fig. 2 shows the percentage of 30-day OHCA survivors by calendar year as a proportion of; i) all EMS-attempted resuscitations and ii) all Utstein comparator group resuscitations. Survival in the EMS-attempted resuscitation group increased significantly over the study period, from 4.2% in 2001 to 16.4% in 2018 ($p < 0.001$). The logistic regression model showed that for this group the odds of surviving 30-days improved by 5% (OR 1.05; 95% CI, 1.04–1.07) per annum in the unadjusted model, and by 9.0% (OR 1.09; 95% CI 1.07–1.10)

Table 1 – Descriptive characteristics of OHCAs of presumed cardiac aetiology attended by SJ-WA in Perth WA between 2001 and 2018 (n = 18,417 cases) across 3-year time intervals.

	2001–2003		2004–2006		2007-2009[a]		2010–2012		2013–2015		2016–2018	
	n = 2439		n = 2529		n = 1897		n = 3083		n = 4032		n = 4437	
Patient age, n (%)												
0–17	30	(1.2)	15	(0.6)	11	(0.6)	33	(1.1)	45	(1.1)	29	(0.7)
18–39	118	(4.8)	158	(6.2)	114	(6.0)	162	(5.3)	299	(7.4)	329	(7.4)
40–64	680	(27.9)	718	(28.4)	590	(31.1)	959	(31.1)	1326	(32.9)	1416	(31.9)
65–79	963	(39.5)	888	(35.1)	623	(32.8)	911	(29.5)	1177	(29.2)	1381	(31.1)
80+	648	(26.6)	750	(29.7)	559	(29.5)	1018	(33.0)	1185	(29.4)	1282	(28.9)
Sex, n (%)												
Male	1580	(64.8)	1668	(66.0)	1233	(65.0)	2032	(65.9)	2647	(65.6)	2860	(64.5)
Female	859	(35.2)	861	(34.0)	664	(35.0)	1051	(34.1)	1385	(34.4)	1577	(35.5)
Arrest location, n (%)												
Public	309	(12.7)	292	(11.5)	212	(11.2)	370	(12.0)	455	(11.3)	417	(9.5)
Other	2130	(87.3)	2237	(88.5)	1685	(88.8)	2713	(88.0)	3577	(88.7)	3952	(90.5)
EMS witnessed arrest n (%)												
Yes	93	(3.8)	113	(4.5)	91	(4.8)	168	(5.4)	245	(6.1)	320	(7.2)
No	2346	(96.2)	2416	(95.5)	1806	(95.2)	2915	(94.6)	3787	(93.9)	4117	(92.8)
Bystander witnessed n (%)												
Yes	703	(28.8)	626	(24.8)	408	(21.5)	688	(22.3)	904	(22.4)	1120	(25.2)
No	1736	(71.2)	1903	(75.2)	1489	(78.5)	2395	(77.7)	3128	(77.6)	3317	(74.8)
Bystander CPR, n (%)												
Yes	505	(21.5)	584	(24.2)	415	(23.0)	906	(31.1)	1331	(35.1)	1584	(38.5)
No	1841	(78.5)	1832	(75.8)	1391	(77.0)	2009	(68.9)	2456	(64.9)	2533	(61.5)
AED shock-given, n (%)												
Yes	2	(0.1)	4	(0.2)	9	(0.5)	32	(1.0)	48	(1.2)	91	(2.1)
No	2437	(99.9)	2525	(99.8)	1888	(99.5)	3051	(99.0)	3984	(98.8)	4346	(97.9)
Initial arrest rhythm, n (%)												
VF/VT	433	(17.8)	406	(16.1)	296	(15.6)	503	(16.3)	577	(14.3)	641	(14.4)
Asystole/PEA	1979	(81.1)	2122	(83.9)	1595	(84.1)	2555	(82.9)	3451	(85.6)	3791	(85.4)
Unknown	27	(1.1)	1	(0.0)	6	(0.3)	25	(0.8)	4	(0.1)	5	(0.1)
Attempted Resus, n (%)												
Yes	1047	(42.9)	978	(38.7)	769	(40.5)	1384	(44.9)	2064	(51.2)	2098	(47.3)
No	1392	(57.1)	1551	(61.3)	1128	(59.5)	1699	(55.1)	1968	(48.8)	2339	(52.7)
EMS response time, n (%)												
< 10 minutes	1558	(63.9)	1559	(61.6)	1143	(60.3)	1994	(64.7)	2963	(73.5)	2985	(67.3)
≥ 10 minutes	876	(35.9)	969	(38.3)	754	(39.7)	1088	(35.3)	1069	(26.5)	1451	(32.7)
Unknown	5	(0.2)	1	(<0.1)	0	(0.0)	1	(0.0)	0	(0.0)	1	(<0.1)
ROSC at ED, n (%)												
Yes	86	(3.5)	115	(4.5)	128	(6.8)	309	(10.1)	504	(12.5)	535	(12.1)
No	2352	(96.5)	2413	(95.5)	1762	(93.2)	2754	(89.9)	3522	(87.5)	3902	(87.9)
Survived 30-days, n (%)												
Yes	63	(2.6)	78	(3.1)	87	(4.6)	167	(5.4)	229	(5.7)	296	(6.7)
No	2376	(97.4)	2451	(96.9)	1810	(95.4)	2916	(94.6)	3803	(94.3)	4141	(93.3)

[a] Data for 2008 excluded.

per annum after adjustment for potential confounders (Table 2a). Survival in the Utstein comparator group showed the greatest improvement over time, from 8.4% in 2001 to 44.0% in 2018 ($p < 0.001$). In this group the odds of surviving 30 days following arrest improved by 12% (OR 1.12; 95% CI, 1.09–1.14) per annum in the unadjusted logistic regression model and by 11% (OR 1.11; 95% CI 1.08–1.14) per annum after adjustment for potential confounders (Table 2b).

Trends in patient and arrest characteristics

Fig. 3 shows the temporal trends in patient and arrest characteristics, as a proportion of all arrests in each respective year. Patients tended to be younger over time, with the odds of belonging to an older age group decreasing by 1.0% annually (OR 0.99; 95% CI, 0.98–0.99). An increasing trend was seen in EMS-witnessed arrests (OR 1.05; 95% CI, 1.03–1.06), bystander CPR (OR 1.06; 95% CI, 1.05–1.07), bystander delivered AED shocks (OR 1.20; 95% CI, 1.16–1.25) and attempted EMS resuscitations (OR 1.03; 95% CI, 1.02–1.03). In contrast, there was a decreasing trend in arrests in public locations (OR 0.98; 95% CI, 0.97–0.99), bystander witnessed arrests (OR 0.99; 95% CI, 0.98–0.99), arrests with an initial VF/VT rhythm (OR 0.98; 95% CI, 0.98–0.99) and EMS response time (OR 0.98; 95% CI, 0.97–0.98). There was no significant trend in patient sex (OR 1.00; 95% CI, 1.00–1.01).

Trends in OHCA incidence

Fig. 4 shows the overall crude, and age-standardised OHCA incidence rates along with the ASIR of the subgroup analyses (EMS-attempted resuscitation, and Utstein comparator group). Supplementary Table 1 show the results of the trend analysis (i.e. Joinpoint

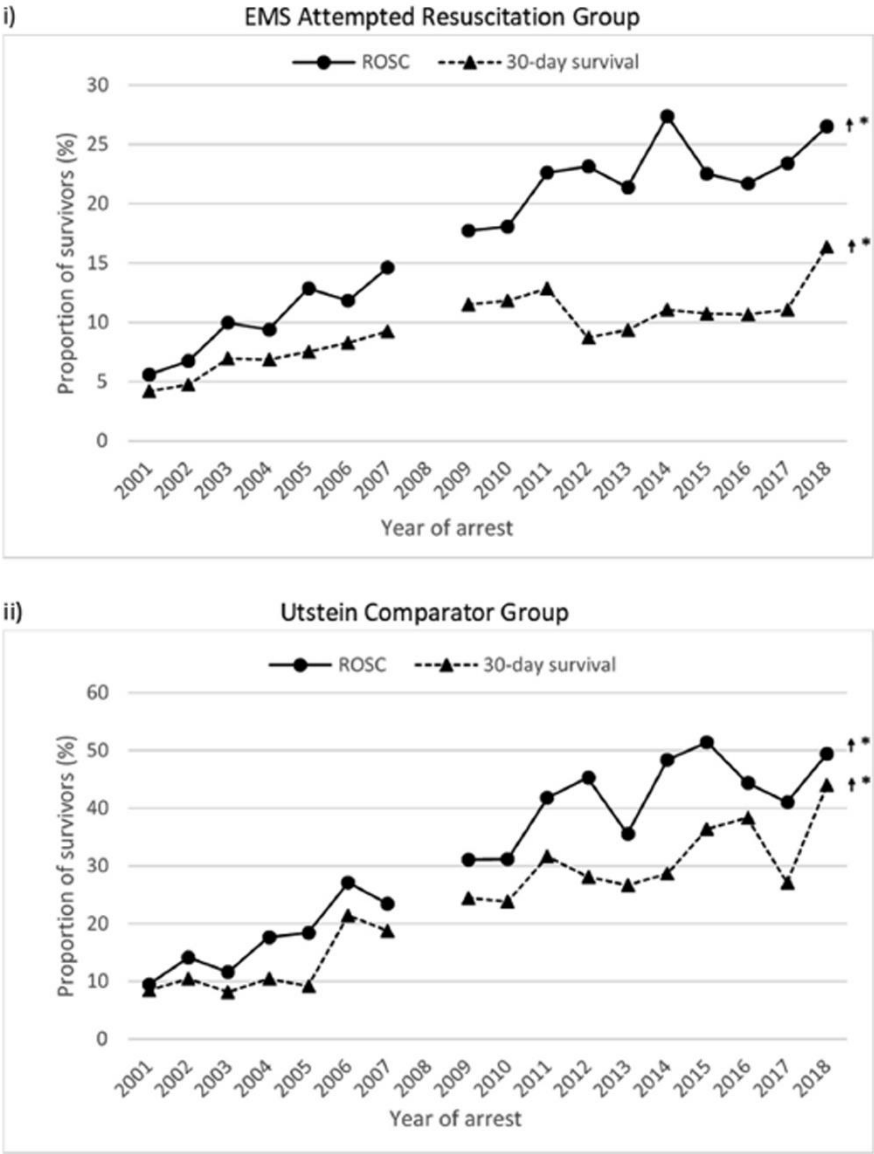

Fig. 2 – Temporal trends in ROSC at ED and 30-day OHCA survival in i) patients with an EMS attempted resuscitation and ii) the Utstein comparator group.
†* Binary logistic regression showing increasing survival over calendar year p < 0.05.

regression results). There were no significant temporal trends in overall crude incidence rate (APC 1.5; 95% CI, −1.1 to 4.2) or ASIR (APC 0.8; 95%, CI −1.9 to 3.5). Likewise, there were no overall significant temporal trends in the ASIR of EMS-attempted resuscitations (APC 0.7; 95% CI, −1.0 to 2.4) or Utstein comparator group arrests (APC 0.2; 95% CI, −3.3 to 3.8). However, ASIR of EMS-attempted resuscitations did show statistically significant intra-study period changes: incidence declined between 2001 and 2004 (APC −7.3; 95% CI, −13.4 to −0.8) and 2015–2018 (APC −8.3, 95% CI, −12.6 to −3.8), but increased between 2011 and 2015 (APC 13.4; 95% CI, 7.7–19.5). Likewise, ASIR of the Utstein comparator group rose significantly after 2007 (APC 4.7; 95% CI, 1.1–8.4). Some age and sex demographic groups showed small (albeit statistically significant) changes in OHCA incidence over time (Supplementary Fig. 1). The largest change occurred in 15–39 year old males with incidence increasing by 12.5% (APC 12.5; 95% CI, 4.8–20.7) per annum after 2011.

Discussion

Our study examined temporal trends in EMS attended OHCAs of presumed cardiac aetiology, in Perth WA, between 2001 and 2018. Overall, there was an upward trend in OHCA survival over the study period. In arrests with EMS attempted resuscitation, 30-day survival increased from 4.2% in 2001 to 16.4% in 2018. The greatest improvement in survival was in the Utstein comparator group (bystander-witnessed arrests presenting with initial shockable arrest

Table 2 – Unadjusted and adjusted odds ratios for OHCA patients achieving ROSC or 30-day survival in (a) EMS attempted resuscitation (n = 8340) or (b) Utstein comparator arrests (n = 1716) between 2001 and 2018.

Table 2a. EMS attempted resuscitation (n = 8340)

	ROSC at Emergency Department				30-day survival			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Year of arrest								
Per year	1.08	(1.07–1.10)	1.11	(1.10–1.13)	1.05	(1.04–1.07)	1.09	(1.07–1.10)
Age group								
0–17	ref	ref		ref	ref		ref	
18–39	1.63	(0.94–2.84)	1.21	(0.66–2.21)	1.72	(0.88–3.33)	0.94	(0.41–2.11)
40–64	1.52	(0.90–2.56)	0.92	(0.52–1.64)	1.54	(0.82–2.89)	0.54	(0.25–1.18)
65–79	1.41	(0.84–2.38)	0.96	(0.54–1.70)	0.99	(0.52–1.87)	0.38	(0.17–0.82)
≥ 80	1.13	(0.67–1.92)	0.83	(0.47–1.48)	0.43	(0.22–0.83)	0.19	(0.09–0.43)
Sex								
Female	ref		ref		ref		ref	
Male	0.95	(0.85–1.07)	0.70	(0.61–0.80)	1.41	(1.19–1.66)	0.81	(0.67–0.99)
Arrest location								
Other	ref		ref		ref		ref	
Public	2.04	(1.79–2.31)	1.58	(1.36–1.84)	3.26	(2.80–3.80)	2.22	(1.83–2.70)
Arrest witness status								
Unwitnessed	ref		ref		ref		ref	
Bystander witnessed	2.35	(2.06–2.66)	1.44	(1.25–1.66)	3.28	(2.70–3.97)	1.36	(1.09–1.69)
EMS witnessed	4.60	(3.90–5.43)	3.37	(2.76–4.12)	9.34	(7.52–11.60)	8.75	(6.55–11.69)
Bystander CPR								
No	ref		ref		ref		ref	
Yes	1.21	(1.08–1.35)	1.11	(0.96–1.28)	1.13	(0.98–1.30)	1.11	(0.89–1.39)
Bystander AED shock								
No	ref		ref		ref		ref	
Yes	5.12	(3.58–7.32)	1.25	(0.84–1.86)	5.71	(3.94–8.26)	1.01	(0.66–1.54)
Presenting arrest rhythm								
Asystole	ref		ref		ref		ref	
PEA	2.89	(2.45–3.41)	2.48	(2.07–2.96)	7.29	(4.91–10.83)	5.37	(3.52–8.20)
VF/VT	5.82	(5.04–6.72)	5.63	(4.79–6.63)	37.62	(26.28–53.83)	34.15	(23.24–50.18)
EMS response time								
Per minute	0.98	(0.97–0.99)	0.98	(0.97–0.99)	0.97	(0.96–0.99)	0.96	(0.95–0.98)

Table 2b. Utstein comparator arrests (n=1716)

	ROSC at Emergency Department				30-day survival			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Year of arrest								
Per year	1.12	(1.10–1.15)	1.11	(1.09–1.14)	1.12	(1.09–1.14)	1.11	(1.08–1.14)
Age group								
0–17	ref		ref		ref		ref	
18–39	1.75	(0.48–6.32)	2.01	(0.49–8.30)	1.51	(0.42–5.46)	1.79	(0.43–7.41)
40–64	0.98	(0.28–3.36)	1.20	(0.30–4.72)	0.76	(0.22–2.63)	0.93	(0.24–3.68)
65–79	0.85	(0.25–2.94)	1.19	(0.30–4.71)	0.48	(0.17–1.65)	0.64	(0.16–2.54)
≥ 80	0.62	(0.18–2.19)	0.90	(0.22–3.65)	0.21	(0.06–0.76)	0.30	(0.07–1.24)
Sex								
Female	ref		ref		ref		ref	
Male	0.82	(0.64–1.06)	0.64	(0.48–0.85)	1.02	(0.77–1.35)	0.75	(0.54–1.04)
Arrest location								
Other	ref		ref		ref		ref	
Public	2.22	(1.81–2.73)	1.98	(1.55–2.53)	3.17	(2.53–3.99)	2.71	(2.07–3.55)
Arrest witness status								
Unwitnessed	NA	NA	NA	NA	NA	NA	NA	NA
Bystander witnessed	NA	NA	NA	NA	NA	NA	NA	NA
EMS witnessed	NA	NA	NA	NA	NA	NA	NA	NA

Bystander CPR								
No	ref		ref		ref		ref	
Yes	2.21	(1.69–2.88)	1.35	(1.01–1.81)	2.95	(2.14–4.08)	1.67	(1.17–2.39)
Bystander AED shock								
No	ref		ref		ref		ref	
Yes	6.16	(4.25–8.92)	2.80	(1.84–4.27)	5.72	(4.05–8.07)	2.25	(1.50–3.38)
Presenting arrest rhythm								
Asystole	NA	NA	NA	NA	NA	NA	NA	NA
PEA	NA	NA	NA	NA	NA	NA	NA	NA
VF/VT	NA	NA	NA	NA	NA	NA	NA	NA
EMS response time								
Per minute	0.94	(0.92–0.97)	0.93	(0.90–0.96)	0.95	(0.92–0.98)	0.93	(0.90–0.97)

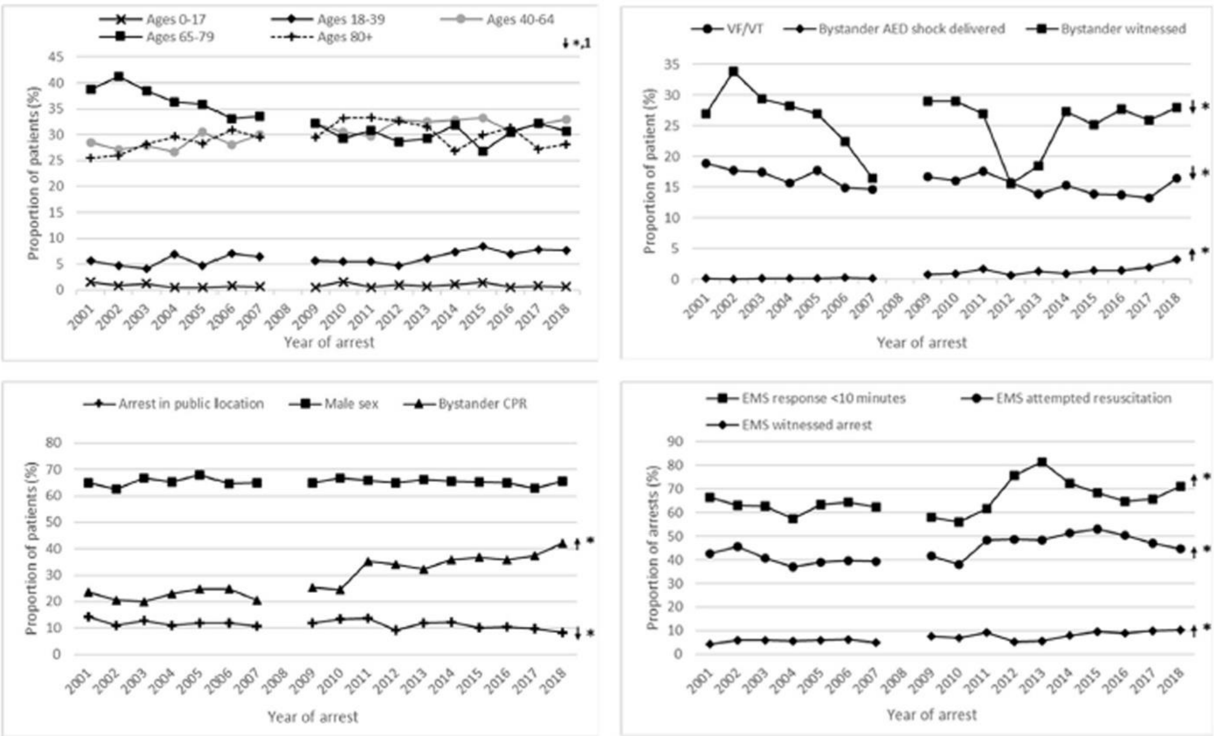

Fig. 3 – Trends over time in patient and arrest characteristics (as a proportion of all EMS attended arrests in each respective year) of OHCA of presumed cardiac aetiology attended by EMS between 2001 and 2018 in Perth WA.
↓*,1 Ordinal logistic regression showing decreasing patient age-group across calendar year $p < 0.05$.
↓* Binary logistic regression showing decreasing trend across calendar year $p < 0.05$.
↑* Binary logistic regression showing increasing trend across calendar year $p < 0.05$.

rhythm), where 30-day survival increased from 8.4% in 2001 to 44.0% in 2018; representing a 5-fold improvement in survival over an 18-year period.

The improvement in the Utstein comparator group survival was particularly noteworthy, as survival in this sub-group of OHCAs is less susceptible to regional variations in EMS policy (with regards to selective resuscitation) or patient/arrest 'case-mix'; thereby providing a more comparable measure of survival trend. We speculate increasing rates of bystander CPR and AED use, coupled with improving EMS response times and provision of high-quality CPR over the study period have acted to increase survival. The benefits of high-quality CPR to OHCA survival has been well established.[21]

Since 2000, resuscitation guidelines have progressively placed greater emphasis on optimizing chest compression (in relation to compression depth and rate) and limiting 'hands-off' periods.[22] Interestingly however, after adjusting our logistic regression models for pre/peri-arrest factors, the trends in 30-day survival and ROSC at ED for the Utstein group remained strong, with the odds of both outcomes increasing 11% annually (both were 12% in unadjusted models). This suggests the improvement in survival may have largely resulted from other, unmeasured factors. Ultimately, we were unable to identify the factors responsible for the large increase in 30-day survival.

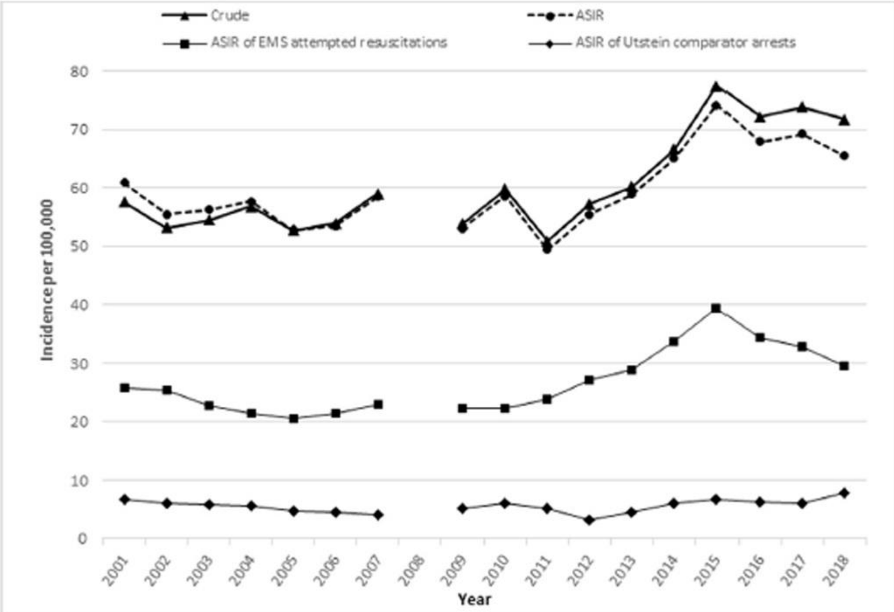

Fig. 4 – Trends in crude incidence, ASIR, ASIR of EMS attempted resuscitations and ASIR of Utstein comparator group arrests of OHCA of presumed cardiac aetiology attended by EMS between 2001 and 2018 in Perth, WA.

There were no significant trends in either crude or ASIRs between 2001 and 2018. A previous study[23] examining OHCA of presumed cardiac aetiology in Perth did not find a significant trend in crude incidence between 1997 and 2010, consistent with our study. This earlier study did however report a significant decrease in the ASIR, though this decrease appears to have exclusively occurred prior to 2002. A study[24] from Victoria, Australia, reported significant declines in the crude incidence and ASIR of OHCA of presumed cardiac aetiology between 2002 and 2012. However, this Victorian study only included adults (≥18 years) and excluded all EMS-witnessed arrests, making direct comparisons with our present study challenging.

Concerningly, our study identified a growing prevalence of OHCA incidence in young males. Between 2011 and 2018, OHCAs in 15–39 year-old males increased at a rate of 12.5% per annum - the largest rate of annual increase of any demographic group. Although we were unable to identify the reason for this increase, a 2012 study[25] reported the most common underlying cause of OHCAs in those between 25 and 35 years of age was coronary artery disease (CAD). We suspect, as others[26–28] have suggested, that the rising prevalence of cardiovascular disease risk factors may be partly responsible for this trend.

Despite encouraging OHCA survival trends, some trends are a cause for concern. Firstly, we found the proportion of OHCA patients presenting with initial shockable arrest rhythms has been steadily decreasing over time; consistent with findings from other Australian[5,29] and international[30,31] studies. Although the association between initial arrest rhythm and survival is well established,[32,33] the reason for this decreasing trend in shockable rhythms is poorly understood. A 2021 study[34] from the Netherlands suggested that comorbidity burden may be associated with lower odds of a shockable arrest, although this relationship was only found in males. Secondly, we found a decreasing trend in both the proportion of bystander-witnessed arrests and arrests occurring in public locations. Both these factors result in a delay to resuscitative efforts, resulting in reduced survival. Lastly, given the generally negative effect comorbidity has on OHCA survival outcomes,[35] projected increases in population comorbidity[36] could result in lower OHCA survival in the future.

Limitations

Our study has several limitations. Firstly, our study excluded all data from 2008. However, this exclusion did not impact reported trends as our regression analyses modelled 'time' (i.e. calendar year) as a continues variable. Secondly, our study only included arrests of 'presumed cardiac aetiology'. We chose to focus on arrests of this aetiology as they make up the bulk of arrests in Western Australia (>70%) and therefore represent the greatest burden to healthcare. Thirdly, we defined the geographical boundary of metropolitan Perth according to the 2016 ABS definition. This may have resulted in the inclusion of some cases (prior to 2016) that were considered, at the time of arrest, to be rural. Lastly, our study did not examine survival outcomes beyond 30 days. However, in a prior study[9] we demonstrated that between 1998 and 2017 there was a significant improvement in 10-year survival, relative to the age- and sex-matched general population, of initial (30-day) OHCA survivors in Perth.

Conclusion

There were no significant trends in the overall incidence of OHCA of presumed cardiac origin in metropolitan Perth between 2001 and 2018, however incidence in 15–39 year-old males increased sharply after 2011. The rates of bystander CPR and the provision of bystander AED shocks increased over the study period, however the proportion of arrests presenting with initial VF/VT rhythms decreased. There was an overall improvement in OHCA survival, with the odds of 30-day survival in the Utstein comparator group (bystander witnessed, initial VF/VT rhythm arrests) improving on average by 12% per annum.

CRediT authorship contribution statement

David Majewski: Conceptualization, Methodology, Validation, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Stephen Ball:** Conceptualization, Methodology, Validation, Data curation, Writing – review & editing. **Paul Bailey:** Conceptualization, Writing – review & editing, Funding acquisition. **Janet Bray:** Conceptualization, Writing – review & editing. **Judith Finn:** Conceptualization, Methodology, Validation, Writing – review & editing, Project administration, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Some of the authors are affiliated with St John WA as follows: Paul Bailey (Medical Director); Judith Finn (Adjunct Research Professor & recipient of research funding); Stephen Ball (Adjunct Research Fellow).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100201.

REFERENCES

1. Kiguchi T, Okubo M, Nishiyama C, et al. Out-of-hospital cardiac arrest across the World: First report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation 2020;152:39–49.
2. Lim SL, Smith K, Dyson K, et al. Incidence and Outcomes of Out-of-Hospital Cardiac Arrest in Singapore and Victoria: A Collaborative Study. J Am Heart Assoc 2020;9:e015981.
3. Paratz ED, Smith K, Ball J, et al. The economic impact of sudden cardiac arrest. Resuscitation 2021;163:49–56.
4. Australian Institute of Health and Welfare. Older Australians [Internet]. Canberra: Australian Institute of Health and Welfare, 2021 [cited 2021 Dec 24]. Available from: https://www.aihw.gov.au/reports/older-people/older-australians
5. Pemberton K, Bosley E. Temporal trends (2002–2014) of incidence and shockable status of adult emergency medical service attended out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland. Emerg Med Austral 2018;30:89–94.
6. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.
7. van Nieuwenhuizen BP, Oving I, Kunst AE, et al. Socio-economic differences in incidence, bystander cardiopulmonary resuscitation and survival from out-of-hospital cardiac arrest: A systematic review. Resuscitation 2019;141:44–62.
8. Raun LH, Jefferson LS, Persse D, Ensor KB. Geospatial analysis for targeting out-of-hospital cardiac arrest intervention. Am J Prev Med 2013;45:137–42.
9. Majewski D, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation 2020;157:108–11.
10. Buick JE, Drennan IR, Scales DC, et al. Improving Temporal Trends in Survival and Neurological Outcomes After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes 2018;11:e003561.
11. Wang C-Y, Wang J-Y, Teng N-C, et al. The Secular Trends in the Incidence Rate and Outcomes of Out-of-Hospital Cardiac Arrest in Taiwan—A Nationwide Population-Based Study. PLoS ONE 2015;10:e0122675.
12. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:1286–300.
13. Australian Bureau of Statistics. 3218.0 - Regional population growth, 2001-02 2003. (Cited 2021 22/08/2021, at: https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/5423FDFDB56DA2EFCA256CFD00041DF6/$File/32180_2001-02.pdf).
14. Australian Bureau of Statistics. 3101.0 – Australian Demographic Statistics, Dec 2019, 2020. (Updated 18/06/202021/04/2020, at: https://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3218.0).
15. Australian Government Department of Health. Emergency Departments; Perth, WA 6000: Healthdirect. (Cited 22 August 2021, at: https://www.healthdirect.gov.au/australian-health-services/results/perth-6000/tihcs-aht-10968/emergency-departments?pageIndex=1&tab=SITE_VISIT).
16. St John WA. Out-of-Hospital Cardiac Arrest Report, 2018. (Cited 19 August 2021, at: https://stjohnwa.com.au/docs/default-source/corporate-publications/ohca-cardiac-arrest-report_web.pdf?sfvrsn=2).
17. Governement of Western Australia DoJ. The Registry of Births, Deaths and Marriages, 2021 May 2021.. (Accessed, at: https://www.wa.gov.au/organisation/department-of-justice/the-registry-of-births-deaths-and-marriages).
18. Australian Bureau of statistics. Standard Population for Use in Age-Standardisation, 2013. (Available, at: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/sep-2020/31010DO003_200106.xls).
19. Laerd Statistics. Ordinal Regression using SPSS Statistics cited 20 May 2021..
20. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.
21. Talikowska M, Tohira H, Finn J. Cardiopulmonary resuscitation quality and patient survival outcome in cardiac arrest: A systematic review and meta-analysis. Resuscitation 2015;96:66–77.

22. Meaney PA, Bobrow BJ, Mancini ME, et al. Cardiopulmonary Resuscitation Quality: Improving Cardiac Resuscitation Outcomes Both Inside and Outside the Hospital. Circulation 2013;128:417–35.
23. Bray JE, Di Palma S, Jacobs I, Straney L, Finn J. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997–2010. Resuscitation 2014;85:757–61.
24. Nehme Z, Bernard S, Cameron P, et al. Using a Cardiac Arrest Registry to Measure the Quality of Emergency Medical Service Care. Circul Cardiovasc Qual Outcomes 2015;8:56–66.
25. Meyer L, Stubbs B, Fahrenbruch C, et al. Incidence, Causes, and Survival Trends From Cardiovascular-Related Sudden Cardiac Arrest in Children and Young Adults 0 to 35 Years of Age. Circulation 2012;126:1363–72.
26. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol 2018;15:230–40.
27. Winther-Jensen M, Christiansen MN, Hassager C, et al. Age-specific trends in incidence and survival of out-of-hospital cardiac arrest from presumed cardiac cause in Denmark 2002–2014. Resuscitation 2020;152:77–85.
28. Gooding HC, Gidding SS, Moran AE, et al. Challenges and Opportunities for the Prevention and Treatment of Cardiovascular Disease Among Young Adults: Report From a National Heart, Lung, and Blood Institute Working Group. J Am Heart Assoc 2020;9:e016115.
29. Alqahtani S, Nehme Z, Williams B, Bernard S, Smith K. Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies. Resuscitation 2020;155:125–33.
30. Hulleman M, Zijlstra JA, Beesems SG, et al. Causes for the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation 2015;96:23–9.
31. Oving I, de Graaf C, Karlsson L, et al. Occurrence of shockable rhythm in out-of-hospital cardiac arrest over time: A report from the COSTA group. Resuscitation 2020;151:67–74.
32. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital Cardiac Arrest. Circul Cardiovasc Qual Outcomes 2010;3:63–81.
33. Majewski D, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation 2021;162:128–34.
34. van Dongen LH, Oving I, Dijkema PW, Beesems SG, Blom MT, Tan HL. Sex differences in the association of comorbidity with shockable initial rhythm in out-of-hospital cardiac arrest. Resuscitation 2021;167:173–9.
35. Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open 2019;9:e031655.
36. Australian Bureau of Statistics. Chronic conditions, 2017-18 financial year, 2018. (Available, at: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/chronic-conditions/latest-release).

3.5 Manuscript Appendix

Table 2. Joinpoint analysis showing the annual percent change (APC) in incidence of OHCA of presumed cardiac aetiology attended by EMS in Perth WA between 2001 and 2018 (Supplementary Table 1).

