Out-of-hospital cardiac arrest of non-cardiac aetiologies:

Incidence and outcomes

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Abstract

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide with many causes and is categorised into presumed cardiac and non-cardiac aetiologies. Presumed cardiac OHCA has been the focus of research over the last three decades. It has benefited from public health interventions such as medication therapies, implantable cardioverter-defibrillator placement for people with dysrhythmias, and community awareness in cardiopulmonary resuscitation (CPR) and defibrillation. Conversely, non-cardiac OHCA has received comparatively little investigation. The incidence and outcomes in this population are not well understood. This lack of understanding may lead to a delay in novel prevention and treatment interventions, or conversely, ongoing resuscitation attempts where the treatments are likely to be futile.

Using data from Victorian Ambulance Cardiac Arrest Registry (VACAR) and international data, this thesis comprises five published studies aiming to describe the incidence and outcomes of non-cardiac OHCA, with particular interest into the precipitating events of a drug overdose and hanging. Paper one examines whether the incidence and survival outcomes of cardiac and non-cardiac OHCA has changed over time in Victoria, Australia between 2000 and 2017. This paper shows that the incidence of OHCA of non-cardiac aetiologies increased by 28.8% in our region over the 18 years while that of presumed cardiac declined by 12.6%. Across precipitating aetiologies, the incidence increased rapidly in hanging, respiratory, neurological, and medical exsanguination over time. Also, survival for non-cardiac OHCA improved modestly over time (overall 6.3%), and this improvement was driven by increased survival in cases with pulseless electrical activity (PEA). In paper two and three, a systematic review of the literature on the incidence and outcomes of OHCA precipitated by drug overdose between 1990 and 2018 was undertaken. This review shows that emergency medical services are expected to treat ≥100,000 cases of OHCA precipitated by drug overdose worldwide every year, of which 9.0% survive to hospital discharge. Since it was unclear in this review whether survival could improve over time

as a result of improvements in bystander CPR and public access defibrillation, paper four describes the long-term epidemiology and outcomes of drug overdose OHCA in Victoria, Australia between 2000 and 2017. This paper shows that survival improved over time with an overall survival rate of 8.8%, and this improvement in survival could be explained by the increased rates of witnessed arrest and PEA. In addition, the majority of survivors reported good functional recovery and health-related of life outcomes at 12-months. To determine whether these improvements could be observed in other non-cardiac OHCA populations, paper five describes changes in the epidemiology and outcomes of hanging-related OHCA in Victoria, Australia, between 2000 and 2017. In this paper, survival did not improve over time with an overall survival rate of 2.9%, and 12-month outcomes for survivors were poor.

This thesis shows that by 2052, the majority of OHCA in our region will be precipitated by non-cardiac aetiologies. This finding suggests that there is a need for cause-specific prevention interventions to counteract the likely increase in the incidence of non-cardiac OHCA cases. Additionally, survival in non-cardiac OHCA is modestly improving in our region, and resuscitation efforts in some non-cardiac populations are not necessarily futile. These findings suggest that there is some potential for improvement in existing treatment interventions in these populations.

Publications during enrolment

1. **Alqahtani S**, Nehme Z, Williams B, Bernard S, Smith K. Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies. Resuscitation 2020;155(10):125-133.

2. **Alqahtani S**, Nehme Z, Williams B, Bernard S, Smith K. Temporal trends in the incidence, characteristics and outcomes of hanging-related out-of-hospital cardiac arrest. Prehosp Emerg Care 2020;24(3):369-77.

3. **Alqahtani S**, Nehme Z, Williams B, Bernard S, Smith K. Long-term trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose. Resuscitation 2019;144(11):17-24.

4. **Alqahtani S**, Nehme Z, Williams B, Smith K. The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: A systematic review and meta-analysis. Resuscitation 2019;134(1):10-18.

5. **Alqahtani S**, Nehme Z, Williams B, Smith K. Emergency medical services and cardiac arrest from drug overdose: A protocol for a systematic review of incidence and survival outcomes. JBI Database System Rev Implement Rep 2019;17(4):500-6.

Conference presentations

1. The Fifth Saudi Scientific Symposium, 2020. Changes in the incidence of out-of-hospital cardiac arrest of non-cardiac aetiologies compared to presumed cardiac during an 18-year period. Sydney, Australia.

2. Paramedics Australasia International Conference 2019. Trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose: An 18-year retrospective study. Hobart, Australia.

3. Paramedics Australasia International Conference 2019. Long-term trends in the incidence, characteristics, and outcomes of hanging related out-of-hospital cardiac arrest. Hobart, Australia.

4. Paramedicine Research Symposium, 2019. Out-of-hospital cardiac arrest precipitated by drug overdose: Changes in characteristics and outcomes over time. Melbourne, Australia.

5. Paramedicine Research Symposium, 2019. Incidence and survival outcomes of hanging-related out-of-hospital cardiac arrest. Melbourne, Australia.

6. Australian Resuscitation Council-Spark of Life Conference 2019. The global incidence and survival outcomes following out-of-hospital cardiac arrest of presumed drug overdose. Sydney, Australia.

7. Australian Resuscitation Council-Spark of Life Conference 2019. Trends in the epidemiology of drug overdose-related out-of-hospital cardiac arrest. Sydney, Australia.

8. Paramedicine Research Symposium, 2018. The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: A systematic review and meta-analysis. Melbourne, Australia.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published in peer-reviewed journals. The core theme of the thesis is epidemiology and outcomes of out-of-hospital cardiac arrest of non-cardiac aetiologies. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Paramedicine, Monash University, under the supervision of Professor Brett Williams, Dr Ziad Nehme and Professor Karen Smith. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapter one, two, three, and four my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature of and % of student contribution	Co-author name(s) % of contribution	Co-author(s), Monash student Yes/No
1	Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies	Published	Concept, methodology, formal analysis and writing original draft (75%)	Ziad Nehme (10%) Brett Williams (5%) Stephen Bernard (5%) Karen Smith (5%)	No No No No
2	Emergency medical services and cardiac arrest from drug overdose: A protocol for a systematic review of incidence and survival outcomes	Published	Concept, methodology, formal analysis and writing original draft (75%)	Ziad Nehme (15%) Brett Williams (5%) Karen Smith (5%)	No No No

2	The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: A systematic review and meta-analysis	Published	Concept, methodology, formal analysis and writing original draft (75%)	Ziad Nehme (15%) Brett Williams (5%) Karen Smith (5%)	No No No
3	Long-term trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose	Published	Concept, methodology, formal analysis and writing original draft (75%)	Ziad Nehme (10%) Brett Williams (5%) Stephen Bernard (5%) Karen Smith (5%)	No No No No
4	Temporal trends in the incidence, characteristics and outcomes of hanging-related out-of-hospital cardiac arrest	Published	Concept, methodology, formal analysis and writing original draft (75%)	Ziad Nehme (10%) Brett Williams (5%) Stephen Bernard (5%) Karen Smith (5%)	No No No No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Saeed Alqahtani

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Abbreviations

CI	Confidence Intervals
CPR	Cardiopulmonary Resuscitation
EMS	Emergency Medical Services
EQ-5D	EuroQol Five Dimensions
GOSE	Glasgow Outcome Scale-Extended
HRQoL	Health-Related Quality of Life
IQR	Interquartile Ranges
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratio
PEA	Pulseless Electrical Activity
ROSC	Return of Spontaneous Circulation
SD	Standard Deviations
SF-12	12-Item Short-Form
VACAR	Victorian Ambulance Cardiac Arrest Registry
VAS	Visual Analogue Scale
VF/VT	Ventricular Fibrillation/Pulseless Ventricular Tachycardia

Definitions

Died at scene	An OHCA that is declared dead at the scene by EMS.
Discharge alive or survival to hospital discharge	An OHCA that is discharged alive from the hospital.
EMS response time	The time from emergency call to EMS arrival at the scene.
EMS-attended	An OHCA that is attended by EMS, irrespective whether treatment was provided.
EMS-treated	An OHCA that received an attempt at resuscitation by EMS.
Event survival or survival to hospital	An OHCA that has a pulse at hospital arrival
Non-shockable rhythms	Rhythms that are not appropriate to receive defibrillation such as PEA and asystole.
OHCA	An absence of signs of circulation as determined by EMS or bystander.
OHCA of non-cardiac aetiologies	The cause of cardiac arrest identified on scene is non-cardiac in origins such as trauma, terminal illness, drug overdose, hanging, respiratory, neurological, drowning, non-traumatic exsanguination, and electrocution.
OHCA of presumed cardiac aetiology	The cause of cardiac arrest identified on scene is presumed to be of cardiac origin.
ROSC	An OHCA that achieves a detectible pulse any time during EMS resuscitation attempt.

