THE UNIVERSITY of ADELAIDE

INCIDENCE, MANAGEMENT, AND OUTCOME OF OUT-OF-HOSPITAL CARDIAC ARREST

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Wittwer MR, Armstrong T, Conway J, Ruknuddeen MI, Zeitz C, Beltrame JF, Arstall MA. In-hospital mode of death after out-of-hospital cardiac arrest. *Resuscitation Plus.* 2022;10: 100229.

Wittwer MR, Aldridge E, Hein C, Thorrowgood M, Zeitz C, Beltrame JF, Arstall MA. Sex differences in incidence and outcome of out-of-hospital cardiac arrest within a local health network. *Frontiers in Cardiovascular Medicine*. 2022;9:1-10.

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ADDITIONAL PUBLICATIONS DURING CANDIDATURE:

Aldridge E, Pathirana M, **Wittwer M**, Sierp S, Leemaqz SY, Roberts CT, Dekker GA, Arstall MA. Prevalence of Metabolic Syndrome in Women After Maternal Complications of Pregnancy: An Observational Cohort Analysis. *Frontiers in Cardiovascular Medicine*. 2022;9:1–9.

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PRESENTATIONS AND ABSTRACTS DURING CANDIDATURE:

NALHN Research Day, Lyell McEwin Hospital, 2021

Poster presentation: Wittwer MR, Hein C, Thorrowgood M, Zeitz C, Beltrame JF, Arstall MA. “Out-of-hospital cardiac arrest in NALHN”.

Cardiac Society of Australia and New Zealand, Virtual Scientific Sessions, 2020

Poster presentation: **Wittwer MR**, Zeitz C, Beltrame JF, Arstall MA. “Mode of death after resuscitated out-of-hospital cardiac arrest”. Published in: *Heart, Lung and Circulation*. 2020;29,S139–40.

Poster presentation: **Wittwer MR**, Thorrowgood M, Zeitz C, Beltrame JF, Arstall MA. "Identifying out-of-hospital cardiac arrests using hospital-based sources". CSANZ Scientific Sessions, 2020. Published in: *Heart, Lung and Circulation*. 2020;29,S133.

Cardiac Society of Australia and New Zealand, Scientific Sessions, Brisbane, 2018

Poster presentation: Wu S, **Wittwer MR**, Beltrame J, Zeitz C, Arstall MA. "Validation and comparison of a clinical score predicting need for emergency angiography in out-of-hospital cardiac arrest survivors". Published in: *Heart, Lung and Circulation*. 2018;27,S201.

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Poster presentation: **Wittwer MR**, Wu S, Beltrame J, Zeitz C, Arstall MA. "Cardiologists accurately identify resuscitated out-of-hospital cardiac arrest cases that do not require emergency cardiac catheterisation". Published in: *Circulation*.2017;136(Suppl 1),A19969

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Poster presentation: **Wittwer MR**, Wu S, Beltrame J, Zeitz C, Arstall MA. "Immediate cardiac catheterisation in out-of-hospital cardiac arrest? Leave it to the cardiologists".

University of Adelaide 3MT competition, Adelaide, 2017.

Oral presentation: "When life's journey ends too soon".

South Australian Medical research institute (SAHMRI) Research Showcase, Adelaide, 2017.

Poster presentation: **Wittwer MR**, Hein C, Thorrowgood M, Zeitz C, Arstall MA. "Incidence, management, and outcome of out-of-hospital cardiac arrest in NALHN".

Australian Resuscitation Council, Spark of Life Conference, Adelaide, 2017

Oral presentation: **Wittwer MR**, Zeitz C, Arstall MA. "Early arterial blood gas in patients with out-of-hospital cardiac arrest".

Poster presentation: **Wittwer MR**, Hein C, Thorrowgood M, Zeitz C, Arstall MA. "Surviving out-of-hospital cardiac arrest in Northern Adelaide".

SA Ambulance education evening, Salisbury, 2017

Invited oral presentation: **Wittwer MR**, Zeitz C, Beltrame J, Arstall MA. "Out-of-hospital cardiac arrest in NALHN".

SA Population Health Conference, 2016

Poster presentation: **Wittwer MR**, Arstall MAA. "Out-of-hospital cardiac arrest in Northern Adelaide".

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ABBREVIATIONS

ACS	Acute coronary syndrome
AHA	American Heart Association
AICD	Automatic implantable cardioverter-defibrillator
AMI	Acute myocardial infarction
ANZCOR	Australian and New Zealand Committee on Resuscitation
ANZICS	Australian and New Zealand Intensive Care Society
ANZICS-APD	Australian and New Zealand Intensive Care Society adult patient database
AUC	Area under the receiver operating characteristic curve
AUS-ROC	Australasian Resuscitation Outcomes Consortium
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CADOSA	Coronary Angiogram Database of South Australia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CQR	Clinical quality registry
CVD	Cardiovascular disease
ECG	Electrocardiogram
ECPR	Extracorpeal cardiopulmonary resuscitation
EMS	Emergency medical service
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems tenth revision Australian modification
ICU	Intensive care unit
IQR	Interquartile range
IHCA	In-hospital cardiac arrest
ILCOR	International Liaison Committee on Resuscitation
MET	Medical emergency team
n	Number
NSTE	No ST-segment elevation
NSTEMI	Non-ST-segment elevation myocardial infarction
OHCA	Out-of-hospital cardiac arrest

OR	Odds ratio
PCI	Percutaneous coronary intervention
PEA	Pulseless electrical activity
RCT	Randomised clinical trial
ROC	Receiver operating characteristic
ROSC	Return of spontaneous circulation
SAAS	SA Ambulance Service
SAAS-CAR	SA Ambulance Service Cardiac Arrest Registry
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SES	Socioeconomic status
STARD	Standards for reporting diagnostic accuracy studies
STE	ST-segment elevation
STEMI	ST-segment elevation myocardial infarction
VACAR	Victorian Ambulance Cardiac Arrest Registry
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WLST	Withdrawal or withholding of life sustaining therapy

ABSTRACT

Introduction: Out-of-hospital cardiac arrest (OHCA) affects 35,000 Australians each year and only 12% will survive to hospital discharge. The first step to improving OHCA survivorship is to develop a registry to track performance, identify areas for improvement, and measure the effectiveness of solutions. The Northern Adelaide Local Health Network (NALHN) services a population at high risk for OHCA in the northern suburbs of Adelaide, South Australia. The primary aim of this thesis was to develop a hospital based registry to determine incidence, management, and outcome of OHCA within NALHN.

Methods: This thesis outlines (a) the development and validation of the NALHN OHCA registry, and (b) retrospective analyses of registry and associated data. The NALHN OHCA registry was developed in accordance with the Utstein-style guidelines as a prospective population-based quality assurance registry of all OHCAs treated at NALHN hospitals. A simple and consistent clinical definition of OHCA was proposed to allow inclusion of non-emergency medical service (EMS) attended OHCAs. Methods of case identification were developed and tested according to the accuracy (sensitivity and positive predictive value) of each source, both individually and combined. Data-linkage was established with the SA Ambulance Service Cardiac Arrest Registry (SAAS-CAR) to quantify age-standardised incidence, baseline characteristics, and outcomes stratified by sex for EMS-treated OHCA, non-EMS witnessed presumed cardiac and obvious non-cardiac sub-cohorts, and hospitalised cohorts. Cardiologist management of cases transported to hospital was assessed by measuring the sensitivity of the decision for emergency coronary angiography with respect to the need for acute revascularisation. Finally, clinical characteristics and outcomes associated with mode of death and adjudicated aetiology were explored in hospitalised patients.

Results: From 2011 onwards, all OHCA cases treated within a NALHN hospital were included in the NALHN OHCA registry. No single data-source identified all OHCAs, but a combination of ED coding and existing clinical registries provided a valid method used to augment EMS-based data. The NALHN catchment area had high incidence of OHCA and there were sex-differences in incidence and outcome, but these were primarily driven by low rates of ventricular fibrillation and differences in underlying aetiology in women. In presumed cardiac patients treated at hospital, emergency coronary angiography was appropriately ruled out, and somewhat effectively ruled in, by both experienced interventional cardiologists and a clinical score. In-hospital mode of death was primarily due

to cardiovascular instability for deaths in the ED, while deaths after admission were due to neurological injury. Mode of death was significantly associated with age, timing of death, and precipitating aetiology, but not sex. Non-cardiac aetiologies represented 40% of the NALHN OHCA cohort and were associated with poor outcome.

Conclusions: The incidence, management, and outcome of OHCA within northern Adelaide was characterised by establishing a high-definition hospital-based registry. The NALHN OHCA registry provides ongoing surveillance of OHCA within northern Adelaide. The results are currently being used to inform development of hospital guidelines, as well as interventions that aim to improve cardiology management and neurological prognostication, and ultimately, OHCA survivorship.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Melanie Ruth Wittwer

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Soli Deo gloria

CHAPTER ONE: INTRODUCTION

1.1 Background and context

1.1.1 Death as a frame of reference for cardiac arrest

Death is both a concept and a reality that may be considered from an endless variety of cultural, spiritual, religious, and biological perspectives. The process of dying involves the progressive cessation of biological functions and activities with death marking the irreversible point of the dying process. Advances in medicine and technology have blurred the lines between life and death such that precise definitions and determinations are increasingly required. Legally, death is defined in South Australia (SA) as (a) irreversible cessation of all function of the brain of the person; or (b) irreversible cessation of circulation of blood in the body of the person.[1] There are no Australian laws that stipulate how death is to be determined but the Australian and New Zealand Intensive Care Society (ANZICS) outline two methods of determining death, neurological and circulatory, in accordance with the Act.[2]

1.1.2 Trajectories of dying

The factors that precipitate death and the process of dying can be complex. Four broad trajectories have been used to describe the ways in which people may die (**Figure 1-1**).[3] Sudden death is, as the name suggests, a sudden unexpected death in a person with high or normal level of functioning e.g. caused by motor vehicle accident, drug overdose, heart attack (acute myocardial infarction, AMI). In this trajectory, the dying process is instant or extremely rapid with a narrow window for intervention and reversal. In contrast, terminal illness, organ failure, and frailty are trajectories characterised by slow to rapid declines in function that eventually result in an expected death. In such cases, acute interventions may be performed to temporarily reverse or halt the dying process, depending on the wishes of the individual and/or their family.

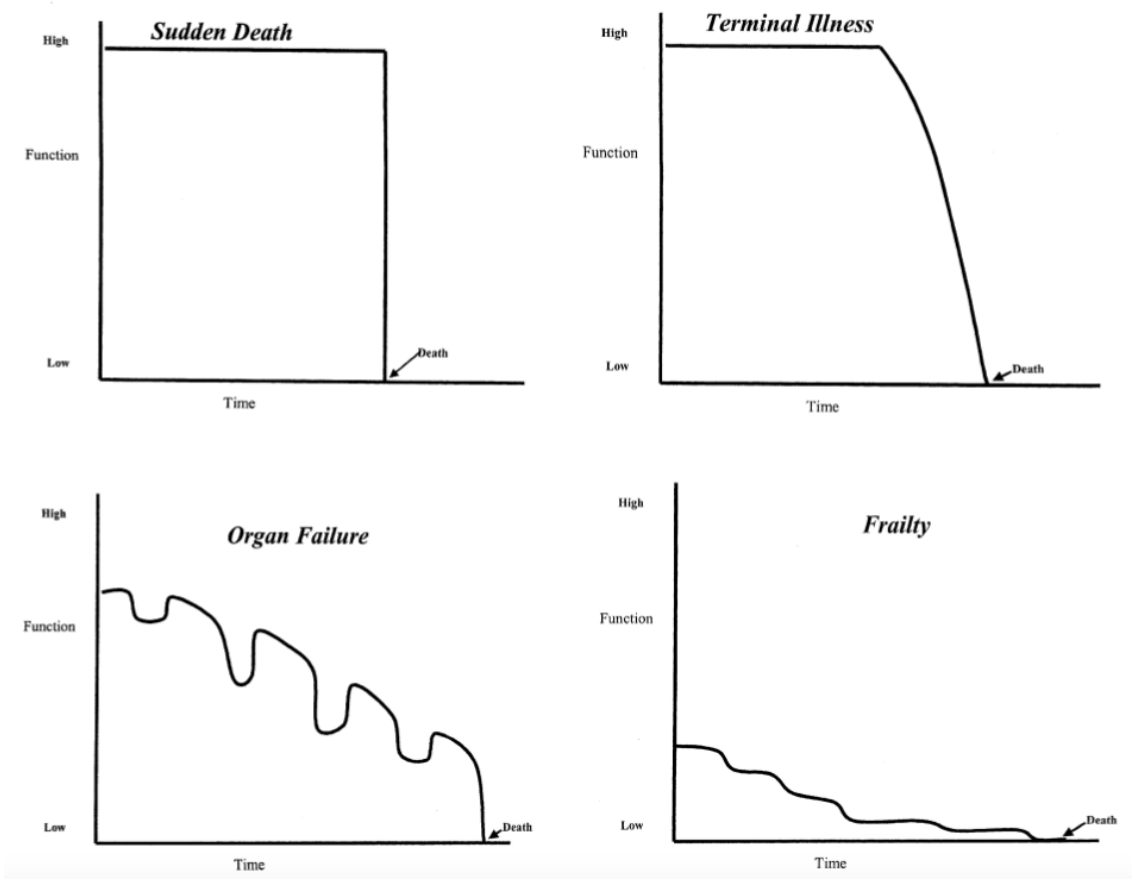

Figure 1-1: Trajectories of dying.
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1.1.3 CARDIAC ARREST

Cardiac arrest is the cessation of normal heart function due to mechanical and/or electrical failure with absence of signs of circulation. Unless circulation is rapidly restored by means of cardiopulmonary resuscitation (CPR), defibrillation, and early advanced care, or in rare cases spontaneously, cardiac arrest becomes synonymous with circulatory death. In patients with neurological death, cardiac arrest inevitably occurs within three minutes after withdrawal of cardiorespiratory support.[2]

Cardiac arrest may be further defined as 'shockable' or 'non-shockable' according to the electrocardiogram (ECG), depending on whether the arrhythmia can be treated using defibrillation (i.e., ventricular fibrillation, VF; ventricular tachycardia, VT) or not (i.e., pulseless electrical activity, PEA; asystole), (**Figure 1-2**). The cause of cardiac arrest may also be defined as cardiac or non-cardiac (see **Chapter 2.4**).

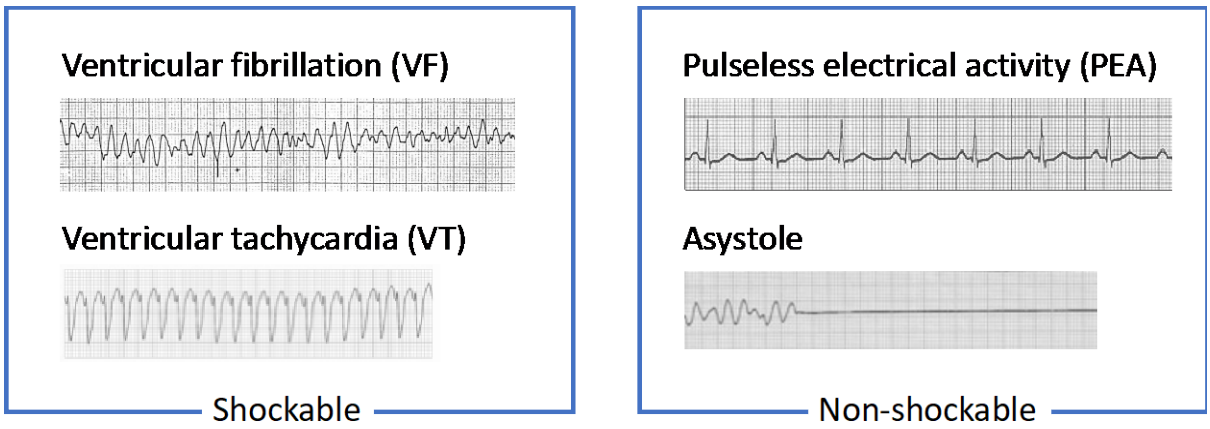

Figure 1-2: Broad categories of shockable and non-shockable initial rhythms.

Cardiac arrest is not a diagnosis, but a clinical event precipitated by an underlying pathophysiology, that falls along the trajectory of dying. Cardiac arrest precedes all circulatory deaths, so it is irrelevant to quantify incidence, management, and outcome of cardiac arrest overall. More important is the investigation of cardiac arrest in specific sub-populations to facilitate (a) implementation of strategies to improve outcomes of preventable deaths, (b) measurement of institutional and provider responses, and (c) assessment of systems of care.

1.1.4 Sudden cardiac death / arrest

Sudden cardiac death (SCD) and sudden cardiac arrest (SCA, resuscitated sudden cardiac death) are sub-populations of interest that represent potential reversible or preventable events. Generally, SCA/SCD is defined as a sudden unexpected cardiac arrest in a person within one hour of symptom onset if witnessed or within 24 hours of symptom onset if unwitnessed.[4–6] SCA and SCD comprise a proportion of the sudden deaths described in the trajectories of dying by Lunney et al[3] (**Figure 1-1**), and generally refer to cardiac arrests from natural cardiovascular causes, excluding obvious non-cardiac causes such as respiratory failure, drug overdose, and trauma.[4,7,8] In Australia, the End Unexplained Cardiac Death (EndUCD) Registry has been established as the first Australian multi-source registry for young cardiac arrest patients aged 1-50.[9] Other SCA/SCD registries, their coverage, and purposes have been covered in a recent review.[10]

1.1.5 Location-based sub-cohorts

In-hospital and out-of-hospital cardiac arrest (IHCA and OHCA, respectively) are broader sub-populations of interest that primarily allow measurement of both institutional and provider responses and systems of care with the common aim of reducing preventable deaths. The Utstein-style guidelines were developed in 1991[11] to provide standardised definitions, core outcomes, and reporting templates for IHCA[12] and OHCA[13], respectively. OHCA is formally defined by absence of circulation in patients attended by emergency medical services (EMS),[13,14] and therefore represents the whole spectrum of cardiac arrest occurring outside the hospital setting. This definition includes SCA, SCD, and other expected and unexpected events (**Figure 1-3**), but excludes patients transported to hospital by private vehicle and obviously deceased patients transported directly to coronial services.

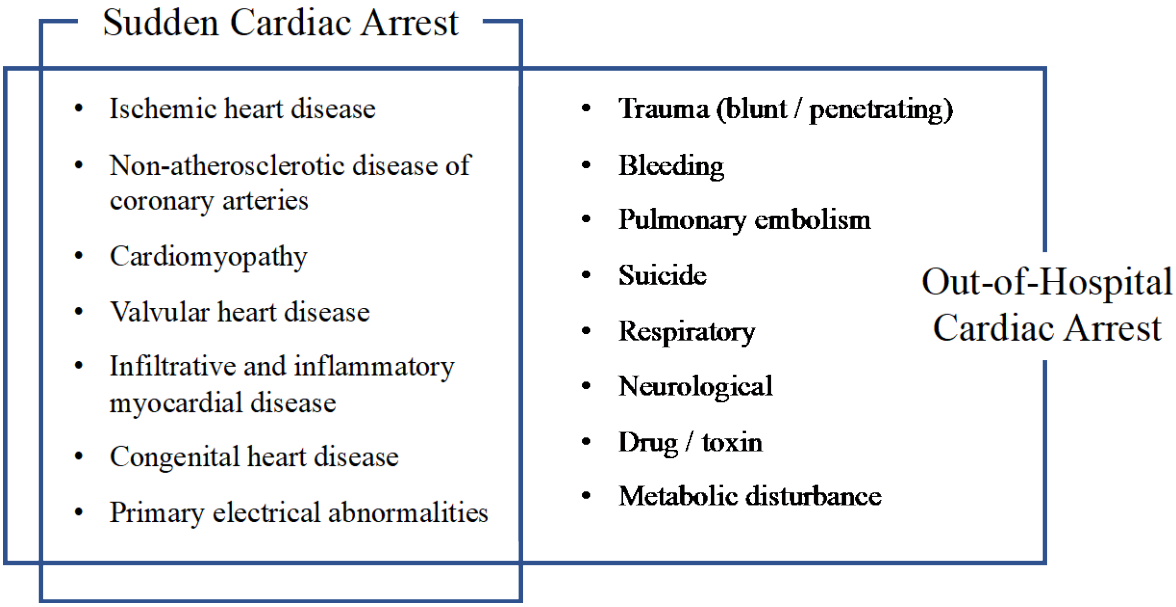

Figure 1-3: A summary of common cardiac and non-cardiac aetiologies of out-of-hospital cardiac arrest.

1.1.6 Scope, significance, and intended outcomes

The Northern Adelaide Local Health Network (NALHN) comprises two public teaching hospitals and other community-based health services within the northern metropolitan area of Adelaide, SA. Northern Adelaide is the highest population growth area in SA and in 2016 the two hospitals serviced a population of approximately 395,000, as well as providing services for over 50,000 people from regional areas. The NALHN catchment is characterised by high rates of cardiovascular disease risk factors, morbidity, and mortality and is one of Australia's most socioeconomically disadvantaged communities.[15]

OHCA represents a medical emergency in patients without access to immediate advanced medical care. Only one in ten patients will survive OHCA and loss of productive years of life and healthcare costs resulting from premature death or disability after cardiac arrest represent a large burden to society.[16] In Australia it was recently estimated that the annual losses in GDP is nearly $100,000 per person, equating to $2 billion dollars per year across Australia, an amount comparable to productivity losses from all cancers combined.[16] There is strong evidence that survival rates can be improved through implementation of quality improvement programs facilitated by robust data collection, analysis, and feedback reporting.[17] Comprehensive and clinically relevant registries are therefore key to improving cardiac arrest survival.[18,19] This thesis describes the rationale, development, and design of the NALHN OHCA registry, which was subsequently used to explore the incidence, management, and outcomes of out-of-hospital cardiac arrest in Northern Adelaide. The end goal of this research is to identify and implement changes to current practice to improve OHCA survivorship within an Australian setting.

1.2 THESIS OVERVIEW

This thesis consists of nine chapters, including a general introduction (Chapter One), a review of the literature (Chapter Two), six research chapters in manuscript format, of which five are published (Chapters Three, Four, Five, Seven, and Eight), and a final general discussion (Chapter Nine) (Figure 4).

Chapter Two aims to provide a review of current literature and knowledge gaps with a focus on Australian OHCA literature. This chapter explores the epidemiology, management, outcomes, precipitating aetiology, sex differences and disparities, and overview of existing registries and methods of OHCA data collection.

Chapter Three describes the rationale, development, and design of the NALHN OHCA registry, including a clinically relevant definition of OHCA developed for the registry which was published in a Letter to the Editor of Resuscitation.[20] The accuracy of the methods used to identify cases were tested and the findings presented in a published manuscript.[21]

Once the NALHN OHCA registry was established, a data-linkage was formed with the SA Ambulance Service Cardiac Arrest Registry (SAAS-CAR) to explore the effect of sex on incidence and outcome of OHCA within NALHN. Chapter Four presents a published manuscript demonstrating that SES and precipitating aetiology, independent of sex, are key factors driving outcome after OHCA.[22]

Chapters Five through Eight explore the in-hospital management and outcome of OHCAs identified within the NALHN OHCA registry. The published manuscript[23] in Chapter Five and study in manuscript format in Chapter Six highlight the accuracy of experienced clinical judgement compared with a clinical score in preventing unnecessary and potentially harmful post-OHCA procedures. A published manuscript in Chapter Seven investigates the timing, location, and mode of death,[24] while a short paper in Chapter Eight provides a description of the entire NALHN OHCA cohort according to adjudicated aetiology.[25]

The final chapter of this thesis presents a discussion of the key findings along with their strengths and limitations. Recommendations for practice, guidelines and future research are presented.

Table 1-1: Thesis overview

Chapter One	Thesis introduction	Context of the study. Thesis structure.
Chapter Two	Literature Review	**Aim:** Present overview of Australian OHCA literature: epidemiology, management, outcomes, precipitating aetiology, sex differences and disparities, and existing registries.
Chapter Three	NALHN OHCA registry protocol	**Aim**: Establish a registry and test methods of case identification. **Manuscript:** Overcoming challenges of establishing a hospital-based out-of-hospital cardiac arrest registry: accuracy of case identification using administrative data and clinical registries.[21]
Chapter Four	NALHN incidence and outcome	**Aim:** Determine sex differences in incidence and outcome. **Manuscript:** Sex differences in incidence and outcome of out-of-hospital cardiac arrest within a local health network.[22]
Chapter Five	In-hospital management	**Aim:** Evaluate in-hospital cardiac management. **Manuscript:** Cardiologists appropriately exclude resuscitated out-of-hospital cardiac arrests from emergency coronary angiography.[23]
Chapter Six	In-hospital management	**Aim:** Evaluate in-hospital cardiac management. **Manuscript:** Comparison and test of a clinical score for predicting acute revascularisation after resuscitated out-of-hospital cardiac arrest. *Unpublished manuscript.*
Chapter Seven	Hospital outcomes	**Aim:** Explore hospital outcomes of timing, location, and mode of death. **Manuscript:** In-hospital mode of death after out-of-hospital cardiac arrest.[24]
Chapter Eight	Hospital outcomes	**Aim:** Explore hospital outcomes according to precipitating aetiology. **Manuscript:** Aetiology of resuscitated out-of-hospital cardiac arrest treated at hospital.[25]
Chapter Nine	Discussion	**Aim:** Provide a critical overview; discuss strengths and limitations; summarise clinical impact and future directions.

CHAPTER TWO: LITERATURE REVIEW

2.1 EPIDEMIOLOGY

2.1.1 DEFINING THE POPULATION

Most of what is currently known about OHCA has been determined from EMS-based registries. Different numerator/denominator combinations have been reported across OHCA sub-populations depending on the aim and objectives of the study, often making direct comparisons between studies difficult. Common numerators (outcome of interest) include bystander CPR, ROSC, transport to hospital, survival to hospital discharge, and survival with favourable neurological outcome. Denominators (population of interest) include EMS-attended, EMS-treated, successfully resuscitated, or hospitalised OHCAs. Sub-populations of interest include non-EMS-witnessed, shockable initial rhythm, and presumed cardiac. A commonly reported group, the Utstein comparator, comprises bystander-witnessed OHCA with initial shockable rhythm.[13] Studies on sudden death or SCA/SCD have been included in limited instances to provide context where OHCA-specific information is lacking.

2.1.2 INCIDENCE

The age-standardised incidence of EMS-attended OHCA per 100,000 population is 98.8 in Australia and 93.6 in SA,[26,27] which is higher than global incidence.[28] This equates to 73 cases per day across Australia. To put this in a broader context, age-standardised incidence of breast cancer, the most common cancer in Australia, is 65 cases per 100,000 population, while the age-standardised rate of acute coronary events is 302 per 100,000 population (http://www.aihw.gov.au). Crude incidence of EMS-treated OHCA per 100,000 population is 45.7 in Australia, and 52.9 in SA[26]; the latter having increased during the preceding 15 years from 35 per 100,000 population.[29] Incidence of OHCA is higher in areas of low socioeconomic status, males, and persons with pre-existing conditions e.g., heart disease.[30,31]

2.1.3 UTSTEIN ELEMENTS

Table 2-1 presents the Utstein core elements for EMS-treated OHCAs across 64% of Australia's population and 14 international registries,[32] as compared with the SAAS-CAR report from the 2016/17 financial year.[33] Rates of initial shockable rhythm and presumed cardiac aetiology were slightly higher within SA, while rates of bystander CPR were lower.

Table 2-1: Comparison of South Australian Utstein core elements with Australian and international data

Utstein element	South Australia 2016/17[33]	Australia 2015[32]	ILCOR 2015[32]
Median age (years)	66	65	64-79
Male sex	67%	68%	57-72%
Private residence	75%	67%	52-85%
EMS-witnessed	14%	15%	6-16%
Bystander witnessed	45%	38%	37-70%
Bystander CPR	63%	77%	19-79%
Initial shockable rhythm	28%	25%	7-38%
Presumed cardiac aetiology	78%	71%	52-95%
Median call to EMS arrival (mins)	8	8	5-11

ILCOR data presented as range across 14 international registries. ILCOR, international liaison committee on resuscitation; EMS, emergency medical services.

2.1.4 SYMPTOMS

Pre-arrest symptoms are difficult to obtain because up to 40% of OHCAs are unwitnessed and OHCA mortality rate can be as high as 90%.[26] An Australian study of presumed cardiac EMS-witnessed OHCAs found that almost half of patients experienced chest pain prior to arrest, while 42% and 38% experienced dyspnoea and altered consciousness, respectively.[34] Although OHCA is frequently described as 'unexpected', it is likely that most patients experience cardiac or other symptoms within four weeks to 24 hours prior to arrest.[35]

2.1.5 Comorbidities

Exploring risk factors for OHCA is complex and somewhat irrelevant given the broad range of associated comorbidities and aetiologies. Instead, most reports focus on burden of pre-existing comorbidities, which has been shown to be negatively associated with survival.[36] An Australian study of EMS-treated OHCAs found a history of hypertension in 32%, diabetes in 17%, COPD in 15%, congestive heart failure in 12%, AMI in 11%, and cancer in 8%.[37] This study was limited to comorbidities obtained from paramedic electronic patient care records and likely under represents the true burden of pre-existing disease because rates reported in international EMS-based[38–40] and hospital-based studies[41–43] are higher. Again, comorbidity varies according to population and reflects underlying aetiology e.g. cardiac aetiologies are associated with lower rates of pre-existing COPD and cancer compared with non-cardiac aetiologies.[40]

2.2 Management

2.2.1 Chain of Survival

Immediately after a patient goes into cardiac arrest, delivery of oxygen and removal of waste by the circulatory system ceases. The brain is highly sensitive to hypoxia (no/low oxygen) and ischaemia (no/low blood flow), and neurons begin to die within minutes after cardiac arrest. For every minute without CPR circulating blood to the brain, the chance of good neurological recovery decreases by 5.5-8%.[44,45]

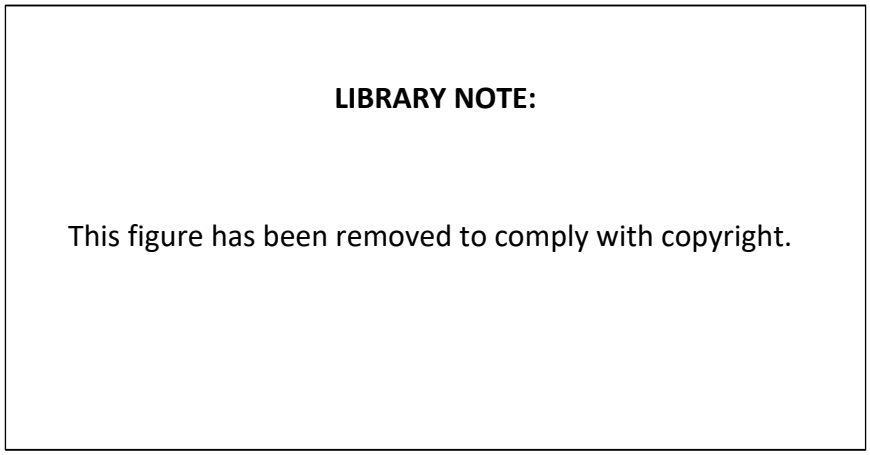

Figure 2-1: Adult OHCA chain of survival.
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Given the time-critical nature of OHCA, American Heart Association introduced the Chain of Survival in 1991[46,47] to emphasise the importance of early recognition and activation of EMS, early CPR, early defibrillation, early advanced resuscitation and transport to hospital, early post-cardiac arrest care, and recovery (**Figure 2-1**). Australian guidelines produced by the Australian and New Zealand Committee on Resuscitation (ANZCOR) are consistent with international guidelines (https://resus.org.au/guidelines/).

2.2.2 Pre-Hospital Termination of Resuscitation

The decision to withhold or terminate resuscitation in the pre-hospital setting remains challenging. A universal termination rule has been developed and implemented in international (but not Australian) guidelines,[48–50] recommending termination when all three criteria are absent: pre-transport ROSC, EMS-witness, and defibrillation. However, the quality of evidence for termination rules is low and the International Liaison Committee on Resuscitation (ILCOR) only makes a conditional recommendation for their use.[51] Each Australian EMS is guided by local protocols and guidelines; SAAS guidelines are based on obvious signs of death, advanced care directives and patient wishes, risk to crew, and appropriate utilisation of resources.[52]

2.2.3 Post-Cardiac Arrest Syndrome

Achieving sustained ROSC in either the pre-hospital or hospital setting is a significant clinical endpoint, but only 40% of patients with ROSC survive to hospital discharge in SA.[33] Hypoxic ischaemic injury may be sustained by organs and tissues, particularly the brain, during the 'no-flow' (pre-CPR) and 'low-flow' (during CPR) intervals. However, a second and more complex phase of recovery may be caused by reperfusion injury caused by the return of blood flow after ROSC. The resulting post cardiac arrest syndrome is characterised by (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, (3) systemic ischaemia/reperfusion response, and often, (4) persistent precipitating pathology.[53] Post-arrest care aims to prevent or treat post cardiac arrest syndrome, which manifests differently according to aetiology and pre-existing comorbidities.[54] Targeted temperature management (TTM) and coronary angiography, discussed in the remainder of this section, are two key post resuscitation strategies to prevent or treat post cardiac arrest syndrome and improve survival.[55,56]

2.2.4 Targeted Temperature Management

Most patients with sustained ROSC who remain comatose will subsequently die due to hypoxic ischaemic brain injury, of which the primary treatment is TTM.[54] Hypothermia decreases brain metabolism, improves glucose control, prevents apoptosis and mitochondrial dysfunction, and decreases inflammatory markers, and has been shown to increase survival outcomes.[57,58] However, recent evidence suggest that avoidance of fever, rather than hypothermia itself, is an important aspect of care in patients who remain comatose after resuscitated OHCA.[59,60]

2.2.5 Cardiac Management – Acute Coronary Syndromes

According to EMS-based assessment, a presumed cardiac aetiology is present in 74% of EMS-treated OHCAs in Australia.[26] In patients surviving to hospital with presumed cardiac aetiology, acute myocardial ischaemia resulting from CAD is thought to be the most common trigger for OHCA (refer to **Chapter 2.4** for discussion of other aetiologies).[61,62] CAD is characterised by the accumulation of atherosclerotic plaques along the lining of the epicardial arteries. Acute Coronary Syndromes (ACS) refer to AMI or unstable angina typically resulting from plaque rupture and/or thrombus occluding the coronary artery. Depending on the severity of the ischaemia, resulting ECG changes, and cardiac troponin level (serum biomarker of myocardial infarction), an AMI may be diagnosed and classified according to ECG characteristics as ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI). The Third Universal Definition of Myocardial Infarction was published in 2012[63] and updated in 2018[64]. Unless stated, the Fourth Definition will be used throughout this thesis (**Figure 2-2**).

2.1.1.1 Coronary Angiography

Cardiac catheterisation procedures are performed in the 'cathlab' and include coronary angiography, a procedure that allows visualisation of the coronary anatomy using contrast dye injected via a catheter inserted into the femoral or radial artery. Depending on the findings, the treating interventional cardiologist may perform percutaneous coronary intervention (PCI) using a balloon with or without stent to restore coronary blood flow.

There are clear guidelines for management of STEMI and NSTEMI within Australia.[65,66] Briefly, STEMI patients presenting <12hrs of symptom onset should have emergency reperfusion (henceforth referred to as 'acute revascularisation' for consistency) with primary PCI <90mins from first medical contact, or else fibrinolytic therapy. Contraindications include age, frailty, and comorbidities. Revascularisation in NSTEMI patients is recommended according to classifications of risk of mortality and recurrent events.

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.
Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.
Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.
Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.
Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.
Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.
Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

Figure 2-2: Fourth universal definition of myocardial injury and myocardial infarction. CABG, coronary artery bypass grafting; cTn, cardiac troponin; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention; URL, upper reference limit. *Used with permission Thygesen et al. Copyright 2018, Oxford University Press.*

2.1.1.2 'Code Blue STEMI' Cathlab Activation

To facilitate guidelines for timely revascularisation in STEMI patients, the 'Code Blue STEMI' system of care has been implemented in SA and is regulated by local guidelines. On provisional diagnosis of STEMI by SAAS paramedics or hospital physicians, a call is made to a cardiac hotline or hospital switchboard, respectively. The on-call interventional cardiologist, designated code STEMI nurse, cathlab nursing team, cardiac physiologist, and radiographer are activated according to their specific roles by pager to prepare the cathlab for patient arrival. Code STEMI key performance indicators are reported through Safety and Quality with quarterly reporting of timing data to comply with door-to-balloon times of <60min and <90min.[65]

2.2.6 Cardiac Management - OHCA

2.2.6.1 Emergency Coronary Angiography

Although there is a clear evidence-based benefit of acute revascularisation for STEMI and high-risk NSTEMI without cardiac arrest, patients with OHCA were routinely excluded from RCTs demonstrating effectiveness of such a strategy. Acute revascularisation in the minority of patients who regain consciousness post-ROSC is not disputed.[67–70] However, the clinical benefit of this strategy in the majority who remain comatose with likely irreversible brain injury has been questioned due to lack of evidence.[69,71–74]

The first report of emergency coronary angiography after resuscitated OHCA was published in 1995.[75] This study was conducted between 1989 and 1994, and of 11 patients with STE and acute revascularisation, 6 (55%) survived to hospital discharge. The first systematic review and meta-analysis of subsequent observational studies found that emergency coronary angiography, compared with a conservative approach, was significantly associated with survival (odds ratio: 2.78; 95% CI: 1.89, 4.10).[76] More recent analyses demonstrate similar results.[77–79] In comatose STEMI undergoing PCI, reported survival in all studies was >65%.[77]

Based on accumulating evidence, international guidelines published in 2000[80] recommended early revascularisation in patients aged <75 years with suspected ACS and signs of shock, and by 2010 the guidelines[81] recommended selective emergency revascularisation despite the absence of STE, chest pain, or consciousness. Consistent with guidelines produced by ILCOR and other international associations,[82–84] ANZCOR guidelines remain broad with

relatively little change between 2010[85] and 2016[54]:

- ANZCOR recommends emergency cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select adult patients with ROSC after OHCA of suspected cardiac origin with ST elevation on ECG (strong recommendation, low-quality evidence).
- ANZCOR suggests emergency cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select adult patients who are comatose with ROSC after OHCA of suspected cardiac origin without ST elevation on ECG (weak recommendation, very-low-quality evidence).

Importantly, early guidelines recognised that traditional ACS diagnostic tools such as patient history and physical examination, ECG, and troponin, even when used in combination, could not be used to reliably exclude ACS in the prehospital and ED settings. However, the time-critical nature of OHCA, clinical complexity, and high mortality continues to fuel the ongoing debate over timing and benefit of acute revascularisation, particularly in comatose patients presenting with initial non-shockable rhythms and absence of post-ROSC STE.

2.2.6.2 Current controversies: OHCA Without ST-elevation

In 1997, Spaulding et al[61] provided the first report of emergency coronary angiography performed irrespective of pre-hospital clinical or ECG findings (referred to as a 'non-selective' approach), the findings of which were later confirmed in a larger study by the same group.[62] Of note, the authors reported that 58% of patients without STE had significant CAD (>50% stenosis) and 26% had successful PCI. The high rate of observed acute myocardial ischaemia in the non-STE cohort appeared to confirm the benefit of non-selective emergency coronary angiography for all OHCA with suspected ischaemia. However, these findings were not replicated in other cohorts[86–88] and the inclusion criteria of several studies raised concerns of selection bias.[76,89] Recently, a systematic review and meta-analysis of unbiased observational studies confirmed that the presence of STE indicates high likelihood of acute revascularisation (high specificity), while absence of STE does not indicate absence of need for acute revascularisation (low sensitivity).[90]

By 2015, the international interventional cardiology community demanded clear evidence of the benefit of emergency coronary angiography in patients without STE from randomised controlled trials (RCT).[91,92] Several RCTs have since been initiated (**Table 2-2**)[93–99]; see Yannopoulos et al[74] for detailed comparison. Previous systematic reviews and meta-analyses suggested that early (<12hrs) coronary angiography was associated with both increased short-term and long-term survival and good neurological recovery.[100,101] Most recently, Verma et al[102] included pilot data from ARREST[94] and DISCO[97] and completed data from COACT[95] and found no difference in survival, neurological status, or rate of PCI (24%) in patients who underwent emergency coronary angiography versus delayed / none. The authors concluded that further work is required to refine patient selection criteria.

Table 2-2: Randomised clinical trials of coronary angiography for OHCA without ST-segment elevation.

Protocol Title	**Clinical Trial Registration**	**Status**
ACCESS	NCT03119571	Terminated prematurely. Results published on clinicaltrials.gov
ARREST[93]	NCT03872960	Pilot data published 2017[94]; expected primary completion November 2021
Cardiac Catheterisation in Cardiac Arrest	NCT02587494	Expected primary completion date December 2018.
COACT	NTR4973	Results published.[95]
COUPE[103]	NCT02641626	Completed. No published results.
DISCO[96]	NCT02309151	Pilot data published 2019[97]; expected primary completion date December 2023
DISCO-noCOMA	NCT04876222	Expected primary completion date May 2023
EMERGE[104]	NCT02876458	Terminated prematurely. Results published.[105]
PEARL	NCT02387398	Terminated prematurely. Results published.[98]
TOMAHAWK[99]	NCT02750462	Completed. Results published.[106]

2.2.6.3 Current controversies: OHCA with Non-Shockable Initial Rhythm

The association between non-shockable initial rhythm and poor outcome is well established, and on this basis a recent scientific statement presented limited evidence of benefit for emergency coronary in such patients.[74] However, autopsy studies demonstrate similar rates of cardiac ischaemia for non-shockable OHCA compared with non-STE,[4,107–109] with up to 32% of patients undergoing acute revascularisation in studies of non-selective emergency coronary angiography.[110,111] Propensity score adjusted analyses also confirm that the overall survival benefit associated with emergency coronary angiography is independent of initial rhythm.[112,113] The role of emergency coronary angiography in patients presenting with initial non-shockable rhythm and without STE is less clear due to a lack evidence in unselected cohorts.[114] In isolation, neither initial non-shockable rhythm nor absence of STE are sufficient to exclude patients from emergency coronary angiography, but more data is needed to determine benefit for patients presenting with both attributes.

2.2.6.4 Treatment Algorithms

Treatment algorithms have been developed to assist clinicians with their decision-making, particularly with respect to comatose patients.[69,72,73,102] In summary, emergency coronary angiography is recommended in patients with STE after consideration of the following unfavourable characteristics: unwitnessed arrest, no-flow >10 minutes, low-flow >20mins, ongoing CPR, age >85, initial non-shockable rhythm, pH <7.2, lactate >7, end stage renal disease, missing brainstem reflexes, and myoclonus or brain oedema. A similar protocol for the management OHCA without STE was developed as part of the most recent systematic review and meta-analysis by Verma et al,[102] with additional recommendations to (a) assess the patient's cardiac and noncardiac status, (b) consult with an interventional cardiologist and primary caregivers, and (c) evaluate expectations of the treatment options.

2.2.6.5 Prediction tools

Another approach researchers have used to determine which patients with OHCA will benefit from emergency coronary angiography is to develop prediction tools based on clinical characteristics and coronary angiography findings. Unfortunately, none of the published tools

have been developed in cohorts associated with a non-selective approach to emergency coronary angiography[115,116] or in OHCA-specific cohorts.[117]

Clinical judgement or 'gestalt' refers to the unstructured method of diagnosis based on recognition of patterns of disease. Historically, clinical judgement has been considered superior to, or at least as good as ACS (without cardiac arrest) diagnostic tools because it takes an individualised, wholistic approach to identification of disease.[118–120] However, a recent multicentre study provided evidence that clinical judgement alone was inaccurate and should not be used independently of validated ACS prediction tools.[121] There are no validated prediction tools for emergency coronary angiography after OHCA and although current practice relies on clinical judgement, the accuracy of this approach is unknown.

2.2.7 Prognostication

Despite advances in post-cardiac arrest care, particularly with respect to TTM and emergency coronary angiography, many patients will have suffered irreversible hypoxic and post-ROSC damage to their organs and tissues and have a high likelihood of in-hospital death or poor neurological recovery. Prognostication is therefore an important tool that aims to avoid the pursuit of futile treatments in the setting of poor outcome as well as prevent inappropriate withdrawal of life-sustaining therapy (WLST) in patients who may achieve good neurological recovery. Similar to emergency coronary angiography, several prediction tools and clinical guidelines have been developed to aid clinicians in their prognostication of patients who remain critically ill post-ROSC, but the most reliable combination and timing of assessments remains unknown.[54,122–126] Unfortunately, the quality of evidence underpinning neurological prognostication tools has been impacted by significant sources of bias such as the self-fulfilling prophesy, sedation, and medications. In particular, the self-fulfilling prophesy is difficult to avoid in Australia because it is unethical and culturally inappropriate to *not* withdraw life-sustaining therapy if such therapy is deemed futile, the decision for which may or may not have been influenced by the prognostic tool being tested.

2.3 OUTCOMES

Outcome reporting for OHCA is guided by the Utstein-style guidelines[13] and the Core Outcome Set for Cardiac Arrest (COSCA).[127] The Utstein core outcomes include event survival (ROSC at hospital), any ROSC, survival to hospital discharge or 30-days, and neurological outcome (cerebral performance category, CPC, and/or modified Rankin Scale, mRS) at discharge in the Utstein comparator (shockable bystander witnessed) and the EMS-treated populations.

2.3.1 SURVIVAL

In Australia, the final outcome for more than 95% of EMS-attended OHCAs is death.[26] This is not to imply that the chain of survival in Australia is failing, but rather that EMS-attended OHCAs without attempted resuscitation (52% of the EMS-attended population) may not be representative of a population with preventable death. Unfortunately, even in Australia, sensationalism has been used to promote OHCA awareness. Out of concern that such sensationalism is misleading to the public I wrote a letter to a major Australian OHCA charity highlighting some of the problems with such a strategy (**Appendix A**).

Overall, about 33% of EMS-treated OHCAs will gain ROSC in the pre-hospital setting across Australia and New Zealand, 28% will have ROSC on arrival to hospital, and 12% will survive to hospital discharge or 30 days.[26] Rates of pre-hospital ROSC are lower in SA and overall survival is reported at 10.5%.[26,33] Survival in the Utstein comparator group was reported as 31% across Australia and New Zealand and 35% in SA, compared with 56% in Seattle, and 47% in Denmark.[26] Of OHCAs transported to hospital in Australia, limited data has revealed that 81% survived to admission and 52-54% survived from admission to discharge.[56,128]

The main factors that influence OHCA survival, also known as Utstein predictors, are well-established and include younger age, public location of cardiac arrest, shockable initial rhythm, bystander witnessed, EMS witnessed, bystander CPR, defibrillation, EMS response time <5mins, pre-hospital ROSC, TTM, cardiac aetiology, and coronary revascularisation.[44,89,129–132] OHCA systems of care that focus on strategies to enhance the coordination of care between each element of the Chain of Survival have been effective in improving outcomes.[133] Over the last 15 years, the system of care implemented by the Victorian Ambulance Service has resulted in a 2.1-fold increase in relative odds of survival to

hospital discharge for EMS-treated patients aged >15 years.[134] The impact of these targeted initiatives on bystander CPR and survival is presented visually in Nehme et al[135].

2.3.2 Neurological outcomes

Survival with good neurological functioning has been recognised as an important patient-focused outcome and has been crudely assessed as a CPC score of 1-2 and/or mRS of 0-3.[13,127] There is no Australian data for neurological outcome after EMS-attended or treated OHCAs. In hospitalised OHCAs of medial aetiology, McKenzie et al[136] found 91% of survivors were discharged with CPC 1-2 , which is higher than two other small single-centre Australian studies.[137,138] In accordance with Australian ethical and cultural practices of WLST, it is likely that fewer patients will be discharged with poor neurological outcomes compared with Asian countries such as Taipei and Korea or even the United States of America where WLST is less common.[32,131,139]

2.3.3 Long-term outcomes

Research has shown that up to 50% of survivors with good neurological recovery may have mild-moderate cognitive impairments such as memory deficit, are at high risk of anxiety, depression and post-traumatic stress disorder, and may continue to suffer problems with fatigue and concentration several years post OHCA.[140–144] Reports on long-term recovery have increased in the last 10 years and an AHA scientific statement on survivorship was published in 2020.[144] Australian data at 12-months post-OHCA suggests that physical and mental health is not significantly different from population norms, good functional recovery is achieved in 65%, mean quality of life approaches full health, and many are able to return to work.[145,146] Although this data appears promising, fatigue and mild cognitive impairment were prevalent in this population with potential for significant impact on work and personal life. The caregiver (includes the partner, spouse, significant other, or primary caregiver) may also report higher levels of anxiety, depression, and post-traumatic stress disorder as compared with the survivor.[147,148]

2.3.4 In-hospital death

2.3.4.1 Withdrawal of life-sustaining treatment

Life-sustaining treatments are those that prolong life but do not treat the underlying cause of cardiac arrest and include cardiopulmonary resuscitation, mechanical ventilation, haemodialysis, left ventricular assist devices, antibiotics, and artificial nutrition and hydration. WLST becomes an important aspect of care after resuscitated OHCA for some patients. End of life care is guided by relevant Australian policies and statements within the ED[149] and for inpatients.[150]

Avoiding inappropriate WLST in patients who may otherwise make a good neurological recovery remains a challenge, especially in Australia where the substitute decision-makers may choose to withdraw care early (<72hrs post-ROSC) rather than prolong suffering. Early WLST is now recognised as a contributor to increased mortality after OHCA in western countries and it has been estimated that up to 21% of patients with early WLST may have otherwise survived with good neurological functioning.[151,152]

2.3.4.2 Mode of Death

In-hospital death after resuscitated OHCA was first described by Herlitz et al in 1995,[153] who reported that 48% of deaths were due to irreversible brain damage compared with myocardial damage alone (10%) or a combination of brain and myocardial damage (42%). To facilitate further development of post-resuscitation systems of care, it is necessary to understand factors associated with both non-survival and survival. Mode of death, or reason for death, has since been reported in a limited number of studies but a lack of consensus on definition and standardised classification has made comparisons and general conclusions difficult (**Table 2-3**).[108,151,154–160] The most common categories include cardiovascular instability, multi-organ failure, and neurological injury; the latter sometimes including brain death. More recently, two unvalidated structured categorisations have been proposed: one defined five categories without consideration of brain death or WLST,[160] while another proposed nine categories but is as yet unpublished.[161] Once standardised classifications are developed, mode of death is likely to become an important endpoint against which the effectiveness or appropriateness of post-ROSC interventions may be measured.

Table 2-3: Published reports of mode of death after resuscitated OHCA.

	Cohort	Site	Inclusion criteria	Age	*n**	Mode of death					
						Cardio-vascular instability	Multi-organ failure	Non-neurological WLST	Neurological WLST	Brain death	Neurological injury (Neurological WLST + brain death)
Laver 2004[154]	OHCA	Single	ICU admission	All	65	23%	9%	-	-	-	68%
Olasveengen 2009[155]	OHCA	Multi	ICU admission	≥18yrs	116	17%	13%	-	-	-	70%
Dragancea 2013[156]	IHCA / OHCA	Single	ICU admission, TTM	All	86	16%	13%	-	-	-	71%
Mulder 2014[158]	OHCA	Single	Sustained ROSC, comatose	≥18yrs	78	9%	-	-	-	10%	-
Callaway 2014[157]	OHCA	Multi	Alive ≥60 mins after arrival	>18yrs	3981	12%	5.8%	10%	61%	11%	72%
Elmer 2016[151]	OHCA	Multi	Alive ≥60 mins after arrival	≥18yrs	4265	20%	-	10%	59%	11%	70%
Chen 2018[108]	IHCA / OHCA	Single	Sustained ROSC	All	982	35%	-	12%	45%	8%	53%
Du Pont-Thibodeau 2018[159]	OHCA	Single	PICU admission	<18yrs	86	19%	-	-	34%	47%	81%
Witten 2018[160]	OHCA	Single	ICU admission	All	226	21%	-	4%	73%	-	73%

ED, Emergency Department; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; WLST, withdrawal of life sustaining therapy. **n*-value represents number of OHCAs included in reports of mode of death in all cases except Dragancea *et al* 2013 and Chen *et al* 2018, where the *n*-value represents both IHCA and OHCA.

2.4 AETIOLOGY

The reversible causes of cardiac arrest may be remembered by the Four Hs and Ts mnemonic[162]:

- Hypoxia
- Hypovolaemia
- Hyperkalaemia, hypokalaemia, hypoglycaemia, hypocalcaemia, acidaemia and other metabolic disorders
- Hypothermia
- Tension pneumothorax
- Tamponade
- Toxins / poisons / drugs
- Thrombosis (myocardial / pulmonary)

While this mnemonic may be useful in the emergency setting, elucidating the underlying aetiology of OHCA is more complex and often multifactorial. This section presents a brief overview of the current knowledge of precipitating aetiologies associated with OHCA.

2.4.1 SUBSTRATE AND TRIGGER

As previously introduced, cardiac arrest represents a clinical event along the pathophysiological continuum of dying, and results from a cumulation of predisposing factors and risks, underlying pathophysiological processes, and anatomic or functional substrates, with a final trigger leading to a common pathway of rhythm disturbance (VF, VT, asystole) or haemodynamic failure (as in PEA).[163–165] In more simple terms, the inability of the heart to maintain a perfusing rhythm is a 'symptom' of an underlying pathology such as acute myocardial infarction, sub-arachnoid haemorrhage, or respiratory arrest, or of an external cause such as trauma or drowning.