	Joinpoint	APC	95% CI
Crude	2001 to 2012	0.0	-1.2 to 1.2
	2012 to 2015	10.8	-4.5 to 28.5
	2015 to 2018	-1.6	-8.1 to 5.4
	2001 to 2018	**1.5**	**-1.1 to 4.2**
ASIR	2001 to 2012	-0.7	-1.9 to 0.6
	2012 to 2015	10.7	-5.3 to 29.3
	2015 to 2018	-3.3	-9.9 to 3.9
	2001 to 2018	**0.8**	**-1.9 to 3.5**
ASIR EMS attempted resus	2001 to 2004	-7.3	-13.4 to -0.8
	2004 to 2011	1.4	-0.9 to 3.8
	2011 to 2015	13.4	7.7 to 19.5
	2015 to 2018	-8.3	-12.6 to -3.8
	2001 to 2018	**0.7**	**-1.0 to 2.4**
ASIR Utstein comparator group	2001 to 2007	-7.5	-15.6 to 1.4
	2007 to 2018	4.7	1.1 to 8.4
	2001 to 2018	**0.2**	**-3.3 to 3.8**
Male 0-14	**2001 to 2018**	**2.3**	**-3.0 to 7.9**
Male 15-39	2001 to 2011	0.6	-5.1 to 6.5
	2011 to 2018	12.5	4.8 to 20.7
	2001 to 2018	**5.3**	**1.2 to 9.6**
Male 40-64	**2001 to 2018**	**3.2**	**2.1 to 4.2**

Male 65-79	2001 to 2011	-3.0	-4.4 to -1.6
	2011 to 2018	2.1	-0.1 to 4.3
	2001 to 2018	**-0.9**	**-2.0 to 0.2**
Male 80+	**2001 to 2018**	**0.4**	**-0.6 to 1.4**
Female 0-14	**2001 to 2018**	**-0.4**	**-0.5 to 4.5**
Female 15-39	**2001 to 2018**	**2.2**	**-0.3 to 4.8**
Female 40-64	**2001 to 2018**	**4.4**	**3.1 to 5.8**
Female 65-79	2001 to 2011	-4.1	-7.1 to -0.9
	2011 to 2018	5.3	0.3 to 10.5
	2001 to 2018	**-0.3**	**-2.7 to 2.2**
Female 80+	**2001 to 2018**	**1.9**	**0.9 to 2.8**

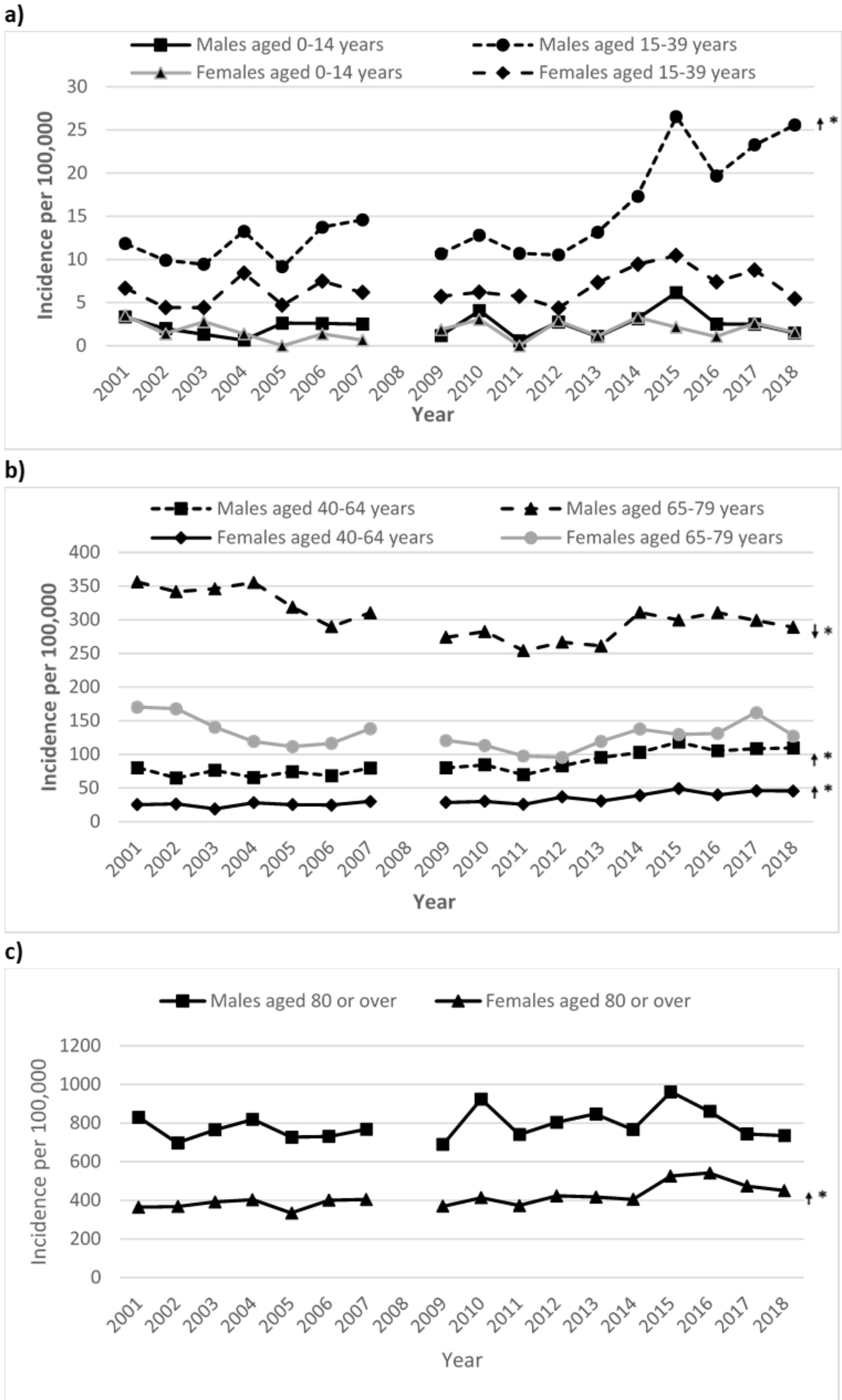

Figure 3. Trends in age- and sex-specific incidence rates of OHCA of presumed cardiac aetiology attended by EMS between 2001 and 2018 in Perth WA in patients; a) under 40 years of age, b) between 40 and 79 years of age and c) patients 80 years or older (Supplementary Figure 1).

↑* Statistically significant positive trend between 2001 and 2018 ($p < 0.05$).

* ↓ Statistically significant negative trend between 2001 and 2018 ($p < 0.05$).

3.6 Summary of Chapter Findings

- 30-day survival in the Utstein comparator group (bystander witnessed arrests with initial shockable arrest rhythm), saw 5-fold improvement over an 18-year period.
- Rates of bystander CPR increased.
  Although very rare events overall, rates of bystander AED delivered shocks
- have increased.
- There was a steady decline in the proportion of ventricular fibrillation (VF)/ventricular tachycardia (VT) arrests.
- OHCA incidence increased substantially in males, aged 15 to 39 years, between 2011 and 2018. The reason for this finding needs further investigation.

Addendums:

- In Table 1 of the manuscript, the variable labelled "Attempted Resus" should be understood to mean a resuscitation attempt by EMS.
- In Figure 2(i) and 2(ii) of the manuscript, the y-axis labels should be interpreted as follows:
  Figure 2(i): Proportion of all OHCA with an EMS attempted resuscitation who attained ROSC at ED/survived to 30 days.
  Figure 2(ii): Proportion of all Utstein comparator group arrests (i.e., OHCA that were bystander witnessed, had an initial shockable arrest rhythm, and an EMS attempted resuscitation) who attained ROSC at ED/survived to 30 days.

Chapter 4 Long term OHCA Survival Overview

4.1 Overview

This chapter examines the long-term survival of initial (30-day) OHCA survivors, relative to the age-and sex-matched general population, in the Perth metropolitan area over a 20-year period. The findings are reported in a manuscript published in the peer-reviewed journal Resuscitation. This manuscript is presented in section 4.4.

> ***Majewski D**, Ball S, Bailey P, Bray J, Finn J. Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving? Resuscitation. 2020;157:108-11.*

4.2 Background and Rationale

The bulk of OHCA research has predominantly focused on short-term survival outcomes (STHD or 30-day survival). However, with global OHCA survival rates increasing over the last 40 years,[2] greater focus on the longer-term prognosis of initial OHCA survivors is needed. Although an increasing number of studies have reported on the longer-term outcomes of initial OHCA survivors, these studies have been unable to address several important questions. Firstly, it is unclear whether an OHCA patient who initially survives their arrest (STHD or 30-day survival) will incur a reduction in life expectancy in comparison to the age- and sex-matched general population. Secondly, it is unclear whether long-term survival has shown improvement over time that is in-excess of any increases in the underlying population life expectancy. To address these questions, this chapter will examine the 10-year survival of OHCA patients (who survived 30 days following their arrest) relative to the age- and sex-matched general population, in the Perth metropolitan area between 1998 and 2017.

4.3 Methodology

<u>Study design</u>:

To address the aims of this chapter I conducted a population-based, retrospective cohort study of all patients ≥16 years of age, who experienced an OHCA in the Perth metropolitan area between 1998 and 2017 and survived at least 30 days following their arrest. To be included in the study patients had to have experienced an arrest of presumed medical aetiology (as defined by the 2015 Utstein guidelines), received an attempted resuscitation by EMS staff (or alternatively received a bystander AED shock) and have been a resident of WA at the time of arrest (to reduce the risk of out-of-state patient migration and therefore loss to follow-up). The study cohort was recruited from the WA OHCA registry.

Data Sources:

As the WA OHCA registry only records patient aetiology according to an earlier version of the Utstein template style, I manually re-coded patient aetiology according to the most recent 2014 Utstein template style for all OHCA between 1999 and 2017 where patients survived at least 30 days. Re-coding of aetiology was performed on the basis of a number of variables recorded in the WA OHCA registry, including: recorded aetiology, problem code, and paramedic ‘free text’ description of the circumstances surrounding the arrest.

Statistical analysis:

To address the objectives of this chapter, an approach was required that could statistically compare the long-term survival of OHCA patients with that of the general population. One possible approach was to match each OHCA patient from the cohort to a control subject (of the same age and sex) sourced from the same underlying general population. However, challenges associated with the identification and recruitment of appropriate[96] controls made this approach impractical. Instead, I utilised a statistical technique known as relative survival[97] which is broadly defined as a ratio of *observed survival* (of the patient cohort) and *expected survival* (of an age- and sex-matched cohort). The major advantage of relative survival is that the *expected survival* can be estimated using population life tables (i.e. without the need to recruit an actual control group).

Both the overall and relative 10-year survival of initial OHCA patients was explored, with estimates of 1-, 5- and 10-year survival post arrest provided. The overall survival was estimated using Kaplan-Meier while relative survival (relative to the age and sex matched general population) was estimated using the Ederer II method[98, 99] and the WA population life tables provided by the ABS. Any changes in the long-term survival of OHCA patients over time was explored by comparing the 10-year relative survival between the first decade (1998 to 2007) and second decade (2008-2017) of the study. Differences in survival between groups was assessed using the Log Rank test at a 5% statistical significance. All statistical analysis was performed using the ‘relsurv’ package in “R”.

4.4 Manuscript

RESUSCITATION 157 (2020) 108 –111

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Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Short paper

Relative long-term survival in out-of-hospital cardiac arrest: Is it really improving?

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Abstract

Aim: To describe the long-term survival of out-of-hospital cardiac arrest (OHCA) patients and to determine whether survival is improving in comparison to the general age- and sex-matched population.

Methods: We utilised the St John Western Australia (WA) OHCA database to retrospectively identify patients aged ≥16 years who experienced an OHCA within the Perth metropolitan area between 1998 and 2017 and survived for at least 30-days post arrest. Patients were excluded if their primary residence was not WA, they did not have an emergency medical services attempted resuscitation (or bystander defibrillation) or did not have an arrest of medical aetiology. Relative survival ratios stratified by decade of arrest were calculated by dividing observed survival of the study cohort by the expected survival of an age- and sex-matched cohort estimated from the Australian Bureau of Statistics life tables for WA.

Results: The OHCA patients who initially survived to 30-days experienced a modest reduction in long-term survival, with 84% (95% CI, 78–90) of patients surviving to 10-years relative to the age- and sex-matched general population. The 10-year relative survival increased from 76% (95% CI, 67–85) to 92% (95% CI, 84–100) between the first (1998–2007) and second (2008–2017) decade of our study.

Conclusion: Relative long-term survival prospects for initial OHCA survivors are moderately lower than that of the general population, however these differences have reduced over time and may be approaching those of the general population.

Keywords: Out-Of-Hospital cardiac arrest, Long-Term survival, Relative survival

Introduction

Long-term survival outcomes (≥1 year) after out-of-hospital cardiac arrest (OHCA) have been reported to be improving.[1] However, it is unclear if these improvements are simply an artefact of increased life expectancy in the general population. Patients who initially survive an OHCA are subsequently exposed to two different potential sources of mortality. The first is the baseline mortality that all individuals within a population are exposed to irrespective of OHCA status (e.g. mortality due to; cancer, trauma, advanced age, etc.); while the second is the excess mortality hazard causally attributed to the OHCA event (e.g. major organ failure, brain damage, post OHCA treatment complications, etc.). Examining excess mortality allows us to address two important questions. Firstly, do OHCA patients who survive at least 30-days post arrest experience a reduction in long-term survival compared to their age- and sex-matched peers; and secondly, has long-term OHCA survival increased over time in excess of population life expectancy increases?

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We applied a statistical method known as relative survival analysis[2] to determine whether the long-term survival of initial OHCA survivors is significantly different to that of the general population. Additionally, we aimed to assess whether the last decade has resulted in improvements in long-term survival of 30-day OHCA survivors, independent of any increases in population life expectancy.

Methods

Study design

We conducted a population-based retrospective cohort study of patients aged ≥16 years who experienced an OHCA in the metropolitan city of Perth, Western Australia (WA), between 1st January 1998 and 31st December 2017. Patients were included if they: had an OHCA of medical aetiology[3]; received an attempted resuscitation by Emergency Medical Services (EMS) or bystander defibrillation; were a primary resident of WA; and survived at least 30 days following the arrest (referred to as 'initial survivors').

Study setting

Perth is the capital and largest city of the state of WA. Metropolitan Perth covers 6400 square kilometres and has a population of 2.06 million.[4] The sole provider of emergency ambulance services in Perth is St John WA (SJ-WA), which operates a single-tiered advanced life support (ALS) ambulance service, staffed by nationally registered paramedics. Patients who are not declared dead at the scene are transported to one of nine hospital emergency departments located within the Perth metropolitan area.

Data sources

This study sourced data from the SJ-WA OHCA Database, which is maintained by the Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU) at Curtin University. Data from patient care records, completed by SJ-WA paramedics, are automatically linked to the computer-aided dispatch data. The OHCA Database contains detailed information about patient demographics, arrest characteristics and EMS response and interventions. Date of death is determined from the WA Death Registry.

Statistical analysis

Observed (or absolute) survival is an estimate of the probability of survival in a cohort of OHCA patients while expected survival is an estimate of the survival probability in a comparable cohort of patients from the general population. Expected survival was estimated using the Ederer II method[5,6] with WA population life tables (provided by the Australian Bureau of Statistics) matched by year of arrest, patient age at arrest and patient sex. Relative survival has been used extensively in cancer research[7] to quantify long-term survival and identify improvements in survival across calendar time.[8] To determine if long-term survival had improved over the study period, relative survival ratios were compared for each decade in the study (1998–2007 vs 2008–2017). Relative survival ratios were also compared by sex (male/female) and age at arrest (16–39, 40–64, 65–79 and ≥80 years). Absolute long-term survival was examined using Kaplan-Meir curves. Statistical analysis was performed using R v3.5.3 (R Core Team; Vienna, Austria) using the 'relsurv' package for estimating relative survival. Group differences were assessed using the Log-Rank test with a statistical significance of <0.05.

Ethics

This study was approved by the Human Research Ethics Committee of Curtin University as a sub-study of the Western Australian Pre-hospital Care Record Linkage Project (HR128/2013).

Results

Between 1998 and 2017 there were 27,069 OHCAs in the Perth metropolitan area attended by SJ-WA. After excluding cases where patients were <16 years old (n = 647), had no EMS attempted resuscitation or bystander defibrillation (n = 15,223), were non-residents of WA (n = 210) or had a non-medical arrest aetiology (n = 1661), 9328 OHCA cases remained. Of these, 871 (9.3%) survived at least 30 days following their arrest and formed the study cohort. The mean patient age at time of arrest was 60.7 years (standard deviation, 15.5), with 79% between the ages of 40 and 79 years; with 75% males. Supplementary Table 1 shows the baseline characteristics of our initial survivor cohort stratified by decade of arrest.

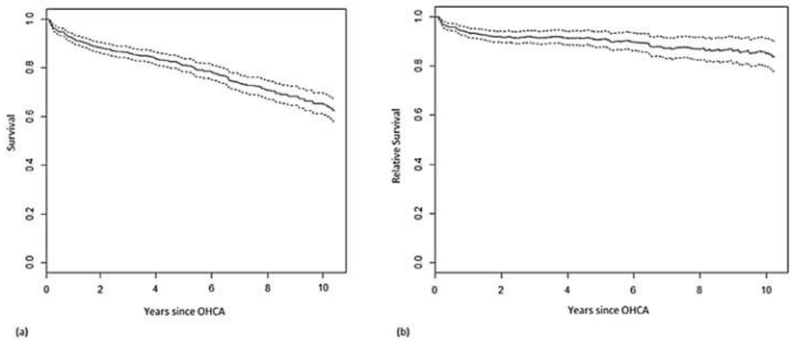

Fig. 1 – a) Ten year Kaplan-Meier survival (with 95% confidence interval), and b) the 10-year relative survival (with 95% confidence interval) of initial (30-day) OHCA survivors.

Fig. 1a shows the 10-year Kaplan Meier survival curve while Fig. 1b shows the 10-year relative survival curve. The Kaplan–Meier estimates for absolute OHCA survival show lower survival compared to the age- and sex-matched general population at one (91% vs 94%), five (81% vs. 91%) and ten (62% vs. 84%) years (Table 1). There was a significant increase (log-rank p = 0.03) in 10-year survival between the first (1998–2007) and second (2008–2017) decade of our study, with the relative survival ratio at 10-years increasing from 0.76 to 0.92 (Fig. 2). Neither patient age (at time of arrest) nor sex were found to be associated with relative long-term OHCA survival (supplementary Fig. 1).

Discussion

In this retrospective cohort study of 871 initial (30-day) OHCA survivors, we found the long-term survival prospects were modestly lower than that of the general population. The 10-year relative survival of OHCA patients was 84% (95% CI, 78–90). Our findings are novel as they estimate the mortality of OHCA patients that is in excess of the general population mortality. In contrast, most other OHCA studies report long-term survival in 'absolute' terms; where continued survival is influenced by both the mortality risk imparted by the arrest itself and the underlying background mortality risk (unrelated to the OHCA). The large difference between relative and absolute survival estimates can be seen in our study where 10-year relative survival was 84% and 10-year absolute survival (obtained using Kaplan Meier) was only 62%.

We found that long-term survival has increased over time, with the 10-year relative survival ratio increasing from 0.76 (95% CI, 0.67–0.85) to 0.92 (95% CI, 0.84–1.00) between the first (1998–2007) and second (2008–2017) decade of our study. Importantly, the 10-year relative survival in the second decade of our study was not statistically significant (95% CI includes '1'); suggesting that long-term survival may be improving to a point where initial OHCA survivors experience similar life spans to their age-and sex-matched peers (without OHCA). Although other studies[9] have also reported increasing trends in long-term survival, ours is the first to find this increase is in excess of any population life expectancy increases. Our results are consistent with previous research[1,10] that the 'fine-tuning' of resuscitation guidelines (and increasing bystander CPR) over the years has yielded substantial benefits in OHCA survival, although

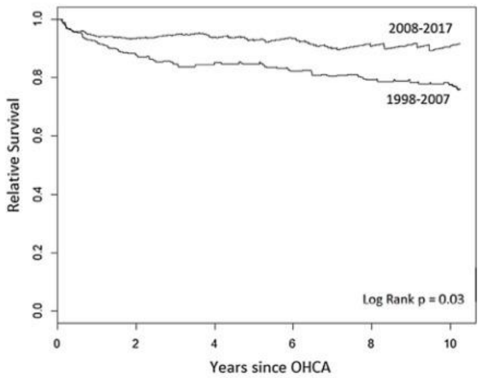

Fig. 2 – Ten year relative survival of initial (30-day) OHCA survivors stratified by decade of arrest.

clearly there may be other underlying causal factors such as change in case-mix.[11]

Previous studies have reported on absolute long-term survival in OHCA cohorts, however few have provided relative measures of survival. A small (n = 79 patients) 2003 study[12] reported reduced long-term survival in OHCA patients compared to age- and sex-matched general population. Interestingly, this study noted that if patients were also matched for comorbidity, survival was statistically not different to that of the general population. The negative association between pre-arrest comorbidity and OHCA outcomes has been described in a recent systematic review.[13] A 2017 study[14] from Melbourne, Australia reported that long-term relative mortality rates in initial OHCA survivors was initially higher than that of the general population but ceased to be significantly different after five years. Our relative long-term survival model found that older age was not significantly associated with survival, suggesting that the significant associations reported in previous studies may be a result of the background mortality risk of age (irrespective of OHCA).

Our study has some limitations. Firstly, our relative survival model assumes that the cohort under consideration is a representative sample of general population from which the population life tables are derived. We were unable to match for other factors potentially influencing outcome, such as comorbidity (or neurological status) as

Table 1 – Relative survival ratios for one, five and ten years post OHCA in those who survive to 30-days.

Relative survival ratio	1 -year		5-year		10-year	
	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI
Overall	0.94	(0.92–0.95)	0.91	(0.88–0.94)	0.84	(0.78–0.90)
Sex						
Male	0.94	(0.92–0.97)	0.92	(0.89–0.96)	0.87	(0.80–0.94)
Female	0.91	(0.87–0.95)	0.87	(0.80–0.94)	0.75	(0.63–0.88)
Age Group						
16–39	0.93	(0.88–0.99)	0.87	(0.79–0.95)	0.84	(0.75–0.94)
40–64	0.97	(0.95–0.96)	0.93	(0.90–0.97)	0.89	(0.84–0.95)
65–79	0.94	(0.90–0.97)	0.92	(0.86–0.99)	0.81	(0.70–0.94)
≥80	0.80	(0.71–0.90)	0.81	(0.64–1.03)	0.66	(0.37–1.21)
Decade of arrest						
1998–2007	0.92	(0.88–0.96)	0.85	(0.79–0.91)	0.76	(0.67–0.85)
2008–2017	0.94	(0.92–0.96)	0.93	(0.89–0.97)	0.92	(0.84–1.00)

such life tables are not available. However, assuming OHCA patient comorbidity is higher than that of the age- and sex-matched general population the bias introduced would tend to result in reduced relative survival. Secondly, our cohort contained few individuals over 80 years of age, meaning that our relative survival ratios by age group may have low statistical power. Lastly, as Perth metropolitan area life tables were unavailable, we used WA state life tables to determine expected survival. However, this is unlikely to bias our results as the majority (92%) of the state's population resides in the Perth metropolitan area.

Conclusion

Despite the pessimism surrounding OHCA survival, our study shows that patients who survive 30-days post arrest experience only a moderate reduction in 10-year survival compared to the general population. Additionally, we found that long-term OHCA survival was improving over time.

Conflicts of interest statement

Prof. Judith Finn receives research support from St John Western Australia (SJ-WA). A/Prof. Paul Bailey is Clinical Services Director at SJ-WA. None of the other authors have any conflicts of interest to declare.

CRediT authorship contribution statement

David Majewski: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing, Visualisation, Project administration. **Stephen Ball:** Conceptualisation, Methodology, Data curation, Validation, Writing - review & editing. **Paul Bailey:** Conceptualisation, Writing - review & editing. **Janet Bray:** Conceptualisation, Writing - review & editing. **Judith Finn:** Conceptualisation, Methodology, Validation, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.10.017.

REFERENCES

1. Yan S, Gan Y, Jiang N, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care (London, Engl) 2020;24:61.
2. Perme MP, Pavlic K. Nonparametric relative survival analysis with the R package relsurv. J Stat Software 2018;2018;87:27.
3. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:1286–300.
4. Australian Bureau of Statistics. 3101.0 – Australian Demographic Statistics, Dec 2019. 2020 (Accessed 21 July 2020 at: https://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3218.0).
5. Lambert PC, Dickman PW, Rutherford MJ. Comparison of different approaches to estimating age standardized net survival. BMC Med Res Methodol 2015;15:64.
6. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note no. 10. End results evaluation section. National Cancer Institute: Bethseda; 1959.
7. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 2008;9:730–56.
8. Dickman Pw, Adami Ho. Interpreting trends in cancer patient survival. J Intern Med 2006;260:103–17.
9. Wong MK, Morrison LJ, Qiu F, et al. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. Circulation 2014;130:1883–90.
10. Larribau R, Deham H, Niquille M, Sarasin FP. Improvement of out-of-hospital cardiac arrest survival rate after implementation of the 2010 resuscitation guidelines. PLoS One 2018;13:e0204169.
11. Bray JE, Di Palma S, Jacobs I, Straney L, Finn J. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997–2010. Resuscitation 2014;85:757–61.
12. Bunch TJ, White RD, Gersh BJ, et al. Long-Term Outcomes of Out-of-Hospital Cardiac Arrest after Successful Early Defibrillation. N Engl J Med 2003;348:2626–33.
13. Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open 2019;9:e031655.
14. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. Heart 2017;103:1104–10.

4.5 Manuscript Appendix

Table 3. Baseline characteristics of cohort by decade of arrest (Supplementary Table 1).

	Total	1998 – 2007		2008 – 2017		Chi squared
Age		n	%	n	%	p-value
16-39	87	12	(5.1)	75	(11.8)	<0.001
40-64	407	90	(38.0)	317	(50.0)	
65-79	279	101	(42.6)	178	(28.1)	
≥80	98	34	(14.3)	64	(10.1)	
Sex						
Male	657	170	(71.8)	487	(76.8)	0.12
Witness status						
Unwitnessed	200	42	(17.7)	158	(24.9)	0.001
Bystander	386	95	(24.6)	291	(75.4)	
EMS	285	100	(42.2)	185	(29.2)	
Arrest location						
Residence	520	144	(60.8)	376	(59.3)	0.70
Public	351	93	(39.2)	258	(40.7)	
Bystander CPR						
Nil	415	149	(62.9)	266	(42.0)	<0.001
Yes	456	88	(37.1)	368	(58.0)	
EMS response time						
< 10 minutes	716	195	(82.3)	521	(82.2)	0.97
≥ 10 minutes	155	42	(17.7)	113	(17.8)	
Bystander defibrillation						
Nil	799	235	(99.2)	564	(89.0)	<0.001
Yes	72	2	(0.8)	70	(11.0)	
Initial Arrest Rhythm						
Shockable	718	201	(84.8)	517	(81.5)	0.26
Non-shockable	153	36	(15.2)	117	(18.5)	

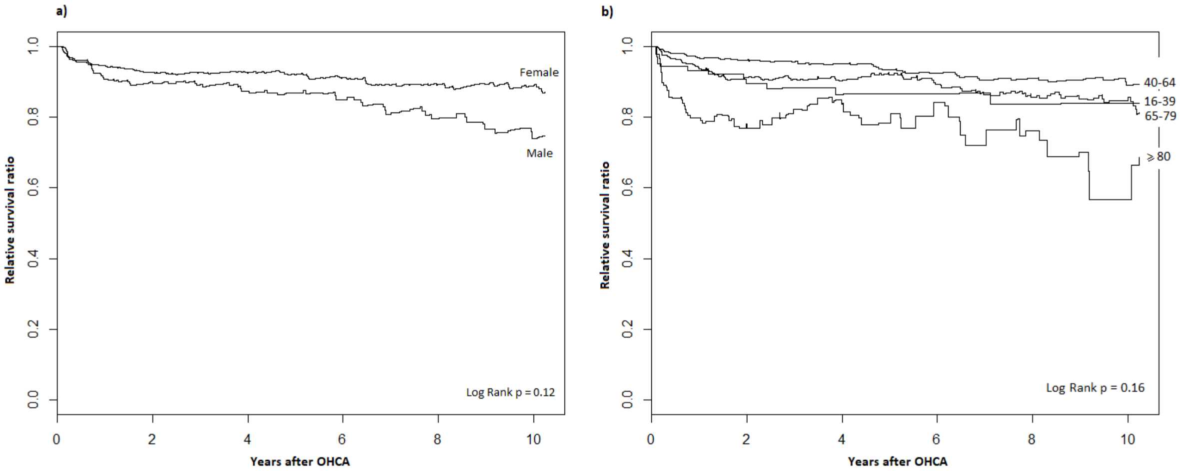

Figure 4. Ten year relative survival curves stratified by (a) sex, and (b) age group at time of arrest (Supplementary Figure 1).

4.6 Summary of Chapter Findings

- OHCA patients, who initially survived 30 days following their arrest, only have a small to moderate reduction in 10-year survival compared to age- and sex-matched general population.

- Long-term OHCA survival has been improving over time, with the improvements being in-excess of any increases in the general population life expectancy.

Chapter 5 Factors associated with Long-term OHCA Survival

5.1 Overview

This chapter explores the association between initial arrest rhythm and the long-term survival of initial (30-day) OHCA survivors, in the Perth metropolitan area over a 20-year period. The findings are reported in a manuscript published in the peer-reviewed journal Resuscitation. This manuscript is presented in section 5.4.

> ***Majewski D**, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34.*

5.2 Background and Rationale

In Chapter 4, I found that 30-day OHCA survivors experienced a small, but statistically significant reduction in long-term survival when compared to the age- and sex-matched general population. However, it is unclear whether this reduction in ongoing survival is inherent to all OHCA survivors, or whether it is associated with prehospital factors. Initial presenting arrest rhythm has been shown to be one of the most important prehospital predictors of short-term (i.e 30-day or STHD) OHCA survival; however its association with longer-term survival outcomes is less well understood.[60] Therefore, this chapter aims to explore the association between initial arrest rhythm and long-term survival in a cohort of initial 30-day OHCA survivors.

5.3 Methodology

<u>Study design</u>:

To address the aim of this chapter I conducted population-based, retrospective cohort study using the same study cohort described in Chapter 4. As a reminder, this cohort consisted of: All EMS attended adult (≥16 years of age) OHCAs of presumed medical aetiology, who survived at least 30 days following their arrest, in Perth between 1998 and 2017.

Statistical analysis:

I had initially planned to use a Cox proportional hazard regression model to explore the long-term mortality risk of initial OHCA survivors, however the assumption of proportional hazards (PH) was violated for the covariate of interest (initial cardiac arrest rhythm). I therefore opted to use the Multi-Resolution Hazard (MRH) estimator function available in the statistical program “R”. The MRH estimator is a semi-parametric, Bayesian based statistical method that can estimate hazard rates with covariates that do not display PH.[100-104]

The association between initial arresting rhythm (i.e. shockable vs non-shockable) and 8-year survival was assessed using a MRH estimator for 1-year intervals of time. Pruning (please see manuscript appendix in Chapter 5 for a detailed explanation) was applied to the MRH model as it has been shown to provide more robust estimates in cases of low interval counts.[105] Both unadjusted and adjusted (for the Utstein factors) mortality hazard rate estimates were produced.

5.4 Manuscript

RESUSCITATION 162 (2021) 128 –134

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Resuscitation

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Clinical paper

Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant?

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Abstract

Objective: To determine whether initial cardiac arrest rhythm remains a prognostic determinant in longer term OHCA survival.

Methods: The St John Western Australian OHCA database was used to identify adults who survived for at least 30 days after an OHCA of presumed medical aetiology, in the Perth metropolitan area between 1998 and 2017. Associations between 8-year OHCA survival and variables of interest were analysed using a Multi-Resolution Hazard (MRH) estimator model with 1-year intervals.

Results: Of the 871 OHCA patients who survived 30 days, 718 (82%) presented with a shockable initial arrest rhythm and 153 (18%) presented with a non-shockable rhythm. Compared to patients with initial shockable arrests, patients with non-shockable arrests experienced increased mortality in the first (HR 3.33, 95% CI 2.12–5.32), second (HR 2.58, 95% CI 1.22–5.15), third (HR 2.21, 95% CI 1.02–4.42) and fourth (HR 2.21, 95% CI 1.02–4.42) year post arrest; however, in subsequent years the initial arrest rhythm ceased to be significantly associated with survival. The overall 8-year survival estimates after adjustment for peri-arrest factors (as potential confounders) were 87% (95% CI 77–93%) for shockable arrests and 73% (95% CI 55–86%) for non-shockable arrests.

Conclusions: Patients with non-shockable (as opposed to shockable) initial arrest rhythms experienced higher mortality in the first 4-years following their OHCA; however, after four years the initial arrest rhythm ceased to be associated with survival.

Keywords: Out of hospital cardiac arrest, Arrest rhythm, Long-term survival

Introduction

Initial cardiac arrest rhythm is one of the strongest predictors of short-term survival after out-of-hospital cardiac arrest (OHCA), with higher survival rates (survival to hospital discharge (STHD)/30-day survival) among patients with an initial shockable rhythm (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]).[1,2] Limited research has also shown that initial arrest rhythm is similarly important for long-term survival.[3,4] However, it is unclear if this association continues indefinitely or reduces over time. In this study we aim to; (i) determine whether long term survival differs by initial arrest rhythm and (ii) examine how mortality risk in initial OHCA survivors changes over time.

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0300-9572/

Methods

Study design

We conducted a population-based retrospective cohort study of patients aged ≥ 16 years who experienced an OHCA in metropolitan Perth, Western Australia (WA), between 1st January 1998 and 31st December 2017, and were attended by St John Western Australia (SJ-WA) emergency medical services (EMS). Patients were included if (i) they survived at least 30 days following arrest, (ii) their primary residence was in WA and (iii) they had an OHCA of presumed medical aetiology.[5] The exposure variable of primary interest was initial cardiac arrest rhythm, described as 'shockable' (i.e. ventricular fibrillation or pulseless ventricular tachycardia (VF/VT)) or 'non-shockable' (i.e. pulseless electrical activity (PEA) or asystole). A shockable initial arrest rhythm was recorded in cases where either the first assessed rhythm by paramedics was VF/VT or a bystander automated external defibrillator (AED) shock was delivered prior to EMS arrival.

Study setting

Perth is the capital and largest city in the state of Western Australia (WA) and currently has a population of 2.06 million people.[6] The sole provider of road based emergency medical services (EMS) in Perth is SJ-WA, which operates a single-tiered advanced life support (ALS) service, staffed by nationally registered paramedics. OHCA patients are transported to one of nine hospital emergency departments within the Perth metropolitan area, unless resuscitative efforts are ceased in the field by paramedics (or not commenced), due to futility or pre-existing not-for-resuscitation orders.

Data sources

This study sourced data from the SJ-WA OHCA database which contains details for all metropolitan OHCAs attended by SJ-WA EMS since 1996 (and all rural OHCAs since 2014). The SJ-WA OHCA database is maintained by the Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU) at Curtin University, using data from patient care records (PCR) completed by SJ-WA paramedics, and linked to computer-aided dispatch data. The database contains patient demographics, arrest characteristics, EMS response intervals and interventions. The so-called 'Utstein variables'[5] are captured in the database, including: patient age and sex, witnessed status (bystander-witnessed; EMS-witnessed; un-witnessed), bystander cardiopulmonary resuscitation (B-CPR), EMS response interval from call answer to arrival on scene, ROSC in the field, and ROSC on arrival at the Emergency Department (ED). The initial cardiac arrest rhythm is recorded on the PCR by the attending paramedic. Date of death was determined by manual look-up in the WA Death Registry.