Shockable rhythms	Rhythms that are appropriate to receive defibrillation such as VF/VT.
Transported with CPR	An OHCA that has an ongoing CPR at scene departure.
Transported with ROSC	An OHCA that has a ROSC at scene departure.

Introduction

Background

Out-of-hospital cardiac arrest (OHCA) remains a public health problem and is a leading cause of death worldwide.[1] It is defined as the absence of signs of systemic circulation as determined by emergency medical services (EMS) or bystanders.[2] Since many causes can lead to an OHCA; they are broadly categorised into presumed cardiac and non-cardiac aetiologies.[3] Historically, OHCA of presumed cardiac aetiology has been the focus of research and benefited significantly from public health interventions.[1] This includes medication therapy and implantable cardioverter-defibrillator placement (ICD) for a population with life-threatening arrhythmias and resuscitation efforts such as cardiopulmonary resuscitation (CPR) and defibrillation. Conversely, OHCA of non-cardiac aetiologies such as that precipitated by drug overdose, hanging, trauma, respiratory, drowning, and electrocution, has received comparatively little investigation. In this population, the incidence and survival outcomes are not well understood. This lack of information may lead to a delay in cause-specific prevention and novel treatment interventions, or conversely, ongoing resuscitation attempts where the treatments are likely to be futile.

Globally, the incidence rate of all causes OHCA has been estimated at 83.7 cases per 100,000 population with a considerable variation across different regions.[4] In Australia, the incidence was 112.9 cases per 100,000 population while it was 98.1 cases in North America, 86.4 cases in Europe, and 52.5 cases in Asia.[4] However, the incidence of OHCA of non-cardiac aetiologies relative to that of presumed cardiac aetiology is unknown. Also, the incidence of cardiac arrest is very dynamic and is rapidly changing over time.[5] As such, monitoring incidence changes over time is an alternative approach. A number of reports from different communities indicate that the incidence of OHCA of presumed cardiac aetiology declined over time and that of non-cardiac aetiologies increased.[6-11] In these reports, the incidence was derived from populations who received an attempt at resuscitation by EMS. Since those who received no attempt at resuscitation by EMS were excluded, the public health burden of non-cardiac aetiologies relative to the that of presumed cardiac remains unclear.

Globally, the rate of survival to hospital discharge has been estimated at 7.6% in 2010, and this remained largely unchanged for nearly 30 years.[12] Over the past ten years, temporal changes in survival rates have been reported in some regions. For example, in the United States, the rate of survival increased from 5.7% to 9.8% between 2005 and 2012 for all OHCA rhythms and from 16.1% to 27.9% for OHCA with shockable rhythms.[13] Similar changes have also been reported in Sweden, Denmark, Japan, and Australia.[10, 11, 14, 15] Authors of these reports indicated that increased rates of bystander CPR and defibrillation were associated with this improvement in survival. It is important to note that these improvements in outcome were reported for OHCA of presumed cardiac aetiology, as OHCA with non-cardiac aetiologies were excluded. One study on cases of non-cardiac aetiologies from Osaka, Japan, reported no changes in 30-day survival between 2005 and 2011 with an overall rate of 5.3%.[9] In that report, bystander CPR was not a predictor of survival. This contradicts findings reported in some non-cardiac populations such as that precipitated by drug overdose which found an association between bystander CPR and survival.[16, 17] Given the heterogeneous nature of OHCA of non-cardiac aetiologies, and that bystander CPR and defibrillation are not a priority in certain events such as that precipitated by trauma,[18] the short-term benefit of resuscitation efforts in some non-cardiac OHCA population is not well understood.

In 2011, a systematic review concluded that resuscitation efforts provide cardiac arrest survivors with good quality of life after hospital discharge in the majority of the included studies (n = 70).[19] In 2015, a landmark study from Victoria, Australia reported a similar conclusion.[20] In that study, the majority of OHCA survivors (55.6%) reported good functional recovery at 12-month follow-up according to Glasgow Outcome Scale-Extended (GOSE), and the majority (≥ 66.0%) reported no problems with mobility, self-care, daily activity, pain and anxiety according to EQ-5D-3L health survey. However, most of OHCA survivors assessed were of presumed cardiac aetiology (84.1%). Few reports have attempted to determine post-arrest outcomes for survivors of some non-cardiac aetiologies but were compromised by small sample sizes and limited to short-term functional outcomes.[21-23] For example, of a 52 hanging-related OHCAs from a single tertiary hospital in South Korea, five were discharged alive with poor neurological outcomes according to cerebral performance category score.[23] As such, long-term functional recovery and health-related quality of life (HRQoL) outcomes for survivors of OHCA of non-cardiac aetiologies have not been sufficiently described.

This thesis aimed to assess changes in the incidence and survival of OHCA of non-cardiac aetiologies relative to that of presumed cardiac aetiology and assess short and long-term benefits of resuscitation efforts in some non-cardiac populations, namely, OHCA precipitated by drug overdose and hanging. The reason these populations were chosen is that worldwide deaths from a drug overdose and hanging have substantially increased over the last three decades compared to other causes.[24]

Thesis structure

This thesis consists of five chapters. The first four chapters are designed to achieve the aims of this thesis as above and include a number of published papers (n = 5). Chapter five discusses the main findings and provides thesis implications and recommendations and conclusions.

Table 1 summarises the content of this thesis.

No	Chapter title	Paper title	Journal/Year published
1	Burden of non-cardiac OHCA in Victoria, Australia	Changes in the incidence of OHCA: Differences between presumed cardiac and non-cardiac aetiologies	Resuscitation/2020
2	Global incidence and outcomes of drug overdose OHCA	Emergency medical services and cardiac arrest from drug overdose: A protocol for a systematic review of incidence and survival outcomes	Joanna Briggs Institute Database of Systematic Reviews Implementation Reports/2019
		Incidence and outcomes of OHCA precipitated by drug overdose: A systematic review and meta-analysis	Resuscitation/2019
3	Epidemiology and outcomes of drug overdose OHCA in Victoria, Australia	Long-term trends in the epidemiology of OHCA precipitated by suspected drug overdose	Resuscitation/2019
4	Epidemiology and outcomes of hanging-related OHCA in Victoria, Australia	Temporal trends in the incidence, characteristics, and outcomes of hanging-related OHCA	Prehospital Emergency Care/2020
5	General discussion of main findings, and thesis implications and recommendations, and conclusion.	N/A	N/A

Abbreviations. OHCA: out-of-hospital cardiac arrest; N/A: not applicable.