2.4.2 DIAGNOSTIC CHALLENGES

The complex interplay between substrate and trigger, or factors influencing the transition from stable to unstable disease state, makes defining the precipitating aetiology difficult. EMS-based assessments of OHCA aetiology, in the absence of obvious causes, are frequently

used as a surrogate for true aetiology in the literature but only represent preliminary diagnoses that require confirmation by autopsy or further in-hospital investigations. Unfortunately, in Australia and many other countries, the majority of deaths occurring outside of the hospital setting do not undergo routine autopsy to confirm underlying aetiology, and death certificate diagnoses are unreliable.[166] As a result, information on precipitating aetiology in the non-hospitalised OHCA population remains limited. For the small proportion survival to hospital admission, in-hospital diagnostic tools include coronary angiography, CT-scans (brain, chest), blood tests, echocardiography, MRI, toxicological screening, and further screening for specific diagnoses as appropriate e.g. flecainide challenge test for Brugada. Even after comprehensive investigations or autopsy a single diagnosis may not be reached, and in some cases several pathological mechanisms are likely.[108]

2.4.3 Categorisation

Many authors have attempted to identify clinically relevant categories for primary cause of cardiac arrest,[4,108,163–165,167,168] with the simplest being (a) primary cardiac, (b) cardiac consequence of non-cardiac condition, and (c) terminal mechanism of inevitable death.[169] Attempts have also been made to additionally stratify cases according to mechanism and risk.[165,170] Table 2-4 demonstrates the lack of consensus between cardiac arrest aetiology classifications proposed in the literature.

Prior to the 2015 update,[13] the Utstein-style guidelines classified all cases without an obvious cause as 'presumed cardiac',[171] which has resulted in over-reporting of cardiac aetiology in the literature. In Australia, 74% of EMS-treated OHCAs are presumed cardiac according to EMS assessment.[26] Three studies have found that an EMS-based cardiac diagnosis was incorrect in 9% of cases,[166,172,173] which raises the question of bias in studies that only include cases based on an EMS-based assessment. Additionally, an Australian study of presumed cardiac cases aged 16-39 years found that 39% had a non-cardiac aetiology on autopsy.[174] In contrast, the two large population-based autopsy studies reported a 60% prevalence of adjudicated cardiac aetiology in cases without obvious non-cardiac aetiology.[4,175] A large French hospital-based study[168] reported the same prevalence of adjudicated cardiac aetiology in admitted OHCAs but prevalence was much lower (25%) in a smaller hospital-based study from the US.[108] Variation in distribution of aetiology observed between hospitals is likely to

reflect (1) the population serviced by that centre (e.g. high vs. low rates of opioid dependence and recreational drug overdose), (2) pre-hospital termination and transport rules, and (3) proportion of cases retrieved to external acute care facilities.

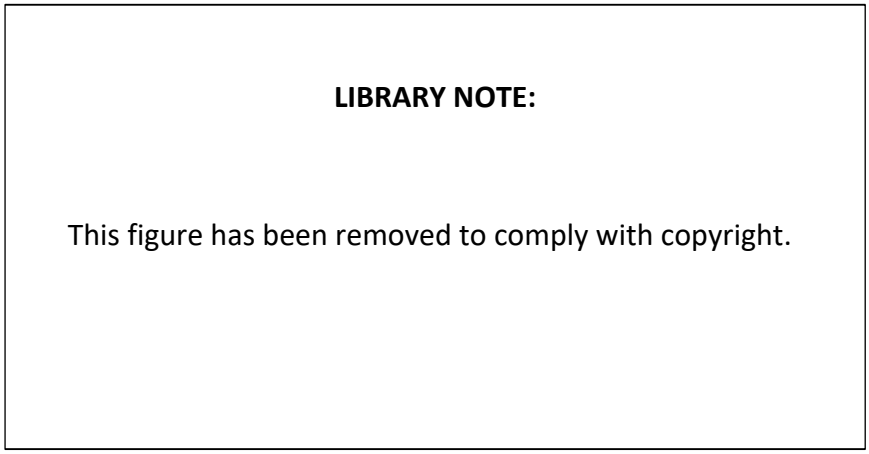

Figure 2-3: Causes of sudden cardiac death (SCD) and rates (A) and age of SCD onset in each disease (B).
ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; LQTS, long-QT syndrome; NIDCM, non–ischemic dilated cardiomyopathy; PUFA, polyunsaturated fatty acids.
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2.4.3.1 Primary cardiac

Cardiac aetiologies are generally considered as due to heart disease, which includes CAD (myocardial injury and infarction[64]), cardiomyopathy, primary arrhythmia, genetic

channelopathy, congenital heart disease, valvular disease, tamponade, myocarditis, and other miscellaneous cardiac causes. Hayashi et al[164] presented a helpful illustration of cardiac aetiology distribution, proposed predisposing factors and risks, substrates, and triggers, and age of onset according to aetiology (**Figure 2-3**). Compared with non-cardiac aetiologies, patients with OHCA resulting from cardiac aetiology, both presumed and adjudicated, are older, more likely to be male, present more often with a shockable initial rhythm, and are more likely to survive to hospital discharge with good neurological outcome.[168,176–178]

2.4.3.2 Non-cardiac

Non-cardiac OHCAs generally represent a cardiac consequence of non-cardiac condition. In accordance with the Utstein-style guidelines, non-cardiac aetiologies include medical aetiologies (respiratory, neurological, metabolic, and other causes), trauma (blunt, penetrating, or burn injury), drug overdose (deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol), drowning, electrocution, and asphyxia (external causes of asphyxia, such as foreign-body airway obstruction, hanging, or strangulation).[13] Even though they comprise up to 40% of the EMS- and hospital-treated populations, non-cardiac causes of OHCA have been routinely excluded from many studies due to low perceived survival and broad diagnostic heterogeneity. An in-depth exploration of all non-cardiac aetiologies is outside the scope of this review. Most non-cardiac OHCAs are of respiratory origin and are typically characterised by progressive asphyxia and hypoxia with gradually deteriorating cardiopulmonary function that results in PEA or asystole. The mechanisms and consequences of the post cardiac arrest syndrome differ compared with cardiac OHCA, and survival rates are lower.[177,179]

2.4.3.3 Terminal mechanism of inevitable death

OHCAs resulting from end-stage medical conditions represent expected deaths and are often excluded from OHCA reporting, along with other obvious non-cardiac aetiologies. Such patients may be categorised as cardiac e.g., end-stage heart failure, or as a cardiac consequence of a non-cardiac condition e.g., end-stage lung disease or end-stage malignancy.

Table 2-4: Proposed aetiological classifications.

Engdahl 2002[167]	**Perkins 2015**[13] *Utstein-style guidelines*	**Geri 2017**[168]	**Chen 2018**[108]	**Tseng 2018**[4] *Adjudicated aetiology of WHO-defined SCD*	**Narayan 2019**[165] *Potential clinical taxonomy*
Cardiac - ischaemic					
Ischaemic cardiac disease	**Cardiac**	**Ischaemic heart disease** Acute coronary syndrome Acute coronary syndrome without occlusion Coronary spasm	**Acute coronary syndrome** Cardiac cath with acute lesion STEMI on ECG	**Acute CAD** Acute coronary lesion AMI **Chronic CAD** Chronic coronary lesion Healed AMI Hypertensive CAD Ischaemic CM	**Acute myocardial ischaemia** Acute coronary occlusion Coronary artery spasm Coronary artery dissection **Prior AMI, no acute ischaemia** HFrEF, HFmEF, HFpEF (Ischaemic CM)
Cardiac – non-ischaemic					
Non-atherosclerotic disease of coronary arteries **Cardiomyopathies** **Valvular heart disease** **Infiltrative and inflammatory myocardial disease** **Congenital heart disease** **Primary electrical abnormalities**	**Cardiac**	**Structural non-ischaemic heart disease** Dilated CM Valvular CM Hypertrophic CM Congenital CM Myocarditis Stress CM Arrhythmogenic right ventricular dysplasia Restrictive CM	**Arrhythmia secondary to CM** Baseline EF <=35% or cardiomegaly on radiography AND VF/VT Post-arrest EF <=20% AND VF/VT **Left ventricular failure (Cardiogenic shock due to acquired or chronic CM)** Cardiogenic shock AND asystole/PEA Pre-arrest EF <=20% AND asystole/PEA	**Cardiomyopathy** Alcoholic CM Amyloidosis Arrhythmogenic right ventricular dysplasia Drug-induced CM HIV CM CM with valve prolapse Noncompaction Nonischaemic / dilated / idiopathic CM Stress CM **Hypertrophy** Hypertensive heart disease Hypertrophic CM Unspecified hypertrophy	**Dilated idiopathic CM** HFrEF, HFmEF, HFpEF (non-ischaemic CM) **Hypertrophic CM** **Inherited CM** Arrhythmogenic right ventricular dysplasia Other Desmosomal proteins Lamin A/C Other proteins

		Primary electrical disease Conduction disorder Brugada Congenital long QT Acquired long QT Early repolarisation Wolff-Parkinson White ScPVCs CPVT **Miscellaneous** Toxic Pacemaker dysfunction Metabolic Ionic major disturbance **Idiopathic ventricular fibrillation**	**Congenital arrhythmia** Brugada Hypertrophic CM Bypass tract Outflow tract tachycardia Long QT **Structural heart disease** Evidence of valvular pathology, HOCM or septal defects Arrhythmogenic right ventricular dysplasia **RV failure** Chronic pulmonary hypertension leading to RV failure AND asystole/PEA Obstructive shock	**Primary electric disease** Complete heart block Congenital long QT Brugada Short QT CPVT Idiopathic VF **Other arrhythmic** Acquired long QT Bicuspid aortic valve MINOCA – acute / healed CIED concern / failure Myocarditis Acute AVR failure Mitral valve prolapse Critical aortic stenosis **Cardiac non-arrhythmic** AMI: pump failure AMI: rupture + tamponade Acute or chronic HF Pericarditis	**Inherited channelopathy** Long QT Brugada Short QT CPVT Idiopathic VF **Congenital heart disease** Related to arrhythmia Cyanotic lesions Tetralogy Transposition of great vessels Univentricular hearts Ebsteins **Sarcoidosis** **Mitral valve prolapse** **Aortic disease**
Non-cardiac					
Trauma **Other bleeding** **Pulmonary embolism** **Suicide** **Lung disease** **Malignancy** **Drug overdose** **Suffocation** **Near drowning** **SIDS**	**Anaphylaxis** **Other medical cause** **Traumatic** **Drug overdose** **Drowning** **Electrocution** **Asphyxia** **Not recorded**	**Neurological disease** **Acute respiratory failure** **Other condition**	**Toxicological** **Asphyxia** **Respiratory failure** **Neurological catastrophe** **Trauma** **Exsanguination** **Distributive shock** **Metabolic derangement** **Other / Unknown**	**Acute renal failure** **Aortic dissection** **Aspiration, asphyxia** **Chemical overdose** **Gastrointestinal** **Metabolic** **Infection** **Neurological catastrophe** **Pulmonary embolism** **Other non-cardiac**	**Obstructive sleep apnoea** **Neuromuscular disorders** **Schizophrenia** **Neurological catastrophe** **Infection** **Metabolic** **Gastrointestinal** **Aspiration, asphyxia** **Disseminated cancer** **Hypercoagulable states**

AMI, acute myocardial infarction; AVR, aortic valve replacement; CAD, coronary artery disease; CM, cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; EF, ejection fraction; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; MINOCA, myocardial infarction with non-obstructive coronary arteries; PEA, pulseless electrical activity; PVC, premature ventricular contractions; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia

2.5 Sex differences and disparities

2.5.1 Definitions

The concepts of sex and gender are related but distinct. According to Australian Government guidelines,[180] sex refers to chromosomal, gonadal, and anatomical biological characteristics, whereas gender refers to a person's social and cultural identity, expression, and experience. Sex and gender disparities refer to inequalities in treatment that are not justified by existing biological or social and cultural differences.

Sex and gender are key determinants of health but are rarely disaggregated in medical research. Australian policies and procedures for reporting sex- and gender-specific health data are minimal,[181] and in addition, the Utstein-style guidelines[13] define the variable 'gender' as 'sex'. As a result, much of the OHCA literature uses the terms sex and gender interchangeably and lacks reporting on sex and gender as separate constructs. In the context of this thesis, and for the sake of consistency, the term 'sex' will be used.

2.5.2 Background

The Framingham study was a landmark prospective cardiovascular disease cohort study with initial enrolment of participants aged 30-62 in 1948. After 26 years of follow-up, Schatzkin et al[6] reported significant sex differences in occurrence of sudden death, defined as any death occurring within one hour of onset of symptoms and without other probable cause of death suggested by medical history. Of all confirmed coronary heart disease (CHD) deaths in this study, females were significantly less likely than males to experience a sudden death (females 34% vs. males 46%, $p<0.05$), and of those with sudden death, females were less likely to present with a diagnosis of prior CHD (females 32% vs. males 53%, $p<0.05$). The authors also found that classic CHD risk factors such as smoking, blood pressure, cholesterol, glucose, and weight were not associated with sudden death in females. The conclusion drawn from this study was that sudden death was the first presentation of CHD in two thirds of females, and this in the absence of traditional CHD risk factors. These two factors have driven subsequent research for the last three decades.

Reports of sex differences for OHCA, as compared with SCA/SCD, are much more recent. In 1999, Perers et al[182] published the first EMS-based report of OHCA sex differences from Sweden. Since then, similar findings have been reported across the globe and confirmed in

three recent meta-analyses.[183–185] Sex differences in OHCA were the subject of a consensus conference on cardiovascular resuscitation research[186] and have been explored in two reviews.[187,188]

2.5.3 Incidence

Reported incidence of OHCA stratified by sex in Australia is limited. The age-standardised rate per 100,000 person-years for EMS-attended OHCAs in Victoria is 111 for males and 56.8 for females.[189] The rate in presumed cardiac OHCA in Victoria and Queensland ranges from 42-46 for females, and 78-103 for males, while the rate for EMS-treated presumed cardiac OHCA in Queensland is 20.8 for females and 53.1 for males.[189,190] Internationally, only three registries have stratified incidence according to sex, but all confirm that males consistently experience OHCA at a rate more than double that of females.[191–193] Incidence rates stratified by age also demonstrate that women have similar incidence to that of men aged 10 years younger.[190,194]

2.5.4 Presentation

2.5.4.1 Utstein core elements

Sex differences in presentation of OHCA have been repeatedly confirmed in Australian and international populations. Women are older, less likely to arrest in a public place, less likely to have a witnessed arrest, less likely to have VF/VT, and less likely to be diagnosed with a presumed cardiac cause of arrest.[183–185,195] In patients with presumed cardiac aetiology, females are less likely to present with ST-elevation on the post-ROSC ECG in some,[43,196,197] but not all studies.[42,198] Although bystander CPR has been reported as 6% lower in females, and in the United States this perceived as due to concerns about sexual assault,[199] most other studies report similar rates between sexes.[184,195] In the broader setting of AMI, women are known to delay seeking treatment[200,201] and it is likely this is also the case for women with OHCA, irrespective of precipitating aetiology.

2.5.4.2 Symptoms

There are no studies that have investigated sex-differences in pre-arrest symptoms of EMS-attended or EMS-treated OHCA. In patients surviving to hospital, women without obvious non-cardiac cause of arrest were more likely to have respiratory or neurological pre-arrest symptoms than men.[196] Symptoms preceding SCD were found in half of males and females, and of those, males were more likely to have chest pain while females were more likely to have dyspnoea and other warning signs such as syncope, palpitation and flu-like symptoms.[35] Observed differences in pre-arrest symptoms, initial rhythm, and ECG characteristics are likely driven by precipitating aetiology.

2.5.4.3 Comorbidities

There is only one pre-hospital study from Denmark that has specifically investigated sex-differences in comorbidities associated with OHCA. Wissenberg et al[38] investigated all EMS-treated OHCAs with presumed cardiac aetiology aged >12years by linking EMS-based data with hospital data to obtain discharge diagnoses from within the previous 10 years. The authors found that more women had a history of COPD and psychiatric illness, whereas more men had a history of cardiovascular disease. Numerically, there was little difference in rates of diabetes and cancer,[38] which has been confirmed in other international OHCA populations.[202–205] Interestingly, in a large Japanese cohort of cardiac and non-cardiac EMS-treated OHCAs there was no difference in rates of documented history of heart disease including coronary artery disease, chronic arrhythmias, congenital heart disease, or pacemaker between males and females.[206] Within an EMS-treated Australian population, women were more likely to have a higher number of comorbidities compared with men.[37] Findings for patients surviving to hospital admission are similar.[41–43,196] Sex-differences in individual comorbidities have not been reported in Australia, nor are they covered in the aforementioned reviews.[187,188]

2.5.4.4 Socioeconomic status

Socioeconomic status (SES) may be derived according to level of education, income, employment, or depravity indices measured at either the individual or area level e.g., individual education attainment versus average level of education associated with a local

government area. OHCA incidence is higher, and survival lower, in individuals and areas characterised by low socioeconomic status (SES) compared to those with higher SES, respectively.[30,207,208] Very few studies have investigated sex differences in SES disparities, and none from Australia. Women of low SES are at significantly higher risk of CHD, CVD, cardiac arrest, and sudden cardiac death, but not stroke, compared with men of low SES even after adjustment for traditional risk factors.[209,210] Women living in a low-income area have been shown to be more likely to experience OHCA compared with men[211] but the sex difference based on education level has only been observed at the individual level[212]; no sex difference has been reported according to area-level deprivation index or average price of real estate.[213,214] In in the unadjusted analyses by Jonsson et al[211] and Wells et al,[212] odds of survival were higher for men living in areas with higher education as well as for men with white collar occupation compared to areas of low education and occupation, respectively, but these disparities were not observed for women. In both studies there was no significant interaction between sex and area-level income and education, or individual-level education or occupation, and the association with survival for males disappeared in adjusted models. Sex does not appear to mediate the effect of SES on incidence or outcome of OHCA once other factors are considered.

2.5.5 MANAGEMENT

2.5.5.1 PRE-HOSPITAL

Pre-hospital management by EMS in Australia, based on a single study,[195] is similar between males and females aged <80 years with no difference in EMS response time or rates of EMS-attempted resuscitations. International registry data[197,215] also demonstrates that there are no differences in administration of drugs and 12-lead ECGs, but there are differences in vascular access with fewer women receiving intravenous lines and more intraosseous access.[197,215] Previous studies[216,217] have hypothesised that women's smaller chest size and lower stiffness increase their likelihood of achieving pre-hospital ROSC because less force is needed to achieve a similar compression depth, resulting in more efficacious CPR. However, this was not confirmed in a more recent studies.[192,218] Despite differences in presentation between males and females, there do not appear to be significant differences or disparities in pre-hospital management by EMS providers.

2.5.5.2 Targeted Temperature Management

Early post-ROSC targeted temperature management is recommended in all comatose OHCAs, although the quality of evidence for after OHCA with non-shockable rhythm is very low.[47] Two studies and meta-analyses have reported lower rates of TTM in females compared with males,[184,185,197,219] but this was not confirmed in other OHCA sub-populations.[193,197,219,220] It is likely that differences in provision of TTM result from lower rates of shockable rhythm and higher death rate prior to TTM initiation in women[193,197]. There are no Australian reports specifically exploring sex differences in TTM.

2.5.5.3 Coronary Angiography and Revascularisation

According to two recent meta-analyses,[184,185] coronary angiography and PCI are performed less often in females compared with males. However, as patients included in most of these studies are selected for coronary angiography according to clinician judgement,[42,43,193,197,198,219] the results are subject to selection bias and must be interpreted with caution. Only one study[196] of a non-selective cohort in Paris found that women with presumed cardiac cause were less likely to receive coronary angiography, even after propensity-score matched analysis and multivariable adjustment. Limited Australian data from selective cohorts remains inconclusive with one study reporting no sex difference[138], and another reporting lower rates of emergency coronary angiography ± PCI in women compared to men.[137] Wittwer at al[221] found no sex difference in rates of coronary angiography (females 66% versus males 72%) in a small single-centre non-selective cohort.

2.5.6 Outcomes

2.5.6.1 Survival

Sex-differences in survival appear to be conflicting, even between meta-analyses.[183–185,220] Blom et al[193] have provided an excellent summary of current research and concluded that survival differences depend on the outcome of interest (survival from cardiac arrest to hospital vs. cardiac arrest to discharge vs. hospital admission to discharge), the sub-group analysed (shockable vs. non-shockable; presumed cardiac vs. all-cause), and whether adjustments were made for covariates and known predictors of survival. Indeed, all the large OHCA registries (n>10,000),[192,215,217,222–224] including an Australian registry,[195] found that

unadjusted survival and favourable neurological prognosis at hospital discharge was consistently higher in men than women. After adjustment for known predictors of survival the sex difference either disappeared[192,195,217,222–224] or favoured women[215]. Several studies[191,192,225,226] have also demonstrated a survival advantage in pre-menopausal women (aged <55 years), attributed to the protective effects of oestrogen. However, these findings have not been supported in other studies,[215,223] including an Australian study.[195]

2.5.6.2 Long-term outcomes

In a large Australian study on outcomes at 12-months post EMS-treated OHCA,[227] women survivors experienced more difficulties with mobility, self-care, performing usual activities, pain, and anxiety/depression compared to men, even after adjustment for confounders. Most other international studies stratified by sex confirm these findings[147,228–232] with only a few reporting no sex difference in return to work or health-related quality of life.[233,234] Men also report experiencing lower levels of participation in society,[147] whereas women are more likely to develop post-traumatic stress disorder.[230] Long-term recovery after OHCA is experienced differently between sexes and tailored interventions are likely to be beneficial.

2.5.6.3 Withdrawal of care

A report from the 2014 Consensus Conference on Cardiovascular Resuscitation Research proposed that poorer cardiac arrest survival in women was due to sex differences in end-of-life care.[186] Subsequent reports from all-cause EMS-treated cohorts found that women were more likely to have WLST, early WLST, and early DNR orders than men,[151,197,235,236] but these differences were not reported in two other studies of presumed cardiac patients admitted to ICU.[41,43] It may be that there are sex-differences in preferences for end-of-life discussions[237,238] or provider-level disparities,[239] as well as differences in prognosis driven by comorbidity and precipitating aetiology; however, OHCA-specific information is lacking.

2.5.6.4 In-hospital death

Only one study has reported sex-differences in mode of death, and it is unknown whether there are sex differences in location or timing of death. Winther-Jensen et al[198] found that

women were more likely to die due to multiorgan failure, with no significant differences in rates of neurological or cardiovascular deaths between sexes.

2.5.7 AETIOLOGY

Sex differences in incidence, presentation, management, and outcome of OHCA are primarily driven by differences in precipitating aetiology. There is only one study of autopsy- and physician-adjudicated aetiology stratified by sex for EMS-treated OHCA, which found that women were less likely to present with a cardiac aetiology and more likely to present with pulmonary and other non-cardiac causes.[176] Combined findings from other autopsy-based SCA/SCD registries and smaller cohort and case-control studies report suggest the following:

1. Women are more likely to arrest due to a non-cardiac aetiology of respiratory or neurological origin[4,8,108,167,176,178,240];
2. Women with confirmed cardiac pathology are:
    a. Less likely to have CAD, dilated cardiomyopathy, or hypertrophic cardiomyopathy, and more likely to have myocarditis, ARVC, and valvular heart disease[8,175,240–242];
    b. Just as likely as men to present with acute cardiac ischaemia.[43,175,242,243]

Two other studies have found contrasting results, but these may be due to a definition of the denominator as 'presumed cardiac' based on a pre-hospital EMS diagnosis, rather than adjudicated cardiac aetiology.[174,196] Currently, there are no reports of adjudicated aetiology from Australia.

2.5.8 MECHANISM

The mechanism underling the observed sex differences in aetiology have been explored in three in-depth reviews.[244–246] Briefly, susceptibility to cardiac arrhythmias varies between men and women due to differences in ion channel expression and function, autonomic regulation, and intracellular calcium handling.[244–249] The reviews postulate that sex hormones, not limited to oestrogen, drive most of these differences. Finally, women are less likely to progress to cardiac arrest due to biological differences in susceptibility, and when they do it is more likely due to an underlying non-cardiac aetiology associated with PEA and asystole compared with men.

2.6 OHCA REGISTRIES

2.6.1 CLINICAL REGISTRIES

The first step to improving OHCA survivorship is to establish a clinical registry that facilitates the clinical outcome feedback loop (**Figure 2-4**).[18,144,250] This loop comprises a) definition and recording of OHCA process and outcome data, b) data analysis, c) identification of areas for improvement, and d) implementation of strategies to improve survival (or other measurable outcome), and so on.[251] Clinical quality registries (CQR) are a type of clinical registry of longitudinal health outcome data pertaining to the entire eligible population of a specific clinical domain. The scope of CQRs and most clinical registries includes health outcome and quality improvement activities facilitated by the clinical outcome feedback loop, as well as medical research.[252] Clinical registries are cost effective[253,254] and have been shown to improve patient care and clinical outcomes in many disease states/conditions,[252] including OHCA.[17,135,255,256]

2.6.1.1 GUIDELINES

Standardised definitions, core outcomes, and reporting templates for cardiac arrest registries are specified by the Utstein-style guidelines.[12,13] More general guidelines outline each aspect of the clinical registry from registry design and data elements, to ethical and legal considerations, as well as operational aspects such as recruitment, data collection, quality assurance, and analysis.[257,258] The Framework for Australia CQRs was developed by the Australian Commission on Safety and Quality in Health Care, and endorsed by Health Ministers in 2014.[259] The Framework covers principals, guidelines, and standards for CQR development including operating principles, requirements specification, infrastructure and technical standards, logical architecture and design, security compliance guidelines, and reporting (**Figure 2-5**). Collection and use of patient data in Australia is guided by the National Statement on Ethical Conduct in Human Research[260] and Australian Code for the Responsible Conduct of Research.[261] CQRs are registered on the Australian Register of Clinical Registries (https://www.safetyandquality.gov.au/australian-register-clinical-registries). Australian CQRs referred to or used in this thesis include the Australasian Resuscitation Outcomes Consortium (Aus-ROC),[262] Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD),[263] and Coronary Angiogram Database of South Australia (CADOSA).[264]

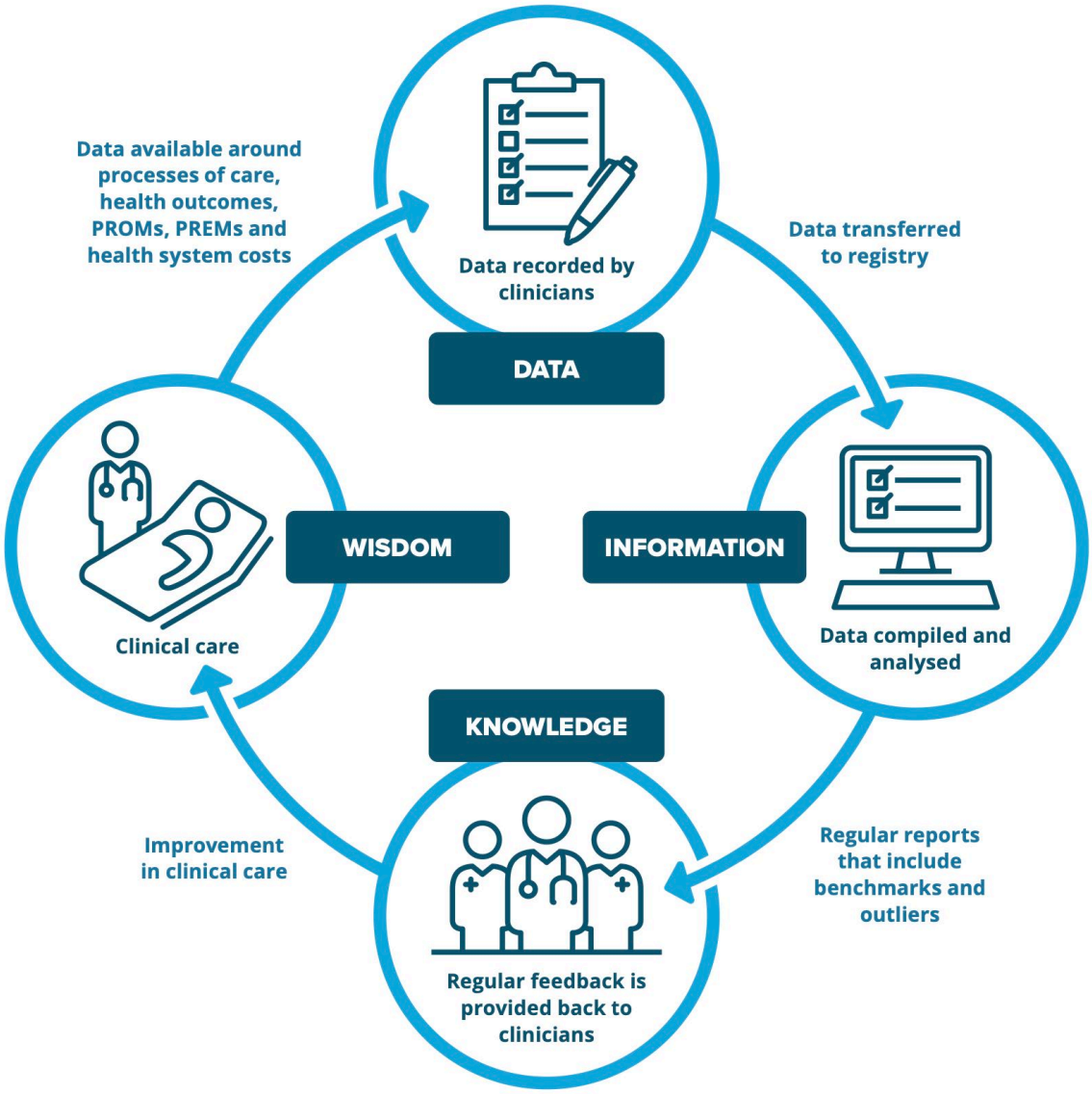

Figure 2-4: The clinical outcome feedback loop.
Reproduced with permission from the National Arrangements for Clinical Quality Registries, developed by the Australian Commission on Safety and Quality in Health Care (ACSQHC). ACSQHC: Sydney 2019.

2.6.2 National and International Registries

Within SA, SAAS-CAR provides EMS-based data on OHCA process of care and outcomes including pre-hospital ROSC and hospital discharge disposition according to the Utstein-style guidelines. Infrastructure and research support underpinning SAAS-CAR is limited with the first and only report available for 2016/17.[33] SAAS-CAR, along with EMS agencies in all states and territories of Australia and New Zealand, contributes to the Aus-ROC epistry.[52,262] Aus-ROC is a CQR established in 2011 that aims to determine risk-adjusted outcomes,

provide benchmarking across providers, and identify system-wide strategies associated with survival.

International EMS-based epistries and regional registries exist in every continent and have been recently summarised.[10,131,265] Combined findings from epistries across Australia and New Zealand, Singapore, South Korea, Japan, Denmark, Norway, Sweden, and United Kingdom were recently reported by ILCOR.[32] Findings from across Europe have been summarised via the European registry on cardiac arrest (EuReCa), which is an intermittent registry with data capture from 28 European countries over two periods of one and three months, respectively.[266,267]

Event survival and survival to hospital discharge are core outcome measures reported in all EMS-based registries. However, in-hospital management and other supplemental outcomes are much more difficult to obtain due to acknowledged challenges in linking patient records between databases.[13,144] Registries that report more detailed in-hospital data are generally limited to specific sub-populations of OHCA such as those undergoing coronary angiography,[62] or TTM.[268,269] There remains a need for population-based information on in-hospital management and outcomes that are not currently collected within the constraints of EMS-based registries.

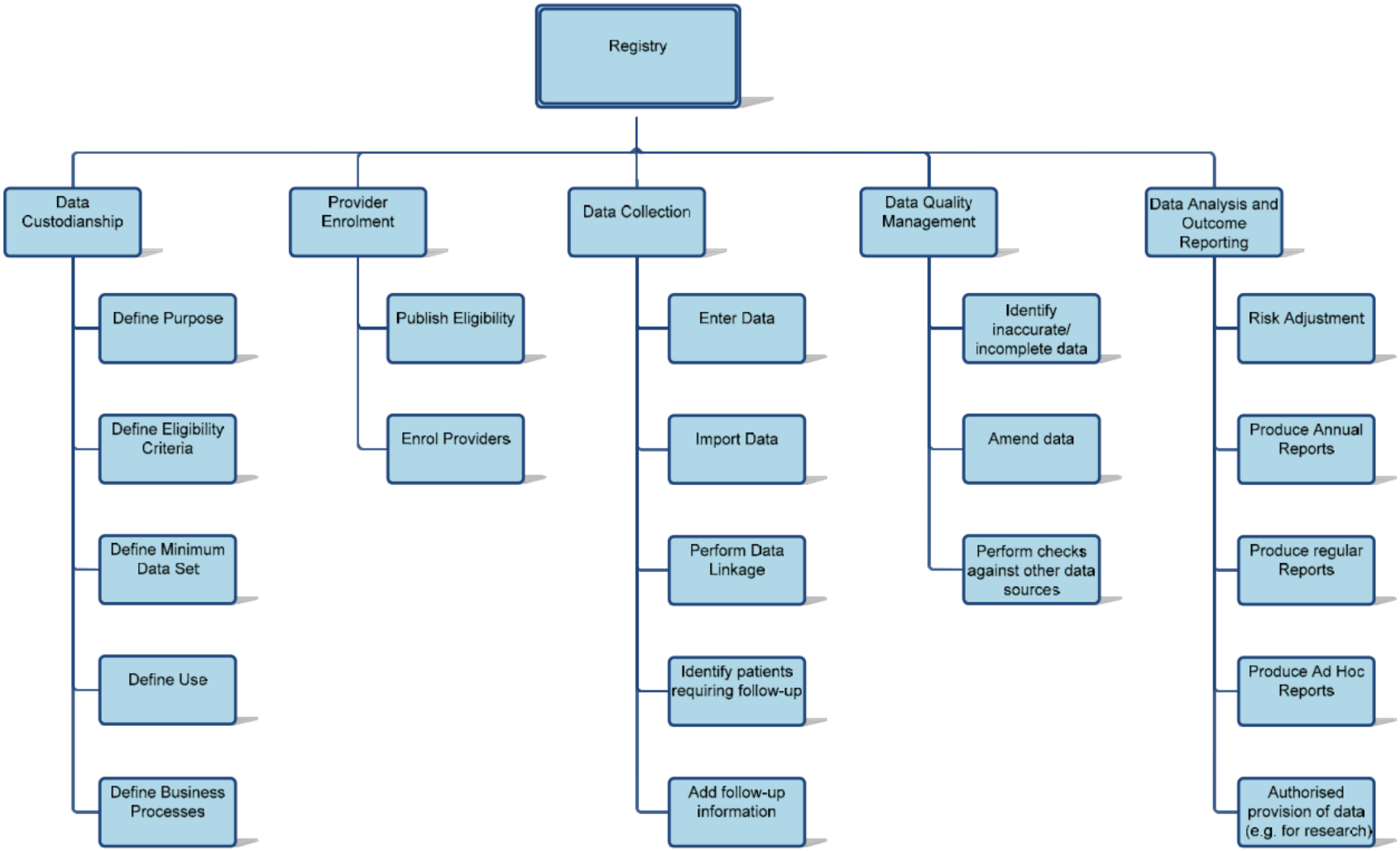

Figure 2-5: Functional overview of Australian clinical quality registries.
Reproduced with permission from the Framework for Australian clinical quality registries, developed by the Australian Commission on Safety and Quality in Health Care (ACSQHC). ACSQHC: Sydney 2014.

CHAPTER THREE: ESTABLISHING THE NALHN OHCA REGISTRY

3.1 Overview of Chapter Three

Chapter Two presented an overview of Australian OHCA literature with respect to epidemiology, management, outcomes, precipitating aetiology, and sex differences and disparities, and highlighted registries as a key mechanism to improve survivorship. This chapter addresses the first research objective of this thesis, which was to establish the NALHN OHCA registry and test methods used to identify cases.

3.2 Introduction

"You can't improve what you don't measure" – Peter Drucker

Accurate and reliable quantification of OHCA incidence, management, and outcomes are essential to make assessments on how effective changes in policy, procedures, or guidelines are at improving patient outcomes. Clinical registries are therefore a fundamental aspect of the OHCA survivorship clinical feedback loop, as described in **Chapter 2.1.6** (**Figure 2-4**). Currently, the Utstein-style guidelines and most international epistries and regional registries are optimised for EMS-based data; this is necessary because the first four links in the chain of survival directly relate to EMS-based provision of care. However, many EMS-based registries are not able to collect additional in-hospital or long-term outcome data due to limitations in data linkage, lack of infrastructure, and concerns about patient confidentiality.[13,144] NALHN represented a unique setting to implement a hospital-based OHCA registry with data linkage to both an EMS cardiac arrest registry and existing CQRs because clinicians and researchers within NALHN have long held a particular interest in OHCA management and have extensive registry experience.[29,200,270–272] This chapter presents the original methods of the NALHN OHCA registry used to generate data for analysis in this thesis, the published manuscript validating the method of case identification, and the proposed methods developed during this doctoral work for future data capture and analysis.

3.2.1 Historical context

Since the opening of the cardiac catheterisation laboratory at a NALHN hospital in April 2006, demographic and procedural data from consecutive patients undergoing emergency angiography with the intent for acute revascularisation (i.e., those for whom a code STEMI was activated, including OHCA patients) were documented in the code STEMI registry. This registry was used to monitor the quality of care according to key performance indicators such as door-to-balloon time and complication and mortality rates.[65,66] From 2011-15, a separate registry was created for code STEMI OHCAs because it became apparent that key performance indicators for STEMI were negatively impacted by inclusion of OHCAs.[273] The NALHN OHCA registry is an expansion of the code STEMI OHCA registry and was developed and refined during this program of doctoral research to facilitate quality improvement activities and further investigations into OHCA management.

3.2.2 Clinically relevant definition of OHCA

The first step in the clinical feedback loop emphasises the importance of relevant, accurate, and reliable definitions for both the study population and each measured outcome. Definitions for OHCA (and conversely, IHCA) are generally based on EMS involvement and confusion remains over the categorisation of OHCAs transported to hospital by private vehicle or occurring on hospital grounds in visitors or staff.[12,13,274] IHCA and OHCA represent the same clinical event occurring along the pathophysiological continuum of dying but as there are differences in location and subsequent epidemiology, process of care, and treatments, it follows that the two are reported separately.[12,13] Recent evidence from a large population-based observational cohort study has nonetheless highlighted the similarities in demographics, comorbidities, initial rhythm, and outcomes between IHCA and OHCA.[275] The definition of 'out-of-hospital' is therefore ultimately driven by the focus of the research. During the early stages of this doctorate, the classification of cardiac arrest location was discussed with hospital clinicians and EMS-personnel, and it became apparent that a clinically relevant differentiation considered the level of care the patient was receiving at the time of arrest. A simple clinical classification of OHCA as *cardiac arrest in persons who do not occupy an ED or inpatient bed* was proposed and justified in a Letter to the Editor published in *Resuscitation* (Appendix B).[20]

3.3 AIMS AND OBJECTIVES

The aim of the NALHN OHCA registry was to improve OHCA survivorship within NALHN.

The specific objectives were to:

- Define quality indicators
- Measure quality of care
- Identify areas to improve quality of care
- Support clinical research
- Serve as a pilot for establishing a state-wide OHCA registry with data linkage between an EMS registry, existing CQRs, and in-hospital medical records.

3.4 METHODS

3.4.1 REGISTRY DESIGN

The NALHN OHCA registry was designed as a prospective hospital-based quality assurance initiative with data capture according to the Utstein-style guidelines[13] and data linkage to both an EMS cardiac arrest registry and two CQRs. OHCA cases not already included in the code STEMI registry between 2011-2015 were identified and data collected retrospectively.

3.4.2 REGISTRY SETTING

SAAS provides a state-wide EMS, described previously.[33,52] Briefly, SAAS operates a two-tier system where non-urgent and scheduled transport of stable patients (non-OHCA) is provided by paramedics trained in basic life support (64% of SAAS paramedics), while critical events are responded to and treated on scene by paramedics trained in advanced life support (29% of paramedics) and/or intensive care paramedics with training in advanced techniques (7% of paramedics).

The NAHLN catchment is a predominately residential area, represents 23% of the population of SA, and is serviced by two teaching hospitals. The Lyell McEwin Hospital (LMH) is the primary treatment centre for OHCA patients within NALHN with 24/7 PCI capability and 15 Intensive Care Unit (ICU) and 26 cardiac unit beds in 2016. Modbury Hospital is a secondary hospital where OHCAs requiring cardiology or ICU management are transferred to LMH once stabilised. Combined, there are approximately 200,000 presentations per year to the ED

and over 61,000 in-patient admissions. Both receiving hospitals have a resuscitation area in the ED with a multidisciplinary health team led by ED specialist physicians. OHCAs occurring within hospital grounds at both hospitals are managed by a Medical Emergency Team (MET) activated by staff via the hospital switchboard according to local protocols. Both SAAS and NALHN hospitals are guided by the ANZCOR resuscitation guidelines.[54]

3.4.3 Inclusion criteria

The NALHN OHCA registry was designed to include consecutive OHCAs aged ≥18 years treated at NALHN hospitals, including patients retrieved from country hospitals. OHCA was defined as *absence of signs of circulation requiring CPR and/or defibrillation in individuals who do not occupy an ED or inpatient hospital bed.*[20] Traumatic OHCAs were included even if retrieved to an external tertiary hospital for further management once stabilised. Paediatric (<18 years) cardiac arrests and Automated Implantable Cardioverter-Defibrillator (AICD) shocks without the need for bystander CPR or ongoing resuscitation were excluded.

3.4.4 Case identification

To be fully functional, a clinical registry must have complete capture of all cases meeting the case definition. There is no single data source that identifies all OHCAs: EMS-based sources such as SAAS-CAR do not, by definition, include cases arriving by private vehicle or on hospital grounds, ED-based sources generally do not include cases transferred directly as in-patients, and in-patient sources do not include cases deceased in ED. Therefore, multiple, pre-existing, overlapping sources were required to identify all cases. The accuracy of each source at identifying OHCA cases in the registry was tested and the findings are presented in the published manuscript of this chapter.[21] Prospective clinician-led identification was not utilised due to constraints in resources and availability of existing data sources.

Proposed method for case identification and data collection:

1. Consecutive data sources are searched for potential cases on a quarterly basis according to pre-defined criteria and relevant key works (Paper One: **Figure 1**).
2. The medical record number, admission date, name, and date of birth of each potential case is recorded.

3. Cases identified as included or excluded from each source are labelled in each consecutive source to avoid duplication.
4. Cases aged <18 years are excluded.
5. Cases are excluded based on review of the electronic clinical summary.
6. Final inclusion/exclusion is based on manual review of the hospital medical record (paper-based clinical record supported by electronic record for pathology and radiology results and patient encounters).
7. Unique study number is assigned to included cases.
8. Data for included cases is imported from linked sources to the registry. The medical record is abstracted for any remaining variables (e.g., mode of death).
9. Subsequent OHCA episodes are recorded for each case using the same study number with the episode number indicated after a decimal point (e.g., 102.4).

Note: A similar method was utilised to retrospectively identify cases not already included in the code STEMI OHCA registry from 2011-2015. The original methods did not include data import from linked sources (step eight) and so all the data for cases presented in this doctoral work were obtained entirely by medical record abstraction. As this was a time-intensive process, each case taking between 30-60minutes to abstract, the proposed methods were updated to include data import from linked sources.

3.4.5 Data sources

3.4.5.1 EMS-based registry – case identification and data-linkage

SAAS-CAR was established in 2009 and includes all OHCA events attended by SAAS throughout the state of SA. Utstein-style data is captured from patient clinical records (paper-based) and merged with ambulance dispatch operational databases, (South Australian Computer Aided Dispatch) to obtain relevant outcomes. Ethics approval covered data-linkage for all EMS-attended OHCAs occurring within a NALHN catchment postcode and received by a NALHN hospital. NALHN postcodes were obtained from the NALHN casemix and Activity Based Funding Unit and updated annually. Cases were manually linked from 2012 onwards when postcode of arrest was available using age, sex, arrest date, and time of call. Linked variables include patient, process, and outcome variables according to the Utstein-style guidelines.[13]

3.4.5.2 Administrative data sources – case identification only

Two administrative data sources based on International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD-10) codes were used to identify cases for the analyses within this thesis. The ICD-10 Australian modification (ICD-10-AM) is an expanded version of the World Health Organisation's ICD-10.

ED data source: HASS EDIS is a real-time patient tracking tool where diagnosis and presenting complaint codes are entered for all ED presentations from a pull-down menu by the treating doctor and triage nurse, respectively. Potential cases admitted to ED are identified from HASS EDIS using the Emergency Department ICD-10-AM Principal Diagnosis Short List (ED Short List) code of cardiac arrest (I46.9) and presenting complaint code of cardiac arrest (0102).

Inpatient data source (original methods only): Primary and secondary ICD-10 codes are assigned by clinical coders to all billable inpatient encounters according to the Australian Coding Standards at the primary treating hospital. Potential inpatient cases were identified by the following ICD-10 codes: Cardiac arrest with successful resuscitation (I46.0), Sudden cardiac death (I46.1), Cardiac arrest unspecified (I46.9), Ventricular fibrillation and ventricular flutter (I49.0), Respiratory arrest (R09.2), and Asphyxiation (T71). The results of the published manuscript in this chapter led to the removal of this source from the proposed method.

3.4.5.3 Clinical registries – case identification and data-linkage

Cardiac registry: The Coronary Angiogram Database of South Australia (CADOSA) is a CQR of all patients undergoing coronary angiography and/or PCI at each tertiary hospital in SA (https://www.cadosa.org).[264,276] CADOSA was established at the LMH in April 2012. To account for changes in CADOSA data variables, the registry was searched for 'Cardiac Arrest within 24 hours prior to procedure' for cases prior to 2016, and 'OHCA' from 2016 onwards. Linked variables include coronary angiography timing, procedure details, and outcomes.

ICU registry: NAHLN participates in the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD), an Australia-wide ICU CQR used for benchmarking of individual ICU performance.[263] A list of OHCAs admitted between 2011 and 2015 had been identified from the ANZICS-APD by ICU clinicians in 2016 (Devanand NA et al, unpublished dataset, 2016). This list was used to identify cases for the NALHN OHCA registry prior to 2016. From 2016 onwards the ANZICS APD was searched using the diagnosis 'cardiac arrest' or 'respiratory arrest'. Linked variables include ICU admission and discharge dates and time.

3.4.6 Data capture

In the initial development stages of the NALHN OHCA registry, data from cases meeting the inclusion criteria were recorded in a Microsoft Excel database based on the original code STEMI OHCA registry. Each row of the database represented a unique presentation and each column a unique data variable. The completed Excel database included OHCA cases from 2011-2016 and formed the basis of the work presented in this thesis. Prior to data analysis, thorough data cleaning and logic checks were preformed within Excel to ensure the validity of the data e.g., checks to confirm that the date and time values were consistent and correct across related variables for each case, age was restricted to 18-110 years, no survival-specific data was entered if the patient was marked as deceased, etc.

The Excel database and data dictionary were used as a template and reference, respectively, to code the NALHN OHCA registry into a REDCap (Research Electronic Data Capture) database, hosted at the University of Adelaide.[277,278] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Preliminary testing of the REDCap database was carried out during this program of doctoral research but was not used to generate the data presented in this thesis.

3.4.7 VARIABLES

The code STEMI OHCA registry was used as a foundation for creating the NALHN OHCA registry as it already contained many relevant variables. Additional core and supplemental Utstein variables were subsequently added to ensure the registry aligned with the Utstein-style guidelines.[13] Other variables of particular interest to the research group such as aetiology and mode of death were also added. The list of data variables available for reporting in this thesis, along with variables recorded from 2017 onwards, is summarised in **Table 3-1**. A data dictionary listing the definition and reference source for each variable was developed to standardise data collection (**Appendix B**). This section presents the outcome variables explored in this thesis.

3.4.7.1 SURVIVAL TO HOSPITAL DISCHARGE

Survival to hospital discharge was derived from the date and time of death or discharge home or to a non-acute facility. Patient retrievals to external acute care facilities were considered as part of the same episode of care and the final discharge disposition was used to derive this outcome. Survival to hospital discharge of the EMS-attended NALHN cohort is reported in **Chapter Four**, while survival to hospital discharge is reported according to precipitating aetiology in **Chapter Eight**.

3.4.7.2 SURVIVAL WITH GOOD NEUROLOGICAL RECOVERY

The neurological outcome of the patient at the time of death or final hospital discharge was defined by the Cerebral Performance Category (CPC) scale according to the medical record. A score of 1-2 was considered as a good neurological outcome.[279] This outcome is reported according to precipitating aetiology in **Chapter Eight**.

3.4.7.3 EMERGENCY CORONARY ANGIOGRAPHY

Emergency coronary angiography was defined as occurring within the first 24 hours after OHCA onset. Selection of patients to emergency versus delayed or no emergency coronary angiography is explored in **Chapters Five** and **Six**.

3.4.7.4 Mode of death

Mode of death categorises the way a patient dies after being resuscitated from OHCA. The categories reported in **Chapter Seven** of this thesis were based on two prior studies and comprised of cardiovascular instability, WLST for non-neurological reasons, WLST due to poor perceived neurological prognosis, and formal brain death.[154,157] The proposed methods include a more comprehensive definition according to a more recent publication.[160]

3.4.7.5 Aetiology

Precipitating aetiology was defined according to documentation in the medical record as well as autopsy reports specifically requested for the purposes of the registry. The code STEMI OHCA registry originally defined 18 different aetiologies, which were re-coded into six primary categories and nine sub-categories and reported in **Chapter Eight**. The primary categories included cardiac, respiratory, neurological, toxicological, other, and unknown, as suggested by Dr J. Elmer, MD (email communication, February 2020). The proposed methods include categories based on more recent publications.[4,108,165,168]

3.4.8 Reporting

The proposed methods include reporting of key outcomes to Cardiology and ICU clinicians on an ad-hoc basis. Once sustainable funding is secured, the registry is intended to be developed into a CQR with appropriate infrastructure to support the provision of timely reports on risk-adjusted outcome analyses to all stakeholders, as well as annual reports detailing aggregated clinical and corporate findings.

3.4.9 Statistical analyses

The registry has been designed to allow both descriptive and quantitative analyses according to the objectives of the quality assurance assessment or research program. Data variables may be recoded and variables with sparse data may be grouped in meaningful ways to facilitate data analysis. The statistical analyses undertaken throughout this doctoral work are presented in each relevant chapter.

Table 3-1: Summary of NALHN OHCA registry variables

Demographics	Pre-arrest cardiac ischaemic symptoms
Age	**ROSC characteristics**
Sex	Sustained ROSC time and location
Ethnicity	12-lead ECG time and defining features
Home postcode	Heart rate
Co-morbidities	Systolic blood pressure
Coronary artery disease	Diastolic blood pressure
Cardiomyopathy	Respiratory rate
Previous cardiac arrest	**Targeted Temperature management**
Cardioverter-defibrillator*	Initial temperature
Channelopathy*	Method of delivery
Family history of heart disease	Location and time initiated
Cerebrovascular disease*	**Hospital management**
Diabetes	Hospital arrival time(s)
Hypertension	ROSC on arrival
Smoking	Glasgow coma scale (GCS)
Lung disease*	pH
Dyslipidaemia	Lactate
Obesity	Glucose
Terminal illness*	Peak Troponin T
Arrest characteristics	Peak Creatine Kinase
Date, time, location of arrest	Cardiogenic shock
Witnessed status	Code STEMI
Bystander response	Intensive care unit
Time of first CPR or defibrillation	**Cardiac catheterisation**
Time of incoming call	Procedure date and time
First monitored rhythm	Consultant
Number of shocks delivered	Intra-aortic balloon pump
Drugs given	Timing of test(s)
Main vascular access type	Discontinuation of treatment
Main airway control type	Vessel stenosis ≥50%
Utstein aetiology	Percutaneous coronary intervention

Cardiac catheterisation (cont.)	**Outcomes**
Other disease findings	Discharge disposition
Small vessel coronary artery disease	Date, time, and location of death
Extent of coronary disease	Cerebral performance category
Left main disease	Modified Rankin scale*
Cardiac diagnosis	Withdrawal of life sustaining therapy
Planned coronary artery bypass grafting	Mode of death
Neurological prognostication	Organ donation
Electroencephalogram (EEG)	Final aetiology
Radionuclide imaging (SPECT)	Unlikely to be true cardiac arrest
Brain computed tomography scan	Cardioverter-defibrillator insertion
Brain magnetic resonance imaging	Alive at 3- and 12-months.
Clinical examination	

*Data variables updated in 2017. ECG, electrocardiogram; ROSC, return of spontaneous circulation.

3.4.10 Ethical considerations

All aspects of the NALHN OHCA registry and associated analyses comply with the ethical principles of respect, beneficence, justice, and good clinical practice according to the to the National Statement on Ethical Conduct in Human Research[260] and Australian Code for the Responsible Conduct of Research.[261] Each case is assigned a unique study number which is linked with identifiable data (name, date of birth, medical record number) in a separate Excel spreadsheet stored on a SA Health shared drive, accessible only by the study investigators. The original Excel database was stored in an identifiable format during the data collection phase on a SA Health shared drive, accessible only by study investigators. Once complete, all identifiers were removed, and the database was stored on the University of Adelaide Box drive in a re-identifiable format for analysis. The current REDCap database necessarily includes identifiable data (medical record number and date of birth) to facilitate data capture, but these are excluded from data exports.

Data linkages with existing registries are performed with the aid of identifiers such as age, date of birth, and medical record number, as well as other characteristics such as date of arrest or date of hospital admission to ensure the accuracy of the linkage. Once the linkage is

complete, all identifiers are removed, and the original data linkage file deleted. The Central Adelaide Local Health Network Human Research Ethics Committee approved the registry as an ongoing quality improvement activity and separate approval was obtained for data linkage with SAAS-CAR (HREC/15/TQEH/89).

3.4.11 Strengths and limitations

The NALHN OHCA registry allows detailed and relevant investigation of local practices that directly inform provision of care to improve survivorship. The observational studies facilitated by this registry will address important clinical questions that often cannot be answered by randomised clinical trials (RCT), even though causal inference cannot be definitively established.