Statistical analysis

Baseline patient characteristics are presented as frequencies and percentages, stratified by initial arrest rhythm (shockable/non-shockable); with differences tested using chi square tests. Follow-up time (in years) was calculated as the difference between the date of arrest and date of death or censoring date (31st December 2018). A Kaplan Meier survival curve, stratified by initial arrest rhythm, was produced to provide a visual representation of the cumulative 8-year survival by arrest rhythm. The relationship between initial arrest rhythm and long-term survival was examined by comparing the hazard rate of patients with shockable, versus non-shockable arrest rhythms. Unadjusted and adjusted 8-year mortality hazard rates and 95% confidence intervals (95% CI) were estimated using a Multi-Resolution Hazard (MRH) estimator with pruning.[7–11] The MRH estimator is a semi-parametric Bayesian statistical method that enables joint estimation of the baseline and covariate hazard rates[7–11] — see Appendix A Supplementary data. Importantly, unlike Cox regression,[12] the MRH method can accept covariates with both proportional and non-proportional hazards and provide a robust estimate of hazard rates in data that may contain long intervals with few 'events'.[7–11] To optimize the fit of the MRH model we chose to use 1-year intervals across the 8-year follow-up period (interval length and follow up period are intrinsically linked in the MRH estimator methodology as described in Appendix A). Each 1-year interval (eight in total) represent the mortality risk for an OHCA survivor for that respective year post arrest. The Utstein covariates included in the adjusted models were: age at arrest (16–39; 40–64; 65–79; ≥80 years), sex (female; male), arrest witness status (bystander-witnessed; EMS-witnessed; unwitnessed), bystander CPR (yes; no), EMS response time (≤10 min; >10 min) and arrest location (public; private residence). For the multivariable models, the first category of each covariate was used as the reference value. Adjusted hazard rate curves for shockable and non-shockable initial arrest rhythms were produced using the MRH estimator to visualise differences in survival outcomes. Statistical analysis was performed using R (https://r-project.org - version 3.5.3) with hazard rates obtained using the R package 'MRH' (https://CRAN.R-project.org/package = MRH). Statistical significance for all analyses and the MRH estimator was set at $p < 0.05$.

Ethics

This study was approved by the Human Research Ethics Committee of Curtin University as a sub-study of the Western Australian Pre-hospital Care Record Linkage Project (HR128/2013).

Results

Study cohort

Between the 1st of January 1998 and the 31st of December 2017 there were 27,069 cases of OHCA attended by SJ-WA in the Perth metropolitan area. After excluding cases where patients were <16 years of age, had no EMS attempted resuscitation or bystander AED defibrillation, were non-residents of WA or had a non-medical arrest aetiology, 9328 OHCA cases remained. Of these, 871 patients survived at least 30 days following arrest (Fig. 1); 718 (82%) with an initial shockable rhythm and 153 (18%) with a non-shockable rhythm (PEA = 124 and Asystole = 29).

Baseline characteristics of cohort

Table 1 shows the baseline characteristics of patients who survived at least 30-days following OHCA, stratified by initial arrest rhythm (shockable vs non-shockable). The mean patient age at time of arrest was 60.7 years, with 79% of patients between the ages of 40 and 79 years. Patients with an initial shockable rhythm (compared to a non-shockable rhythm) were more likely to: be under 65 years of age

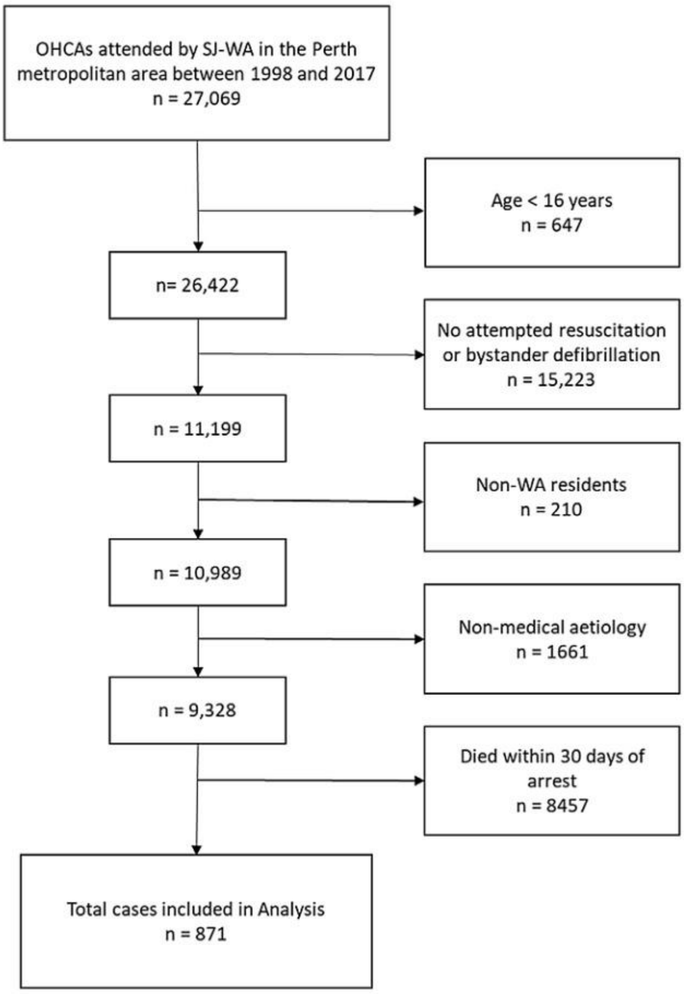

Fig. 1 – Flow chart of study cohort.

(58.5% vs 47.7%, p = 0.001), male (79.1% vs 75.4%, $p < 0.001$), have arrested in a public location (44.7% vs 19.6%, $p < 0.001$), received bystander CPR (57.9% vs 26.1%, $p < 0.001$) and have a witnessed (bystander or EMS) arrest (79.5% vs 70.0%, $p < 0.001$). Bystanders administered an AED shock in 72 (10%) of the shockable patients. Of the 153 patients with a non-shockable initial rhythm, 15 (9.8%) subsequently converted to a shockable rhythm prior to achieving ROSC.

Relationship between initial arrest rhythm and 8-year OHCA survival

Unadjusted

The Kaplan Meier estimates for 8-year OHCA survival (from time of arrest) are displayed in Fig. 2 and show a statistically significant difference between OHCA patients with a shockable versus non-shockable initial arrest rhythm (log-rank test, $p < 0.001$). The unadjusted MRH model estimates for 8-year survival were similarly higher for shockable (75%, 95% CI 71–79%) than for non-shockable (47%, 95% CI 38–57%) arrest rhythms, with the effect being most pronounced in the first few years following OHCA (Fig. 3a). The unadjusted 8-year MRH model detailing the mortality hazard ratios by 1-year intervals for initial shockable and non-shockable arrest rhythms are shown in Table 2. Mortality was significantly higher for non-shockable arrests (compared to shockable arrests) in each of the first four years following arrest, with the mortality hazard ratio in the first, second, third and fourth year being 4.10 (95% CI 2.62–6.37), 3.10 (95% CI 1.43–6.37), 2.56 (95% CI 1.20–5.08) and 2.56 (95% CI 1.20–5.08) respectively. However, there was no statistically significant association between initial arrest rhythm and subsequent survival for the remaining four years (i.e. years 5–8).

Table 1 – Baseline characteristics of OHCA patients in the study cohort stratified by initial cardiac arrest rhythm.

	VF/VT Initial Arrest Rhythm		PEA/Asystole Initial Arrest Rhythm		Total		Chi-squared (degrees of freedom - *df*)	p-value
	n = 718		n = 153					
Age, n (%)								
16–39	70	(9.7)	17	(11.1)	87	(10.0)	15.85 (3 *df*)	0.001
40–64	351	(48.9)	56	(36.6)	407	(46.7)		
65–79	229	(31.9)	50	(32.7)	279	(0.32)		
≥80	68	(9.5)	30	(19.6)	98	(11.3)		
Sex, n (%)								
Male	568	(79.1)	89	(75.4)	568	(75.4)	29.84 (1 *df*)	<0.001
Witness status, n (%)								
Unwitnessed	154	(21.5)	46	(30.1)	200	(23.0)	21.40 (2 *df*)	<0.001
Bystander	344	(47.9)	42	(27.4)	386	(44.3)		
EMS	220	(30.6)	65	(42.5)	285	(32.7)		
Arrest location, n (%)								
Residence	397	(55.3)	123	(80.4)	520	(59.7)	33.03 (1 *df*)	<0.001
Public	321	(44.7)	30	(19.6)	351	(40.3)		
Bystander CPR, n (%)								
No	302	(42.1)	113	(73.9)	415	(47.6)	51.11 (2 *df*)	<0.001
Yes	416	(57.9)	40	(26.1)	456	(52.4)		
EMS response time, n (%)								
<10 min	588	(81.9)	128	(83.7)	716	(82.2)	0.27 (2 *df*)	0.604
≥10 min	130	(18.1)	25	(16.3)	155	(17.8)		
Arrest Decade, n (%)								
1998–2007	201	(28.0)	36	(27.2)	237	(27.2)	1.27 (2 *df*)	0.260
2008–2017	517	(72.0)	117	(72.8)	634	(72.8)		

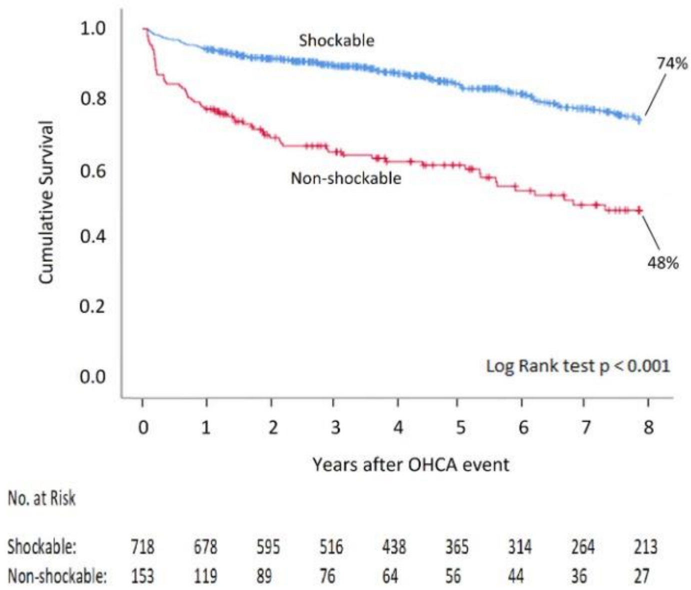

Fig. 2 – Eight-year Kaplan Meier survival curve by initial cardiac arrest rhythm (log rank test p < 0.001).

Adjusted

The adjusted 8-year survival estimates were 87% (95% CI 77–93) for shockable arrests and 73% (95% CI 55–86) for non-shockable arrests. Fig. 3b) shows the adjusted 8-year mortality rate curve for shockable and non-shockable arrest rhythms; while Table 2 provides the 8-year mortality hazard ratio by 1-year intervals. The 8-year mortality rate curve shows an increased mortality rate for non-shockable arrests in the initial years following OHCA, before approximating the shockable mortality rate curve (Fig. 3b). The 1-year interval mortality hazards ratio estimates for patients presenting

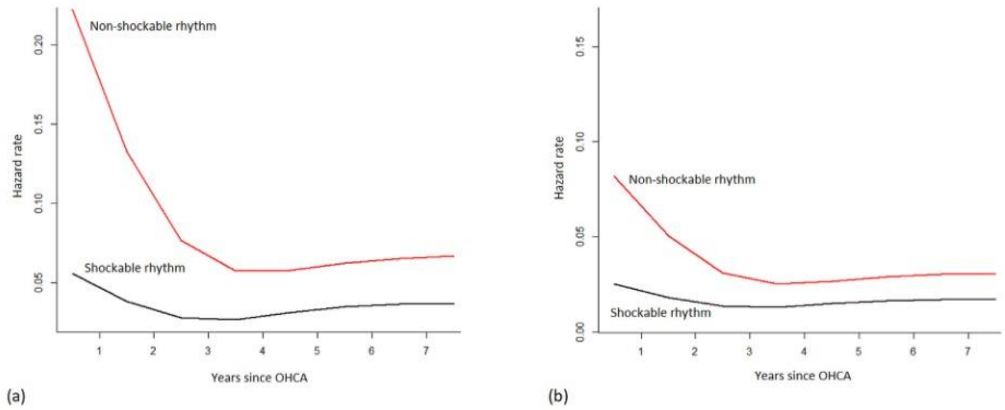

Fig. 3 – (a) Unadjusted hazard rate curve for shockable and non-shockable arrest rhythms; (b) Adjusted hazard rate curve for shockable and non-shockable arrest rhythms.

Table 2 – Unadjusted and adjusted 8-year mortality hazard rate estimates for initial 30-day OHCA survivors (n = 871).

	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Age				
16–39	ref		ref	
40–64	0.67	(0.37–1.26)	0.64	(0.37–1.23)
65–79	1.94	(1.11–3.55)	1.88	(1.11–3.49)
≥80	5.41	(3.02–10.07)	4.91	(2.73–9.37)
Gender				
Female	ref		ref	
Male	0.76	(0.56–1.04)	1.30	(0.94–1.79)
Witness status				
Bystander	ref		ref	
EMS	1.30	(0.90–1.91)	1.01	(0.64–1.63)
Unwitnessed	1.57	(1.15–2.14)	1.10	(0.74–1.62)
Arrest location				
Public	ref		ref	
Private residence	1.56	(1.16–2.13)	1.11	(0.80–1.58)
Bystander CPR				
Yes	ref		ref	
No	1.75	(1.32–2.34)	1.11	(0.74–1.66)
EMS response time				
<10 min	ref		ref	
≥10 min	1.06	(0.72–1.51)	1.43	(0.95–2.13)
Arrest Rhythm				
VF/pVT	ref		ref	
PEA/Asystole				
Year 1	4.10	(2.62–6.37)	3.33	(2.12–5.32)
Year 2	3.10	(1.43–6.37)	2.58	(1.22–5.15)
Year 3	2.56	(1.20–5.08)	2.21	(1.02–4.42)
Year 4	2.56	(1.20–5.08)	2.21	(1.02–4.42)
Year 5	1.83	(0.98–3.08)	1.79	(0.95–3.10)
Year 6	1.83	(0.98–3.08)	1.79	(0.95–3.10)
Year 7	1.83	(0.98–3.08)	1.79	(0.95–3.10)
Year 8	1.83	(0.98–3.08)	1.79	(0.95–3.10)

with non-shockable arrest rhythm (compared to shockable arrest rhythms) were significantly higher for the first four years following arrest, with the mortality hazard in the first, second, third and fourth years being 3.33 (95% CI 2.12–5.32), 2.58 (95% CI 1.22–5.15), 2.21 (95% CI 1.02–4.42) and 2.21 (95% CI, 1.02–4.42) respectively. There was no statistically significant association between initial arrest rhythm and subsequent survival for the remaining four years (i.e. years 5–8).

Discussion

In this retrospective cohort study of initial 30-day OHCA survivors, we compared the long-term survival prospects of patients presenting with shockable and non-shockable arrest rhythms. We found that despite surviving 30-days, patients with non-shockable arrests continued to experience disproportionately higher mortality than patients with an initial shockable arrest. However, this increased mortality risk was time limited; with survival after four years post arrest being statistically no different for shockable and non-shockable arrest patients. The findings of this study are novel, as they not only describe the overall differences in long term survival between shockable and non-shockable arrests, but detail how the mortality risk for shockable and non-shockable arrests evolves over time. As there are limited studies describing the relationship of long term OHCA survival and peri-arrest factors, we included a range of peri-arrest factors (see methods) to adjust for any potential confounding. Of the peri-arrest factors included, only older age (≥65 years) was found to be associated with an increased mortality risk.

The overall adjusted 8-year MRH survival estimates (from time of arrest) for our cohort of 30-day OHCA survivors was 87% for shockable arrest rhythms and 73% for non-shockable arrest rhythms. The mortality rate for shockable arrest rhythms appeared to be relatively stable over time; with little variation over the 8-year period. In contrast, the non-shockable arrest rhythm mortality rate was more dynamic; where, despite an initial downward trend, it remained significantly elevated over the initial four years following arrest before finally stabilising. Our findings suggest that the use of 30-day survival as an outcome measurement may not reflect an accurate picture of 'survival' for all OHCAs. Given this, we believe future revisions of the Utstein guidelines[5] may benefit from recommending additional, longer term survival variables which provide a more realistic measure of OHCA survival.

To the best of our knowledge no prior studies have directly examined the relationship between initial arrest rhythm mortality rate over time; although a few have examined the relationship between initial arrest rhythm and long term survival. A 2017 study[4] from Melbourne (Australia) reported adjusted 10-year survival for shockable arrests was 70.8% while those for non-shockable arrests were 59.8% and 63.8% for PEA and asystole, respectively. However, the authors of this study stratified their Cox PH model by arrest rhythm (due to non-PH). This meant that they were unable to describe the association between initial arrest rhythm and long term OHCA survival. A 2012 study[13] from the US reported five-year survival as 73% for shockable arrests and 43% for non-shockable arrests. These estimates were lower than those from our own study even though ours had a longer follow-up (8 years vs 5 years). Importantly both these studies, like our own, reported that non-shockable arrests were negatively associated with long term survival. The main point of difference however, is that we demonstrate that this reduction in survival is time-limited; with the mortality hazard rate beyond 4-years being indistinguishable for shockable and non-shockable arrests.

Patients with initial non-shockable cardiac arrest rhythms are generally considered to have poor outcomes;[14] and within our study cohort most (82%) of the OHCA 30-day survivors had a shockable initial arrest rhythm. The initial arrest rhythm likely reflects the underlying aetiology, with non-shockable rhythms being more common in OHCA with non-ischemic aetiologies.[15] However, our results do show that OHCA patients with an initial non-shockable rhythm do survive, and many are still alive several years later. Such findings will hopefully help to reduce the risk of prognostication bias; which occurs when resuscitative efforts are prematurely terminated on the basis of a perceived futility, ultimately guaranteeing a negative outcome (i.e. the 'self-fulfilling prophecy').[16–18]

The use of mortality hazard rates to model OHCA survival offers a number of unique advantages over the more traditional survival analysis techniques. Firstly, cumulative survival (or hazard) models tend to obscure temporal changes in mortality hazard.[9] In contrast, hazard rate functions more readily expose changes (or patterns) in mortality rate over time.[19] Secondly, the hazard rate function can help identify the time point/s when two competing groups (e.g. shockable and non-shockable arrests) begin to experience comparable mortality risks. This situation can be readily observed in our study where the Kaplan Meier curves (Fig. 2) show a clear difference in survival at 8-years between shockable and non-shockable arrests. Therefore, examining the Kaplan Meier curves alone could lead to an erroneous conclusion; that initial arrest rhythm has a persistent effect on long term OHCA survival. However, our 8-year hazard rate curves (Fig. 3) demonstrate that the increased mortality risk in non-shockable arrest victims (relative to their shockable arrest counterparts) is time-limited; with the mortality hazard rates after four years post arrest being statistically no different to that seen in shockable arrest victims. Our analysis demonstrated that peri-arrest factors, such as initial arrest rhythm, may not always demonstrate proportional hazards. Applying a Cox PH regression model in cases were the PH assumptions are not met, or even tested, is statistically inappropriate and may produce erroneous results (see Supplementary file).[20]

Limitations

Our study has a number of limitations. Firstly, due to the relatively small number of 30-day OHCA survivors with an initial arrest rhythm of PEA or Asystole ($n = 153$), we grouped the initial arrest rhythm into either shockable or non-shockable which prevented us describing the effect of individual rhythms on long term OHCA survival. Secondly, although the MRH estimator (with pruning) used in this study has been shown to perform well in cases of low 'event' counts, we acknowledge that the estimates for the earlier survival period of our study will be more accurate then those near the end. Thirdly, our study did not describe the neurological status of our long term OHCA survivor cohort. However, a 2017 WA study[21] reported that a high proportion of OHCA patients who survived to hospital discharge had a good neurological outcome (93% had a Cerebral Performance Category of either one or two). Finally, we used the WA death registry records to determine the date of death. There is therefore a risk that we failed to capture out-of-state deaths; leading to increased survival estimates. To reduce the risk of this potential bias in our study, we restricted our cohort to OHCA patients who were WA residents at the time of their arrest. Moreover, previous studies have shown that incomplete ascertainment of deaths after cardiac events is very low in WA.[22,23]

Conclusion

Our study found that although patients with non-shockable (as opposed to shockable) arrests experience an increased initial mortality risk, this risk does not persist over time. Using the MRH estimator we found that after four years the mortality hazard rates for shockable and non-shockable arrest were not statistically different. Future studies examining factors related to OHCA survival over time should consider using this statistic over Cox proportional-hazard models.

Conflicts of interest

Professor Judith Finn receives research support from SJ-WA. A/Prof. Paul Bailey is Medical Director at SJ-WA. None of the other authors have any conflicts of interest to declare.

CRediT authorship contribution statement

David Majewski: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Stephen Ball:** Conceptualization, Methodology, Data curation, Validation, Writing - review & editing. **Paul Bailey:** Conceptualization, Writing - review & editing. **Janet Bray:** Conceptualization, Writing - review & editing. **Judith Finn:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.02.030.

REFERENCES

1. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63–81.
2. Rajan S, Folke F, Hansen SM, et al. Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology. Resuscitation 2017;114:157–63.
3. Shuvy M, Morrison LJ, Koh M, et al. Long-term clinical outcomes and predictors for survivors of out-of-hospital cardiac arrest. Resuscitation 2017;112:59–64.
4. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. Heart 2017;103:1104–10.
5. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:1286–300.
6. Australian Bureau of Statistics. 3101.0 — Australian Demographic Statistics, Dec 2019. 2020 (Accessed 21 July 2020, at https://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3218.0).
7. Bouman P, Dukic V, Meng X-L. A Bayesian mulitresolution hazard model with application to AIDS reporting delay study. Stat Sin 2005;15:325–57.
8. Bouman P, Meng X-L, Dignam J, Dukić V. A multiresolution hazard model for multicenter survival studies: application to tamoxifen treatment in early stage breast cancer. J Am Stat Assoc 2007;102:1145–57.
9. Dukić V, Dignam J. Bayesian hierarchical multiresolution hazard model for the study of time-dependent failure patterns in early stage breast cancer. Bayesian Anal 2007;2:591–610.
10. Hagar Y, Albers D, Pivovarov R, Chase H, Dukic V, Elhadad N. Survival analysis with electronic health record data: experiments with chronic kidney disease. Stat Anal Data Min 2014;7:385–403.
11. Hagar Y, Dignam JJ, Dukic V. Flexible modeling of the hazard rate and treatment effects in long-term survival studies. Stat Methods Med Res 2017;26:2455–80.
12. Sedgwick P. Cox proportional hazards regression. BMJ 2013;347:f4919.
13. Dumas F, Rea TD. Long-term prognosis following resuscitation from out-of-hospital cardiac arrest: role of aetiology and presenting arrest rhythm. Resuscitation 2012;83:1001–5.
14. Daya MR, Zive DM. Subsequent shockable rhythm and survival from out-of-hospital cardiac arrest: another piece of the puzzle? Resuscitation 2017;114:A14–5.
15. Kauppila JP, Hantula A, Kortelainen M-L, et al. Association of initial recorded rhythm and underlying cardiac disease in sudden cardiac arrest. Resuscitation 2018;122:76–8.
16. Grunau B, Puyat J, Wong H, et al. Gains of continuing resuscitation in refractory out-of-hospital cardiac arrest: a model-based analysis to identify deaths due to intra-arrest prognostication. Prehosp Emerg Care 2018;22:198–207.
17. Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation 2016;102:127–35.
18. Steinberg A, Elmer J. Prognostication after cardiac arrest: are we thinking fast or thinking slow? Resuscitation 2020;149:228–9.
19. Aalen OO, Gjessing HK. Understanding the shape of the hazard rate: a process point of view. Stat Sci 2001;16:1–14.
20. Delgado J, Pereira A, Villamor N, Lopez-Guillermo A, Rozman C. Survival analysis in hematologic malignancies: recommendations for clinicians. Haematologica 2014;99:1410–20.
21. McKenzie N, Cheetham S, Williams TA, et al. Neurological outcome in adult out-of-hospital cardiac arrest (OHCA) patients – not all doom and gloom. 11th International Spark of Life Conference 2017 (Accessed 26 July 2020, at https://resus.org.au/2017-spark-life-conference/).
22. Bradshaw PJ, Jamrozik K, Jelfs P, Le M. Mobile Australians: a moving target for epidemiologists. Med J Aust 2000;172:566.
23. Finn J, Smith K, Jacobs IG. Out of hospital cardiac arrest outcomes — is linkage to the National Death Index a viable option to determine survival rates? Paramedics Australasia Conference Abstracts 2013;10 (Accessed at https://ajp.paramedics.org/index.php/ajp/article/view/26/31).

5.5 Manuscript Appendix

Appendix A

Rationale for applying MRH methodology

An examination of the Schoenfeld residuals in our study cohort revealed that the assumption of PH for shockable and non-shockable arrest rhythm was violated. The non-compliance of initial arrest rhythm with the PH assumption of the Cox model has been reported by others.[1] This has important implications for long term survival OHCA studies which commonly utilise Cox PH regression for multivariate analysis. A key assumption of this method is that all covariates must exhibit PH over the study period. Options to satisfy the PH assumption have traditionally been limited to either performing a time dependent Cox regression analysis or stratified (by initial arrest rhythm) Cox regression analysis. However, modelling arrest rhythm as a time dependent covariate would be statistically inappropriate as can be seen from our findings (i.e. the hazards are only non-proportional for a limited time). On the other hand stratifying the model by initial arrest rhythm would not permit evaluation of the stratification covariate. Likewise, applying a Cox PH regression model in cases were the PH assumptions are not met, or even tested, is statistically inappropriate and may produce erroneous results.[2] In cases where PH are not met, we would recommend the use of the MRH estimator to model long term survival. The MHR estimator method has been mathematically validated and tested with real-world and simulated data and found to provide comparable results to more established statistical techniques.[3-7] Covariates with non-PHs can be included in the MRH estimator model by applying a non-proportional hazard function [npn()] modifier while all covariates with PH can be included without the modifier.

For our study, default MRH estimator settings in R were used, while the model 'resolution' was set at M=3. All unadjusted and adjusted MRH estimator models within our study converged within 100,000 Markov chain Monte Carlo (MCMC) iterations. Pruning was applied to both adjusted and unadjusted models to improve model performance (as confirmed using model diagnostic measures as the Deviance Information Criterion (DIC), Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Simplified MRH primer

The following is a simplified primer for the MRH estimator method used in this paper. It has been written to aid the reader of the accompanying paper develop a basic conceptual understanding of the MRH method. The mathematical complexities of the MRH method have been intentionally simplified or omitted in this document. For a detailed mathematical explanation of the MRH method please refer to the papers cited here[3-7].

The MRH model estimates the mortality hazard rate function *h(t),* by approximating a piece-wise hazard function composed of 2^M (where *M* can be any positive integer) intervals; with each interval containing a constant estimate of the hazard rate for that interval. Prior to running the MRH model using the statistical software package R, a value for '*M'* must be selected by the user. As already mentioned, the value of 'M' determines the number of hazard interval splits in the final MRH model according to the expression 2^M. However, the *duration* of each one of these intervals is itself dependent on both the value of *M* and the length of the study follow-up where;

$Interval\ duration = \frac{length\ of\ follow{-}up}{2^M}$. Therefore, selections for the follow-up length and the value of *M* should be made concurrently, with selection guided by two important considerations. Firstly, the selection of both values should result in clinically meaningful interval lengths; and secondly they should be selected to produce intervals of sufficient duration so that every interval contains at least a few 'events'. With these considerations in mind, we selected a follow-up length of 8-years and an *M=3.* This resulted in eight (2^3), 1-year intervals, with each interval containing a constant hazard rate estimate (See figure 1 below).

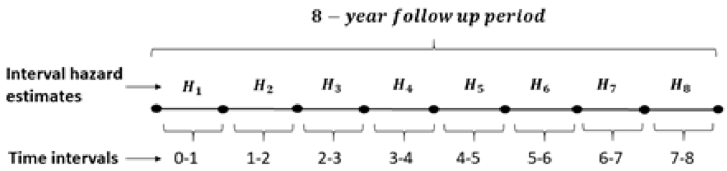

Figure 5. MRH partition of the follow-up length (Supplementary Figure 1).

$$h(t) \cong h(t_i) = \begin{cases} H_1 & for & 0 \le t < 1 \\ H_2 & for & 1 \le t < 2 \\ H_3 & for & 2 \le t < 3 \\ H_4 & for & 3 \le t < 4 \\ H_5 & for & 4 \le t < 5 \\ H_6 & for & 5 \le t < 6 \\ H_7 & for & 6 \le t < 7 \\ H_8 & for & 7 \le t \le 8 \end{cases}$$

Where the sum of the interval hazards gives the cumulative hazard rate H:

$$H_{cumalative} = \sum_{i=1}^{8} H_i = H_1 + H_2 + H_3 + H_4 + H_5 + H_6 + H_7 + H_8$$

Therefore, the MRH method provides an approximation for the 8-year hazard rate function (a continuous function) by utilizing a discrete piece-wise function; with each time interval represented by an estimate of a constant hazard.

In the following section we describe *how* the MRH method estimates the hazard rate for each of the eight intervals shown in figure 1. The MRH method is based on an iterative binary partition of the time axes modelled using a binary 'probability tree'. More precisely, the MRH model is represented by a number of discrete 'levels' (in our case 4), with each 'level' (from 0 to 3) containing the 8-year follow-up period partitioned into progressively smaller sub-intervals according 2^M (where M=0 -> M=3). Hence, our MRH model is composed of the following four levels; level 0 contains a single $[2^0]$ 8-year observation interval, level 1 contains two $[2^1]$ 4-year intervals, level 2 contains four $[2^2]$ 2-year intervals and lastly level 3 contains eight $[2^3]$ 1-year intervals (our final level from figure 1). This probability-tree model is shown in Figure 2 below were $H_{j,i}$ represents the *i-th* interval hazard of the *j-th* level.

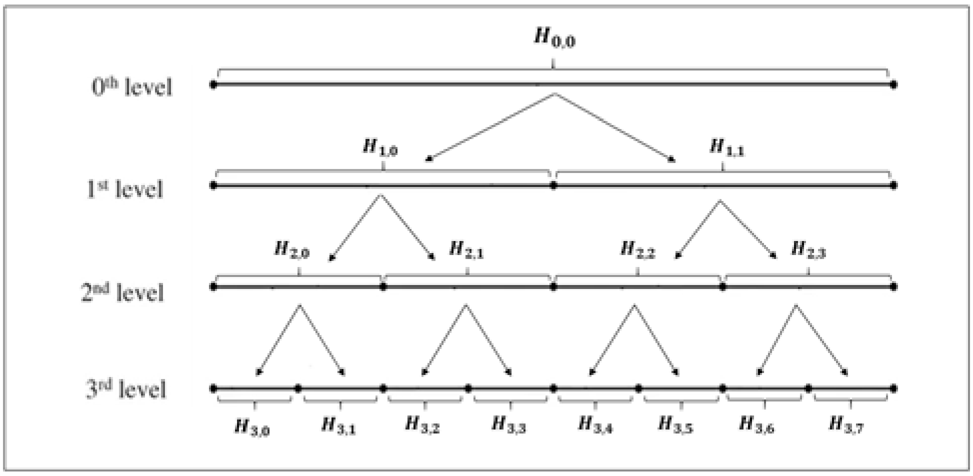

Figure 6. The MRH tree with follow-up time split into smaller sub-intervals at each subsequent level (Supplementary Figure 2).

In this section we explain how the hazards for each of the time intervals (across all levels) shown in figure 2 are estimated. The MRH method uses a semiparametric Bayesian approach to estimate hazard rates for all intervals, with the Bayesian aspect practically implemented using a Markov Chain Monte Carlo sampling algorithm. Hazard rates are continually estimated for each interval in every level (figure 2) starting from level 0 down to the final level 3. The MRH method estimates the hazard rate for each interval by sampling from a hypothetical probability distribution (developed by the MRH) specific for that interval. These hypothetical probability distributions are modelled on some underlying ‘assumed’ probability distribution (e.g. Poisson) which are standardised to the observations of our data sample (i.e. the distribution is fitted to our cohort sample) for that specific time interval. This again highlights why it is crucial that each interval within our data set contain at least some failure events (so that the hypothetical distribution can be standardized). Returning to the hazard estimate process, once a hazard is sampled from the probability distribution for that interval, it is compared to the estimate from the proceeding ‘level’ and then used to ‘adjust’ the probability distribution for the original interval. For example, the estimate for interval $H_{2,0}$ (Figure 2) is determined by sampling from the probability distribution for that interval, comparing it to the estimate from the proceeding interval $H_{1,0}$, and then ‘adjusting’ the probability distribution for that interval (interval $H_{2,0}$) based on whether the estimate is above or below. This ‘retrospective’ nature of the MRH method is why it can provide strong hazard estimates even when interval event counts are low, as it basically ‘borrows’ information from the proceeding interval (which has a larger time length and therefore more ‘events’). This process is undertaken for all intervals starting from level 0 and ending at level 3. The process is then repeated through many iterations with each iteration effectively updating each hazard interval estimate. Over many iterations this results in increasingly ‘better’ hazard approximations. Finally, the MRH method has an optional ‘pruning’ function. The MRH pruning function merges adjacent ‘intervals’ in any of the ‘M’ levels of the Polya tree that are deemed to be statistically similar. By appropriately merging adjacent time intervals the event count for the merged interval is increased, ultimately reducing estimate uncertainty. The advantage of the MRH pruning technique is that it provides robust estimates even in situations where interval ‘event’ counts are low.

5.6 Summary of Chapter Findings

- 30-day OHCA survivors have a substantially greater mortality risk in the initial years following an arrest if they had a non-shockable (as opposed to shockable) initial arrest rhythm.

- Besides initial arrest rhythm and patient age, there were no other measured prehospital factors that were associated with an increased long-term mortality risk.

Chapter 6 Pre-arrest Comorbidity and OHCA Outcomes Overview

6.1 Overview

This chapter explores the association between pre-arrest comorbidity and OHCA outcomes by performing a systematic review of the literature. The findings of this research are reported in a manuscript published in the peer-reviewed journal BMJ Open.

> ***Majewski D**, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.*

6.2 Background and Rationale

One of the findings in Chapter 3 was that even after accounting for Utstein variables, a steep temporal trend in OHCA survival was still evident. Previous studies[26, 44] have indicated that prehospital factors explain between 41%[44] and 51%[26] of the variation in STHD across EMS services, suggesting that a large part of the variation in survival outcome may be attributed to other un-accounted for factors. Several studies have proposed that patient comorbidity may play a substantial role in OHCA survival, whether directly, or as a confounder of initial arrest rhythm.[44, 106, 107] However, to date, there remains no clear consensus in the resuscitation community on this issue. Therefore, I undertook a systematic review of the literature to determine the association between pre-arrest comorbidity and OHCA patient survival and neurological outcomes.