Chapter 1. Burden of non-cardiac OHCA arrest in Victoria, Australia

Background

Prevention is the primary goal of the public health response to OHCA.[1] While the cause of cardiac arrest is mostly of presumed cardiac aetiology, and life-threatening arrhythmias precipitate the majority of these cases, most of the primary and secondary prevention interventions involve the use of beta-blockers and ICD placement.[1, 5] As a result, the incidence of OHCA of presumed cardiac aetiology has declined over time, and this is primarily driven by a reduction in the incidence of VF/VT.[6, 25, 26] Despite this, more than one million people from the United States, Europe, Japan, and Australia experience a cardiac arrest every year.[15, 27-29] The reason for this is not clear, but other causes of OHCA such as that precipitated by non-cardiac aetiologies may be increasing and undermining the reductions being made in presumed cardiac populations. To confirm this, there is a need to understand temporal changes in the incidence of OHCA of non-cardiac aetiologies relative to that of presumed cardiac aetiology. This understanding is essential for informing public health prevention interventions.

Aims

This chapter comprising a published paper aimed to assess temporal changes in the incidence of OHCA of non-cardiac compared to that of presumed cardiac. These changes will be evaluated across the overall population and among key subgroups of age, sex, region, arrest characteristics, precipitating non-cardiac aetiologies, and survival to hospital discharge.

Manuscript 1. Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies

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Clinical paper

Changes in the incidence of out-of-hospital cardiac arrest: Differences between cardiac and non-cardiac aetiologies

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Abstract

Aim: We aimed to assess temporal changes in the incidence of OHCAs of presumed cardiac and non-cardiac aetiologies.

Methods: We conducted a retrospective cohort study of OHCAs in Victoria, Australia between 2000–2017. Annual adjusted incidence rates in presumed cardiac and non-cardiac OHCA were calculated with 95% confidence intervals (95% CI), assuming a Poisson distribution. Annual percent changes in the adjusted rates were calculated from Poisson regression models.

Results: During an 18-year period, 90,688 emergency medical service (EMS)-attended OHCAs were included. Of those, 64,422 (71.0%) were of presumed cardiac and 26,266 (29.0%) were of non-cardiac aetiology. Over the 18-year period, there was a 12.6% (95% CI: 10.8%, 14.4%) relative decline in presumed cardiac events and this was driven largely by a reduction in cases with an initial shockable rhythm (23.4%; 95% CI: 19.8%, 27.0%) and cases in patients aged 65–79 years (48.6%; 95% CI: 45.0%, 50.4%). Conversely, there was a 28.8% (95% CI: 27.0%, 32.4%) relative increase in non-cardiac events over the 18-year period, and this was driven by an increase in initial pulseless electrical activity events (93.6%; 95% CI: 86.4%, 100.8%) and cases in patients aged ≥80 years (93.6%; 95% CI: 86.4%, 100.8%). Precipitating events with the largest 18-year increase in incidence were non-traumatic exsanguination (115.2%; 95% CI: 95.4%, 133.2%), respiratory (66.6%; 95% CI: 59.4%, 73.8%), and neurological (63.0%; 95% CI: 50.4%, 77.4%).

Conclusion: Our data indicates that by 2052, non-cardiac aetiologies could be the leading cause of OHCA in our region. These findings have important EMS-system and public health implications.

Keywords: Out-of-hospital cardiac arrest, Incidence, Survival, Cardiopulmonary resuscitation, Emergency medical services.

Background

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death and disability in industrialised countries.[1] Figures from the United States and Europe combined show that more than 700,000 people experience a cardiac arrest every year of whom around 50,000 survive to hospital discharge.[2–4] The corresponding figure from Australia is approximately 25,000 cases per year of which around 1500 are discharged alive.[5] However, the incidence of cardiac arrest

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is also changing over time.[6] Understanding temporal changes in the incidence of OHCA is important for informing future research and public health interventions.

Cardiac arrest is often dichotomised into presumed cardiac and non-cardiac aetiologies.[7] For presumed cardiac OHCA, international data suggests that the incidence is declining over time, and survival is increasing as a result of better prevention and treatment interventions.[8–11] This includes implantable cardioverter defibrillator (ICD) placement for at risk populations, and greater community engagement in cardiopulmonary resuscitation (CPR) and defibrillation. Conversely, there is some data that suggests that the incidence of OHCA precipitated by non-cardiac aetiologies is increasing, and survival is not improving.[12,13] However, these studies exclude OHCA patients who do not receive an attempt at resuscitation by emergency medical services (EMS). As such, it is difficult to know whether these changes reflect the true burden of OHCA in the community. In addition, while changes in incidence have been reported for both presumed cardiac and non-cardiac aetiologies, it is unclear which patient or arrest characteristics are contributing to these changes over time.

The aim of this study was to assess temporal changes in the incidence of OHCAs precipitated by presumed cardiac and non-cardiac aetiologies, across the overall population and among key subgroups of age, sex, witness status, arrest location, initial rhythm, bystander CPR, EMS treatment status, aetiology of arrest and survival outcome.

Methods

Study design

This was a retrospective population-based study. All OHCA that were attended by EMS between 1st January 2000 and 31st December 2017 were included. We excluded cardiac arrest of presumed sudden infant death syndrome (SIDS) as they involve only infant populations and by their very definition have no survivors. Data was obtained from the Victorian Ambulance Cardiac Arrest Registry (VACAR). The registry is a quality assurance project and the use and collection of its data was approved by the Victorian Department of Health Human Research Ethics Committee. This study has ethics approval from the Monash University Human Research Ethics Committee (Project number: 9600).

Settings

Ambulance Victoria is the sole provider of EMS in the state of Victoria, Australia, servicing approximately 6.3 million people across more than 227,000 km^2. Paramedics with advanced life support and intensive care skills respond simultaneously to OHCA events. In some areas across the state, community volunteers and fire-fighters with basic life support skills also respond to suspected cardiac arrests. Paramedics operate under clinical practice guidelines which are aligned to the guidelines of the Australian Resuscitation Council (www.resus.org.au). In adults with cardiac arrest, paramedics can withhold resuscitation in the field if there are obvious signs of death or the initial rhythm is asystole and the time between collapse and EMS arrival exceeds 10 min.

Data source and definitions

Since 1999, the VACAR has recorded data on all OHCA cases attended by EMS. A detailed description of the registry has been described elsewhere.[10] Briefly, the registry captures potential cardiac arrests from paper-based and electronic treatment records completed by paramedics through a sensitive search strategy. Most of data variables are recorded according to the Utstein style which uses uniform definitions for reporting OHCA elements.[14] The cause of cardiac arrest is presumed to be of cardiac origin unless an obvious non-cardiac cause is identified on scene (e.g. drug overdose, respiratory, trauma). EMS-attended OHCA refers to all cases of OHCA attended by the EMS, irrespective of whether treatment was provided. EMS-treated OHCA refers to cases that receive any attempt at resuscitation by EMS.

Statistical analysis

Baseline characteristics over time in presumed cardiac and non-cardiac OHCA were summarised using descriptive statistics. Continuous variables were reported as mean and standard deviations (SD) or median and interquartile ranges (IQR) and categorical variables were reported as counts and proportions. Trends in baseline characteristics over time were assessed using linear and logistic regression as appropriate.

Annual crude and age- and sex-adjusted incidence rates in presumed cardiac and non-cardiac OHCA were calculated per 100,000 person-years (and 95% confidence intervals [CI]) assuming a Poisson distribution. Crude rates were calculated by dividing the number of OHCA cases in each year by the population at risk during that year. Adjusted rates were calculated using the direct method. First, annual age and sex-specific rates were calculated as the number of OHCA cases across each 5-year age and sex band divided by the total population across that 5-year age and sex band. Second, we applied these rates to the age and sex distribution of the 2001 Australian standard population. Population figures were obtained from the Australian bureau of statistics (www.abs.gov.au). Annual changes in the adjusted incidence rates were then stratified according to age groups (0–14, 15–44, 45–64, 65–79, and $\geq$ 80 years), gender (male and female), region (rural and metropolitan), arrest characteristics (witnessed status, public location, ventricular fibrillation/pulseless ventricular tachycardia [VF/VT], pulseless electrical activity [PEA], asystole and bystander CPR), EMS treatment status (treated and not treated), and survival to hospital discharge. In OHCA of non-cardiac aetiology, we also examined annual changes in the adjusted incidence rates across precipitating events.