There remain several limitations inherent to all observational registries. Firstly, although the NALHN OHCA registry has been designed as a prospective registry with data linkage to existing sources, the analyses presented in this thesis were generated from data collected retrospectively from medical record abstraction. As a result, the findings presented are dependent on the accuracy of documentation by medical staff in the medical record and whether information was missing from paper or electronic sources. Secondly, the use of data linkage with existing registries is expected to improve the efficiency of the NALHN OHCA registry. However, clinical registries are subject to limitations in availability of data e.g., CADOSA data is only available >6months after presentation date. Finally, further limitations with respect to the methods of case identification are discussed in the published manuscript presented in this chapter.

3.5 Manuscript, Paper One

The following paper, "Overcoming challenges of establishing a hospital-based out-of-hospital cardiac arrest registry: accuracy of case identification using administrative data and clinical registries" was published in *Resuscitation Plus* in 2021.[21]

Statement of Authorship

Title of Paper	Overcoming challenges of establishing a hospital-based out-of-hospital cardiac arrest registry: accuracy of case identification using administrative data and clinical registries
Publication Status	[X] Published [ ] Accepted for Publication [ ] Submitted for Publication [ ] Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Melanie Wittwer		
Contribution to the Paper	Conception and design of the project; data acquisition; analysis and interpretation of data; drafting significant parts of the article or critically revising it so as to contribute to the interpretation		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	11th May 2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mohammed Ishaq Ruknuddeen		
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Clinical paper

Overcoming challenges of establishing a hospital-based out-of-hospital cardiac arrest registry: accuracy of case identification using administrative data and clinical registries

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Abstract

Introduction: Comprehensive identification of out-of-hospital cardiac arrest (OHCA) cases for inclusion in registries remains challenging due to the inherent diversity of OHCA aetiology, presentation, and management. The Northern Adelaide Local Health Network (NALHN) OHCA registry identifies OHCAs presenting to NALHN hospitals using existing data sources to monitor in-hospital treatment and survival. This study aimed to investigate the accuracy of hospital-based data sources for identifying OHCA cases treated at hospital.

Methods: Retrospective analysis of all OHCAs aged >18 years included in the NALHN OHCA registry between 2011–16. Registry cases are identified from an emergency medical service (EMS) OHCA registry, Emergency Department (ED) and ICD-10 coding datasets, and key-word searches of two in-hospital clinical registries. Sensitivity and positive predictive values (PPV) of each hospital-based data source were analysed with respect to (a) the number of cases expected to be identified by that source, (b) total OHCA. Non-OHCAs yielded by each source were explored and a sub-analysis of ICD-10 codes was performed.

Results: Between 2011–16, the four hospital-based sources yielded 992 cases, of which 383 were confirmed as OHCA. The ED coding dataset was the most accurate with a sensitivity and PPV of 78%. The ICD-10 coding dataset had good sensitivity but low PPV (33%). The ED coding dataset, combined with the two in-hospital clinical registries, identified 93% of OHCAs.

Conclusions: No single dataset identified all OHCAs presenting to NALHN hospitals. Combined hospital-based data sources provide a valid method of identifying OHCAs treated at hospital that may be adapted to augment EMS-based data.

Keywords: Out-of-hospital cardiac arrest, Registry, ICD-10, Administrative data, Utstein template, Validation

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Introduction

Out-of-hospital cardiac arrest (OHCA) survival in Australia is only 12% and remains a challenge in medicine.[1] The Global Resuscitation Alliance statement proposes registries as a primary mechanism to improve cardiac arrest survival.[2] Compared with procedure-based registries which have one common entry point (e.g. the procedure), injury- and disease-based registries may have multiple entry points where cases are identified by clinicians or administrative data. The majority of OHCA registries comprise of cases identified by emergency medical services (EMS) but most exclude non-EMS attended OHCAs and lack data on in-hospital management.[3–9] Administrative data, such as the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) codes, are designed to allow international comparisons in reporting health trends and statistics but do not reliably identify OHCAs.[10,11] Registries that use comprehensive and valid methods of case identification facilitate improved understanding of epidemiology, process of care, and outcome but remain a particular challenge for OHCA. This paper describes the methods used to identify OHCA cases included in the hospital-based Northern Adelaide Local Health Network (NALHN) OHCA registry. The primary objective was to determine the accuracy of each hospital-based source for identifying OHCA presenting to NALHN hospitals with respect to (a) expected OHCAs (e.g. ICU dataset was analysed with respect to patients admitted to ICU) and (b) total OHCA. Cases identified as OHCA were confirmed by manual hospital medical record review. Secondary objectives included classification of non-OHCAs yielded by each source, and a sub-analysis of ICD-10 coding in admitted patients. Our findings may provide insights for others establishing hospital-based OHCA registries.

Methods

Study design

This is a retrospective analysis of methods used to identify cases for inclusion in the NALHN OHCA registry, a hospital-based cohort registry of all OHCAs aged ≥18 years treated at NALHN hospitals from 2011 onward. Registry variables include all core elements of the Utstein template with additional items on cardiac management, neurological prognostication, and aetiology.

Setting

NALHN comprises two public hospitals that service the northern metropolitan area of Adelaide, South Australia. The Lyell McEwin Hospital is the primary cardiac arrest centre with 15 Intensive Care Unit (ICU) and 26 cardiac unit beds, and Modbury Hospital is a secondary teaching hospital. Combined, there are approximately 200,000 presentations per year to the ED and over 61,000 in-patient admissions. South Australia has a single state-wide two-tier EMS where OHCA patients are treated by SAAS paramedics on-scene. Both receiving hospitals have a resuscitation area in the ED with a multidisciplinary health team led by ED specialist physicians. Traumatic arrests are generally retrieved to an external tertiary hospital for further management once stabilised by EMS or ED staff. SAAS and NALHN hospitals follow the 2010 (revised in 2015) ANZCOR resuscitation guidelines.[12]

Inclusion and exclusion criteria

Cardiac arrest is defined as the *absence of signs of circulation*.[13,14] According to the Utstein definition we included all OHCAs aged ≥18 years receiving chest compressions or external defibrillation, whether for severe bradycardia with pulses and poor perfusion, as well as ROSC pre-EMS or Medical Emergency Team (MET) arrival.[14] OHCA was defined as *cardiac arrest occurring in individuals who do not occupy an ED or inpatient hospital bed*.[15] This definition distinguishes between patients who are not receiving advanced care at the time of cardiac arrest and those already under advanced care that aims to (1) prevent cardiac arrest, and (2) provide immediate and timely resuscitation if required, rather than a distinction based on emergency responder (EMS vs. MET). The registry therefore includes all arrests transported to hospital by EMS or private car, including arrests in the community, medical clinics, rehabilitation facilities, nursing homes, and inter-hospital transfers, as well as any arrest on hospital grounds involving staff, visitors, and outpatients, including arrests in the ED waiting room or ambulance bay prior to handover to an ED physician. Paediatric (<18 years) cardiac arrests were excluded because NALHN does not have a paediatric Intensive Care Unit (ICU) and patients are generally retrieved to an external tertiary hospital once stabilised. Automated Implantable Cardioverter-Defibrillator (AICD) shocks without the need for bystander CPR or ongoing resuscitation were also excluded.

Data sources

EMS-based registry

Data linkage with SAAS-CAR was limited to EMS-attended OHCAs occurring within a NALHN catchment postcode and received by a NALHN hospital. Cases were manually linked using age, sex, arrest date, and time of call. Data were not available prior to 2012.

Administrative datasets

The ICD-10 Australian modification (ICD-10-AM) is an expanded version of the World Health Organisation's ICD-10. The ED coding dataset comprised of the Emergency Department ICD-10-AM Principal Diagnosis Short List (ED Short List) code of cardiac arrest (I46.9) and presenting complaint code of cardiac arrest (0102) extracted from HASS EDIS, a real-time patient tracking tool used in EDs across Australia. The diagnosis and presenting complaint codes were entered from a pull-down menu by the treating doctor and triage nurse, respectively.

The ICD-10 dataset includes the following primary or secondary diagnoses assigned to billable in-patient encounters by clinical coders according to the Australian Coding Standards at the primary treating hospital: Cardiac arrest with successful resuscitation (I46.0), Sudden cardiac death (I46.1), Cardiac arrest unspecified (I46.9), Ventricular fibrillation and ventricular flutter (I49.0), Respiratory arrest (R09.2), and Asphyxiation (T71). We included T71 to maximise sensitivity but excluded Ventricular tachycardia (I47.2) from the final coding set due to the high yield and low expected true positive rates. A post-hoc search of I47.2 yielded 608 cases from 2011 to 2016, of which 75 (12%) were matched to existing cases in the NALHN OHCA registry.

Table 1 – Characteristics of all adult OHCA cases arriving to NALHN facilities 2011–16, *n*=393.

Age	60±18
Male gender	262 (67%)
Possible syncopal episode with CPR (e.g. unmonitored arrest, bradyarrhythmia)	23 (6%)
Arrest location	
Home/residence (EMS-attended)	246 (63%)
Other (EMS-attended)	126 (32%)
Vehicle/carpark (non-EMS attended)	14 (4%)
Hospital grounds (non-EMS attended)	6 (2%)
Arrest within NALHN catchment postcode	321 (82%)
Witnessed	
Bystander	194 (49%)
Medical	94 (24%)
Unwitnessed	105 (27%)
Bystander CPR	216/299 (72%)
Initial shockable rhythm	183 (47%)
Sustained ROSC	351 (89%)
ROSC pre-SAAS	20 (5%)
Presenting Emergency Department	
Lyell McEwin Hospital	317 (81%)
Modbury Hospital	40 (10%)
Non-NALHN	36 (9%)
Presumed cardiac aetiology on arrival to emergency	285 (73%)
Glasgow coma scale >3 on arrival to emergency	105/390 (27%)
Admitted to NALHN facility	316 (80%)
Primary treating: Lyell McEwin Hospital	313 (99%)
Primary treating: Modbury Hospital	3 (1%)
Coronary angiography at Lyell McEwin Hospital	163 (42%)
Targeted temperature management (pre- and in-hospital)	143 (36%)
Admitted to NALHN intensive care/critical care unit	253 (64%)
NALHN discharge disposition	
Retrieved to acute care facility <24h	12 (3%)
Deceased in NALHN Emergency Department	69 (18%)
NALHN inpatient — survived[a]	148 (38%)
NALHN inpatient — deceased[a]	164 (42%)
Aetiology of arrest according to hospital medical record or autopsy	
Cardiac	203 (52%)
Respiratory	72 (18%)
Neurological	12 (3%)
Toxicological	24 (6%)
Other	38 (10%)
Unknown	44 (11%)
Overall survival to hospital discharge[a]	170 (43%)

Data presented as mean±standard deviation, or count (percentage). Percentages may not add up to 100% due to rounding.
CPR, cardiopulmonary resuscitation; EMS, emergency medical service; NALHN, Northern Adelaide Local Health Network; ROSC, return of spontaneous circulation.
[a] Includes patients retrieved to non-NALHN hospital(s) during episode of care.

Clinical registries

Cardiac catheterisation registries included the cardiac catheterisation record book, the 'Code STEMI' database, and the Coronary Angiogram Database of South Australia (CADOSA),[16,17] and were searched for "OHCA" or similar terms. NAHLN participates in the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), an Australia-wide ICU registry used for benchmarking of individual ICU performance.[18] The registry had been used retrospectively to identify an OHCA cohort admitted between 2011–2015, and for 2016 was searched using the diagnosis 'cardiac arrest' or 'respiratory arrest'.

Case identification method and quality control

The medical record number, admission date, name, and date of birth of each case identified from the hospital-based source was recorded, then (1) cases identified as included or excluded from each source were labelled in each consecutive source to avoid duplication, (2) age-based exclusion, (3) exclusion based on electronic summary, (4) inclusion based on manual hospital medical record review, (5) unique identification number assigned; identifiers stored in separate electronic file, (6) medical record abstraction; data import from linked sources, (7) annual review, training, and ongoing education for all data variables and definitions; annual monitoring of 10% of records; inbuilt database checks. Clinician-led identification was not utilised due to constraints in resources and availability of existing data sources.

Statistical analysis

Sensitivity and positive predictive values (PPV) of each hospital-based data source used to identify cases for the NALHN OHCA registry were investigated between 2011–16. The proportion of OHCA and non-OHCA cases yielded from each hospital-based data source was compared to (a) the number of OHCAs expected to be identified by each source, e.g., by limiting the analysis of the ED dataset to cases admitted to ED, and (b) total OHCA. The exact proportion of true negatives for each source was not calculated; however, specificity and negative predictive values were >95% for each data source using estimations of annual ED presentations, in-patient admissions, ICU admissions, and cardiac catheterisation procedures, respectively. A sensitivity analysis was performed excluding cases with ROSC pre-EMS and non-EMS attended OHCAs and accuracy for each dataset was compared. Standards for reporting diagnostic accuracy studies (STARD) were followed.[19] The classification of non-OHCAs yielded by each source was also explored and a sub-analysis of ICD-10 coding was performed for admitted patients. Analyses were performed using MedCalc Statistical Software version 19.2 (MedCalc Software bv, Ostend, Belgium).

Results

Between 2011–16, the NALHN OHCA registry included 393 OHCAs confirmed by manual hospital record review. Patient characteristics are presented for the total cohort (Table 1) and sensitivity analysis inclusion and exclusion groups (Table S1).

Hospital-based source accuracy

The four hospital-based data sources used to identify cases yielded 992 potential cases, of which 383 were true OHCA (Fig. 1). The EMS reference source yielded an additional 10 (3%) unique OHCAs between 2012–16. Of the 257 cases that arrested within a NALHN postcode and were attended by EMS between 2012–16, 195 (77%) were identified by the EMS registry (see Table S1 for characteristics of cases 'missed' by SAAS-CAR). The number of cases yielded, true positives, and accuracy for each source are presented with respect to the number of cases expected to be identified by each source (Table 2) and total OHCA (Table 3). The ED coding dataset was sensitive for both OHCAs admitted to ED (85%), and total OHCA

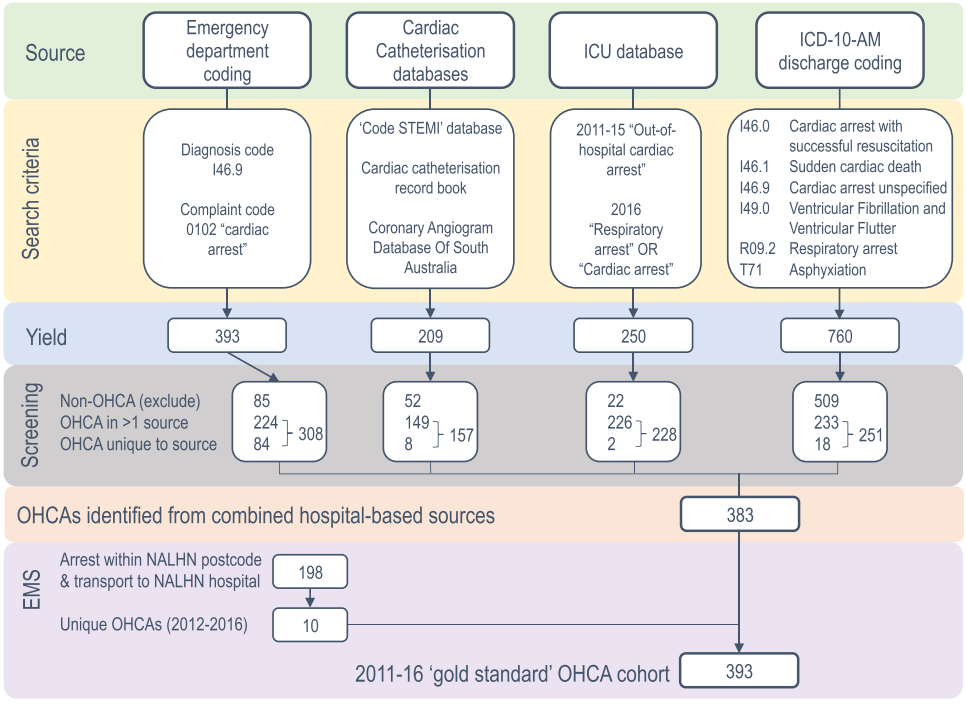

Fig. 1 – Cases in the NALHN OHCA registry identified from hospital-based and EMS-based sources. Data displayed is from 2011 to 2016. Cases yielded from each source are cross-referenced with each subsequent source to avoid duplication. Data from the EMS-based source was limited to arrests within NALHN catchment postcode with transport to NALHN hospital between 2012–2016. EMS, emergency medical service; ICU, Intensive Care Unit; OHCA, out-of-hospital cardiac arrest; NALHN, Northern Adelaide Local Health Network.

Table 2 – Accuracy of hospital-based sources with respect to total OHCA cases in the NALHN OHCA registry expected to be identified by each source, 2011–16.

	Total yield (*n*)	True positive (*n*)	Total OHCA (*n*)	Sensitivity (%)	PPV (%)
Emergency Department coding dataset	390	305	357 admitted to Emergency Department	85.4	78.2
Cardiac catheterisation registries	197	145	163 underwent cardiac catheterisation	88.96	73.6
Intensive Care Unit registry	250	228	253 admitted to Intensive Care Unit	90.1	91.2
ICD-10 coding dataset	760	251	316 admitted as in-patient	79.4	33.0

ED, Emergency Department; ICU, Intensive Care Unit. Sensitivity = true positive/total OHCA; PPV, Positive Predictive Value = true positive/total yield. Refer Fig. 2 for search criteria used to generate each source.

Table 3 – Accuracy of hospital-based sources with respect to total OHCA in the NALHN OHCA registry, 2011–16.

	Total yield (*n*)	True positive (*n*)	Total OHCA (*n*)	Sensitivity (%)	PPV (%)
Emergency Department coding dataset	393	308	393	78.4	78.4
Cardiac catheterisation registries	209	157	393	40.0	75.1
Intensive Care Unit registry	250	228	393	58.0	91.2
ICD-10 coding dataset	760	251	393	63.9	33.0

Sensitivity = true positive/total OHCA; PPV, Positive Predictive Value = true positive/total yield. Refer Fig. 2 for search criteria used to generate each source.

(78%), while the ICD-10 coding dataset had a sensitivity of 79% for admitted OHCAs at the cost of low PPV (33%). Combining the ED coding dataset with the two clinical registries identified 93% of total OHCAs. The sensitivity analysis revealed similar sensitivity and PPVs for each dataset (Tables S2 and S3).

Non-OHCAs

Table 4 presents a categorisation of cases yielded by each hospital-based source that were not OHCA. ED arrests were further defined as arrests occurring in patients occupying an ED bed or under active care

Table 4 – Excluded cases yielded by each hospital-based source searched for potential OHCA cases.

	<18 years of age	ED arrest	In-hospital arrest	AICD shock	Not cardiac arrest
Emergency Department coding dataset (*n*=85)	17 (20%)	**41 (48%)**	4 (5%)	-	23 (27%)
Cardiac catheterisation registries (*n*=52)	1 (2%)	17 (33%)	**21 (40%)**	2 (4%)	11 (21%)
Intensive Care Unit registry (*n*=22)	2 (9%)	9 (41%)	**10 (45%)**	-	1 (5%)
ICD-10 coding dataset (*n*=509)	12 (2%)	46 (9%)	**291 (57%)**	17 (3%)	143 (28%)

Data presented as *n* (% total non-OHCA). Bold values represent highest values of excluded cases (non-OHCA) for each source. Note: percentages may not add up to 100% due to rounding. ED, Emergency Department; AICD, Automated Implantable Cardioverter-Defibrillator.

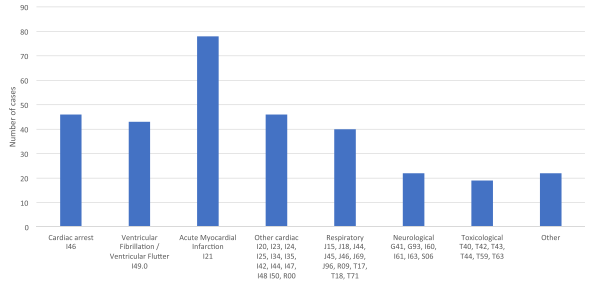

Fig. 2 – Primary ICD-10 code categories assigned to out-of-hospital cardiac arrest in-patient encounters grouped according to major diagnosis groups (*n*=316).

by emergency physicians after handover from EMS or MET and prior to in-patient hospital admission. Of note, the ICD-10 coding dataset yielded more in-hospital cardiac arrests than OHCAs (291 vs. 251), and the ED coding dataset yielded a high proportion of ED arrests (48%). Cases in the 'not cardiac arrest' group represented a broad range of diagnoses such as conscious arrhythmias and unconscious collapse.

Primary and secondary ICD-10 codes

The most common primary ICD-10-AM code for admitted patients in the NALHN OHCA registry (n=316) was acute myocardial infarction (I21) followed by cardiac arrest (I46) (Fig. 2, Table S4). When the ICD-10 coding set was used to identify admitted OHCA cases using only primary codes, sensitivity and PPV were 32.9% and 61.5%, respectively. The primary diagnosis code of cardiac arrest (I46) had a 14.6% sensitivity and 82.1% PPV for admitted OHCA, compared to 66.8% sensitivity and 40.1% PPV for OHCA when both primary and secondary diagnoses of I46 were searched. A breakdown of cases identified by each ICD-10-AM code in the coding set can be found in Table S5.

Discussion

Although EMS-based registries remain a primary source of OHCA identification and data, hospital-based sources provide additional identification of non-EMS attended OHCAs, as well as data on in-hospital management and outcomes. In this paper we describe the methods used to identify cases in the NALHN OHCA registry using a simple and consistent definition of OHCA.[15] To address the overarching aims of the registry, this definition allowed the inclusion of OHCAs that arrive by private vehicle and thus was not based on the emergency response (EMS vs MET) but rather whether the patient was receiving in-patient care at the time of cardiac arrest. Our analysis of existing hospital-based sources found that the ED coding set identified the most OHCAs overall. Sensitivity analyses excluded non-EMS-attended and -resuscitated OHCAs resulted in similar accuracy for each data source. We confirmed that ICD-10 codes do not provide efficient identification of OHCA cases. Hospital-based data sources, ideally in combination with EMS-based sources, provide a valid method of identifying OHCA cases treated at hospital.

Validation of hospital-based methods of OHCA identification

Due to the heterogenous nature of OHCA presentations and limitations of coding, there is no single data source that correctly identifies all OHCA cases. Combined hospital-based sources identified 97% of OHCAs treated at a NALHN hospital with the remainder identified by the EMS-based registry. Overall, the ED coding dataset yielded the most OHCAs with a sensitivity of 78% for total OHCA and 85% for OHCAs admitted to ED. Existing clinical registries, especially the ICU registry, were highly accurate within their respective patient subgroups, and when combined with the ED coding set, identified 93% of total OHCAs. To the best of our knowledge the NALHN OHCA registry is the first of its kind. Other hospital-based registries either exclude non-EMS attended arrests and patients without ROSC, or do not adequately describe methods of identification, accuracy, and reliability to enable comparison.[7,20,21] Multiple-source sudden cardiac death registries that additionally utilise autopsy registers and death certificate screening are nearest to comprehensive case capture but are generally limited by their exclusion of non-cardiac cases.[22] Existing data sources are a valid method of hospital-based OHCA identification that minimises the potential burden associated with clinician-led identification.

Limitations of EMS-based registries

Current prospective OHCA data sources are predominately EMS-based.[3–9] Except for PAROS,[5] most OHCA registries do not capture non-EMS-attended OHCAs such as hospital arrivals by private vehicle, arrests on hospital grounds individuals not occupying an ED or inpatient bed, or clearly deceased cases of sudden cardiac death transported directly to coronial services. The latter may be further identified from autopsy registers or by death certificates as in multiple-source SCD registries.[22,23] Although cases may be identified using multiple strategies by EMS personnel and many are linked to hospital records or death registries, missing data remains an issue.[24] Some registries do not routinely audit for missing data and up to 25% of eligible cases have been reported as missing.[25,26] Using hospital-based sources we identified 59 of 254 (23%) eligible cases that were missing from the EMS-based registry, though this number is expected to decrease as the definition of cardiac arrest is standardised between

the registries. We also identified 21 (5%) non-EMS attended OHCAs, the majority of which occurred during transport in private vehicles and on arrival to hospital carparks. By combining an EMS-based registry with existing hospital-based sources of OHCA identification we begin to improve identification of non-EMS attended arrests for inclusion in registries in a manner that is not overly resource-intensive.

Limitations of ICD-10 coding

This is the first study to demonstrate that neither single nor primary ICD-10-AM codes are valid methods of identifying hospital-admitted OHCAs. We found that multiple primary and secondary ICD-10-AM codes identified 79% of admitted cases and 64% of all NALHN presentations, albeit with a PPV of only 33% and only 18/251 (7%) unique cases not found in other sources. Only two other North American studies have used ICD-9 coding datasets applied to ED encounters to identify OHCAs and sensitivity varied from 40% to 87%.[20,27] Of note, ICD-10-AM codes are only assigned to in-patient and not ED encounters, so the ED coding dataset used in this study (which incorporates a short version of the ICD-10-AM) may be more useful for future comparisons. Unlike these studies, we did not include I47.2 Ventricular tachycardia because the false positive rate (identification of mainly in-hospital arrests) was expected to be exceptionally high. Although the most common primary diagnosis code for admitted OHCAs was acute myocardial infarction (I21), likely because the I46 code cannot be applied to resuscitated OHCAs when the underlying cause is documented, this code would also not be sensitive enough to identify OHCAs effectively. Future iterations of the ICD-10 coding system should differentiate between IHCA and OHCA to allow effective monitoring of disease trends and allocation of hospital resources.[11]

Study limitations

The NALHN OHCA registry was designed to overcome limitations of incomplete case capture inherent to other types of registries but is also, by design, subject to limitations. The registry was designed for thorough investigation of cases treated at NALHN hospitals but does not provide information on cases attended by EMS in the community that were declared dead on scene or transported to other acute care facilities. Although traumatic OHCAs were not excluded from the registry, bias may be introduced because most are retrieved by EMS to a non-NALHN acute care facility. We included cases according to the Utstein definition[14] and identified 23 (6%) unmonitored events may have been syncopal episodes and not true cardiac arrest according to the treating hospital clinician. The data sources used may not be translatable to a national and international setting. Although ICD-10 codes are designed to allow international comparisons they may be subject to local variations in coding practices. The registry is currently limited to a local cohort, but the small size has allowed us to more effectively test a method that can be adapted for larger population-based registries. Data-linkage with SAAS-CAR was not available for 2011 due to data capture issues, and in future will be expanded to include arrests outside the NALHN catchment. Both NALHN and SAAS-CAR primarily use paper-based records whereas other institutions may be able to conduct electronic searches using appropriate keywords to increase case capture. Confirmation of OHCA and collection of many core data variables requires manual hospital record review, which may be subject to confounding and bias when compared to prospective data collection by a clinician directly involved in the patient care. However, such a method is not feasible in our or other settings and remains subject to missed cases due to the highly varied and time critical nature of OHCA presentations.

Conclusion

We have overcome the challenges of establishing a hospital-based OHCA registry by using existing hospital-based sources as well as linkage with an EMS-based registry. Our analysis confirms that ICD-10 codes do not efficiently identify OHCAs and should not be used in the calculation of cardiac arrest incidence. We found that the ED coding set had the highest sensitivity for total OHCA cases in the NALHN OHCA registry. The methods presented here may be adapted to augment EMS-based data or used where EMS registries are not established or data-linkage with EMS is prohibitive.

Funding

None to declare.

Conflicts of interest

None to declare.

Ethics information

The Central Adelaide Local Health Network Human Research Ethics Committee approved the registry as an ongoing quality improvement activity and separate approval was obtained for data linkage with the South Australian Ambulance Service Cardiac Arrest Registry (SAAS-CAR).

CRediT authorship contribution statement

Melanie R. Wittwer: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. **Mohammed Ishaq Ruknuddeen:** Methodology, Resources, Writing - review & editing. **Mel Thorrowgood:** Resources, Writing - review & editing. **Chris Zeitz:** Supervision, Writing - review & editing. **John F. Beltrame:** Supervision, Writing - review & editing. **Margaret A. Arstall:** Conceptualization, Supervision, Writing - review & editing.

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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.resplu.2021.100136.

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3.6 Summary of Chapter Three

Chapter Three presents the rationale, development, and design of the NALHN OHCA registry, including a published definition of OHCA and published manuscript investigating accuracy of case identification. The NALHN OHCA registry is the first hospital-based OHCA registry to collect Utstein-style data on consecutive OHCA cases treated at hospital. Throughout this program of doctoral research, the registry was used to investigate the incidence, management, and outcome of OHCA within NALHN to identify strategies to improve survivorship within an Australian setting. In accordance with the principles of the clinical feedback loop, the methods have undergone several iterations and will continue to do so to ensure that the most relevant information is collected in a time-efficient and sustainable manner. Pilot implementation of the REDCap database and associated data dictionary is currently ongoing but is hoped to improve the ease and reproducibility of data collection. The registry was established to overcome limitations with respect to the original code STEMI OHCA registry, as well as limitations in data capture by the EMS-based registry, SAAS-CAR, and has the potential to form the basis of a state-wide CQR. This model may be adapted to augment EMS-based data or used where EMS registries are not established or data-linkage with EMS is prohibitive.

CHAPTER FOUR: SEX DIFFERENCES IN INCIDENCE AND OUTCOME OF OHCA WITHIN NALHN

4.1 Overview of Chapter Four

Chapter Three summarised the NALHN OHCA registry protocol and validated the methods of case identification. A data-linkage was subsequently formed with the SA Ambulance Service Cardiac Arrest Registry (SAAS-CAR) to characterise the burden of OHCA within NALHN using both pre-hospital and in-hospital data. This chapter addresses the third research objective of this thesis, which was to determine sex differences in incidence and outcome of OHCA within NALHN.

4.2 Background and context

Sex and gender differences in incidence, presentation, management, outcome, and aetiology of OHCA are well established. However, on closer inspection, these differences were only observed in cohorts with a pre-hospital presumed cardiac diagnosis and low or no representation of non-cardiac patients.[184] Since pre-hospital diagnoses are incorrect in up to 20% of cases,[25] further investigation into sex differences based on adjudicated aetiology is warranted. In addition, the roles of precipitating aetiology and SES in mediating these sex differences remain under-researched. Overall, women are less likely to survive after OHCA than men, and this is likely explained by a higher prevalence of confirmed non-cardiac aetiology and non-shockable initial rhythm compared to men, both of which are associated with poor outcomes.[176,177,179] The study presented in this chapter was designed to provide an overview of the sex differences in incidence and outcome of OHCA within NALHN, with a focus on precipitating aetiology and SES. In the context of this thesis, the study also establishes the overall incidence and survival rate of OHCA within NALHN across cohorts of interest.

4.3 Manuscript, Paper Two

The following paper, "Sex differences in incidence and outcome of out-of-hospital cardiac arrest within a local health network" was published in *Frontiers in Cardiovascular Medicine* in 2022.[22] Supplementary materials are provided in **Appendix C**.

Statement of Authorship

Title of Paper	Sex differences in incidence and outcome of out-of-hospital cardiac arrest within a local health network
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Wittwer MR, Aldridge E, Hein C, Thorrowgood M, Zeitz C, Beltrame JF, Arstall MA. Sex differences in incidence and outcome of out-of-hospital cardiac arrest within a local health network. Frontiers in Cardiovascular Medicine. 2022;9:1-10.

Principal Author

Name of Principal Author (Candidate)	Melanie Wittwer		
Contribution to the Paper	Conception and design of the project; data acquisition; analysis and interpretation of data; drafting significant parts of the article or critically revising it so as to contribute to the interpretation		
Overall percentage (%)	65%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/03/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Emily Aldridge		
Contribution to the Paper	Conception and design of the project; analysis and interpretation of data; drafting significant parts of the article and critically revising it so as to contribute to the interpretation.		
Signature		Date	21/03/2022

Name of Co-Author	Cindy Hein		
Contribution to the Paper	Data acquisition; critical revision.		
Signature		Date	21/03/2022

Name of Co-Author	Mel Thorrowgood		
Contribution to the Paper	Data acquisition; critical revision.		
Signature		Date	22/3/22

Name of Co-Author	Chris Zeitz		
Contribution to the Paper	Research data input; contribution of knowledge; critical revision.		
Signature		Date	23/3/22

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Contribution to the Paper	Research data input; contribution of knowledge; critical revision.		
Signature		Date	23/3/22

Name of Co-Author	Margaret A Arstall		
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Signature		Date	21/03/2022

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ORIGINAL RESEARCH
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Sex Differences in Incidence and Outcome of Out-of-Hospital Cardiac Arrest Within a Local Health Network

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Introduction: Sex and gender differences in presentation and characteristics of out-of-hospital cardiac arrest (OHCA) are established in cohorts with presumed cardiac aetiology but not non-cardiac etiology. This study investigated the effect of sex on incidence and outcome of OHCA according to presumed and adjudicated aetiology within a local health network.

Methods: Population-based observational cohort study of emergency medical services (EMS) attended OHCAs within an Australian local health network. Cases identified from an EMS registry between 2012-2016 were linked to a hospital registry. Age-standardised incidence and baseline characteristics were stratified by sex for EMS-treated OHCA, non-EMS witnessed presumed cardiac and obvious non-cardiac sub-cohorts, and hospitalised cases. Logistic regression was used to explore the primary outcome of survival to hospital discharge.

Results: We identified 2,024 EMS-attended and 780 EMS-treated OHCAs. The non-EMS witnessed sub-cohorts comprised 504 presumed cardiac and 168 obvious non-cardiac OHCAs. Adjudicated aetiology was recorded in 123 hospitalised cases. Age-standardised incidence for women was almost half that of men across all groups. Across cohorts, women were generally older and arrested with a non-shockable initial rhythm in an area of low socioeconomic status. There was no sex difference in the primary outcome for the main EMS-treated cohort or in the non-cardiac sub-cohorts. The sex difference in outcome in the presumed cardiac sub-cohort was not present after multivariable adjustment.

Conclusions: There are sex differences in incidence and outcome of EMS-treated OHCA that appear to be driven by differences in susceptibility to cardiac arrhythmias and underlying etiology, rather than treatment delays or disparities.

Keywords: out-of-hospital cardiac arrest, sex, gender, outcomes - health care, aetiology (etiology), socioeconomic status, epidemiology

INTRODUCTION

Incidence, characteristics, and outcomes of out-of-hospital cardiac arrest (OHCA) differ according to sex. Women represent around 40% of the OHCA population attended by emergency medical services (EMS) but present with fewer established predictors of survival including increased age, unwitnessed arrest, arrest within a private residence, and non-shockable initial rhythm compared with men (1, 2). Precipitating non-cardiac aetiology leading to OHCA, as confirmed by diagnostic testing or autopsy, is also more common in women than men, and is associated with fewer survival predictors, such as shockable initial rhythm, and poor overall survival (3–9). Nonetheless, sex differences in outcomes have not been investigated according to adjudicated cardiac and non-cardiac etiology. Recent meta-analyses found that adult women were up to 50% less likely to survive to hospital discharge or 30 days after OHCA compared with men (2, 10). Adjusting for known survival predictors fully accounts for observed sex differences in survival to hospital discharge in Australian and international populations (1, 11–14). It is likely that the high rates of non-cardiac aetiology and associated non-shockable initial rhythm in women play a key role in driving the relationship with poor outcome after OHCA, but this area remains under-researched. Socioeconomic status (SES) is another important determinant of cardiovascular health, particularly in women (15, 16). Low SES is associated with a high incidence of OHCA and poor survival (17); however, limited studies suggest that low SES is associated with poor survival in men but not women (18, 19).

The primary study objective was to investigate the effect of sex on survival to discharge in a cohort of EMS-treated OHCAs and sub-cohorts of non-EMS-witnessed presumed cardiac and obvious non-cardiac cases. The secondary objectives were to report incidence stratified by age and sex, explore the effect of SES on survival according to sex, and to investigate sex differences in adjudicated aetiology in the sub-cohort transported to hospital.

METHODS

Study Design

This was a retrospective observational study of all adult OHCAs within the Northern Adelaide Local Health Network (NALHN), South Australia. The study cohorts were generated by linking an EMS-based and a hospital-based OHCA registry for all cases occurring within a NALHN catchment as defined by postcode. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (20) were followed and the Central Adelaide Local Health Network Human Research Ethics Committee approved the study [HREC/15/TQEH/89].

Study Setting

The SA Ambulance Service (SAAS) provides a two-tier EMS where patients are treated by paramedics on scene across the state of South Australia (SA). NALHN comprises two public hospitals that service a population of 395,000 across 631 km^2 within the northern metropolitan area of Adelaide, SA. Compared with the rest of Australia, both SA and NALHN are characterised by low SES and are ranked in the 37th and 19th percentiles according to the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD), respectively (21). SAAS and NALHN hospitals follow the ANZCOR resuscitation guidelines (22). Cardiac catheterisation and targeted temperature management are performed at the discretion of treating clinicians according to local guidelines.

Data Sources and Definitions

The SAAS Cardiac Arrest Registry (SAAS-CAR), described previously (23), was searched from 2012–16 for all cases aged ≥18 years within NALHN using the postcode associated with arrest location. Patients without attempted resuscitation by EMS had high rates of missing data (85 missing for initial rhythm, 63 witness status, 63% bystander CPR) and were included for incidence rate calculations only. The main cohort comprised all EMS-treated OHCAs including obvious non-cardiac aetiologies such as trauma, asphyxia, exsanguination, overdose etc., while the sub-cohorts comprised EMS-treated, non-EMS-witnessed OHCA with (presumed cardiac) or without obvious non-cardiac cause. Attempted resuscitation was defined as any chest compressions or any defibrillation by paramedics. Arrest location (e.g., private residence) and response times were not available due to limitations in data capture within the study period. The primary outcome of survival to hospital discharge was extracted for cases transported to non-NALHN hospitals.

The Northern Adelaide Local Health Network (NALHN) OHCA registry is a hospital-based quality assurance initiative (24). Variables are obtained from linkage with existing clinical registries and abstraction from the hospital medical record. Ethnicity was frequently documented as unknown and therefore excluded from this analysis. The hospitalised sub-cohort was formed by manually linking cases with the NALHN OHCA registry using age, sex, arrest date, and time of call.

The 2011 IRSAD was generated from census data by the Australian Bureau of Statistics (abs.gov.au) according to postal area code (POA) and linked to postcode of arrest. Although residential postcodes better reflect individual SES, they were not available for analysis. Higher national deciles indicate low levels of disadvantage and high levels of advantage.

Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes included incidence per 100,000 person-years, whether the patient was transported to hospital (excluding patients transferred for certification of death), and survival with good neurological recovery (cerebral performance category, CPC, 1-2) in hospitalised patients.

Statistical Analysis

Crude and age-standardised incidence rates per 100,000 person-years were explored according to sex for EMS-attended OHCAs with attempted resuscitation aged ≤20 years, to match with available population data. To account for dynamic changes in the at-risk population over the study period, enumerated NALHN population data (Australian Bureau of Statistics, compiled and presented by.id) was averaged between data available for

2011 and 2016 (25). Adjusted rates were calculated using the direct method across 5-year age groups from 20 to >85 years and applied to the 2001 Australian standard population. Age was missing, presumed at random, in eight cases so an inflation factor was calculated as the percentage of missing data and applied to both crude and age-adjusted incidence rates (**Supplementary Table 1**).

Descriptive statistics were used to explore differences between males and females in all cohorts. Comparisons between sexes were performed using Wilcoxon Sum Rank Tests, Chi-Squared Tests or Fisher's Exact Tests as appropriate for skewed continuous and categorical variables.

Exploratory binary logistic regressions investigated the association between sex and survival to hospital discharge for both the main cohort and presumed cardiac sub-cohort, while adjusting for available survival predictors (age, witness status, bystander CPR, and shockable rhythm). The obvious non-cardiac sub-cohort was too small and survival rate too low to permit multivariable analysis. Interactions between sex and each covariate were tested in the adjusted models and removed if insignificant. Odds ratios (OR), 95% confidence intervals (95%CI), and comparison and global *P*-value are presented.

P-values less than or equal to 0.05 were regarded as significant and adjustments were not made for multiple comparisons. Analyses were performed using SPSS 26 (IBM SPSS Statistics, Armonk, NY, USA).

RESULTS

There were 9,026 EMS-attended cardiac arrests aged ≥18 years identified from SAAS-CAR between 2012–16, of which 2,024 (23%) occurred within a NALHN postcode and 780 were EMS-treated (**Figure 1**). There was no difference in proportion of males vs. females receiving attempted resuscitation (38% vs. 39% of all attended arrests, $p > 0.05$). In the sub-cohorts of non-EMS witnessed cases, 504 were of presumed cardiac origin and 168 were of obvious non-cardiac origin. The hospitalised sub-cohort consisted of 123 cases with adjudicated aetiology documented in the NALHN OHCA registry, excluding 24 with unknown etiology.

Crude and age-adjusted incidence rates of OHCAs aged ≥20 years according to sex are presented in **Table 1**. Incidence in women was similar to that of men 10–20 years younger for EMS-attended and EMS-treated OHCAs (**Figure 2**).

EMS-Treated Cohorts

Sex differences in characteristics of the main adult EMS-treated OHCA cohort and sub-cohorts are presented in **Table 2**. Women represented 35% of the main cohort, 33% of the presumed cardiac sub-cohort, and 38% of the non-cardiac sub-cohort, were a median 4–6 years older than men on presentation, and had similar rates of presumed cardiac diagnosis as men. Women in the main cohort and presumed cardiac sub-cohort, but not the obvious non-cardiac sub-cohort were less likely to present with VF/VT and more likely to present with asystole than men. OHCA was more likely to occur in an area associated with higher levels of disadvantage (lowest 5 deciles) in women than men in the presumed cardiac sub-cohort, but this difference was not observed for the main or non-cardiac cohorts.

There was no significant sex difference in unadjusted survival to hospital discharge observed in the main cohort (9% women vs. 13% men; OR: 0.66, 95% CI: 0.40-1.08, $p = 0.099$). Exploratory analyses were performed and an interaction between sex and shockable rhythm, but not sex and age, SES, or other predictors, was observed. On multivariable analysis, higher odds of survival were associated with shockable rhythm in both males and females, decreasing age, bystander witness, and EMS witness, as well as IRSAD deciles, such that for every increase in IRSAD decile the odds of survival increased by 11% (**Table 3**). There was no difference in survival from hospital arrival to discharge in all cases transported to hospital, including non-NALHN hospitals (women 29% vs. men 42%, $p = 0.14$).

In unadjusted analyses of the presumed cardiac sub-cohort, women were less likely than men to survive to hospital discharge (7% women vs. 15% men; OR: 0.45, 95%CI 0.23–0.87, $p = 0.018$). No interactions were observed between sex and age, SES, or other predictors. Multivariable analysis revealed that sex was not associated with higher odds of survival to hospital discharge (OR: 0.76, 95% CI 0.35–1.64, $p = 0.48$), nor was bystander CPR (OR: 1.02, 95% CI 0.49-2.11, $p = 0.96$). Decreasing age (OR: 0.97, 95% CI 0.95–0.99, $p = 0.013$), bystander witness (OR: 3.04, 95% CI 1.47–6.27, $p = 0.003$), shockable rhythm (OR: 16.1, 95% CI 6.99-37.0, $p < 0.001$), and increasing IRSAD deciles (OR: 1.13, 95%CI: 1.00, 1.28, $p = 0.046$) were associated with higher odds of survival to hospital discharge.

Hospital-Treated Sub-cohort

Sex differences in survival to hospital discharge were explored according to adjudicated aetiology (cardiac vs. non-cardiac, excluding unknown) in a small sub-cohort of non-EMS witnessed OHCAs transported to NALHN hospitals (**Table 4**). Cardiac aetiology represented 68% of known adjudicated diagnoses (57% including unknown diagnoses) and was significantly more prevalent in men than women (76% vs. 50%, $p = 0.01$). Women with cardiac aetiology were younger than men, but there were no other statistically significant sex differences in arrest characteristics or outcomes within groups. In cases with a pre-hospital presumed cardiac diagnosis, precipitating aetiology was confirmed as cardiac in fewer women than men when cases with unknown diagnoses were included (53% vs. 75%, $p = 0.029$).

DISCUSSION

We report sex differences in incidence and outcome of consecutive EMS-attended and -treated OHCA within a local health network. Within these populations, women were almost half as likely to experience OHCA compared with men after age-standardisation. Although women in the sub-cohort with non-EMS-witnessed presumed cardiac OHCA were less likely to survive to hospital discharge than men in unadjusted analyses, this association was not present in the adjusted model. Exploratory

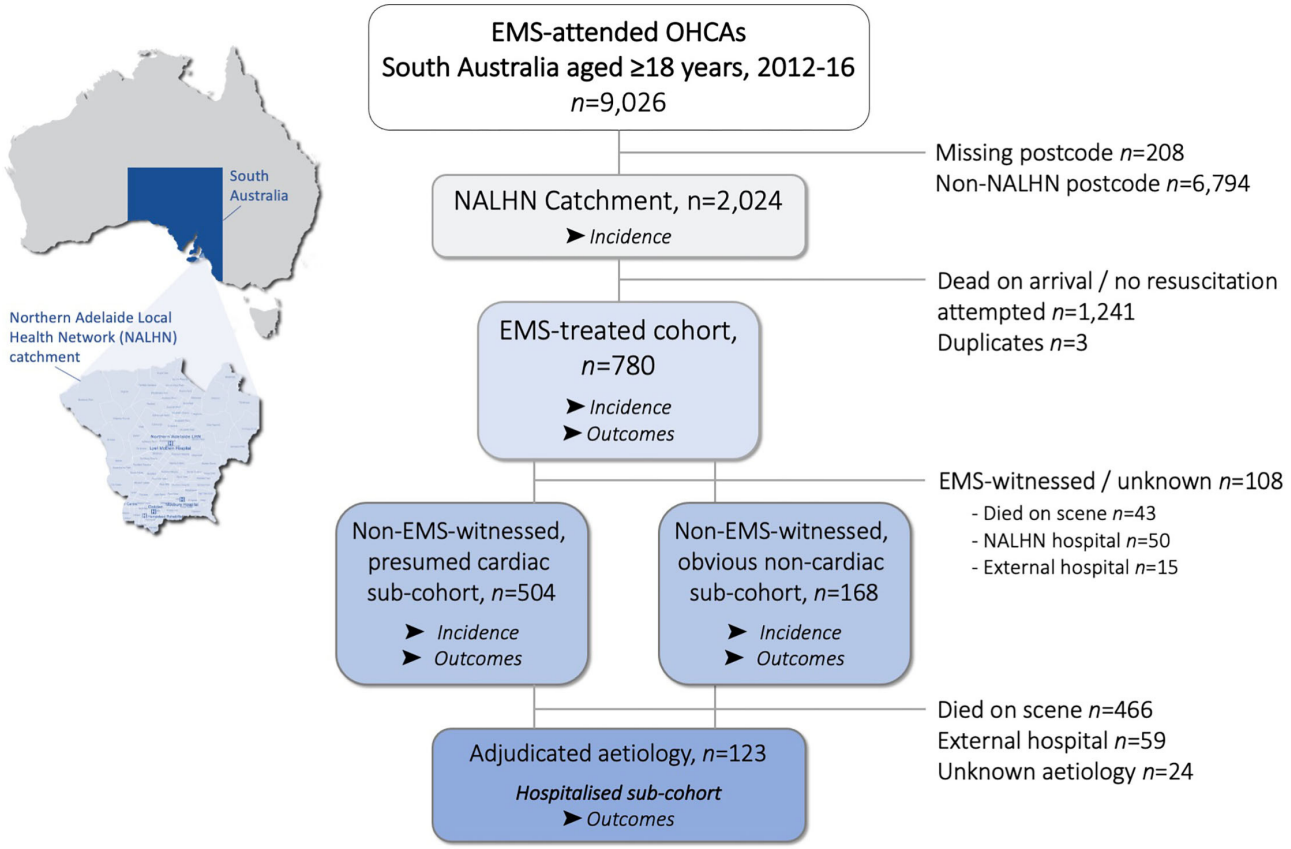

FIGURE 1 | Flowchart of out-of-hospital cardiac arrests (OHCA) aged ≥18 years occurring within the Northern Adelaide Local Health Network (NALHN) catchment area in South Australia, Australia from 2012–2016.

TABLE 1 | Incidence of OHCA aged ≥20 years within NALHN according to sex, 2012–2016.

	Total	Females	Male
EMS-attended*	***n* = 1,970**	***n* = 691**	***n* = 1,279**
Crude	148.7	100.3	199.6
Age-standardised	139.9	96.0	184.3
EMS-treated cohort*	***n* = 772**	***n* = 273**	***n* = 499**
Crude	57.3	39.2	76.4
Age-standardised	54.6	38.1	71.8
Non-EMS witnessed presumed cardiac sub-cohort	***n* = 501**	***n* = 163**	***n* = 338**
Crude	36.8	23.4	50.9
Age-standardised	34.7	22.8	47.2
Non-EMS witnessed obvious non-cardiac sub-cohort*	***n* = 161**	***n* = 63**	***n* = 98**
Crude	12.3	9.0	15.8
Age-standardised	12.2	9.0	15.6

*Data is presented per 100,000 person-years. *Inflation factor applied to crude and age-standardised incidence rates, excepting female EMS-treated rates and non-EMS witnessed obvious non-cardiac rates for females.*

analyses highlighted the discrepancy between presumed and adjudicated aetiologies and pointed to a survival advantage for hospitalised women with adjudicated non-cardiac aetiology.

Sex Differences in Incidence

Few studies have reported sex differences in age-standardised incidence of EMS-attended and EMS-treated adult OHCAs, irrespective of etiology. Unadjusted and age-adjusted

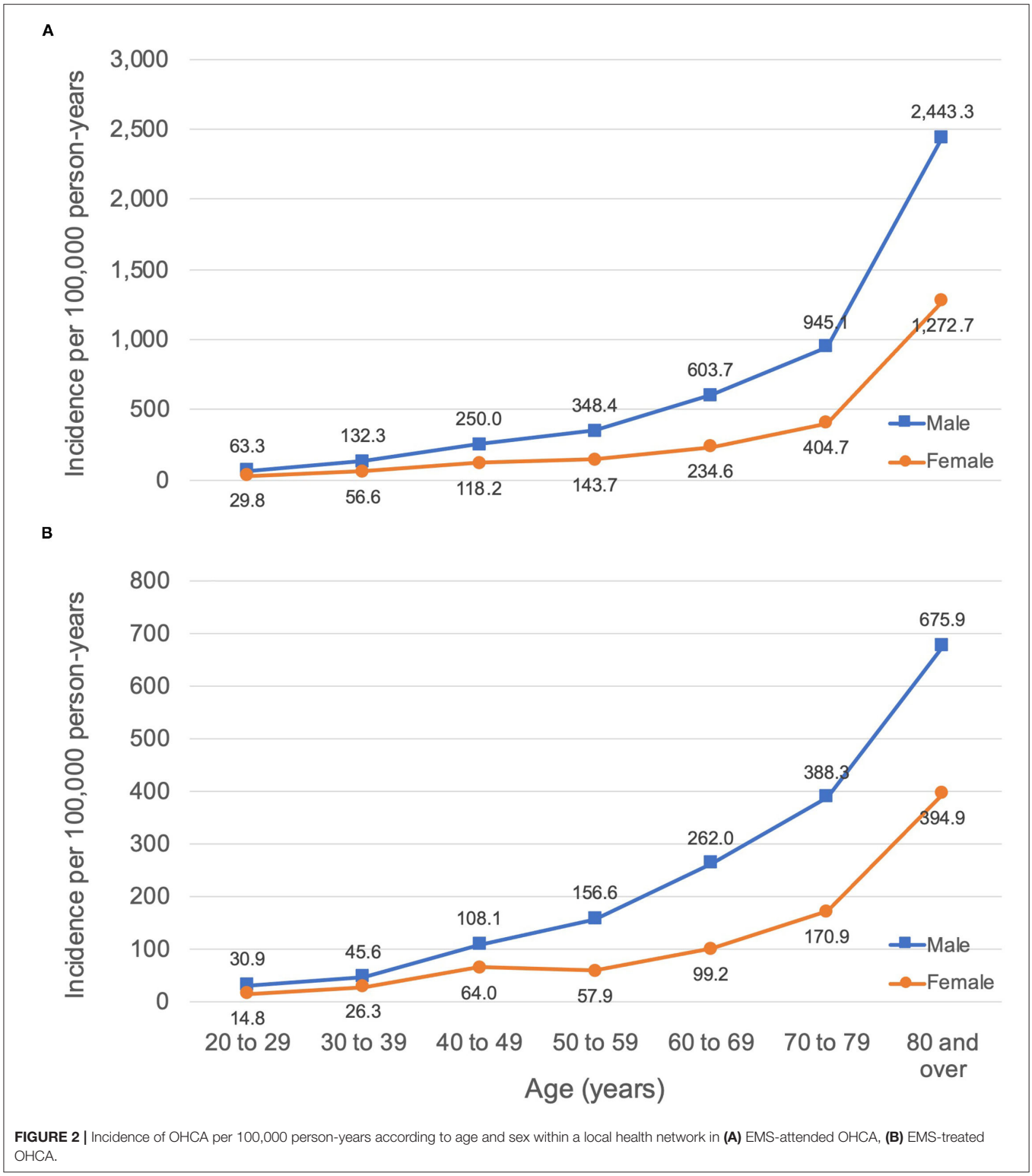

FIGURE 2 | Incidence of OHCA per 100,000 person-years according to age and sex within a local health network in **(A)** EMS-attended OHCA, **(B)** EMS-treated OHCA.

rates stratified by sex were consistent with comparable previous studies, confirming that men consistently experience OHCA at a rate more than double that of women (13, 26–28). Similar to the delayed onset of cardiovascular disease in women, our data and that of others suggests that the incidence of OHCA in women of any given age group is similar to that of men 10 years younger (27–29).

TABLE 2 | Characteristics of EMS-treated OHCAs within NALHN according to sex.