6.3 Methodology

<u>Study design</u>

Originally, I had planned to use the WA OHCA registry to conduct a retrospective cohort study with patient comorbidity status ascertained from the EMS PCR. However, on examining a sample of OHCA cases, I noted that the comorbidity status was generally non-specific, with many cases having a recorded comorbidity of ‘other’. Given this, I decided not to proceed with this study design. Instead, I decided to address the aims of this chapter by conducting a systematic review of the literature. To identify relevant studies, the databases MEDLINE, Ovid Embase, Scopus, CINAHL, Cochrane Library and MedNar were searched from inception to 31 December 2021. To be included in the review studies had to: 1) include cases of OHCA of medical aetiology,[25] and 2) provide a quantitative comparison between pre-arrest patient comorbidity and either OHCA survival (30-day or STHD) or neurological outcome post arrest (or both). Study types excluded from this review included: editorials, case studies/case reports/case series, commentaries, conference abstracts, opinion pieces and letters. The Newcastle-Ottawa Quality Assessment Scale for cohort studies was used to assess the risk of bias. A meta-analysis of the included studies was planned if clinically appropriate and if the statistical heterogeneity across the studies was under 50% (i.e. $I^2<0.5$).

6.4 Manuscript

Open access Original research

BMJ Open

Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes

David Majewski, Stephen Ball, Judith Finn

To cite: Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. *BMJ Open* 2019;**9**:e031655. doi:10.1136/bmjopen-2019-031655

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ABSTRACT

Objectives To assess the current evidence on the effect pre-arrest comorbidity has on survival and neurological outcomes following out-of-hospital cardiac arrest (OHCA).
Design Systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Data sources MEDLINE, Ovid Embase, Scopus, CINAHL, Cochrane Library and MedNar were searched from inception to 31 December 2018.
Eligibility criteria Studies included if they examined the association between prearrest comorbidity and OHCA survival and neurological outcomes in adult or paediatric populations.
Data extraction and synthesis Data were extracted from individual studies but not pooled due to heterogeneity. Quality of included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.
Results This review included 29 observational studies. There were high levels of clinical heterogeneity between studies with regards to patient recruitment, inclusion criteria, outcome measures and statistical methods used which ultimately resulted in a high risk of bias. Comorbidities reported across the studies were diverse, with some studies reporting individual comorbidities while others reported comorbidity burden using tools like the Charlson Comorbidity Index. Generally, prearrest comorbidity was associated with both reduced survival and poorer neurological outcomes following OHCA with 79% (74/94) of all reported adjusted results across 23 studies showing effect estimates suggesting lower survival with 42% (40/94) of these being statistically significant. OHCA survival was particularly reduced in patients with a prior history of diabetes (four out of six studies). However, a prearrest history of myocardial infarction appeared to be associated with increased survival in one of four studies.
Conclusions Prearrest comorbidity is generally associated with unfavourable OHCA outcomes, however differences between individual studies makes comparisons difficult. Due to the clinical and statistical heterogeneity across the studies, no meta-analysis was conducted. Future studies should follow a more standardised approach to investigating the impact of comorbidity on OHCA outcomes.
PROSPERO registration number CRD42018087578

Strengths and limitations of this study

- ► To the best of our knowledge, this is the first systematic review examining the relationship between prearrest comorbidity and out-of-hospital cardiac arrest (OHCA) outcomes (survival or neurological).
- ► This study identifies the limitations of current research in the area of prearrest comorbidity and OHCA outcomes, and provides direction for future research.
- ► Significant clinical heterogeneity between studies prevented a meta-analysis.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a sudden and commonly fatal medical emergency.[1 2] Although a number of patient-specific and arrest-specific factors have been identified that influence patient survival,[3 4] these factors fail to fully explain the variability in outcomes.[5 6] The effect of prearrest comorbidity on outcomes in patients with OHCA is poorly understood.[7]

It has been suggested that a better understanding of the effect that comorbidity has on OHCA outcomes could lead to a number of benefits such as: improved understanding of the epidemiology of cardiac arrest,[8] more informed end-of-life planning,[9 10] improved public health policies to preemptively manage 'at risk' populations[8 11] and improved prognostication.[3 7 9 12] A number of authors have investigated the association between prearrest comorbidity and OHCA survival with some reporting comorbidity to be negatively associated with survival,[6 13] while others reporting no relationship.[14] Regarding neurological outcomes, similar variability in findings has been observed, with some authors reporting a negative relationship[15] and others reporting no relationship.[10 12] However, despite the variability in findings and continued interest in the topic, no systematic review examining the association of prearrest comorbidity and OHCA outcome has been conducted to date. This systematic review provides an overview of the current evidence regarding the association between prearrest comorbidity and patient survival and neurological outcomes following OHCA.

METHODS

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[16] was followed in this systematic review.

Review question

In patients with OHCA, do preexisting chronic health conditions result in poorer survival to hospital discharge and neurological outcomes?

Eligibility criteria

To be eligible for inclusion in this systematic review, studies had to include: (1) cases of OHCA of medical aetiology[17] and (2) quantitative comparison between comorbidity and OHCA outcome (either survival or neurological outcome). Survival outcome could include survival to hospital discharge or 30-day survival, both being survival metrics recommended by the Utstein report.[17] No restrictions were placed on the tool used to measure comorbidity or neurological outcome, and both adult and paediatric cases were included. No publication date or language restrictions were applied. There were no ethical requirements for inclusion in this systematic review.

All comparative study types were considered for inclusion except: (1) editorials, case studies/case reports/case series, commentaries, conference abstracts, opinion pieces and letters; (2) in-hospital cardiac arrests or arrests that occurred during interhospital transfer; (3) cardiac arrests with a primary aetiology of trauma, drug-related, drowning, electrocution or asphyxia as defined by the 2015 Utstein OHCA reporting guidelines.[17]

Data on individual cancer sub-types were excluded as this level of detail was beyond the scope of this review. Data on prior surgeries, medication use or conditions that are congenital, idiopathic, of short duration and/or unlikely to have long term implications were not considered to constitute a comorbidity for this review.

Data sources

The databases Ovid MEDLINE, Ovid Embase, Scopus, CINAHL and Cochrane Library were searched for all eligible studies from inception to 31 December 2018. The search engine MedNar was searched until 31 December 2018 for grey literature. Reference lists from all relevant studies were searched to identify any additional studies.

Patient and public involvement

No patient or public were involved in the design or planning of this study.

Search strategy

Search terms were grouped into two broad categories of 'OHCA' and 'comorbidity' and combined using the Boolean operator 'AND'. The search strategies for each of the databases have been provided in online supplementary appendix 1.

Study selections

Titles and abstracts were initially screened by a single author (DM) to identify potentially relevant papers. Full-text review was then performed by two authors (DM and SB) independently to identify studies that met the eligibility criteria, with disagreements resolved by a third reviewer (JF). As a subsequent check to ensure a high level of sensitivity, JF rescreened all titles and abstracts. Any papers identified from this second screen then underwent full-text review by two authors (DM and SB) and were included if they met eligibility criteria (by mutual agreement of DM and SB).

Data collection

Data were extracted by DM from the relevant studies and entered into an Excel spreadsheet. Data extracted included information on authors, title, publication year, study location, study period, aims, study design, comorbidity, type of comorbidity measurement, patient survival and/or neurological outcome. Additionally, prehospital resuscitation factors (eg, witness status and bystander cardiopulmonary resuscitation) were extracted where available. Where a study provided relevant outcomes graphically (eg, in a forest plot) but did not provide corresponding effect estimates, the authors of those studies were contacted for additional data.

Risk of bias in individual studies

Risk of bias of individual studies was independently assessed by two authors (DM and SB) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, and any disagreements were resolved by mutual consensus.

Summary measures

We planned to use ORs to compare survival or neurological outcomes between cases with and without comorbidities. In studies that did not provide ORs, crude ORs were calculated wherever possible. Studies that provided mortality OR were converted to survival OR by calculating the reciprocal of the mortality OR for both unadjusted and adjusted values. Studies that provided statistics other than OR (eg, hazard ratios) were not included in forest plots. Where cerebral performance categories (CPC)[18] were reported, we used CPC of 1 or 2 as an indicator of good neurological outcome. ORs for survival to hospital discharge and 30-day survival were considered equivalent and grouped together. For both survival and neurological outcomes, results were included in a forest plot only if two or more studies reported ORs on the same comorbidity. RevMan V.5.3 was used to obtain relevant figures such as forest plots.[19] Where individual studies provided different descriptors for the same or similar comorbidity, we planned to group these where appropriate (eg, hyperlipidaemia and hypercholesterolaemia). Any results exclusively associated with an initial non-shockable cardiac arrest rhythm were excluded. Where multiple results were reported by a single study for the same exposure but for varying subgroup (for example by initial cardiac arrest rhythm), only one set of results were utilised to prevent duplication. Given the well documented prognostic influence of specific other covariates on OHCA outcomes,[4 20 21] adjusted results were preferentially used.

RESULTS

Study selection

The initial search identified 6395 citations. After removal of duplicates 3132 remained. A total of 75 potential studies were identified after title and abstract screening against inclusion/exclusion criteria. After full-text review, 29 studies were included. These results are summarised in the PRISMA flow diagram (figure 1). Of the 46 excluded studies, 24 were excluded because they did not directly document a comparison between OHCA outcome and at least one comorbid condition or did not allow for the direct calculation of such a relationship. Our search also identified two studies[22 23] that conducted relevant analysis however did not report these results and were therefore excluded from this review. Our initial article search identified three papers from Taiwan[24–26] with significant cohort overlap. To avoid duplication of results only the paper[26] with the most comprehensive analysis of comorbidity was included within this review. Similarly, of two papers from Australia[9 27] with significant cohort overlap, only one paper[9] was included in the review.

Study characteristics

A summary of all included studies is provided in tables 1 and 2. Studies presented in table 1 (n=21) directly investigated the effect of comorbidity on OHCA outcome, while those in table 2 (n=8) had alternative primary aims but still provided information on the association between comorbidity and OHCA outcomes. Results from each of the individual studies are shown online supplementary table 1 (for survival to hospital discharge outcomes) and online supplementary table 2 (for neurological outcomes). There were 18 studies conducted in Europe,[3 5 10 13 15 28–40] four in the USA,[8 12 41 42] three in Asia,[20 26 43] two multinational studies,[11 14] one in Australia[9] and one in Canada.[44] The number of patients enrolled in each study varied from n=63[30] to n=2 47 684.[41] Patient inclusion age varied between studies, with 19 studies restricted to adults (≥16 years),[3 8 9 12 20 26 28 29 31 33 36–44] one[10] restricted to 70 years or over, seven placing no age restrictions[5 11 13 15 32 34 35] and two studies being unclear about age.[14 30] Cohort recruitment points varied greatly also, with 15 studies using scene of arrest as the enrolment point,[5 8–11 13 20 31–33 38–40 42 44] 6 using emergency department (ED) admission[12 15 26 35–37] and 8 using hospital admission.[3 14 28–30 34 41 43] Cardiac arrest aetiology was identified as either cardiac or non-traumatic in 12 studies,[5 8–12 20 26 31 33 36 41] while the remaining studies either placed no restriction or were unclear. Patient clinical inclusion characteristics were highly variable between the studies. Eight studies placed no restrictions[9–11 20 26 31 40 44] on inclusion criteria while 21 studies restricted inclusion to patients with one or more clinical characteristics. These clinical characteristics included such factors as initial presenting cardiac rhythm,[5 8 32 34 42] whether the arrest was witnessed,[33 38] Glasgow Coma Scale score after successful resuscitation,[3 28 29] presence of a particular medical condition and/or admittance to a specific hospital department[12 14 15 30 35–37 41 43] and/or certain procedures or treatments received (eg, hypothermia; coronary angiograph).[3 28 43]

A number of studies had overlapping cohorts (overlapping geographical regions and recruitment dates). This included two studies from the Netherlands[5 10] and two from Sweden.[13 34] However, all four studies were included in this review as they differed sufficiently in inclusion criteria, study aims or recruitment period. Four studies from Denmark[29 37 39 40] had overlapping cohorts but generally examined different outcomes. Where the same or similar outcomes were examined, results from only one of the studies was used in this review. A fifth Danish study[3] was also included as the cohort overlap with the other four Danish studies was minimal. Three included US studies[8 12 42] have a possible cohort overlap, with a fourth study[41] that sourced its cohort from a nationwide inpatient sample. However, this overlap would be 20% at most and therefore it was decided to include all four studies.

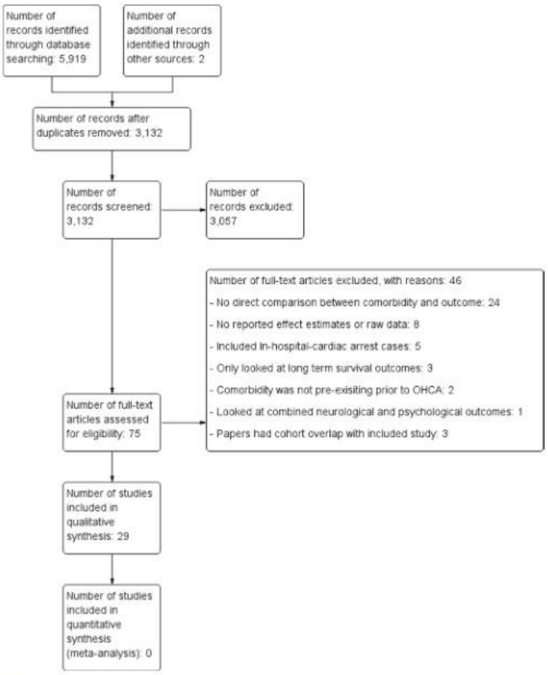

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies. OHCA, out-of-hospital cardiac arrest.

Table 1 Characteristics of included studies that directly investigated the influence of comorbidity on OHCA outcomes

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Andrew *et al* 2017[9]	Australia	Retrospective cohort	15 953	Jan 2007–Dec 2014	Survival to hospital discharge	CCI=0,1,2,3,≥4, hypertension, diabetes, myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive disease, cancer, metastatic cancer, dementia, peripheral vascular disease, peptic ulcer, HIV/AIDS, skin ulcers, connective tissue disease.	Ambulance patient care records.	All non-traumatic arrests with an attempted resuscitation.	≥16
Beesems *et al* 2015[10]	Netherlands	Prospective cohort	851	Jan 2009–Dec 2011	Survival with good neurological outcome (CPC 1–2)	CCI ≥4.	Patients general practitioner.	All non-traumatic arrest patients without DNR orders and in whom resuscitation was started.	≥70
Blom *et al* 2013[5]	Netherlands	Prospective cohort	1172	2005–2008	30-day survival Neurological outcome at hospital discharge	Cardiovascular disease, obstructive pulmonary disease.	Presence of at least two condition-specific pharmacy prescriptions.	All VF/VT OHCA of presumed cardiac aetiology in whom resuscitation was attempted.	Any
Carew *et al* 2007[42]	USA	Retrospective cohort	1043	Jan 1999– Dec 2003	Survival to hospital discharge	Number of chronic conditions.	Ambulance patient care records.	All VF cardiac arrest patients who had an arrest of presumed cardiac aetiology/heart disease.	≥18
Corrada *et al* 2013[30]	Italy	Prospective cohort	63	2004–2009	Neurological outcome at discharge	Heart disease.	Unclear.	OHCA patients admitted to cardiac intensive care unit alive.	Unclear
de Vreede-Swagemakers *et al* 1998[31]	Netherlands	Prospective cohort	288	Jan 1991–Dec 1995	Survival to hospital discharge	Cardiac history.	Patients general practitioner.	All OHCA where CPR was attempted by EMS and arrest was not due to trauma or intoxication or patient in terminal stage of disease.	20–75
Dickey and Adgey 1992[32]	Northern Ireland (UK)	Prospective cohort	281	Jan 1966–Dec 1987	In-hospital mortality	Cerebrovascular accident, myocardial infarction.	Unclear.	All OHCA patients with an initial rhythm of VF.	Any

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Dumas *et al* 2017[8]	USA	Prospective cohort	1166	Jan 2007– Dec 2013	Survival to hospital discharge, neurological outcome at discharge (CPC)	CCI=0,1,2,3, atrial fibrillation, cancer, cerebrovascular accident, congestive cardiac failure, coronary artery disease, diabetes, gastrointestinal disease, heart disease, HIV, hypercholesterolaemia, hypertension, kidney disease, liver disease, lung disease, mental health, metabolic disease, myocardial infarction, non-cardiac history, non-neurological history, peripheral artery disease, prior cardiac arrest, tissue/inflammatory disease, valvulopathy.	Ambulance patient care records.	Non-traumatic OHCA with initial rhythm of VF.	≥18
Herlitz *et al* 1995[34]	Sweden	Prospective cohort	488	1981–1992	In-hospital mortality	Myocardial infarction, angina pectoris, hypertension, diabetes, congestive heart failure, cerebrovascular disease, asthma.	Unclear.	All OHCA patients with initial rhythm of VF who were hospitalised alive.	Any
Hirlekar *et al* 2018[38]	Sweden	Retrospective cohort	12012	2011–2015	30-day survival	CCI=0–2, 3–4, 5–6,>6, cancer, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disorder/rheumatic, dementia, diabetes, diabetes (with complications), liver disease (mild), myocardial infarction, paraplegia/hemiplegia, peptic ulcer disease, peripheral vascular disease, renal disease.	National Patient Registry.	All bystander-witnessed patients with OHCA.	≥18

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Iqbal *et al* 2015[15]	UK	Prospective cohort	174	2011–2013	Neurological outcome (modified Rankin Scale, mRS) at discharge	CCI.	National Institute for Cardiovascular Outcomes Research database.	All OHCA patients who were brought to emergency department with ROSC.	Any
Kang *et al* 2017[20]	South Korea	Retrospective cohort	341	Jan 2009 – Dec 2014	Survival to hospital discharge, neurological outcome (CPC)	Cancer.	Electronic medical records.	All non-traumatic OHCA. Cases of hanging, intoxication and drowning were excluded.	≥18
Larsson *et al* 2005[13]	Sweden	Prospective cohort	1377	Oct 1980–Oct 2003	Survival to hospital discharge	Angina pectoris, diabetes, myocardial infarction.	Hospital records and general practitioner.	All OHCA in whom resuscitation was attempted and patients were admitted to hospital alive.	Any
Lee *et al* 2018[11]	Japan, Singapre, South Korea, Malaysia, Taiwan, Thailand UAE	Retrospective cohort	19 044	2009–2012	Survival to hospital discharge, neurological outcome at discharge (CPC)	1, 2 or three conditions, heart disease	Hospital records, ambulance reports and ambulance dispatch records.	All non-traumatic OHCA where resuscitation was commenced and where patient's medical history was known.	Any
Parry *et al* 2017[44]	Canada	Retrospective cohort	10 097	2012–2014	Survival to hospital discharge, neurological outcome (mRS)	Diabetes	In-hospital records.	All OHCA's treated by ambulance services that had data on diabetes status.	≥18
Roedl *et al* 2017[35]	Austria	Prospective cohort	1068	Jan 2005–Jan 2012	6-month neurological outcome (CPC)	CCI=1,≥4, liver cirrhosis.	Hospital screening.	All OHCA patients admitted to the emergency department after ROSC.	Any

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Salam *et al* 2018[3]	Denmark	Prospective cohort	666	Jun 2002–2011	30-day mortality	CCI ≥1, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, chronic kidney disease, connective tissue disease, coronary disease, dementia, diabetes, diabetes (with complications), gastric/duodenal ulcer, hemiplegia, hypercholesterolaemia, hypertension, liver disease, malignant haematological disease, acute myocardial infarction, peripheral artery disease, psychiatric disorder, pulmonary disease.	National patient registry and chart review.	Comatosed patients (GCS<8), who were successfully resuscitated from OHCA, admitted and treated with TTM (32–36 C) for 24 hours.	≥18
Søholm *et al* 2015[40]	Denmark	Retrospective cohort	2527	2007–2011	Survival to hospital discharge	CCI 1, 2,≥3, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, diabetes, diabetes (with complications), hemiplegia, ischaemic heart disease, liver disease (mild), moderate/severe liver disease, moderate/severe renal disease, peptic ulcer, peripheral vascular disease, rheumatological disease.	National Patient Registry.	All OHCA of any aetiology with attempted resuscitation by EMS.	≥18

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Terman *et al* 2015[12]	USA	Retrospective cohort	588/558	Jan 2005–Sept 2012	Neurological outcome (CPC)	CCI (continuous), CCI=1, CCI=2, AIDS, any tumour, cardiovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disease, dementia, diabetes, diabetes (with end organ damage), hemiplegia, leukaemia/ lymphonma, mild liver disease, moderate/ severe liver disease, moderate/severe renal disease, myocardial infarction, peptic ulcer disease, peripheral occlusive vascular disease, tumour (metastatic).	Electronic health records.	All non-traumatic OHCA patients that presented to the emergency department.	≥18
Winther-Jensen *et al* 2016[14]	Europe, Australia	Post hoc analysis of clinical trial	939	2010–2013	Neurological outcome (CPC) at 6 months	Modified CCI (mCCI): mCCI=1, mCCI=2, mCCI ≥3.	Unclear.	Comatosed patients with OHCA admitted to one of 36 intensive care units with ROSC.	Unclear
Winther-Jensen *et al* 2018[39]	Denmark	Retrospective cohort	993	2007–2011	30-day mortality Neurological outcome (CPC) at discharge	Cancer.	National Patient Register.	All patients with OHCA attended to by EMS and successfully resuscitated.	≥18

CCI, Charlson Comorbidity Index; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; GCS, Glasgow Coma Scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, therapeutic temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 Characteristics of included studies that did not directly compare effect of comorbidity to OHCA outcome

Study ID	Country	Study design	Cases	Enrolment Period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Beitland *et al* 2016[28]	Norway	Prospective cohort	245	Sept 2010–Jan 2014	Survival with good neurological outcome at 6 months.	Diabetes (type II) and chronic hypertension.	Hospital records	All patient with GCS <8 on admission who received TTM within 24 hours of ICU stay.	≥18
Bro-Jeppesen *et al* 2012[29]	Denmark	Prospective cohort	360	Jun 2004–Dec 2010	30-day mortality.	No comorbidities.	Unclear	All patients admitted to hospital with ROSC, GCS <9 and no cardiogenic shock.	≥18
Chen *et al* 2017[26]	Taiwan	Retrospective cohort	5338	2005–2012	Survival to hospital discharge.	CCI=1, ≥2, angina, tumour, acute myocardial infarction, cerebrovascular disease, congestive heart failure, coronary artery disease, diabetes.	Taiwan National Health Insurance database	All non-traumatic OHCA patients admitted to the emergency department.	≥18
Eid *et al* 2017[41]	USA	Cross sectional	247 684	1995–2013	Neurological outcome at hospital discharge.	mCCI=1, 2, 3, ≥4.	Nationwide Inpatient Survey (NIS)	All OHCA patients (non-traumatic) who achieved ROSC and were hospitalised.	≥18
Fabbri *et al* 2006[33]	Italy	Prospective cohort	479	Jul 1994–Dec 2004	Neurological outcome at discharge.	Hypertension, diabetes, congestive cardiac failure, myocardial infarction.	Unclear	All bystander witnessed OHCA of presumed cardiac origin.	≥18
Oh *et al* 2018[43]	Korea	Retrospective cohort	295	Mar 2007–Dec 2013	Neurological outcome (CPC).	Non-diabetic.	Registry and electronic records	All OHCA patients who achieved ROSC and were admitted to the emergency intensive care unit and were administered therapeutic cooling.	≥18
Sharma *et al* 2016[36]	Netherlands	Retrospective cohort	195	Mar 2012–Apr 2014	Survival to hospital discharge.	Atrial fibrillation, cerebrovascular accident, congestive heart failure, diabetes, dyslipidaemia/ cardiovascular conditions, hypertension, myocardial infarction, ventricular fibrillation.	Hospital records	OHCA of cardiac presumed cardiac origin in patients that survived to emergency department admission (survived means either in ROSC or ongoing CPR).	Adults

Continued

Table 2 Continued

Study ID	Country	Study design	Cases	Enrolment Period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Søholm *et al* 2014[37]	Denmark	Prospective cohort	1016	2007–2011	30-day mortality.	CCI	Hospital records	All OHCA of any aetiology where patient was either in ROSC or had ongoing CPR on emergency department admission.	>18

CCI, Charlson Comorbidity Index; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; GCS, Glasgow Coma Scale; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, therapeutic temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

Risk of bias within studies

Generally, the quality of studies varied greatly in regards to selection criteria and comparability. More specifically, most studies were found to be of high risk of bias with respect to comparability (ie, adjustment for confounders) and representativeness of the exposed cohort with no single study scoring well in both categories (online supplementary table 3). The majority of studies ascertained comorbidity data from hospital records however many were not clear on the type of hospital record (eg, patient clinical records or hospital billing/statistical records) or whether the record referred to prior hospitalisations or treatments. Only 12 studies[3 5 10 13 15 20 26 31 38–41] obtained history from sources that could be considered to have a low risk of exposure ascertainment bias. All studies were judged to be of low risk of bias with respect to selection of non-exposed cohort and follow-up length.

Results of individual studies

The relevant results of individual studies are reported under each of the corresponding outcome subheadings 'Survival to hospital discharge' and 'Neurological outcomes after OHCA'. A request for additional data was sent to the authors of two studies[9 44] with data subsequently being provided for one[9] of these studies.

Survival to hospital discharge

Comorbidity and survival to hospital discharge/30-day survival results were provided by 19 studies.[3 5 8 9 11 13 20 26 29 31 32 34 36–40 42 44] Of these, six studies[3 8 9 26 37 38] used the Charlson Comorbidity Index (CCI)[45] as a predictor of survival. The use of CCI scores varied greatly, with some studies comparing individual CCI scores and others comparing ranges of CCI. Fifteen studies[5 8 9 11 13 20 26 31 32 34 36 38–40 44] examined the presence or absence of individual comorbid conditions as the predictor of survival.

Adjusted survival to hospital discharge results

There were 15 studies[3 5 8 9 11 13 26 29 31 34 37–39 42 44] that provided a total of 71 adjusted analyses on the association between comorbidity and survival to hospital discharge. Three studies found statistically significant decreased survival in all CCI models (where CCI >0).[8 9 37] Two studies[3 26] found that survival was not statistically different in those with a CCI ≥1 (compared with CCI=0) although these studies restricted their cohort to patients either successfully resuscitated and admitted to hospital[3] or admitted to the ED.[26] Another paper found that only higher CCI scores showed significant negative relationships.[38] Three studies[8 9 38] demonstrated monotonic trends, whereby each increase in CCI (ie, increased comorbidity), was associated with a further reduction in survival. Most individual comorbidities were predictive of lower survival. Four[9 13 34 38] out of six studies[9 13 26 34 38 44] found statistically significant lower survival to hospital discharge in patients with a prearrest history of diabetes. One[26] out of four studies[9 13 26 38] demonstrated that a history of myocardial infarction (MI)

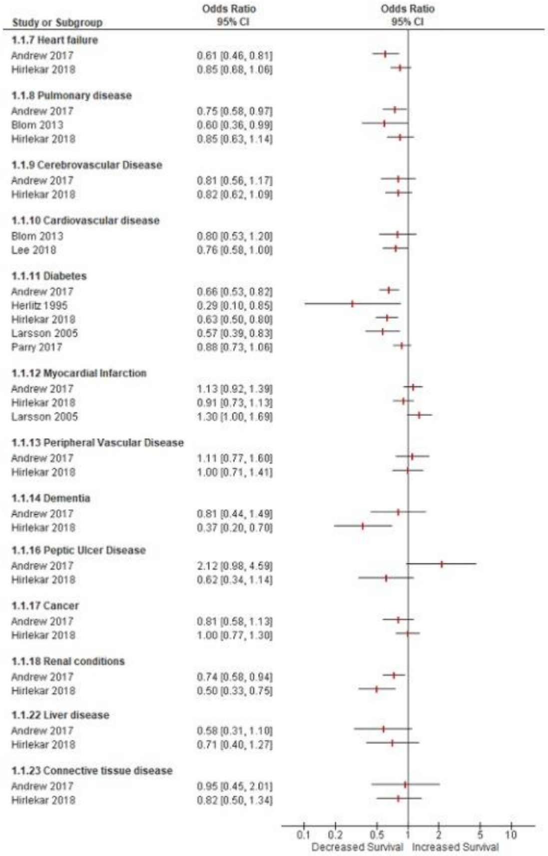

Figure 2 Forest plot showing adjusted ORs of individual comorbidities on survival to hospital discharge.

was associated with higher survival after OHCA (mortality HR: 0.80 CI: 0.68 to 0.94). One of two studies showed a slight, but non-significant, survival benefit in patients with peripheral vascular disease (figure 2).[9 38] One[13] of two[13 26] studies that looked at a prearrest history of angina pectoris showed a statistically significant increase in survival to hospital discharge. Looking more broadly at heart disease and survival following OHCA, two studies[11 26] found no significant relationship, while another found a statistically significant negative association with survival.[31] Three studies reported on the effect of cancer on survival to hospital discharge with all three studies finding no significant effect on survival.[9 38 39] One study[42] that looked at the relationship between the number of comorbid conditions and survival found that an increasing cumulative number of comorbidities resulted in decreased survival (figure 3). Finally, a single study found that patients with no prearrest comorbidity were significantly more likely to survive to hospital discharge than those with prearrest comorbidity.[29]

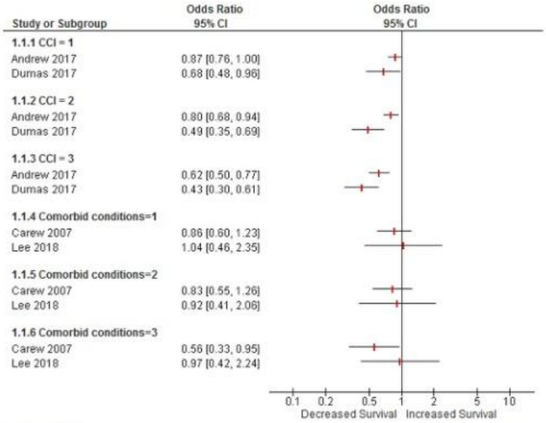

Figure 3 Forest plot showing adjusted ORs of comorbidity burden on survival to hospital discharge.

Unadjusted results for survival to hospital discharge

There were 17 studies that reported a total of 97 unadjusted analyses on the association between comorbidity and survival to hospital discharge.[3 5 8 9 11 20 26 29 31 32 34 36 37 39 40 42 44] Individual papers reported between 1[3 20 29 31 37 44] and 22[8] unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 17 studies, 51% (49/97) showed a statistically significant reduction in survival to hospital discharge for individuals who had a prearrest comorbidity while 4% (4/97) showed significantly higher survival. Of the remaining 44/97 non-significant results, 86% (38/44) had point estimates indicating reduced survival. Forest plots for unadjusted survival outcomes have been provided as supplementary figures (online supplementary figure 1 and online supplementary figure 2).

Neurological outcomes after OHCA

The effect of prearrest comorbidity on neurological outcome following OHCA was reported in 16 studies.[5 8 10–12 14 15 20 28 30 33 35 39 41 43 44] One study provided functional outcomes after hospital discharge, but was not included in this section as the neurological outcomes could not be deduced from the paper.[9] Eleven studies measured neurological outcome at discharge,[5 8 10–12 15 20 30 39 41 44] four studies measured it at 6 months,[14 28 35 43] and one study assessed at both discharge and 12 months.[33] Comorbidity was assessed using the CCI in six of the studies[8 10 12 15 35 41] and a modified version of the CCI was used by an additional paper.[14] The remaining nine studies[5 11 20 28 30 33 39 43 44] used the presence or absence of individual comorbidity as the predictor.

These 16 studies reported neurological outcome as either good or bad, with 12 of these[5 8 10–12 14 20 28 30 35 39 43] using a CPC of 1 or 2 to indicate good neurological outcome. Two studies used the modified Rankin Scale (mRS) as an indicator of neurological outcome with one study[15] defining a good neurological outcome as a mRS of 0–3

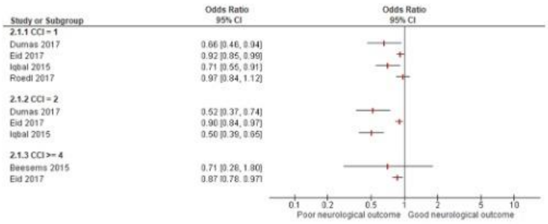

Figure 4 Forest plot showing adjusted ORs of comorbidity burden on neurological outcome.

and the other[44] defining it as a mRS of 0–2. Of the two remaining studies, one defined good outcome as patients discharged alive without International Classification of Diseases codes indicating coma, permanent anoxic brain injury or persistent vegetative state[41] and the other study defined good outcome using the Overall Performance Categories scores of 1 or 2.[33]

Adjusted results

A total of 23 adjusted analyses relating to the association between comorbidity and neurological outcome following OHCA were reported by 11 studies.[8 10–12 14 15 33 35 39 41 43] In comparison with CCI=0, a CCI=1 was significantly associated with a poorer neurological outcome in three[8 15 41] studies (figure 4) while two other studies found no significant relationship.[12 35] Similarly, CCI=2 (relative to CCI=0) was significantly associated with a poorer neurological outcome in three studies[8 15 41]; while another study found no significant relationship.[12] A 2016 study[14] showed effect estimates for the modified CCI=2 favouring a good neurological outcome, although this was not significant. Two studies found that a CCI ≥4 was associated with poor neurological outcomes[10 41]; however, this was statistically significant in only one of these studies.[41] Five studies reported individual comorbid conditions in relation to neurological outcomes (online supplementary table 2).[11 33 35 39 43]

Unadjusted results

Eleven studies provided a total of 31 unadjusted analyses on the association between comorbidity and neurological outcomes following OHCA.[5 10–12 20 28 30 33 35 41 44] Individual studies reported between 1[5 10 20 30 35 44] and 14[12] unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 11 studies, 29% (9/31) of results showed statistically significant poorer neurological outcomes for individuals who had a prearrest comorbidity while 3% (1/31) showed a statistically significant positive neurological outcome. Of the remaining 21 non-significant results, 62% (13/21) had point estimates indicating poorer neurological outcomes. Forest plots for unadjusted neurological outcomes have been provided as online supplementary figure 3.

DISCUSSION

This review identified 29 studies that examined the association between OHCA outcome and prearrest comorbidity. To our knowledge, this is the first systematic review to assess the association between prearrest comorbidity on both survival and neurological outcomes in patients with OHCA. We identified only one other systematic review, from 2013,[7] that overlapped the scope of our review, with several important differences. This other review[7] was restricted to patients over 70 years of age, did not examine neurological outcomes and considered comorbidity as one of a number of predictors of survival (ie, it did not focus specifically on comorbidity). This previous review[7] identified only a single paper that examined comorbidity as a predictor for survival, and concluded that more studies on comorbidity and survival were needed.