Annual percent changes in adjusted incidence rates were calculated from Poisson regression models with 95% CI. Differences in annual percent changes in the incidence of presumed cardiac and non-cardiac OHCA were assessed using the Chow test. A two-tailed p value of $<$0.05 was considered statistically significant. All statistical analyses were performed on STATA statistical software version 16.0 (Statacorp, College Station, Texas, USA).

Results

The population selection flow-chart is shown in Fig S1. The registry captured a total of 91,061 OHCAs between 2000 and 2017. After excluding cases of presumed SIDS (n = 373), 90,688 EMS-attended OHCAs were included. Of the EMS-attended cases, 64,422 (71.0%) were presumed cardiac and 26,266 (29.0%) were of non-cardiac aetiology.

Changes in baseline characteristics over time

Table 1 presents temporal changes in baseline characteristics of presumed cardiac and non-cardiac OHCA. In presumed cardiac cases, the overall crude incidence did not change over time. Mean age, the proportion witnessed, occurring in a public location, and presenting in VF/VT all declined over time. In comparison, the rate of bystander CPR nearly doubled over the study period from 21.3% in 2000-05 to 39.5% in 2012-17. In non-cardiac OHCA, the crude incidence rate increased significantly over time with an overall rate of 27.2 cases per 100,000 person-years (95% CI: 26.9, 27.5). Mean age, the proportion witnessed, and presenting in PEA all increased over the study period. The rate of bystander CPR has more than doubled during an 18-year period, increasing from 12.7% in 2000-05 to 28.3% in 2012-17.

Changes in the adjusted incidence rates of OHCA

Fig. 1 shows annual changes in the adjusted incidence rates of OHCA. The adjusted incidence rate for all OHCA was 83.7 cases per 100,000 person-years (95% CI: 83.4, 84.0), and this did not change over time. However, the adjusted rate declined over time in presumed cardiac cases with an overall rate of 60.0 cases per 100,000 person-years (95% CI: 59.7, 60.2) and increased in non-cardiac cases with an overall rate of 23.8 cases per 100,000 person years (95% CI: 23.6, 23.9). The annual adjusted rate in presumed cardiac cases declined by −0.7% (95% CI: −0.6%, −0.8%), while non-cardiac cases increased by 1.6% (95% CI: 1.5%, 1.8%) (both $p < 0.001$).

Changes in the adjusted incidence rates across stratifications

Annual changes in the adjusted incidence rates per 100,000 person-years across stratifications of presumed cardiac and non-cardiac OHCA are shown in Table 2 and Fig. 2. Across most stratifications, the adjusted incidence rates declined in presumed cardiac cases, and increased in non-cardiac cases. Across all stratifications, annual percent changes in the adjusted incidence rates differed significantly between presumed cardiac and non-cardiac OHCA ($p < 0.001$). In presumed cardiac OHCA, the annual adjusted incidence rate declined by −2.7% (95% CI: −2.5%, −2.8%) in patients aged 65−79 years, −1.7% (95% CI: −1.6%, −1.8%) in metropolitan region, and −1.3% (95% CI: −1.1%, −1.5%) in patients with initial VF/VT. In comparison, the annual adjusted rate increased by 1.7% (95% CI: 1.5%, 1.9%) in rural regions and 4.3% (95% CI: 4.2%, 4.5%) in bystander CPR. In non-cardiac OHCA, the annual adjusted incidence rate increased by 5.2%

Table 1 – Baseline characteristics of presumed cardiac OHCA and non-cardiac over time.

	Overall	2000-05	2006-11	2012-17	P-for trend	Missing, n (%)
Presumed cardiac OHCA						
Number of cases, (%)	64,422 (100.0)	19,505 (30.3)	20,920 (32.5)	23,997 (37.2)		
Crude rate per 100,000 person-years, (95% CI)	66.7 (66.2, 67.2)	67.4 (66.5, 68.4)	65.7 (64.8, 66.6)	67.0 (66.1, 67.8)	0.991	0
Mean age, (SD)	69.4 (16.8)	69.6 (16.0)	68.8 (17.4)	69.1 (17.3)	0.001	494 (0.8)
Male gender, n (%)	41,571 (64.6)	12,575 (64.7)	13,465 (64.4)	15,531 (64.8)	0.723	90 (0.1)
Witnessed arrest, n (%)	23,086 (36.2)	7134 (37.1)	7495 (36.0)	8457 (35,5)	<0.001	578 (0.9)
Public location, n (%)	6878 (10.7)	2212 (11.3)	2220 (10.6)	2446 (10.2)	<0.001	3 (0.0)
Initial rhythm, n (%)						779 (1.2)
VF/VT	12,077 (19.0)	3854 (20.2)	3815 (18.4)	4408 (18.5)	<0.001	
PEA	7527 (11.8)	2356 (12.3)	2289 (11.1)	2882 (12.1)	0.502	
Asystole	44,039 (69.2)	12,893 (67.5)	14,581 (70.5)	16,565 (69.4)	<0.001	
Bystander CPR, n (%)	19,233 (29.9)	4153 (21.3)	5606 (62.8)	9474 (39.5)	<0.001	1 (0.0)
Total EMS response time, Median (IQR)	8.0 (6.0, 11.2)	7.0 (6.0, 10.0)	8.3 (6.3, 12.0)	8.3 (6.3, 12.2)	<0.001	999 (1.6)
EMS response time per region, Median (IQR)						1000 (1.6)
Rural	10.0 (7.0, 16.0)	9.0 (6.0, 14.0)	10.0 (7.0, 16.0)	10.4 (7.2, 16.5)	<0.001	
Metropolitan	7.6 (6.0, 10.0)	7.0 (5.6, 9.0)	7.9 (6.1, 10.6)	7.7 (6.0, 10.6)	<0.001	
Non-cardiac OHCA						
Number of cases, (%)	26,266 (100.0)	7094 (27.0)	8803 (33.5)	10,369 (39.5)		
Crude rate per 100,000 person-years, (95% CI)	27.2 (26.9, 27.5)	24.5 (24.0, 25.1)	27.6 (27.0, 28.2)	28.9 (28.4, 29.5)	<0.001	0
Mean age, (SD)	51.7 (22.5)	47.6 (22.0)	52.0 (22.5)	54.0 (22.5)	<0.001	1930 (7.3)
Male gender, n (%)	18,046 (69.7)	4878 (70.7)	6046 (69.6)	7122 (69.2)	0.050	378 (1.4)
Witnessed arrest, n (%)	10,472 (40.7)	2512 (36.5)	3468 (39.9)	4492 (44.3)	<0.001	549 (2.1)
Public location, n (%)	7551 (28.8)	2386 (33.6)	2519 (28.6)	2646 (25.5)	<0.001	2 (0.0)
Initial rhythm, n (%)						409 (1.6)
VF/VT	771 (3.0)	278 (4.0)	254 (2.9)	239 (2.3)	<0.001	
PEA	4110 (15.9)	876 (12.7)	1264 (14.6)	1970 (19.2)	<0.001	
Asystole	20,976 (81.1)	5751 (83.3)	7157 (82.5)	8068 (78.5)	<0.001	
Bystander CPR, n (%)	5408 (20.6)	902 (12.7)	1577 (17.9)	2929 (28.3)	<0.001	0
Total EMS response time, Median (IQR)	8.4 (6.2, 12.5)	8.0 (6.0, 11.0)	9.0 (6.7, 13.0)	8.8 (6.5, 13.4)	<0.001	363 (1.4)
EMS response time per region, Median (IQR)						364 (1.4)
Rural	12.0 (8.0, 19.0)	11.0 (7.0, 17.0)	12.0 (8.0, 19.6)	12.2 (8.1, 19.0)	<0.001	
Metropolitan	7.8 (6.0, 10.5)	7.0 (5.9, 9.0)	8.1 (6.3, 11.1)	7.9 (6.1, 10.8)	<0.001	

Abbreviations. OHCA: out-of-hospital cardiac arrest. CI: confidence intervals. SD: standard deviation. VF/VT: ventricular fibrillation/pulseless ventricular tachycardiac. PEA: pulseless electrical activity. CPR: cardiopulmonary resuscitation. EMS: emergency medical services. IQR: interquartile ranges.