Characteristics	EMS-treated cohort $n = 780$			Non-EMS witnessed sub-cohorts					
				Presumed cardiac $n = 504$			Obvious non-cardiac $n = 168$		
	Sex		Missing	Sex		Missing	Sex		Missing
	Female $n = 273$	Male $n = 507$		Female $n = 165$	Male $n = 339$		Female $n = 63$	Male $n = 105$	
Age	68 [49–82]	64 [50–76]*	8 (1%)	72 [53-82]	67 [56-77]	–	53 [42-71]	47 [35-65]	–
IRSAD decile ≤5	205 (75%)	377 (74%)	–	134 (81%)	247 (73%)*	–	43 (67%)	83 (79%)	–
Witnessed			4 (0.5%)			–			–
EMS-witnessed	42 (15%)	61 (12%)	–	–	–	–	–	–	–
Bystander	102 (38%)	221 (44%)	–	77 (47%)	117 (52%)	–	25 (39%)	44 (42%)	–
Unwitnessed	127 (47%)	223 (44%)	–	88 (53%)	222 (48%)	–	39 (61%)	61 (58%)	–
Bystander CPR	148 (56%)	291 (59%)	28 (3.7%)	107 (66%)	217 (65%)	7 (1.4%)	39 (61%)	71 (69%)	
Initial rhythm			8 (1%)			3 (0.6%)			1 (0.6%)
VF/VT	50 (19%)	158 (32%)*	–	33 (21%)	137 (41%)*		5 (8%)	5 (5%)	–
PEA	79 (29%)	220 (44%)	–	38 (23%)	61 (18%)		21 (33%)	31 (30%)	–
Asystole	139 (52%)	126 (25%)*	–	92 (56%)	140 (41%)*		37 (59%)	68 (65%)	–
Presumed cardiac	192 (71%)	385 (76%)	1 (0.1%)	165 (100%)	339 (100%)	–	0 (0%)	0 (0%)	–
NALHN Hospital	71/92 (77%)	126/178 (71%)		34/42 (81%)	87/119 (73%)	–	13/20 (65%)	13/25 (52%)	–
Transported to hospital	92 (34%)	178 (35%)		42 (25%)	119 (35%)*	–	20 (31%)	25 (24%)	–
Survived to discharge	24 (9%)	65 (13%)	8 (1%)	12 (7%)	50 (15%)*	1 (0.2%)	4 (6%)	3 (3%)	2 (1.2%)

*Data presented as median [interquartile range] and number (percentage). *P-value <0.05; p-values reflect data that excludes missing values. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage; NALHN, Northern Adelaide Local Health Network; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.*

TABLE 3 | Multivariable logistic regression model: predictors of survival to hospital discharge after EMS-treated OHCA (main cohort), $n = 751$.

Characteristics	Comparison	Odds Ratio (95% CI)	*p*-value
Female sex	Shockable vs. non-shockable	1.26 (1.09–1.46)*	0.001
Male sex	Shockable vs. non-shockable	1.46 (1.30–1.65)	<0.001
Age, per *y*		0.98 (0.96-1.00)	0.012
IRSAD decile		1.11 (1.00–1.23)	0.041
Bystander witnessed vs. unwitnessed		3.00 (1.56–5.77)	<0.001
EMS witnessed vs. unwitnessed		6.77 (2.97–15.5)	<0.001
Presumed cardiac cause		0.83 (0.39–1.76)	0.621

**Interaction p < 0.05. EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage.*

Sex Differences in Survival

Women in the presumed cardiac sub-cohort were 55% less likely to survive to hospital discharge than men in unadjusted analyses. Once adjusted for available predictors of survival that differ between males and females (age, SES, witness status, and initial rhythm) the sex difference in outcome disappeared. It is likely that a smaller magnitude of difference in outcome between sexes exists for the main cohort of EMS-treated OHCAs, but the sample may not have been sufficiently powered. Only a few studies have reported sex differences in outcome of all-cause OHCA with the survival rate for men ranging from 1 to 5.5% higher than women (13, 30–32). Attenuation of the magnitude of difference in outcome between sexes may be due to the inclusion of obvious non-cardiac etiologies such as asphyxia, exsanguination, and overdose, the outcomes of which may not differ between males and females. Although we found that outcomes were similar between sexes in the small non-cardiac sub-cohort, this hypothesis has only been investigated in one other study of patients presenting with shockable rhythm and requires further validation (33). Previous reports of sex differences in survival appear contradictory; however, all of the larger OHCA registries ($n > 10{,}000$) report unadjusted survival and favourable neurological prognosis at hospital discharge as consistently higher in men than women, with no difference (1, 11–14, 30) or even a favouring of women (34) after adjustment, irrespective of differences in population subsets. The observed sex differences in survival across our cohorts were explained by the older age of women, their higher rate of arrest in a low SES

TABLE 4 | Characteristics of EMS-treated, non-EMS witnessed OHCAs treated at NALHN hospital according to adjudicated aetiology and sex, $n = 123$.

	Cardiac $n = 84$		Non-cardiac $n = 39$	
Characteristics	**Female $n = 18$**	**Male $n = 66$**	**Female $n = 18$**	**Male $n = 21$**
Age	51 [41–65]	65 [54–72]*	53 [43–70]	50 [34–67]
IRSAD decile ≤5	14 (78%)	47 (71%)	11 (61%)	15 (71%)
Bystander witnessed	11 (61%)	53 (80%)	8 (44%)	11 (52%)
Bystander CPR	15 (83%)	47 (71%)	13 (72%)	16 (76%)
Initial rhythm				
VF/VT	14 (78%)	56 (85%)	1 (6%)	2 (10%)
PEA	0 (0%)	3 (5%)	7 (39%)	5 (24%)
Asystole	4 (22%)	7 (11%)	10 (56%)	14 (67%)
Pre-hospital presumed cardiac diagnosis	18 (100%)	65 (98%)	7 (39%)	12 (57%)
GCS 3 on arrival	15 (83%)	49/64 (77%)	16 (89%)	20 (95%)
Sustained ROSC	16 (89%)	61 (92%)	18 (100%)	20 (95%)
ST-elevation	6/16 (38%)	25/60 (42%)	1/16 (6%)	4/19 (21%)
Inpatient admission	16 (89%)	59 (89%)	15 (83%)	19 (90%)
Survived to discharge	7 (39%)	37 (56%)	4 (22%)	1 (5%)
Neurological recovery (CPC 1-2) at discharge	7 (39%)	35/65 (54%)	4 (22%)	1 (5%)
12-month survival	7 (39%)	35 (53%)	4 (22%)	1 (5%)

*Data presented as median [interquartile range] and number (percentage). *P-value < 0.05; p-values reflect data that excludes missing values. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage; NALHN, Northern Adelaide Local Health Network; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.*

area with an initial non-shockable rhythm, and lower likelihood of a confirmed cardiac aetiology than men. Our results confirm a different distribution of risk factors, such as age and SES, and precipitating etiologies between sexes rather than a male survival advantage.

Interaction Between Sex and Established Predictors of Survival

There were no significant interactions in adjusted models between sex and age, bystander witness, or bystander CPR, respectively. Similar to Bray et al. (1) our findings did not show increased survival in younger Australian women. We did not observe any sex differences in pre-hospital treatment such as bystander CPR or EMS resuscitation, which is in contrast to some previous studies (1, 35). In the main EMS-treated cohort, but not the presumed cardiac sub-cohort, we observed a significant interaction between sex and initial rhythm where the relationship between shockable rhythm and survival was stronger in men than women. Although women are 50% less likely to present with a shockable rhythm after adjustment for established predictors of survival, (27, 30, 36) we again confirm that non-shockable initial rhythm predicts poor outcome regardless of sex (1, 12, 30, 34, 37). Poor survival in women is therefore directly related to their lower incidence of shockable initial rhythm, which, in our population, is likely due to sex differences in susceptibility to cardiac arrhythmias and underlying aetiology (38, 39), rather than treatment delays or disparities.

Effect of Socioeconomic Status on Survival

Consistent with international studies, we found that SES was a predictor of survival after OHCA in adjusted analyses (40, 41). Each increase in SES decile (more advantaged) was associated with an 11% increase in odds of survival to hospital discharge after EMS-treated OHCA (adjusted OR: 1.11, 95% CI 1.00–1.23). Women with a presumed cardiac OHCA were more likely to arrest in a postcode associated with low SES but this was not the case for the full cohort that included obvious non-cardiac etiologies such as asphyxia, exsanguination, and overdose. However, the interaction between sex and SES was not significant and differences in survival rate across low and high SES did not vary between men and women. Wells et al. (18) found no interaction between sex and individual-level education or occupation in a cohort of EMS-treated non-traumatic OHCAs with shockable initial rhythm. Similarly, Jonsson et al. (19) reported no interaction between sex and area-level income and area-level education in all EMS-treated OHCAs, excluding EMS-witnessed. These findings are somewhat surprising given that a stronger association between low SES risk of cardiac arrest and sudden cardiac death has been observed in women compared with men, even after adjustment for traditional risk factors (42). Importantly, our results should be considered as hypothesis-generating only as the study population is biased and over-representative of low SES (IRSAD ≤5 in 75% of the study population). The importance of SES in determining outcome of OHCA has been highlighted in this study and should be explored in larger state-wide and national analyses.

Sex Differences According to Adjudicated Etiology

Cause of arrest documented by EMS providers does not reflect true aetiology in many cases and these discrepancies may contribute to observed differences in outcome between sexes

(43). We performed an in-depth exploration of aetiology as documented in the hospital medical record or autopsy report for the hospitalised sub-cohort. The sample was underpowered to detect a significant difference in outcome and should be considered as hypothesis generating only. The results suggest that survival after adjudicated cardiac OHCA is higher in men, whereas survival after non-cardiac OHCA is higher in women. Only 53% of hospitalised women with a pre-hospital presumed cardiac diagnosis were confirmed as cardiac, which highlights the importance of investigating and recording the aetiology as confirmed in the medical record or by autopsy.

Limitations

This is a small retrospective study conducted within a local health network in Australia and care should be taken when generalising the findings. Crude and age-adjusted incidence calculations were made using enumerated population data that was averaged between 2011 and 2016 to account for dynamic population changes and may not accurately reflect the true at-risk population. OHCA incidence calculations may be underestimated due to missing cases within SAAS-CAR during the study period (24). Arrest location and EMS response times are important predictors of survival that may have influenced outcome but were not available within SAAS-CAR during the study period. Arrest postcode was used as a surrogate for patient SES but may not reflect the patient's true level of advantage and disadvantage. Finally, investigation of sex differences in outcome of EMS-treated OHCA was limited due to small sample size and the findings should be confirmed in a larger sample. Nonetheless, this study provides important findings on sex differences in incidence and outcome of OHCA according to both presumed and confirmed cardiac and non-cardiac etiology.

CONCLUSIONS

Women were less than half as likely to experience OHCA than men and the incidence of OHCA in women of any given age group was similar to that of men 10 years younger within a local health network. The effect of sex on survival to discharge after EMS-treated OHCA was influenced by precipitating etiology. Women with non-EMS witnessed presumed cardiac OHCA were more likely to present with unfavourable predictors of survival and were more likely to arrest in location associated with low SES, but there was no sex difference in adjusted survival. Analysis of adjudicated aetiology in the hospitalised sub-cohort suggests that survival after non-cardiac OHCA may be higher in women than men, but this finding requires further validation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because access to participant identifiable data is subject to relevant institutional approval(s). Requests to access the datasets should be directed to MW, melanie.wittwer@adelaide.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MW: conceptualisation, methodology, investigation, formal analysis, and writing—original draft. EA: conceptualisation and writing—original draft. CH: data curation, writing—review, and editing. MT: data curation, writing—review, and editing. CZ: supervision, writing—review, and editing. JB: supervision, writing—review, and editing. MA: conceptualisation, supervision, writing—review, and editing. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read, critically reviewed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.870696/full#supplementary-material

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4.4 Summary of Chapter Four

This chapter provides an overview of sex differences in the incidence and outcome of EMS-attended, EMS-treated, and hospitalised OHCA within NALHN. The age-adjusted incidence of EMS-attended, and crude incidence of EMS-treated OHCA in this population was higher than state and national reports.[26,27] Although our findings are not directly comparable because we excluded patients aged <20 years to match with available population data, incidence within NALHN nonetheless remained higher than in other Australian populations aged ≥18.[28,190] Our results support previous Australian and international findings of higher incidence in low SES areas and highlight the need for overall reduction of chronic disease and risk factor burdens contributing to increased rates of OHCA in this area.[30,190,280] Despite a high incidence and high level of socioeconomic disadvantage within NALHN, survival rates were comparable with other areas across Australia, which reflects positively on the system of care in place during the study period.[26,27] The significant association between SES and outcome was independent of sex, but these results should be confirmed in analyses of cohorts with coverage across the full spectrum of SES.

This study also confirms that women within the NALHN population were almost half as likely as men to experience OHCA, and their lower survival rate was driven by a lower prevalence of shockable initial rhythm. Although the rates of presumed cardiac cause were similar between sexes in the main EMS-treated cohort, our in-depth exploration of aetiology according to hospital medical record review and autopsy reports revealed that women in the hospitalised sub-cohort were less likely to have their presumed cardiac diagnosis confirmed as cardiac than men. Overall, the study highlights the importance of aetiology and physiology as drivers of the observed sex differences in OHCA characteristics and outcome, rather than treatment delays or disparities. Ongoing investigations into sex differences in adjudicated aetiology using the NALHN OHCA registry may clarify this relationship.

CHAPTER FIVE: IN-HOSPITAL CARDIAC MANAGEMENT OF OHCA – ACCURACY OF CLINICAL GESTALT

5.1 Overview of Chapter Five

Chapter Four described the epidemiology and outcome of OHCA within NALHN and demonstrated that factors such as younger age, initial shockable rhythm, and higher socioeconomic status were associated with survival independent of sex. Survival is also associated with rapid identification and reversal of ongoing precipitating aetiology. This chapter addresses the third research objective of this thesis, which was to evaluate in-hospital cardiac management.

5.2 Background and Context

Patients without obvious non-cardiac aetiology represent three-quarters of the OHCA population surviving to hospital and 40% of these will have an acute coronary occlusion amenable to revascularisation as the likely trigger. A landmark study by Dumas et al[62] in 2010 demonstrated that non-selective emergency revascularisation was associated with better survival after presumed cardiac OHCA, and that 58% of patients without ST-segment elevation on the post-ROSC ECG had significant CAD (>50% stenosis). These findings sparked a change in protocol within NALHN. Between 2011 and 2013, all OHCA patients with ROSC underwent emergency coronary angiography via Code Blue STEMI unless there was a clear, non-cardiac cause of arrest, evidence of futility, or contraindication. Not all NALHN interventional cardiologists agreed with this approach, however, and by 2014 coronary angiography was performed at the discretion of the treating interventionist in accordance with ACS guidelines (**Chapter 2.2**). Two factors contributing to this change included perceived futility likely augmented by a small study demonstrating only 6% survival in intubated and ventilated OHCA patients undergoing primary PCI at the Royal Adelaide Hospital,[80] and low rates of 'unexpected' acute coronary occlusions observed by treating interventionists. However, there remained concerns interventionists miss or delay reperfusion of acute ischaemic events because the ECG, cardiac troponin, and other clinical indicators are not as accurate in the setting of OHCA as for ACS without cardiac arrest.

Clinical judgement or 'gestalt' refers to the decision-making process that forms an overall impression of risk (i.e., need for emergency coronary angiography) based on the recognition of patterns in patient history, presentation, and initial diagnostic tests. In the setting of ACS, a recent multi-centre study found that clinician gestalt did not "rule in" or "rule out" ACS with sufficient accuracy or safety and should not be relied upon in clinical practice without the

addition of validated diagnostic tools.[121,281] The study presented in this chapter was designed to confirm that experienced interventionists appropriately select patients for emergency coronary angiography without missing acutely ischaemic events requiring revascularisation.

5.3 Research Aims and Hypotheses

Based on individual clinical judgement of presenting information, it was hypothesised that interventional cardiologists with >5 years of experience managing OHCA patients would:

1 Identify patients requiring acute revascularisation with 100% sensitivity;
2 Demonstrate a high level of inter-cardiologist agreement for
    a. ECG diagnosis,
    b. Working diagnosis, and
    c. Coronary angiography timing;
3 Demonstrate a high level of intra-cardiologist agreement between individual working diagnosis and aetiology.

After further consideration of the primary clinical message to be presented in the published manuscript the following exclusions were made to Paper Four: patients admitted in 2014 were excluded to avoid selection bias resulting from change in hospital protocol; patients without coronary angiography were excluded; results of interrater agreement for ECG diagnosis and working diagnosis were excluded; individual agreement between working diagnosis and aetiology were excluded; area under the receiver operating characteristics curves (AUC) were excluded.

The full methods, published paper, and additional results are presented in this chapter.

5.4 Methods overview

This clinical evaluation study was conducted at the Lyell McEwin Hospital, a tertiary teaching hospital in South Australia. Institutional ethical review was not sought for the study because it met criteria for exemption from such review according to institutional policy. The standards for reporting diagnostic accuracy studies (STARD 2015) were followed (**Appendix D**).[282]

The NALHN OHCA registry was used to identify all patients admitted between 2011-2014. This timeframe reflects the point to which the dataset was completed when the study commenced. Patients transferred from a regional hospital, cases with no coronary angiography and unknown aetiology, patients with insufficient clinical documentation, and potentially identifiable patients were excluded. Obvious non-cardiac patients were included as controls.

A copy of the initial clinical information recorded within the first two hours post-cardiac arrest was collected from the medical record. This timeframe was chosen to reflect the information available to the on-call interventionist prior to the decision for emergency coronary angiography and included:

- SA Ambulance case card
- Post-resuscitation ECG and/or subsequent ECGs captured in the Emergency Department
- Emergency Department observation chart
- Emergency Department note or admission note within 60mins of arrival
- Chest x-ray report, arterial or venous blood gas, bedside echocardiography, CT brain etc. if performed within 30mins of arrival

References to treatment decisions were removed and notes were de-identified prior to independent review by three experienced interventional cardiologists who were thus blinded to outcome. A case report form was completed by each cardiologist for each patient (**Appendix D**). Results were re-identified and linked with the NALHN OHCA registry to obtain patient and arrest characteristics, adjudicated aetiology, and outcome data.

5.4.1 Primary Outcome

The decision for emergency coronary angiography made for each patient by each cardiologist was evaluated as a diagnostic test. The overarching aim of the study was to ensure that interventionists didn't miss or delay reperfusion of acute ischaemic events, so the sensitivity of their decision was identified as the important test characteristic and needed to reach 100%.

> **Sensitivity,** or true positive rate, was the number of patients selected for emergency coronary angiography by each cardiologist that required revascularisation in real life, divided by the total number of patients that underwent revascularisation. A sensitivity

less than 100% indicates that the cardiologist chose delayed/no coronary angiography based on the clinical summary provided in a patient(s) that required acute revascularisation.

Conversely, **specificity**, or true negative rate, was the number of patients selected for delayed/no coronary angiography by each cardiologist that did not require revascularisation in real life, divided by the total number of patients that did not undergo revascularisation. A specificity less than 100% indicates that the cardiologist chose emergency coronary angiography in patients that did not require acute revascularisation.

5.4.2 Additional Data Analyses

Interrater agreement of ECG diagnosis and working diagnosis, and agreement between individual working and adjudicated aetiology, was calculated using Randolph's free-marginal multi-rater kappa, where κ-values of 0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–1.0 represent poor, low, moderate, good, and very good levels of agreement, respectively.[283,284] Results were stratified as presumed cardiac and no obvious non-cardiac (controls).

The diagnostic performance of the cardiologist's decision for emergency coronary angiography was also determined by calculating the areas under the receiver operating characteristics curves (AUC) using logistic regression and adjusting for clustering on patient. An AUC of 1 represents a perfect test and an area of .5 represents a worthless test, where values of 0.9-1, 0.8-0.9, 0.7-0.8, 0.6-0.7, and 0.5-0.6 may be classified as excellent, good, fair, poor, and no better than chance, respectively.

Statistical analyses were performed using SPSS, version 26 (SPSS Inc., Chicago, IL, USA) and MedCalc version 20.009 (MedCalc Software, Mariakerke, Belgium).

5.5 Manuscript, Paper Three

The following paper, "Cardiologists Appropriately Exclude Resuscitated Out-of-Hospital Cardiac Arrests from Emergency Coronary Angiography" was published in *Journal of the American College of Emergency Physicians* in 2020.[23]

Statement of Authorship

Title of Paper	Cardiologists appropriately exclude resuscitated out-of-hospital cardiac arrests from emergency coronary angiography.
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Contribution to the Paper	Conception and design of the project; data acquisition; analysis and interpretation of data; drafting significant parts of the article or critically revising it so as to contribute to the interpretation.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

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ii. permission is granted for the candidate in include the publication in the thesis; and

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ORIGINAL RESEARCH

Cardiology

Cardiologists appropriately exclude resuscitated out-of-hospital cardiac arrests from emergency coronary angiography

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Abstract

Objective: Emergency coronary angiography after resuscitated out-of-hospital cardiac arrest as a selective or non-selective diagnostic procedure with or without intervention continues to be the subject of debate. This study sought to determine if cardiologists reliably select patients using clinical judgement for emergency coronary angiography without missing acutely ischemic cases requiring revascularization.

Methods: Presenting clinical details and ECGs (within 2 hours) from 52 consecutive out-of-hospital cardiac arrest patients who underwent non-selective coronary angiography were compiled retrospectively. Three out-of-hospital cardiac arrest-experienced interventional cardiologists, blinded to patient outcome, independently determined working diagnosis, and decision for emergency coronary angiography using clinical judgement. Sensitivity of the cardiologists' decision was assessed with respect to the outcome of acute revascularization. Inter-rater differences, consensus in clinical assessment, and influence of working diagnosis were also investigated.

Results: Sensitivity of individual cardiologist's decision for emergency coronary angiography with respect to acute revascularization was very high (adjusted overall sensitivity = 95.8%, 95% CI = 89–100, cardiologist range = 93%–100%), and perfect for the consensus of 2 or more cardiologists (100%, 95% CI = 79.4–100). There was no statistical difference in the sensitivity of this decision between cardiologists ($P < 0.05$), and inter-rater agreement was moderate (78% overall agreement, $\kappa = 0.56$).

Conclusions: Experienced cardiologists recommend emergency coronary angiography in all resuscitated out-of-hospital cardiac arrest requiring acute revascularization and appropriately excluded one-third of patients. Rather than advocating a non-selective, or conversely, a restrictive strategy with respect to coronary angiography after out-of-hospital cardiac arrest, the findings support an individualized approach by a

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multidisciplinary emergency team that includes experienced cardiologists. The results should be confirmed in a larger prospective study.

KEYWORDS
coronary angiography, out-of-hospital cardiac arrest, percutaneous coronary intervention

1 | INTRODUCTION

1.1 | Background

Out-of-hospital cardiac arrest affects an estimated 20,000 individuals each year in Australia with a crude incidence of 102.5 per 100,000 population.[1] Only 21% to 36% of those who receive attempted resuscitation by ambulance personnel have return of spontaneous circulation on arrival to hospital.[1] The leading cause of non-traumatic out-of-hospital cardiac arrest is acute myocardial infarction resulting from an acutely occluded coronary artery. Australian guidelines recommend emergency coronary angiography with percutaneous coronary intervention as indicated in patients with ST-segment elevation on the post-resuscitation ECG or a high clinical suspicion of ischaemia.[2] However, due to the complex diagnostic and prognostic setting, determining suitability for emergency coronary angiography in the absence of ST-segment elevation is difficult because standard indicators such as clinical history and cardiac biomarkers are often unknown or difficult to interpret. Retrospective data have consistently shown that if all non-traumatic out-of-hospital cardiac arrests are taken for emergency coronary angiography (non-selective approach), 74%–82% with ST-segment elevation and 26%–46% of those without ST-segment elevation will undergo acute revascularization for an occluded coronary artery.[3,4] Several prospective clinical trials are currently underway in an attempt to provide definitive evidence for the selective versus non-selective angiography debate.[5] The recent COACT trial found no difference in survival at 90 days between emergency versus delayed coronary angiography in non-ST-segment elevation patients with a shockable arrest rhythm who were unconscious on hospital arrival.[6]

1.2 | Importance

The time-sensitive aim in undertaking emergency coronary angiography is to revascularize a culprit lesion responsible for the out-of-hospital cardiac arrest to prevent further myocardial injury. Conversely, coronary angiography may be deferred when there is no expected benefit. Whether cardiologists, as part of the multidisciplinary emergency management team, achieve these aims appropriately using a selective approach based on clinical judgement is currently unknown. There is no single benchmark to assess the appropriateness of emergency coronary angiography in the setting of out-of-hospital cardiac arrest; however, for the purposes of this study acute revascularization was chosen as the gold standard against which to assess a selective cardiologist-led approach.

1.3 | Goals of this investigation

This study sought to determine if experienced interventional cardiologists use clinical judgement to reliably select patients for emergency coronary angiography without missing acutely ischemic cases requiring revascularization. The primary objective investigated whether the decision for emergency coronary angiography, based on the initial clinical summary and ECG, is highly sensitive for acute revascularization. Secondary objectives included (1) inter-rater differences, (2) cardiologist consensus in clinical assessment, and (3) influence of working diagnosis.

2 | METHODS

2.1 | Study design and setting

This clinical evaluation study was conducted at the Lyell McEwin Hospital, a tertiary teaching hospital in South Australia. Institutional ethical review was not sought for the study because it met criteria for exemption from such review according to institutional policy. The standards for reporting diagnostic accuracy studies (STARD 2015) were followed.[7]

South Australia has a single state-wide emergency medical services system where out-of-hospital cardiac arrest patients are treated by paramedics on-scene and a 12-lead ECG is taken out-of-hospital after achieving stable return of spontaneous circulation. A ”Code STEMI” may be called either in the ambulance by an intensive care paramedic, or by a physician in the emergency department to activate the on-call interventional cardiologist and cardiac catheterization team. The Lyell McEwin Hospital is the single cardiac arrest center for northern Adelaide and services a population of 398,000. Both the South Australian Ambulance Service and Lyell McEwin Hospital follow the 2010 (now 2015) ANZCOR resuscitation guidelines endorsed by the Australian Resuscitation Council and the New Zealand Resuscitation Council.[2] Emergency physicians routinely refer out-of-hospital cardiac arrest patients without obvious non-cardiac cause for review by the cardiology team before activating ”code STEMI.” The decision to proceed with coronary angiography is ultimately made by the interventionist.

During the study inclusion period (2011–2013), hospital protocol required all out-of-hospital cardiac arrest patients with return of spontaneous circulation to undergo emergency coronary angiography via code STEMI (non-selective approach) unless there was a clear, non-cardiac cause of arrest, evidence of futility, or contraindication. Since this time, a selective approach has been adopted by the hospital, and subsequent patients were not eligible for inclusion due to selection bias.

The Bottom Line

Coronary angiography after out-of-hospital cardiac arrest has been associated with improved outcome, but the optimal timing is unknown. This retrospective analysis of 52 out-of-hospital cardiac patients demonstrated that experienced interventional cardiologists accurately identified patients who required emergency revascularization based on clinical summary and ECG.

2.2 | Selection of participants

The hospital out-of-hospital cardiac arrest registry was searched to identify patients admitted during the non-selective era of 2011–2013 who underwent coronary angiography (emergency or delayed >6 hours). The registry collects comprehensive patient data from consecutive patients in accordance with the Utstein template,[8] including findings from coronary angiography. Cases were excluded on the following grounds: (1) no coronary angiography indicated due to obvious non-cardiac cause, evidence of futility, or contraindication on initial hospital assessment, failed cardiac catheterization attempt, (2) identifiable case (eg, unusually young age, transfer from remote hospital), and (3) no ECG available.

2.3 | Measurements

For all included patients, the initial clinical summary from up to the first 2 hours post-arrival was copied from the medical record and de-identified. At minimum, the summary included the ambulance case card, emergency department clinical record, and observations, arterial blood gas result(s) and post-return of spontaneous circulation ECGs. References to treating physicians, patient management, and working diagnosis were removed. The initial clinical summary reflects the information available to the on-call interventionist at initial consultation prior to the decision for emergency coronary angiography, or within the first 2 hours for patients with delayed coronary angiography.

Three interventional cardiologists were selected to participate in this study and all had >5 years experience as interventional team leaders with previous experience in other centers. Each cardiologist independently reviewed the initial clinical summary for each patient and used clinical judgment to complete a case report form. Working diagnosis was categorized as likely ischemia, other cardiac cause, and non-cardiac cause. Recommendation for coronary angiography was dichotomized into emergency (<6 hours post-arrest) or not emergency (delayed 6–24 hours, within next office hours, or not indicated). Results were re-identified and linked with complete registry data.

2.4 | Outcomes

The primary outcome was sensitivity of the experienced cardiologist-led decision for emergency coronary angiography, based on the initial clinical summary and ECG, with respect to the real-life outcome of acute revascularization (percutaneous coronary intervention, including planned or failed percutaneous coronary intervention, or coronary artery bypass grafting, coronary artery bypass grafting). Secondary outcomes included (1) inter-rater differences, (2) cardiologist consensus in decision making, and (3) influence of working diagnosis.

2.5 | Analysis

Normally distributed continuous data are presented as mean ± SD and comparisons between groups made using Student *t* test. Categorical data are presented as frequency and percentage and comparisons between groups made using Fisher's exact test and Pearson chi-square test, as appropriate.

The cardiologist's decision for emergency coronary angiography was evaluated as a diagnostic test. Ideally, the cardiologist would always recommend emergency coronary angiography in patients who required acute revascularization. Thus, the sensitivity of the decision (probability that the cardiologists select emergency coronary angiography when the patient requires acute revascularization) was identified as the important test characteristic.

Sensitivity and specificity of the decision for emergency coronary angiography with respect to acute revascularization was calculated for each cardiologist individually, as well as combined. Related-samples Cochran's Q test was used to assess differences in the distributions of sensitivity and specificity between cardiologists. If the *P*-value was <0.5, post hoc McNemar's tests with Bonferroni correction ($P < 0.0125$) were used to identify significant differences between cardiologist pairwise. Combined cardiologist sensitivity and specificity were calculated and adjusted for clustering on patient using the variance inflation factor, which takes into account the cluster size-weighted average cluster size and the intra-class correlation coefficient.[9]

Agreement between individual cardiologist decision and acute revascularization was evaluated using McNemar's tests and combined agreement was evaluated using logistic generalized estimating equation (GEE) models to account for clustering. Post hoc McNemar's exact conditional tests found sufficient power (>0.80) to detect significant agreement.

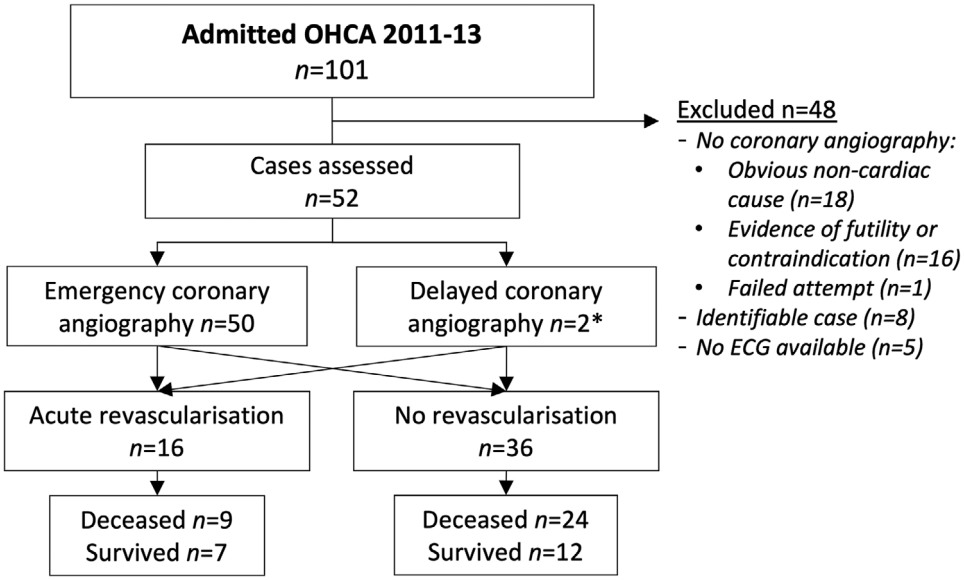

FIGURE 1 Flow diagram of real-life treatment pathway and outcome of patients included in the final cohort for analysis. *One case with missed post-return of spontaneous circulation ST-elevation and acute thrombus considered too unstable for percutaneous coronary intervention was included in the acute revascularization group for study purposes

Inter-rater agreement was measured using Randolph's free-marginal multi-rater kappa, where κ-values of 0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–1.0 represent poor, low, moderate, good, and very good levels of agreement, respectively.[10,11]

A 2-tailed $P < 0.05$ was considered statistically significant, except where stated. Analyses were performed using SPSS 24 (IBM SPSS Statistics, Armonk, NY), and SAS 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Characteristics of study subjects

A search of the hospital out-of-hospital cardiac arrest registry identified 101 patients admitted between 2011 and 2013, and of those, 52 were included (Figure 1). The final cohort was predominately male, aged 58 ± 15 years, bystander-witnessed arrest in 65%, shockable rhythm in 69%, return of spontaneous circulation within 20 minutes in 28%, ST-segment elevation in 33%, and 37% survived to hospital discharge all with good neurological recovery (cerebral performance category 1–2). Coronary angiography revealed coronary artery dissection in 63%, 29% received percutaneous coronary intervention, and 37% were diagnosed with an acute myocardial infarction according to the fourth universal definition (Table 1).[12] Percutaneous coronary intervention was only performed in patients with a diagnosis of acute myocardial infarction. One case with missed post-return of spontaneous circulation ST-segment elevation, delayed coronary angiography, and acute thrombus considered too unstable for percutaneous coronary intervention, was re-categorized into the acute revascularization group for study analyses. No cases had failed revascularization attempts or plans for coronary artery bypass grafting.

3.2 | Main results

The primary study endpoint, sensitivity of the decision for emergency coronary angiography with respect to acute revascularization, is presented in Table 2. We considered the results of all cardiologists individually as well as pooled together. Adjusted overall sensitivity was very high (95.8%, 95% CI = 89–100). Both cardiologists 1 and 2 recommended no emergency coronary angiography in separate cases requiring acute revascularization; however, they each specified that additional diagnostic tests were required to assist with the decision making process. Agreement between the individual decision and outcome of acute revascularization was significant for each cardiologist as well as overall ($P < 0.01$).

3.3 | Secondary outcomes

3.3.1 | Inter-rater differences

There was no statistical difference in overall sensitivity between cardiologists with respect to acute revascularization (related-samples Cochran's Q test, $P > 0.05$), but there was a significant difference in specificity between cardiologist 2 and 3 (post-hoc McNemar's test with Bonferroni correction, $P < 0.01$). Inter-rater agreement of the selection of emergency versus no emergency coronary angiography was moderate (78% overall agreement, $K = 0.56$). In 63% of cases, there was 100% agreement.

TABLE 1 Medical history, arrest characteristics, management, and outcome of patients included in analysis (n = 52)

Patient characteristics	
Male sex	34 (65)
Age (y)	58 ± 15
Independent living	50 (96)
Known ischemic heart disease	18 (35)
Diabetes	16 (31)
Hypertension	33 (64)
Family history cardiac disease	13 (25)
Current smoker	16 (31)
Dyslipidemia	21 (40)
Witnessed arrest	
Bystander	34 (65)
EMS	4 (8)
Unwitnessed	14 (27)
Bystander CPR (excludes EMS-witnessed)	34 (71) (n = 48)
Shockable rhythm	36 (69)
Time to return of spontaneous circulation ≤20 mins	14 (28) (n = 50*)
Post-return of spontaneous circulation ST-segment elevation	17 (33)
Spontaneous circulation on arrival	42 (81)
Business hours	39 (75)
Coronary angiogram	
Emergency	51 (98)
Delayed (>6 h)	1 (2)
Arrest to coronary angiography (min)	120 [99–146]
Presenting hospital to coronary angiography (min)	66 [52–87]
Obstructive coronary artery disease	33 (63)
Percutaneous coronary intervention	15 (29)
Etiology	
Cardiac ischemic	18 (35)
Cardiac other	23 (44)
Non-cardiac	11 (21)
Acute myocardial infarction	19 (37)
Survived	19 (37)
Cerebral performance category 1–2 ("good outcome")	19 (37)

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ROSC, return of spontaneous circulation.
Data presented as n (%), mean ± SD or median [interquartile range].
*ROSC time unknown in 2 cases.

3.3.2 | Consensus

Consensus in clinical management was defined as when 2 or more cardiologists selected the same approach. Sensitivity of the consensus decision for emergency coronary angiography was 100% (95% CI = 79.4–100) with respect to acute revascularization (Figure 2). None of the cases chosen by consensus for no emergency coronary angiography required acute revascularization.

TABLE 2 Sensitivity and specificity of cardiologist selection of emergency coronary angiography according to acute revascularization

Assessor	Sensitivity True positive rate	Specificity True negative rate
Cardiologist 1	93.8 (69.8–99.8)	44.4 (27.9–61.9)
Cardiologist 2	93.8 (69.8–99.8)	61.1 (43.5–76.9)
Cardiologist 3	100 (79.4–100)	30.6 (16.4–48.1)
Overall	95.8 (89–100)	45 (35–55.7)

3.3.3 | Influence of working diagnosis

Table 3 presents the number of cases each cardiologist diagnosed as "likely ischemic," "other cardiac," and "non-cardiac," as well as the proportion in each category they selected for emergency coronary angiography. The diagnosis made by cardiologist 3 and consensus (diagnosis made by 2 or more cardiologists) was "likely ischemic" for all patients who required acute revascularization, and all such patients were selected for emergency coronary angiography. Cardiologists 1 and 2 diagnosed one case each that required acute revascularization as "other cardiac" and did not select emergency coronary angiography. As documented above, both cases were assessed as requiring additional diagnostic tests to assist with the decision making process.

4 | LIMITATIONS

Our study was a single-center observational cohort study, and as such, the results should be interpreted in the light of inherent limitations. Bias may have been introduced because over one third (30/82) of presumed cardiac cases were excluded because (1) coronary angiography was not performed due to evidence of futility or contraindication, (2) cases were considered identifiable, and (3) ECGs were missing. However, of the 16 cases excluded for the first reason above, the final etiology was cardiac ischemic in 2 deceased patients, both of whom had multiple comorbidities with poor neurological prognosis; other diagnoses in this group included cardiac non-ischemic (n = 7), non-cardiac (n = 5), and unknown (n = 2). The initial clinical summary was collated from the medical record and reflects up to 2 hours post-arrival, but this may not be an accurate representation of what information is available or communicated to the on-call interventionists at initial consultation and handover. Our results are from experienced interventionists and may not be applicable to more junior clinicians.

Unlike other similar studies, our primary outcome was not analyzed with respect to acute myocardial infarction. This was because the diagnostic criteria for acute myocardial infarction in out-of-hospital cardiac arrest are not entirely clear (ie, non-acute myocardial infarction

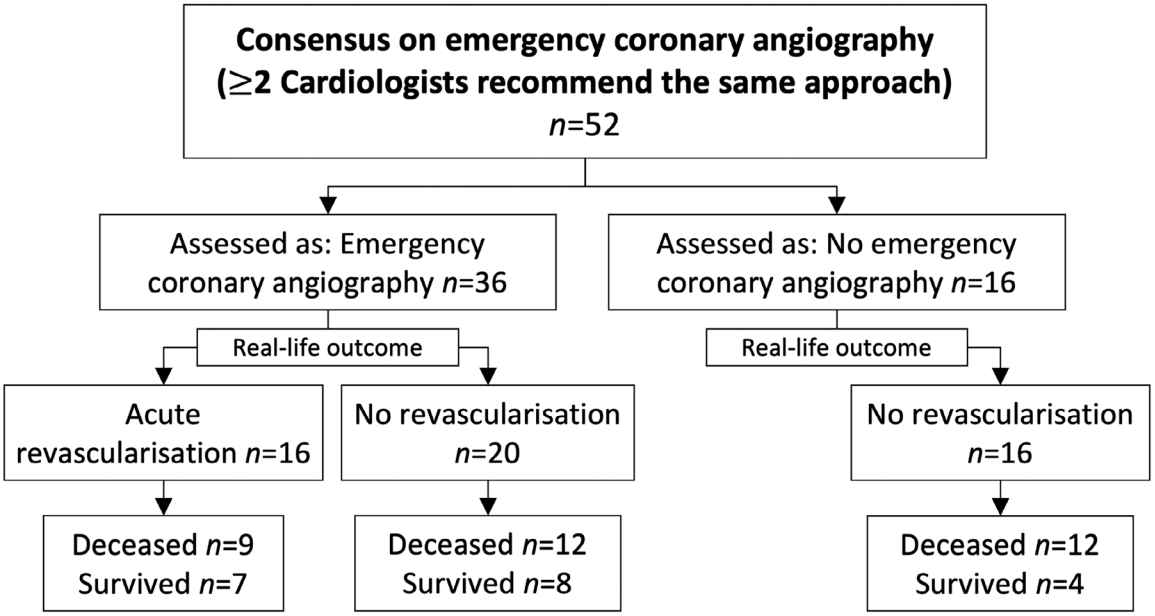

FIGURE 2 Flow diagram of emergency versus no emergency coronary angiography recommended by 2 or more cardiologists (consensus) with revascularization outcome and survival to hospital discharge

patients may still have troponin rise; history of chest pain is often unknown, etc), and because acute myocardial infarction may exclude patients with other non-obstructive ischemic diagnoses such as global ischemia in the setting of multiple lesions, and spasm. We acknowledge that acute revascularization is a subjective measure but there is as yet no single gold standard for assessing appropriateness of emergency coronary angiography in this setting.

5 | DISCUSSION

Experienced cardiologists used clinical judgment to reliably select retrospective out-of-hospital cardiac arrest patients for emergency coronary angiography without missing acutely ischemic cases requiring revascularization. Although revascularization of an acutely occluded coronary artery is not the only reason why a patient may be selected for emergency coronary angiography, it nonetheless remains a time-critical endpoint useful for assessing appropriateness. If a selective clinician-led approach had been used in the study cohort, 16 (31%) patients could potentially have avoided emergency coronary angiography. Interventional cardiologists may be involved early in the decision making process after resuscitated out-of-hospital cardiac arrest because they appropriately identify patients in whom emergency coronary angiography can be safely deferred. The Australian emergency care system is similar in design and function to others outside Australia, making our findings readily generalizable.

Out-of-hospital cardiac arrest represents a complex diagnostic and prognostic setting where the trigger may be multifactorial with several plausible causes. It was outside the scope of this study to investigate factors influencing the decision for emergency coronary angiography.

TABLE 3 Selection of emergency coronary angiography by experienced cardiologists according to their working diagnosis based on the initial clinical summary and ECG

Working diagnosis	n	Selected for emergency coronary angiogram(%)
Cardiologist 1		
Likely ischemic	32	31 (97)
Other cardiac	16	4 (25)
Non-cardiac	4	0 (0)
Cardiologist 2		
Likely ischemic	37	28 (76)
Other cardiac	11	1 (9)
Non-cardiac	4	0 (0)
Cardiologist 3		
Likely ischemic	40	40 (100)
Other cardiac	3	1 (33)
Non-cardiac	9	0 (0)
Consensus diagnosis		
Likely ischemic	38	34 (89)
Other cardiac	9	2 (22)
Non-cardiac	3	0 (0)
No consensus	2	0 (0)

However, the results found that two or more cardiologists (consensus) made the same diagnosis of "likely ischemic" with a recommendation for emergency coronary angiography in all patients who required acute

revascularization. No patients with a ''non-cardiac'' working diagnosis were selected for emergency coronary angiography, again confirming this cardiologist-led approach.

There are no other studies that have assessed the performance of clinical judgment in this area. Studies assessing clinical prediction rules demonstrate that post-return of spontaneous circulation ST-segment elevation alone is not a useful marker for emergency coronary angiography with a sensitivity of 64%–88% for acute myocardial infarction,[4,15] and only 56%–70% for percutaneous coronary intervention,[3,4,14] lower than the current study. Intracranial hemorrhage may also present with post-return of spontaneous circulation ST-segment elevation in up to 78% of patients, but rarely in two contiguous leads.[16] Elevated cardiac troponin on admission is another key diagnostic indicator for acute myocardial infarction; however, it performs poorly in the setting of out-of-hospital cardiac arrest because global ischemia also results in myocardial damage.[17,18] Only a few studies have gone further and investigated other clinical markers but applicability is limited due to inclusion criteria.[19–21] A clinical score >1 based on pre-arrest chest pain (1 patient), shockable rhythm (1 patient), and post-return of spontaneous circulation ST-segment elevation in any lead (2 patients) had a sensitivity of 93% for acute myocardial infarction.[19] Although scoring systems are useful clinical aids to improve diagnostic accuracy, clinical judgment appears to perform better in this setting.

The results of this study do not dismiss emergency coronary angiography without acute revascularization as a negative finding. Rather, coronary angiography provides a single procedure that aids in the time-critical diagnosis of ischemic versus non-ischemic heart disease, pulmonary embolism, and cardiomyopathy. In the setting of post-return of spontaneous circulation ST-segment elevation, an emergency coronary angiography without intervention will likely result in one of many useful diagnoses including Takotsubo cardiomyopathy, myocarditis, spontaneous coronary artery dissection, myocardial infarction with non-obstructive coronary arteries, and type II myocardial infarction, to name a few.

In summary, our study tested whether interventional cardiologists identify out-of-hospital cardiac arrest patients who might benefit from emergency coronary angiography using clinical judgment. Experienced cardiologists from our institution recommended emergency coronary angiography in all patients who required acute revascularization, as well as appropriately excluding a proportion of patients. A prospective multicenter cohort investigating the qualitative aspects of judgment rational that includes emergency physicians and cardiologists with varying levels of experience should be performed to confirm and broaden the applicability of these findings. An individualized approach to coronary angiography after out-of-hospital cardiac arrest may be appropriate when experienced interventionists, who understand the risks and benefits of coronary angiography and acute revascularization, are involved early in the decision making process.

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AUTHOR CONTRIBUTIONS

CZ, MRW, and MAA conceived and designed the study. MRW and SW extracted the preliminary data. SR, KM, and CZ provided the data assessments. MRW performed the data collection and analysis under supervision of CZ, JFB, and MAA. MRW drafted the manuscript and all authors contributed substantially to its revision. MRW takes responsibility for the paper as a whole.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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5.6 Additional Results

5.6.1 Patient characteristics

There were 143 admitted patients identified from the NALHN OHCA registry between 2011 and 2014, of which 88 presumed cardiac patients and 20 obvious non-cardiac patients (controls) were included in the additional analyses after exclusions (**Figure 5-1**).

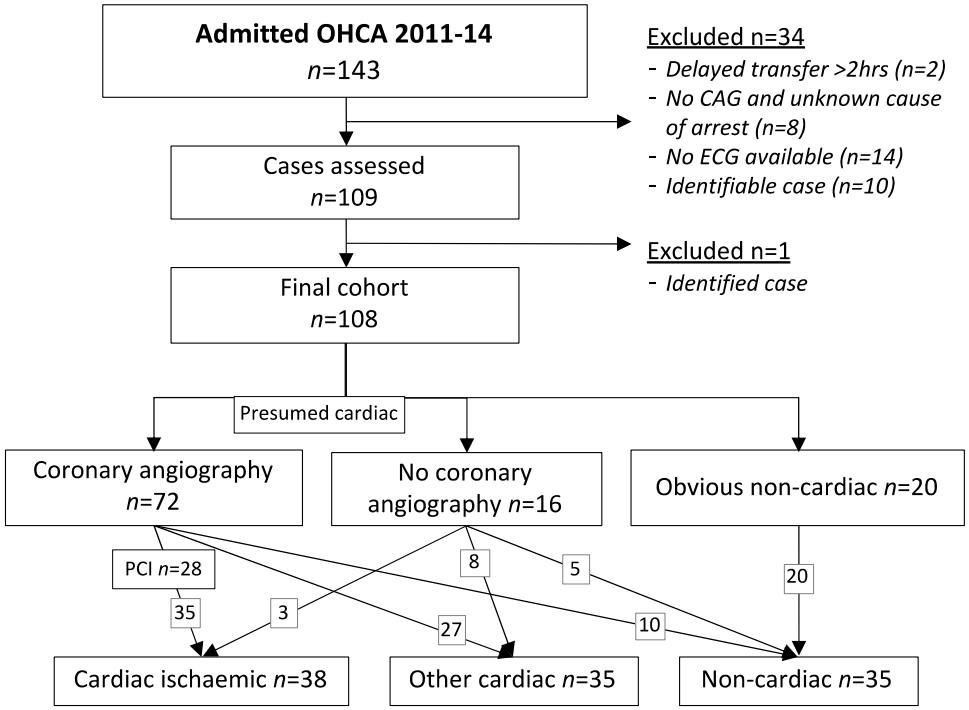

Figure 5-1: Flow chart of real-life treatment pathway and adjudicated aetiology of OHCA patients included in the final cohort for diagnosis and decision-making by interventional cardiologists.

5.6.2 Interrater Agreement - ECG Diagnosis

In patients where more than one ECG was taken during the first two hours post-cardiac arrest inter-cardiologist agreement was only calculated when all three cardiologists selected the same ECG as the diagnostic ECG (n=66). ECG diagnosis was re-coded into 5 categories for analysis: evidence of ST-elevation, ST-depression, broad QRS (+/- BBB), other, and normal. Inter-cardiologist agreement in presumed cardiac patients for ECGs from presumed cardiac patients was good (81% overall agreement, K=0.76, n=48) and moderate in controls (59% overall agreement, K=0.49, n=18).

5.6.3 Interrater Agreement - Working Diagnosis

Working diagnosis was re-coded into three categories for analysis: presumed ischaemic, cardiac non-ischaemic, non-cardiac. Inter-cardiologist agreement in presumed cardiac patients was moderate (69% overall agreement, K=0.53) but in controls was very good (90% overall agreement, K=0.85). Inter-cardiologist agreement was lower than expected so a sub-analysis was performed according to aetiology in the presumed cardiac cohort. Inter-cardiologist agreement was highest in patients with cardiac ischaemic aetiology (90% overall agreement, K=0.86, n=38) compared to low agreement for cardiac non-ischaemic (52% overall agreement, K=0.29, n=35) and non-cardiac (53% overall agreement, K=0.30, n=15).

5.6.4 Agreement Between Working Diagnosis and Adjudicated Aetiology

Agreement between working diagnosis and adjudicated aetiology in presumed cardiac patients was moderate overall, and low-moderate for each cardiologist individually (62% overall agreement, cardiologist range 58-65%; K=0.43, cardiologist range 0.37-0.47). In controls, agreement was very good overall as well as for each cardiologist individually (93% overall agreement, cardiologist range 90-95%; K=0.9, cardiologist range 0.85-0.92).

5.6.5 Diagnostic performance of decision for emergency coronary angiography

In addition to calculating sensitivity and specificity of the decision for emergency coronary angiography in the published manuscript, the overall AUC was calculated and found to be fair with respect to predicting acute revascularisation (AUC 0.71, 95% CI 0.66-0.77, cardiologist range 0.65-0.81). The consensus decision, defined as the decision recommended by 2 or more cardiologists for each patient, was also a fair predictor of acute revascularisation (AUC 0.72, 95% CI 0.59-0.86).

5.7 Summary of Chapter Five

The analyses presented in this chapter found that interventional cardiologists 'ruled out' emergency coronary angiography in patients who did not require acute revascularisation using clinical gestalt, but the accuracy of their decision-making was dependent on precipitating aetiology. Cardiologists had the greatest difficulty diagnosing and predicting the benefit of emergency coronary angiography in patients that were of non-ischaemic cardiac origin. Although a previous study demonstrated that experienced clinicians may identify patients with acute MI more accurately than less experienced clinicians,[118] our results were similar to that of Oliver et al[121] who concluded that clinician gestalt did not rule in or rule out ACS with sufficient accuracy or safety.

The additional analyses of a larger cohort presented in this chapter support and enhance the findings presented in the published manuscript. Inter-cardiologist agreement on ECG diagnosis reached 81% overall agreement in presumed cardiac patients but was much lower in controls. These results highlight the complexity of ECG interpretation in the post-ROSC setting and further confirm that the ECG cannot be used to guide management of OHCA in isolation. The investigation of working diagnosis revealed that cardiologists were least accurate in diagnosing patients who presented with a presumed cardiac aetiology and were later found to have a non-ischaemic cardiac aetiology. Cardiac ischaemic indicators such as shockable initial rhythm and or STE may have been present in these patients, but they were not ultimately found to have an acute coronary occlusion or culprit lesion.

Guidelines for management of the conscious patient with suspected ischaemia and unconscious patient with STE are clear and not disputed. Although this study demonstrated that a selective approach to emergency coronary angiography is associated with low rate of missed acute ischaemia, it was not designed to investigate the most contentious population of comatose patients without STE. The findings presented in this chapter may have been driven by overrepresentation of patients with STE and acute ischaemia compared to patients without STE and should be interpreted with caution. A sub-analysis of patients with STE vs. no STE was not performed due to small numbers. A prospective multicentre cohort should be performed with emergency physicians and cardiologists of varying experience levels in patients presenting without STE and/or shockable initial rhythm to confirm and broaden the applicability of these findings.

CHAPTER SIX: IN-HOSPITAL CARDIAC MANAGEMENT OF OHCA – ACCURACY OF A CLINICAL SCORE

6.1 Overview of Chapter Six

The study presented in Chapter Five provided some evidence to suggest that experienced interventional cardiologists appropriately manage resuscitated OHCAs with presumed cardiac aetiology. Whether clinical gestalt is superior to clinical prediction tools for determining which patients will benefit from emergency coronary angiography has not been investigated in this setting. This chapter continues to address the third research objective of this thesis, which was to evaluate the in-hospital management of OHCA by cardiologists with respect to emergency coronary angiography.