Our review found that generally the presence of prearrest comorbidity among patients with OHCA was associated with decreased survival to hospital discharge. Of the 15 included studies that presented adjusted analyses for survival to hospital discharge, 38% (27/71) reported a statistically significant negative association between comorbidity and survival, while only 3% (2/71) found a significant positive association. Furthermore, of the 42/71 remaining non-significant analyses, 62% (26/42) had point estimates indicating reduced survival, further demonstrating an overall pattern of poorer survival outcomes. Additionally, increased levels of comorbidity burden, measured using the CCI, were generally associated with a trend of decreasing survival (figure 3). With reference to individual comorbid conditions, a history of diabetes was associated with statistically significant reduced rates of survival in four[9 13 34 38] out of six studies. Despite this, no meta-analysis could be conducted between any of the studies as a result of significant clinical heterogeneity. As such, we believe the use of prearrest comorbidity as a prognostication tool for OHCA survival is unlikely to be useful which is consistent with the International Liaison Committee on Resuscitation statement.[46]

In contrast, a patient's prearrest history of MI was shown to be suggestive of increased survival to hospital discharge in three[9 13 26] out of four[9 13 26 38] studies reporting on the condition, with one[26] of the studies reporting statistically significant results. Furthermore, one[13] of two[13 26] studies found that patients with a history of angina, a condition with a similar underlying pathology to MI, had statistically increased odds of survival. The reasons for these apparent survival benefits are unclear, however it has been suggested that certain medications such as statins, routinely prescribed to patients with these conditions, may be responsible for this effect.[47–49]

The presence of prearrest comorbidity was generally associated with worse neurological outcome after OHCA. A total of 23 adjusted neurological outcome results were reported across 11[8 10–12 14 15 33 35 39 41 43] of the 29 included studies. Overall, 56% (13/23) of these adjusted results showed that individuals with prearrest comorbidity had statistically poorer neurological outcomes while no results reported statistically positive neurological outcomes. Of the remaining 10 non-significant results, 80% (8/10) had point estimates indicating reduced neurological outcome. As with survival, we found similar variation in results between studies. When looking at cumulative comorbidity burden using CCI there was no corresponding pattern between increasing CCI and increasing odds of poorer neurological outcome. Furthermore, there was greater variation in results between studies examining neurological outcome by corresponding CCI level (figure 4) than for survival. We suspect this discrepancy could be explained by the fact that CCI is a mortality risk indicator[45] and therefore may be ineffective in assessing the effect of comorbidity burden on neurological outcomes.

Limitations

Limitations of included studies

A number of limitations within the studies included in this review were identified. First, a large proportion of studies did not stipulate specific health conditions, instead using broad descriptors such as 'heart history' or 'respiratory disease'. This ultimately made it difficult to interpret results, since many different diseases could fall within those broad descriptions. Second, many of the included studies did not adequately quantify the severity of the comorbidities within their cohorts. This was particularly noteworthy in conditions that can have a large range of physiological presentations and mortality risks such as diabetes or liver disease. Some studies did attempt to account for this. Some dichotomised conditions by severity, such as those that stratified diabetes as either 'diabetes' or 'diabetes with complications'.[3 38 40] One study attempted to account for comorbidity severity by using the Sequential Organ Failure Assessment scores,[35] while others adjusted for comorbidity severity using the CCI. Given the CCI was designed to predict 1 year mortality risk based on the presence of a predefined list of comorbid conditions, we believe it is an acceptable tool that assesses both the number of comorbidities and severity of those conditions and recommend its use in future studies on comorbidity and OHCA survival. Third, a number of authors only reported comorbidities that were found to be significantly associated with survival which resulted in a high risk of reporting bias. Lastly, the vast majority of studies were vague regarding the completeness of patient medical histories and/or only focused on a limited number of conditions. The use of incomplete or inaccurate patient history may result in large variability between studies as seen in patients with peptic ulcer disease (figure 2). This was identified as a major risk of bias in the majority of studies. Furthermore, three studies obtained prearrest comorbidity history from ambulance patient care record forms alone.[8 9 42] Comorbidity data from ambulance records may be ascertained by paramedics from a variety of sources including bystander reports and/or current patient medications which are likely to be inaccurate or incomplete.

A high degree of clinical heterogeneity was found between studies which is consistent with findings of other related OHCA systematic reviews.[7 50 51] A substantial source of clinical heterogeneity resulted from participant recruitment and inclusion criteria. Some studies included all participants in OHCA, while others specified eligibility criteria such as witnessed arrest or shockable initial rhythm. Others only recruited participants that reached specific resuscitation milestones such as ROSC, survival to ED or hospital admission. Furthermore, a number of studies only included patients with specific acute or chronic complications/conditions or those meeting specific eligibility criteria for clinical interventions. Ultimately, this heterogeneity made it inappropriate to compare outcomes between studies and prevented a meta-analysis from being conducted. This review highlights a clear need for a more standardised approach in reporting of comparative observational OHCA studies to enable the true effect of comorbidity on outcomes to be determined. Achieving this would require standardised patient study recruitment start and end points, consistent inclusion criteria, complete comorbidity histories and uniform statistical outcome reporting. To allow for future meta-analysis in observational OHCA studies we also suggest the development of a standardised guide for statistical adjustment for arrest and resuscitation factors.

Limitations of this review

This review had several limitations. First, while every effort was made to identify all relevant studies in our search we acknowledge that some relevant studies may have been inadvertently missed. Second, as the definition of comorbidity covers a broad range of conditions and severity, a set of criteria was developed to determine what would constitute 'comorbidity' for this review (see methods section). Where studies were vague or broad in their identification of comorbid conditions, clinical judgement was used to group conditions that we believed are the same or similar. Third, comorbidities were only included in forest plots if adjusted results were available from at least two studies that provided relevant ORs. Many studies provided results for both individual comorbid conditions as well as CCI. Ultimately this meant that the same patient populations may have been used in both results. Additionally, this review only used survival to hospital discharge/30-day survival as the measure for survival and did not report shorter or longer term outcomes.

Lastly, this review predominately utilised adjusted results to reduce the effects that patient-specific and arrest-specific resuscitation factors would have on the variability of results between studies. However, the list of adjustment factors varied greatly between studies (online supplementary table 1 and online supplementary table 2), with some only adjusting for one or two resuscitation factors while others adjusted for multiple prearrest/peri-arrest/postarrest factors. Despite this, given the clinical variability between studies we believe these results still provide a more robust representation of the effect of comorbidity than crude results alone.

CONCLUSIONS

Despite variability between studies and reported outcomes, it appears that prearrest comorbidity is generally associated with both lower survival and poorer neurological outcomes following OHCA. Survival to hospital discharge was found to be particularly negatively associated with a prearrest history of diabetes. Few studies had point estimates of a positive association between comorbidity and survival, with the most consistent result being for MI (three of four studies having point estimates of a positive association, although only one statistically significant association). There were high levels of clinical heterogeneity between studies which precluded meta-analyses of results. Given our findings, we believe using comorbidity as a prognostication tool for determining OHCA outcomes is unlikely to be useful.

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REFERENCES

1 Chamberlain D. Predictors of survival from out-of-hospital cardiac arrest. *Heart* 2010;96:1785–6.
2 Sandroni C, Cavallaro F, Callaway CW, *et al*. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: patients treated with therapeutic hypothermia. *Resuscitation* 2013;84:1324–38.
3 Salam I, Thomsen JH, Kjaergaard J, *et al*. Importance of comorbidities in comatose survivors of shockable and non-shockable out-of-hospital cardiac arrest treated with target temperature management. *Scand Cardiovasc J* 2018;52:133–40.
4 Sasson C, Rogers MA, Dahl J, *et al*. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2010;3:63–81.
5 Blom MT, Warnier MJ, Bardai A, *et al*. Reduced in-hospital survival rates of out-of-hospital cardiac arrest victims with obstructive pulmonary disease. *Resuscitation* 2013;84:569–74.
6 Hallstrom AP, Cobb LA, Yu BH. Influence of comorbidity on the outcome of patients treated for out-of-hospital ventricular fibrillation. *Circulation* 1996;93:2019–22.
7 van de Glind EMM, van Munster BC, van de Wetering FT, *et al*. Pre-arrest predictors of survival after resuscitation from out-of-hospital cardiac arrest in the elderly a systematic review. *BMC Geriatr* 2013;13:68.
8 Dumas F, Blackwood J, White L, *et al*. The relationship between chronic health conditions and outcome following out-of-hospital ventricular fibrillation cardiac arrest. *Resuscitation* 2017;120:71–6.
9 Andrew E, Nehme Z, Bernard S, *et al*. The influence of comorbidity on survival and long-term outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2017;110:42–7.
10 Beesems SG, Blom MT, van der Pas MHA, *et al*. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. *Resuscitation* 2015;94:33–9.
11 Lee MH, Fook-Chong S, Wah W, *et al*. Effect of known history of heart disease on survival outcomes after out-of-hospital cardiac arrests. *Emerg Med Australas* 2018;30:67–76.
12 Terman SW, Shields TA, Hume B, *et al*. The influence of age and chronic medical conditions on neurological outcomes in out of hospital cardiac arrest. *Resuscitation* 2015;89:169–76.
13 Larsson M, Thorén A-B, Herlitz J. A history of diabetes is associated with an adverse outcome among patients admitted to hospital alive after an out-of-hospital cardiac arrest. *Resuscitation* 2005;66:303–7.
14 Winther-Jensen M, Kjaergaard J, Nielsen N, *et al*. Comorbidity burden is not associated with higher mortality after out-of-hospital cardiac arrest. *Scand Cardiovasc J* 2016;50:305–10.
15 Iqbal MB, Al-Hussaini A, Rosser G, *et al*. Predictors of survival and favorable functional outcomes after an out-of-hospital cardiac arrest in patients systematically brought to a dedicated heart attack center (from the Harefield cardiac arrest study). *Am J Cardiol* 2015;115:730–7.
16 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
17 Perkins GD, Jacobs IG, Nadkarni VM, *et al*. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International liaison Committee on resuscitation (American heart association, European resuscitation Council, Australian and New Zealand Council on resuscitation, heart and stroke Foundation of Canada, InterAmerican heart Foundation, resuscitation Council of southern Africa, resuscitation Council of Asia); and the American heart association emergency cardiovascular care Committee and the Council on cardiopulmonary, critical care, perioperative and resuscitation. *Circulation* 2015;132:1286–300.
18 Anon. A randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods, and patient characteristics. brain resuscitation clinical trial I study Group. *Am J Emerg Med* 1986;4:72–86.
19 The Cochrane Collaboration. *Review Manager (RevMan) [Computer program]. Version 5.3*. Copenhagen: The Nordic Cochrane Centre, 2014.
20 Kang SB, Kim KS, Suh GJ, *et al*. Long-term survival of out-of-hospital cardiac arrest patients with malignancy. *Am J Emerg Med* 2017;35:1457–61.
21 Mathiesen WT, Bjørshol CA, Kvaløy JT, *et al*. Effects of modifiable prehospital factors on survival after out-of-hospital cardiac arrest in rural versus urban areas. *Crit Care* 2018;22.
22 Patel AA, Arabi AR, Alzaeem H, *et al*. Clinical profile, management, and outcome in patients with out of hospital cardiac arrest: insights from a 20-year registry. *Int J Gen Med* 2014;7:373–81.
23 Geri G, Savary G, Legriel S, *et al*. Influence of body mass index on the prognosis of patients successfully resuscitated from out-of-hospital cardiac arrest treated by therapeutic hypothermia. *Resuscitation* 2016;109:49–55.
24 Wang C-Y, Wang J-Y, Teng N-C, *et al*. The secular trends in the incidence rate and outcomes of out-of-hospital cardiac arrest in Taiwan--a nationwide population-based study. *PLoS One* 2015;10:e0122675.
25 Lai C-Y, Lin F-H, Chu H, *et al*. Survival factors of hospitalized out-of-hospital cardiac arrest patients in Taiwan: a retrospective study. *PLoS One* 2018;13:e0191954.
26 Chen Y-C, Hung M-S, Chang C-H, *et al*. Major interventions are associated with survival of out of hospital cardiac arrest patients – a population based survey. *Signa Vitae* 2017;13:108–15.10.22514/SV132.112017.17
27 Nehme Z, Nair R, Andrew E, *et al*. Effect of diabetes and pre-hospital blood glucose level on survival and recovery after out-of-hospital cardiac arrest. *Crit Care Resusc* 2016;18:69–77.
28 Beitland S, Nakstad ER, Staer-Jensen H, *et al*. Impact of acute kidney injury on patient outcome in out-of-hospital cardiac arrest: a prospective observational study. *Acta Anaesthesiol Scand* 2016;60:1170–81.

29 Bro-Jeppesen J, Kjaergaard J, Wanscher M, *et al*. Emergency coronary angiography in comatose cardiac arrest patients: do real-life experiences support the guidelines? *Eur Heart J Acute Cardiovasc Care* 2012;1:291–301.
30 Corrada E, Mennuni MG, Grieco N, *et al*. Neurological recovery after out-of-hospital cardiac arrest: hospital admission predictors and one-year survival in an urban cardiac network experience. *Minerva Cardioangiol* 2013;61:451–60.
31 de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, *et al*. Circumstances and causes of out-of-hospital cardiac arrest in sudden death survivors. *Heart* 1998;79:356–61.
32 Dickey W, Adgey AA. Mortality within hospital after resuscitation from ventricular fibrillation outside Hospital. *Heart* 1992;67:334–8.
33 Fabbri A, Marchesini G, Spada M, *et al*. Monitoring intervention programmes for out-of-hospital cardiac arrest in a mixed urban and rural setting. *Resuscitation* 2006;71:180–7.
34 Herlitz J, Ekström L, Wennerblom B, *et al*. Hospital mortality after out-of-hospital cardiac arrest among patients found in ventricular fibrillation. *Resuscitation* 1995;29:11–21.
35 Roedl K, Wallmüller C, Drolz A, *et al*. Outcome of in- and out-of-hospital cardiac arrest survivors with liver cirrhosis. *Ann Intensive Care* 2017;7:103.
36 Sharma AS, Pijls RWM, Weerwind PW, *et al*. Out-of-hospital cardiac arrest: the prospect of E-CPR in the Maastricht region. *Netherlands Heart Journal* 2016;24:120–6.
37 Søholm H, Bro-Jeppesen J, Lippert FK, *et al*. Resuscitation of patients suffering from sudden cardiac arrests in nursing homes is not futile. *Resuscitation* 2014;85:369–75.
38 Hirlekar G, Jonsson M, Karlsson T, *et al*. Comorbidity and survival in out-of-hospital cardiac arrest. *Resuscitation* 2018;133:118–23.
39 Winther-Jensen M, Kjaergaard J, Hassager C, *et al*. Cancer is not associated with higher short or long-term mortality after successful resuscitation from out-of-hospital cardiac arrest when adjusting for prognostic factors. *Eur Heart J Acute Cardiovasc Care* 2018:2048872618794090.
40 Søholm H, Hassager C, Lippert F, *et al*. Factors associated with successful resuscitation after out-of-hospital cardiac arrest and temporal trends in survival and comorbidity. *Ann Emerg Med* 2015;65:523–31.
41 Eid SM, Abougergi MS, Albaeni A, *et al*. Survival, expenditure and disposition in patients following out-of-hospital cardiac arrest: 1995–2013. *Resuscitation* 2017;113:13–20.
42 Carew HT, Zhang W, Rea TD. Chronic health conditions and survival after out-of-hospital ventricular fibrillation cardiac arrest. *Heart* 2007;93:728–31.
43 Oh SJ, Kim JJ, Jang JH, *et al*. Age is related to neurological outcome in patients with out-of-hospital cardiac arrest (OHCA) receiving therapeutic hypothermia (th). *Am J Emerg Med* 2018;36:243–7.
44 Parry M, Danielson K, Brennenstuhl S, *et al*. The association between diabetes status and survival following an out-of-hospital cardiac arrest: a retrospective cohort study. *Resuscitation* 2017;113:21–6.
45 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
46 Nolan JP, Neumar RW, Adrie C, *et al*. Post-Cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A scientific statement from the International liaison Committee on resuscitation; the American heart association emergency cardiovascular care Committee; the Council on cardiovascular surgery and anesthesia; the Council on cardiopulmonary, perioperative, and critical care; the Council on clinical cardiology; the Council on stroke. *Resuscitation* 2008;79:350–79.
47 Hung S-W, Chu C-M, Su C-F, *et al*. Effect of preceding medications on resuscitation outcome of out-of-hospital cardiac arrest. *J Investig Med* 2017;65:689–93.
48 Khoury Abdulla R, Kheder E, Yeow R, *et al*. The impact of statin therapy on survival for inhospital cardiac arrest. *J Investig Med* 2017;65:e4.
49 Rahimi K, Majoni W, Merhi A, *et al*. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. *Eur Heart J* 2012;33:1571–81.
50 Whitehead L, Perkins GD, Clarey A, *et al*. A systematic review of the outcomes reported in cardiac arrest clinical trials: the need for a core outcome set. *Resuscitation* 2015;88:150–7.
51 Shah KSV, Shah ASV, Bhopal R. Systematic review and meta-analysis of out-of-hospital cardiac arrest and race or ethnicity: black us populations fare worse. *Eur J Prev Cardiol* 2014;21:619–38.

6.5 Manuscript Appendix

Table 4. Survival to hospital discharge/30-day survival data (Supplementary Table 1).

Supplementary Table 1: Survival to hospital discharge/30-day survival following out of hospital cardiac arrest

Author	Predictor	Crude OR (95% CI)	Adjusted OR (95% CI)	Factors included in multivariate analysis
Andrew 2017	CCI = 1	0.77 (0.69, 0.87)	0.87 (0.76, 0.99)	Age, gender, witnessed status, bystander CPR, presumed cardiac aetiology, public location, initial rhythm
	CCI = 2	0.56 (0.49, 0.63)	0.80 (0.68, 0.94)	
	CCI = 3	0.37 (0.31, 0.45)	0.62 (0.50, 0.78)	
	CCI $\geq$ 4	0.29 (0.23, 0.36)	0.53 (0.41, 0.68)	
	Hypertension[a]	0.94 (0.77, 1.15)	0.96 (0.82, 1.12)	Age, gender, witnessed status, bystander CPR, presumed cardiac aetiology, public location
	Diabetes[a]	0.51 (0.42, 0.62)	0.66 (0.53, 0.81)	
	Myocardial Infarction[a]	0.81 (0.68, 0.96)	1.13 (0.92, 1.37)	
	Cerebrovascular disease[a]	0.56 (0.41, 0.77)	0.81 (0.56, 1.16)	
	Congestive heart failure[a]	0.36 (0.28, 0.46)	0.61 (0.46, 0.82)	
	COPD[a]	0.58 (0.46, 0.72)	0.75 (0.58, 0.97)	
	Metastatic cancer[a]	0.13 (0.02, 0.97)	0.71 (0.50, 1.00)	
	Cancer[a]	0.57 (0.42, 0.76)	0.81 (0.58, 1.13)	
	Dementia[a]	0.31 (0.17, 0.54)	0.81(0.44, 1.50)	
	Peripheral vascular disease[a]	0.71 (0.52, 0.98)	1.11 (0.77, 1.60)	
	Peptic ulcer[a]	1.28 (0.64, 2.56)	2.12 (0.98, 4.60)	
	HIV/AIDS[a]	4.13 (0.37, 45.6)	1.05 (0.69, 1.60)	
	Skin ulcers[a]	0.46 (0.15, 1.35)	0.79 (0.42, 1.49)	
	Renal disease[a]	0.35 (0.23, 0.53)	0.74 (0.58, 0.94)	
	Liver disease[a]	0.27 (0.08, 0.89)	0.58 (0.31, 1.10)	
	Connective tissue disease[a]	0.77 (0.4, 1.50)	0.95 (0.45, 2.00)	
	Depression[a]	0.88 (0.65, 1.20)	0.99 (0.69, 1.42)	
Blom 2013	Chronic obstructive pulmonary disease	0.4 (0.3, 0.7)[b]	0.6 (0.4, 0.99)[b]	Age, gender, CVD, OHCA public location, witness status, bystander CPR, AED use, and EMS response time
	Cardiovascular disease	0.5 (0.3, 0.7)[b]	0.8 (0.5, 1.2)[b]	Age, gender, OPD,OHCA public location, witness status, bystander CPR, AED use, and EMS response time
Bro-Jeppesen 2012	No comorbidity	0.3 (0.1, 0.6) [c,d]	0.4 (0.2, 0.8) [c,d]	Unclear

	Kidney Disease	0.75 (0.48, 1.19)	NR	
	Prior cardiac arrest	0.54 (0.19, 1.53)	NR	
	Coronary artery disease	0.68 (0.44, 0.85)	NR	
	Peripheral artery disease	0.71 (0.38, 1.32)	NR	
	Valulopathy	0.71 (0.34, 1.49)	NR	
	Hypertension	0.88 (0.70, 1.11)	NR	
	Hypercholesterolemia	1.24 (0.82, 1.88)	NR	
	Gastro-intestinal Disease	0.72 (0.49, 1.07)	NR	
	Cancer	0.28 (0.16, 0.49)	NR	
	Mental Health	0.73 (0.5, 1.07)	NR	
	HIV	NR	NR	
	Tissue/inflammatory disease	0.93 (0.44, 1.97)	NR	
Herlitz 1995[e,g]	Myocardial infarction	0.86 (0.6, 1.22)	NR	
	Angina Pectoris	0.85 (0.59, 1.21)	NR	
	Hypertension	0.91 (0.61, 1.36)	NR	
	Diabetes	0.45 (0.26, 0.79)	0.29 (0.1, 0.85)[h]	Clinical history, chronic medication, Interval time to defibrillation, bystander CPR, time of day, nurse present, no of shocks, and status on admission.
	Congestive heart failure	0.6 (0.41, 0.87)	NR	
	Cerebrovascular Disease	0.49 (0.27, 0.87)	NR	
	Asthma	0.61 (0.29, 1.31)	NR	
Hirlekar, 2018	CCI = 0-2 (ref)	NR	Reference	Year of OHCA, age, gender, initial rhythm, location, bystander CPR, mechanical chest compression, aetiology, adrenalin treatment, intubation and anti-arrhythmic medications, time to CPR, and EMS response time.
	CCI = 3-4	NR	0.85 (0.66, 1.09)[a,b]	
	CCI = 5-6	NR	0.62 (0.42, 0.92)[a,b]	
	CCI > 6	NR	0.54 (0.32, 0.88)[a,b]	
	Myocardial Infarction	NR	0.91 (0.73, 1.13)[a,b]	
	Congestive heart failure	NR	0.85 (0.68, 1.06)[a,b]	
	Peripheral vascular disease	NR	1.00 (0.71, 1.37)[a,b]	
	Cerebrovascular disease	NR	0.82 (0.61, 1.09)[a,b]	
	Dementia	NR	0.37 (0.19, 0.70)[a,b]	

	Chronic pulmonary disease	NR	0.85 (0.64, 1.14)[a,b]	
	Connective tissue disease/rheumatic	NR	0.82 (0.51, 1.34)[a,b]	
	Peptic ulcer disease	NR	0.62 (0.33, 1.14)[a,b]	
	Liver disease (mild)	NR	0.71 (0.39, 1.27)[a,b]	
	Diabetes	NR	0.63 (0.49, 0.80)[a,b]	
	Diabetes (with complications)	NR	0.69 (0.49, 0.99)[a,b]	
	Paraplegia/Hemiplegia	NR	0.7 (0.32, 1.52)[a,b]	
	Renal Disease	NR	0.5 (0.34, 0.75)[a,b]	
	Cancer	NR	1.00 (0.77, 1.31)[a,b]	
	Metabolic Disease	0.55 (0.29, 1.04)	NR	
Kang 2017	Cancer	0.78 (0.38, 1.59)	NR	
Larsson 2005	Diabetes	NR	0.57 (0.39, 0.80)	Age, history of myocardial infarction, angina pectoris, hypertension and heart failure, cardiac arrest aetiology.
	Angina Pectoris	NR	1.3 (1.01, 1.7)	Age, history of myocardial infarction, diabetes, hypertension and heart failure, cardiac arrest aetiology.
	Myocardial infarction	NR	1.3 (1.00, 1.7)	Age, history of diabetes, angina pectoris, hypertension and heart failure, cardiac arrest aetiology.
Lee 2018	Heart disease	1.16 (1.03, 1.30)	0.76 (0.58, 1.00)	Age >65, gender, number of comorbidities, location, witnessed status, initial rhythm, bystander CPR, pre hospital defibrillation, pre hospital advanced airway, time of call, and EMS response time.
	Heart disease[a]	0.69 (0.57, 0.84)	0.67 (0.47, 0.95)	
	0 comorbidity	Reference	Reference	
	1 comorbidity	0.71 (0.58, 0.87)	1.04 (0.46, 2.35)	
	2 comorbidity	0.62 (0.48, 0.80)	0.92 (0.41, 2.09)	
	3 comorbidity	0.47 (0.25, 0.90)	0.97 (0.42, 2.25)	
Parry, 2017	Diabetes	0.70 (0.60, 0.83)	0.88 (0.72, 1.06)[a]	Age, gender, witness status, location, bystander CPR, initial arrest rhythm and aetiology of arrest.
Salam 2018	CCI ≥ 1	1.68 (1.23, 2.30)[a,c]	0.82 (0.55, 1.23)[a,c]	Age, gender, witnessed arrest, bystander CPR, EMS response time, and time to ROSC

Sharma 2016	Diabetes	0.58 (0.27, 1.25)	NR	
	Hypertension	0.95 (0.52, 1.73)	NR	
	Dyslipedaemia/Cardiovascular conditions	0.89 (0.42, 1.91)	NR	
	Cerebrovascular accident	0.77 (0.21, 2.81)	NR	
	Congestive heart failure	0.35 (0.13, 0.91)	NR	
	Myocardial infarction	0.71 (0.38, 1.33)	NR	
Søholm 2014	CCI	1.28 (1.20, 1.38)[c]	1.15 (1.06, 1.25)[c]	Age, gender, rhythm, bystander CPR, EMS response time, time to ROSC, CCI, witnessed status, cardiac aetiology, and therapeutic hypothermia
Søholm 2015	Cerebrovascular disease	0.49 (0.32, 0.73)	NR	
	Congestive heart failure	0.85 (0.61, 1.17)	NR	
	Diabetes	0.59 (0.39, 0.87)	NR	
	Diabetes (with complications)	0.56 (0.35, 0.91)	NR	
	Hemiplegia	0.73 (0.18, 2.92)	NR	
	Ischemic heart disease	0.76 (0.55, 1.04)	NR	
	Liver disease (mild)	0.48 (0.17, 1.33)	NR	
	Liver disease (moderate/severe)	0.73 (0.07, 8.06)	NR	
	Renal disease (moderate/severe)	0.89 (0.49, 1.59)	NR	
	Peptic ulcer	0.76 (0.43, 1.34)	NR	
	Peripheral vascular disease	0.54 (0.27, 1.09)	NR	
	Rheumatologic disease	0.73 (0.25, 2.14)	NR	
Winther-Jensen 2018	Cancer	1.35 (1.07, 1.71)[c]	0.98 (0.76, 1.27)[c]	Age, CCI≥3, gender, initial rhythm, time to ROSC, and witness status.

a. Shockable rhythm
b. 30 day survival outcome
c. Data presented as 30 day mortality Hazard Ratio's (HR)
d. Patients subgroup had underlying STEMI
e. All patients with initial rhythm of VF
f. Data presented as mortality Hazard Ratio's (HR)
g. Cohort admitted to hospital alive
h. Results converted to survival OR

Table 5. Neurological outcome data (Supplementary Table 2).

Supplementary Table 2: Good neurological outcome (CPC 1-2) following out-of-hospital-cardiac-arrest

Author	Predictor	Period post cardiac arrest	Crude OR (95% CI)	Adjusted OR (95% CI)	Factors included in multivariate analysis
Beesems 2015	CCI ≥ 4	Discharge	0.54 (0.25, 1.13)[a]	0.71 (0.28, 1.80)	Age, gender, initial rhythm, witnessed arrest, bystander CPR, AED applied to patient, and time to defibrillator application.
Beitland 2016[a]	Diabetes, type II	6 months	2.61 (0.75, 9.16)[b]	NR	
	Hypertension		1.67 (0.74, 3.78)[b]	NR	
Blom 2013[c]	Obstructive pulmonary disease	Discharge	1.23 (0.28, 5.45)[a]	NR	
Corrada 2013	Heart Disease	Discharge	0.24 (0.07, 0.83)	NR	
Dumas 2017[e]	CCI = 0	Discharge	Reference	Reference	Age, gender, response time, location, witnessed arrest and bystander CPR.
	CCI = 1	Discharge	NR	0.66 (0.47, 0.94)	
	CCI = 2	Discharge	NR	0.52 (0.37, 0.74)	
	CCI = 3	Discharge	NR	0.38 (0.26, 0.55)	
Eid 2016[e]	CCI = 0	Discharge	Reference	Reference	Age, gender, race, primary payer, patient income, time of arrest, initial rhythm, and hospital characteristics.
	CCI = 1	Discharge	1.03 (0.98, 1.08)[f]	0.92 (0.86, 0.99)[f]	
	CCI = 2	Discharge	1.03 (0.98, 1.09)[f]	0.90 (0.84, 0.97)[f]	
	CCI = 3	Discharge	1.01 (0.94, 1.08)[f]	0.99 (0.90, 1.08)[f]	
	CCI ≥ 4	Discharge	0.83 (0.78, 0.90)[f]	0.87 (0.79, 0.97)[f]	
Fabbri 2006[g,n]	Hypertension	Discharge	0.38 (0.17, 0.86)	0.34 (0.14, 0.83)	Age, gender, comorbidity, seasonality, day/week, time, urban setting, home location, EMS response time, initial rhythm.
	Diabetes	Discharge	0.36 (0.16, 0.82)	NR	
	Congestive heart failure	Discharge	0.04 (0.03, 0.31)	0.37 (0.14, 0.99)	
	Myocardial infarction	Discharge	0.28 (0.11, 0.72)	0.40 (0.16, 1.00)	
	Diabetes	12 months	NR	0.30 (0.10, 0.91)	
	Congestive heart failure	12 months	NR	0.06 (0.01, 0.50)	
	Myocardial infarction	12 months	NR	0.05 (0.01, 0.49)	

Iqbal 2015[h]	CCI	Discharge	NR	0.71 (0.55, 0.91)[i]	CCI, cardiogenic shock, shockable as initial rhythm, bystander CPR, adrenaline administration, duration of resuscitation, Intra-aortic balloon pump use, and inotrope use.
Kang 2017	Cancer	Discharge	0.67 (0.13, 3.44)	NR	Age, gender, witnessed cardiac arrest.
Lee 2018[n]	Heart Disease	Discharge	1.44 (1.22, 1.69)	0.81 (0.55, 1.18)	Age >65, gender, number of comorbidities, location, witnessed arrest, initial rhythm, bystander CPR, pre hospital defibrillation, pre hospital advanced airway, time of call, time to EMS arrival.
	Heart disease	Discharge	0.95 (0.71, 1.28)[k]	1.30 (0.64, 2.61)[k]	
Oh 2018	Non-Diabetic	6 months	NR	15.21 (1.85, 125.3)	Unclear
Parry, 2017[j]	Diabetes	Discharge	0.70 (0.43, 1.14)	NA	
Roedl 2017	CCI = 1	6 months	NR	0.97 (0.84, 1.12)	Liver cirrhosis, age, gender, OHCA, witnessed arrest, time to ROSC, presence of shockable rhythm, cardiac cause of CA, mechanical ventilation, SOFA on admission, initiation of MTH, cumulative adrenaline dosage.
	Cirrhosis	6 months	0.26 (0.13, 0.53)	0.13 (0.04, 0.36)	Comorbidity, age, sex, OHCA, witnessed CA, time to ROSC, presence of shockable rhythm, cardiac cause of CA, mechanical ventilation, SOFA on admission, initiation of MTH, cumulative adrenaline dosage.
Terman 2015[n]	CCI	Discharge	0.88 (0.79, 0.99)	1.0 (0.87, 1.2)	Initial rhythm, witnessed arrest, bystander witnessed, bystander CPR, sex, arrest aetiology, mild therapeutic hypothermia treatment, cardiac catheterization and age.
	CCI		0.79 (0.66, 0.94)[k]	0.89 (0.7, 1.1)[k]	
	Myocardial infarction		1.4 (0.8, 2.5)	NR	
	Congestive cardiac failure		0.8 (0.4, 1.6)	NR	
	Peripheral vascular disease		0.9 (0.3, 3.1)	NR	
	Cardiovascular disease		0.8 (0.4, 1.9)	NR	
	Chronic pulmonary disease		1.5 (0.9, 2.6)	NR	
	Mild liver disease		0.8 (0.1, 7.0)	NR	
	Diabetes		0.6 (0.3, 1.1)	NR	
	Hemiplegia		1.7 (0.2, 16)	NR	
	Renal disease (moderate-severe)		0.6 (0.2, 1.6)	NR	
	Diabetes with end organ damage		0.8 (0.2, 2.9)	NR	

	Cancer		0.6 (0.3, 1.1)	NR	
	Liver disease (moderate-severe)		0.4 (0.05, 2.9)	NR	
	Metastatic cancer		0.3 (0.04, 2.0)	NR	
Winther-Jensen 2016[l]	mCCI=1	6 months	NR	0.81 (0.35, 1.79)	Sex, age, primary rhythm, location of arrest, witnessed arrest, STEMI, time to ROSC and bystander CPR.
	mCCI=2		NR	2.21 (0.85, 5.39)	
	mCCI ≥ 3		NR	0.74 (0.11, 3.01)	
Winther-Jensen 2018[m]	Cancer	Discharge	NR	1.16 (0.47, 3.32)	Age, CCI≥3, sex, initial rhythm, time to ROSC, witnessed arrest.

a. Cohort consisted of patients admitted to hospital with GCS<8
b. Reference category: patients who do not have predictor
c. Neurological outcome conditional on all patients being discharged from hospital alive
d. Conditioned on cohort being admitted to hospital alive.
e. Cohort had initial rhythm of VF
f. Neurological outcome considered good if patient was not comatose, did not sustain permanent anoxic brain injury and not discharged in permanent vegetative state
g. Conditioned on cohort being admitted to ICU.
h. Conditioned on cohort admitted to the emergency department alive.
i. Neurological outcome assessed using modified Rankin Scale (mRS) and were favourable outcome was mRS-3⁺
j. Neurological outcome assessed using modified Rankin Scale (mRS) and were favourable outcome was mRS-2⁺
k. Shockable initial rhythm
l. Cohort conditioned on those admitted to the ICU with ROSC
m. Conditioned on cohort being successfully resuscitated by emergency medical services.
n. In cases where two variants of same measure are given (i.e. neurological outcome at discharge vs 6 months or shockable vs non shockable rhythm) only one result chosen for analysis to avoid duplication of results.