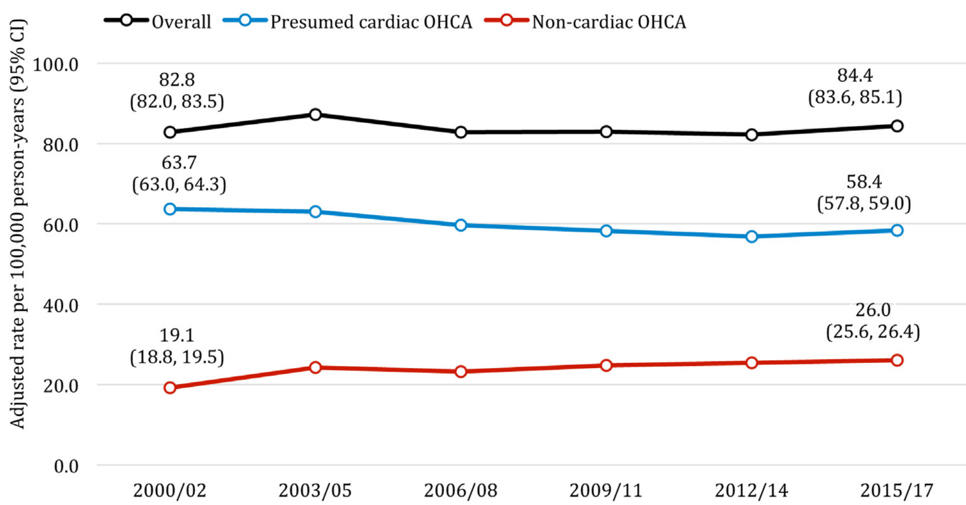

Fig. 1 – Annual changes in the adjusted incidence rates of presumed cardiac OHCA and non-cardiac.

(95% CI: 4.8%, 5.6%) in patients aged ≥80 years, 5.2% (95% CI: 4.9%, 5.4%) in rural regions, 0.3% (95% CI: 0.1%, 0.4%) in metropolitan region, and 5.2% (95% CI: 4.8%, 5.6%) in cases with initial PEA. In addition, the adjusted rate of bystander CPR increased by 8.3% (95% CI: 8.0%, 8.6%) per year.

Table 3 presents adjusted incidence rates across precipitating events. The adjusted incidence rate increased significantly over time in the majority of the causes of non-cardiac OHCA.

Changes in the adjusted incidence rates of OHCA survivors

Table 2 and Fig. 3 show annual changes in the adjusted incidence rate of survivors to hospital discharge stratified by initial rhythm. In presumed cardiac OHCA with initial VF/VT, the overall adjusted incidence rate of survivors was 3.2 cases per 100,000 person-years (95% CI: 3.1, 3.3), increasing by 5.4% (95% CI: 5.0%, 5.8%) per year. In non-cardiac OHCA with initial PEA, the overall adjusted incidence rate of survivors was 0.3 cases per 100,000 person-years (95% CI: 0.3, 0.3), increasing by 8.5% (95% CI: 7.3%, 9.8%) per year. Annual percent changes in the adjusted incidence rate of survivors differed significantly across cardiac and non-cardiac OHCA across all rhythms ($p < 0.001$).

Discussion

During an 18-year period, the overall incidence of OHCA did not change in Victoria, Australia. However, this was the result of opposing trends in the temporal incidence of presumed cardiac and non-cardiac OHCA. Over the study period, the incidence declined by 12.6% in presumed cardiac OHCA and increased by 28.8% in non-cardiac OHCA. If these trends continue as observed, our models estimate that non-cardiac aetiologies will be the leading cause of OHCA by 2052 (with an estimated incidence rate of 44.9 cases per 100,000 person-years). In presumed cardiac OHCA, the incidence of initial VF/VT declined by 23.4% over the 18-year period, while the relative rate of survival nearly doubled (97.2%). In non-cardiac OHCA, the incidence of initial PEA increased by 93.6% over the 18-year period, and the relative rate of survival also increased by 153.0%. In both populations, a substantial increase in the incidence has been observed in rural regions relative to that in the metropolitan region.

While we reported no temporal changes in the overall incidence of OHCA, a number of regional studies reported changes to the overall incidence of OHCA. For example, in a nationwide study from Japan, the incidence rate per 100,000 person-years increased from 80.7 in 2005 to 90.4 in 2009.[9] Similarly, population-based estimates obtained from the Resuscitation Outcomes Consortium indicate that the incidence rate of OHCA also increased in North America. In 2008, Nichol and colleagues reported a rate of 95.9 cases per 100,000 person-years.[15] In 2016, the rate was estimated at 110.8 cases per 100,000 person-years.[16] In these studies, the confounding effect of age and sex was not adjusted for in the calculation of incidence. In addition, it is unclear if these increases reflect an increase in the incidence rate of presumed cardiac or non-cardiac aetiologies, or both. Unlike the findings reported in Japan and North America, our incidence rates were age- and sex-adjusted, which adjust for changes in the age and sex structure of the population over time.

In presumed cardiac OHCA, there was a reduction in the incidence rate over the study period. This finding is consistent with a study from Perth, Australia, which reported an annual reduction in the incidence of presumed cardiac OHCA by 0.8 cases per 100,000 person-years between 1997 and 2011.[17] The authors of that study indicated that the reduction was driven largely by fewer events occurring in patients aged 65–84 years. Although we observed a similar finding, other subgroups also contributed to the reduction in presumed cardiac cases including a reduction in the incidence of initial VF/VT. Similar explanations have been proposed by other authors in different regions.[18–20] For example, a study from Seattle, United States, showed that the incidence rate of presumed cardiac OHCA declined between 1980 and 2000, from 139.0–90.0 cases per 100,000 person-years, and this was associated with a large reduction in the incidence of initial VF/VT.[18]

Although the incidence of initial VF/VT declined in our presumed cardiac OHCAs, the rate of survival improved substantially. Similarly, in Denmark, survival from initial VF/VT doubled between 2001 and 2010, despite a reduction in the proportion of EMS treated events from 32.2% to 28.7%.[11] In Sweden, there was a 10.0% absolute reduction in the incidence of VF/VT between 1992 and 2011, but the rate of

Table 2 – Annual changes in the adjusted incidence rates across stratifications.