6.2 Manuscript, Paper Four

The following paper, "Validation and test of a clinical score for predicting acute revascularisation after resuscitated out-of-hospital cardiac arrest" has not been submitted for journal publication.

Statement of Authorship

Title of Paper	Validation and test of a clinical score for predicting acute revascularisation after resuscitated out-of-hospital cardiac arrest
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted work written in manuscript style
Publication Details	n/a

Principal Author

Name of Principal Author (Candidate)	Melanie Wittwer		
Contribution to the Paper	Conception and design of the project; data acquisition; analysis and interpretation of data; drafting, revision, and finalisation of manuscript; corresponding author.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/03/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Sunny Wu		
Contribution to the Paper	Data acquisition; analysis and interpretation of data; drafting of manuscript.		
Signature		Date	21/03/2022

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Contribution to the Paper	Conception and design of the project; research data input; contribution of knowledge; critical revision		
Signature		Date	23/3/22

Name of Co-Author	John F Beltrame		
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Signature		Date	23/3/22

Name of Co-Author	Margaret A Arstall		
Contribution to the Paper	Conception and design of the project; research data input; contribution of knowledge; critical revision; supervision		
Signature		Date	21/03/2022

Validation and test of a clinical score for predicting acute revascularisation after resuscitated out-of-hospital cardiac arrest

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Abstract

Introduction: Emergency coronary angiography with or without revascularisation is associated with improved survival after out-of-hospital cardiac arrest (OHCA). This study aimed to validate and test the performance of a clinical prediction score at ruling in and ruling out acute revascularisation in resuscitated OHCA of presumed cardiac origin.

Methods: Three cohorts were retrospectively identified from a hospital OHCA registry: a validation cohort of all presumed cardiac patients with non-selective coronary angiography during 2011-13, a test cohort of all presumed cardiac patients, and a control cohort of obvious non-cardiac patients, both admitted during 2016; patients with missing data were excluded. The score comprised STE in any lead including aVR (2 points), shockable initial rhythm (1 point), and chest pain (1 point). Score performance was assessed by calculating the AUC for the primary outcome of acute revascularisation. Optimal score cut points were determined by the Youden Index and sensitivity and specificity values obtained.

Results: The validation cohort comprised 52 patients, the test cohort 32 patients, and control cohort 21 patients. Patient demographics were similar for presumed cardiac cohorts. The score predicted acute revascularisation with an AUC of 0.94 (95% CI 0.83-0.99, $p<0.001$) and a score ≥3 had a sensitivity of 94% and specificity of 83%. A score of 0 ruled out 19% and 16% of presumed cardiac patients. No patients in the control cohort scored ≥3.

Conclusions: A simple clinical prediction score was effective at ruling out acute revascularisation in resuscitated OHCA of presumed cardiac aetiology.

Introduction

Strategies to enhance out-of-hospital cardiac arrest (OHCA) systems of care have significantly improved survival of resuscitated patients within Australia.[1,2] Access to emergency coronary angiography is one such strategy that is associated with improved survival, particularly for patients with acute coronary occlusion amenable to revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass graft.[1–3] Significant coronary artery disease leading to acute myocardial infarction (AMI) is a common trigger of cardiac arrest in patients surviving to hospital without an obvious non-cardiac aetiology.[4,5] Current guidelines recommend emergency coronary angiography in resuscitated patients presenting to hospital with ST-segment elevation (STE) on the post-resuscitation ECG regardless of coma.[6] However, this strategy is not without risk and recent evidence suggests that patients without a clear AMI diagnosis and/or without STE may not benefit from an emergency strategy when compared with delayed coronary angiography.[7,8]

Clinical prediction scores are effective at 'ruling in' or 'ruling out' AMI in patients without cardiac arrest.[9] In 2016, Zeyons et al[10] developed a scoring system with the aim to improve selection of OHCA patients with return of spontaneous circulation (ROSC) for emergency coronary angiography. The "Zeyons Score" comprises of STE in any lead including aVR (2 points); pre-arrest chest pain (1 point); and shockable initial rhythm (1 point). A score of ≥2 predicted AMI-related OHCA with 93% sensitivity while a score of 0 ruled out AMI-related OHCA in 20% of the cohort. However, major limitations of the study design were (a) the use of a reference standard (primary outcome) that is not routinely used in clinical practice, and (b) selection of patients for emergency coronary angiography by the treating cardiologist, which may have resulted in selection bias and overestimation of accuracy. Whilst there is no gold standard against which to assess the appropriateness of emergency coronary angiography in the setting of OHCA, the primary benefit of this strategy appears to be associated with acute revascularisation.[5,11,12] The aim of this study was to validate the Zeyons Score as a predictor of acute revascularisation in a cohort of patients with a presumed cardiac diagnosis admitted during an era of routine coronary angiography. The secondary aims were (1) to validate the score in the same cohort with respect to (a) the universal definition of type 1 myocardial infarction[13] and (b) 'AMI-related OHCA' as defined by Zeyons et al,[10] and (2) to test the performance of the score against clinical practice in consecutive patients admitted during an era of selective coronary angiography. Validation of this score will assist in ruling in or ruling out emergency angiography in resuscitated OHCA patients.

Methods

Study design

This was an observational retrospective study of consecutive patients identified from the NALHN OHCA registry, which includes all OHCA patients aged >=18 years treated at hospital facilities within the Northern Adelaide Local Health Network (NALHN).[14] All patients undergoing coronary angiography between 2011-13 were included in the validation cohort; failed cardiac catheterisation attempts, potentially identifiable patients (eg, unusually young age, transfer from remote hospital), and patients without a post-ROSC ECG were excluded. Patients with sustained ROSC (≥20 minutes) admitted during 2016 were divided into a test cohort of patients with a presumed cardiac diagnosis on arrival to hospital, and a control cohort of patients with obvious non-cardiac aetiology (e.g., asphyxia, drug overdose, exsanguination); patients with missing or uninterpretable post-ROSC ECGs were excluded. Institutional ethical review was not sought for the study because it met criteria for exemption from such review according to institutional policy. The standards for reporting diagnostic accuracy studies (STARD 2015) were followed (**Appendix E**).[15]

Patient management

The Lyell McEwin Hospital (LMH) is the primary cardiac arrest centre for the northern metropolitan area of Adelaide, South Australia, with 24/7 PCI-capability and 13 intensive care unit and 26 cardiac unit beds. SA Ambulance Service provides a single state-wide two-tier emergency medical service (EMS) where OHCAs are treated by paramedics on-scene. A 12-lead ECG is taken in all patients who gain stable ROSC in the pre-hospital or emergency department (ED) setting, and a Code Blue STEMI may be called by EMS or ED physicians to activate the on-call interventionalist and catheterisation lab team.

During 2011-13, all OHCA patients with a presumed cardiac diagnosis on arrival to hospital underwent routine emergency (<6 hours) coronary angiography +/- acute revascularisation via code STEMI unless there was evidence of futility, contraindication, or if a non-cardiac diagnosis became apparent on initial investigation. From 2014 onward, emergency coronary angiography +/- acute revascularisation was performed at the discretion of the on-call interventional cardiologist according to Australian guidelines.[6,16]

Data collection

The following variables were extracted from the NALHN OHCA registry for analysis:

- Primary outcome: acute revascularisation, defined as planned or attempted PCI and/or transfer to external tertiary facility for coronary artery bypass grafting;
- Patient and process variables;
- De-identified ECG copies.

The first available interpretable ECG taken <2 hours post-cardiac arrest was analysed as the index ECG by an independent examiner blinded to patient management and outcomes.

The index coronary angiogram and troponin results for the validation cohort were extracted from the medical record and analysed according to a case report form (Appendix E) by an experienced interventional cardiologist blinded to patient outcomes. Patients were classified according to the Fourth Universal Myocardial Infarction Definition[13] as type 1 myocardial infarction (including type 3 myocardial infarction if the patient was deceased prior to troponin measurement), type 2 myocardial infarction, no myocardial infarction, or undetermined. In accordance with Zeyons et al,[10] patients were also classified as AMI-related OHCA (group 1): defined by the presence of a recent coronary occlusion on the angiogram (a thrombus) or the ability to cross easily through the occlusion – associated with a thrombolysis in myocardial infarction (TIMI) 0 or 1 flow or a pattern of irregular unstable lesion (type II of the Ambrose classification) coupled with a significant troponin increase; Chronic CAD-related OHCA without AMI (group 2): defined by the presence of significant but stable mainly concentric lesions on coronary angiography, without evidence of thrombus, staining, or angiographic appearance of ruptured plaque; and Non-CAD-related OHCA (group 3): defined either by the presence of a normal angiogram or angiography findings indicating an obviously stable CAD with an independent cause of arrest identified (clearly identifiable after angiography). Significant CAD was defined as >= 70% stenosis on the coronary angiogram.

Zeyons Score

The Zeyons Score was calculated as STE with or without reciprocal changes present in two or more contiguous precordial leads or in two or more adjacent limb leads ⩾0.2 mV in men or ⩾0.15 mV in women in leads V2–V3 and/or ⩾0.1 mV in other leads and/or isolated STE

in the aVR lead ⩾0.1 mV (2 points); pre-cardiac arrest chest pain (1 point); and shockable initial rhythm (1 point). Unknown pre-cardiac arrest chest pain was considered to be negative, and no point was given.

Statistical Analysis

Normally distributed continuous data are presented as mean ± standard deviation and categorical data as frequency and percentage. The diagnostic performance of the Zeyons Score according to primary and secondary outcomes was determined by calculating the area under the receiver operating characteristic (ROC) curves (AUC). An AUC of 1 represents a perfect test and an area of .5 represents a worthless test, where values of 0.9-1, 0.8-0.9, 0.7-0.8, 0.6-0.7, and 0.5-0.6 may be classified as excellent, good, fair, poor, and no better than chance, respectively. Optimal Zeyons Score cut points with respect to each outcome were determined using the Youden index and sensitivity and specificity calculated. Sensitivity, or true positive rate, was the number of patients with an optimal Zeyons Score who required acute revascularisation divided by the total number of patients requiring acute revascularisation. A sensitivity less than 100% indicates that some patients requiring acute revascularisation scored less than the optimal cut point. Conversely, specificity, or true negative rate, was the number of patients that scored less than the optimal cut point who did not undergo acute revascularisation divided by the total number of patients that did not undergo acute revascularisation. A specificity less than 100% indicates that some patients who did not undergo acute revascularisation scored higher than the optimal cut point. Statistical analyses were performed using SPSS, version 26 (SPSS Inc., Chicago, IL, USA) and MedCalc version 20.009 (MedCalc Software, Mariakerke, Belgium).

Results

Cohort characteristics

The validation cohort comprised of 52 patients with a presumed cardiac diagnosis on hospital arrival that underwent coronary angiography between 2011-13; the reasons for exclusion have been previously described (**Figure 1, Paper Three**[17]) and are presented in Figure 1. Of 66 patients with ROSC admitted in 2016, 13 had no ECGs available, leaving 32 patients with a presumed cardiac diagnosis (test cohort) and 21 patients with an obvious non-cardiac

diagnosis (control cohort) for analysis (Figure 2). Table 1 describes the patient characteristics and outcomes of each cohort, of which more than half were male and average age ranged from 50-68 years. Consistent with a presumed cardiac diagnosis, the validation and test cohorts had numerically higher rates of pre-existing medical conditions, pre-arrest chest pain, shockable initial rhythm, STE in any lead including aVR, and peak cardiac troponin >99th centile compared with controls.

Zeyons Score validation

In the validation cohort of patients presenting with a presumed cardiac OHCA undergoing non-selective coronary angiography, the Zeyons Score was an excellent predictor of both acute revascularisation and type 1 myocardial infarction, and a good predictor of AMI-related OHCA as defined by Zeyons et al[10] (Figure 3; Table 2). A score >=3, determined as the optimal cut point according to the Youden index, had a sensitivity of 94% and specificity of 83% with respect to the primary outcome (Table 2). The lowest values of sensitivity and specificity were observed with respect to AMI-related OHCA. One patient with missed STE and acute thrombus considered too unstable for PCI was included in the acute revascularisation group for analysis purposes. The rates of acute revascularisation according to Zeyons Scores of 0, 1-2, and 3-4, are presented in Figure 1, while clinical and angiographic characteristics are presented in Table 3. Of note, 19% of the cohort had a Zeyons Score of 0 and none of these patients required acute revascularisation and none were diagnosed with type 1 myocardial infarction. One out of 21 (5%) patients with a score of 1-2, had a shockable initial rhythm but no STE and underwent acute revascularisation.

Performance of the Zeyons Score in test cohort

The Zeyons Score was tested in a cohort of consecutive patients with a presumed cardiac diagnosis on arrival to hospital, of which 66% were selected by the on-call interventionalist to undergo coronary angiography. The score was a good predictor of acute revascularisation (AUC 0.81, 95% CI 0.64-0.97, p<0.01) (Table 2). A score >=3, determined as the optimal cut point according to the Youden index, had a sensitivity of 66% and specificity of 85% for the primary outcome. The rates of acute revascularisation according to Zeyons Scores of 0, 1-2, and 3-4, are presented in Figure 2. Of note, all five patients (16% of the total cohort) had a

Zeyons Score of 0 and none required acute revascularisation. Four out of twelve (25%) patients with a score of 1-2 underwent acute revascularisation, all of which had an initial shockable rhythm without STE. As coronary angiography was only performed in a select cohort, the accuracy of the Zeyons Score could not be tested against an angiographically confirmed diagnosis of type 1 myocardial infarction or AMI-related OHCA.

Test of the Zeyons Score in control cohort

The performance of the Zeyons Score was tested in a control cohort of patients with obvious non-cardiac aetiology. No controls presented with pre-cardiac arrest chest pain; one presented with a shockable initial rhythm secondary to acute ketoacidosis (Table 1). Of the five patients presenting with STE, one was due to drug overdose and four had positive STE in aVR alone. In all controls the Zeyons Score was <3 (Figure 2).

Discussion

This study retrospectively validated and assessed the performance of the clinical prediction score developed by Zeyons et al[10] in three small cohorts and found that it was highly effective at ruling out, and quite effective at ruling in, acute revascularisation after resuscitated OHCA. Overall, the score was an excellent predictor of both acute revascularisation (AUC 94, 95% CI 83-99) and type 1 myocardial infarction (AUC 92, 95% CI 81-98) in the validation cohort of patients with a presumed cardiac aetiology undergoing non-selective coronary angiography irrespective of initial cardiac arrest rhythm or ECG findings. The accuracy of AMI-related OHCA prediction in this cohort was lower but similar to that reported by Zeyons et al[10] (AUC 0.86 vs 0.85, respectively). A Zeyons Score ≥3, determined as the optimal cut point, predicted acute revascularisation with 94% sensitivity and 83% sensitivity. The score did not perform as well in the test cohort, but no patients with an obvious non-cardiac aetiology (e.g., asphyxia, drug overdose, exsanguination) scored ≥3. Importantly, no patients with a score of 0 (up to 19% of the study cohorts) required acute revascularisation. This study validates the Zeyons Score as a useful tool to assist decision-making for emergency angiography in resuscitated OHCA patients with a presumed cardiac aetiology.

According to Zeyons et al,[10] the main implication of their study was that a score of 0 could be used to rule out 20% of the population from emergency coronary angiography with 100% specificity. Similarly, in the current study 19% of the validation cohort and 16% of the test cohort scored 0 and none required acute revascularisation. Although recent randomised trials have confirmed the lack of overall benefit of emergency coronary angiography in patients without STE, it is well established that up to 30% will have an acute coronary occlusion or culprit lesion responsible for the OHCA and investigations into sub-sets of patients who may benefit from this strategy are ongoing.[8,18] The Zeyons Score may therefore be beneficial in further ruling out the need for emergency coronary angiography in patients without any pre-arrest chest pain, shockable initial rhythm, or STE (Zeyons Score =0). There was no evidence of STE, but the initial rhythm was shockable in all patients with a score of 1-2 that underwent acute revascularisation (5% of the validation and 25% of the test cohorts with a score of 1-2). Our results therefore highlight the significance of initial shockable rhythm as a predictor of acute cardiac ischaemia.

The accuracy of clinical predictions tools used to determine which patients will benefit from emergency coronary angiography i.e., those who require acute revascularisation, has not been compared to unstructured clinical judgement or 'gestalt'. Wittwer et al[17] reported a sensitivity of 100% for acute revascularisation according to the decision made by at least two out of three experienced interventional cardiologists (consensus decision), which is higher than the current study. In the additional analyses of the study presented in Chapter Five of this thesis, an AUC of 0.71 overall and 0.72 for the consensus decision was reported for acute revascularisation, which is lower than the AUC of the Zeyons Score in the current study. Although the consensus decision reported by Wittwer et al[17] was highly sensitive for acute revascularisation, the 95% confidence intervals ranged from 79.4-100% and individual sensitivity ranged from 94-100%, likely corresponding to higher than clinically acceptable 'miss' rates. On the other hand, the cardiologists' consensus decision ruled out acute revascularisation in 31% of the cohort studied,[17] whereas the Zeyons Score only ruled out 20% of the same cohort. This small single-centre study suggests that the Zeyons Score, compared with clinical judgement alone, may be more accurate at ruling in but not ruling out acute cardiac ischaemia amenable to revascularisation. Other studies in the setting of ACS without cardiac arrest have demonstrated similar findings and suggest that relying on clinical judgement alone does not meet current standards of care.[19]

Neither prediction scores nor clinician judgement, when analysed at a single time-point, captures the complexity of OHCA management, which may evolve over time depending on the results of additional diagnostic tests and neurological prognostication. Poor neurological prognosis is a contraindication for emergency coronary angiography with data suggesting a lack of benefit in these patients.[20,21] Although guidelines for cardiac management of resuscitated OHCAs remain unclear for patients presenting without STE and results of large randomised clinical trials remain forthcoming, several treatment protocols have been developed to aid clinicians in their decision-making.[8,22–24]

Limitations

This was a small retrospective study, and the results must be interpreted with caution. A validation study typically requires 100 cases and >=200 controls but inclusion of such large numbers was not possible due to the strategy of selective emergency coronary angiography implemented from 2014 onwards within NALHN. The validation cohort was chosen to minimise selection bias, but it was not possible to eliminate all bias due to the study design. Not all patients presenting in 2016 with a presumed cardiac diagnosis (test cohort) underwent coronary angiography or autopsy to confirm presence or absence of acute coronary ischaemia, which may have resulted in underestimation of the score's diagnostic performance. Further validation of the score in a larger, prospective, non-selective cohort is required.

Conclusion

A simple clinical score incorporating STE in any lead including aVR, shockable initial rhythm, and chest pain was very good at ruling out acute cardiac ischaemia requiring emergency coronary angiography and revascularisation in OHCA patients with a presumed cardiac diagnosis on hospital arrival. Alongside clinical judgement, this score may assist decision making for emergency coronary angiography.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures and Tables

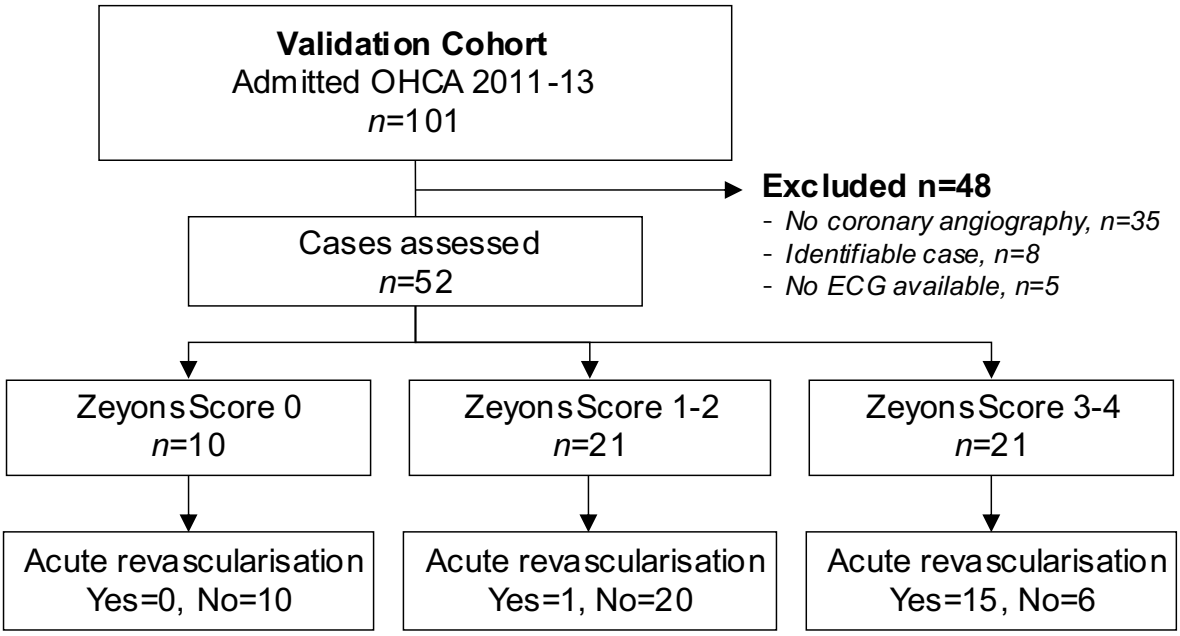

Figure 1: STARD diagram of the primary outcome of acute revascularisation according to the Zeyons Score in the validation cohort.

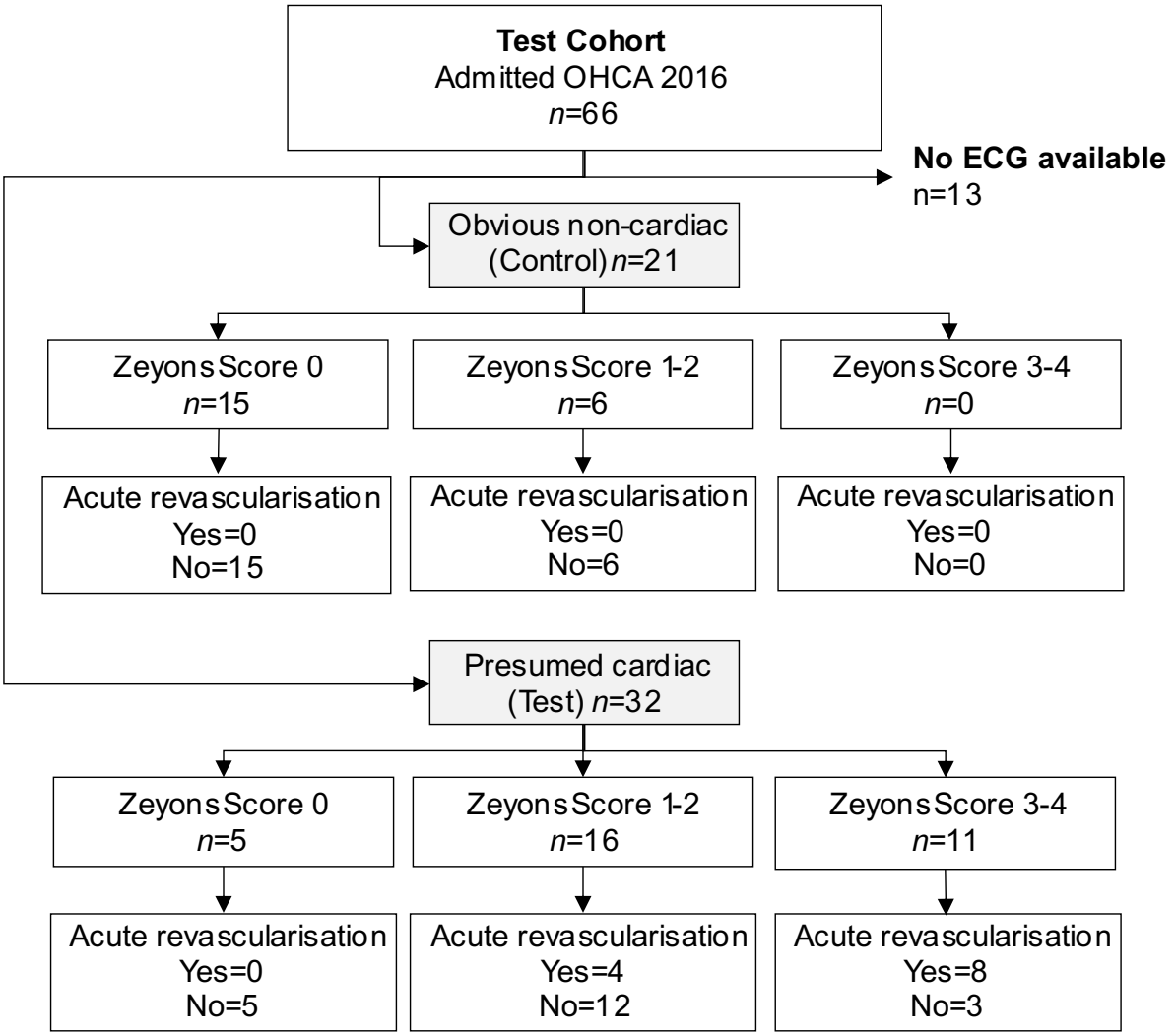

Figure 2: STARD diagram of the primary outcome of acute revascularisation according to the Zeyons Score in the test cohort, divided according to presumed or obvious aetiology.

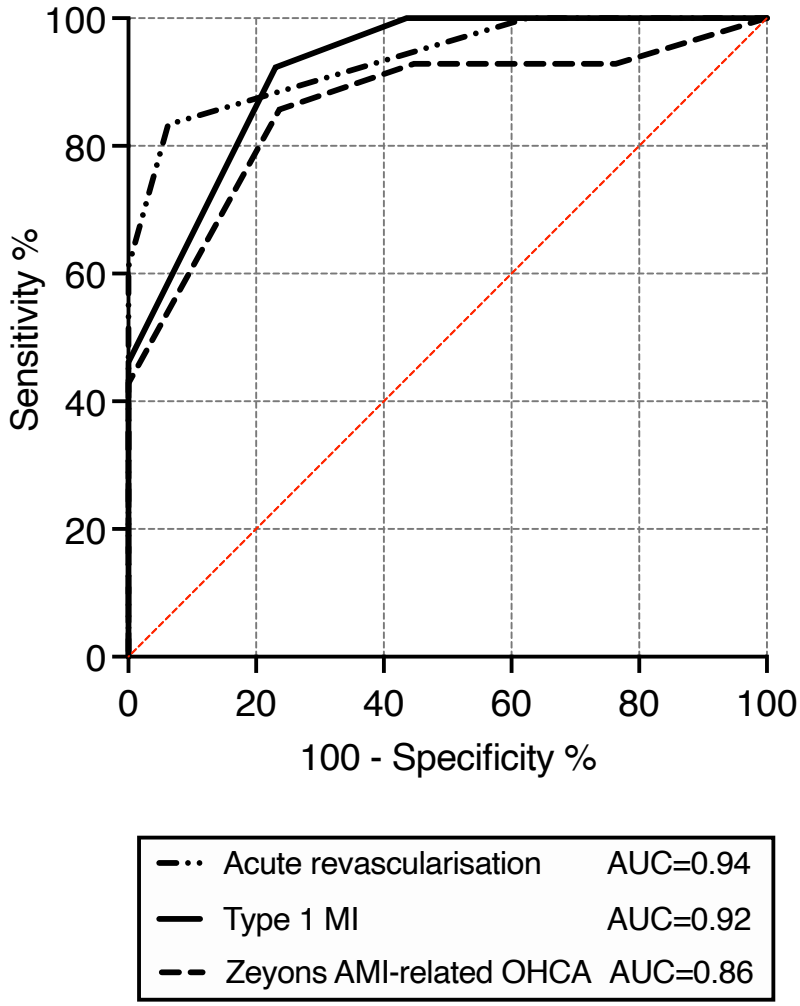

Figure 3: Comparison of the receiver operating characteristics curve of the Zeyons Score combining ST elevation in any lead (2 points), chest pain before out-of-hospital cardiac arrest (1 point), and a shockable initial rhythm (1 point) in predicting acute revascularisation (dash-dot-dot line), type 1 myocardial infarction (plain line), and AMI-related OHCA (dashed line).

Table 1: Description of validation, control, and test cohorts

Patient characteristics	**Validation** ***n*=52**	**Test** ***n*=32**	**Control** ***n*=21**
Age (years)	58 ± 15	68 ± 11	50 ± 19
Male sex	34 (65)	21 (66)	13 (62)
Pre-existing medical history			
Ischaemic heart disease	18 (35)	14 (44)	2 (10)
Hypertension	33 (64)	17 (53)	4 (19)
Diabetes	16 (31)	10 (31)	2 (10)
Dyslipidaemia	21 (40)	13 (41)	3 (14)
Obesity	8 (15)	11 (34)	3 (14)
Family history of cardiac disease	13 (25)	3 (9)	0 (0)
Current smoker	16 (31)	9 (28)	5 (24)
Pre-arrest chest pain	10 (19)	7 (22)	0 (0)
Bystander/EMS witnessed	38 (73)	28 (88)	12 (57)
Bystander CPR (non-EMS-witnessed)	34/48 (71)	14/23 (61)	13/16 (81)
Shockable initial rhythm	36 (69)	22 (69)	1 (5)
Refractory arrest	31/50 (62)	10 (31)	3 (21)
STE in any lead including aVR	26 (50)	15 (47)	5 (24)
Peak troponin >99th centile*	41/50 (82)	21/29 (72)	7/16 (44)
Cardiac catheterisation	52 (100)	21 (66)	0 (0)
Acute revascularisation	16 (31)	8 (25)	0 (0)
Survived with good neurological outcome (Cerebral performance category 1-2)	19 (37)	20 (63)	7 (33)

Data presented as *n* (%) or mean ± standard deviation. Percentages may not add up to 100 due to rounding. *Values reflect missing data. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; STE, ST-segment elevation.

Table 2: Performance of the Zeyons Score according to primary and secondary outcomes

Outcomes	Score Criterion	Sensitivity % (95% CI)	Specificity % (95% CI)	C-statistic AUC (95% CI)
Validation cohort (n=52)				
Acute revascularisation	≥3	94 (70-100)	83 (67-94)	94 (83-99)*
Type 1 myocardial infarction	≥3	92 (64-100)	77 (61-89)	92 (81-98)*
AMI-related OHCA	≥3	86 (57-98)	76 (60-89)	86 (74-94)*
Test cohort (n=32)				
Acute revascularisation	≥3	67 (35-90)	85 (62-97)	81 (64-97)*

*p-value <0.01 compared with AUC 50. AUC, area under the receiver operating characteristic curve; CI, confidence interval; AMI, acute myocardial infarction.

Table 3 Clinical and angiographic characteristics according to Zeyons Score in the 2011-13 validation cohort, n=52

	Zeyons Score		
	0 (*n*=10)	**1-2** (*n*=21)	**3-4** (*n*=21)
Age	67 ± 11	54 ± 16	58 ± 14
Male sex	5 (50)	12 (57)	17 (81)
Pre-arrest chest pain	0 (0)	4 (19)	6 (29)
Bystander/EMS witnessed	3 (30)	16 (76)	19 (90)
Shockable initial rhythm	0 (0)	16 (76)	21 (100)
Refractory cardiac arrest*	6/9 (67)	10 (48)	15/20 (75)
STE in any lead including aVR	0 (0)	3 (14)	8 (38)
Peak troponin >99th centile	8/9 (89)	15/20 (75)	18 (86)
Coronary artery disease			
Normal or minor	4 (40)	15 (71)	3 (14)
One-vessel disease	1 (10)	0 (0)	7 (33)
Two-vessel disease	2 (20)	3 (14)	5 (24)
Three-vessel disease	3 (30)	3 (14)	6 (29)
Infarct-related artery			
Left main	0 (0)	0 (0)	2 (10)
Left anterior descending	0 (0)	0 (0)	8 (38)
Circumflex	1(10)*	1 (5)	3 (14)
Right coronary artery	0 (0)	0 (0)	1 (5)
Universal definition of myocardial infarction			
Myocardial infarction type 1	0 (0)	1 (5)	12 (57)
Myocardial infarction type 2	1 (10)	0 (0)	2 (10)
No myocardial infarction	7 (70)	18 (86)	6 (29)
Undetermined / other	2 (20)	1 (5)	1 (5)

Data presented as *n* (%) or mean ± standard deviation. Percentages may not add up to 100 due to rounding. *Suspected spontaneous coronary artery dissection. EMS, emergency medical services; STE, ST-segment elevation

6.3 Summary of Chapter Six

Emergency coronary angiography after resuscitated OHCA in patients without obvious non-cardiac aetiology is beneficial for three important reasons as described by Yannopoulos et al[74]: (1) it provides a single procedure that aids in the time-critical diagnosis of ischemic versus non-ischemic heart disease, pulmonary embolism, and cardiomyopathy; (2) it facilitates reversal of an acute ischaemic aetiology by means of revascularisation; and (3) it allows further support and stabilisation of patients by means of circulatory assist devices. A fourth reason is that emergency coronary angiography often forms part of a more aggressive protocol of post-resuscitation care which focuses on early diagnosis and management and has been shown to improve survival.[56,79,285]

At the time the Zeyons Score was published there was very little evidence about the benefit of an emergency versus delayed approach to coronary angiography after resuscitated OHCA without STE. However, Zeyons et al[116] acknowledged that the score may be more useful for ruling out, than ruling in AMI. In the NALHN cohort, the score predicted (ruled in) acute revascularisation with greater accuracy than clinical judgement according to ROC analysis of AUC but did not rule out as many patients. Although presumed cardiac OHCAs are appropriately managed by experienced interventional cardiologists, the addition of a clinical score seems advantageous especially when less experienced clinicians are involved in patient care.

CHAPTER SEVEN: IN-HOSPITAL DEATH AFTER OHCA

7.1 Overview of Chapter Seven

The chapters presented so far have explored patient and arrest factors associated with survival after OHCA, such as age, sex, and initial rhythm, and in-hospital management strategies aimed at improving survival, such as emergency coronary angiography, and acute revascularisation. Emerging but less well-defined clinical endpoints for assessing the effectiveness of post-resuscitation care are the reasons and mechanisms of in-hospital death. This chapter addresses the fifth research objective of this thesis, which was to explore hospital outcomes of timing, location, and mode of death in NALHN OHCA patients treated at hospital.

7.2 Background and Context

The core outcome set for reporting on effectiveness studies of cardiac arrest (COSCA) in adults includes survival to hospital discharge or 30 days, neurological function as measured by the modified Rankin Scale at hospital discharge or 30 days, and health-related quality of life measured by ≥1 tools at 90 days and at periodic intervals up to 1 year after cardiac arrest.[127] These indices effectively distinguish between varying patient-level outcomes in survivors, but do not distinguish between varying reasons for death, such as neurological injury, cardiovascular collapse, and multiorgan failure, in non-survivors. The reason for death, or mode of death, as distinct from cause / aetiology of arrest, is emerging as an important clinical endpoint for effectiveness studies of cardiac arrest.[156,286,287] The study presented in this chapter was designed as a preliminary investigation into in-hospital death within NALHN.

7.3 Manuscript, Paper Five

The following paper, "In-hospital mode of death after out-of-hospital cardiac arrest" was published in *Resuscitation Plus* in 2022.[24]

Statement of Authorship

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Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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Clinical paper

In-hospital mode of death after out-of-hospital cardiac arrest

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Abstract

Introduction: Factors associated with in-hospital mortality after out-of-hospital cardiac arrest (OHCA), such as mode of death and withdrawal of life-sustaining treatment (WLST), are not well established. This study aimed to compare clinical characteristics, timing of WLST and death, and precipitating aetiology between modes of death for OHCAs treated at hospital within a local health network.

Methods: Retrospective cohort study of adult non-traumatic OHCAs included in a hospital based OHCA registry between 2011 and 2016 and deceased at hospital discharge, excluding cases retrieved to external hospitals. Mode of death was defined as (1) cardiovascular instability, (2) non-neurological WLST, (3) neurological WLST, and (4) formal brain death. Relevant data were extracted from the registry and stratified according to mode of death and timing of death as early (within the emergency department) or late (after admission).

Results: Mode of death data was available for 69 early and 144 late deaths. Cardiovascular instability was the primary mode for 75% of early deaths, while 72% of late deaths were attributed to neurological injury (47% neurological WLST and 24% brain death, combined). Cardiovascular instability was associated with cardiac aetiology, brain death was associated with younger age and highest rates of organ donation, and neurological WLST was associated with highest rates of targeted temperature management, and longest time from arrest to death ($p < 0.05$).

Conclusions: This is the first study to compare clinical characteristics of adult patients resuscitated from OHCA according to in-hospital mode of death. A consensus on the definition of mode of death with standardised classification is needed.

Keywords: Out of hospital cardiac arrest, Mode of death, Cause of death, Aetiology, WLST, Brain death

Introduction

Out-of-hospital cardiac arrest (OHCA) remains associated with high mortality in spite of ongoing systems-based improvements.[1] Post-cardiac arrest syndrome has long been recognised as the major contributor to high mortality observed for patients who gain sustained return of spontaneous circulation (ROSC $\geq$ 20 min).[2] The four key components of post cardiac arrest syndrome include post-OHCA brain injury, post-OHCA myocardial dysfunction, systemic ischaemic-reperfusion injury, and persistent precipitating aetiology. Post-resuscitation guidelines therefore centre on addressing each of these components.[3–5] Understanding the reason for in-hospital death after OHCA and the contribution of associated factors such as post cardiac arrest syndrome, is useful for identifying organ donation candidates,[6] developing tools to aid prognostication, and ultimately for improving survival.

Previous research has identified that the mode of death for 70% of in-hospital deaths after resuscitated OHCA is neurological injury, which encompasses the spectrum of brain injury resulting in withholding or withdrawal of life-sustaining therapy (WLST) for perceived poor neurological prognosis, through to brain death. Other reported

Abbreviations: DNR, Do not resuscitate, ICU, Intensive care unit, NALHN, Northern Adelaide Local Health Network, OHCA, Out-of-hospital cardiac arrest, ROSC, Return of spontaneous circulation, SAAS, SA Ambulance Service, TTM, Targeted temperature management, WLST, Withdrawal of life sustaining treatment.

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modes of death include cardiovascular instability and multi-organ failure[7–14]; however, the literature on mode of death is limited. Factors associated with survival and non-survival, such as witnessed arrest and shockable initial rhythm, are established but the clinical characteristics and precipitating aetiology associated with specific modes of death have not been described in an adult population. Additionally, some evidence suggests that mode of death may differ between sexes, in part driven by higher rates of early WLST (<72 h post ROSC) in women compared with men.[7,15,16] Therefore, this study aimed to compare clinical characteristics, timing of WLST and death, and precipitating aetiology between modes of death for non-traumatic adult OHCAs with (a) early death in the emergency department (ED) and (b) late death after admission. Our secondary aim was to explore sex differences in mode of death, and timing of WLST and death.

Methods

Design

This is a retrospective observational cohort study of the Northern Adelaide Local Health Network (NALHN) OHCA registry, a hospital-based quality assurance initiative with data capture according to the Utstein style, described previously.[17,18] Briefly, potential cases are identified from existing EMS-based and hospital-based sources and eligible cases are included after full medical record review. Demographic, management, and outcome data are abstracted from the medical record into the registry. The current analysis included all adult, non-traumatic OHCAs treated at NALHN facilities and deceased at hospital discharge between 2011 and 2016. Patients retrieved to an external hospital were excluded. The Central Adelaide Local Health Network Human Research Ethics Committee approved the registry and subsequent analyses as an ongoing quality improvement activity [Q20170304].

Setting

NALHN comprises two public hospitals that service a population of 450,000 within the northern metropolitan and regional areas of Adelaide, South Australia. There is a single state-wide two-tier emergency medical service (SA Ambulance Service, SAAS) where patients are treated by paramedics on scene with transport under CPR according to local protocol. Both receiving hospitals have a resuscitation area in the ED with a multidisciplinary health team led by ED specialist physicians. The Lyell McEwin Hospital is the primary cardiac arrest centre with 24/7 PCI-capability and 13 intensive care unit (ICU) and 26 cardiac unit beds. SAAS and NALHN hospitals are guided by the ANZCOR resuscitation guidelines.[3] WLST covers both withholding and withdrawal of life-sustaining therapy including intubation, inotropes, and other life-sustaining medications.[19] Briefly, the decision for WLST is made between the physician and substitute decision maker according to known or perceived patient wishes. Timing and methods chosen for prognostication are left at the discretion of the treating physician. Following WLST, patients are palliated per local guidelines.

Measures

Primary and secondary outcome measures were extracted from the registry and analysed for patients deceased within ED and deceased after admission. Mode of death was documented in the registry according to the circumstances of death described in the medical record. Mode of death categories were based on previous studies[7–9,20] and included: (1) cardiovascular instability, including haemodynamic instability, recurrent arrest, and intractable shock; (2) WLST for non-neurological reasons are varied and may include multi-system organ failure, underlying comorbidities, advanced directive, substitute decision maker wishes etc. (non-neurological WLST); (3) WLST due to poor perceived neurological prognosis (neurological WLST); (4) formal brain death. Secondary outcome measures included sex, patient demographics, arrest characteristics, hospital management, WLST, location and timing of death, and aetiology. Clinical and multimodal methods of neurological prognostication and "Do Not Resuscitate" (DNR) orders were not consistently documented in the registry and could not be included in the current analysis.

Statistics

Continuous data is presented as median ± interquartile range and comparisons between groups made using Mann-Whitney U test or Kruskal-Wallis test. Categorical data is presented as frequency and percentage and comparisons between groups made using Fisher's exact test or Fisher-Freeman-Halton exact test with post-hoc pairwise z-tests performed as appropriate. Analyses were performed using SPSS 28 (IBM SPSS Statistics, Armonk, NY, USA).

Results

A search of the NALHN OHCA registry between 2011 and 2016 revealed 223 OHCA cases deceased at hospital discharge. Seven cases retrieved to a non-NALHN hospital were excluded, leaving a final cohort 69 cases deceased in ED and 147 cases deceased after admission, 144 with full details on mode of death (Fig. 1). Overall, the ED death rate was 18% with 32% of all deaths occurring in the ED, while the admitted death rate was 46%.

Early deaths in ED

Characteristics of patients deceased in ED stratified according to mode of death are presented in Table 1. Overall, 54% of patients were male with a median age of 72 years; 39% gained sustained ROSC $\geq$ 20 min, and median time from arrest to death was 1.5 h. Mode of death was due to cardiovascular instability in 75% of cases, non-neurological WLST in 16%, and neurological WLST in 10%. The

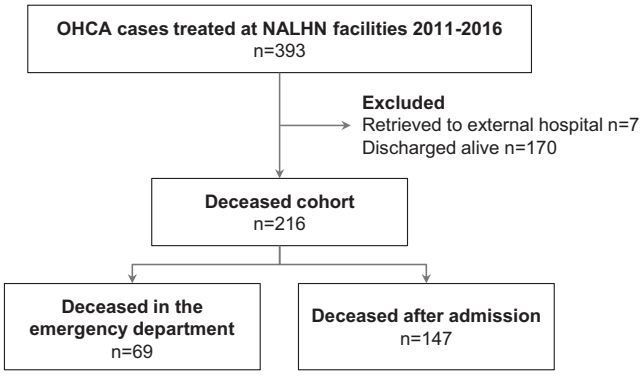

Fig. 1 – Flow-chart of included patients with early death in the emergency department and late death after admission.

Table 1 – Patient characteristics of resuscitated OHCAs with early death in the emergency department within a local health network, stratified by mode of death.

	Overall $n = 69$	Cardiovascular instability $n = 52$	WLST $n = 17$	*p*-value
Male	37 (54%)	31 (60%)	6 (35%)	0.099
Age	72 [58–84]	70 [53–80]	79 [68–86]	0.023
Arrest at home or residence	36 (52%)	25 (48%)	11 (65%)	0.27
Witnessed status				
Bystander	18 (26%)	14 (27%)	4 (24%)	>0.99
Emergency medical services	34 (49%)	29 (56%)	5 (29%)	0.093
Unwitnessed	17 (25%)	9 (17%)	8 (47%)	0.022
Bystander CPR	22/34 (65%)	14/22 (63%)	8/12 (67%)	>0.99*
Initial shockable rhythm	13 (19%)	11 (21%)	2 (12%)	0.50
Sustained ROSC $\geq$ 20mins	27 (39%)	10 (19%)	17 (100%)	<0.001
Arrest to death (h)	1.5 [0.9–2.3] ($n = 68$)	1.2 [0.8–1.9] ($n = 51$)	2.4 [1.7–4.2]	<0.001*
Aetiology				<0.01
Cardiac	57 (39%)	16 (64%)	6 (29%)	
Respiratory	42 (29%)	3 (12%)	9 (43%)	
Neurological	8 (5%)	1 (4%)	0 (0%)	
Toxicological	7 (5%)	0 (0%)	3 (14%)	
Other	15 (10%)	5 (20%)	2 (10%)	
Unknown	18 (12%)	0 (0%)	1 (5%)	
Organ donation	2 (3%)	1 (2%)	1 (6%)	–

Data presented as number (percentage), or median [interquartile range]. *P-values reflect data that excludes missing values. ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

Table 2 – Patient characteristics of OHCAs admitted to hospital within a local health network, stratified by mode of death.

	Overall $n = 144$	Cardiovascular instability $n = 20$	Non-neurological WLST $n = 21$	Neurological WLST $n = 68$	Brain death $n = 35$	*p*-value
Male	96 (67%)	14 (70%)	13 (62%)	45 (66%)	24 (69%)	0.96
Age	61 [47–73]	67 [48–78]	70 [53–75]	65 [52–76]	47 [33–60]	<0.001
Arrest at home or residence	115 (80%)	16 (80%)	19 (90%)	51 (75%)	29 (83%)	0.47
Witnessed						0.76
Bystander	72 (50%)	10 (50%)	11 (52%)	35 (51%)	16 (46%)	
Emergency medical services	14 (10%)	1 (5%)	4 (19%)	6 (9%)	3 (9%)	
Unwitnessed	58 (40%)	9 (45%)	6 (29%)	27 (40%)	16 (46%)	
Bystander CPR	81/130 (62%)	15/19 (79%)	12/17 (71%)	33/62 (53%)	21/32 (66%)	0.18
Initial shockable rhythm	51 (35%)	11 (55%)	7 (33%)	26 (38%)	7 (20%)	0.06
Cardiac catheterisation	55 (38%)	10 (50%)	7 (33%)	26 (38%)	12 (34%)	0.67
Cardiac intervention	19/55 (35%)	6/10 (60%)	3/7 (43%)	7/26 (27%)	3/12 (25%)	0.27
Temperature management	80 (37%)	6 (30%)	6 (29%)	50 (74%)	15 (43%)	<0.001
Neurological prognostication						
Brain Computed Tomography	71 (49%)	8 (40%)	6 (29%)	37 (54%)	20 (57%)	0.12
Brain MRI	23 (16%)	1 (5%)	1 (5%)	18 (26%)	3 (9%)	0.016
Brain perfusion scan	10 (7%)	-	-	-	10 (29%)	-
WLST <72 h after ROSC	46/86 (53%)	-	15/20 (75%)	31/66 (47%)	-	0.04*
ROSC to WLST (h)	70 [33–99] ($n = 86$)	-	30 [12–67] ($n = 20$)	74 [46–102] (n = 66)	-	<0.01*
Death in Intensive Care Unit	125 (87%)	18 (90%)	18 (86%)	54 (79%)	35 (100%)	0.012
Arrest to death (h)	57 [30–103] ($n = 141$)	15 [8–45]	36 [14–84] ($n = 19$)	85 [48–143] ($n = 67$)	48 [36–66]	<0.001
Organ donation	23 (16%)	1 (5%)	1 (5%)	6 (9%)	15 (43%)	<0.001

Data presented as number (percentage), or median [interquartile range]. *P-values reflect data that excludes missing values. MRI, magnetic resonance imaging; ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

two WLST categories were combined for analyses due to low numbers. Patients with WLST were older and more likely to have an unwitnessed arrest and longer time from arrest to death compared with patients deceased due to cardiovascular instability.

Late deaths after admission

Characteristics of patients surviving to hospital admission with sustained ROSC, stratified according to mode of death, are presented in Table 2. Overall, 67% were male with a median age of 61 years. In contrast to the ED cohort, most OHCAs occurred in the home, only 10% were EMS-witnessed, and 35% presented with an initial shockable rhythm. On arrival to the hospital 93% were comatose (Glasgow Coma Scale, GCS = 3), lactate was recorded in 58% of cases and found to be elevated > 7 mmol/L in 64%, and pH was recorded in 79% of cases and was > 7.2 in 18%. There were no differences in these prognostic indicators across modes of death ($p > 0.05$). All cases were admitted to ICU except for two cases admitted directly to the ward for poor outlook and palliation.

The primary mode of death was neurological WLST in 47% of cases, followed by brain death in 24%, non-neurological WLST in 15%, and cardiovascular instability in 14% (Table 2). Neurological injury, comprising neurological WLST and brain death, represented the primary mode of death in 72% of all admitted OHCAs. The distribution of age, but not sex, was significantly different across modes of death where brain death represented the youngest cohort with a median age of 47 years ($p < 0.01$). Rates of targeted temperature management (TTM) were highest for neurological WLST ($p < 0.05$) but did not significantly differ between other modes of death. Time from arrest to death was longest for neurological WLST ($p < 0.01$) but did not significantly differ between other modes of death (Fig. 2). Other arrest characteristics were similar across modes of death. There were no significant sex differences for rates of WLST, early WLST, and time from arrest to death (Table 3).

OHCA aetiology

Patients deceased in ED due to cardiovascular instability were more likely to have a precipitating cardiac aetiology, and less likely to have an unknown aetiology compared to deaths due to WLST ($p < 0.05$). Similar to cases deceased in ED (Table 1), the distribution of precipitating aetiology in admitted cases was 39% cardiac, 28% respiratory, 6% neurological, 5% toxicological, and 23% other/unknown. Fig. 3 presents the distribution of aetiology according to mode of death in admitted OHCAs. Cardiac aetiology was more prevalent for deaths due to cardiovascular instability when compared with confirmed brain deaths ($p < 0.05$), but not when compared to other modes of death ($p > 0.05$). There was no significant difference between modes for other aetiologies ($p > 0.05$).

Discussion

This study investigated the clinical characteristics, timing of WLST and death, and precipitating aetiology associated with mode of death in adult OHCAs transported to hospital within a local health network. The primary mode of death in 75% of ED deaths was cardiovascular instability (haemodynamic instability, recurrent arrest, and intractable shock), while in 72% of admitted deaths it was neurological injury (neurological WLST and brain death). Mode of death was significantly associated with age, timing of death, and precipitating aetiology, but not sex.

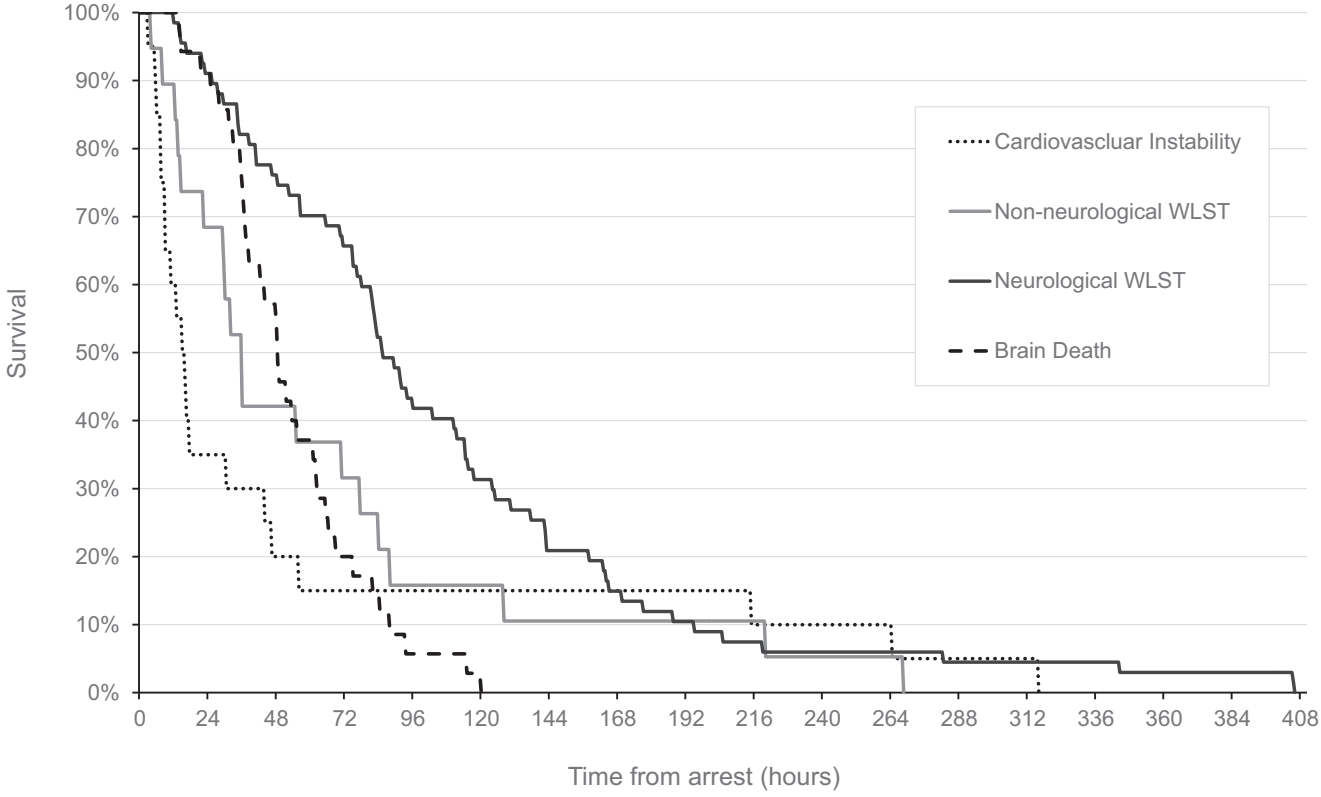

Fig. 2 – Survival percentage according to time from arrest (h) for OHCAs with sustained ROSC admitted to hospital within a local health network, stratified by mode of death (n = 144). WLST, withdrawal of life-sustaining therapy.