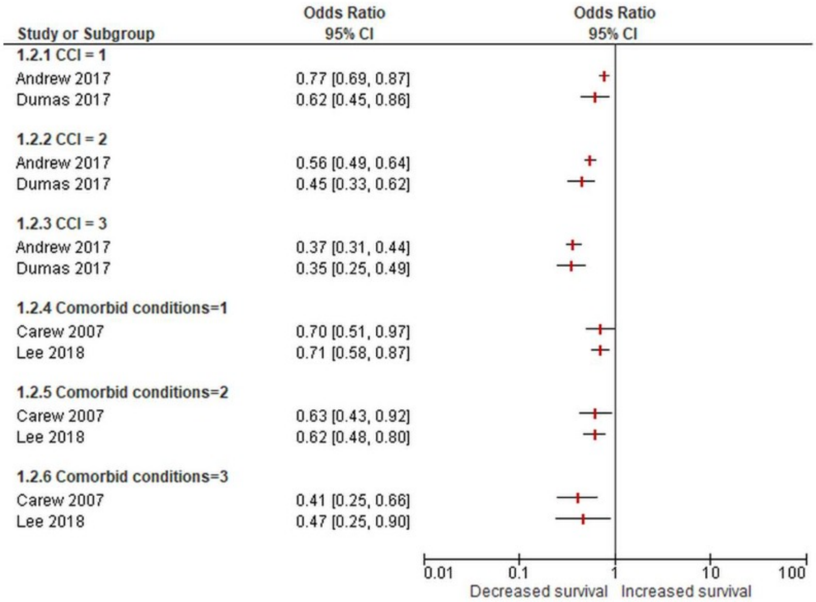
Table 6. Newcastle-Ottawa quality assessment scale for cohort studies (Supplementary Table 3).

Supplementary Table 3: Newcastle-Ottawa quality assessment scale for cohort studies.

		Andrew 2017	Beesems 2015	Beitland 2016	Blom 2013	Bro-Jeppesen 2012	Carew 2007	Chen 2017	Corrada 2013	De Vreede-Swagemaker 1998	Dickey 1992	Dumas 2017	Eid 2017	Fabbri 2006	Herlitz 1995	Hirlekar 2018	Iqbal 2015	Kang 2017	Larsson 2005	Lee 2018	Oh 2018	Parry 2017	Roedl 2017	Salam 2018	Søholm 2015	Terman 2015	Winther-Jensen 2016	Winther-Jenson 2018	Sharma 2016	Søholm 2014
Selection	Representativeness of the exposed cohort[a]	*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-	-	*	-	-	-	-	-
	Selection of the non-exposed cohort[b]	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Ascertainment of exposure[c]	-	*	-	*	-	-	*	-	*	-	-	*	-	-	*	*	*	*	-	-	-	-	*	*	-	-	*	-	-
	Demonstration that outcome of interest was not present at start of study[d]	*	-	-	*	*	*	*	-	*	*	*	-	-	*	*	-	*	*	*	-	*	-	*	*	-	-	*	*	*
Comparability	Comparability of cohorts on the basis of the design or analysis[e]	-	-	-	**	-	*	-	-	-	-	*	-	-	-	**	-	-	-	**	-	-	-	-	-	-	-	-	-	**
Outcome	Assessment of outcome[f]	*	-	-	*	*	*	*	-	*	*	*	-	-	*	*	-	*	*	*	-	*	-	*	*	*	-	*	*	*
	Was follow-up long enough for outcomes to occur[g]	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	Adequacy of follow-up of cohorts[h]	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*

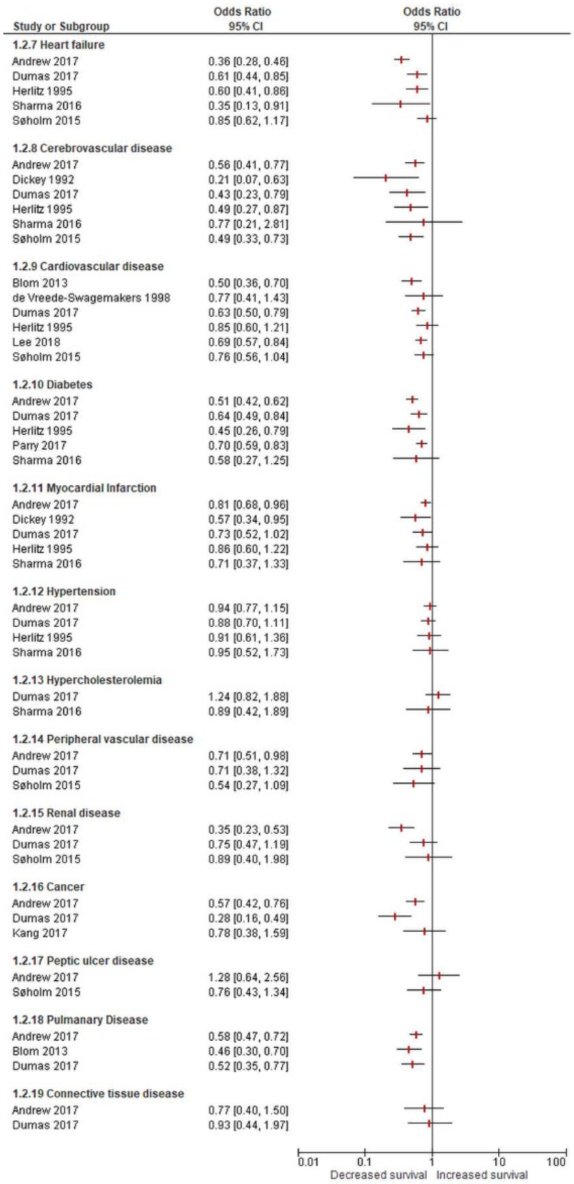
a. Awarded single star if cohort included all OHCA patients and did not restrict cohort (i.e to initial cardiac rhythm, conditional survival or age)
b. All studies awarded one star as comorbidity was random and not pre-defined.

c. Awarded one star if comorbidity was likely ascertained from source preceding arrest (i.e. not simply determined during incident of arrest)
d. Awarded one star for all articles looking at survival as death could not be present before arrest.
e. Awarded one star if model adjusted for: Age, gender, initial arrest rhythm, witness status, by-stander cpr and EMS response time. Additional star awarded to any additional adjustments.
f. Awarded one star if outcome is survival to hospital discharge or 30 day survival or for neurological outcome one star was awarded if assessment was carried out by health professional.
g. One star awarded if outcome assed to discharge or 30-days.
h. One star awarded if loss to follow-up was less than 5%.



Supplementary figure 1. Forest plot showing unadjusted odds ratios of individual comorbidities on survival to hospital discharge.

Figure 7. Forest plot showing unadjusted odds ratios of individual comorbidities on survival to hospital discharge (Supplementary Figure 1).



Supplementary figure 2: Forest plot showing unadjusted odds ratios of comorbidity burden on survival to hospital discharge.

Majewski D, *et al. BMJ Open* 2019; 9:e031655. doi: 10.1136/bmjopen-2019-031655

Figure 8. Forest plot showing unadjusted odds ratios of comorbidity burden on survival to hospital discharge (Supplementary Figure 2).

6.6 Update of Literature Review

The initial literature search strategy identified eligible studies up to the 31st of December, 2018. To update this review with recent literature, I re-ran the search strategy to identify any additional studies from the last run date (31st December, 2018) to the 31st December 2021. The search identified four eligible studies which are outlined in Table 7 below.

Table 7. Characteristics of studies identified in the updated search that examine pre-arrest comorbidity and OHCA outcomes.

Study ID	**Country**	**Study Design**	**Cases**	**Enrolment Period**	**Reported Outcome**	**Comorbidity**	**Source of comorbidity data**	**Inclusion Criteria**	**Age (years)**
Jung et al 2019*	South Korea	Cross-sectional	11,610	2012 – 2016	Survival to hospital discharge, neurological outcome (CPC)	Hypertension	Medical record review	All EMS treated of presumed cardiac aetiology that survived to hospital admission.	≥ 19
Mohr et al 2020*	Denmark	Retrospective cohort	28,955	2001-2014	30-day survival	Diabetes	Danish National Patient Registry	All OHCA of presumed cardiac origin that had EMS or bystander attempted CPR.	≥ 18
Dumas et al 2021	France	Prospective cohort	777	Jan 2012 – Sep 2017	Early mortality at hospital discharge	CCI=1-3, CCI ≥ 4	Prospectively collected during ICU stay	All non-traumatic OHCA who achieved ROSC and were admitted to a French cardiac arrest-receiving centre	Adults
Van Dongen et al. 2021 *	North Holland province, Netherlands	Retrospective cohort	3760	2010-2016	Survival to hospital discharge	Heart disease	Patients general practitioner	All EMS-attended OHCA of presumed cardiac origin	≥ 18

The studies listed in Table 7 all investigated the association between comorbidity and OHCA outcome, however they differed with respect to cohort definition, assessment of comorbidity burden, reported outcome and statistical analysis. The study by Jung et al.[108] recruited OHCA patients who survived to hospital admission and reported on the association between pre-arrest hypertension and both, survival outcome (STHD) and neurological outcome (defined as CPC of 1 or 2). Jung et al.[108] found that hypertension was associated with increased odds of both STHD (adjusted Odds Ratio (aOR) 1.13; 95% confidence interval (CI), 1.01-1.27) and good neurological outcome (aOR 1.18; 95% CI: 1.04-1.35) after adjusting for confounding factors and other co-morbidities (diabetes, chronic heart disease, chronic renal disease). The authors concluded that a pre-arrest history of hypertension appeared to be a prognostic factor for positive OHCA outcomes.[108] Although the authors of this study were unable to explain the reason for this finding, they speculated that patients with a history of hypertension may be more aware of ischemic heart symptoms and therefore alert EMS services sooner.

The study by Mohr et al.[109] recruited all OHCAs, with an EMS attempted resuscitation or bystander CPR, and investigated the association between pre-arrest diabetes and 30-day OHCA survival. The patient cohort in this study could potentially have some overlap with that of an earlier study[13] (also reporting on diabetes) included in the systematic review (small potential overlap in study region and study period). However, the earlier study only provided unadjusted results for the effects of diabetes on mortality. The authors[109] reported that pre-arrest diabetes was significantly associated with reduced 30-day OHCA survival in both, the crude (aOR 0.56; 95% CI, 0.49-0.64) and adjusted (adjusted for prehospital factors and other comorbidities) models (aOR 0.56; 95% CI, 0.48-0.65).

The study by Dumas et al.[110] recruited all non-traumatic OHCA, who achieved ROSC, and were admitted to a cardiac arrest receiving centre. This study, reporting on the association between pre-arrest comorbidity (assessed using the CCI) and early mortality at hospital discharge, found that a CCI of 1-3 and a CCI $\geq$ 4 were both associated with significantly higher mortality at hospital discharge (compared to a CCI of 0). The authors also reported that only chronic obstructive pulmonary disease (of all component conditions assessed by CCI) was independently associated with a significantly higher risk of mortality. This study also reported that comorbidity burden was associated with poorer neurological outcomes, however the authors did not provide any data supporting this finding in the manuscript.

Lastly, the study by Van Dongen et al.[111] recruited all EMS attended OHCA of presumed cardiac aetiology and reported the association between pre-arrest heart disease and STHD. This study also had a potential cohort overlap (patients aged $\geq$ 70 years) with an earlier study[112] included in my systematic review, however the earlier study only reported on neurological outcomes while this study reported only survival outcomes. Van Dongen et al.[111] reported that although a pre-arrest diagnosis of heart disease was associated with increased odds of surviving to hospital admission, there were no significant associations with survival to hospital discharge in either the crude (Odds Ratio (OR) 0.96; 95%, 0.82-1.11) or adjusted (aOR 1.09; 95% CI, 0.90-1.32) models.

The four[108-111] new studies identified in the updated literature search appear congruent with the earlier findings of the published systematic review, namely that; i) a pre-arrest history of diabetes or a CCI $\geq$ 1 are generally associated with poorer OHCA survival and, ii) a pre-arrest history of heart disease tends not to be significantly associated with OHCA survival. Finally, these four studies display the same substantial clinical heterogeneity as the studies included in my original systematic review.

6.7 Summary of Chapter Findings

- There is weak evidence to suggest that overall, pre-arrest comorbidity may be associated with reduced survival and poorer neurological outcomes.

- Overall, a pre-arrest history of diabetes was generally associated with reduced OHCA survival, while a pre-arrest history of heart disease was generally not associated with OHCA survival.

- There was substantial clinical heterogeneity between the included studies in relation to: patient recruitment, inclusion criteria, outcome measures and statistical methods utilized for analysis.

Chapter 7 Measuring OHCA Survival Outcomes

7.1 Overview

This chapter explores the equivalence of two commonly reported OHCA survival outcomes; STHD and 30-days survival. The findings of this study are reported in an article published in the peer review journal Resuscitation. This article is presented in section 7.4.

> ***Majewski D**, Ball S, Bailey P, McKenzie N, Bray J, Morgan A, Finn J. Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies. Resuscitation. 2021;166:43-8.*

7.2 Background and Rationale

The 2015 'Utstein Resuscitation Registry Template for OHCA' recommends OHCA registries report patient survival outcome as either STHD, or alternatively 30-day survival.[25] As a result, these two outcomes are considered to have a de facto equivalence, with many studies combining the two outcomes.[17-19] However, to date, no studies have assessed the true equivalence of these survival outcomes, nor have they explored the potential benefits or pitfalls of either metric. As the WA OHCA Registry routinely records both STHD and 30-day survival, the aim of this chapter was to examine the equivalence of these two survival outcomes in the context of the WA OHCA database.

7.3 Methodology

<u>Study design</u>:

To address the research aims of this chapter, I conducted a population-based, retrospective cohort study of patients who experienced an EMS-attended OHCA (of any aetiology in Perth, WA), between the 1st of January 1999 and the 31st of December 2018. To be included in the study patients had to have: received either an EMS attempted resuscitation or bystander AED shock and been transported (by EMS) and admitted to a hospital ED (with either a ROSC or CPR in progress). The rational for only including those patients transported to the ED (with either ROSC or CPR in progress) was to ensure that all patients within the study cohort would have been eligible to receive a 'survival-to-hospital discharge' status (i.e. yes/no). The outcomes of interest were 30-day survival, and STHD. The study cohort was sourced from the WA OHCA registry.

Statistical Analysis:

To test the equivalence of the two survival metrics (i.e. STHD and 30-day survival), both the 'agreement' (i.e. concordance) and systematic bias,[113] were assessed. The agreement (reported as a percentage) refers to how often the two survival metrics, STHD and 30-day survival, agreed on the 'survival status' (i.e. survived/died) for each individual patient. The systematic bias refers to any intrinsic bias in either of the survival metrics that potentially favours reporting one survival status (i.e. survived or died) over the other. This type of bias is particularly important in this study as the two survival metrics (STHD and 30-day survival) actually assess different survival milestones, opening the possibility that one metric may indeed favour one type of outcome. The systematic bias was assessed using McNemar's test with a significant p-value indicating the presence of bias (i.e. p-value < 0.05).[113, 114] Lastly, the characteristics of discordant cases were explored by tabulating discordant cases against a range of demographic and peri-arrest factors.

7.4 Manuscript

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Short paper

Survival to hospital discharge is equivalent to 30-day survival as a primary survival outcome for out-of-hospital cardiac arrest studies

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Abstract

Aim: The 2015 Utstein guidelines stated that 30-day survival could be used as an alternative to survival to hospital discharge (STHD) as the primary survival outcome in out-of-hospital cardiac arrest (OHCA) studies. We sought to ascertain the equivalence (concordance) of these two survival outcome measures.

Methods: We conducted a population-based retrospective cohort study of OHCA patients who were attended by St John Western Australia (SJ-WA) paramedics in Perth, WA between 1999 and 2018. OHCA patients were included if they received either an attempted resuscitation by SJ-WA or bystander defibrillation; were a resident of WA; and were transported to a hospital emergency department (ED). STHD was determined through hospital record review and 30-day survival via the WA Death Registry and cemetery registration data.

Results: The study cohort comprised a total of 7953 OHCA patients, predominantly male (70%), with a median (IQR) age of 63 (46–77 years), a presumed cardiac arrest aetiology (78.9%), and the majority occurred in a private residence (66.8%). Survival rates were identical for STHD and 30-day survival, with both being (13.78%, 95% CI: 13.02–14.54%) (p = 0.99). The overall concordance between the two survival rates was 99.6%. There were only 30 (0.4%) discordant cases in total: 15 cases with STHD-yes but 30-day survival-no; and 15 cases with STHD-no but 30-day survival-yes.

Conclusion: We found that STHD and 30-day survival were equivalent survival metrics in our OHCA Registry. However, given potential dierences in health systems, we suggest that 30-day survival is likely to enable more reliable comparisons across jurisdictions.

Keywords: Out-of-hospital cardiac arrest Survival to hospital discharge 30-day survival Registry

Introduction

Standardisation of definitions for reporting survival outcomes after out-of-hospital cardiac arrest (OHCA) is necessary to enable meaningful comparisons between studies and across different jurisdictions.[1–3] The first version of the guidelines for uniform reporting of OHCA data and the "Utstein Style Reporting Template" were produced in 1991 by an International Taskforce of resuscitation experts.[4] Whilst acknowledging that the best outcomes to report might differ between various systems and locations, the Taskforce specified 'discharged alive (yes/no)' and 'alive at 1 year (yes/no)' as core clinical outcomes.[4] Subsequent iterations in 2004[5] and 2015[6] by the International Liaison Committee on Resuscitation

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(ILCOR)[7] saw 'survival to hospital discharge' (STHD) remain as a core outcome, but 1-year survival became a supplementary outcome. The 2015 Utstein guidelines,[6] for the first time, stated that 30-day survival could be used as an alternative to STHD. However, the equivalence of these two survival outcome measures is not well established.

Whilst the capture of prehospital data for OHCA registries is *relatively* straight forward for many Emergency Medical Services (EMS), especially for those using electronic patient care records, determining in-hospital mortality and longer-term survival outcomes can be more challenging. For example, if ascertainment of STHD requires manual hospital record review (e.g. by a research nurse), the salary costs can be prohibitive, especially in an EMS serving a large number of hospitals.[8] For some jurisdictions, it may be more feasible to ascertain date of death from the local death registry, thereby facilitating determination of 30-day survival. However, this relies on the completeness of the death registry data, since loss to follow-up can introduce bias.[9]

We sought to ascertain the equivalence (concordance) between STHD and 30-day survival as primary survival outcomes for OHCA; and to explore the characteristics of discordant cases. We anticipated that our study results could help inform comparisons of OHCA outcomes between jurisdictions, and more broadly inform registry science.

Methods

Study design

We conducted a population-based retrospective cohort study of OHCA patients who were attended by EMS in Perth, Western Australia (WA), between 1st January 1999 and 31st December 2018. Patients were included if: they received either an attempted resuscitation by EMS, or bystander defibrillation; were a resident of WA; and were transported to a hospital emergency department (ED). The two outcomes of interest were rates of STHD and 30-day survival.

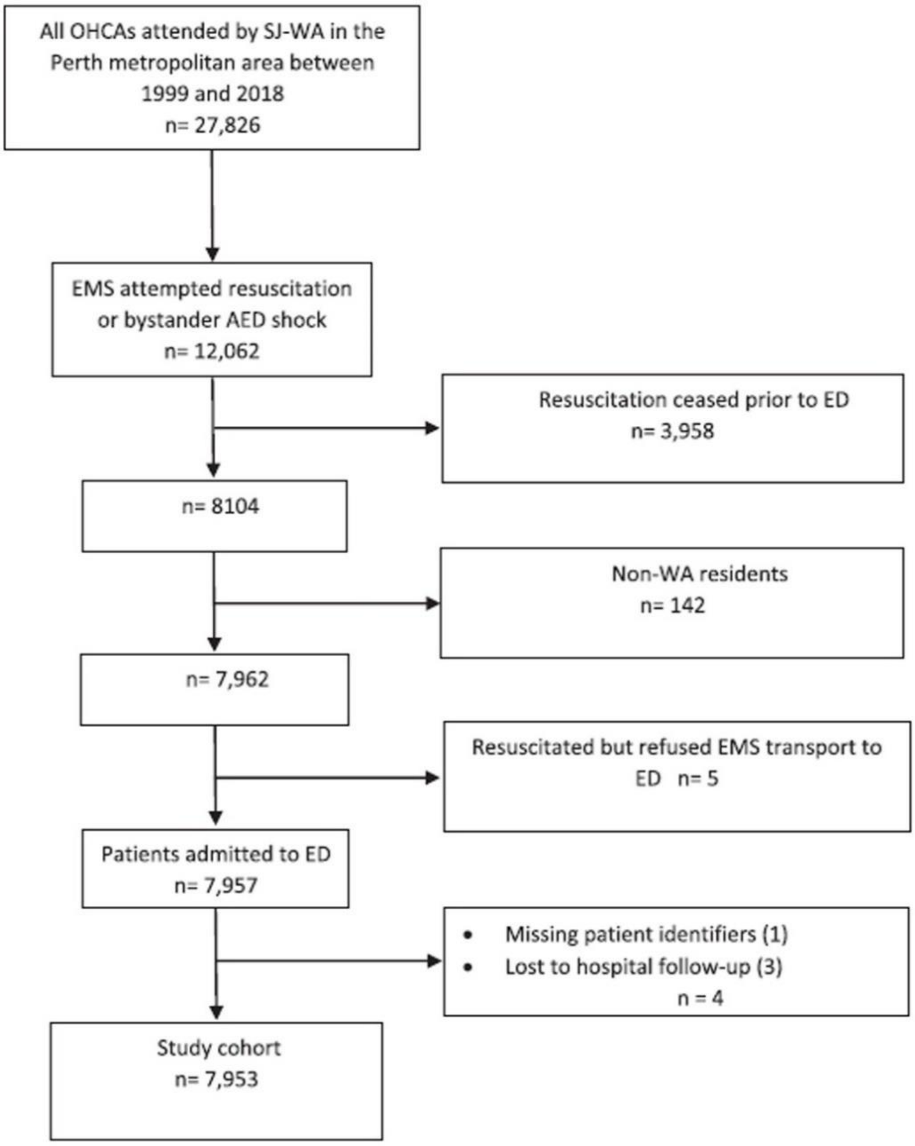

Fig. 1 – Flow diagram of study cohort.

Study setting

Perth is the capital city of WA; with an area covering 6400 square kilometres and an estimated resident population of 2.09 million at 30 June 2019.[10] St John WA (SJ-WA)[11] is the sole EMS provider in WA; and operates a single-tiered advanced life support (ALS) ambulance service, staffed by nationally registered paramedics. Within Perth, OHCA patients who are not declared dead at the scene are transported to one of nine hospital emergency departments (ED).[12]

Data sources

Data were sourced from the SJ-WA OHCA Registry[13], which is maintained by the Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU) at Curtin University. The OHCA Registry contains detailed information drawn from the SJ-WA patient care records (PCRs) and computer-aided dispatch data; including patient demographics, arrest characteristics, EMS interventions and initial survival status (ROSC, survival to ED). STHD is routinely determined by manual review of the patient's hospital record by a research nurse (NM). Thirty-day survival is primarily ascertained using the WA Death Registry;[14] with both the Metropolitan Cemeteries Board[15] database and the SJ-WA PCR being used as secondary data sources. For patients with a match in the death registry, 30-day survival is based simply on the recorded date of death, relative to the date of the arrest. Where a patient has no match in the death registry they are considered to have survived 30 days if (i) there is no indication in the ambulance PCR that the patient died in ED (i.e. in the presence of the attending paramedics) and (ii) the patient does not appear in the WA Metropolitan Cemeteries Board database with a death date recorded within 30 days of their arrest.

Statistical analysis

Baseline patient characteristics were presented as frequencies and percentages, or medians and interquartile ranges (IQR). Agreement in the overall percentage of the two survival outcome rates (STHD and 30-day survival) was tested using the McNemar test.[16] The characteristics of discordant cases were described for a range of demographic and peri-arrest factors. All statistical analyses were performed using SPSS v26 (IBM Inc., Armonk, NY, USA). Results were considered statistically significant for P values < 0.05.

Ethics

This study was approved by the Human Research Ethics Committee (HREC) of Curtin University (HR128/2013); with separate HREC approvals from each of the metropolitan hospitals for medical record review.

Table 1 – Study cohort patient characteristics.

	N = 7953	
ROSC, n (%)		
Yes	2504	(31.5)
Age, n (%)		
0–17	453	(5.7)
18–39	984	(12.4)
40–64	2672	(33.6)
65–79	2252	(28.3)
≥80	1585	(19.9)
Unknown	7	(0.1)
Sex, n (%)		
Male	5567	(70.0)
Witness status, n (%)		
Unwitnessed	3105	(39.0)
Bystander	3621	(45.5)
EMS	1217	(15.3)
Unknown	10	(0.1)
Arrest location, n (%)		
Private residence	5315	(66.8)
Public	2107	(26.5)
Aged care	531	(6.7)
Initial arrest rhythm		
VF	2823	(35.5)
VT	106	(1.3)
PEA	2458	(30.9)
Asystole	2399	(30.2)
Unknown	167	(2.1)
Bystander CPR, n (%)		
Yes	4148	(52.2)
Bystander AED shock, n (%)		
Yes	183	(2.3)
EMS response time, n (%)		
<5 min	963	(12.1)
5–10 min	4190	(52.7)
>10 min	2796	(35.2)
Missing	4	(0.1)
Aetiology, n (%)		
Presumed cardiac	6271	(78.9)
Respiratory	347	(4.4)
Drug overdose	275	(3.5)
Trauma	764	(9.6)
Malignancy	66	(0.8)
Other	230	(2.9)
Arrest year, n (%) [a]		
1999–2003	1127	(14.2)
2004–2008	1388	(17.5)
2009–2013	2286	(28.7)
2014–2018	3152	(39.6)
Hospital length of stay, Median (IQR)		
For STHD (days)	9	(4–17)
For 30-day survivors (days)	9	(4–17)

a The Perth population grew from 1.46 million in 2001 to 2.06 million in 2018, representing a 41% increase. (Australian Bureau of statistics. Population Estimates by Local Government Area, 2001 to 2020 [Cited 1st June 2021]. Available from: https://stat.data.abs.gov.au/Index.aspx?DataSetCode=ABS_ANNUAL_ERP_ASGS2016#).

Results

Between 1999 and 2018 there were 27,826 cases of OHCA attended by SJ-WA in Perth, with 12,062 patients receiving an attempted EMS resuscitation or bystander defibrillation. After applying our inclusion/exclusion criteria, 7953 cases remained (Fig. 1). Table 1 shows the baseline characteristics of the study cohort, which had a median (IQR) age of 63 years (46–77), and was predominantly: male (70%), had a presumed cardiac aetiology (78.9%), and occurred in a private residence (66.8%).

The overall percentage survival was identical for STHD and 30-day survival (13.78%, 95% CI: 13.02–14.54%) (McNemar test; $\chi^2 < 0.001$, $p = 0.999$). There were n = 30 discordant cases in total; 15 cases with STHD-yes but 30-day survival-no; and 15 cases with STHD-no but 30-day survival-yes (Supplementary Table 1). Of the 15 discordant cases where STHD-yes and 30-day survival-no, most (11/15) survived at least twice as long as their hospital length of stay;

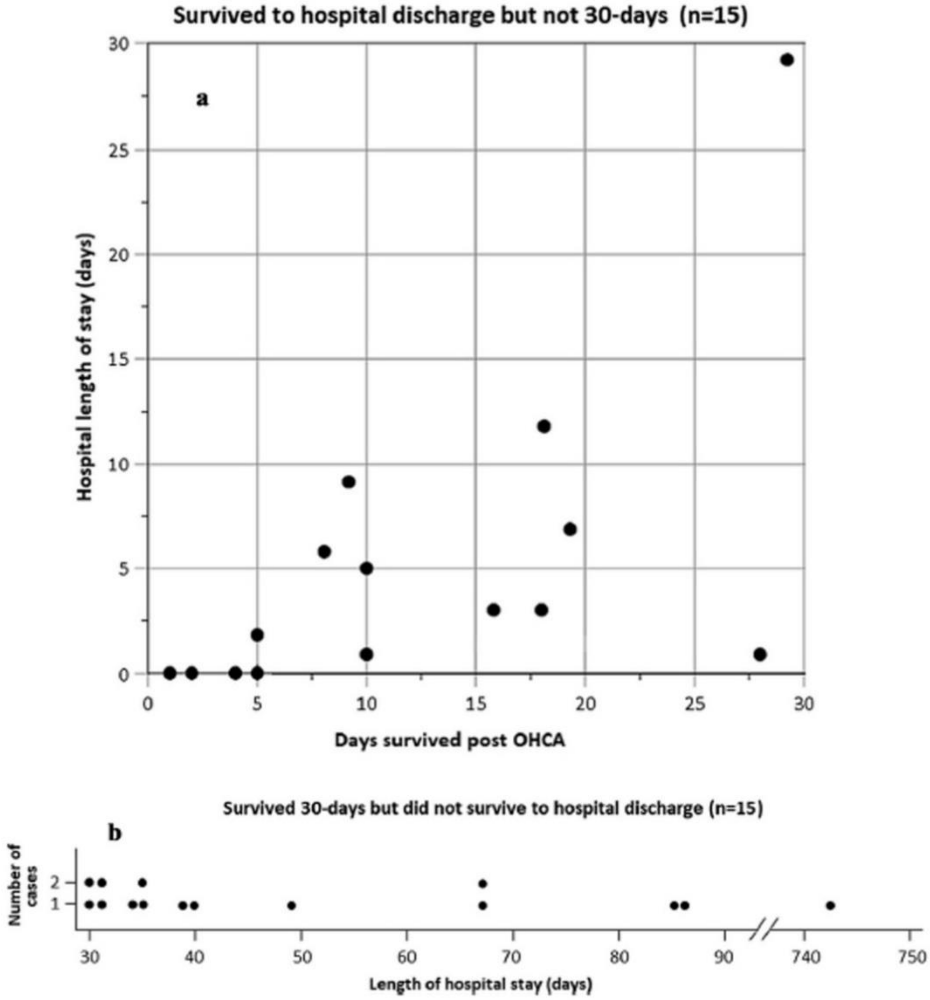

Fig. 2 – Hospital length of stay in days for the n = 30 discordant cases (a) Length of hospital length of stay and days survived post-arrest in patients who survived to hospital discharge but did not survive to 30-days. (b) Length of survival in patients who survived 30-days but who do not survive to hospital discharge.

but two patients died on the same day they were discharged (Fig. 2a). These n = 15 discordant cases (STHD-yes; 30-day survival-no) had a shorter median hospital length of stay (3 days, IQR 0–7 days) compared to the length of stay for all STHD cases overall (9 days, IQR 4–17 days). For the other n = 15 discordant cases (STHD-no; 30-day survival-yes), median survival from time of arrest was 39 days (IQR, 31–67), (Fig. 2b). Supplementary Table 2 shows the characteristics of both groups of discordant cases. Because of the small numbers involved, no statistical tests about differences between the groups were made.

Discussion

Our population-based cohort study of (n = 7953) OHCA patients transported to ED by EMS over 20 years, showed that survival-to-hospital-discharge (13.78%) and 30-day survival (13.78%) were equivalent. There were only n = 30 (0.38%) cases with discordant survival outcomes, i.e. 30 cases with different yes/no values for STHD and 30-day survival. We have established that for our OHCA Registry, it is acceptable to use either metric as the primary survival outcome.

A 2015 systematic review of OHCA randomised controlled studies (n = 141) showed that STHD was the most commonly reported survival outcome (73%);[17] with 23% reporting 1-month survival and 16% reporting 1-year survival.[17] More recently, the COSCA initiative (Core Outcome Set for Cardiac Arrest) stated that STHD and survival to 30 days were considered to be better indicators of patient survival than shorter-term outcomes, such as survival to admission.[9] However, the COSCA authors cautioned that STHD is "limited by cultural differences (whether patients are discharged home to die or die predominantly in the hospital) and health system differences (efficiency of discharge processes; whether long-term care is provided in the hospital or in home care settings)".[9] They suggested that "survival to specific intervals (e.g. 30 days) after arrest can avoid some of these limitations", enabling more robust comparisons across different health systems.[9] Notwithstanding such benefits, some OHCA Registries may not have access to the local death registry, or it may be incomplete. Furthermore, manually reviewing medical records enables the collection of additional clinical information, such as post-resuscitation care and neurological outcomes. As such, each EMS OHCA Registry will need to assess the cost/benefit/feasibility for the two options.

Limitations

Our study has some limitations. Firstly, there is a possibility that OHCA patients discharged from hospital prior to 30-days post-arrest may have died interstate (despite our exclusion of patients known to be non-WA residents). However, we previously showed (in 2009) that only 3/55 (5.5%) of the WA OHCA patients who had STHD subsequently died interstate; none of whom died within 30 days post-arrest.[18] Secondly, a total of 6 cases in the current study cohort were not identified in the WA Death Registry but were identified through the use of the Cemeteries Board database. While this is not a limitation per se, it does show that we could have missed n = 6 deaths if we relied solely on the WA Death Registry; a cautionary message for other jurisdictions. We did not report the neurological status of survivors, however we have previously shown that the majority (93%) of OHCA patients in Perth who STHD have a good cerebral performance category score (CPC 1–2) at hospital discharge.[19] Finally, we acknowledge that our results may not be applicable to other OHCA registries with different cultural backgrounds and health systems.

Conclusions

We found that STHD and 30-day survival were equivalent survival metrics in our population-based OHCA Registry. However, given potential differences in health systems, we suggest that 30-day survival is likely to enable more reliable comparisons across jurisdictions.

CRediT authorship contribution statement

David Majewski: Conceptualization, Methodology, Validation, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Stephen Ball:** Conceptualization, Methodology, Validation, Data curation, Writing - review & editing. **Paul Bailey:** Conceptualization, Writing - review & editing, Funding acquisition. **Nicole Mckenzie:** Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing. **Janet Bray:** Conceptualization, Writing - review & editing. **Alani Morgan:** Conceptualization, Data curation, Writing - review & editing. **Judith Finn:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Project administration, Supervision, Funding acquisition.

Declaration of Competing Interest

Some of the authors are affiliated with St John WA as follows: Paul Bailey (Medical Director); Judith Finn (Adjunct Research Professor & recipient of research funding); Stephen Ball (Adjunct Research Fellow).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.07.023.