	Adjusted incidence rate per 100,000 person-years (95% CI)				P for trend
	Overall	2000-5	2006-11	2012-17	
Presumed cardiac OHCA					
Number of cases	64,422	19,505	20.920	23,997	
Per age groups					
0–14 years	2.5 (2.4, 2.6)	2.7 (2.5, 3.0)	2.8 (2.5, 3.0)	2.0 (1.9, 2.2)	<0.001
15–44 years	11.5 (11.4, 11.7)	9.7 (9.5, 10.0)	11.3 (11.0, 11.6)	13.5 (13.2, 13.8)	<0.001
45–64 years	69.1 (68.5, 69.6)	66.6 (65.6, 67.6)	66.7 (65.8, 67.7)	73.9 (72.9, 74.9)	<0.001
65–79 years	224.8 (223.2, 226.4)	267.3 (264.2, 270.3)	217.1(214.3, 219.8)	190.1 (187.5, 192.7)	<0.001
≥ 80 years	566.3 (561.8, 570.8)	583.5 (575.6, 591.5)	573.9 (566.0, 581.8)	541.4 (533.8, 549.2)	<0.001
Per gender					
Male	77.9 (77.5, 78.3)	83.0 (82.3, 83.8)	76.2 (75.5, 76.9)	74.4 (73.7, 75.2)	<0.001
Female	42.3 (42.0, 42.6)	44.0 (43.5, 44.5)	42.0 (41.5, 42.5)	41.0 (40.5, 41.5)	<0.001
Per region					
Metropolitan	43.0 (42.8, 43.3)	48.2 (47.8, 48.6)	41.4 (41.0, 41.8)	39.5 (39.1, 39.9)	<0.001
Rural	16.9 (16.8, 17.1)	15.1 (14.9, 15.3)	17.6 (17.3, 17.8)	18.1 (17.8, 18.3)	<0.001
Per arrest characteristics					
Witnessed arrest	21.7 (21.5, 21.8)	23.5 (23.2, 23.8)	21.2 (20.9, 21.5)	20.0 (19.8, 20.3)	<0.001
Public location	6.6 (6.5, 6.7)	7.2 (7.0, 7.3)	6.4 (6.3, 6.6)	6.2 (6.0, 6.3)	<0.001
VF/VT	11.6 (11.5, 11.7)	12.8 (12.6, 13.0)	11.0 (10.8, 11.2)	10.9 (10.7, 11.1)	<0.001
PEA	6.9 (6.8, 7.0)	7.7 (7.6, 7.9)	6.4 (6.2, 6.5)	6.7 (6.6, 6.9)	<0.001
Asystole	40.7 (40.5, 40.9)	41.5 (41.2, 41.9)	40.9 (40.5, 41.3)	39.6 (39.2, 40.0)	<0.001
Bystander CPR	17.6 (17.5, 17.8)	13.8 (13.6, 14.0)	16.0 (15.8, 16.2)	23.1 (22.8, 23.4)	<0.001
Per EMS treatment status					
Treated	29.9 (29.7, 30.0)	31.8 (31.5, 32.2)	28.2 (27.9, 28.5)	29.6 (29.3, 29.9)	<0.001
Not treated	30.1 (29.9, 30.3)	31.5 (31.2, 31.9)	30.8 (30.5, 31.1)	28.0 (27.7, 28.3)	<0.001
Per initial rhythm survival rate,[a]					
VF/VT	3.2 (3.1, 3.3)	2.2 (2.1, 2.2)	3.3 (3.2, 3.4)	4.1 (4.0, 4.2)	<0.001
PEA	0.4 (0.4, 0.4)	0.4 (0.4, 0.4)	0.3 (0.3, 0.4)	0.4 (0.4, 0.4)	0.250
Asystole	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.2 (0.2, 0.3)	0.2 (0.2, 0.2)	0.422
Non-cardiac OHCA					
Number of cases	26,266	7094	8803	10,369	
Per age group					
0–14 years	3.5 (3.4, 3.7)	3.5 (3.2, 3.7)	3.7 (3.5, 4.0)	3.4 (3.2, 3.6)	0.331
15–44 years	22.4 (22.2, 22.6)	23.3 (22.9, 23.8)	21.5 (21.1, 21.9)	22.4 (22.0, 22.8)	0.043
45–64 years	26.4 (26.0, 26.8)	21.5 (21.0, 22.1)	27.2 (26.6, 27.8)	30.5 (29.8, 31.1)	<0.001
65–79 years	47.1 (46.4, 47.8)	41.6 (40.4, 42.8)	48.8 (47.5, 50.1)	50.9 (49.5, 52.2)	<0.001
≥ 80 years	87.5 (85.7, 89.2)	60.6 (58.1, 63.3)	91.4 (88.3, 94.6)	110.3(106.9, 113.8)	<0.001
Per gender					
Male	33.2 (33.0, 33.5)	30.7 (30.3, 31.2)	33.3 (32.8, 33.7)	35.7 (35.2, 36.2)	<0.001
Female	14.5 (14.3, 14.6)	12.7 (12.5, 13.0)	14.7 (14.4, 15.0)	15.9 (15.6, 16.2)	<0.001
Per region					
Metropolitan	17.0 (16.8, 17.1)	16.8 (16.5, 17.0)	17.2 (16.9, 17.4)	17.0 (16.8, 17.1)	<0.001
Rural	6.8 (6.7, 6.9)	4.9 (4.8, 5.0)	6.8 (6.6, 6.9)	8.7 (8.5, 8.9)	<0.001
Per arrest characteristics					
Witnessed arrest	9.1 (9.0, 9.2)	7.6 (7.4, 7.8)	9.1 (9.0, 9.3)	10.7 (10.5, 10.8)	<0.001
Public location	6.0 (5.9, 6.1)	6.3 (6.2, 6.5)	5.7 (5.5, 5.8)	6.1 (6.0, 6.2)	0.684
VF/VT	0.8 (0.7, 0.8)	0.9 (.09, 1.0)	0.7 (0.7, 0.8)	0.6 (0.6, 0.7)	<0.001
PEA	3.8 (3.7, 3.9)	2.8 (2.7, 2.9)	3.6 (3.6, 3.7)	5.0 (4.8, 5.1)	<0.001
Asystole	18.8 (18.7, 18.9)	17.3 (17.1, 17.5)	19.2 (19.0, 19.5)	19.9 (19.6, 20.2)	<0.001
Bystander CPR	5.1 (5.0, 5.2)	3.0 (2.9, 3.1)	4.6 (4.5, 4.7)	7.7 (7.6, 7.9)	<0.001
Per EMS treatment status					
Treated	9.4 (9.3, 9.5)	7.8 (7.6, 7.9)	9.3 (9.1, 9.5)	11.1 (10.9, 11.3)	<0.001
Not treated	14.4 (14.2, 14.5)	13.9 (13.7, 14.1)	14.6 (14.4, 14.8)	14.6 (14.4, 14.8)	<0.001
Per initial rhythm survival rate[b]					
VF/VT	0.1 (0.1, 0.2)	0.1 (0.1, 0.1)	0.2 (0.2, 0.2)	0.1 (0.1, 0.2)	0.295
PEA	0.3 (0.3, 0.3)	0.2 (0.1, 0.2)	0.3 (0.3, 0.4)	0.5 (0.4, 0.5)	<0.001
Asystole	0.2 (0.2, 0.2)	0.2 (0.1, 0.2)	0.2 (0.2, 0.3)	0.1 (0.1, 0.1)	0.005

Abbreviations. CI: confidence intervals. OHCA: out-of-hospital cardiac arrest. VF/VT: ventricular fibrillation/pulseless ventricular tachycardia. PEA: pulseless electrical activity.

[a] Adjusted survival to hospital discharge rate per initial rhythm in EMS-treated cases of presumed cardiac OHCA, n = 30,928 (VF/VT: n = 12,004; PEA: n = 6928; Asystole: n = 11,996).

[b] Adjusted survival to hospital discharge rate per initial rhythm in EMS-treated cases of non-cardiac OHCA, n = 9476 (VF/VT: n = 724; PEA: n = 3529; Asystole: n = 5223).