Table 3 – Sex differences in mode of death, timing of WLST, and location and timing of death in OHCAs with sustained ROSC admitted to hospital within a local health network (n = 147).

	Missing data	Male	Female	*p*-value
		n = 98	*n* = 49	
WLST		58 (59%)	31 (63%)	0.72
WLST <72 h after ROSC	3 (3%)	29 (51%)	17 (59%)	0.65
ROSC to WLST (h)	2 (2%)	71 [33–101]	67 [37–96]	0.63
Death in Intensive Care Unit	-	86 (88%)	41 (84%)	0.61
Arrest to death (h)	3 (2%)	55 [30–103]	62 [36–110]	0.48

Data presented as number (percentage) or median [interquartile range]. p-values reflect data that excludes missing values. ROSC, return of spontaneous circulation; WLST, withdrawal of life-sustaining therapy.

Early in-hospital death

The ED mortality rate was 18% and 32% of all hospital deaths occurred in ED, which is consistent with recently published Australian rates of 19% and 33%, respectively, reported over a similar period.[21] In the current study, cardiovascular instability was the primary mode of death in the ED and likely reflects a high burden of recurrent arrest. Most deaths due to cardiovascular instability occurred within the first 2 h post-OHCA and only 19% gained sustained ROSC. Extracorporeal cardiopulmonary resuscitation (ECPR) is not available within the current setting, but our results highlight the importance of such an intervention given that almost two thirds of these patients had a potentially reversible precipitating cardiac aetiology. WLST for neurological and non-neurological reasons occurred at a lower rate than reported by Kempster et al.[21] we also reported a slightly lower prevalence of cardiac aetiology and higher prevalence of respiratory aetiology in these patients, which is consistent with a high rate of respiratory OHCA in our cohort.[22]

Mode of death after admission

Consistent with previous literature, we found that neurological injury was the leading mode of death in OHCAs surviving to hospital admission, irrespective of precipitating aetiology.[8,9,11,23] Interestingly, brain death alone accounted for 24% of admitted deaths compared to previous reports in older studies of 3.7–19% in adult populations, and 47% in a paediatric population.[6,7,14,24] Only a small proportion of patients with brain death had an OHCA due to a neurological aetiology, and although this was not statistically different, the majority were of cardiac and respiratory origin, reflecting a progression of hypoxic brain injury to brain death. The higher rate of brain death observed may therefore be driven by the lower median age of this group and increased pre- and in-hospital resuscitative efforts, highlighting the importance of assessing the potential for organ donation in non-survivors.[6]

Consistent with guidelines available during the study timeframe, neurological WLST was associated with highest rates of TTM in this cohort. Neurological WLST was also associated with the longest time from arrest to death (median 3.5 days), which is similar to a report from a paediatric population.[14] Despite this finding, WLST occurred ≤72 h in 53% of cases, likely reflecting Australian cultural practice to withdraw care early rather than prolong suffering.

Deaths due to cardiovascular instability represented only 14% of admitted patients compared to other reports of 20–23 %[7,8] which may reflect differences in definitions or practice within our institutions e.g., unstable cases with poor outlook may not be transferred directly to the ICU with resulting death in the ED. Finally, rates of other established outcome predictors such as sex, arrest location, witness sta-

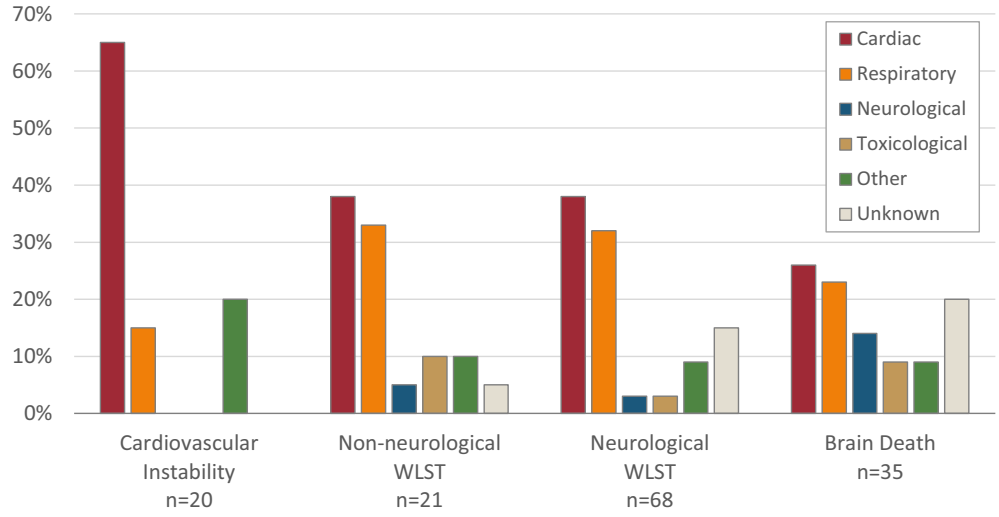

Fig. 3 – Mode of death in OHCAs deceased after admission to hospital within a local health network, stratified according to underlying aetiology as documented in hospital medical records and autopsy reports (n = 144). WLST, withdrawal of life-sustaining therapy.

tus, bystander CPR, and cardiac catheterisation were similar across modes of death. Our findings confirm previous work and continue to emphasise the need for strategies to improve neurological outcomes such avoiding fever[25] and delaying neurological prognostication for ≥72 h post-ROSC.[7,26]

No sex differences in mode of death or WLST practice

Previous research has identified that women are less likely to survive to hospital discharge after OHCA, and it has been postulated that this is due to increased withdrawal of treatment[15,27]. However, women surviving to admission in our small study had similar rates of WLST and early WLST compared to men, which is in contrast to some previous studies[7,16] but not others.[28] Similarly, we found that the distribution of sexes across the modes of death in both the ED and admitted populations was not statistically significant. Future studies in larger populations should continue to stratify according to sex, particularly considering the differences in OHCA aetiology in females compared with males.[10].

Defining Mode of Death

Few studies have explored mode of death after OHCA, and these in diverse sub-populations with varying definitions of mode of death, which limits direct comparison.[7–14] Witten et al.[11] recently proposed five clearly defined categories with good interrater agreement based on retrospective review of the medical record. This definition still requires external validation and should be expanded to include brain death.[29] A simpler categorisation may consist of *death despite full treatment, death following WLST, and brain death*, which could be supplemented with additional information on neurological prognostication, reasons for WLST, and precipitating aetiology. Consensus on the definition of mode of death with a standardised classification is needed to provide a clear distinction from cause of death defined in the Utstein template, which is likely to reflect precipitating OHCA aetiology e.g. acute myocardial infarction, rather than mode of death.[6,17].

Limitations

The findings of this small study must be interpreted in the light of the following limitations. Firstly, data variables in the registry were entered in the registry by retrospective case note abstraction and may be subject to inherent bias. The complex nature of OHCA meant it was often difficult to categorise mode of death even when the clinical documentation was adequate, as noted by others.[11] Secondly, only four categories of mode of death were defined in the registry and it was not possible to separate out deaths caused by respiratory or multiorgan failure, DNRs, or detailed reasons for WLST. A prospective study is required to address the current subjectivity associated with mode of death categorisation. Thirdly, this study was performed within a local health network in Australia and the findings may not be readily generalisable to other settings, particularly other countries with differing medical services and end-of-life culture.[30] Finally, the results should be interpreted within the context of the study period as practice changes may have occurred over the last > 5 years; we have nonetheless highlighted the consistency of our findings with other reports. The strength of this study is that it is the first to report mode of death and WLST after OHCA in patients treated at hospital in Australia, and the first to compare clinical characteristics across modes in adult patients.

Conclusions

In summary, the leading mode of death in OHCAs surviving to hospital and deceased in the ED was cardiovascular instability, while death after admission was primarily due to neurological injury. This report from within a local health network is the first to describe clinical characteristics associated with mode of death in an adult OHCA population. Mode of death was found to be associated with timing of death and precipitating aetiology, but not sex. Mode of death provides critical information for the assessment of post-cardiac arrest management but consensus regarding definition and standardised classifications are still needed.

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CRediT authorship contribution statement

Melanie R Wittwer: Conceptualization, Methodology, Investigation, Writing – original draft. **Thomas Armstrong:** Investigation, Writing – original draft. **Jordan Conway:** Investigation, Writing – original draft. **Mohammed Ishaq Ruknuddeen:** Methodology, Writing – review & editing. **Chris Zeitz:** Supervision, Writing – review & editing. **John F Beltrame:** Supervision, Writing – review & editing. **Margaret A Arstall:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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7.4 Summary of Chapter Seven

This investigation into in-hospital death after OHCA within NALHN provided important insights into patient and arrest factors associated with modes of death occurring within the ED and admitted patients, as well as challenges associated with the collection and classification of mode of death. The primary mode of death in the ED was cardiovascular instability, comprising haemodynamic instability, recurrent arrest, and intractable shock. In contrast, the primary mode of death in admitted patients was neurological injury, comprising neurological WLST and brain death. These findings have important implications for aspects of post-resuscitation care that target refractory arrest and neurological recovery, as well as for assessing the appropriateness of interventions such as coronary angiography in patients with poor neurological prognosis.The findings confirm previous work and additionally demonstrate that rates of established outcome predictors such as sex, arrest location, witness status, bystander CPR, and cardiac catheterisation were similar across modes of death in patients who gained sustained ROSC. The main differences between groups were observed for factors such as age and aetiology, where brain death was associated with lower age, and cardiovascular instability was associated with a precipitating cardiac aetiology. Mode of death represents a promising endpoint for effectiveness studies in cardiac arrest that may improve identification of organ donation candidates, selection of patients for post-cardiac arrest interventions, development of prognostication tools, and ultimately, OHCA survivorship. Further work is required to define and validate clinically meaningful categorisations of mode of death in this setting.

CHAPTER EIGHT: AETIOLOGY OF OHCA TREATED AT HOSPITAL

8.1 Overview of Chapter Eight

As presented throughout the preceding chapters of this thesis, precipitating aetiology plays a central role in the epidemiology, management, and outcome of OHCA. This chapter addresses the seventh objective of this thesis, which was to explore hospital outcomes according to precipitating aetiology in consecutive patients treated at hospital with sustained ROSC (≥20minutes).

8.2 Introduction and Context

OHCA aetiology represents the complex interplay between substrate and trigger, or factors influencing the transition from stable to unstable disease state and is often difficult to define. For this reason and others, including absence of routine autopsy, limitations in data capture, and focus of the Utstein-style guidelines on the pre-hospital setting, aetiology is typically derived from assessment by EMS and reported as presumed cardiac and obvious non-cardiac (or not at all). However, the published manuscript presented in **Chapter Four** found that only 53% of women and 75% of men with a pre-hospital presumed cardiac diagnosis were confirmed as cardiac after in-hospital or autopsy investigations.[22] This lack of accuracy is concerning, not only because it has significant impact on the outcomes of both observational and effectiveness studies, but also because it has resulted in under-reporting of non-cardiac aetiology in the literature. Patient and arrest factors associated with adjudicated aetiology have not been reported across the spectrums of aetiology in a resuscitated OHCA population.

8.3 Manuscript, Paper Six

The following short paper, "Aetiology of out-of-hospital cardiac arrest treated at hospital" was published in *Resuscitation* in 2021.[25]

Statement of Authorship

Title of Paper	Aetiology of resuscitated out-of-hospital cardiac arrest treated at hospital
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Melanie Wittwer		
Contribution to the Paper	Conception and design of the project; data acquisition; analysis and interpretation of data; drafting, revision, and finalisation of manuscript; corresponding author.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21/03/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conception and design of the project; contribution of knowledge; critical revision; supervision		
Signature		Date	21/03/2022

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Short paper

Aetiology of resuscitated out-of-hospital cardiac arrest treated at hospital

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Abstract

Introduction: Precipitating aetiology of out-of-hospital cardiac arrest (OHCA), as confirmed by diagnostic testing or autopsy, provides important insights into burden of OHCA and has potential implications for improving OHCA survivorship. This study aimed to describe the aetiology of non-traumatic resuscitated OHCAs treated at hospital within a local health network according to available documentation, and to investigate dierences in outcome between aetiologies.

Methods: Observational retrospective cohort study of consecutive OHCA treated at hospital within a local health network between 2011–2016. Cases without sustained ROSC (≥20 minutes), unverified cardiac arrest, and retrievals to external acute care facilities were excluded. A single aetiology was determined from the hospital medical record and available autopsy results. Survival to hospital discharge was compared between adjudicated aetiologies.

Results: In the 314 included cases, distribution of precipitating aetiology was 53% cardiac, 18% respiratory, 3% neurological, 6% toxicological, 9% other, and 11% unknown. A presumed cardiac pre-hospital diagnosis was assigned in 235 (84%) cases, 20% of which were incorrect after exclusion of unknown cases. Rates of survival to hospital discharge varied significantly across aetiologies: cardiac 64%, respiratory 21%, neurological 0%, toxicological 58%, other 32% ($p < 0.001$). A two-fold dierence in survival was observed between cardiac and non-cardiac aetiologies (64% versus 29%, excluding unknown, $p < 0.001$).

Conclusions: Non-cardiac aetiologies represented a substantial burden of resuscitated OHCA treated at hospital within a local health network and were associated with poor outcome. The results confirmed that true aetiology was not evident on initial examination in 1 in 5 cases with a pre-hospital cardiac diagnosis.

Keywords: Out-of-hospital cardiac arrest, Aetiology, Outcome

Introduction

In Australia there are over 26,600 out-of-hospital cardiac arrests (OHCA) each year and although survival rates are improving, in-hospital mortality remains high.[1,2] A key to improving survival in successfully resuscitated patients is rapid identification and reversal of any ongoing precipitating pathophysiology. Aetiology is typically reported in the literature as presumed cardiac and obvious non-cardiac, or medical and non-medical, based on prehospital assessment by emergency medical services (EMS).[3,4] However, in the absence of obvious causes such as trauma, homicide, suicide, or obvious drug overdose, EMS-based assessments only represent preliminary diagnoses that may not reflect true aetiology. An autopsy study of presumed cardiac OHCAs aged < 40 years confirmed a non-cardiac diagnosis in 39% of cases,[5] which highlights the importance of autopsy or further in-hospital investigations for the determination of aetiology. Population-based autopsy studies suggest that 40% of sudden cardiac deaths (SCD) are caused by non-cardiac aetiologies,[6,7] but few studies have reported on aetiology as confirmed by in-hospital investigations in the minority of OHCAs achieving sustained return of spontaneous circulation (ROSC).[8–10] In addition, information on frequency and outcome after non-cardiac OHCAs is lacking because these cases are routinely excluded from many

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investigations due to low perceived survival and broad diagnostic heterogeneity. This study aimed to describe the characteristics and outcome of non-traumatic resuscitated OHCAs treated at hospital within a local health network according to precipitating aetiology.

Methods

Study design and setting

This is a retrospective observational cohort study of the Northern Adelaide Local Health Network (NALHN) OHCA registry, which includes all OHCAs age ≥ 18 years treated at either of the two public teaching hospitals within NALHN.[11] OHCA was defined as absence of signs of circulation requiring chest compressions or external defibrillation in individuals who did not occupy an emergency department (ED) or inpatient bed.[12] We identified all adult, non-traumatic OHCAs with sustained ROSC (≥20mins) treated at NALHN facilities between 2011–2016. Cases without sustained ROSC, bystander CPR with ROSC pre-EMS, retrieval to external acute facilities, and likely syncopal episodes were excluded. The local ethics committee approved the registry and subsequent analyses as an ongoing quality improvement activity [Q20170304].

Aetiology classification

NALHN hospitals follow the Australian Resuscitation Council resuscitation guidelines,[13] which focus on rapid identification and treatment of precipitating aetiology. Investigations are guided by patient history and examination and are performed according to discretion of the treating physician. Investigations in cases without obvious cause may include emergency coronary angiography, computed tomography (CT) of brain, chest (including pulmonary angiography), abdomen and/or pelvis, pathology, echocardiography, repeat electrocardiograms, and toxicological screening. Additional cardiac tests include cardiac magnetic resonance imaging (MRI), electrophysiological tests, Holter monitor, provocative tests with flecainide and adrenaline, and genetic testing.

The single clearly documented or most likely aetiology according to the hospital medical record and available autopsy results was recorded in the NALHN OHCA registry by a single investigator and extracted for this analysis. In cases where more than one aetiology was likely the case was adjudicated by a senior expert and either a single aetiology was selected, or the aetiology was designated as 'unknown'. Six primary categories and nine sub-categories were defined:

1. Cardiac – acute myocardial infarction (AMI);[14] chronic or previous ischaemia without evidence of AMI; non-ischaemic structural heart disease; primary arrhythmia.
2. Respiratory – primary respiratory failure; hanging; other: e.g., choking, asthma, drowning.
3. Neurological – subarachnoid haemorrhage (SAH), intracranial haemorrhage (ICH), ischaemic stroke, and other e.g., seizure.
4. Toxicological – deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol.
5. Other – metabolic derangement; pulmonary embolism; other: e.g. anaphylaxis, hypovolemia, sepsis.
6. Unknown.

Data variables

Outcome measures and clinical covariates were analysed according to aetiology. The primary outcome was survival to hospital discharge. Secondary outcomes included survival with good neurological recovery (cerebral performance category 1–2) and survival at 12 months.

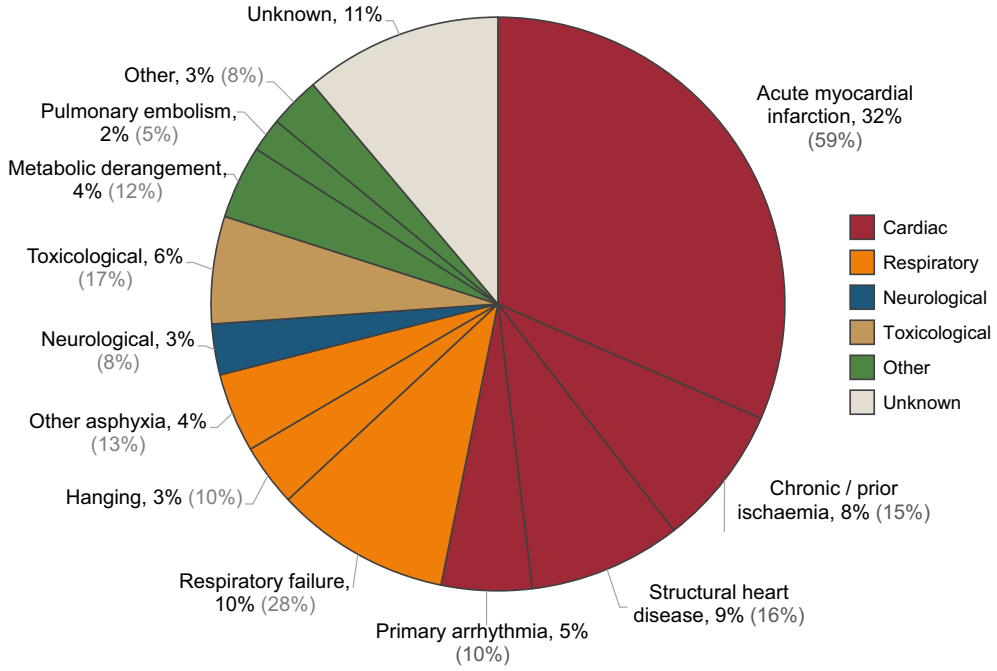

Fig. 1 – Adjudicated aetiology of consecutive non-traumatic resuscitated OHCA treated at hospital within a local health network, n = 314. Percentage values in black reflect % of total cohort (n = 314); percentage values in grey reflect % of cardiac aetiology (n = 167) and % of non-cardiac aetiology (excludes unknown; n = 112), respectively.

Table 1 – Characteristics of resuscitated non-traumatic out-of-hospital cardiac arrests treated at hospital according to adjudicated aetiology, n = 314.

	Cardiac n = 167	Respiratory n = 56	Neurological n = 9	Toxicological n = 19	Other n = 28	Unknown n = 35	p-value*	Non-cardiac† n = 112	p-value‡
Age	61 [53–74]	59 [41–73]	73 [61–74]	39 [29–43]	63 [54–72]	65 [50–81]	<0.001	59 [39–72]	<0.001
Male	120 (72%)	35 (63%)	7 (78%)	13 (68%)	16 (57%)	20 (57%)	0.347	71 (63%)	0.149
Arrest at private location	93 (56%)	45 (80%)	8 (89%)	17 (89%)	23 (82%)	23 (66%)	<0.001	93 (83%)	<0.001
Witnessed status									
Bystander witnessed	100 (60%)	22 (39%)	3 (33%)	5 (26%)	15 (54%)	15 (43%)	<0.01	45 (40%)	<0.001
EMS-witnessed	37 (22%)	11 (20%)	3 (33%)	2 (11%)	9 (32%)	4 (11%)	0.270	25 (22%)	>0.999
Unwitnessed	30 (18%)	23 (41%)	3 (33%)	12 (63%)	4 (14%)	16 (46%)	<0.001	42 (38%)	<0.001
Bystander CPR	101/130 (78%)	29/45 (64%)	3/6 (50%)	12/17 (71%)	14/19 (74%)	16/31 (52%)	0.051	58/87 (67%)	0.086
Initial rhythm									
VF/VT	140 (84%)	1 (2%)	2 (22%)	1 (5%)	7 (25%)	10 (29%)	<0.001	11 (10%)	<0.001
PEA	12 (7%)	28 (50%)	2 (22%)	10 (53%)	8 (29%)	13 (37%)	<0.001	48 (45%)	<0.001
Asystole	14 (8%)	24 (43%)	4 (44%)	8 (42%)	11 (39%)	12 (34%)	<0.001	47 (44%)	<0.001
Unknown	1 (1%)	3 (5%)	1 (11%)	0 (0%)	2 (7%)	0 (0%)	n/a	n/a	
Non-shockable initial rhythm to shockable	2/26 (8%)	6/ (12%)	0/7 (0%)	2/18 (11%)	2/20 (10%)	4/25 (16%)	0.948	10/99 (10%)	>0.999
Defibrillation	142 (85%)	7 (13%)	2 (22%)	3 (16%)	10 (36%)	14 (40%)	<0.001	22 (20%)	<0.001
Arrival mode: EMS vs. private vehicle	157 (94%)	54 (96%)	9 (100%)	19 (100%)	27 (96%)	32 (91%)	0.863	109 (97%)	0.254
Pre-hospital presumed cardiac diagnosis	166 (99%)	17 (30%)	4 (44%)	3 (16%)	17 (61%)	28 (80%)	<0.001	41 (37%)	<0.001
GCS 3 on arrival to emergency department	101/165 (61%)	44 (80%)	9 (100%)	15 (79%)	22 (79%)	34 (97%)	<0.001	90 (81%)	<0.001
Arrest to ROSC (minutes)	22 [13–34] (n = 161)	26 [14–35]	23 [15–40]	19 [17–33]	32 [12–47]	27 [21–33]	0.442	26 [14–39]	0.240
Post-ROSC ST-elevation	67/162 (41%)	5/48 (10%)	0/7 (0%)	1/18 (6%)	1/27 (4%)	4/30 (13%)	<0.001	7 (7%)	<0.001
Elevated Troponin T	156/164 (96%)	31/39 (79%)	6/8 (75%)	9/13 (69%)	19/23 (83%)	24/26 (92%)	<0.001	65/83 (78%)	<0.001
Elevated Creatinine Kinase	111/145 (77%)	12/32 (38%)	2/4 (50%)	10/10 (100%)	12/17 (71%)	13/19 (68%)	<0.001	36/63 (57%)	<0.01
Temperature management	88/167 (53%)	22 (39%)	2 (22%)	5 (26%)	7 (25%)	13 (37%)	0.013	36 (32%)	<0.001
Coronary angiography	129 (77%)	3 (5%)	1 (11%)	2 (11%)	8 (29%)	12 (34%)	<0.001	14 (13%)	<0.001
Intensive care unit length of stay	3 [2–4] (n = 125)	3 [2–4] (n = 48)	2 [2–3] (n = 7)	3 [2–5] (n = 15)	3 [1–4] (n = 24)	4 [3–5] (n = 23)	0.090	3 [2–4] (n = 94)	0.360
Survived to hospital discharge	107 (64%)	12 (21%)	0 (0%)	11 (58%)	9 (32%)	5 (14%)	<0.001	32 (29%)	<0.001
CPC 1–2 at hospital discharge	105 (63%	12 (21%)	0 (0%)	11 (58%)	9 (32%)	5 (14%)	<0.001	32 (29%)	<0.001
Survival at 12 months	105 (63%)	11 (20%)	0 (0%)	10 (53%)	8 (29%)	5 (14%)	<0.001	29 (26%)	<0.001

Data presented as number (percentage) and median [interquartile range]. CPC, cerebral performance category score of 1–2 indicates good neurological recovery; CPR, cardiopulmonary resuscitation; GCS, Glasgow coma scale; EMS, emergency medical services; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VT, ventricular tachycardia; VF, ventricular fibrillation.

* p-value comparing across all categories.

† Excludes cases with unknown aetiology.

‡ p-value comparing cardiac with non-cardiac, excluding unknown cases.

Covariates included patient demographics, arrest characteristics, and hospital management.

Statistical analysis

Continuous data is presented as median ± interquartile range and categorical data is presented as frequency and percentage. Comparisons between groups were made using Mann-Whitney U test and Kruskal-Wallis test for continuous data, and Fisher's exact test and Fisher-Freeman-Halton exact test for categorical data. Analyses were performed using SPSS 26 (IBM SPSS Statistics, Armonk, NY, USA).

Results

From 2011-2016, 393 OHCAs were treated at a NALHN hospital. After excluding 42 without sustained ROSC, 22 with ROSC pre-EMS arrival, 11 retrieved to an external acute care facility, and 4 likely syncopal events, 314 were included in the final analysis.

Fig. 1 depicts the distribution of precipitating aetiology, identified as cardiac in 53% of cases (60% of cases with known aetiology), 18% respiratory, 3% neurological, 6% toxicological, 9% other, and 11% unknown. Within sub-categories, 59% of cardiac-related OHCA were due to AMI, while 51% of non-cardiac aetiologies were respiratory (Fig. 1).

Many demographic, in-hospital management, and outcome variables differed according to primary aetiology categories (Table 1). A presumed cardiac pre-hospital diagnosis was assigned in 235 (84%) cases, 20% of which were incorrect after exclusion of cases with unknown aetiology (Table 1). Survival rates according to aetiology sub-categories ranged from 0% hanging and neurological catastrophe, to 68% for AMI (Fig. 2). No statistical analyses were performed according to aetiology sub-category due to the large number of categories and low n-values.

A sub-analysis in Table 1 compared the characteristics of patients with non-cardiac and cardiac aetiologies, excluding cases with unknown aetiology. Non-cardiac aetiology was associated with younger age, lower rates of known predictors of survival, and lower rates of all survival outcomes.

Discussion

This is the first study to explore characteristics and outcome of resuscitated non-traumatic OHCA treated at hospital according to precipitating aetiology. Retrospective analysis of the medical record and autopsy results confirmed that 40% of cases with known aetiology were of non-cardiac origin, the most common being respiratory and toxicological. Survival to hospital discharge was highest for cardiac aetiologies and varied from 0 to 58% for non-cardiac aetiologies.

Cardiac causes of OHCA and sudden cardiac death (SCD) are well-described in the literature, but few studies have described the burden and outcomes of non-cardiac OHCA. Our results are consistent with reports of adjudicated aetiology in both population-based autopsy cohorts and hospitalised cohorts that found 40–60% of included cases were of non-cardiac origin.[6–10] After taking into consideration the differences in inclusion criteria, these studies suggest that the true burden of non-cardiac OHCA with attempted resuscitation lies up to 50–60% and may be increasing.[2] In support of this premise, we also found that a pre-hospital presumed cardiac diagnosis, commonly used as a surrogate to estimate incidence and outcome of cardiac-related OHCA and SCD, was incorrect in 20% of cases. These findings have important implications for early prevention, recognition, and treatment of non-cardiac OHCA in a setting that has primarily targeted cardiac aetiologies such as AMI and heart failure.[15–17]

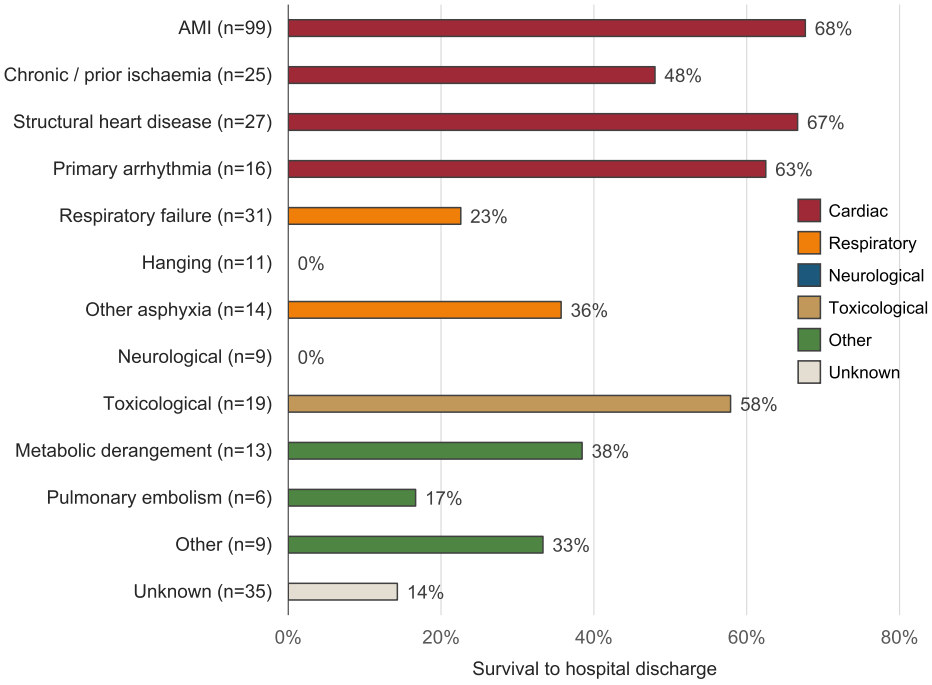

Fig. 2 – Rates of survival to hospital discharge after non-traumatic resuscitated OHCA treated at hospital according to precipitating aetiology.

Our study revealed a broad distribution of precipitating aetiologies. Consistent with previous reports,[8,9] we found that 59% of cardiac-related OHCA were due to AMI and only a small number were due to a primary arrhythmia. Overall, respiratory causes accounted for half of all non-cardiac aetiologies, which is higher than other studies.[6,9,10,18,19] There are no standardised criteria for determining precipitating aetiology, which limits comparisons between studies especially in non-cardiac cases and cases with multiple potential causes.

Survival to hospital discharge varied significantly according to primary and sub-categories of aetiology. A cardiac aetiology was associated with high rates of survival predictors such as VF/VT and coronary angiography, and unsurprisingly, the best survival outcomes. None of the small number of cases with OHCA due to hanging or neurological aetiologies survived to hospital discharge, which is consistent with previous findings.[18,20]. Survival after other respiratory causes such as respiratory failure, choking, and asthma was also low, reflecting the impact of prolonged anoxia on neurological outcome.[21,22]

Limitations

This study provides an overview of broad categories of precipitating aetiology within a local health network but is limited in interpretation and applicability due to the retrospective design. The data is $\geq$ 5 years old and rates of non-cardiac aetiology may have increased in more recent years.[2] Aetiology categorisation was dependent on (a) diagnostic tests performed at the discretion of the treating clinician, (b) accuracy of the medical record, (c) availability of autopsy results, and (d) interpretation by a single investigator with adjudication by a senior expert for complex cases. Every effort was made to determine the single most likely precipitating aetiology, but this may have been subjective in cases where multiple aetiologies were contributory. Traumatic arrests were excluded as they are generally retrieved directly to an external acute care facility for management. Nonetheless, this in-depth analysis of aetiology provides valuable insights into factors influencing survivorship within a hospitalised OHCA population.

Conclusion

Our study highlights the diversity of precipitating aetiology in patients with non-traumatic resuscitated OHCA treated at hospital within a local health network. Adjudicated non-cardiac aetiologies were predominately of respiratory origin, represented 40% of the cohort, and were associated with poorer outcome compared with cardiac-related OHCA. EMS-based diagnoses underestimated the burden of non-cardiac OHCA. Our results emphasise the importance of standardised criteria for determining precipitating aetiology according to autopsy or in-hospital investigations to drive optimal post-resuscitation research and care.

CRediT authorship contribution statement

M.R. Wittwer: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **C. Zeitz:** Supervision, Writing – review & editing. **J.F. Beltrame:** Supervision, Writing – review & editing. **M.A. Arstall:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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8.4 Summary of Chapter Eight

The findings presented in this final results chapter represent an overall characterisation of patients included in the NALHN OHCA registry according to precipitating aetiology. Patient and arrest factors, markers of cardiac ischaemia, management strategies, and outcomes differed significantly across broad aetiological categories. The results confirmed that non-cardiac aetiologies, such as asphyxia, drug overdose, and stroke etc., represent up to 40% of the population of OHCA with sustained ROSC treated at hospital. Overall, non-cardiac aetiologies were associated with poor outcome when compared to cardiac aetiologies such as AMI and primary arrhythmia. Importantly, 37% of the cohort with an adjudicated non-cardiac aetiology initially presented with a presumed cardiac diagnosis. These findings have important implications for the prevention, recognition, and management of non-cardiac OHCA in a setting that has primarily targeted cardiac aetiologies such as AMI and heart failure.[56,288,289]

CHAPTER NINE: DISCUSSION AND CONCLUSIONS

9.1 Overview of Chapter Nine

This chapter provides a summary and discussion of the main findings of this thesis. Following this, the strengths and limitations are discussed. Finally, implications for translation into clinical practice are presented and future directions outlined.

9.2 Introduction

The overarching aim of this program of doctoral research was to develop a hospital based OHCA registry to determine incidence, management, and outcome of OHCA within the Northern Adelaide Local Health Network. Specifically, the knowledge gaps around in-hospital management, in-hospital death, and contributing factors, including adjudicated aetiology, were addressed, and data was disaggregated according to sex to account for biological and sociocultural differences between men and women.

This program of doctoral work started by addressing the challenges of establishing a hospital based OHCA registry. The registry was then used to investigate the incidence and outcome of OHCA within NALHN and explore important in-hospital factors associated with OHCA survivorship. From these analyses, key strategies were identified to improve current practice and important suggestions were made regarding future research.

9.3 Overview of key findings

The five key objectives were addressed as follows:

1. Establish a hospital based OHCA registry and test methods for case identification.

The NALHN OHCA registry was developed by expanding the code STEMI OHCA registry to include all OHCA patients treated at NALHN hospitals. Once the registry was initially established, it was further developed in accordance with the clinical outcome feedback loop (**Chapter 2.6.1**). As presented in **Chapter Three**, systematic changes were made to ensure ongoing sustainability and capacity for expansion into a CQR with adoption at other South Australian hospitals.

Firstly, a simple, consistent, and clinically based definition of IHCA and OHCA was developed to overcome inconsistencies observed between existing registries and between clinicians. OHCA was therefore defined as *absence of signs of circulation requiring CPR and/or defibrillation in individuals who do not occupy an ED or inpatient hospital bed*.

Secondly, the accuracy of each data source at identifying confirmed OHCA cases was investigated. The study presented in **Chapter Three** found that commonly used ICD-10 codes (e.g., 'cardiac arrest' and 'ventricular fibrillation') assigned to billable hospital in-patient encounters had a low positive predictive value for OHCA cases. Instead, a combination of codes assigned to ED encounters and key-word search of two existing clinical registries was found to be the most efficient method with acceptable accuracy for identifying OHCA cases.

Thirdly, a comprehensive data dictionary was developed and refined throughout this program of doctoral research (**Appendix B**). Specifically, the definition and categorisation of mode of death underwent significant revisions in consultation with ICU collaborators based on recent publications and preprints.[159–161] Similarly, the categories of aetiology were developed from the rather basic categories reported in the published manuscript in **Chapter Seven**[25] to more well-defined and clinically relevant categories based on recent publications.[4,108,165,168]

Finally, the method of data collection was refined to include data linkages with existing clinical registries to increase efficiency by minimising the amount of data to be manually abstracted from the medical record. This process of continued developing and refining the NALHN OHCA registry provides a strong foundation for improving OHCA survivorship within NALHN, and ultimately, across South Australia.

2. Determine incidence of OHCA within NALHN and explore reasons for sex-differences in incidence and outcome.

The published manuscript presented in **Chapter Four** provides the first report of OHCA incidence within NALHN. The age-standardised rates of EMS-attended and EMS-treated OHCA were 139.9 and 54.6 per 100,000 population, respectively. Incidence in women was half that of men across populations with an attenuation only observed in the obvious non-cardiac cohort. Overall, the lower survival rate observed for women was driven by a lower prevalence of shockable initial rhythm. Even though such findings have been addressed in

several larger cohorts, it was important to confirm whether such sex differences in incidence and outcome were also prevalent within NALHN.

The reasons for the observed sex differences in incidence and outcome of OHCA are multifactorial, but the picture emerging from this doctoral work, and confirmed by existing literature, is that:

1 The decreased incidence of OHCA in women is because they are biologically less susceptible to cardiac arrhythmias.[244–246]
2 Most reports suggest that compared with men, women who do arrest are more likely to do so for non-cardiac reasons e.g. respiratory and neurological.[4,8,108,167,176,178,240] However, this difference was not observed in the published manuscript presented in **Chapter Eight** that investigated adjudicated aetiology in a hospitalised cohort.[25]
3 It is likely that the rates of initial shockable/non-shockable rhythm are similar for both men and women with a non-cardiac OHCA.[22] Overall, non-cardiac aetiologies are associated with high rates of non-shockable initial rhythm (PEA and asystole) compared with cardiac aetiologies.[176,290]
4 Women with a non-cardiac OHCA have similarly low survival rates as men,[22,225,291] likely because their rates of shockable/non-shockable initial rhythm are similar.
5 Conversely, women with an adjudicated cardiac OHCA are less likely to present with an initial shockable rhythm,[193,222,290] and therefore are less likely to survive overall.
6 Women with an adjudicated cardiac OHCA and initial shockable rhythm/non-shockable rhythm, are just as likely to survive to hospital discharge compared to men with the same initial rhythm.[222]

These findings are summarised in **Figure 9-1**.

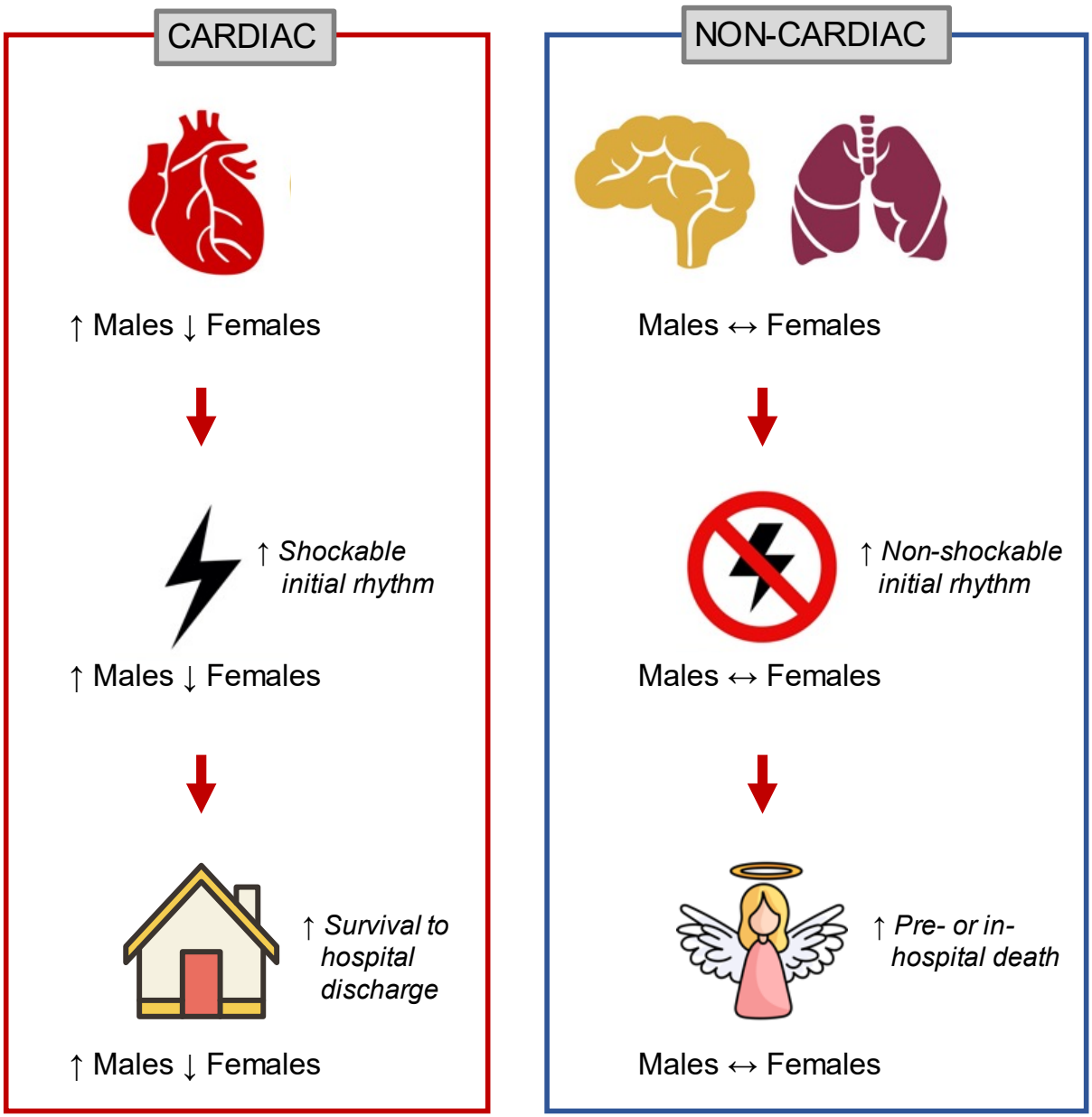

Figure 9-1: Sex differences in outcome of OHCA according to precipitating aetiology.

3. Evaluate in-hospital cardiac management of OHCA within NALHN.

Emergency coronary angiography with revascularisation of an acutely occluded coronary artery has been an essential management strategy for patients with suspected cardiac OHCA for the last three decades. However, as discussed in **Chapter 2.2**, the timing and benefit of emergency coronary angiography continues to be the subject of debate because of the time-critical nature of OHCA, clinical complexity, and high mortality. The investigations presented in **Chapters Five** and **Six** were undertaken to determine the accuracy of clinician gestalt and a clinical score at ruling in or out emergency coronary angiography in patients

requiring acute revascularisation. Overall, both experienced interventional cardiologists and the Zeyons Score appropriately ruled out, and somewhat effectively ruled in, emergency coronary angiography in patients with presumed cardiac OHCA. There were discrepancies observed within each study, particularly with respect to precipitating aetiology where clinicians had the greatest difficulty diagnosing and predicting the benefit of emergency coronary angiography in patients with OHCA of non-ischaemic cardiac origin. These studies were important because they confirmed the complexity of OHCA management and explored challenges associated with predicting benefit of coronary angiography.

4. Explore hospital outcomes of timing, location, and mode of death.

The published manuscript presented in **Chapter Seven** is the first study internationally to assess patient characteristics associated with modes of death in an adult OHCA cohort treated both within the ED and as inpatients. The median time to death in ED was 1.5 hours and the leading mode of was cardiovascular instability. In contrast, median time to death was 57 hours for admitted patients with 71% of deaths due to neurological WLST and brain death, combined. Mode of death was significantly associated with age, timing of death, and precipitating aetiology, but not sex. Since mode of death is emerging as an important clinical endpoint for effectiveness studies in cardiac arrest, this report provides a useful baseline to inform future research. As such, the importance of developing standard definitions and categorisations of mode of death to allow comparisons between studies was also highlighted.

5. Explore hospital outcomes according to precipitating aetiology.

The published short paper presented in **Chapter Eight** is the first to explore patient characteristics and outcomes according to adjudicated precipitating aetiology in an Australian cohort. The code STEMI OHCA registry originally defined 18 different aetiologies, which were re-coded into six primary categories: cardiac, respiratory, neurological, toxicological, other, and unknown, as suggested by Dr J. Elmer, MD (email communication, February 2020), and nine sub-categories. Adjudicated non-cardiac aetiologies represented 40% of the hospitalised NALHN OHCA cohort and a two-fold difference in survival was observed when compared with cardiac aetiologies. Consistent with the only two other similar reports,[108,168] these results highlighted the heterogeneity of patient characteristics and outcomes across

aetiologies and emphasised the importance of disaggregation of data according to aetiology as confirmed by autopsy or in-hospital investigations. Importantly, this short paper characterised the entire NALHN OHCA registry cohort, thus forming the foundation for assessing the effect of changes to clinical practice and informing future research.

9.3.1 SUMMARY – KEY FINDINGS

- ICD-10 codes assigned to billable hospital in-patient encounters have a low positive predictive value for identification of OHCA cases.
- OHCA-related codes assigned to ED encounters, both alone and in combination with existing clinical registries and EMS-based sources, provide a valid and efficient method of identifying consecutive OHCA cases treated at hospital.
- Sex differences in incidence and outcome of OHCA are driven by differences in aetiology, rather than treatment delays or disparities.
- Emergency coronary angiography for resuscitated presumed cardiac OHCA was appropriately ruled out, and somewhat effectively ruled in, by both experienced interventional cardiologists and a clinical score.
- The leading mode of death in the ED was cardiovascular instability, while in admitted patients it was neurological injury (neurological WLST and brain death combined).
- Mode of death in the ED and after admission was significantly associated with age, timing of death, and precipitating aetiology, but not sex.
- Non-cardiac aetiologies represented 40% of the NALHN OHCA cohort and were associated with poor outcome.
- A pre-hospital ‘presumed cardiac’ diagnosis was incorrect in 1 out of 5 OHCA patients surviving to hospital admission within NALHN.

9.4 Strengths and limitations

This section discusses the strengths and limitations of this doctoral work overall.

This research had several strengths. The strengths of each individual study have already been covered in the associated chapters and will not be readdressed in this section. Firstly, the key strength of this research is that the NALHN OHCA registry is, as far as can be determined, the only Australian hospital based OHCA registry of consecutive OHCAs, irrespective of presumed or confirmed aetiology. As a result, Australian data for in-hospital management and outcome of this population has been made publicly available for the first time. Secondly, this research was based on a clinically relevant definition of OHCA that includes patients transported to hospital by private vehicle. Thirdly, the design of the registry, with linkages to both EMS-based data and existing in-hospital clinical registries, has allowed in-depth analysis of patient-level factors contributing to outcome. Specifically, this research has promoted the importance of (1) reporting outcomes according to adjudicated aetiology, and (2) including mode of death as an outcome for both observational and effectiveness studies. Finally, this doctoral work provides a firm foundation for establishing a state-wide registry as well as useful information for informing hospital-based data collection in an Australian context.

This research must be interpreted in the light of several limitations that have already been outlined in each of the published works. They are presented briefly here for reference: (a) the retrospective design may be subject to inherent bias, (b) the data presented is dependent on the accuracy, availability, and interpretation of documentation within the medical record, (c) changes in practice may have occurred over the last > 5 years, and (d) findings are specific to NALHN and may not be readily generalisable to other settings.

9.5 Implications of findings and recommendations for future research

The key findings of this research led to the identification of several implications for the translation of this research into clinical practice as well as recommendations for future research. This section presents the implications for practice and future research.

9.5.1 Future directions of the NALHN OHCA registry

The need for a state-wide data on the in-hospital management and long-term outcome of OHCA patients has been increasingly recognised. For this reason, the NALHN OHCA registry was developed with the end-goal of expansion into a state-wide CQR. Further refinement of the registry is required to achieve this goal, but this program of doctoral work has highlighted the importance of the following elements:

1. A clear, consistent, and clinically based definition of IHCA and OHCA is essential to developing a registry that provides meaningful information for treating clinicians and other key stakeholders.
2. Complete case capture requires, at a minimum, identification of cases from SAAS-CAR and a combination of codes assigned to ED encounters to ensure that non-EMS attended OHCAs are included.
3. Most core OHCA data elements may be obtained from SAAS-CAR and the two other state-based clinical registries, CADOSA and ANZICS-APD, without the need for manual medical record abstraction.

The importance of relevant and comprehensive characterisation of OHCA patients across South Australia, with data covering all aspects of the patient journey from arrest to long-term recovery, cannot be underestimated. Such data will allow accurate reporting of incidence statistics used to assess burden of illness and healthcare system performance and will also facilitate the identification of strategies to improve overall survivorship.

9.5.2 Identifying non-EMS attended OHCAs

Although the definition of OHCA developed as part of this program of doctoral work may not be relevant to registries that are solely EMS-based, it is highly relevant for population- and hospital-based registries that include patients not attended by EMS, such as PAROS.[292] Non-admitted persons represent 1% of the reported IHCA population[293–296] and it is likely that non-EMS attended OHCAs likely represent a similar proportion, but these patients remain underreported in the literature. The published manuscript presented in **Chapter Three** found that non-EMS attended OHCAs represented 6% of all OHCAs treated at hospital, and 4% arrived by private vehicle.[21] The number of OHCAs presenting to hospital by private vehicle rather than ambulance has not been reported previously in Australia and represents a preventable public health issue that requires further investigation.

9.5.3 Effect of socioeconomic status within NALHN

Socioeconomic disadvantage in Australia is associated with higher rates of health risk factors, chronic conditions, and premature death.[297] OHCA incidence is also higher in individuals and areas characterised by low SES compared to those with higher SES, respectively.[30,190,280,298] The incidence of EMS-attended OHCA within NALHN was notably higher than state and national averages (98.8 versus 139.9 EMS-attended OHCA per 100,000 person-years across Australia and NALHN, respectively).[22,26,27,189] However, unlike other reports of lower survival in low SES areas from international cohorts,[207,208] the survival rates within NALHN were comparable with other rates reported across Australia[22,26,27]. A more comprehensive investigation into the effect of SES on short- and long-term survival after OHCA, with aggregation according to sex, in a large Australian population is required to explore this further. To date, there have been no studies systematically investigating the effect of SES on OHCA outcomes in Australia.

The findings presented within **Chapter Four** and **Eight** are important because they can be used to advocate for the implementation of strategies specific to NALHN. Despite a high incidence, the system of care in place during the study period was effective at achieving survival rates comparable with Australian averages. Population-based strategies to reduce the high incidence of OHCA in NALHN may therefore include:

- Increasing uptake of interventions aimed at reducing the prevalence of chronic disease and the burden of risk factors for OHCA, such as the Get Healthy information and coaching service provided by Wellbeing SA (www.gethealthy.sa.gov.au),
- Funding education campaigns to increase the recognition of OHCA symptoms,
- Facilitating programs to enhance CPR training in schools and workplaces or other community engagement opportunities to increase the rates of bystander CPR.

Trends over time analyses of OHCA outcomes would provide important insight on the success of such strategies.

9.5.4 Cardiac management of OHCA

In the time from when this program of doctoral work was commenced there has been a significant increase in the literature investigating the post-OHCA benefit of emergency coronary angiography with or without revascularisation. Several reviews and an American

Heart Association scientific statement explore this issue thoroughly.[69,71–74] The investigations presented in **Chapters Five** and **Six** found that both the clinical gestalt of experienced cardiologists and the Zeyons Score were quite accurate at ruling out emergency coronary angiography in this population. However, there were important limitations to these findings and neither met the clinically acceptable 'miss' rates of ≤1%.[121,299] The published manuscript presented in **Chapter Eight** confirmed the complexities associated with selecting patients for emergency coronary angiography. Of patients with an adjudicated non-cardiac aetiology, 7% had evidence of STE (not including aVR in this analysis) and 78% had troponin elevated 99th centile.[25] A protocol that facilitates both clinical gestalt and clinical predictors was therefore developed with the aim of standardising care within and across SA hospitals (**Appendix F**).This protocol is currently under review by senior interventional cardiologists and departmental directors and will be developed according to the clinical feedback loop.

The debate over the timing and benefit of emergency coronary angiography, particularly in comatose patients presenting with initial non-shockable rhythms and absence of post-ROSC STE, continues. Future research in this area will focus on refining the selection criteria to identify OHCA patients who will benefit the most from a strategy of emergency coronary angiography.

9.5.5 Importance of adjudicated aetiology

A major strength of the NALHN OHCA registry is its capacity for performing analyses according to adjudicated aetiology, rather than presumed aetiology documented by EMS in the pre-hospital setting. A presumed cardiac diagnosis was found to be incorrect in up to 20% of admitted patients with an available adjudicated aetiology and may therefore represent a confounding factor in both outcome and effectiveness studies.[25] To date, there are some heterogenous recommendations but no standardised definitions or criteria for categorising precipitating aetiology across the whole spectrum of cardiac and non-cardiac (or medial and non-medical) causes (**Table 2-4**).[4,13,108,165,167,168] As a result of the current state of heterogeneity it is difficult to make valid comparisons between studies, which limits the applicability of important research findings. The categorisations defined in the NALHN OHCA registry provide a good foundation and future research should focus on developing and reporting on outcomes aggregated according to adjudicated aetiology where possible.

In the published manuscript presented in **Chapter Four** a presumed cardiac diagnosis was found to be incorrect in significantly more women than men (53% versus 75%, respectively).[22] To this day there remains ongoing debate about whether women have poorer outcomes after OHCA compared with men, and why. The reasons for differences in reported outcomes between sexes may be explained by differences in the outcome of interest, analysis of different sub-groups, and differences in multivariate adjustment.[193] The findings presented in this doctoral work further highlight that such discrepancies may also develop from using presumed rather than adjudicated aetiology.