REFERENCES

1. Eisenberg MS, Bergner L, Hearne T. Out-of-hospital cardiac arrest: a review of major studies and a proposed uniform reporting system. Am J Public Health 1980;70:236–40.
2. Newman MM. Comparing apples with apples: Time for a standard definition of survival from out-of-hospital cardiac arrest. Curr Emerg Cardiac Care 1990;1:3–4.
3. Eisenberg MS, Cummins RO, Larsen MP. Numerators, denominators, and survival rates: reporting survival from out-of-hospital cardiac arrest. Am J Emerg Med 1991;9:544–6.
4. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of- hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84:960–75.
5. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart

Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63:233–49.
6. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328–40.
7. International Liaison Committee on Resuscitation. About ILCOR. (updated 2021; cited 14 Feb 2021). (Available from: https://www.ilcor.org/about).
8. Becker LB, Aufderheide TP, Geocadin RG, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation 2011;124:2158–77.
9. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation 2018;127:147–63.
10. Australian Bureau of Statistics (ABS). Regional population 2018-19 financial year, 2020 (cited 12 Feb 2021). (Available from: https://www.abs.gov.au/statistics/people/population/regional-population/2018-19#capital-cities).
11. St John WA. 2019/2020 Annual Report (cited 20 Jan 21). (Available from: https://stjohnwa.com.au/docs/default-source/corporate-publications/annual-report-2019-2020-digital.pdf?sfvrsn=f762e9b2_2).
12. WA Department of Health. Emergency department live activity (updated 2021; cited 12 Feb 2021). (Available from: https://ww2.health.wa.gov.au/Reports-and-publications/Emergency-Department-activity/Data?report=ed_activity_now).
13. St John WA. Out-of-Hospital Cardiac Arrest Report, 2019 (cited 20 Jan 2021). (Available from: https://stjohnwa.com.au/docs/default-source/corporate-publications/ohca-annual-report-2019_digital.pdf?sfvrsn=da1be9b2_2).
14. WA Department of Justice. The Registry of Births, Deaths and Marriages (cited 20 Jan 21). (Available from: https://www.wa.gov.au/organisation/department-of-justice/the-registry-of-births-deaths-and-marriages).
15. The Government of Western Australia. Metropolitan Cemeteries Board (cited 14 Feb 21). (Available from: https://www.mcb.wa.gov.au/).
16. Bland M. An Introduction to Medical Statistics. 4th ed. Oxford, UK: Oxford University Press; 2015.
17. Yan S, Gan Y, Jiang N, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Critic Care (London, England) 2020;24. https://doi.org/10.1186/s13054-020-2773-2.
18. Jacobs I, Smith K, Finn J. Assessment of the accuracy of linkage of Victorian and Western Australian Ambulance out-of-hospital cardiac arrest patient records to the AIHW Australian National Death index (NDI): Report prepared for the Council of Ambulance Authorities (CAA). The University of Western Australia; 2011.
19. McKenzie N, Cheetham S, Williams TA, et al. Neurological Outcome In Adult Out-Of-Hospital Cardiac Arrest (OHCA) Patients – Not All Doom and Gloom! 11th International Spark of Life Conference, Adelaide, Australia. Australian Resusitation Council; 2017.

7.5 Manuscript Appendix

Table 8. Agreement between survival to hospital discharge and 30-day survival (Supplementary Table 1).

		30-day survival		
		Yes	No	Total
STHD	Yes	1081	15	1096 (13.78%)
	No	15	6842	6857 (86.22%)
	Total	1096 (13.78%)	6857 (86.22%)	7953 (100%)

McNemar test: Chi-square < 0.001, Asymptotic Significance p > 0.999

Table 9. Comparison of characteristics between 'types' of discordant cases (Supplementary Table 2).

	STHD = Yes; 30-day survival=No n = 15		30-day survival = Yes; STHD=No n = 15	
Bystander AED shock, n (%)				
Yes	2	(13.3)	0	(0.0)
Sex, n (%)				
Male	9	(60.0)	12	(80.0)
Initial cardiac arrest rhythm				
VF	6	(40.0)	4	(26.7)
VT	0	(0.0)	0	(0.0)
PEA	5	(33.3)	8	(53.3)
Asystole	3	(20.0)	3	(20.0)
Unknown	1	(6.7)	0	(0.0)
Arrest aetiology				
Presumed cardiac	12	(80.0)	11	(73.3)
Respiratory	2	(13.3)	1	(6.7)
Drug overdose	1	(6.7)	1	(6.7)
Trauma	0	(0.0)	2	(13.3)
ROSC				
Yes	14	(93.3)	12	(80.0)
No	1	(6.7)	3	(20.0)
Arrest witness status				
EMS witnessed	3	(20.0)	2	(13.3)
Bystander witnessed	9	(60.0)	5	(33.3)
Unwitnessed	3	(20.0)	8	(53.3)
Ambulance response time				
≤ 10 mins	12	(80.0)	11	(73.3)
>10 mins	3	(20.0)	4	(26.7)
Arrest location				
Private residence	8	(53.3)	11	(73.3)
Public	2	(13.3)	4	(26.7)
Aged or residential care	5	(33.3)	0	(0.0)
Bystander CPR				
Yes	8	(53.3)	7	(46.7)
No	7	(46.7)	8	(53.3)
Patient age group				
0-17	0	(0.0)	2	(13.3)
18-39	1	(6.7)	5	(33.3)
40-64	4	(26.7)	4	(26.7)
65-79	4	(26.7)	2	(13.3)
≥80	6	(40.0)	2	(13.3)
Arrest year				
1999-2003	2	(13.3)	1	(6.7)
2004-2008	1	(6.7)	2	(13.3)
2009-2013	2	(13.3)	7	(46.7)
2014-2018	10	(66.7)	5	(33.3)
Length of hospital stay, median days (IQR)	3	(0-7)	39	(31-67)
Overall survival, median days (IQR)	10	(5-18)	39	(31-67)

7.6 Post-hoc Comments Regarding Results

The percent agreement between the two survival metrics (STHD and 30-day survival) were found to be 99.6%. Given the very high level of agreement between the two survival metrics, as well as the large sample size (n = 7,953), statistical assessment of the agreement using Cohen's kappa coefficient was unnecessary.[115] The McNemar test, assessing the systematic bias between the two survival metrics (STHD and 30-day survival), produced a highly non-significant p-value (i.e. $p > 0.999$), suggesting there is likely no systematic bias present.

7.7 Summary of Chapter Findings

- In the WA OHCA registry, survival-to-hospital discharge, and 30-day OHCA survival were found to be highly concordant (99.6%) and therefore, could be considered equivalent survival metrics.
- There were no characteristic patterns observed in the 30 discordant OHCA cases nor any significant evidence of systematic bias between the measures.

Chapter 8 Thesis Discussion

8.1 Overview

The primary objective of this thesis was to investigate the prognostic determinants of long-term OHCA survival through an exploration of the epidemiology of OHCA in the Perth metropolitan area. This objective was addressed by five individual studies, all of which have been published in peer reviewed journals and presented in Chapters 3-7 of this thesis. In the following sections I discuss the key findings of these studies, their relation to each other, and to the overall aim of this thesis. Lastly, I discuss the limitations of my research, as well as recommendations for future research, before providing my final concluding remarks.

8.2 Discussion of Key Findings

8.2.1 Trends in OHCA survival

In Chapter 3, I analysed the temporal trends in 30-day OHCA survival in the Perth metropolitan area between 2001 and 2018. Overall, I found there was a substantial improvement in 30-day OHCA survival between 2001 and 2018. The greatest improvement was in the Utstein comparator group, where 30-day survival increased from 8.4% in 2001 to 44% in 2018; corresponding to a 5-fold improvement over an 18-year period. The upward trend in survival is not unique to Perth. A 2021 study from Taipei reported that the percentage of OHCA patients who STHD increased almost two-fold between 2008-2009 (5.4%) and 2016-2017 (10.1%).[116] In another study from Toronto (Canada), survival-to-hospital discharge doubled between 2006 (4.8%) and 2013 (9.4%).[117] In Singapore, both the overall 30-day survival, and Utstein comparator group 30-day survival increased between 2011 and 2016, from 3.6% to 6.5%, and 11.6% to 23.1% respectively.[118] Similar to the findings of my study, most studies reported substantial increase over time in the provision of bystander CPR[116-118] and bystander AED[117, 118] use, likely contributing to the improvement in survival.[117] More broadly, a 2020 systematic review[2] found that OHCA survival increased over the last 40 years, from a pooled STHD rate of 8.6% during the 1976-1999 period (based on 80 studies with a combined cohort of 4851 patients) to a pooled rate of 9.9% during the 2010-2019 period (based on 25 studies with a combined cohort of 10,483 patients).

I found the proportion of OHCA presenting with shockable rhythms has been steadily declining over time in the Perth metropolitan area. This decline is particularly concerning given the strong positive association between shockable rhythms and OHCA survival;[60] and the fact that 'programs aimed at enhancing early defibrillation, although effective, could have less benefit than anticipated'.[119] This declining trend in shockable rhythm is not unique to Perth, with several other Australian[120, 121] and international[43, 122] jurisdictions reporting similar findings.[43, 123] The reason for this trend is not well understood although several possible explanatory factors have been proposed such as: increasing patient comorbidity,[124] use of Beta blocker medicications[125] and other treatments for coronary artery disease,[126] increasing EMS response times,[127] or simply changes in patient case mix (e.g. patient age and sex).[126, 128] Although determining the reason for this change was not an objective of my thesis, I can confidently state (based on the study data) that changes in EMS response times were not a factor. In fact, EMS response times in Perth had decreased slightly over the 2001 to 2018 period.

8.2.2 Relative Long-term OHCA survival

Studies investigating the long-term survival of OHCA patients have traditionally examined survival in 'absolute' terms. However, this is open to the possibility that a component of the long-term mortality of OHCA patients is independent of the OHCA event itself. That is, some mortality is likely to be unrelated to any impacts of the OHCA event, or to the antecedents of the cardiac arrest, including any comorbidities, lifestyle factors or genetic factors that are associated with OHCA patients; but instead potentially attributable to the population background mortality. To put it simply, when we follow a cohort over time, people can die for a wide variety of reasons, some of which are independent of our factor of interest. Extending this concept to the context of temporal trends, an improvement in long-term OHCA survival over time could be partially (or even entirely) due to a change in background population mortality. For these reasons, it is important to estimate OHCA survival *relative to* the background population survival, in order to determine the mortality that is specifically associated with OHCA patients.

Between 1998 and 2017 the 10-year relative survival of initial (30-day) OHCA survivors in the Perth metropolitan area was 84% (relative to the age- and sex-matched general population); suggesting that OHCA patients who survived the initial 30 days following their arrest experienced a modest reduction in life expectancy. The mechanisms responsible for this reduction in lifespan are not apparent; and, as described above, could be due not only to the effects of the cardiac arrest itself, but potentially also attributable to a range of health factors that are associated with OHCA patients. To the best of my knowledge, my study is the first to use relative survival analysis to explore the long-term survival of OHCA patients. The only other related study was a 2018 Dutch study[129] that compared the 10-year survival of a cohort of initial OHCA survivors to the theoretical 10-year survival of an age- and sex-matched comparator group determined from Dutch census bureau data. However, this study only consisted of an older patient cohort (≥ 75 years of age) and did not indicate the statistical methods used to calculate the 'theoretical' survival of the age- and sex-matched cohort.

Looking at how long-term OHCA survival has changed over time, I found that 10-year relative survival has significantly increased, from 76% (between 1998 and 2007) to 92% (between 2008 and 2017). Importantly, long-term survival is approaching that of the general population, with the upper 95% confidence limit of the relative survival estimate for the 2008-2017 period overlapping "1" (i.e 95% CI: 0.84 to 1.00); thus suggesting that long-term survival in the 2008-2017 period is not significantly different to the age- and sex- matched general population. Although improvements in long-term OHCA survival over time have also been reported by other studies,[2, 130] these studies do not adjust for improvements in survival that potentially could have resulted from increases in the population life expectancy, ultimately limiting the inferences that could be confidently made with respect to the temporal trends. Increases in the underlying population life-expectancy can be substantial, with the ABS reporting that life expectancy in WA increased by 1.4 and 0.8 years, for males and females respectively, between 2009 and 2019.[131]

8.2.3 Prognostic Determinants of Long-term OHCA Survival

Numerous prehospital factors have been demonstrated to be important prognostic determinants of 30-day OHCA survival, including patient age, witness status, bystander CPR, arrest location, EMS response time, bystander defibrillation and initial cardiac arrest rhythm.[26, 35] Of these factors, initial presenting arrest rhythm has been shown to be most strongly associated with 30-day survival.[60] To investigate whether the 'ongoing' mortality risk identified in the relative survival study (Chapter 4) was associated with the presenting cardiac arrest rhythm - a strong predictor of 30-day survival - I explored the long-term mortality rate by initial presenting arrest rhythm in Chapter 5. As my study cohort would only include patients who had already survived 30 days, I hypothesised that the initial arrest rhythm would have no effect on longer term survival. However, this hypothesis was not supported by my results. In the first year following an OHCA, I found that patients who presented with a non-shockable arrest rhythm had a mortality hazard rate 4.1 times higher than patients who had presented with a shockable rhythm. Even after adjusting for prehospital (i.e. Utstein factors), the mortality rate remained 3.3 times higher, suggesting that the initial presenting cardiac arrest rhythm was indeed an important determinant of OHCA mortality well beyond the initial 30 days following an arrest.

There have been other studies[132] that have explored the crude associations between arrest rhythm and long-term OHCA survival. A 2022 systematic review[132] (that included my study)[133] using unadjusted results reported that compared to patients with non-shockable rhythms, those with shockable rhythms had significantly greater odds of survival in the first (based on 11 studies) to third year (based on 3 studies) following an arrest, before showing no significant difference at five years. The negative association between non-shockable arrest rhythms and long-term OHCA survival (in initial 30-day OHCA survivors) has also been reported in a 2021 study[134] by Baldi et al which explored the association of Utstein variables to long-term OHCA survival. Looking at other factors associated with long-term OHCA mortality, I only found that older age (65-79, and ≥ 80) was associated with an increased mortality rate. Curiously, looking at the mortality hazard rate graphs (Chapter 5, Figure 3), I found that after the mortality rates reduced to their minima (between years 3 and 4), the rates began to slowly increase across years 4 to 8, with the increase greatest in the unadjusted MRH model. I do not believe the upward trend in the mortality rate after year four has any association with the arrest itself, but most probably represents the increased mortality risk of advancing age taking effect as the cohort ages.

The findings of my research relating to the long-term survival of OHCA patients have several important implications. Firstly, I found that OHCA patients who survive at least 30 days following their arrest, experience a modest overall reduction in life-expectancy when compared to their age- and sex matched peers from the general population. Secondly, unlike OHCA patients who present with a shockable arrest rhythm, those that present with a non-shockable arrest rhythm continue to have a substantial ongoing risk of death 30 days after their arrest. This suggests longer-term OHCA survival (i.e. over 30 days) outcomes may present a more detailed picture of actual OHCA survival, particularly for patients who arrest with non-shockable rhythms.

8.2.4 Statistical Considerations

A novel aspect of this thesis was the use of an alternative statistical technique to investigate long-term OHCA survival. I will initially provide a brief description of the statistical method applied in this research followed by a discussion of its advantages in the context of this thesis, and more broadly in the context of OHCA research.

Initially, I had attempted to use a Cox proportional hazards regression model to explore long-term OHCA survival in relation to initial arrest rhythm. However, the assumption of proportional hazards (PH) was violated for the covariate of interest (initial cardiac arrest rhythm). To overcome this complication, I identified an alternative statistical method to perform my analysis – the Multiresolution hazard (MRH) estimator. The MRH estimator is a semi-parametric, Polya tree-based, Bayesian statistical method that can estimate hazard rates jointly with covariates of interest.[100-104] Most importantly, this method can accept covariates that do not meet the PH assumption. As the only published descriptions of this method are highly mathematical, I have developed a primer to provide a basic (heavily simplified) overview of the technique (see manuscript appendix in Chapter 5).

An important assumption of the Cox model is that PH remain constant over time.[135] Non-compliance of the PH assumption is a relatively common issue, and has been reported in other cardiac arrest studies.[136-138] Testing for the PH assumption can be achieved using a variety of techniques, such as log(−log) plots, scaled/ranked Schoenfeld residuals or by modelling time-dependent covariates in a Cox PH model.[139] In cases where PH assumptions are not met, options to satisfy the PH assumption are limited. One option is to use a Cox PH regression but stratify the analysis by the non-PH covariate. However, this option would not allow evaluation of the stratified covariate. Another option is to use a conditional Cox PH model. The application of conditional Cox PH models to overcome issues of PH non-compliance has been verified mathematically.[140] However this method requires large study cohorts with almost complete patient follow-up.[141]

Unfortunately, many researchers fail to properly adjust for, or even assess PH assumptions when using Cox PH regression. A systematic review[142] of 58 randomised control trials of pharmacological cancer treatments, reported that 19% of studies displayed non-PH. Another review which examined the reporting and testing of non-PH assumption in n=318 arthroplasty studies reported that over 20% of studies likely included a non-PH covariate in a Cox model and failed to mention the PH assumptions or even adjust for it.[143] This problem also extends to OHCA research, with several studies[144-146] utilising Cox PH models without addressing PH assumption.

8.2.5 Pre-Arrest Comorbidity and OHCA Outcomes

As previously mentioned, prehospital Utstein factors are important determinants of OHCA survival. That being said, previous studies[26, 44] have suggested that these factors may only explain about 50% of the variations in OHCA survival outcomes between different EMS jurisdictions – indicating the possibility that other less researched factors, such as patient pre-arrest comorbidity, may play pivotal role in OHCA survival. I initially had planned to undertake a retrospective cohort study using the WA OHCA Registry to explore the association between pre-arrest comorbidity and OHCA survival. However, on inspection of the WA OHCA Registry I found the reporting of comorbidity was inconsistent, with a substantial portion of cases only indicating the presence of 'unspecified' comorbidity without clarification of the type or severity. Obviously including such undifferentiated exposures in a study of comorbidity would be of little research value and excluding them would result in selection bias. Therefore, I ultimately decided to abandon this study design. Instead, I decided to undertake a systematic review of existing literature, as no review on this topic had been previously conducted.

My systematic review, exploring the associations between pre-arrest comorbidity and OHCA outcomes, allowed me to make several general observations. Firstly, the CCI appeared to be a reasonable predictor of OHCA outcomes. Specifically, increasing levels of comorbidity burden (represented by increasing CCI) were generally associated with reduced survival and poorer neurological outcomes.[147] Secondly, there tended to be more extreme variability between individual unadjusted results than in the adjusted (adjusted for a variety of prehospital factors) results. This is consistent with the notion that prehospital factors have a large effect on OHCA outcomes. Therefore, I would suggest future studies preference, where possible, the use of adjusted results and reporting of comorbidity burden using CCI.

Looking at individual comorbid conditions, I found that out of the seven studies[11, 38, 109, 148-150] reporting adjusted results for diabetes, five[11, 38, 109, 148, 149] reported significant negative associations with OHCA survival. Similarly, out of two studies[151, 152] reporting adjusted results for diabetes and neurological outcome, both studies found that diabetes resulted in a poorer neurological outcome. The negative association between diabetes and OHCA outcomes was also reported by a 2018 systematic review.[153] The other interesting finding from my systematic review was that a pre-arrest history of heart disease was generally not associated with OHCA outcomes. Although the reason for this is not known, one might hypothesise that patients with a history of heart disease (particularly with a prior myocardial infarction (MI)) are more cognisant of their increased mortality risk, and therefore less likely to ignore any warning signs. Importantly, it's possible that for some patients an OHCA may be the first sign of an undiagnosed coronary artery disease.[154, 155]

The heterogeneity between included studies was seen across several aspects of the study characteristics such as: patient recruitment and inclusion criteria, reporting outcomes, statistical analysis, and pre-arrest comorbidity definitions. As a result, a meta-analysis of individual reported results was not appropriate. In addition to the clinical heterogeneity, there was considerable variation in the methods used by individual studies to ascertain pre-arrest comorbidity status, with several studies using ambulance PCRs. The appropriateness of ascertain pre-arrest comorbidity using EMS PCR's is debatable, as arrests often occur in the presence of bystanders who may be unfamiliar with a patient's medical history.[156] Another challenge in ascertaining pre-arrest comorbidity is the determination of disease severity. A good example of this is diabetes, where the burden of disease covers a spectrum, from diabetes that is managed by diet alone to diabetes with associated end-organ damage. Obviously such differences in underlying disease severity are likely to impact on OHCA outcomes,[153] but are rarely captured in paramedic clinical records.

8.2.6 Measuring OHCA Survival

One of the most important Utstein variables for reporting in OHCA registries is survival outcome; with STHD recommended as the primary outcome and 30-day survival the alternate. The Utstein style reporting template provides two options for reporting survival outcome in recognition that for different EMS one outcome may be easier to obtain than the other. However, to the best of my knowledge, no previous studies have examined the equivalence between these two OHCA metrics. Notwithstanding this, it's clear that many previous studies[17-19] have used the metrics interchangeably. Given this, in Chapter 7, I investigated the equivalence between the survival metrics STHD and 30-day OHCA survival within the context of the WA OHCA registry. I found the recommended reporting outcomes, STHD and 30-day survival, can be considered equivalent outcome metrics. This finding has important implications, both for the global resuscitation community and for the WA OHCA registry. Firstly, as some EMSs can only report 30-day survival outcomes (possibly due to costs associated with performing hospital follow-up), the findings of this study provides some assurance that the metrics are likely comparable. Additionally, studies reporting WA OHCA survival (either STHD or 30-day survival) can be directly comparable with interstate or international studies - irrespective of whether those studies report STHD or 30-day survival.

Previous studies that have reported both STHD and 30-day survival outcomes for the same cohort of patients, have shown the overall survival percentages to be very similar. An OHCA report from Queensland, Australia, reported that in 2019, 14.4% of OHCA patients had STHD and 14.3% survived 30 days.[157] A 2008 Danish study,[158] comparing OHCA survival before and after the implementation of new resuscitation guidelines, reported that of 372 OHCA patients treated between 2004 and 2005, 7.8% (n=29) had STHD and 8.3% (n=31) as having survived 30 days.[158] This same study also reported that of 419 OHCAs treated between 2006 and 2007, 16.0% (n=67) had STHD and likewise another 16.0% (n=67) survived 30 days. A Serbian study[159] reported that in a cohort of 287 OHCA patients admitted to hospital, 18.8% (n=54) had STHD and 18.5% (n=53) survived to 30 days. However, although the overall proportion of OHCA survivors recorded in each of these reports/studies are similar for the two metrics, the level of concordance between the metrics is unclear. More precisely, these reports do not detail the level of agreement between the two outcomes. This means that although the overall reported percentages may be similar (or even the same), there could potentially be little or even no agreement between the reported outcomes for *individual* cases. Though this may not present a substantial issue for reporting crude survival (as no matter whether STHD or 30-day survival is reported, the values would be similar/the same), it could present a serious issue for multivariable analysis if there were differences in the case mix of patients who survive to hospital discharge, versus those who survive to 30 days.

In my study, I found that not only did STHD and 30-day survival in WA have a very high level of agreement in the overall percentage of survival (both 13.78 %), but there was also a high level of concordance (99.6 %), with only 30 patients being discordant between STHD and 30-day survival among a total of x patients who survived to ED admission. Although these survival metrics were highly concordant in WA, this may not be true for other registries. Therefore, it's important to discuss the potential sources of discordance. One potential source occurs when 30-day survival outcome is ascertained solely using death records, and therefore no match in the death records would result in a reported outcome status of 'survived', when in reality the case may have simply been a loss to follow-up. The other source of discordance relates to variations in hospital capabilities,[160, 161] treatment protocols[162] and discharge policies,[163] which can affect how early

OHCA patients are discharged from hospital, and therefore the chances of patients being discharged alive. For example, if a hospital tends towards earlier discharge, OHCA patients may be more likely to survive to discharge (due to reduced time at risk in hospital). Given the potential differences in hospital discharge policies, reporting 30-day survival instead of STHD may be more appropriate. The authors of the COSCA initiative (Core Outcome Set for Cardiac Arrest) have also suggested that the use of survival milestones defined by time may reduce the potential biases.[164]

8.3 Limitations

In this section I will discuss the limitations of my thesis. Firstly, industrial action by paramedics in 2008 resulted in an unknown number of missing cases for that year. The missing cases related to OHCAs that were declared deceased on scene, and therefore not transported to the ED by EMS. Including 2008 data (with an unknown number of 'missing' OHCA cases) would have resulted in biased estimates for that year (e.g. lower OHCA incidence rates and higher survival rate due to unknown number of 'at-risk' patients). Given this, I excluded all 2008 data for the study (presented in Chapter 3) examining the temporal trends in OHCA. However, exclusion of 2008 data is unlikely to have an impact on the findings of my study as the regression analysis I applied modelled time (i.e. year) as a continuous variable.

Secondly, an assumption of relative survival analysis is that the estimated survival of the age- and sex-matched peers from the general population is assumed to be free of the condition being examined (i.e. OHCA). Obviously, the life tables used for the relative survival analysis in Chapter 4 would include mortality from OHCA, potentially resulting in some bias. However, a study[165] from Sweden that investigated the potential bias of using population life tables in the relative survival analysis of cancer patients in Sweden found that the bias introduced by using population life tables is sufficiently small that it can be ignored. Additionally, I explored the temporal 'trend' in long term OHCA survival by comparing the changes in relative survival between two time periods (i.e. between 1998-2017 and 2008-2017). Although I was able to identify a substantial improvement in survival between the first, and second time period I am unable to rule out complex intra-period changes that could have occurred over the 20-year study period. Furthermore, in Chapter 5 where I explored the association between initial arrest rhythm and long-term OHCA survival, my analysis did not adjust for patient pre-arrest comorbidity. As a result, I could not determine whether pre-arrest comorbidity itself was a factor in both the non-shockable arrest rhythm and reduction in long-term OHCA survival.

Thirdly, all population-based cohort studies in this thesis were conducted in the Perth metropolitan area, therefore findings may not be applicable to other jurisdictions. For example, the observed concordance between 30-day survival and STHD in the WA OHCA registry may not apply to OHCA occurring in regional WA. Similarly, the findings from my study may not be applicable to other national or international jurisdictions.

Lastly, this thesis did not examine the neurological outcomes of OHCA survivors. However, a colleague has described the neurological outcomes of OHCA survivors in Perth in a recent study;[88] reporting that between 2004 and 2019, 92.7% of patients who STHD had a CPC score of between 1 and 2.

8.4 Recommendations for Future Research and Practice

1) In this thesis I found that the odds of 30-day survival in OHCA (of presumed cardiac aetiology) improved at a rate of 11% per annum between 2001 and 2018 even after adjustment for prehospital factors. Future studies should aim to identify the likely source of this 11% annual improvement over this study period.
2) I demonstrated that patients who arrest with non-shockable rhythms are at a substantially greater risk of mortality in the initial few years following an arrest compared to those who presented with shockable rhythms. Additionally, I identified a declining trend in the proportion of OHCA presenting with shockable initial rhythms in Perth. In combination, these two factors may act to detract from the current trend of increasing survival. To address this, research should focus on identifying the cause behind the decline in shockable arrests over time as this continues to be an important question in OHCA research.
3) Future studies should aim to enhance our understanding of the causes of death in initial OHCA survivors as well as the impact of post-resuscitation interventions (such as implantable defibrillators) on long-term patient survival.
4) A clear understanding of the association between pre-arrest comorbidity and OHCA outcomes has unfortunately not emerged from a systematic search of the literature. However, my systematic review has identified that a more standardised approach needs to

be followed for OHCA studies reporting on pre-arrest comorbidity so that the results of individual studies could be synthesised in a meta-analysis.

5) I found the OHCA outcomes, STHD and 30-day survival, to be equivalent survival metrics, with a high level of concordance. However, as mentioned in the limitations, the findings of this study may not be true for other jurisdictions. As such, I recommend jurisdictions conduct similar studies to confirm survival concordance. Furthermore, it should be recognised that changes in hospital policy or processes over time could impact survival concordance and therefore ongoing monitoring should be conducted.
6) This thesis identified that the proportion of OHCA witnessed by EMS has significantly increased between 2001 and 2018. The reason for this trend is not clear and warrants further investigation.

8.5 Concluding remarks

In this thesis, I explored the determinants of long-term OHCA survival through a detailed analysis of the epidemiology of OHCA in the Perth metropolitan area. I found that both short- and long-term OHCA survival have steadily increased in the Perth metropolitan area, with 30-day survival in the ‘Utstein comparator group’ showing a 5-fold improvement over an 18-year period. Together with the finding that improvements in OHCA survival have exceeded improvements in general population life expectancy, these findings are consistent with there being positive impacts from concerted efforts to strengthen the ‘OHCA chain of survival’. However, I also found that non-shockable arrest rhythms were associated with lower chances of longer-term OHCA survival - even in patients who survive 30 days following an arrest. Furthermore, the proportion of arrests presenting with shockable rhythms appears to be declining over time, which could possibly detract from future gains in survival. Despite this, the improvements in several modifiable Utstein factors over time, along with increasing rates of survival, should provide encouragement for achieving future improvements in OHCA survival.

Chapter 9 References

1. Bray J, Howell S, Ball S, Doan T, Bosley E, Smith K, et al. The epidemiology of out-of-hospital cardiac arrest in Australia and New Zealand: A binational report from the Australasian Resuscitation Outcomes Consortium (Aus-ROC). Resuscitation. 2022;172:74-83.
2. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Critical Care. 2020;24(1):61.
3. Coute RA, Nathanson BH, Mader TJ, McNally B, Kurz MC. Trend analysis of disability-adjusted life years following adult out-of-hospital cardiac arrest in the United States: A study from the CARES Surveillance Group. Resuscitation. 2021;163:124-9.
4. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics - 2022 Update: A Report From the American Heart Association. Circulation. 2022;145(8):e153-e639.
5. Paratz ED, Smith K, Ball J, van Heusden A, Zentner D, Parsons S, et al. The economic impact of sudden cardiac arrest. Resuscitation. 2021;163:49-56.
6. Hollenberg J, Svensson L, Rosenqvist M. Out-of-hospital cardiac arrest: 10 years of progress in research and treatment. Journal of internal medicine. 2013;273(6):572-83.
7. Institute of Medicine (IOM). Chapter 6: Strategies to Improve Cardiac Arrest Survival: A Time to Act. In: A GRMMS, editor. Resuscitation Research and Continuous Quality Improvement. Washington, DC: The National Academy Press.
8. Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, et al. Epidemiology of Sudden Cardiac Death: Global and Regional Perspectives. Heart, Lung and Circulation. 2019;28(1):6-14.
9. Carew HT, Zhang W, Rea TD. Chronic health conditions and survival after out-of-hospital ventricular fibrillation cardiac arrest. Heart. 2007;93(6):728-31.
10. Hallstrom AP, Cobb LA, Yu BH. Influence of comorbidity on the outcome of patients treated for out-of-hospital ventricular fibrillation. Circulation. 1996;93(11):2019-22.
11. Hirlekar G, Jonsson M, Karlsson T, Hollenberg J, Albertsson P, Herlitz J. Comorbidity and survival in out-of-hospital cardiac arrest. Resuscitation. 2018;133:118-23.
12. Beesems SG, Blom MT, van der Pas MH, Hulleman M, van de Glind EM, van Munster BC, et al. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. Resuscitation. 2015;94:33-9.

13. Søholm H, Hassager C, Lippert F, Winther-Jensen M, Thomsen JH, Friberg H, et al. Factors associated with successful resuscitation after out-of-hospital cardiac arrest and temporal trends in survival and comorbidity. Annals of emergency medicine. 2015;65(5):523-31. e2.
14. Rajagopalan B, Shen WK, Patton K, Kutyifa V, Di Biase L, Al-Ahmad A, et al. Surviving sudden cardiac arrest—successes, challenges, and opportunities. Journal of Interventional Cardiac Electrophysiology. 2021.
15. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest. Circulation. 2015;132(13):1286-300.
16. Yeung J, Matsuyama T, Bray J, Reynolds J, Skrifvars MB. Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest? — A systematic review. Resuscitation. 2019;137:102-15.
17. Kiguchi T, Okubo M, Nishiyama C, Maconochie I, Ong MEH, Kern KB, et al. Out-of-hospital cardiac arrest across the World: First report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation. 2020;152:39-49.
18. Gräsner J-T, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, et al. EuReCa ONE - 27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. Resuscitation. 2016;105:188-95.
19. Beck B, Bray J, Cameron P, Smith K, Walker T, Grantham H, et al. Regional variation in the characteristics, incidence and outcomes of out-of-hospital cardiac arrest in Australia and New Zealand: Results from the Aus-ROC Epistry. Resuscitation. 2018;126:49-57.
20. American Heart Association. Heart Attack and Sudden Cardiac Arrest Differences [Internet]. [cited 2022 Mar 21]. Available from: https://www.heart.org/en/health-topics/heart-attack/about-heart-attacks/heart-attack-or-sudden-cardiac-arrest-how-are-they-different.
21. Committee on the Treatment of Cardiac Arrest: Current S, Future D, Board on Health Sciences P, Institute of M. The National Academies Collection: Reports funded by National Institutes of Health. In: Graham R, McCoy MA, Schultz AM, editors. Strategies to Improve Cardiac Arrest Survival: A Time to Act. Washington (DC): National Academies Press (US). Copyright 2015 by the National Academy of Sciences. All rights reserved.; 2015.
22. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on

Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation. 2015;96:328-40.

23. Høybye M, Stankovic N, Holmberg M, Christensen HC, Granfeldt A, Andersen LW. In-Hospital vs. Out-of-Hospital Cardiac Arrest: Patient Characteristics and Survival. Resuscitation. 2021;158:157-65.

24. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300(12):1423-31.

25. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015;132(13):1286-300.

26. Dyson K, Brown SP, May S, Smith K, Koster RW, Beesems SG, et al. International variation in survival after out-of-hospital cardiac arrest: A validation study of the Utstein template. Resuscitation. 2019;138:168-81.

27. Nolan J, Soar J, Eikeland H. The chain of survival. Resuscitation. 2006;71(3):270-1.

28. Merchant RM, Topjian AA, Panchal AR, Cheng A, Aziz K, Berg KM, et al. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16_suppl_2):S337-S57.

29. American Heart Association. Out of Hospital Chain of Survival [Internet]. [cited 2022 Mar 21]. Available from: https://cpr.heart.org/en/resources/cpr-facts-and-stats/out-of-hospital-chain-of-survival.

30. Perkins GD, Neumar R, Monsieurs KG, Lim SH, Castren M, Nolan JP, et al. The International Liaison Committee on Resuscitation-Review of the last 25 years and vision for the future. Resuscitation. 2017;121:104-16.

31. Nolan JP, Maconochie I, Soar J, Olasveengen TM, Greif R, Wyckoff MH, et al. Executive Summary: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency

Cardiovascular Care Science With Treatment Recommendations. Circulation. 2020;142(16_suppl_1):S2-S27.
32. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett P, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. Task Force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Ann Emerg Med. 1991;20(8):861-74.
33. Otto Q, Nolan JP, Chamberlain DA, Cummins RO, Soar J. Utstein Style for emergency care — the first 30 years. Resuscitation. 2021;163:16-25.
34. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries.: A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation. 2004;63(3):233-49.
35. Ong MEH, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. Lancet. 2018;391(10124):980-8.
36. Andersen LW, Bivens MJ, Giberson T, Giberson B, Mottley JL, Gautam S, et al. The relationship between age and outcome in out-of-hospital cardiac arrest patients. Resuscitation. 2015;94:49-54.
37. Nakamura F, Kajino K, Kitamura T, Daya MR, Ong MEH, Matsuyama T, et al. Impact of age on survival of patients with out-of-hospital cardiac arrest transported to tertiary emergency medical institutions in Osaka, Japan. Geriatrics & Gerontology International. 2019;19(11):1088-95.
38. Andrew E, Nehme Z, Bernard S, Smith K. The influence of comorbidity on survival and long-term outcomes after out-of-hospital cardiac arrest. Resuscitation. 2017;110:42-7.
39. Chamberlain RC, Barnetson C, Clegg GR, Halbesma N. Association of measures of socioeconomic position with survival following out-of-hospital cardiac arrest: A systematic review. Resuscitation. 2020;157:49-59.
40. Myat A, Song K-J, Rea T. Out-of-hospital cardiac arrest: current concepts. The Lancet. 2018;391(10124):970-9.
41. Lei H, Hu J, Liu L, Xu D. Sex differences in survival after out-of-hospital cardiac arrest: a meta-analysis. Critical Care. 2020;24(1):613.