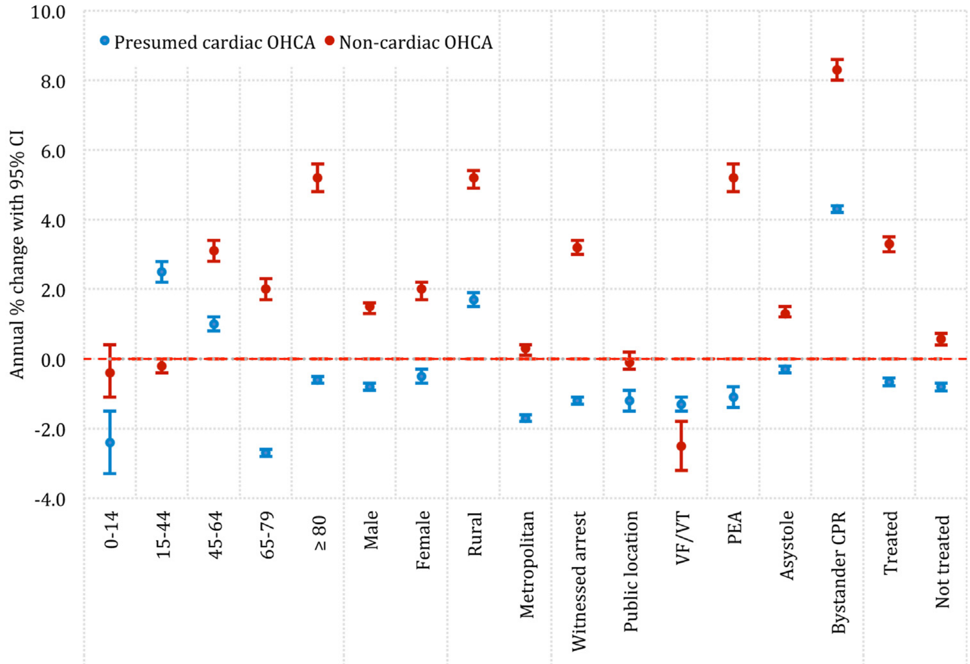

Fig. 2 – Annual percent changes in the adjusted incidence rates of presumed cardiac OHCA compared to non-cardiac per age group, gender, region, arrest characteristics, and EMS treatment status.

Table 3 – Annual adjusted incidence rates of non-cardiac OHCA per precipitating aetiology.

	Incidence rate per 100,000 person-years, (95% CI)				Annual % change (95% CI)	P for trend
	Overall	2000-05	2006-11	2012-17		
Trauma, n = 6849	5.3 (5.2, 5.4)	5.1 (5.0, 5.2)	5.2 (5.0, 5.3)	5.7 (5.6, 5.8)	1.2 (0.9, 1.4)	<0.001
Terminal illness, n = 5365	4.9 (4.8, 5.0)	4.5 (4.3, 4.6)	5.3 (5.2, 5.4)	4.9 (4.8, 5.1)	1.4 (1.1, 1.7)	<0.001
Drug overdose, n = 4543	4.6 (4.5, 4.6)	5.1 (4.9, 5.2)	4.3 (4.1, 4.4)	4.4 (4.3, 4.5)	−0.9 (−0.6, −1.2)	<0.001
Hanging, n = 3891	3.8 (3.7, 3.9)	3.2 (3.1, 3.3)	3.7 (3.6, 3.8)	4.5 (4.3, 4.6)	3.0 (2.7, 3.3)	<0.001
Respiratory, n = 3464	3.2 (3.1, 3.3)	2.4 (2.3, 2.5)	3.4 (3.3, 3.5)	3.8 (3.7, 3.9)	3.7 (3.3, 4.1)	<0.001
Neurological, n=808	0.8 (0.8, 0.8)	0.6 (0.5, 0.6)	0.9 (0.9, 1.0)	0.9 (0.8, 0.9)	3.5 (2.8, 4.3)	<0.001
Drowning, n = 549	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.4, 0.5)	0.5 (0.5, 0.6)	0.6 (-0.3, 1.5)	0.177
Non-traumatic exsanguination, n = 477	0.4 (0.4, 0.5)	0.3 (0.2, 0.3)	0.4 (0.4, 0.4)	0.6 (0,6, 0.7)	6.4 (5.3, 7.4)	<0.001
Other causes, n = 320	0.3 (0.3, 0.3)	0.2 (0.1, 0.2)	0.3 (0.3, 0.4)	0.4 (0.4, 0.4)	5.9 (4.6, 7.2)	<0.001

Abbreviations. CI: confidence intervals.

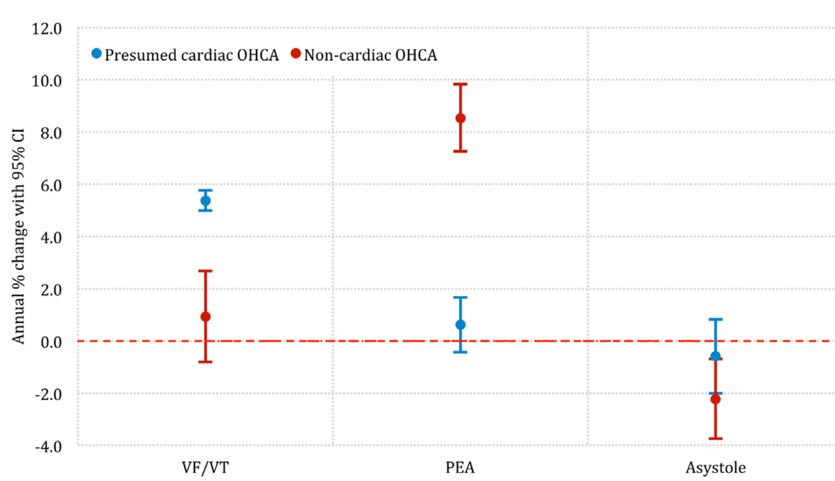

Fig. 3 – Annual percent changes in the adjusted rates of survival to hospital discharge of presumed cardiac OHCA compared to non-cardiac per initial rhythm.

survival nearly tripled.[21] These increases in survival have been linked to recent improvements in the links of the chain of survival.[11,21] This includes increasing the rate of bystander CPR. In presumed cardiac OHCA, the rate of bystander CPR nearly doubled in our study. It is possible that the proportion of patients with VF/VT who received bystander CPR increased over time, and this could be associated with improved survival.

A number of studies also reported changes in the incidence of non-cardiac OHCA, including one from US and Japan.[12,13] However, the populations included in these studies were those who received an attempt at resuscitation by EMS, and those who were aged ≥20 years. Additionally, these studies did not report which precipitating events were responsible for this increase. An important finding in our study is that the incidence of initial PEA in non-cardiac OHCA doubled over time with a near two-fold increase in survival. A higher rate of initial PEA may be explained by the increased rate of witnessed arrests and bystander CPR in these populations. Initial PEA is also a known predictor of survival in non-cardiac OHCA populations (relative to asystole).[22,23] Our findings differ from an earlier report from our region which showed that the incidence of PEA declined between 2003 and 2013, with no improvements in survival.[24] In that report, 71.1% of the included population were of presumed cardiac aetiology.

Our study shows that the incidence of non-cardiac OHCA increased in both regions over the 18-year period; however, this increase was larger in rural regions (93.6%) relative to that in the metropolitan region (5.4%). Conversely, the incidence of presumed cardiac OHCA increased over the study period by 30.6% in rural regions while it declined by 30.6% in the metropolitan region. Our findings appear comparable to a 4-year nationwide study from South Korea, which showed that presumed cardiac OHCAs increased at a greater rate in rural areas (50.8%) compared with metropolitan areas (15.8%).[25] There may be a number of reasons for this. In many developed countries, rural populations have poorer access to health care services, preventive screening, and health education compared with metropolitan populations.[26,27] For instance, a mass media campaign targeting knowledge and awareness of heart attacks symptoms was associated with a significant reduction in OHCA incidence in metropolitan areas of Victoria.[28] Unfortunately, rural areas received a much smaller version of this public awareness campaign and its effect on OHCA is yet to be determined. Novel strategies which target high-risk rural areas with knowledge of heart attack and OHCA warning symptoms may be useful as preventive measures.