Further, while it is established that there are sex and gender differences in risk factors, clinical factors, biology, psychosocial factors, and outcomes in the setting of cardiovascular disease with and without cardiac arrest, very little is known about patients with non-cardiac aetiologies in the setting of OHCA because they are routinely excluded from analyses.[184] On review of the literature, only two studies of EMS-attended OHCA from Japan were found to have reported outcomes according to sex, and this in obvious non-cardiac cohorts where the diagnosis was based on assessment by the treating physician and EMS personnel. There was no sex difference in 30-day survival or survival with good neurological outcome in one study restricted to patients with an initial shockable rhythm,[291] while the other study reported a small female advantage for 30-day survival (3.9% male versus 4.4% female) but not survival with good neurological outcome.[225] Unfortunately, the study presented in **Chapter Eight** of adjudicated aetiology in hospitalised patients was too small to perform a sub-analysis of outcome according to sex. Larger studies investigating outcomes disaggregated according to adjudicated aetiology and patient sex are required to ensure that the quality of care and appropriate allocation of resources are maintained for all OHCA patients, both within NALHN and more broadly.

9.5.6 Mode of death as an emerging clinical endpoint

Four key findings have emerged from the research into mode of death after OHCA that have the potential to change, or have already changed, clinical practice. Firstly, cardiovascular instability was found to be the primary mode of death within ED and almost two thirds of these patients had a potentially reversible precipitating cardiac aetiology. Extracorpeal cardiopulmonary resuscitation (ECPR) is a key mechanism to improve survival of such

patients but is not currently available within NALHN.[300,301] The results of this study demonstrate a clear need to advocate for ECPR capability within NALHN.

Secondly, early WLST (<72hrs), performed in 53% of admitted patients with WLST in this study, is now recognised as a contributor to increased mortality after OHCA in western countries and it has been estimated that up to 21% of patients with early WLST may have otherwise survived with good neurological functioning.[151,152] ANZCOR guidelines were updated in 2016 to recommend against neurological prognostication <72 hours, whereas earlier guidelines were less clear.[54,85] Although the majority of patients included in this analysis were deceased prior to the guideline update, the results nonetheless highlight the need for change in clinical practice. Overall, more than half of the deaths in this cohort were preceded by a withdrawal of treatment, which is similar to previous reports in an ICU population[302]. Limited Australian data has shown that 47-49% of all deaths in the ICU, regardless of reason for admission, were preceded by a withdrawal of treatment[303,304]. These rates are similar to those seen in Northern America and Europe, but much higher when compared to Asia and the Middle East, reflecting cultural differences in WLST practice[139]. A collaboration was established with ICU clinicians during this program of doctoral research which has facilitated increased awareness of WLST practice in OHCA patients and will likely lead to a prospective study investigating timing and reasons for WLST within NALHN/SA.

Thirdly, previous reports have found that women are more likely to have WLST, early WLST, and early DNR orders compared with men.[151,197,235,236] Considering that women are also less likely to present with OHCA precipitated by a cardiac aetiology, it was interesting that there were no sex differences observed in the timing, location, and mode of death. This may be because the published manuscript presented in **Chapter Eight** revealed that the distribution of adjudicated aetiologies were similar between men and women in this cohort.[25] Alternately, the results may confirm that there are no sex differences in the end-of-life discussions or provider-level disparities as observed both within and outside the OHCA setting.[41,43,237–239] Further work disaggregated according to sex in larger populations is required to confirm these findings.

Finally, collection of detailed mechanisms of death in cardiac arrest studies has been repeatedly advocated but is currently limited by a lack of consensus on definition and standardised classification of mode of death.[160,286,287] Although the Utstein-style guidelines

include *cause of death as officially recorded in the patient's medical records or death certificate* as a supplemental data item, such sources are more likely to reflect the underlying aetiology e.g., acute myocardial infarction rather than the mode of death.[13] The research presented in **Chapter Seven** highlights the challenges faced in retrospective determination of mode of death and supports the validation of proposed criteria in prospective cohorts.

9.5.7 Summary – implications and future research

- Development of the NALHN OHCA registry into a state-wide CQR.
- Investigation into OHCA patients presenting to hospital by private vehicle rather than by EMS.
- Population-based strategies to reduce the high incidence of OHCA in NALHN.
- Introduction of the cardiac management of OHCA protocol as part of the clinical feedback loop to improve OHCA survivorship.
- Advocate for ECPR capability within NALHN.
- Prospective study investigating timing and reasons for WLST.
- Further work disaggregated according to sex and adjudicated aetiology in larger populations.

9.6 Concluding remarks

The NALHN OHCA registry, the first of its type in Australia, was established and developed as part of an ongoing clinical feedback loop to improve OHCA survivorship within NALHN. The analyses of the registry presented in this doctoral work describe the current incidence, management, and outcome of OHCA within NALHN, and provide a strong foundation for ongoing research and quality improvement. Key gaps in knowledge about sex differences, aetiology, mode of death, and withdrawal of treatment were addressed, and several implications for the translation of this research into clinical practice as well as recommendations for future research were outlined. This research represents the first three stages of the clinical feedback loop, and it is hoped that this ongoing process of measurement, analysis, implementation, and refinement will improve OHCA survivorship within an Australian setting.

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APPENDICES

APPENDIX A – CHAPTER TWO SUPPLEMENTARY MATERIAL

Letter to Take Heart Australia

Government of South Australia
SA Health

A Campus of Northern Adelaide Local Health Network

Lyell McEwin Hospital

Haydown Road
Elizabeth Vale SA 5112

ABN 46 371 200 573

www.lmh.sa.gov.au

15th May 2017

Dear Associate Professor Middleton,

We would like to commend you on the Take Heart Australia initiative. There is much to be done in Australia to increase awareness about sudden cardiac arrest and we strongly support your endeavours to get CPR training into schools.

We notice that the Take Heart Australia website is the first hit for a google search of "cardiac arrest Australia", but that the section highlighting "Some Important Facts about Cardiac Arrest Survival" may be misleading for the public.

The quoted 9% survival rate in Australia looks rather bad compared with 62% in Seattle, but these figures are not comparing apples with apples.

In 2014, Seattle reported a survival rate of 62% for a specific subgroup of OHCA patients, that is, EMS-treated witnessed VF/VT arrest. For the same patient group, survival in Victoria in 2015/16 (Victorian Ambulance Cardiac Arrest Registry 2015-2016 Annual Report) was 35% compared to 46% in Seattle (2016 Annual Report to the King County Council).

Australia-wide figures will shortly be available through the AUS-ROC epistry. An abstract recently presented at the ARC Spark of Life conference found that 60% of bystander-witnessed cardiac arrests received bystander CPR.

As this page is the first place someone from the community is directed, we think it's important to provide an accurate reflection of current information.

The presence of Take Heart Australia on social media is really encouraging and we look forward to a time when >75% of Australians are trained in CPR.

Kind regards,

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APPENDIX B – CHAPTER THREE SUPPLEMENTARY MATERIAL

Letter to the Editor

NALHN OHCA Registry Data Dictionary

Statement of Authorship

Title of Paper	Providing a simple and consistent solution for the definition of in- versus out-of-hospital cardiac arrest
Publication Status	[X] Published [ ] Accepted for Publication [ ] Submitted for Publication [ ] Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Melanie Wittwer		
Contribution to the Paper	Developed concept in consultation with co-authors, drafted and prepared final manuscript for submission.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	7th November 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Chris Zeitz		
Contribution to the Paper	Concept development, critical evaluation, and final editing of manuscript.		
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Signature		Date	23/3/22

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Margaret A Arstall		
Contribution to the Paper	Supervision, critical evaluation, and final editing of manuscript		
Signature		Date	7th November 2021

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Letter to the Editor

Providing a simple and consistent solution for the definition of in- versus out-of-hospital cardiac arrest

To the Editor,

Accurate reporting of cardiac arrest incidence is essential to inform about the burden of illness and healthcare system performance. Based on epidemiological and clinical differences, cardiac arrest is further defined as in-hospital or out-of-hospital.[1,2] This distinction by location at first seems clear but there is significant variation in definition of numerator and denominator with significant impacts on cardiac arrest incidence and survival.

Out-of-hospital cardiac arrest (OHCA) is generally defined as resuscitation by an emergency medical service (EMS) and the denominator is the population served by the EMS[1] (Table 1). Effective data linkage between EMS and hospital systems is needed to ensure that non-EMS attended OHCAs transported to hospital by private vehicle are included in OHCA incidence reports.

In-hospital cardiac arrest (IHCA) was defined by the 1997 Utstein guidelines as 'all patients who occupy a hospital bed'.[3] The 2019 Utstein update,[2] as well as the 2013 American Heart Association (AHA) consensus,[4] additionally include arrests within a hospital facility in non-admitted persons such as outpatients (including emergency department (ED) arrests), employees, and visitors. However, both the 1997 Utstein guideline and 2013 AHA consensus, but not the 2019 Utstein guideline, exclude cardiac arrest in non-admitted persons from the numerator and denominator of IHCA incidence calculations because it is impossible to know the true number of non-admitted persons within a hospital facility to include in the denominator.

The distinction between IHCA and OHCA needs to be clear and exhaustive, such that patients excluded from one classification are included in the other. We therefore propose a simple definition:

IHCA: *Cardiac arrest in persons who occupy an ED or inpatient hospital bed*

OHCA: *Cardiac arrest in persons who do not occupy an ED or inpatient hospital bed*

Although arrests within a hospital facility in outpatients, employees and visitors have been previously defined as IHCA, we argue that they are better placed within the OHCA definition. The hospital setting may expedite resuscitation, similar to EMS-witnessed OHCA, but in essence an arrest in the hospital cafeteria or carpark is equivalent to an arrest outside the hospital. Conversely, admitted and ED patients are under expert medical care that aims to prevent cardiac arrest while providing immediate and timely resuscitation as required. ED arrests fit the categorisation of IHCA because they display similar clinical features to IHCA compared with OHCA, as recently demonstrated by Mikati et al.[5]

The inconsistency in the current definition and reporting of OHCA and IHCA makes benchmarking and research projects in these fields near impossible. Our definition is both a call to action and a simple solution for investigating differences in epidemiology, prevention, and treatment of IHCA and OHCA, and between registries.

Table 1 – Issues with current definition of cardiac arrest location for reporting incidence.

	Numerator	Denominator	Common data source	Issues
OHCA[1]	EMS-resuscitation	Population served by EMS	EMS database	Non-EMS attended OHCAs missed
IHCA[2–4]	Patients in a hospital bed +/– outpatients, employees, visitors	Admitted patients (includes day cases)	Hospital code database	Inconsistent definition Non-admitted patients under-reported

OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; EMS, emergency medical services.

Conflicts of interest

None.

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None.

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NALHN OHCA Registry Data Dictionary

Version 3, dated 6th August 2020

[C] and [S] indicate Utstein template core and supplementary data variables, respectively
*Variable added in 2017

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Branching Logic (Show field only if...)**
Patient number (patient_n)	None	[auto-fill]	
LMH MRN (lmh_ur) Indicate the MRN assigned to the patient by the Lyell McEwin Hospital, if applicable	None	XXXXXX	
Modbury MRN (mod_ur) Indicate the MRN assigned to the patient by Modbury Hospital, if applicable	None	XXXXXX	
Age (years) (age) **[C]** Indicate the patient's age on the date of arrest (calculated from date of birth)	None	XX	
Sex (sex) **[C]** Indicate the patient's sex at birth	None	1, Male | 2, Female	

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Ethnicity (ethnicity) Indicate the ethnicity as determined by the patient/family/medical record. If no ethnitiicy is specified in admission notes, enter 'Caucasian'. If the patient is of mixed race, select the most appropriate category	Caucasian: Having origins in Europe, the Middle East or North Africa for example, England, Ireland, Germany, Sweden, Italy, Greece, Russia, Egypt, Morocco, Sudan, Iran, Turkey etc. including Australians and North Americans (ABS Groups 1.1.01, 1.2.02, 2, 3, 4, 8.1.02, 8.1.03, 8.1.04) Aboriginal / Torres Strait Islander: A person identifying themselves as being of Aboriginal and/ or Torres Strait Islander origin (ABS groups 1.11.02, 1.1.03, 1.1.04, 1.1.05) Pacific Islander: Having origins in any of the original peoples of Hawaii, Guam, New Zealand, Samoa, or other Pacific Islands (ABS groups 1.2.01, 1.3, 1.4, 1.5) South-East Asian: Having origins in any of the original peoples of mainland or maritime South-East Asia for example, Burma, Cambodia, Vietnam, Indonesia, Singapore etc. (ABS group 5) North-East Asian: Having origins in any of the original peoples of China, Japan, Korea, Mongolia, and Tibet (ABS group 6) Southern and Central Asian: Having origins in any of the original peoples of Southern and Central Asia including India, Pakistan, Sri Lanka, Afghanistan, Turkmenistan etc. (ABS group 7) Native American: Having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment) for example, American Indian and Alaskan Native (ABS groups 8.1.06, 8.1.07, 8.2) Hispanic: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race (ABS groups 8.1.05, 8.3, 8.4) Sub-Saharan Africa: Having origins in any of the black racial groups of Africa (ABS groups 8.1.01, 9) *Source: Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG), 2019. [Appx 1].*	1, Caucasian | 2, Aboriginal / Torres Strait Islander | 3, Pacific Islander | 4, South-East Asian | 5, North-East Asian | 6, Southern and Central Asian | 7, Native American | 8, Hispanic | 9, Sub-Saharan Africa	
Postcode (home) (home_postcode) Indicate the Australian Postcode of the patient's primary residence If the patient does not have an Australian residence or is homeless, enter as '0000'	None	XXXX	

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Nursing home resident (nursing_home) Indicate whether the patient was a nursing home resident at the time of arrest	None	1, Yes | 2, No / unknown / not documented	
Independent Living (indep_living) **[S]** Indicate if the patient was able to perform all activities of daily living without the assistance of caregivers before the arrest	None	1, Yes | 2, No / unknown / not documented	
Coronary artery disease (hx_ihd) **[S]** Indicate if the patient has a history of AMI, angina, PCI or CABG	None	1, Yes | 2, No / unknown / not documented	
Cardiomyopathy (hx_cm) **[S]** Indicate if the patient has a history of cardiomyopathy	Cardiomyopathy is a disease of the heart muscle and refers to deterioration of the function of the myocardium, in which the heart muscle is abnormally enlarged, thickened, and/or stiffened. Types of cardiomyopathy include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia and Takotsubo cardiomyopathy etc. *Source: CADOSA full data specifications version 5.0*	1, Yes | 2, No / unknown / not documented	
Cardiomyopathy type* (hx_cm_type) **[S]** Indicate the type and cause of cardiomyopathy as documented in the medical record E.g. dilated cardiomyopathy caused by alcohol abuse	None	[free text]	[hx_cm] = '1'
Previous cardiac arrest* (hx_ca) [S] Indicate if the patient has a history of cardiac arrest	Cardiac arrest includes pulseless clinical scenarios that require cardiopulmonary resuscitation (requiring two or more chest compressions, or open heart massage) and/or requiring emergency defibrillation. *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Yes | 2, No / unknown / not documented	

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Year most recent arrest* (hx_ca_year) [S] Indicate the year that the patient most recently experienced a cardiac arrest	None	YYYY	[hx_ca] = '1'
Cardioverter-defibrillator (hx_cd) [**S]** Indicate if the patient had an internal or external cardioverter-defibrillator implanted prior to the current episode	None	1, Yes | 2, No / unknown / not documented	
Genetic Channelopathy* (hx_channel) **[S]** Indicate if the patient has ever been diagnosed with a genetic ion channelopathy	Genetic channelopathy is defined as a pre-existing diagnosis of Long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia (CPVT) and idiopathic ventricular fibrillation. *Source: Napolitano et al. Sudden cardiac death and genetic ion channelopathies. Circulation (2012) 125:2027–34.*	1, Yes | 2, No / unknown / not documented	
Genetic channelopathy type* (hx_channel_type) **[S]** Indicate the channelopathy sub-type	None	1, Long QT | 2, Brugada | 3, Short QT | 4, CPVT | 5, Idiopathic VF	[hx_channel] = '1'
Family history of heart disease (hx_famhx) **[S]** Indicate if the patient has a first-degree relative with a history of AMI, angina, sudden cardiac arrest or sudden cardiac death without obvious cause, PCI, CABG	None	1, Yes | 2, No / unknown / not documented	
Cerebrovascular disease* (hx_cerebrovascular) **[S]** Indicate if the patient has a history of cerebrovascular disease	Cerebrovascular Disease is defined as a current or previous history of: - Ischemic stroke: infarction of central nervous system tissue whether symptomatic or silent (asymptomatic). -TIA: transient episode (<24hrs) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. - Non-invasive or invasive arterial imaging test demonstrating 50% stenosis of any major extracranial or intracranial vessels to the brain. - Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. Does not include chronic (nonvascular) neurological diseases or other acute neurological insults e.g. metabolic/anoxic ischemic encephalopathy. *Source: Weintraub et al. ACCF/AHA 2011 Key Data Elements and Definitions of a Base Cardiovascular Vocabulary for Electronic Health Records. Circulation (2011) 124:103-23.*	1, Yes | 2, No / unknown / not documented	

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Diabetes (hx_diabetes) **[S]** Indicate if the patient has a history of diabetes mellitus regardless of duration of disease or need for anti-diabetic agents	Diabetes mellitus as diagnosed by a physician or can be defined as HbA1c ≥ 6.5%, fasting glucose ≥ 7.0mmol/L, and random glucose ≥11.1mmol/L. It does not include gestational diabetes. *Source: American Diabetes Association Care. (2011) 34:S4-10.*	1, Yes | 2, No / unknown / not documented	
Hypertension (hx_ht) **[S]** Indicate if the patient has a history of hypertension	Hypertension is defined by any one of the following: 1. History of hypertension diagnosed and treated with medication, diet and/or exercise 2. Prior documentation of blood pressure greater than 140mmHg systolic and/or 90mmHg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure greater than 130mmHg systolic and/or 80mmHg diastolic on at least two occasions for patients with diabetes or chronic kidney disease 3. Currently on pharmacologic therapy for treatment of hypertension *Source: Cannon et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. JACC (2001) 38:2114–30.*	1, Yes | 2, No / unknown / not documented	
Current smoker (hx_smoking) [S] Indicate whether the patient has smoked cigarettes for more than one year. This includes daily, non-daily or occasional smoking.	Includes cigarette smoke only. Does not include vape	1, Yes | 2, No / unknown / not documented	
Chronic lung disease* (hx_copd) [S] Indicate if the patient has a history of chronic lung disease	Chronic lung disease can include patients with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema. It can also include a patient who is currently being chronically treated with inhaled or oral pharmacological therapy (e.g., beta-adrenergic agonist, anti-inflammatory agent, leukotriene receptor antagonist, or steroid). Patients with asthma or seasonal allergies are not considered to have chronic lung disease. A history of chronic inhalation reactive disease (asbestosis, mesothelioma, black lung disease or pneumoconiosis) may qualify as chronic lung disease. Radiation induced pneumonitis or radiation fibrosis also qualifies as chronic lung disease. A history of atelectasis is a transient condition and does not qualify. *Source: CADOSA full data specifications version 5.0.*	1, Yes | 2, No / unknown / not documented	

Demographics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Dyslipidaemia (hx_dyslipid) **[S]** Indicate if the patient has a history of dyslipidemia diagnosed and/or treated by a physician	Physician documented or treated hypercholesterolemia, hyperlipidaemia, or one of the following: 1. Total cholesterol ≥5.18mmol/L; or 2. Low-density lipoprotein (LDL) ≥3.37mmol/L; or 3. High-density lipoprotein <1.04mmol/L *Source: National Heart, Lung and Blood Institute, National Cholesterol Education Program.*	1, Yes | 2, No / unknown / not documented	
Obesity (hx_obesity) **[S]** Indicate if the patient has a history of obesity	Obesity is defined as BMI >30. This may be documented in the dietician notes if currently obese.	1, Yes | 2, No / unknown / not documented	
Terminal illness* (hx_terminal) [S] Indicate if the patient has a terminal illness with a life expectancy <6 months	Life expectancy of <6 months e.g. due to cancer, or end stage lung, kidney or heart disease: Death due to "terminal" condition is one in which death is expected and for which there is evidence of poor function or functional decline prior to death. Both conditions need to be met. Terminal condition will most often be considered in patients with advanced cancer. An individual whose function is declining and for whom death is expected should be classified as terminal illness. *Source: Morrison et al. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. Resuscitation (2008) 78:161–9.*	1, Yes | 2, No / unknown / not documented	

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Date of arrest (arrest_date) **[C]** Indicate the date the patient arrested	None	ddmmyyyy	
Arrest location (arrest_location) **[C]** Indicate the location of the arrest	Home / Residence: apartment, boarding house, institutional place of residence, halfway house, group home, dormitory building, private home, residential house, home premises, private driveway, private garage, private garden, private walkway, swimming pool within private residence or garden, and yard of home. Workplace / Industrial: any location in which the patient is carrying out duties associated with their work, building under construction, dockyard, dry dock, factory building or premises, garage (place of work), industrial yard, loading platform in factory or store, industrial plant, mine, quarry, railway yard, shop (place of work), warehouse, and workhouse. Sports / Recreation event: amusement park, sport field or court of all types, resort of all types, gymnasium, holiday camp, ice palace, playground, public park, racetrack, riding school, rifle range, skating rink, stadium, public swimming pool, recreational locations within an educational institution (playground, gymnasium). Excludes occurrence in private home / residence. Street / Highway: all public roadways, and sidewalk or road not associated with a residence or business. Public building: any building used by the general public, including bank, café, state, casino, church, cinema, clubhouse, commercial shop, courthouse, dance hall, farm, fire station, day-care, hotel, jail, market, movie theatre, music hall, nightclub, office building, opera house, parking garage, post office, public hall, restaurant, broadcasting station, and store. Excludes home garage (see Home/Residence), industrial building/workplace (see Workplace / Industrial), and physician's office (see Medical Facility). Assisted living / Nursing home: all medical residential institutions that are licensed as nursing homes or assisted-living centres. Educational institution: Primary, secondary, and tertiary education campuses whether public or private Ambulance: ambulance barouche whether inside or outside the ambulance. Medical facility (non-hospital): medical clinic, doctor's rooms, dialysis clinic, free standing clinic. Hospital (not admitted): staff, visitors, outpatients, ED triage, ED waiting room Other: to be used when location is not included in the above categories. When this option is selected, please indicate / describe the location type in the free text field. *Derived from: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Home / Residence | 2, Workplace / Industrial | 3, Sports / Recreation event | 4, Street / Highway | 5, Public building | 6, Assisted living / Nursing Home | 7, Educational institution | 8, Ambulance | 9, Medical facility (non-hospital) | 10, Hospital (not admitted) | 11, Other (please specify) | 12, Unknown	

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Postcode of arrest (arrest_postcode) Indicate the postcode of the location of arrest If the postcode is unknown or not recorded enter '0000' If the patient arrested while in transit enter the postcode of the final destination	None	XXXX	
Is approximate time of arrest known? (arrest_time_known) Indicate whether the time of arrest is known or can be estimated from the medical record	None	1, Yes | 0, No	
Date and time of arrest (arrest_datetime) **[C]** Indicate the date/time of arrest if known or estimated (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[arrest_time_known] = '1'
Witnessed status (arrest_witnessed) **[C]** Indicate whether the arrest was witnessed by a bystander, EMS/MET or unwitnessed	Witnessed status is defined by: Bystander witnessed: a cardiac arrest that is seen or heard by another person or is monitored. Bystanders are all non-EMS/MET witnessed groups. By this definition, physicians, nurses, or paramedics who witness a cardiac arrest and initiate CPR but are not part of the organized rescue team are characterized as bystanders, and the arrest is not described as EMS witnessed. EMS/MET witnessed: EMS/MET personnel respond to a medical emergency in an official capacity as part of an organized medical response team. *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Bystander witnessed | 2, EMS / MET witnessed | 3, Unwitnessed | 4, Unknown | not recorded	

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Bystander response (arrest_bystandercpr) **[C]** Indicate whether the bystander performed CPR	Bystander CPR is CPR performed by a person who is not responding as part of an organized emergency response system to a cardiac arrest. Physicians, nurses, and paramedics may be described as performing bystander CPR if they are not part of the emergency response system involved in the victim's resuscitation. Bystander CPR may be compression only or compression with ventilations (the act of inflating the patient's lungs by rescue breathing with or without a bag-mask device or any other mechanical device). *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	0, No CPR | 1, Any CPR including compression only | 2, Unknown | not recorded	[arrest_witnessed] = '1' or [arrest_witnessed] = '3' or [arrest_witnessed] = '4'
Bystander AED (arrest_bystanderaed) **[C]** Indicate whether the bystander used an automated external defibrillator (AED)	None	0, None used | 1, Used but no shock delivered | 2, Used with shock delivered | 3, Unknown | not recorded	[arrest_witnessed] = '1' or [arrest_witnessed] = '3' or [arrest_witnessed] = '4'
Is approximate time of first CPR (or first shock if no CPR) known? (arrest_cpr_known) **[C]** Indicate whether the time of first CPR (or first shock if no CPR) is known. If time of first CPR is not recorded and/or there was no bystander CPR, time of SAAS or MET arrival may be used in place of 'time of first CPR'	None	1, Yes | 0, No	
Date and time of first CPR (or first shock if no CPR) (arrest_first_cpr) **[C]** Indicate the date and time of first CPR (or first shock if no CPR) (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours) If time of first CPR is not recorded and/or there was no bystander CPR, time of SAAS or MET arrival may be used in place of 'time of first CPR'	None	ddmmyyyy hh:mm	[arrest_cpr_known] = '1'
Estimated time from arrest to first CPR (or shock if no CPR)? (arrest_cpr_10min) Indicate the estimated time from arrest to first CPR (or first shock if no CPR)	None	0, <=10mins | 1, >10mins | 2, Unknown | not recorded	[arrest_time_known] = '0' or [arrest_cpr_known] = '0'

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Date and time EMS called (arrest_ems_call) **[C]** Indicate the time SAAS, MET or Resus team called (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours). Provide best estimate if not documented.	None	ddmmyyyy hh:mm	[arrest_witnessed] = '2'
Date and time EMS arrive (arrest_ems_arrive) **[C]** Indicate the time SAAS, MET or Resus team arrive at patient (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours). Provide best estimate if not documented.	None	ddmmyyyy hh:mm	
First monitored rhythm (arrest_rhythm) **[C]** Indicate the first cardiac rhythm present when the monitor or defibrillator was attached to the patient after a cardiac arrest	When CPR is started because of the absence of signs of circulation despite electrocardiographic evidence of electrical activity (ie, pulseless electrical activity), it should be recorded as pulseless electrical activity even if the electrocardiographic rhythm is slow. Asystole is defined by a period of at least 6 seconds with- out any electrical activity of >0.2 mV (which could represent atrial complexes). *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Ventricular Fibrillation (VF) | 2, Pulseless Ventricular Tachycardia (VT) | 3, Pulseless Electrical Activity (PEA) | 4, Asystole | 5, Bradycardia | 6, AED - shockable | 7, AED - non-shockable | 8, ROSC achieved before rhythm determined | 9, Unknown | not recorded	
EMS defibrillation (arrest_emsdefib) **[C]** Indicate if EMS (SAAS, Medstar, MET, Resus) provided defibrillation	None	1, Yes | 0, No	
Date and time of first shock by AED or EMS (arrest_shock_datetime) **[C]** Indicate the date and time of the first shock delivered by AED or EMS (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[arrest_bystanderaed] = '2' or [ems_met_defib] = '1'

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Total number of shocks delivered during the resuscitation episode (arrest_defib) **[S]** Indicate the total number of shocks delivered before sustained ROSC Do not include shocks delivered if patient re-arrests after sustained ROSC	None	0, Unknown | not documented | 1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7 | 8, 8 | 9, 9 | 10, 10 | 11, 11 | 12, 12 | 13, 13 | 14, 14 | 15, 15 | 16, 16 | 17, 17 | 18, 18 | 19, 19 | 20, 20 | 21, >20	[bystander_aed] = '1' or [ems_met_defib] = '1'
Drugs given during resuscitation episode (arrest_drugs) **[C]** Indicate which drugs were given during the resuscitation episode	Resuscitation episode is defined as the period from arrest to stabilisation after sustained ROSC. Do not include the following: drugs given pre-arrest, drugs given once patient has been stabilised after sustained ROSC, drugs given if the patient re-arrests after sustained ROSC.	0, None given | 1, Adrenaline | 2, Amiodarone | 3, Vasopressin | 4, Other | 5, Unknown | not recorded	
Date and time first drug given (arrest_drugs_datetime) **[S]** Indicate the date and time when vascular access is obtained and the first drug given (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[arrest_drugs] <> "0"
Main vascular access type (arrest_drugs_ access) **[S]** Indicate the main vascular access type for drug delivery during the resuscitation episode	None	0, No access | 1, Central line | 2, Peripheral IV | 3, IO (intraoesseous) | 4, Endotracheal | 5, Unknown | not recorded	[arrest_drugs] <> "0"
Inotrope infusion* (arrest_inotrope) Indicate whether the patient was initiated on inotrope infusion to maintain blood pressure. Applies to all patients who do not achieve sustained ROSC or where infusion is initiated within the first hour post-ROSC.	Blood pressure management aims to maintain systolic blood pressure >100mmHg or mean arterial pressure >65mmHg. Adrenaline (epinephrine) 1 microgram / 1ml saline 0.9% intravenous / intraoesseous titrated to effect. *Source: SA Ambulance service CPG-121-ICP version 1, effective date 07/11/2018.*	1, Yes | 2, No / unknown / not documented	

Arrest characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Main airway control type (arrest_airway) **[S]** Indicate the main airway control type during the resuscitation episode If patient has OPA or LMA and then ETT, select ETT	Resuscitation episode' is defined as the period from arrest to stabilisation after sustained ROSC. Do not include the following: airway control initiated after the patient has been stabilised post sustained ROSC, airway control initiated if patient re-arrests in ED or as in-patient after sustained ROSC.	0, None | 1, Oropharyngeal airway (OPA, guedel) | 2, Supraglottic airway (LMA, laryngeal mask) | 3, Endotracheal tube | 4, Surgical airway | 5, Multiple | 6, Unknown | not recorded	
Pathogenesis (arrest_pathogenesis) **[C]** Indicate the most likely cause of arrest documented in the pre- or early-hospital phase	Pathogenesis is defined as the following: Medical: includes cases in which the cause of the cardiac arrest is presumed to be cardiac Medical other: anaphylaxis, asthma, GI bleed etc. Medical no obvious: in which there is no obvious cause of the cardiac arrest Traumatic: cardiac arrest directly caused by blunt, penetrating, or burn injury Drug overdose: evidence that the cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol Drowning: victim is found submersed in water without an alternative causation Asphyxial: external causes of asphyxia, such as foreign-body airway obstruction, hanging, or strangulation *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Medical cardiac | 2, Medical other | 3, Medical (no obvious cause) | 4, Traumatic cause | 5, Drug overdose | 6, Drowning | 7, Electrocution | 8, Asphyxial | 9, Not recorded	
Cardiac ischaemic symptoms prior to arrest (arrest_ischaemia) Indicate if the patient experienced any cardiac ischaemic symptoms within 24hrs prior to the arrest	Ischaemic symptoms / angina may be described at rest or on exertion: 1. Chest pain: burning, squeezing, tightness, sharp, heavy or 'other' 2. Jaw pain 3. Arm pain 4. Other equivalent discomfort suggestive of cardiac ischaemia e.g. chest pain with associated tachypnea, rapid palpitations, pre-syncope, nausea/vomiting, sweating, chest wall tenderness, dyspnoea, 'other' 5. No ischaemic symptoms / angina described pre-arrest 6. Ischaemic symptoms / angina unknown or not documented pre-arrest *Source: CADOSA full data specifications version 5.0.*	1, Chest pain or pressure (burning, squeezing, tightness, sharp, heavy etc.) | 2, Jaw pain | 3, Arm pain | 4, Other equivalent discomfort suggestive of cardiac ischaemia | 5, None | 6, Unknown | not documented	

ROSC Characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Any return of spontaneous circulation (ROSC) (rosc_any) **[C]** Indicate if any return of spontaneous circulation has been recorded	ROSC is defined as signs of life comprising a palpable pulse or generating a blood pressure without the use of a ventricular assist device. *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Yes | 0, No	
Sustained ROSC achieved (>20mins) (rosc_sustained) **[C]** Indicate if first ROSC has been sustained for >20mins regardless of whether the patient re-arrests after 20mins	Sustained ROSC is defined as signs of life comprising a palpable pulse or generating a blood pressure for >20mins without the use of a ventricular assist device. *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Yes | 0, No	[rosc_any] = '1'
Time of first sustained ROSC is known (rosc_datetime_known) Indicate whether the time of first sustained ROSC is known. Best estimate is acceptable	None	1, Yes | 0, No	[rosc_sustained] = '1'
Date and time of first sustained ROSC (rosc_datetime) Indicate date and time of first sustained ROSC (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours). Best estimate is acceptable	None	ddmmyyyy hh:mm	[rosc_sustained] = '1'
Sustained ROSC location (rosc_location) Indicate where primary resuscitation was taking place when sustained ROSC was achieved	None	1, Pre-EMS | 2, EMS before handover to emergency department physicians | 3, Emergency department	[rosc_sustained] = '1'
Date and time of first ECG post sustained ROSC (rosc_ecgdatetime) **[S]** Indicate date and time of first 12-lead ECG taken after first sustained ROSC (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours). Sometimes this will be documented in the medical record observation charts even if the physical copy is not available.	None	ddmmyyyy hh:mm	[rosc_sustained] = '1'

ROSC Characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
ECGs copied (rosc_ecgcopy) Indicate whether all ECGs within first 2hrs post-ROSC have been photocopied and filed in relevant folder for assessment	None	1, Yes | 0, No - there are no ECGs available	[rosc_any] = '1'
ECG characteristic (rosc_ecgcharacteristic) **[S]** Indicate the physician assessment of the post-ROSC ECG primary characteristic. The ECG should be independently analysed by an experienced cardiologist and the findings entered. Do not use assessments documented in the medical record.	ST-elevation criteria for V2-V3: >2mm males; >1.5mm females AND/OR ≥2 contiguous leads: >1mm	1, ST-elevation | 2, ST-elevation in aVR | 3, ST-depression | 4, Wide QRS (+BBB) | 5, Wide QRS (-BBB) | 6, Long QTc | 7, Other (please specify) | 8, Normal | 9, Unknown	[rosc_ecgcopy] = '1'
ECG Characteristic (Other) (rosc_ecgch_other) Indicate the physician assessment of the post-ROSC ECG primary characteristic if specified as 'other'	None	[free text]	[rosc_ecgcharacteristic] = '7'
ECG rhythm (rosc_ecgrhythm) Indicate the physician assessment of the post-ROSC ECG primary rhythm. The ECG should be independently analysed by an experienced cardiologist and the findings entered. Do not use assessments documented in the medical record.	None	1, Sinus | 2, Sinus tachycardia | 3, Atrial fibrillation / flutter (AF / AFl) | 4, Other / unknown	[rosc_ecgcopy] = '1'
Was a Glascow Coma Scale (GCS) measurement taken after ROSC but before sedation (e.g. fentanyl, midazolam, propofol)? (rosc_gcs) Indicate whether a GCS measurement was documented after ROSC prior to sedation	Sedation may be initiated pre- or post-ROSC to assist with intubation or maintenance of supraglottic airway. Small aliquots of fentanyl are followed by midazolam as required. *Source: SA Ambulance Service CPG-116-ICP version 2, effective date 06/11/2018.*	1, Yes | 0, No	[rosc_sustained] = '1'

ROSC Characteristics			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
GCS total score* (rosc_gcs) Indicate first measurement or earliest of Glascow Coma Scale (GCS) after sustained ROSC. Do not include measurements if patient is under sedation.	Consciousness is composed of wakefulness and awareness. The ability to establish wakefulness in the unresponsive patient after cardiac arrest is of central importance because patients who awaken earlier after ROSC typically have better outcomes. A total Glasgow Coma Scale score <9 is traditionally used as the cut-off for coma. *Source: Geocadin et al. Standards for studies of neurological prognostication in comatose survivors of cardiac arrest. Circulation (2019) 140:e517–e542.*	0, Unknown | not documented | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7 | 8, 8 | 9, 9 | 10, 10 | 11, 11 | 12, 12 | 13, 13 | 14, 14 | 15, 15	[rosc_gcs] = "1"
GCS - Eye sub-scale* (rosc_gcs_e) Indicate first measurement or earliest of Glascow Coma Scale (GCS) Eye sub-scale after sustained ROSC. Do not include measurements if patient is under sedation.		1, 1 | 2, 2 | 3, 3 | 4, 4 | 0, Unknown | not documented	[rosc_gcs] = "1"
GCS - Verbal sub-scale* (rosc_gcs_v) Indicate first measurement or earliest of Glascow Coma Scale (GCS) Verbal sub-scale after sustained ROSC. Do not include measurements if patient is under sedation		1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 0, Unknown | not documented	[rosc_gcs] = "1"
GCS - Motor sub-scale* (rosc_gcs_m) Indicate first measurement or earliest of Glascow Coma Scale (GCS) Motor sub-scale after sustained ROSC. Do not include measurements if patient is under sedation.	As a sign of poor neurological outcome, a GCS Motor score ≤ 2 at 72 h has low specificity but its sensitivity is high—around 70–80% —and it can therefore be used to identify patients with the most severe HIBI needing neuroprognostication. *Source: Sandroni, C., D'Arrigo, S. and Nolan, J. P. Prognostication after cardiac arrest. Critical Care (2018) 22:1–9.*	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 0, Unknown | not documented	[rosc_gcs] = "1"
Glucose (rosc_glucose) Indicate the first measurement or earliest record of glucose in mmol/L after first sustained ROSC	There is a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurological outcome Blood glucose should be maintained between 4-10mmol/L *Sources: (1) Nolan et al. Section 5 of the European Resuscitation Council guidelines for resuscitation 2015. Resuscitation (201); 95:202–22.* (2) *SA Ambulance Service CPG-121-ICP version 1, effective date 07/11/2018.*	mmol/L	[rosc_bloodgas] = '1' or [rosc_bloodgas] = '2'

Temperature management			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Initial temperature (ttm_temp) Indicate the first measurement or earliest record of temperature (in degrees Celcius) within 1 hour after first sustained ROSC	None	degrees Celsius	
Targeted temperature management (TTM) (ttm) **[C]** Indicate whether targeted temperature management (TTM) was provided	Definition: measures taken to reduce the patient's body temperature to 32-34deg or 34-36deg by either non-invasive means (administration of cold intravenous saline, external cold pack application to armpits and groin, cooling blanket, torso vest or leg wrap devices) or by invasive means (use of a cooling catheter inserted in the femoral vein) within 24hrs post-ROSC. *Adapted from: McNally et al. CARES: Cardiac Arrest Registry to Enhance Survival. Annals of Emergency Medicine (2009) 54:674-68.*	1, Yes | 2, No | 3, Unknown | not documented	
Non-invasive TTM (ttm_noninv) Indicate whether non-invasive TTM was provided	Non-invasive TTM: cold intravenous saline, external cold pack application to armpits and groin, use of a cooling blanket, torso vest or leg wrap devices *Source: McNally et al. CARES: Cardiac Arrest Registry to Enhance Survival. Annals of Emergency Medicine (2009) 54:674-68.*	1, Yes | 0, No	[ttm] = '1'
Invasive TTM (ttm_inv) Indicate whether invasive TTM was provided	Invasive TTM: use of a cooling catheter inserted in the femoral vein *Source: McNally et al. CARES: Cardiac Arrest Registry to Enhance Survival. Annals of Emergency Medicine (2009) 54:674-68.*	1, Yes | 0, No	[ttm] = '1'
Location TTM initiated (ttm_location) **[C]** Indicate the location where TTM was first initiated	None	1, Pre-hospital | 2, Emergency department | 3, Cardiac care unit (CVIS/CCU/CSU) | 4, Intensive care unit (ICU) | 5, Other (specify)	[ttm] = '1'
Location TTM initiate (other) (ttm_location_other) **[C]** Indicate the location where TTM was first initiated if 'other' is selected	None	[free text]	[ttm_location] = '5'
Date and time TTM initiated (ttm_datetime) **[C]** Indicate date and time TTM initiated (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[ttm] = '1'

Hospital management			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Presenting hospital is NALHN hospital (hosp_nalhn) Indicate whether the presenting hospital is a NALHN hospital (Lyell McEwin or Modbury)	None	1, Yes | 0, No	
Presenting hospital name (hosp_name) Indicate the name of the presenting hospital	None	[free text]	[hosp_nalhn] = '0'
Date and time of arrival at presenting hospital (hosp_arr_datetime) Indicate date and time of arrival at presenting hospital (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	
Spontaneous circulation (ROSC) on arrival (hosp_circ) **[C]** Indicate whether spontaneous circulation (ROSC) was documented on arrival to first hospital	Spontaneous circulation (ROSC) is defined as signs of life comprising a palpable pulse or generating a blood pressure without the use of a ventricular assist device. *Source: Perkins et al. Update and simplification of the Utstein templates for resuscitation registries. Resuscitation (2014) 63:233–49.*	1, Yes | 0, No	
Blood gas recorded within 1hr after sustained ROSC (hosp_bloodgas) Indicate whether venous or arterial blood gas results were recorded within 1 hour of first sustained ROSC	Patients with unfavourable resuscitation features are less likely to benefit from coronary intervention e.g. evidence of unresponsive hypoperfusion and microcirculatory failure (pH and lactate levels). A lactate level of 7 mmol/l corresponds to a pH of 7.2 (72) and suggests a very poor prognosis post-resuscitation. Lactic acidosis is independently associated with a 3-fold increase in mortality secondary to multiorgan failure, including severe anoxic brain injury with poor neurological outcome. *Source: Rab et al. Cardiac Arrest: A treatment algorithm for emergent invasive cardiac procedures in the resuscitated comatose patient. JACC (2015); 66:62–73.*	0, None | 1, Venous blood gas | 2, Arterial blood gas	[rosc_sustained] = '1'
Blood gas – pH (hosp_ph) **[S]** Indicate the first measurement or earliest record of pH (blood gas) after first sustained ROSC	None	X.XX	[rosc_bloodgas] = '1' or [rosc_bloodgas] = '2'

Hospital management			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Blood gas – lactate (hosp_lactate) **[S]** Indicate the first measurement or earliest record of lactate in mmol/L (blood gas) after first sustained ROSC	None	mmol/L	[rosc_bloodgas] = '1' or [rosc_bloodgas] = '2'
Troponin T measured (hosp_troponint) Indicate whether Troponin T was measured	None	1, Yes | 0, No	
Peak Troponin T (hosp_ptroponin) Indicate the peak Troponin T value in ng/L recorded recorded between first medical contact and hospital discharge. Note: Enter the value. If the value is reported using a "<" symbol (eg, "<0.02"), record the number only (eg, "0.02").	Troponin T rise above the 99th percentile URL indicates myocardial injury and is used for the diagnosis of myocardial infarction *Source: Thygesen et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J (2019) 40:237-69.*	ng/L	[hosp_troponint] = '1'
Creatinine Kinase measured (hosp_ck) Indicate whether Creatinine Kinase (CK) was measured	None	1, Yes | 0, No	
Peak Creatinine Kinase (hosp_pck) Indicate the peak Creatine Kinase (CK) value in U/L recorded after the index event, either from a transferring hospital or index hospital.	CK rise above the 99th percentile URL also indicates myocardial injury but is less sensitive and less specific compared to Troponin T. *Source: Thygesen et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J (2019) 40:237-69.*	U/L	[hosp_ck] = '1'
Cardiogenic shock (hosp_cgshock) Indicate whether the patient was in cardiogenic shock on arrival to presenting hospital	Ineffective cardiac output caused by a primary cardiac disorder. Systolic blood pressure of <90mmHg for >30 min or support to maintain SBP >=90mmHg AND impaired end-organ perfusion (altered mental status, cold/clammy skin and extremities, urine output <30 mL/h, or lactate >2.0 mmol/L) *Source: Diepen et al. Contemporary Management of Cardiogenic Shock. Circulation (2017) 136:e1-37.*	1, Yes | 0, No	
Code STEMI activated (hosp_stemi) Indicate whether code STEMI was activated	None	1, Yes | 0, No	

Hospital management			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Code STEMI date and time (hosp_stemi_datetime) Indicate date and time of code STEMI activation (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[hosp_stemi]='1'
Date and time of arrival to NALHN hospital (hosp_arr_nalhn) Indicate date and time of arrival to NALHN hospital (Lyell McEwin or Modbury) (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[hosp_nalhn] = '0'
Arrival location (hosp_adm_loc) Indicate the location of arrival to NALHN hospital when NALHN was not the initial hospital	None	1, Emergency Department | 2, Direct admission: CVIS (cardiac catheterisation lab) | 3, Direct admission: ICU | 4, Direct admission: General ward	[hosp_nalhn] = '0'
Coronary reperfusion (hosp_reperfusion) **[C]** Indicate whether coronary reperfusion was attempted	None	0, None | 1, Angiography only | 2, Thrombolysis only | 3, Thrombolysis + PCI/CABG | 4, PCI	
Admission to ICU / critical care unit (hosp_icu) Indicate whether the patient was admitted to NALHN intensive care unit or critical care unit	None	1, Yes | 0, No	
ICU admission date and time (hosp_icu_datetime) Indicate the date and time the patient was first admitted to NALHN intensive care unit or critical care unit (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	

Neurological prognostication			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Electroencephalogram (EEG)* (neuro_eeg) **[S]** Indicate whether an Electroencephalogram (EEG) was performed	EEG is the recording of cortical surface activity. EEG may be recorded once (a 20- to 30-minute recording is typical) or continuously over time. To date, lack of reactivity has correlated with poor outcome. *Source: Geocadin et al. Standards for studies of neurological prognostication in comatose survivors of cardiac arrest. Circulation (2019) 140:e517–e542.*	1, Yes | 2, No | 3, Not applicable (ACD, NFR, not admitted, deceased without WLST < 72hrs)	[rosc_sustained] = '1'
Electroencephalogram (EEG) tests* (neuro_eeg_n) **[S]** Indicate how many Electroencephalogram (EEG) measurements were performed	None	1, 1 | 2, 2 | 3, 3 | 4, 4	[neuro_eeg] = "1"
Electroencephalogram (EEG) date and time (neuro_eeg_datetime) **[S]** Indicate the date and time of the Electroencephalogram (EEG) measurement (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours) If there is more than one measurement only record the date and time of the final measurement.	None	ddmmyyyy hh:mm	[neuro_eeg] = "1"
Electroencephalogram (EEG) led to treatment withdrawal (neuro_eeg_wd) **[S]** Indicate whether the Electroencephalogram (EEG) measurement(s) led to withdrawal of life sustaining therapy	None	1, Yes | 0, No	[neuro_eeg] = "1"
Radionuclide imaging (SPECT) (neuro_nm) **[S]** Indicate whether radionuclide imaging was performed to aid prognostication or confirm brain death	Tc-99m HMPAO is a radionuclide that demonstrates perfusion and crosses the blood–brain barrier to then be retained by brain parenchyma. The absence of radionuclide intracranially is compared to the presence of radionuclide extra cranially using single photon emission computerised tomography (SPECT). *Source: Australian and New Zealand Intensive Care Society. (2019) The statement on death and organ donation (Edition 4).*	1, Yes | 2, No | 3, Not applicable (ACD, NFR, not admitted, deceased without WLST < 72hrs)	[rosc_sustained] = '1'
Number of Radionuclide imaging tests (neuro_nm_n) **[S]** Indicate how many radionuclide imaging measurements were performed	None	1, 1 | 2, 2 | 3, 3 | 4, 4	[neuro_nm] = "1"

Neurological prognostication			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Radionuclide imaging date and time (neuro_nm_datetime) **[S]** Indicate the date and time of the radionuclide imaging measurement (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours) If there is more than one measurement only record the date and time of the final measurement.	None	ddmmyyyy hh:mm	[neuro_nm] = "1"
Radionuclide imaging led to treatment withdrawal (neuro_nm_wd) **[S]** Indicate whether the final radionuclide imaging led to withdrawal of life sustaining therapy or confirmation of brain death	None	1, WLST | 2, Brain death | 3, Normal / other	[neuro_nm] = "1"
Brain CT (neuro_ct) **[S]** Indicate whether Brain CT was performed to aid prognostication or confirm brain death	Computed tomography (CT) is often performed early in the admission to rule out a cerebral cause of the arrest (e.g., intracerebral haemorrhage) but is typically not helpful for prognostication until several days after arrest, given the typical delay in the imaging appearance of hypoxic/ischemic changes early after arrest. *Sources: (1) Geocadin et al. Standards for studies of neurological prognostication in comatose survivors of cardiac arrest. Circulation (2019) 140:e517–e542. (2) Australian and New Zealand Intensive Care Society. (2019) The statement on death and organ donation (Edition 4).*	1, Yes | 2, No | 3, Not applicable (ACD, NFR, not admitted, deceased without WLST < 72hrs)	[rosc_sustained] = '1'
Number of Brain CTs (neuro_ct_n) **[S]** Indicate how many Brain CT measurements were performed	None	1, 1 | 2, 2 | 3, 3 | 4, 4	[neuro_ct] = "1"
Brain CT date and time (neuro_ct_datetime) **[S]** Indicate the date and time of the Brain CT measurement (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours) If there is more than one measurement only record the date and time of the final measurement.	None	ddmmyyyy hh:mm	[neuro_ct] = "1"
Brain CT led to treatment withdrawal (neuro_ct_wd) **[S]** Indicate whether the final Brain CT led to withdrawal of life sustaining therapy or confirmation of brain death	None	1, Yes | 0, No	[neuro_ct] = "1"

Neurological prognostication			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Brain MRI (neuro_mri) **[S]** Indicate whether Brain MRI was performed to aid prognostication or confirm brain death	Magnetic resonance imaging (MRI) can be normal in the first 1 to 2 days after arrest and is best performed 3 to 5 days after arrest. *Source: Geocadin et al. Standards for studies of neurological prognostication in comatose survivors of cardiac arrest. Circulation (2019) 140:e517–e542.*	1, Yes | 2, No | 3, Not applicable (ACD, NFR, not admitted, deceased without WLST < 72hrs)	[rosc_sustained] = '1'
Number of Brain MRI tests (neuro_mri_n) **[S]** Indicate how many Brain MRI measurements were performed	None	1, 1 | 2, 2 | 3, 3 | 4, 4	[neuro_mri] = "1"
Brain MRI date and time (neuro_mri_datetime) **[S]** Indicate the date and time of the Brain MRI measurement (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours) If there is more than one measurement record the date and time of the final measurement.	None	ddmmyyyy hh:mm	[neuro_mri] = "1"
Brain MRI led to treatment withdrawal (neuro_mri_wd) **[S]** Indicate whether the final Brain MRI led to withdrawal of life sustaining therapy or confirmation of brain death	None	1, Yes | 0, No	[neuro_mri] = "1"
Clinical examination only (neuro_clin) **[S]** Indicate whether a clinical neurological examination was performed leading to WLST or confirmation of brain death	Clinical prognostication leading to withdrawal of treatment includes one or more of the following: • Glasgow Coma Scale Motor score < 2 • Absent bilateral corneal reflex • Absent bilateral pupillary reflex Neurological determination of death is carried out by two doctors, one of whom should be a specialist, who must each independently determine death according to the ANZICS statement. *Sources: (1) Sandroni C, D'Arrigo S, Nolan JP. Prognostication after cardiac arrest. Crit Care (2018) 22:1–9. (2) Australian and New Zealand Intensive Care Society (2019). The Statement on Death and Organ Donation (Edition 4).*	1, WLST | 2, Brain death | 3, No / not applicable	[rosc_sustained] = '1'
Clinical examination date and time (neuro_clin_datetime) **[S]** Indicate the date and time of the clinical examination that lead to withdrawal of life sustaining therapy (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[neuro_clin] = '1'

Cardiac catheterisation			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Procedure date and time [C] N/A CADOSA element: 7000 Indicate the date and time the procedure started. The time of the procedure is the time that the skin incision, vascular access, or its equivalent, was made in order to start the procedure. Note(s): Indicate the date/time (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	The time the procedure started is defined as the time at which local anaesthetic was first administered for vascular access, or the time of the first attempt at vascular access for the cardiac catheterization (use whichever is available and whichever earlier).	N/A	
PCI N/A CADOSA element: 7050 Indicate if the patient had a percutaneous coronary intervention (PCI) attempted and/or performed during this cath lab visit. Note(s): Code 'Yes' when a guidewire is introduced for the purpose of PCI.	A percutaneous coronary intervention (PCI) is the placement of an angioplasty guide wire, balloon, or other device (e.g. stent, atherectomy, brachytherapy, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization.	N/A	
Supervising consultant name N/A CADOSA element: 6000 Indicate the name of the Supervising Consultant for the diagnostic catheterisation.	None	N/A	

Cardiac catheterisation

Variable and Coding instructions	Supporting definitions	Data options	Show if…
IABP or other mechanical ventricular support device [S] N/A CADOSA element: 7423 Indicate the mechanical ventricular support device used.	Cardiopulmonary Support (CPS): extracorporeal device that allows for rapid cardiopulmonary support of the critically ill patient in the intensive care unit. It provides immediate and complete support of cardiac and pulmonary functions to maintain perfusion to vital organs in patients who are severely physiologically compromised (e.g., in cardiogenic shock, adult respiratory distress syndrome or pulmonary oedema). Extracorporeal membrane oxygenation (ECMO): also extracorporeal life support (ECLS), is an extracorporeal technique of providing both cardiac and respiratory support to persons whose heart and lungs are unable to provide an adequate amount of gas exchange to sustain life. Impella: Left or right Ventricular Support: The Impella device is a minimally invasive, catheter based cardiac assist device. It is the smallest rotary blood pump in the world. The pump is inserted percutaneously through the femoral artery and into the left ventricle. Intra-aortic balloon pump (IABP): mechanical device that helps the heart pump blood. Left or right ventricular assist device (LVAD): electromechanical circulatory device that is used to partially or completely replace the function of a failing heart. Percutaneous Heart Pump (PHP): provides hemodynamic support for compromised patients. TandemHeart: The TandemHeart Percutaneous Ventricular Assist Device (pVAD) differs from other assist devices in that it can be inserted either by cardiovascular surgeons in the operating room or by cardiologists in the cardiac catheterization laboratory. The TandemHeart pVAD is a continuous-flow centrifugal assist device placed outside the body (extracorporeally).	N/A	
Native vessel with stenosis >=50% N/A CADOSA element: 7506 Indicate if any of the native coronary territories had no disease (i.e. stenosis 0%). Note(s): It is acceptable to use prior cath lab visit information, as long as there have been no changes in coronary anatomy. This includes stenosis determined via cardiac catheterization at another facility.	None	N/A	