42. Feng D, Li C, Yang X, Wang L. Gender differences and survival after an out-of-hospital cardiac arrest: a systematic review and meta-analysis. Internal and Emergency Medicine. 2021;16(3):765-75.
43. Oving I, de Graaf C, Karlsson L, Jonsson M, Kramer-Johansen J, Berglund E, et al. Occurrence of shockable rhythm in out-of-hospital cardiac arrest over time: A report from the COSTA group. Resuscitation. 2020;151:67-74.
44. Rea TD, Cook AJ, Stiell IG, Powell J, Bigham B, Callaway CW, et al. Predicting survival after out-of-hospital cardiac arrest: role of the Utstein data elements. Annals of emergency medicine. 2010;55(3):249-57.
45. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circulation Cardiovascular quality and outcomes. 2010;3(1):63-81.
46. Rhee BY, Kim B, Lee YH. Effects of Prehospital Factors on Survival of Out-Of-Hospital Cardiac Arrest Patients: Age-Dependent Patterns. International journal of environmental research and public health. 2020;17(15).
47. Cheng FJ, Wu WT, Hung SC, Ho YN, Tsai MT, Chiu IM, et al. Pre-hospital Prognostic Factors of Out-of-Hospital Cardiac Arrest: The Difference Between Pediatric and Adult. Frontiers in pediatrics. 2021;9:723327.
48. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating Effectiveness of Cardiac Arrest Interventions. Circulation. 1997;96(10):3308-13.
49. Herlitz J, Engdahl J, Svensson L, Young M, Angquist KA, Holmberg S. A short delay from out of hospital cardiac arrest to call for ambulance increases survival. European heart journal. 2003;24(19):1750-5.
50. Merchant RM, Topjian AA, Panchal AR, Cheng A, Aziz K, Berg KM, et al. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16_suppl_2):S337-S57.
51. Talikowska M, Tohira H, Finn J. Cardiopulmonary resuscitation quality and patient survival outcome in cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2015;96:66-77.
52. Song J, Guo W, Lu X, Kang X, Song Y, Gong D. The effect of bystander cardiopulmonary resuscitation on the survival of out-of-hospital cardiac arrests: a systematic review and meta-analysis. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2018;26(1):86.

53. Tanaka H, Ong MEH, Siddiqui FJ, Ma MHM, Kaneko H, Lee KW, et al. Modifiable Factors Associated With Survival After Out-of-Hospital Cardiac Arrest in the Pan-Asian Resuscitation Outcomes Study. Annals of Emergency Medicine. 2018;71(5):608-17.e15.
54. Holmberg MJ, Vognsen M, Andersen MS, Donnino MW, Andersen LW. Bystander automated external defibrillator use and clinical outcomes after out-of-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2017;120:77-87.
55. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(16_suppl_2):S366-S468.
56. Kurz MC, Schmicker RH, Leroux B, Nichol G, Aufderheide TP, Cheskes S, et al. Advanced vs. Basic Life Support in the Treatment of Out-of-Hospital Cardiopulmonary Arrest in the Resuscitation Outcomes Consortium. Resuscitation. 2018;128:132-7.
57. Martinell L, Larsson M, Bång A, Karlsson T, Lindqvist J, Thorén AB, et al. Survival in out-of-hospital cardiac arrest before and after use of advanced postresuscitation care: a survey focusing on incidence, patient characteristics, survival, and estimated cerebral function after postresuscitation care. The American journal of emergency medicine. 2010;28(5):543-51.
58. Alves N, Mota M, Cunha M, Ribeiro JM. Impact of emergent coronary angiography after out-of-the-hospital cardiac arrest without ST-segment elevation – A systematic review and meta-analysis. International Journal of Cardiology. 2022.
59. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation. 2021;167:160-72.
60. Al-Dury N, Ravn-Fischer A, Hollenberg J, Israelsson J, Nordberg P, Strömsöe A, et al. Identifying the relative importance of predictors of survival in out of hospital cardiac arrest: a machine learning study. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2020;28(1):60.
61. Lee CC, Tsai MS, Fang CC, Chen YJ, Hui-Ming M, Huang CH, et al. Effects of pre-arrest comorbidities on 90-day survival of patients resuscitated from out-of-hospital cardiac arrest. Emergency medicine journal : EMJ. 2011;28(5):432-6.
62. Department of Planning Lands and Heritage. Perth and Peel@3.5million [Internet]. [cited 2022 Jan 18]. Available from: https://www.dplh.wa.gov.au/getmedia/404a6895-f6ec-4829-87df-8de5b80075b8/FUT-PP-Perth_and_Peel_Sub_Region_March2018_v2.

63. Australian Bureau of statistics. Population Estimates by Local Government Area, 2001 to 2020 [Internet]. 2021 [cited 2021 Jun 1]. Available from: https://stat.data.abs.gov.au/Index.aspx?DataSetCode=ABS_ANNUAL_ERP_ASGS2016#.
64. Australian Bureau of Statistics. Region summary: Greater Perth [Internet]. [cited 2022 Mar 5]. Available from: https://dbr.abs.gov.au/region.html?lyr=gccsa&rgn=5GPER.
65. St John WA. Annual Report 2019/20 [Internet]. [cited 2022 Feb 15]. Available from: https://stjohnwa.com.au/docs/default-source/corporate-publications/annual-report-2019-2020-digital.pdf?sfvrsn=f762e9b2_2.
66. St John WA. Annual Report 2018/2019 [Internet]. [cited 2022 Mar 24]. Available from: https://stjohnwa.com.au/docs/default-source/corporate-publications/annual-report-2019.pdf?sfvrsn=10.
67. Priority Dispatch. Medical Priority Dispatch System (MPDS) Information Sheet 2019 [Internet]. [cited 2022 Feb 20]. Available from: https://prioritydispatch-media.s3.amazonaws.com/prioritydispatch.net/salessheets/PDC_MPDS_Sales_Sheet_v8_web.pdf.
68. Brooks IA, Grantham H, Spencer C, Archer F. A review of the literature: the transition of entry-level paramedic education in Australia from vocational to higher education (1961–2017). Australasian Journal of Paramedicine. 2018;15(2).
69. Australian Health Practitioner Regulation Agency. Ahpra Paramedicine Board [Internet]. [cited 2022 Mar 8]. Available from: https://www.paramedicineboard.gov.au/.
70. St John WA. Clinical Practice Guidelines - Cardiac Arrest [Internet]. [updated 2017; cited 2022 Mar 5]. Available from: http://clinical.stjohnwa.com.au/clinical-practice-guidelines/circulation/cardiac-arrest.
71. St John WA. Skills Matrix [Internet]. [updated 2020; cited 2022 Mar 15]. Available from: https://clinical.stjohnwa.com.au/general/skills-matrix.
72. St John WA. Clinical Practice Guidelines [Internet]. [cited 2022 Mar 5]. Available from: http://clinical.stjohnwa.com.au/clinical-practice-guidelines.
73. Australian Resuscitation Council. ANZCOR Adult Cardiorespiratory Arrest Flowchart [Internet]. [updated 2016; cited 2022 Mar 3]. Available from: https://resus.org.au/download/flowcharts/anzcor-adult-cardiorespiratory-arrest-flowchart-jan-2016.pdf.
74. St John WA. Determination of Death (TOR/ROLE) [Internet]. [updated 2021; cited 2022 Mar 22]. Available from: https://clinical.stjohnwa.com.au/clinical-practice-guidelines/circulation/determination-of-death-(tor-role).

75. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011;82(9):1138-43.
76. Boyle M. 7th International Spark of Life Resuscitation Conference. Australasian Journal of Paramedicine. 2009;7(2).
77. Jolife AB. LUCAS Chest Compression System [Internet]. [cited 2022 Mar 24]. Available from: https://www.lucas-cpr.com.
78. St John Ambulance WA. Annual Report 2013/14 [Internet]. [cited 2022 Mar 28]. Available from: https://stjohnwa.com.au/docs/corporate-publications/2013_2014_annual_report.pdf?sfvrsn=362e75d2_2.
79. International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 2: Adult basic life support. Resuscitation. 2005;67(2-3):187-201.
80. Talikowska M. The relationship between the quality of cardiopulmonary resuscitation (CPR) performed by paramedics and survival outcomes from out-of-hospital cardiac arrest (OHCA) [dissertation] Bentley (Au): Curtin University; 2017 [Cited 20th January 2022]. Available from: https://espace.curtin.edu.au/handle/20.500.11937/65985.
81. Talikowska M, Tohira H, Brink D, Bailey P, Finn PJ. Paramedic-reported barriers towards use of CPR feedback devices in Perth, Western Australia. Journal of Paramedic Practice. 2016;8(12):597-606.
82. Australian Government Department of Health. Emergency Departments; Perth, WA 6000 [Internet]. [cited 2021 Aug 22]. Available from: https://www.healthdirect.gov.au/australian-health-services/results/perth-6000/tihcs-aht-10968/emergency-departments?pageIndex=1&tab=SITE_VISIT.
83. McKenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, et al. Arterial carbon dioxide tension has a non-linear association with survival after out-of-hospital cardiac arrest: A multicentre observational study. Resuscitation. 2021;162:82-90.
84. McKenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, et al. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: A multicentre observational study. Resuscitation. 2021;158:130-8.
85. Australian and New Zealand Commitee on Resuscitation. ANZCOR Guideline 11.7 - Post-Resuscitation Therapy in Adult Advanced Life Support [Internet]. [cited 2020 Aug 8]. Available from: https://www.resus.org.nz/assets/Guidelines/Adult-ALS/ANZCOR-Guideline-11.7-Jan16.pdf.

86. Australasian College for Emergency Medicine. How the FACEM Training Program works [Internet]. [cited cited 2022 Mar 25. Available from: https://acem.org.au/Content-Sources/Training/How-the-FACEM-Training-Program-works.
87. College of Intensive Care Medicine of Australia and New Zealand. About Us [Cited: 25th March 2022]. Available from: https://www.cicm.org.au/About/About-Us.
88. McKenzie N, Ball S, Bailey P, Finn L, Arendts G, Celenza A, et al. Neurological outcome in adult out-of-hospital cardiac arrest – Not all doom and gloom! Resuscitation. 2021;167:227-32.
89. Safar P. Cerebral resuscitation after cardiac arrest: a review. Circulation. 1986;74(6 Pt 2):Iv138-53.
90. Hirakawa A, Hatakeyama T, Kobayashi D, Nishiyama C, Kada A, Kiguchi T, et al. Real-time feedback, debriefing, and retraining system of cardiopulmonary resuscitation for out-of-hospital cardiac arrests: a study protocol for a cluster parallel-group randomized controlled trial. Trials. 2018;19(1):510.
91. Bray JE, Di Palma S, Jacobs I, Straney L, Finn J. Trends in the incidence of presumed cardiac out-of-hospital cardiac arrest in Perth, Western Australia, 1997-2010. Resuscitation. 2014;85(6):757-61.
92. Geri G, Passouant O, Dumas F, Bougouin W, Champigneulle B, Arnaout M, et al. Etiological diagnoses of out-of-hospital cardiac arrest survivors admitted to the intensive care unit: Insights from a French registry. Resuscitation. 2017;117:66-72.
93. Australian Bureau of Statistics. Standard Population for Use in Age-Standardisation [Internet]. [updated 2013; cited 2021 May 18]. Available from: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/sep-2020/31010DO003_200106.xls.
94. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19(3):335-51.
95. Rea F, Pagan E, Monzio Compagnoni M, Cantarutti A, Pugni P, Bagnardi V, et al. Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies. Epidemiology Biostatistics and Public Health. 2017;14:e12616-1.
96. Mansournia MA, Jewell NP, Greenland S. Case–control matching: effects, misconceptions, and recommendations. European Journal of Epidemiology. 2018;33(1):5-14.
97. Perme MP, Pavlic K. Nonparametric Relative Survival Analysis with the R Package relsurv. Journal of Statistical Software. 2018;87(8):1 - 27.

98. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note no. 10. End results evaluation section. National Cancer Institute: Bethseda. 1959.
99. Lambert PC, Dickman PW, Rutherford MJ. Comparison of different approaches to estimating age standardized net survival. BMC Medical Research Methodology. 2015;15(1):64.
100. Bouman P, Dukic V, Meng X-L. A Bayesian mulitresolution hazard model with application to AIDS reporting delay study. Statistica Sinica. 2005;15(2):325-57.
101. Bouman P, Meng X-L, Dignam J, Dukić V. A Multiresolution Hazard Model for Multicenter Survival Studies: Application to Tamoxifen Treatment in Early Stage Breast Cancer. J Am Stat Assoc. 2007;102(480):1145-57.
102. Dukić V, Dignam J. Bayesian Hierarchical Multiresolution Hazard Model for the Study of Time-Dependent Failure Patterns in Early Stage Breast Cancer. Bayesian Anal. 2007;2(3):591-610.
103. Hagar Y, Albers D, Pivovarov R, Chase H, Dukic V, Elhadad N. Survival analysis with electronic health record data: Experiments with chronic kidney disease. Statistical Analysis and Data Mining: The ASA Data Science Journal. 2014;7(5):385-403.
104. Hagar Y, Dignam JJ, Dukic V. Flexible modeling of the hazard rate and treatment effects in long-term survival studies. Statistical Methods in Medical Research. 2017;26(5):2455-80.
105. Hagar Y, Dukic VM. Analyzing Non-proportional Hazards: Use of the MRH Package. arXiv: Computation. 2016.
106. Koyama S, Gibo K, Yamaguchi Y, Okubo M. Variation in survival after out-of-hospital cardiac arrest between receiving hospitals in Japan: an observational study. BMJ Open. 2019;9(11):e033919.
107. Grubb N, Fox K, Elton R. In-hospital mortality after out-of-hospital cardiac arrest. The Lancet. 1995;346(8972):417-21.
108. Jung E, Park JH, Ro YS, Song KJ, Ryu HH, Lee SC, et al. Effect of hypertension across the age group on survival outcomes in out-of-hospital cardiac arrest. American Journal of Emergency Medicine. 2019;37(4):608-14.
109. Mohr GH, Sondergaard KB, Pallisgaard JL, Moller SG, Wissenberg M, Karlsson L, et al. Survival of patients with and without diabetes following out-of-hospital cardiac arrest: A nationwide Danish study. European heart journal Acute cardiovascular care. 2020;9(6):599-607.
110. Dumas F, Paoli A, Paul M, Savary G, Jaubert P, Chocron R, et al. Association between previous health condition and outcome after cardiac arrest. Resuscitation. 2021;167:267-73.

111. Van Dongen LH, Blom MT, De Haas SCM, Van Weert HCPM, Elders P, Tan H. Higher chances of survival to hospital admission after out-of-hospital cardiac arrest in patients with previously diagnosed heart disease. Open Heart. 2021;8(2).
112. Beesems SG, Blom MT, van der Pas MHA, Hulleman M, van de Glind EMM, van Munster BC, et al. Comorbidity and favorable neurologic outcome after out-of-hospital cardiac arrest in patients of 70 years and older. Resuscitation. 2015;94:33-9.
113. Watson PF, Petrie A. Method agreement analysis: A review of correct methodology. Theriogenology. 2010;73(9):1167-79.
114. Pembury Smith MQR, Ruxton GD. Effective use of the McNemar test. Behavioral Ecology and Sociobiology. 2020;74(11):133.
115. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.
116. Lin H-Y, Chien Y-C, Lee B-C, Wu Y-L, Liu Y-P, Wang T-L, et al. Outcomes of out-of-hospital cardiac arrests after a decade of system-wide initiatives optimising community chain of survival in Taipei city. Resuscitation. 2022;172:149-58.
117. Buick JE, Drennan IR, Scales DC, Brooks SC, Byers A, Cheskes S, et al. Improving Temporal Trends in Survival and Neurological Outcomes After Out-of-Hospital Cardiac Arrest. Circulation Cardiovascular quality and outcomes. 2018;11(1):e003561.
118. Ho AFW, De Souza NNA, Blewer AL, Wah W, Shahidah N, White AE, et al. Implementation of a National 5-Year Plan for Prehospital Emergency Care in Singapore and Impact on Out-of-Hospital Cardiac Arrest Outcomes From 2011 to 2016. Journal of the American Heart Association. 2020;9(21):e015368.
119. Christenson JM. Why Is the Incidence of VF Decreasing? [Internet] Waltham: Massachusetts Medical Society; 2004 [cited 2022 Feb 10]. Available from: https://www.jwatch.org/em200405120000004/2004/05/12/why-incidence-vf-decreasing.
120. Pemberton K, Bosley E. Temporal trends (2002–2014) of incidence and shockable status of adult emergency medical service attended out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland. Emergency Medicine Australasia. 2018;30(1):89-94.
121. Alqahtani S, Nehme Z, Williams B, Bernard S, Smith K. Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies. Resuscitation. 2020;155:125-33.
122. Hulleman M, Zijlstra JA, Beesems SG, Blom MT, van Hoeijen DA, Waalewijn RA, et al. Causes for the declining proportion of ventricular fibrillation in out-of-hospital cardiac arrest. Resuscitation. 2015;96:23-9.

123. Adielsson A, Djärv T, Rawshani A, Lundin S, Herlitz J. Changes over time in 30-day survival and the incidence of shockable rhythms after in-hospital cardiac arrest - A population-based registry study of nearly 24,000 cases. Resuscitation. 2020;157:135-40.
124. van Dongen LH, Oving I, Dijkema PW, Beesems SG, Blom MT, Tan HL. Sex differences in the association of comorbidity with shockable initial rhythm in out-of-hospital cardiac arrest. Resuscitation. 2021;167:173-9.
125. Barcella CA, Eroglu TE, Hulleman M, Granfeldt A, Souverein PC, Mohr GH, et al. Association of beta-blockers and first-registered heart rhythm in out-of-hospital cardiac arrest: Real-world data from population-based cohorts across two European countries. Europace. 2020;22(8):1206-15.
126. Keller SP, Halperin HR. Cardiac Arrest: the Changing Incidence of Ventricular Fibrillation. Current Treatment Options in Cardiovascular Medicine. 2015;17(7):29.
127. Holmén J, Herlitz J, Ricksten SE, Strömsöe A, Hagberg E, Axelsson C, et al. Shortening ambulance response time increases survival in out-of-hospital cardiac arrest. Journal of the American Heart Association. 2020;9(21):e017048.
128. Herlitz J, Engdahl J, Svensson L, Young M, Ängquist K-A, Holmberg S. Decrease in the occurrence of ventricular fibrillation as the initially observed arrhythmia after out-of-hospital cardiac arrest during 11 years in Sweden. Resuscitation. 2004;60(3):283-90.
129. Hiemstra B, Bergman R, Absalom AR, van der Naalt J, van der Harst P, de Vos R, et al. Long-term outcome of elderly out-of-hospital cardiac arrest survivors as compared with their younger counterparts and the general population. Therapeutic Advances in Cardiovascular Disease. 2018;12(12):341-9.
130. Wong MK, Morrison LJ, Qiu F, Austin PC, Cheskes S, Dorian P, et al. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. Circulation. 2014;130(21):1883-90.
131. Australian Bureau of Statistics. Life expectancy continues to increase in Australia [Internet]. [updated 2020; cited 2022 Feb 7]. Available from: https://www.abs.gov.au/media-centre/media-releases/life-expectancy-continues-increase-australia.
132. Chin YH, Yaow CYL, Teoh SE, Foo MZQ, Luo N, Graves N, et al. Long-term outcomes after out-of-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2022;171:15-29.
133. Majewski D, Ball S, Bailey P, Bray J, Finn J. Long-term survival among OHCA patients who survive to 30 days: Does initial arrest rhythm remain a prognostic determinant? Resuscitation. 2021;162:128-34.

134. Baldi E, Compagnoni S, Buratti S, Primi R, Bendotti S, Currao A, et al. Long-Term Outcome After Out-of-Hospital Cardiac Arrest: An Utstein-Based Analysis. Front Cardiovasc Med. 2021;8:764043-.
135. Bewick V, Cheek L, Ball J. Statistics review 12: survival analysis. Crit Care. 2004;8(5):389-94.
136. Andrew E, Nehme Z, Wolfe R, Bernard S, Smith K. Long-term survival following out-of-hospital cardiac arrest. Heart. 2017;103(14):1104-10.
137. Mandigers L, Termorshuizen F, de Keizer NF, Rietdijk W, Gommers D, Dos Reis Miranda D, et al. Higher 1-year mortality in women admitted to intensive care units after cardiac arrest: A nationwide overview from the Netherlands between 2010 and 2018. Journal of critical care. 2021;64:176-83.
138. Kvakkestad KM, Sandvik L, Andersen GØ, Sunde K, Halvorsen S. Long-term survival in patients with acute myocardial infarction and out-of-hospital cardiac arrest: A prospective cohort study. Resuscitation. 2018;122:41-7.
139. Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pélissier S. Variables with time-varying effects and the Cox model: Some statistical concepts illustrated with a prognostic factor study in breast cancer. BMC Medical Research Methodology. 2010;10(1):20.
140. Jung SH, Lee HY, Chow SC. Statistical Methods for Conditional Survival Analysis. J Biopharm Stat. 2018;28(5):927-38.
141. Hieke S, Kleber M, König C, Engelhardt M, Schumacher M. Conditional Survival: A Useful Concept to Provide Information on How Prognosis Evolves over Time. Clinical Cancer Research. 2015;21(7):1530.
142. Rulli E, Ghilotti F, Biagioli E, Porcu L, Marabese M, D'Incalci M, et al. Assessment of proportional hazard assumption in aggregate data: a systematic review on statistical methodology in clinical trials using time-to-event endpoint. British Journal of Cancer. 2018;119(12):1456-63.
143. Kuitunen I, Ponkilainen VT, Uimonen MM, Eskelinen A, Reito A. Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. BMC Musculoskeletal Disorders. 2021;22(1):489.
144. Rey JR, Caro-Codón J, Rodríguez Sotelo L, López-de-Sa E, Rosillo SO, González Fernández Ó, et al. Long term clinical outcomes in survivors after out-of-hospital cardiac arrest. European Journal of Internal Medicine. 2020;74:49-54.

145. Storm C, Krannich A, Schachtner T, Engels M, Schindler R, Kahl A, et al. Impact of acute kidney injury on neurological outcome and long-term survival after cardiac arrest – A 10 year observational follow up. Journal of critical care. 2018;47:254-9.
146. Jamme M, Ait Hamou Z, Ben Hadj Salem O, Guillemet L, Bougouin W, Pène F, et al. Long term renal recovery in survivors after OHCA. Resuscitation. 2019;141:144-50.
147. Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.
148. Herlitz J, Ekström L, Wennerblom B, Axelsson Å, Bång A, Holmberg S. Hospital mortality after out-of-hospital cardiac arrest among patients found in ventricular fibrillation. Resuscitation. 1995;29(1):11-21.
149. Larsson M, Thorén AB, Herlitz J. A history of diabetes is associated with an adverse outcome among patients admitted to hospital alive after an out-of-hospital cardiac arrest. Resuscitation. 2005;66(3):303-7.
150. Parry M, Danielson K, Brennenstuhl S, Drennan IR, Morrison LJ. The association between diabetes status and survival following an out-of-hospital cardiac arrest: A retrospective cohort study. Resuscitation. 2017;113:21-6.
151. Fabbri A, Marchesini G, Spada M, Iervese T, Dente M, Galvani M, et al. Monitoring intervention programmes for out-of-hospital cardiac arrest in a mixed urban and rural setting. Resuscitation. 2006;71(2):180-7.
152. Oh SJ, Kim JJ, Jang JH, Hwang IC, Woo JH, Lim YS, et al. Age is related to neurological outcome in patients with out-of-hospital cardiac arrest (OHCA) receiving therapeutic hypothermia (TH). American Journal of Emergency Medicine. 2018;36(2):243-7.
153. Voruganti DC, Chennamadhavuni A, Garje R, Shantha GPS, Schweizer ML, Girotra S, et al. Association between diabetes mellitus and poor patient outcomes after out-of-hospital cardiac arrest: A systematic review and meta-analysis. Scientific Reports. 2018;8(1):17921.
154. Davies SW. Clinical presentation and diagnosis of coronary artery disease: stable angina. British medical bulletin. 2001;59:17-27.
155. Sara JD, Eleid MF, Gulati R, Holmes DR, Jr. Sudden cardiac death from the perspective of coronary artery disease. Mayo Clinic proceedings. 2014;89(12):1685-98.
156. Haskins B, Smith K, Cameron P, Bernard S, Nehme Z, Murphy-Smith J, et al. The impact of bystander relation and medical training on out-of-hospital cardiac arrest outcomes. Resuscitation. 2020;150:72-9.

157. Queensland Ambulance Service. Out of Hospital Cardiac Arrest in Queensland: 2019 Annual Report [Internet]. [cited 2021 Jan 10]. Available from: https://www.ambulance.qld.gov.au/docs/QAS_OHCA_Annual_Report_%202019.pdf.
158. Steinmetz J, Barnung S, Nielsen SL, Risom M, Rasmussen LS. Improved survival after an out-of-hospital cardiac arrest using new guidelines. Acta Anaesthesiologica Scandinavica. 2008;52(7):908-13.
159. Nikolovski SS, Lazic AD, Fiser ZZ, Obradovic IA, Randjelovic SS, Tijanic JZ, et al. Initial Outcomes and Survival of Out-of-Hospital Cardiac Arrest: EuReCa Serbia Multicenter Cohort Study. Cureus. 2021;13(10):e18555.
160. Nakahara S, Nagao T, Nishi R, Sakamoto T. Task-shift Model in Pre-hospital Care and Standardized Nationwide Data Collection in Japan: Improved Outcomes for Out-of-hospital Cardiac Arrest Patients. JMA J. 2021;4(1):8-16.
161. Lai C-Y, Lin F-H, Chu H, Ku C-H, Tsai S-H, Chung C-H, et al. Survival factors of hospitalized out-of-hospital cardiac arrest patients in Taiwan: A retrospective study. PLoS One. 2018;13(2):e0191954-e.
162. Wnent J, Seewald S, Heringlake M, Lemke H, Brauer K, Lefering R, et al. Choice of hospital after out-of-hospital cardiac arrest - a decision with far-reaching consequences: a study in a large German city. Critical Care. 2012;16(5):R164.
163. Drye EE, Normand S-LT, Wang Y, Ross JS, Schreiner GC, Han L, et al. Comparison of Hospital Risk-Standardized Mortality Rates Calculated by Using In-Hospital and 30-Day Models: An Observational Study With Implications for Hospital Profiling. Annals of Internal Medicine. 2012;156(1_Part_1):19-26.
164. Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Circulation. 2018;137(22):e783-e801.
165. Talbäck M, Dickman PW. Estimating expected survival probabilities for relative survival analysis – Exploring the impact of including cancer patient mortality in the calculations. European Journal of Cancer. 2011;47(17):2626-32.

APPENDICES

Appendix A PROSPERO Registration

PROSPERO
International prospective register of systematic reviews

Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes

David Majewski, Judith Finn, Stephen Ball

Citation

David Majewski, Judith Finn, Stephen Ball. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. PROSPERO 2018 CRD42018087578 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018087578

Review question

In out of hospital cardiac arrest patients do pre-existing chronic health conditions result in poorer survival rates and neurological outcomes?

Searches

We will search the following electronic databases: MEDLINE (1950-), EMBASE (1966-), CINAHL (1937-), Scopus, The Cochrane Library and grey literature via Mednar. Review articles may be used to find other relevant articles. Reference lists from relevant articles will be used to identify additional relevant sources.

No date or language restrictions will be placed on the studies included in the review.

Types of study to be included

The following types of studies will be included: Randomised controlled trials, Cohort Studies, Cross-sectional studies and Case-Control studies and any other type of comparative study.

All commentaries, editorials, letters, case studies, abstracts and reviews will be excluded.

Condition or domain being studied

Out-of-hospital cardiac arrest (OHCA).

Participants/population

Inclusion: Patients who experienced an OHCA of medical aetiology (as defined by 2015 Utstein recommended guidelines)

Exclusion: In-hospital cardiac arrests.

Intervention(s), exposure(s)

Pre-existing comorbidity (chronic health condition); as described in the studies.

Comparator(s)/control

Level of comorbidity.

Main outcome(s)

Survival to hospital discharge.

Additional outcome(s)

Neurological outcome

Measures of effect

Data extraction (selection and coding)

All title and abstracts will be reviewed by one author (DM) to identify relevant studies. Full text articles will then be independently reviewed by DM and SB to ensure eligibility and that all criteria is met using pre-determined forms. Differences will be discussed at group meeting with DM, SB and JF and resolved by consensus.

Risk of bias (quality) assessment

GRADE (Grading of Recommendations Assessment, Development and Evaluation) for observational studies will be used to evaluate the quality of studies included within the review.

Strategy for data synthesis

Data from individual studies will be assessed for Heterogeneity using the I^2 statistic and combined using RevMan v.5.3 if heterogeneity is below 50% and studies are deemed appropriate to be combined.

Analysis of subgroups or subsets

Sub group analysis will be performed for the following patient groups:
Male and Female
Presenting initial rhythm (shockable and non-shockable)
Children and Adults

Contact details for further information

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Organisational affiliation of the review

Curtin University
https://healthsciences.curtin.edu.au/health-sciences-research/research-institutes-centres/precru/

Review team members and their organisational affiliations

Dr David Majewski. Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU), School of Nursing, Midwifery and Paramedicine, Curtin University
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Dr Stephen Ball. Prehospital, Resuscitation and Emergency Care Research Unit (PRECRU), School of Nursing, Midwifery and Paramedicine, Curtin University

Type and method of review

Meta-analysis, Prognostic, Systematic review

Anticipated or actual start date

01 February 2018

Anticipated completion date

08 June 2018

Funding sources/sponsors

- Research Training Program (RTP) stipend
- Curtin University RTP stipend top-up scholarship
- Curtin PRECRU top up scholarship

Conflicts of interest

Professor Judith Finn receives salary from St John Ambulance WA
Yes

Language

English

Country

Australia

Stage of review

Review Completed published

Details of final report/publication(s) or preprints if available

Majewski D, Ball S, Finn J. Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes. BMJ Open. 2019;9(11):e031655.
https://bmjopen.bmj.com/content/9/11/e031655

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Cardiopulmonary Resuscitation; Comorbidity; Humans; Out-of-Hospital Cardiac Arrest

Date of registration in PROSPERO

06 February 2018

Date of first submission

01 February 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

06 February 2018
17 April 2018
19 December 2018
03 July 2021
13 July 2021

Appendix B Systematic Review Search Strategy

Supplementary appendix 1

Medline (Ovid) search strategy

Line	Search Statement
1	(Out of Hospital Cardiac Arrest).mp
2	OHCA.mp
3	Exp Heart arrest/
4	(Cardiac Arrest).mp
5	Exp Resuscitation/
6	Resus*.mp
7	(Cardio pulmonary resuscitation).mp
8	Cpr.mp
9	Prehospital.mp
10	Ambulance.mp
11	(Emergency Medical Services).mp
12	EMS.mp
13	Emergency Medical Services/
14	Ambulance/
15	3 or 4 or 5 or 6 or 7 or 8
16	9 or 10 or 11 or 12 or 13 or 14
17	15 and 16
18	1 or 2 or 17
19	exp epidemiological factors/
20	Risk factors/
21	comorbid*.mp
22	(medical histor*).mp
23	(health histor*).mp
24	(risk factor?).mp
25	(chronic condition?).mp
26	(chronic diseas*).mp
27	(chronic health).mp
28	Preexisting.mp
29	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	18 and 29

Embase (Ovid) search strategy

Line	Search Statement
1.	"out of hospital cardiac arrest"/
2.	out of hospital cardiac arrest.mp.
3.	ohca.mp.
4.	exp heart arrest/
5.	cardiac arrest.mp.
6.	resuscitation/
7.	resus*.mp.
8.	cardio pulmonary resuscitation.mp.
9.	cpr.mp.
10.	emergency health service/
11.	first aid/
12.	emergency care/
13.	prehospital.mp.

Majewski D, *et al. BMJ Open* 2019; 9:e031655. doi: 10.1136/bmjopen-2019-031655

14.	ambulance.mp.
15.	emergency medical services.mp.
16.	ems.mp.
17.	ambulance/
18.	4 or 5 or 6 or 7 or 8 or 9
19.	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20.	18 and 19
21.	1 or 2 or 3 or 20
22.	epidemiology/
23.	causality/
24.	comorbidity/
25.	risk factor/
26.	comorbid*.mp.
27.	medical histor*.mp.
28.	health histor*.mp.
29.	risk factor?.mp.
30.	chronic condition?.mp.
31.	chronic diseas*.mp.
32.	chronic health.mp.
33.	pre-existing.mp.
34.	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35.	21 and 34

CINAHL search strategy

Line	Search Statement
1	(Out of Hospital Cardiac Arrest).mp
2	OHCA.mp
3	Exp Heart Arrest/
4	(Cardiac arrest).mp
5	Cpr.mp
6	Advanced cardiac life support/
7	Bystander cpr/
8	Exp Resuscitation/
9	Resus*.mp
10	(Cardio pulmonary resuscitation).mp
11	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	emergency medical services/
13	first aid/
14	exp emergency care/
15	Emergency Medical Technicians/
16	Prehospital.mp
17	Ambulance.mp
18	(Emergency Medical Services).mp
19	EMS.mp
20	Ambulance/
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	11 and 21
23	1 or 2 or 22
24	comorbidity/
25	exp Risk factors/

26	comorbid*.mp
27	(medical histor*).mp
28	(health histor*).mp
29	(risk factor?).mp
30	(chronic condition?).mp
31	(chronic diseas*).mp
32	(chronic health).mp
33	24 and 25 and 26 and 27 and 28 and 29 and 30 and 31 and 32
34	23 and 33

Cochrane search strategy

Line	Search Statement
#1	MeSH descriptor: [Out-of-Hospital Cardiac Arrest] explode all trees
#2	("out-of-hospital cardiac arrest"):kw
#3	(OHCA):kw
#4	#1 OR #2 OR #3
#5	(cardiac arrest):kw
#6	(resusitation):kw
#7	(cpr):kw
#8	MeSH descriptor: [Emergency Medical Technicians] explode all trees
#9	MeSH descriptor: [Emergency Medical Services] explode all trees
#10	(ambulance):kw
#11	(paramedic):kw
#12	#5 OR #6 OR #7
#13	#8 OR #9 OR #10 OR #11
#14	#12 AND #13
#15	#4 OR #14
#16	MeSH descriptor: [Comorbidity] explode all trees
#17	(comorbid*):kw
#18	(chronic health):kw
#19	(chronic disease):kw
#20	(medical histor*):kw
#21	#16 OR #17 OR #18 OR #19 OR #20
#22	#15 AND #21

Scopus search strategy

TITLE-ABS-KEY (("Pre-existing" OR "comorbid*" OR "chronic *" OR "medical history" OR "risk factor*") AND (("out of hospital cardiac arrest" OR "ohca") OR (("cardiac arrest") AND ("prehospital" OR "pre-hospital" OR "ems" OR "ambulanc*" OR "emergenc* *" OR "paramed*"))))