Cardiac catheterisation

Variable and Coding instructions	Supporting definitions	Data	Show if…
Graft vessel with stenosis >=50% N/A CADOSA element: 7525 Indicate if any graft vessel had a lesion >= 50%. Note(s): Identify the disease found in vessels >=2mm. Identify disease found in vessels <2mm when PCI is intended for the lesion and/or the patient's anatomy is <2mm. It is acceptable to use prior cath lab visit information, as long as there have been no changes in coronary anatomy. This includes stenosis determined via cardiac catheterization at another facility. This does not include collaterals.	Stenosis represents the percentage diameter reduction, ranging from 0 to 100, associated with the identified vessels. Percent stenosis at its maximal point is estimated to be the amount of reduction in the diameter of the "normal" reference vessel proximal to the lesion. In instances where multiple lesions are present, enter the single highest percent stenosis noted.	N/A	
Other disease findings N/A CADOSA element: 6250 Indicate other coronary artery disease findings.	No CAD (smooth): Coronary arteries and vessels with an entirely normal and smooth angiographic appearance Minor plaques <50%: Minor CAD - stenosis <50% judged angiographically None: No other disease findings.	N/A	
Small vessel CAD N/A CADOSA element: 6251 Indicate if small vessel CAD is present.	Small vessel CAD: Stenosis ≥ 50% judged angiographically present in the coronary vessels small or moderate in size (less than 2 mm in diameter).	N/A	
Extent of coronary disease N/A CADOSA element: 6252 Indicate the number of diseased vessels. Note(s): Left anterior descending territory includes the left anterior descending (LAD), diagonal and septal arteries. Left Circumflex territory includes the circumflex (Cx) trunk and obtuse marginal vessels posterior descending artery (if left-dominant system). Right Coronary Territory includes the right coronary artery (RCA) posterior descending artery (if right- dominant system). The Left main coronary artery (LMCA) supplies both the LAD & Cx systems and therefore is at least double vessel disease, and would be triple vessel disease if RCA also involved. LAD-Diagonal is one coronary system as is Cx-OM and the RCA.	Non-Obstructive CAD: All coronary territories with stenosis < 50%. 1 Vessel Disease: Lesion of ≥ 50% stenosis in 1 coronary territory. 2 Vessel Disease: Lesion of ≥ 50% stenosis in 2 coronary territories. 3 Vessel Disease: Lesion of ≥ 50% stenosis in 3 coronary territories.	N/A	

Cardiac catheterisation

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Left main disease N/A CADOSA element: 6253 Where the patient has multi vessel disease, indicate if the patient has left main disease (defined as a lesion of ≥50%)	None	N/A	
Obstructive coronary artery disease N/A CADOSA element: 6300 Indicate if the cardiac diagnosis includes obstructive atherosclerotic coronary artery disease (CAD).	Obstructive CAD: atherosclerotic plaque identified on coronary angiography resulting in >=50% luminal narrowing involving at least one epicardial coronary artery. *Source: Scanlon et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. Circulation (1999) 99: 2345-57.*	N/A	
Slow flow N/A CADOSA element: 6301 Indicate if the cardiac diagnosis includes Slow Flow.	Slow Flow: presence of delayed opacification of epicardial vessels in the absence of atherosclerotic CAD. *Source: Beltrame et al. The coronary slow flow phenomenon--a new coronary microvascular disorder. Cardiology (2002) 97:197-202.*	N/A	
Variant angina N/A CADOSA element: 6302 Indicate if the cardiac diagnosis includes variant angina.	Variant Angina: angina pectoris (or angina equivalent) that typically occurs spontaneously and, nearly always occurs at rest. It is frequently associated with transient ST- segment elevation and is caused by constriction (spasm) of a coronary artery. *Source: Weintraub et al. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records. JACC (2011) 124:103-23.*	N/A	
Takotsubo N/A CADOSA element: 6303 Indicate if the cardiac diagnosis includes Takotsubo Note(s): Takotsubo cardiomyopathy, also known as transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, Gebrochenes-Herz-Syndrom, and simply stress cardiomyopathy, is a type of non-ischemic cardiomyopathy in which there is a sudden temporary weakening of the myocardium.	Takotsubo: transient cardiac syndrome that involves left ventricular apical akinesis and mimics acute coronary syndrome. It was first described in Japan in 1990 by Sato et al. Patients often present with chest pain, have ST-segment elevation on electrocardiogram, and elevated cardiac enzyme levels consistent with a myocardial infarction. However, the coronary angiogram reveals left ventricular apical ballooning and no significant coronary artery stenosis. *Source: Sato et al. Clinical Aspect of Myocardial Injury: From Ischaemia to Heart Failure. Tokyo: Kagakuhyoronsha Publishing Co; 1990. p56-64.*	N/A	

Cardiac catheterisation

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Muscle bridge N/A CADOSA element: 6304 Indicate if the cardiac diagnosis includes muscle bridge.	Muscle bridge: a band of myocardial tissue over one or more of the large epicardial coronary vessels.	N/A	
Cardiomyopathy N/A CADOSA element: 6305 Indicate if the cardiac diagnosis includes cardiomyopathy independent of the coronary artery angiographic findings.	Cardiomyopathy refers to deterioration of the function of the myocardium, in which the heart muscle is abnormally enlarged, thickened, and/or stiffened. Do not code Takotsubo cardiomyopathy as cardiomyopathy but as Takotsubo (6303).	N/A	
Valvular heart disease N/A CADOSA element: 6306 Indicate if the cardiac diagnosis includes valvular heart disease.	Valvular heart disease includes the following diagnoses independent of coronary angiographic findings: (i) aortic stenosis (AVA ≤ 1.0 m2) (ii) mitral stenosis (MVA ≤ 1.0 m2) (iii) mitral valve prolapse (iv) grade ≥ 2 aortic or mitral regurgitation.	N/A	
Spontaneous coronary dissection N/A CADOSA element: 6307 Indicate if the cardiac diagnosis includes spontaneous coronary dissection independent of the coronary artery angiographic findings.	Spontaneous Coronary Dissection (SCAD) can occur spontaneously or as a consequence of chest trauma, cardiac surgery, coronary angiography, coronary intervention, or as extension of aortic dissection. Dissection of the coronary artery results in separation of the layers of the arterial wall, creating a false lumen. The separation may be between the intima and the media, or between the media and the adventitia. Haemorrhage into the false lumen can impinge upon the true lumen of the coronary artery, impairing blood flow and causing myocardial ischemia, infarction, or sudden death. *Source: Kamran et al. Spontaneous coronary artery dissection: case series and review. J Invasive Cardiol (2008) 20:553-9.*	N/A	
Congenital heart disease N/A CADOSA element: 6308 Indicate if the cardiac diagnosis includes congenital heart disease independent of the coronary artery angiographic findings.	Congenital heart disease refers to any problem with the heart's structure and function due to abnormal heart development before birth. Congenital means present at birth.	N/A	

Cardiac catheterisation

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Primary pulmonary hypertension N/A CADOSA element: 6309 Indicate if the cardiac diagnosis includes primary pulmonary hypertension Note(s): Pulmonary hypertension is abnormally high blood pressure in the arteries of the lungs. Do not include pulmonary hypertension secondary to congenital heart disease.	Pulmonary hypertension is conventionally divided into primary and secondary types. Primary pulmonary hypertension is considered idiopathic (of unknown origin). It occurs sporadically with no family history of the disorder and in a familial form. Secondary pulmonary hypertension may be due to congenital heart disease, pulmonary embolism, portal hypertension, collagen vascular disorders (such as lupus), sarcoidosis, and HIV infection. *Source: Rich. Pulmonary hypertension. In: Bonow ROL, Mann DL, Zipes DP, Libby P, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia, Pa: Saunders Elsevier; 2011: ch78.*	N/A	
Myocarditis N/A CADOSA element: 6310 Indicate if the cardiac diagnosis includes myocarditis independent of the coronary artery angiographic findings.	Myocarditis refers to inflammation of the heart muscle. It is characterized by inflammation of myocytes resulting from infectious, toxic, and autoimmune aetiologies. *Source: Liu & Schultheiss. Myocarditis. In: Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia, Pa: Saunders Elsevier; 2007: ch66.*	N/A	
Pericarditis N/A CADOSA element: 6311 Indicate if the cardiac diagnosis includes pericarditis independent of the coronary artery angiographic findings.	Pericarditis includes the following diagnoses independent of the coronary artery angiographic findings: (i) acute pericarditis (pleuritic/positional chest pain ± inflammatory markers) (ii) constrictive pericarditis	N/A	
Microvascular disease N/A CADOSA element: 6312 Indicate if the cardiac diagnosis includes coronary microvascular disease.	Microvascular disease refers to dysfunction of the microscopic coronary vessels. It is characterized by chest pain suggestive of myocardial ischemia, and angiographically normal epicardial coronary arteries. Clinical syndromes may include microvascular angina or cardiac syndrome X Assessment typically involves measuring coronary-artery flow reserve or coronary reactivity. *Source: Beltrame. Chest Pain and Normal Angiography. In: E B, ed. Braunwald's Heart Disease Edition. Philadelphia: Elsevier; 2006.*	N/A	
Spasm N/A CADOSA element: 6313 Indicate if the cardiac diagnosis includes coronary artery spasm (sudden narrowing of one of the coronary arteries).	Coronary artery spasm is defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation. *Source: Beltrame et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J (2017) 38:2565–8.*	N/A	

Cardiac catheterisation			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
MINOCA N/A CADOSA element: 6314 Indicate if the cardiac diagnosis includes myocardial infarction with non-obstructive coronary artery disease.	Myocardial infarction with nonobstructive coronary arteries (MINOCA) is clinically defined by the presence of the universal acute myocardial infarction (AMI) criteria, absence of obstructive coronary artery disease (≥50% stenosis), and no overt cause for the clinical presentation at the time of angiography (eg, classic features for takotsubo cardiomyopathy). *Sources: (1) Agewall et al. Working Group on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J (2017) 38:143–53. (2) Pasupathy et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation (2015) 131:861-70.*	N/A	
Transfer for CABG N/A CADOSA element: 10111 Indicate if the patient was transferred for the purpose of performing a coronary artery bypass graft.	None	N/A	
CABG planned N/A CADOSA element: 10112 Indicate if the patient has a CABG planned after discharge. Note(s): A planned CABG could include a documented plan for the patient to receive a CABG, a patient referral for a CABG or a CABG date scheduled.	None	N/A	

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Patient admission (outc_admission) Indicate the patient admission status	None	1, Resuscitation terminated in NALHN ED | 2, Transferred to another acute care facility from NALHN ED | 3, Admitted to NALHN hospital	
Patient deceased during episode of care (includes death in another hospital) (outc_deceased) **[C]** Indicate whether the patient died during the episode of care (includes death in another acute care hospital, extended care or rehabilitation facility)	None	1, Yes | 0, No	[outc_admission] >1
Deceased date and time (outc_deceased_datetime) Indicate the date and time of death (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[outc_deceased] = "0" or [outc_admission] > "1"
Location of death (outc_death_location) Indicate the location of death	None	1, Emergency department | 2, Cardiac investigation suite (CVIS) / cardiology ward | 3, Intensive / critical care unit | 4, General ward | 5, Other hospital	[outc_deceased] = "0" or [outc_admission] > "1"
ICU discharge date and time (outc_icu_dc) Indicate the ICU discharge date and time (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[hosp_icu] = '1' and [outc_death_location] <> "3"

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
NALHN discharge disposition (outc_nalhn_dc) Indicate the NALHN discharge disposition	1. Home, includes nursing home if previous resident 2. An extended care rehab unit typically provides a high level of intensive therapy as well as specialized nursing and physician care. This discharge setting may also be called subacute care or long-term acute care (LTACH) 3. Other acute care hospital 4. Nursing homes are establishments which provide long-term care involving regular basic nursing care to chronically ill, frail, disabled or convalescent persons or senile inpatients 5. Hospices are establishments providing palliative care to terminally ill patients. Only freestanding hospices which do not provide any other form of acute care are included in this category 6. Other discharge location 7. The patient was discharged or eloped against medical advice *Source: CADOSA full data specifications version 5.0.*	1, Home (includes nursing home if previous resident) | 2, Extended care / rehab | 3, Other acute care hospital | 4, Nursing home | 5, Hospice | 6, Other discharge location | 7, Left against medical advice (AMA)	[outc_deceased] = "0" or [outc_admission] > "1"
NALHN discharge date and time (outc_discharge) Indicate the NALHN discharge date and time (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[outc_nalhn_dc] <> ""
Other acute care hospital discharge date and time (outc_tf_datetime) Indicate the final hospital discharge date and time if not NALHN hospital (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[outc_nalhn_dc] = 3

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Cerebral performance category (outc_cpc) **[C]** Indicate the Cerebral performance category at discharge as determined from the medical record	CPC 1: Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities). CPC 2: Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes. CPC 3: Conscious. Dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence, to those who are paralyzed and can communicate only with their eyes, as in the "locked in" syndrome. CPC 4: Unconscious. Unaware of surroundings, no cognition. No verbal and/or psychologic interaction with environment. CPC 5: Brain dead, circulation preserved. Death at discharge. *Source: Rittenberger et al. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. Resuscitation (2011) 82:1036-40.*	1, Good cerebral performance | 2, Moderate cerebral disability | 3, Severe neurological disability | 4, Coma or vegetative state | 5, Dead	
Modified rankin scale (outc_mrs) **[C]** Indicate the modified Rankin Score at discharge as determined from the medical record	No significant disability: Able to carry out all usual activities (work, leisure, caregiver roles), despite some symptoms. Slight disability: Able to look after own affairs without assistance, but unable to carry out all previous activities. Moderate disability: Requires some help (preparing a simple meal, household chores, shopping, money management, local travel), but able to walk unassisted. Moderately severe disability: Unable to attend to own bodily needs (eating, toilet, daily hygiene) without assistance, and unable to walk unassisted. Severe disability: Requires constant nursing care and attention, bedridden, incontinent. *Source: Rittenberger et al. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. Resuscitation (2011) 82:1036-40.*	0, No symptoms. | 1, No significant disability | 2, Slight disability | 3, Moderate disability | 4, Moderately severe disability | 5, Severe disability | 6, Dead.	

Outcomes

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Advanced care directive (ACD) or not for resuscitation (NFR) order activated (outc_nfr) Indicate whether an Advanced Care Directive (ACD) or not for resuscitation (NFR) order was activated after arrival to hospital and before death or discharge	None	1, Yes | 0, No	
Date and time ACD discovered or NFR activated (outc_nfr_datetime) Indicate date and time the Advanced Care Directive (ACD) or not for resuscitation (NFR) order was activated (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[outc_nfr]='1'
Withdrawal of life sustaining therapy (WLST) (outc_death_wlst) **[S]** Indicate whether withdrawal of life sustaining therapy (WLST) was completed	Withdrawal of life sustaining therapy may include extubation, or if the patient is not intubated, the cessation of inotropes, or if the patient is neither intubated or on inotropes, the cessation of other life-sustaining medications	1, Yes | 0, No	[outc_death_location] <> ""
Withdrawal of life sustaining therapy (WLST) date and time (outc_wlst_datetime) **[S]** Indicate the date and time of WLST (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours).	None	ddmmyyyy hh:mm	[outc_death_wlst] = '1'
Reason for WLST (outc_wlst_reason) Indicate the reason for WLST as best determined from the medical record	Pre-existing advanced directives: advanced care directive (ACD) and not for resuscitation order (NFR). Confirmed brain death: clinical examination for neurological determination of death with or without imaging Poor neurological progress: perceived neurological injury and assumed poor prognosis as determined by one or more of the following: clinical examination, brain imaging (radionuclide imaging, CT, MRI), EEG Other non-neurological reasons: overt hemodynamic or other instability that makes ongoing medical care futile in the assessment of the treating clinician. *Adapted from: Elmer et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation (2016) 102:127-35.*	1, Pre-existing advanced directives | 2, Confirmed brain death | 3, Poor neurological progress | 4, Other non-neurological reason | 5, Other (please specify)	[outc_death_wlst] = '1'

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Reason for WLST other (outc_wlst_other) Indicate the reason for WLST if specified as 'other' as best determined from the medical record	None	[free text]	[outc_wlst_reason] = '6'
Mode of death (outc_death_mode) Indicate the mode of death	Sudden cardiac death: Recurrent cardiac arrest without sustained ROSC with or without extraordinary measure (e.g. ECPR) in place. Progressive, refractory hemodynamic shock: Progressive, refractory hemodynamic shock despite aggressive ICU care, or withdrawal of care based on same. Hemodynamically stable patients (e.g. maintaining their mean arterial blood pressure) on aggressive ICU care (e.g. full vasopressor support) should not be included in this category. Respiratory failure: Respiratory failure or withdrawal of care based on same. Respiratory failure may be related to hypoxemia, hypercapnia or the combination thereof. Patients who are oxygenating sufficiently on highest ventilator settings should not be included in this category. Hypoxic brain injury WLST: Withdrawal of care based on expectations of a poor neurological recovery based on EEG, brain imaging, and/or clinical examination stating that the prognosis for neurologic recovery is very poor. If an assessment off sedation is not done, there must be other evidence of severe neurologic injury. Brain death: Confirmed brain death secondary to neurological catastrophe e.g. intracranial haemorrhage, subarachnoid haemorrhage, or progression of hypoxic brain injury to brain death. Comorbid WLST: Withdrawal of care or refusal of life-sustaining therapy based on the expectation of a poor quality of life. This may be related to a pre-existing or newly discovered terminal illness or other serious medical condition (e.g. dementia or cancer). To categorize patients with multiple potential causes of death (e.g. refractory hemodynamic shock, respiratory failure and multi system organ failure), an attempt should be made to identify the primary cause of death or reason for withdrawal of care. *Adapted from: Witten et al. Reasons for death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. Resuscitation (2019) 136:93-9.*	1, Sudden cardiac death | 2, Progressive, refractory hemodynamic shock | 3, Respiratory failure | 4, Hypoxic brain injury | 5, Brain death | 6, Comorbid WLST	[outc_death_location] <> ""

Outcomes

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Organ donation (outc_organdonation) **[S]** Indicate whether ≥1 solid organs were donated for transplantation	None	1, Yes | 0, No	[outc_death_location] <> ""
Coroner's case (outc_coroner) Indicate whether the case was sent to the coroner's office	None	0, No | 1, Yes - request pending | 2, Yes - completed	[outc_death_location] <> ""
Cause of arrest (primary category) (outc_cause_primary) Indicate the most likely primary cause of arrest as determined from the medical record	Terminal mechanism of inevitable death is defined as life expectancy <6 months e.g. in the setting of end stage COPD on home O2, end stage heart failure, end stage kidney disease, or cancer with <6mth prognosis Note: Determining the underlying cause of arrest can be difficult as the cause is often multifactorial. An attempt should be made to identify the primary cause of arrest according to the underlying substrate, rather than the trigger. E.g. An acute gastrointestinal bleed with a precipitous drop in haemoglobin may result in myocardial injury and type 2 MI, triggering a cardiac arrest. The cause of arrest is non-traumatic exsanguination, not type 2 MI.	1, Cardiac ischaemic | 2, Cardiac non-ischaemic | 3, Respiratory | 4, Toxicological | 5, Neurological | 6, Other | 7, Multiple | 8, Terminal mechanism of inevitable death | 9, Unknown	
Cardiac ischaemic (outc_cause_1) Indicate the type of cardiac ischaemic cause as determined from the medical record	Acute MI (Type 1): MI caused by atherosclerotic plaque disruption with thrombosis. Post-mortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI regardless of cTn values. Criteria: (1) Rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following: (2) a. Ischaemic symptoms; b. ECG changes; c. Pathological Q waves; d. Imaging evidence; e. Angiography, intracoronary imaging or autopsy Acute MI (Type 3): Cardiac death in patients with ischaemic symptoms and ECG changes before cTn values become available or abnormal. Type 2 MI includes Chronic CAD; Coronary artery spasm / coronary microvascular dysfunction; Coronary embolism; Spontaneous Coronary Dissection (SCAD). Does not include SCAD as a consequence of chest trauma, cardiac surgery, coronary angiography, coronary intervention, or as extension of aortic dissection. MINOCA: ischaemic mechanism responsible for the myocyte injury without evidence of obstructive CAD Ischaemic cardiomyopathy: previous MI without evidence of acute ischaemia *Source: Thygesen et al. Fourth universal definition of myocardial infarction (2018). Eur Hear J. 2019. 40:237-69.*	1, Acute coronary occlusion (Type 1 and 3 MI) | 2, Type 2 MI without underlying non-cardiac cause | 3, MINOCA | 4, Ischaemic cardiomyopathy	[outc_cause_primary] = '1'

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Cardiac non-ischaemic (outc_cause_2) Indicate the type of cardiac non-ischaemic cause as determined from the medical record	None	1, Cardiomyopathy | 2, Genetic channelopathy |3, Other arrhythmia | 4, Structural heart disease	[outc_cause_primary] = '2'
Cardiomyopathy sub-type (outc_cause_2a) Indicate the sub-type of cardiomyopathy as determined from the medical record	Hypertrophic Cardiomyopathy (HCM): Presence of increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease) sufficient to cause the observed abnormality (myocardial hypertrophy). In up to 60% of adults this autosomal dominant trait is caused by mutations in cardiac sarcomere protein genes. Dilated Cardiomyopathy (DCM): Presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. E.g. Familial, alcohol-induced, myocarditis etc. Restrictive Cardiomyopathy (RCM): Restrictive ventricular physiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness. E.g. Familial, amyloid, cancer, radiation, drugs etc. Arrhythmogenic right ventricular dysplasia (ARVD): progressive fibrofatty replacement of RV myocardium and RV dysfunction, regional or global, usually demonstrated by echocardiography or cardiac MRI. Unclassified: E.g. takotsubo cardiomyopathy *Source: Elliot et al. Classification of the Cardiomyopathies. Euro H J (2008) 29:270-6. [Appx 2]*	1, Hypertrophic (HCM) | 2, Dilated (DCM) | 3, Restrictive (RCM) | 4, ARVD | 5, Unclassified	[outc_cause_2] = '1'
Genetic Channelopathy sub-type (outc_cause_2b) Indicate the sub-type of genetic channelopathy cause as determined from the medical record	Long QT should be considered in all patients presenting with QTc >440 milliseconds in male patients and >460 milliseconds in female patients. Brugada is characterized by intermittent right precordial lead 'coved' ST-segment elevation and right bundle-branch block, which is unmasked by pharmacological challenge with flecainide. Short QT has been reported in only ~70 cases worldwide, with the mean QTc value in the entire population of 310 milliseconds. Catecholaminergic polymorphic ventricular tachycardia (CPVT) presents with unremarkable resting ECG and bidirectional or polymorphic ventricular tachycardia reproducibly triggered by exercise or acute emotion. Idiopathic VF may be considered when sudden death occurs in the absence of an identifiable cause. *Source: Napolitano et al. Sudden cardiac death and genetic ion channelopathies. Circulation (2012) 125:2027–34.*	1, Long QT | 2, Brugada | 3, Short QT | 4, CPVT | 5, Idiopathic VF	[outc_cause_2] = '2'

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Other arrhythmia sub-type (outc_cause_2c) Indicate the sub-type of other arrhythmic cause as determined from the medical record	Myocardial scarring may occur without prior MI in the setting of non-ischemic cardiomyopathies due to replacement fibrosis, or in the course of cardiac surgical repairs, such as surgical correction of Tetralogy of Fallot. Bradyarrhythmia is a slow heart rate primarily due to conduction abnormalities. Do not include bradycardia due to previous MI, medications or metabolic problems here.	1, Scar-related VF without prior MI | 2, Bradyarrhythmia	[outc_cause_2] = '3'
Structural heart disease sub-type (outc_cause_2d) Indicate the sub-type of structural heart disease cause as determined from the medical record	Structural heart disease: structural or functional abnormalities of the heart, or blood vessels supplying the heart, that impair normal functioning. Do not include here congenital hypertrophic cardiomyopathies (HCM) or arrhythmogenic right ventricular dysplasia (ARVD). Valvular: mitral valve prolapse; aortic and mitral stenosis; bicuspid aortic valve etc. Congenital: Atrial and ventricular septal defect, left atrial appendage etc.	1, Valvular | 2, Congenital	[outc_cause_2] = '4'
Respiratory (outc_cause_3) Indicate the type of respiratory cause as determined from the medical record	None	1, Choking / asphyxiation / strangulation / foreign body aspiration | 2, Asthma | 3, Drowning | 4, COPD | 5, Pneumonia | 6, Mucous plugging | 7, Diffuse alveolar haemorrhage (DAH) | 8, Post ROSC hypoxia or CO2>60 without other aetiology	[outc_cause_primary] = '3'
Toxicological (outc_cause_4) Indicate the type of toxicological cause as determined from the medical record	None	1, Poison / toxin | 2, Drug overdose (including drug-induced long QT) | 3, Bradycardia or cariogenic shock due to medications	[outc_cause_primary] = '4'

Outcomes			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Neurological (outc_cause_5) Indicate the sub-type of neurological cause as determined from the medical record	Hemorrhagic stroke (SAH and ICH): A stroke with documentation on imaging e.g., CT or MRI of haemorrhage in the cerebral parenchyma, or a subdural or subarachnoid haemorrhage Ischaemic stroke: A focal neurological deficit that results from a thrombus or embolus (and not due to haemorrhage) that appears and is still partially evident for more than 24 hours *Source: Cannon et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. JACC (2001) 38:2114–30.*	1, Subarachnoid haemorrhage (SAH) | 2, Intracranial haemorrhage (ICH) | 3, Ischaemic stroke | 4, Other neurological event	[outc_cause_primary] = '5'
Other (outc_cause_6) Indicate the sub-type of other cause as determined from the medical record. Make every effort to categorise patients in existing aetiologies rather than using 'Not listed'.	Cardiac tamponade: includes pericarditis, malignant effusions, aortic dissection, cardiac rupture	1, Metabolic - hypo/hyperkalaemia | 2, Metabolic - hypo/hyperglycaemia | 3, Metabolic - pH disruption | 4, Metabolic - diabetic ketoacidosis | 5, Metabolic – temperature dysregulation (hyper-, hypothermia) | 6, Gastrointestinal - GI haemorrhage | 7, Gastrointestinal - incarcerated/strangulated hernia | 8, Gastrointestinal - bowel obstruction | 9, Gastrointestinal - hepatorenal failure / pancreatitis | 10, Gastrointestinal - Liver failure | 11, Non-traumatic exsanguination | 12, Dehydration | 13, Anaphylaxis (without large airway obstruction) | 14, Septic shock; overwhelming infection | 15, Major aortic disease (aneurysm rupture, dissection) | 16, Electrocution | 17, Pulmonary embolism | 18, Trauma (blunt / penetrating) | 19, Cardiac tamponade | 20, Not listed	[outc_cause_primary] = '6'
Specify 'Not listed' cause of arrest (outc_cause_6_other) Indicate the cause 'Not listed' as determined from the medical record.	None	[free text]	[outc_cause_6] = "21"

Outcomes

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Cause: Multiple (outc_cause_7) Indicate the two most likely causes of arrest as determined from the medical record. Make every effort to categorise patients with a single aetiology where possible.	Please see relevant definitions as above	1, Cardiac ischaemic | 2, Cardiomyopathy | 3, Genetic channelopathy | 4, Other arrhythmia | 5, Non-ischaemic heart disease | 6, Respiratory | 7, Toxicological | 8, Neurological catastrophe | 9, Other	[outc_cause_primary] = '7'
Likely syncopal episode (outc_syncopal) Indicate whether the event was likely to be a syncopal episode with CPR rather than true cardiac arrest	Syncope is defined as sudden loss of consciousness with loss of postural tone, not related to anaesthesia, with spontaneous recovery as reported by patient or observer. Patients may experience syncope when supine. *Source: Weintraub et al. ACCF/AHA 2011 Key Data Elements and Definitions of a Base Cardiovascular Vocabulary for Electronic Health Records. Circulation (2011) 124:103-23.*	1, Yes | 0, No	
Cardiac device implanted (AICD) during admission (outc_aicd) Indicate whether a cardioverter-defibrillator was implanted during the admission	None	1, Yes | 0, No	[outc_deceased] = "0" or [outc_admission] > "1"
Alive at 3 months post-arrest (outc_alive_3m) Indicate whether the patient is alive at 3 months post-arrest date	None	1, Yes | 0, No	[outc_deceased] = "0" or [outc_admission] > "1"
Alive at 12 months post-arrest (outc_alive_12m) **[S]** Indicate whether the patient is alive at 12 months post-arrest date	None	1, Yes | 0, No	[outc_alive_3m] = '1'
Special considerations for enrolment in follow-up studies (outc_followup) Indicate whether there are any special considerations for enrolment in follow-up studies e.g. country patient, interpreter required, mental illness etc.	None	[free text]	[outc_deceased] = "0" or [outc_admission] > "1"

Completion

Variable and Coding instructions	Supporting definitions	Data options	Show if…
Notes for remaining data collection (complete_todo) Indicate whether there are any notes for remaining data collection e.g. ECGs to be copied and filed; 12 month alive status to confirm; coroner report	None	[free text]	
Date of case completion (complete_date) Indicate the date the data entry was completed	None	ddmmyyyy	
Medical record volume number (complete_mrn_vol) Indicate the volume number(s) of the medical record that contain the index admission	None	[free text]	
Patient summary (complete_comments) Provide a case summary: background, arrest summary, hospital management summary, and outcome	e.g. 37yo male with significant comorbidities, witnessed arrest on sidewalk with bystander CPR, 2x defib by SAAS, ROSC on scene, 2x stent to LAD, uneventful recovery e.g. 89yo female hx COPD, CHF. Neighbours found collapsed called SAAS, pea arrest witnessed by SAAS on transfer to ambulance barouche, re-arrest enroute, intubated with nil resp effort. Hypoxic brain injury, normal coronaries. NFR order, deceased. Unknown cause ?exacerbation of CHF or COPD, known CO2 retainer, likely PEA hypoxic arrest with bradycardia.	[free text]	

Trial [optional]			
Variable and Coding instructions	**Supporting definitions**	**Data options**	**Show if…**
Date and time of first recorded observations after sustained ROSC (rosc_obs) Indicate date and time of first recorded observations between 5-10 minutes after first sustained ROSC (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[rosc_sustained] = '1'
Heart rate (HR; pulse rate) (rosc_hr) Indicate the earliest heart rate (in beats per minute) recorded between 5-10 minutes after first sustained ROSC	None	bpm	[rosc_sustained] = '1'
Systolic blood pressure (SBP) (rosc_sbp) Indicate the earliest systolic blood pressure (in mmHg) recorded between 5-10 minutes after first sustained ROSC	None	mmHg	[rosc_sustained] = '1'
Diastolic blood pressure (DBP) (rosc_dbp) Indicate the earliest diastolic blood pressure (in mmHg) recorded between 5-10 minutes after first sustained ROSC	None	mmHg	[rosc_sustained] = '1'
Respiratory rate (RR) (rosc_rr) Indicate the earliest respiratory rate (in breaths per minute) recorded between 5-10 minutes after first sustained ROSC	None	bpm	[rosc_sustained] = '1'
Date and time of observations recorded 1 hour after sustained ROSC (rosc_obs_1hr) Indicate date and time of observations 1 hour +/- 10 minutes after first sustained ROSC (dd/mm/yyyy hours:minutes) using the military 24-hour clock, beginning at midnight (0000 hours)	None	ddmmyyyy hh:mm	[rosc_sustained] = '1'
1hr Heart rate (HR; pulse rate) (rosc_hr_1hr) Indicate heart rate (in beats per minute) recorded 1 hour +/- 10 minutes after first sustained ROSC	None	bpm	[rosc_sustained] = '1'
1hr Systolic blood pressure (SBP) (rosc_sbp_1hr) Indicate systolic blood pressure (in mmHg)recorded 1 hour +/- 10 minutes after first sustained ROSC	None	mmHg	[rosc_sustained] = '1'
1hr Diastolic blood pressure (DBP) (rosc_dbp_1hr) Indicate diastolic blood pressure (in mmHg) recorded 1 hour +/- 10 minutes after first sustained ROSC	None	mmHg	[rosc_sustained] = '1'
1hr Respiratory rate (RR) (rosc_rr_1hr) Indicate respiratory rate (in breaths per minute) recorded 1 hour +/- 10 minutes after first sustained ROSC	None	bpm	[rosc_sustained] = '1'

Australian Bureau of Statistics

1249.0 Australian Standard Classification of Cultural and Ethnic Groups, 2019

Released at 11.30am (Canberra time) 18 December 2019

Table 1.3 Classification structure: Broad groups, narrow groups, and cultural and ethnic groups

Broad group	Narrow group	Cultural and ethnic group	
1	**OCEANIAN**		
	11	**Australian Peoples**	
		1101	Australian
		1102	Australian Aboriginal
		1103	Australian South Sea Islander
		1104	Torres Strait Islander
		1105	Norfolk Islander
	12	**New Zealand Peoples**	
		1201	Maori
		1202	New Zealander
	13	**Melanesian and Papuan**	
		1301	New Caledonian
		1302	Ni-Vanuatu
		1303	Papua New Guinean
		1304	Solomon Islander
		1399	Melanesian and Papuan, nec
	14	**Micronesian**	
		1401	I-Kiribati
		1402	Nauruan
		1499	Micronesian, nec
	15	**Polynesian**	
		1501	Cook Islander
		1502	Fijian
		1503	Niuean
		1504	Samoan
		1505	Tongan
		1506	Hawaiian

Appendix 1: Australian Standard Classification of Cultural and Ethnic Groups

2 NORTH-WEST EUROPEAN

21 British

2101	English
2102	Scottish
2103	Welsh
2104	Channel Islander
2105	Manx
2199	British, nec

22 Irish

2201	Irish

23 Western European

2301	Austrian
2303	Dutch
2304	Flemish
2305	French
2306	German
2307	Swiss
2311	Belgian
2312	Frisian
2313	Luxembourg
2399	Western European, nec

24 Northern European

2401	Danish
2402	Finnish
2403	Icelandic
2404	Norwegian
2405	Swedish
2499	Northern European, nec

3 SOUTHERN AND EASTERN EUROPEAN

31 Southern European

3101	Basque
3102	Catalan
3103	Italian
3104	Maltese
3105	Portuguese
3106	Spanish
3107	Gibraltarian
3199	Southern European, nec

32 South Eastern European

3201	Albanian
3202	Bosnian
3203	Bulgarian
3204	Croatian
3205	Greek
3206	Macedonian
3207	Moldovan
3208	Montenegrin
3211	Romanian
3212	Roma Gypsy
3213	Serbian
3214	Slovene
3215	Cypriot
3216	Vlach
3299	South Eastern European, nec

33 Eastern European

3301	Belarusan
3302	Czech
3303	Estonian
3304	Hungarian
3305	Latvian
3306	Lithuanian
3307	Polish
3308	Russian
3311	Slovak
3312	Ukrainian
3313	Sorb/Wend
3399	Eastern European, nec

Appendix 1: Australian Standard Classification of Cultural and Ethnic Groups

4 NORTH AFRICAN AND MIDDLE EASTERN

41 Arab

4101	Algerian
4102	Egyptian
4103	Iraqi
4104	Jordanian
4105	Kuwaiti
4106	Lebanese
4107	Libyan
4108	Moroccan
4111	Palestinian
4112	Saudi Arabian
4113	Syrian
4114	Tunisian
4115	Yemeni
4116	Bahraini
4117	Emirati
4118	Omani
4121	Qatari
4199	Arab, nec

42 Jewish

4201	Jewish

43 Peoples of the Sudan

4301	Bari
4302	Darfur
4303	Dinka
4304	Nuer
4305	South Sudanese
4306	Sudanese
4399	Peoples of the Sudan, nec

49 Other North African and Middle Eastern

4902	Berber
4903	Coptic
4904	Iranian
4905	Kurdish
4907	Turkish
4908	Assyrian
4911	Chaldean
4912	Mandaean
4913	Nubian
4914	Yezidi
4999	Other North African and Middle Eastern, nec

5 SOUTH-EAST ASIAN

51 Mainland South-East Asian

5101	Anglo-Burmese
5102	Burmese
5103	Hmong
5104	Khmer (Cambodian)
5105	Lao
5106	Thai
5107	Vietnamese
5108	Karen
5111	Mon
5112	Chin
5113	Rohingya
5199	Mainland South-East Asian, nec

52 Maritime South-East Asian

5201	Filipino
5202	Indonesian
5203	Javanese
5204	Madurese
5205	Malay
5206	Sundanese
5207	Timorese
5208	Acehnese
5211	Balinese
5212	Bruneian
5213	Kadazan
5214	Singaporean
5215	Temoq
5299	Maritime South-East Asian, nec

6 NORTH-EAST ASIAN

61 Chinese Asian

6101	Chinese
6102	Taiwanese
6199	Chinese Asian, nec

69 Other North-East Asian

6901	Japanese
6902	Korean
6903	Mongolian
6904	Tibetan
6999	Other North-East Asian, nec

Appendix 1: Australian Standard Classification of Cultural and Ethnic Groups

7 SOUTHERN AND CENTRAL ASIAN

71 Southern Asian

7101	Anglo-Indian
7102	Bengali
7103	Burgher
7104	Gujarati
7106	Indian
7107	Malayali
7111	Nepalese
7112	Pakistani
7113	Punjabi
7114	Sikh
7115	Sinhalese
7117	Maldivian
7118	Bangladeshi
7121	Bhutanese
7122	Fijian Indian
7123	Kashmiri
7124	Parsi
7125	Sindhi
7126	Sri Lankan
7127	Sri Lankan Tamil
7128	Indian Tamil
7131	Tamil, nfd
7132	Telugu
7199	Southern Asian, nec

72 Central Asian

7201	Afghan
7202	Armenian
7203	Georgian
7204	Kazakh
7205	Pathan
7206	Uzbek
7207	Azeri
7208	Hazara
7211	Tajik
7212	Tatar
7213	Turkmen
7214	Uighur
7215	Kyrgyz
7299	Central Asian, nec

8 PEOPLES OF THE AMERICAS

81 North American

8101	African American
8102	American
8103	Canadian
8104	French Canadian
8105	Hispanic North American
8106	Native North American Indian
8107	Bermudan
8199	North American, nec

82 South American

8201	Argentinian
8202	Bolivian
8203	Brazilian
8204	Chilean
8205	Colombian
8206	Ecuadorian
8207	Guyanese
8208	Peruvian
8211	Uruguayan
8212	Venezuelan
8213	Paraguayan
8299	South American, nec

83 Central American

8301	Mexican
8302	Nicaraguan
8303	Salvadoran
8304	Costa Rican
8305	Guatemalan
8306	Mayan
8399	Central American, nec

84 Caribbean Islander

8401	Cuban
8402	Jamaican
8403	Trinidadian Tobagonian
8404	Barbadian
8405	Puerto Rican
8499	Caribbean Islander, nec

Appendix 1: Australian Standard Classification of Cultural and Ethnic Groups

9 SUB-SAHARAN AFRICAN

91 Central and West African

9101	Akan
9102	Fulani
9103	Ghanaian
9104	Nigerian
9105	Yoruba
9106	Ivorean
9107	Liberian
9108	Sierra Leonean
9111	Acholi
9112	Cameroonian
9113	Congolese
9114	Gio
9115	Igbo
9116	Krahn
9117	Mandinka
9118	Senegalese
9121	Themne
9122	Togolese
9199	Central and West African, nec

92 Southern and East African

9201	Afrikaner
9202	Angolan
9203	Eritrean
9204	Ethiopian
9205	Kenyan
9206	Malawian
9207	Mauritian
9208	Mozambican
9211	Namibian
9212	Oromo
9213	Seychellois
9214	Somali
9215	South African
9216	Tanzanian
9217	Ugandan
9218	Zambian
9221	Zimbabwean
9222	Amhara
9223	Batswana
9225	Hutu
9226	Masai
9228	Tigrayan
9231	Tigre
9232	Zulu
9233	Burundian
9234	Kunama
9235	Madi
9236	Ogaden
9237	Rwandan
9238	Shona
9241	Swahili
9242	Swazilander
9299	Southern and East African, nec

Appendix 2: Cardiomyopathy sub-types. Elliot et al 2008. Classification of the Cardiomyopathies. Euro H J.

Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

APPENDIX C – CHAPTER FOUR SUPPLEMENTARY MATERIAL\

Paper Two supplementary material

frontiers

Supplementary Material

Table S1: Inflation factors for incidence calculations

EMS-attended	**Total**	**Females**	**Males**
Number of cases	1970	691	1279
Age missing	54	8	46
Inflation factor	1.0274	1.0116	1.0360
Uninflated crude incidence (per 100,000 person-years)	144.7	99.1	192.6
Uninflated age-standardised incidence (per 100,000 person-years)	136.2	94.9	199.6
EMS-treated cohort			
Number of cases	772	273	499
Age missing	8	0	8
Inflation factor	1.0103	n/a	1.0160
Uninflated crude incidence (per 100,000 person-years)	56.7	39.2	75.2
Uninflated age-standardised incidence (per 100,000 person-years)	54.1	38.1	71.8
Non-EMS witnessed presumed cardiac sub-cohort			
Number of cases	501	163	338
Age missing	0	0	0
Inflation factor	n/a	n/a	n/a
Non-EMS witnessed obvious non-cardiac sub-cohort			
Number of cases	161	63	98
Age missing	7	0	7
Inflation factor	1.0434	n/a	1.0714
Uninflated crude incidence (per 100,000 person-years)	11.8	9.0	14.8
Uninflated age-standardised incidence (per 100,000 person-years)	11.7	9.0	14.6

APPENDIX D – CHAPTER FIVE SUPPLEMENTARY MATERIAL

STARD Checklist

Case Report Form – Patient management in OHCA

Section & Topic	No	Item	Reported on manuscript page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	2
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	2
Participants	**6**	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	3
Test methods	**10a**	Index test, in sufficient detail to allow replication	3
	10b	Reference standard, in sufficient detail to allow replication	3
	11	Rationale for choosing the reference standard (if alternatives exist)	3
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	3
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	3
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	3
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	3
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	3
	15	How indeterminate index test or reference standard results were handled	3
	16	How missing data on the index test and reference standard were handled	3
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n/a
	18	Intended sample size and how it was determined	3
RESULTS			
Participants	**19**	Flow of participants, using a diagram	4
	20	Baseline demographic and clinical characteristics of participants	5
	21a	Distribution of severity of disease in those with the target condition	4
	21b	Distribution of alternative diagnoses in those without the target condition	4
	22	Time interval and any clinical interventions between index test and reference standard	n/a
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	n/a
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	5
	25	Any adverse events from performing the index test or the reference standard	n/a
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	5
	27	Implications for practice, including the intended use and clinical role of the index test	7
OTHER INFORMATION			
	28	Registration number and name of registry	n/a
	29	Where the full study protocol can be accessed	n/a
	30	Sources of funding and other support; role of funders	n/a

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Patient Management in OHCA

*Required

1. Your Initials *

2. Patient number *

Decision making

3. Choose a qualifying ECG and write the time the ECG was taken, or the number on the ECG (e.g. 10:45am or #2) *

This is either the first ECG taken (e.g. if all subsequent ECGs are similar), or the ECG that best reflects the likely condition of the patient (e.g. STE only visable on the 3rd ECG). If there is only one ECG available just put #1

4. What is the primary rhythm of the qualifying ECG? *

Tick all that apply.

- [ ] Sinus
- [ ] Atrial fibrillation / flutter
- [ ] Complete heart block
- [ ] Other:

5. What are the characteristics of the qualifying ECG? If the ECG is not clear, describe it as best you can or use the 'other' selection *

Mark only one oval.

- ◯ Narrow QRS
- ◯ Broad QRS (+ BBB)
- ◯ Broad QRS (- BBB)
- ◯ Evidence of old infarct – presence of q-waves
- ◯ Evidence of ST-segment elevation (V2-V3: >2mm males; >1.5mm females AND/OR ≥2 contiguous leads: >1mm)
- ◯ Evidence of ST-segment depression
- ◯ Normal
- ◯ Other:

6. Is the patient in cardiogenic shock? *

Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ Unclear

7. What time did the patient present to emergency?

Mark only one oval.

- ◯ Mon-Fri 8am - 5pm
- ◯ Mon-Fri after hours
- ◯ Weekend/public holiday 8am - 5pm
- ◯ Weekend/public holiday after hours

8. What is your working diagnosis for the cause of OHCA based on all the information available? *

Tick all that apply.

- [ ] STEMI
- [ ] NSTEMI
- [ ] Highly suspicious of ischaemia
- [ ] Other cardiac cause (specify below in 'other')
- [ ] Non-cardiac cause (specify below in 'other')
- [ ] Other:

9. What is your recommendation? *

Take into consideration day/time of presentation

Mark only one oval.

- ◯ Immediately to cathlab
- ◯ Delayed cathlab (<24 hours)
- ◯ Delayed cathlab (>24hrs e.g. next office hours)
- ◯ No cathlab indicated but review decision within 24hrs
- ◯ Cathlab not indicated

10. If applicable: What time frame do you recommend for delayed cathlab <24hrs? *

Select as many as apply; N/A if not applicable

Tick all that apply.

- ☐ Within 6 hours
- ☐ Within 12 hours
- ☐ Within 24 hours
- ☐ Next office hours
- ☐ Dependent on other tests e.g. echo, CT head (please specify below)
- ☐ Dependent on clinical progress
- ☐ N/A
- ☐ Other: _____

11. What is your reasoning for the timing of the intervention (or otherwise) *

_____

12. Do you remember the details about the in-hospital management and outcomes of this patient? *

Mark only one oval.

- ◯ Yes
- ◯ No

APPENDIX E – CHAPTER SIX SUPPLEMENTARY MATERIAL

STARD Checklist

Case Report Form – Coronary Angiogram Analysis

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3
	4	Study objectives and hypotheses	3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4
Participants	**6**	Eligibility criteria	4
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4
	9	Whether participants formed a consecutive, random or convenience series	4
Test methods	**10a**	Index test, in sufficient detail to allow replication	5-6
	10b	Reference standard, in sufficient detail to allow replication	5
	11	Rationale for choosing the reference standard (if alternatives exist)	3
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	5
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	n/a
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	4
	16	How missing data on the index test and reference standard were handled	4
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n/a
	18	Intended sample size and how it was determined	n/a
RESULTS			
Participants	**19**	Flow of participants, using a diagram	15
	20	Baseline demographic and clinical characteristics of participants	18
	21a	Distribution of severity of disease in those with the target condition	20
	21b	Distribution of alternative diagnoses in those without the target condition	n/a
	22	Time interval and any clinical interventions between index test and reference standard	n/a
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	19
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	19
	25	Any adverse events from performing the index test or the reference standard	n/a
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	10
	27	Implications for practice, including the intended use and clinical role of the index test	8-9
OTHER INFORMATION			
	28	Registration number and name of registry	n/a
	29	Where the full study protocol can be accessed	n/a
	30	Sources of funding and other support; role of funders	n/a

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Coronary Angiogram Analysis

Patient Number

% Stenosis

	Normal / minor	30-49%	50-69%	70-99%	100%
Left main					
Prox LAD					
Mid/Distal LAD, Diag branches					
Circ, OMs, LPA, LPL branches					
RCA, RPDA, RPL, AM branches					
Ramus					
Aberrant					

TIMI III flow

	0	1	2	3
Left main				
Prox LAD				
Mid/Distal LAD, Diag branches				
Circ, OMs, LPA, LPL branches				
RCA, RPDA, RPL, AM branches				
Ramus				
Aberrant				

If >=70% stenosis then

* angiographic evidence of thrombus at the site of occlusion or through the ability of opening the occluded artery by passing a guidewire easily through the lesion

	Lesion is acute / recent*	Lesion is chronic
Left main	○	○
Prox LAD	○	○
Mid/Distal LAD, Diag branches	○	○
Circ, OMs, LPA, LPL branches	○	○
RCA, RPDA, RPL, AM branches	○	○
Ramus	○	○
Aberrant	○	○

IRA and PCI

	infarct related artery	PCI
Left main	☐	☐
Prox LAD	☐	☐
Mid/Distal LAD, Diag branches	☐	☐
Circ, OMs, LPA, LPL branches	☐	☐
RCA, RPDA, RPL, AM branches	☐	☐
Ramus	☐	☐
Aberrant	☐	☐

Other disease findings

- ☐ No CAD
- ☐ Minor plaques <50%
- ☐ Small vessel CAD >=50%
- ☐ None

Other comments

Verdict

- ○ Type 1 MI (or 3 if deceased without troponin measurement)
- ○ Type 2 MI - myocardial oxygen supply/demand imbalance
- ○ Other MI (Specify)
- ○ Not MI
- ○ Not determined

Zeyon Score paper equivalent

- ○ Group 1: AMI-related OHCA - Presence of a recent coronary occlusion (thrombus) OR the ability to gross easily through the occlusion with TIMI 0-1 flow or a pattern of irregular unstable lesion (type II Ambrose) AND significant troponin increase
- ○ Group 2: Chronic CAD-related OHCA without AMI - Presence of significant but stable mainly concentric lesions, without evidence of thrombus, staining, or angiographic appearance of ruptured plaque
- ○ Group 3: non CAD-related OHCA - Normal angiogram or findings indicating an obviously stable CAD with an independent cause of arrest (clearly identifiable after angiography)

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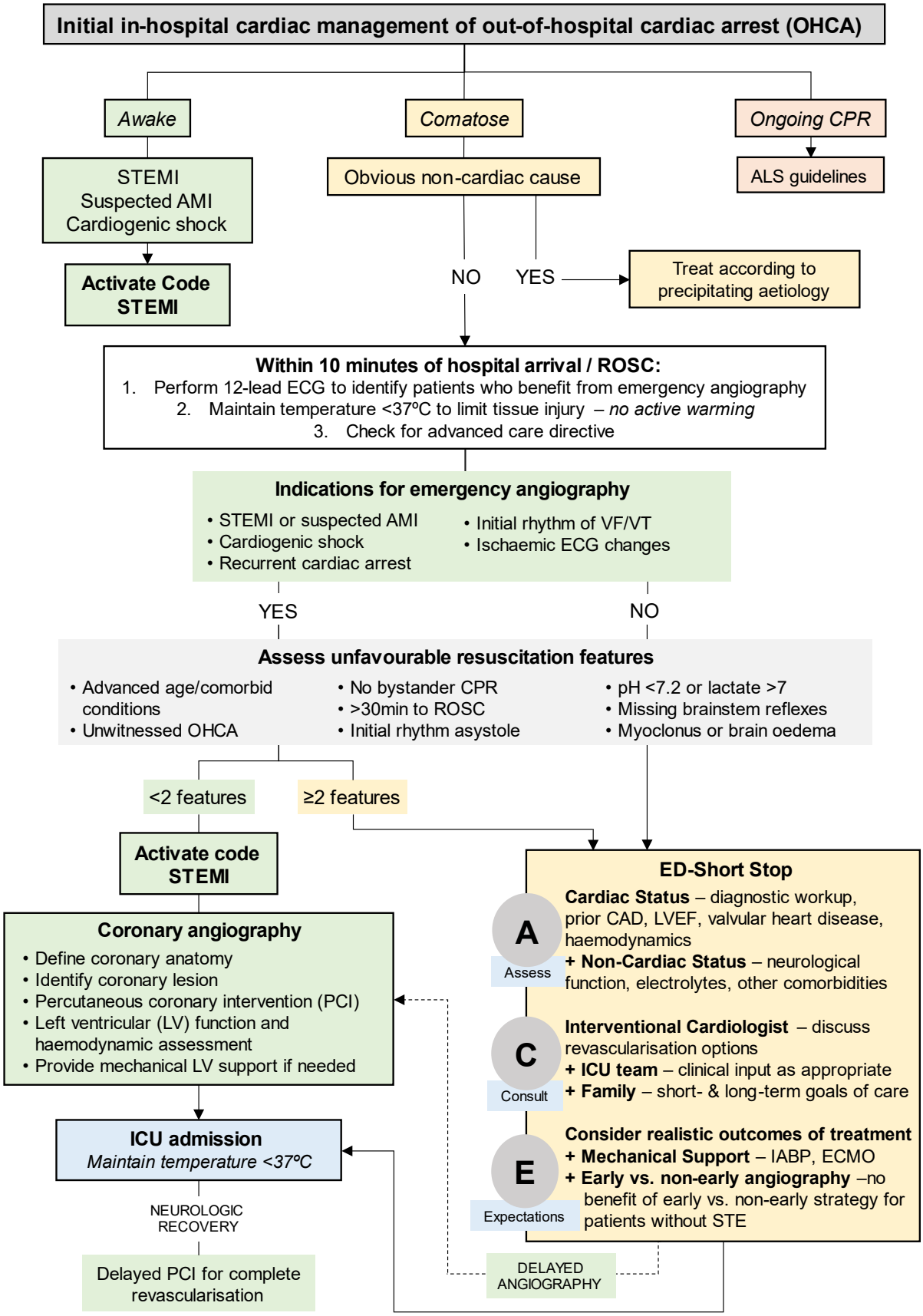
APPENDIX F – CHAPTER NINE SUPPLEMENTARY MATERIAL

Cardiac management of OHCA protocol



Adapted from Rab T et al. J Am Coll Cardiol. 2015; 66(1):62-73, Jentzer JC et al. J Am Coll Cardiol Intv. 2019;12(8):697-708, and Verma BR et al. J Am Coll Cardiol Intv. 2020;13(19):2193-205

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