Our study has important implications for the direction of public health interventions targeting OHCA. The majority of evidence-based prevention interventions developed over the last three decades are cardiovascular-specific, and include the use antiarrhythmic drugs, fatty acids and lipids therapies, revascularisation, and ICD placement for at risk individuals.[29] In addition, international data suggests that the incidence of myocardial infarction is also declining over time, supported by better prevention interventions.[30,31] While these factors could explain the reduction in incidence of presumed cardiac OHCA, our modelling suggests that non-cardiac aetiologies will become the leading cause of OHCA by 2052. Suicide (particularly from hanging) is on the rise in many regions,[32,33] and existing community-based strategies appear to be ineffective at curbing the rate of suicide in our community.[34] In addition, increased prescribing of anti-coagulants could also lead to a concomitant rise in deaths from major haemorrhage,[35–37] and this could explain the increase in medical exsanguination cases in our study. Increased efforts are therefore needed to better understand the epidemiological and social determinants contributing to non-cardiac OHCAs, and the development of novel public health strategies to reduce their frequency.

As the incidence of VF/VT declines, so does the absolute number of survivors from OHCA. Interestingly, our modelling suggests that by 2052, the rate of initial VF/VT will make up just 10.8% of all EMS-attended cases of presumed cardiac aetiology. Unfortunately, survival rates from initial asystole and PEA are generally low, and there is ongoing concern that many survivors experience poor neurological outcomes.[24] A recent randomised controlled trial indicates that the early use of therapeutic hypothermia in these populations could improve the number of neurologically intact survivors from OHCA with an initial non-shockable rhythm.[38] There is also a need to examine the role of new resuscitation approaches which optimise the early recognition and treatment of reversible causes of OHCA in the field. A recent example is the development of trauma-specific resuscitation protocols for patients with traumatic OHCA, which emphasise oxygenation, control of major haemorrhage and volume replacement, before CPR.[39] Unfortunately, the evidence supporting these resuscitation approaches remain weak, and ongoing research is needed to determine their value.

Limitations

Our study is limited by its retrospective study design which suffers from inherent methodological limitations. The cause of cardiac arrest in our population was presumed by paramedics. As such, paramedics are likely to misclassify the cause of some cardiac arrests. In an autopsy study from San Francisco, US, approximately 40% of presumed cardiac OHCA were misclassified.[40] While we adjust for age and sex, other population-based factors are also likely to contribute to changes in the incidence of OHCA in the future. Finally, while we had a low rate of missing data for most variables (usually <2.1%), patient age was missing in 7.3% of all non-cardiac OHCA.

Conclusion

Our data indicates that by 2052, non-cardiac aetiologies could be the leading cause of OHCA in our region. Evidence-based prevention interventions are needed to reduce the incidence of non-cardiac OHCA. Our data also indicates that the incidence of shockable rhythms is declining in both presumed cardiac and non-cardiac OHCA populations, and the incidence of initial PEA is increasing. Increased research efforts are therefore needed to identify novel treatment approaches in patients with initial non-shockable rhythms, which help to improve the rate of neurologically intact survival. Resuscitation approaches which optimise the early identification and correction of reversible non-cardiac causes of OHCA also require further investigation.

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Declaration

Along with myself, Dr Ziad Nehme, Prof Brett Williams, Prof Stephen Bernard, and Prof Karen Smith, confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

Conflict of interest

None to declare.

CRediT authorship contribution statement

Saeed Alqahtani: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Ziad Nehme:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing - review & editing, Supervision. **Brett Williams:** Writing - review & editing, Supervision. **Stephen Bernard:** Writing - review & editing. **Karen Smith:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing - review & editing, Supervision.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2020.07.016.

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Manuscript 1 Appendix. Supplementary Data

Supplementary

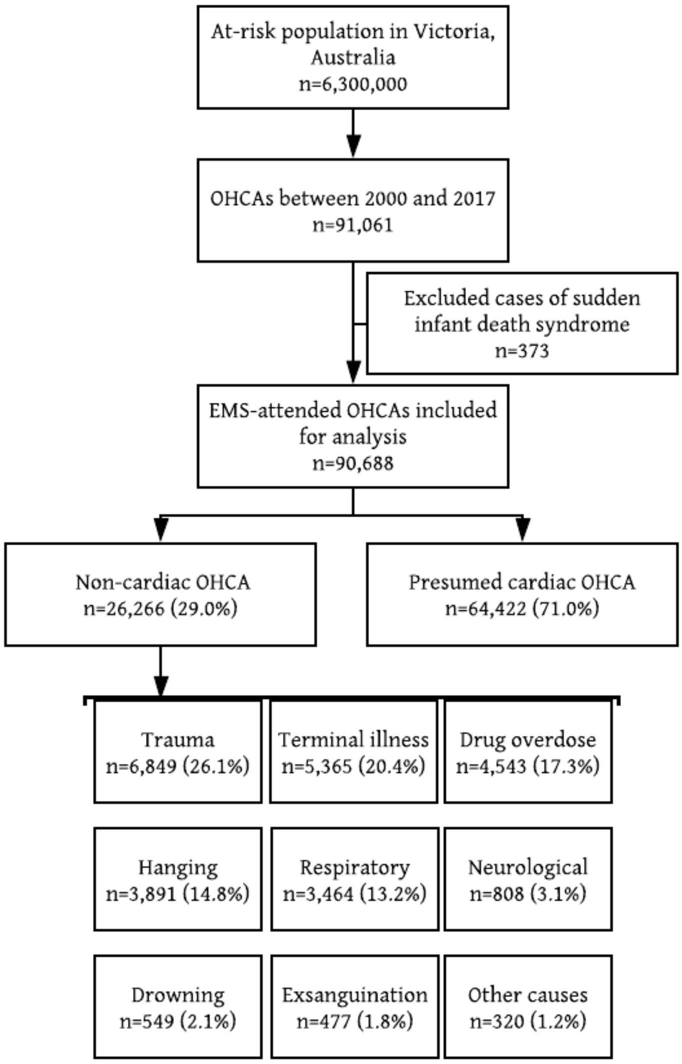

Figure S1. Flowchart of the included cases.

Summary of findings

In Victoria, Australia, nearly one-third of OHCA was precipitated by non-cardiac aetiologies between 2000 and 2017. However, the incidence increased by 28.8% over the 18 years. Also, across most of the precipitating aetiologies, the incidence increased over the 18 years, and this increase ranged between 54.0% and 115.2% in some of these aetiologies such as that precipitated by non-traumatic exsanguination, respiratory, neurological, and hanging. Interestingly, the adjusted rate of survival for all cardiac rhythms modestly increased from 5.3% in 2000-05 to 7.4% in 2012-17. Cases with initial PEA drive this increase in the overall survival, whose survival increased by 153.0% over the 18 years. Finally, over the 18 years, the incidence increased by 57.6% in cases that were witnessed, 149.4% in cases that received bystander CPR, and 93.6% in cases presented with PEA.

Chapter 2. Global incidence and outcomes of drug overdose OHCA

Background

In the previous chapter, the overall incidence of drug overdose OHCA declined over the 18 years in Victoria, Australia, but there was some evidence that the incidence increased between 2006-11 and 2012-17. In addition, short- and long-term outcomes in this population have not been reported. Drug overdose OHCA is characterised by deliberate or accidental use of prescribed medications, recreational drugs or ethanol.[2] In some regions, one-third of OHCA in young adults (16-39 years) is precipitated by drug overdose.[30, 31] While restricting access to illicit drugs and bystander CPR and defibrillation are critical public health strategies to reduce the incidence of drug overdose OHCA and improve survival, the incidence and survival outcomes varied across regions.[16, 17, 32] Unfortunately, it is unclear if these variabilities are related to differences in the effectiveness of prevention and treatment interventions across the studied regions or only due to chance. Understanding these variabilities is important for informing public health prevention and treatment interventions.

Aims

The aim of this chapter which consists of two published papers, was to review the literature on the global incidence and survival outcomes of drug overdose OHCA. The first paper is a systematic review protocol. In this protocol, the search strategy, inclusion criteria, types of included studies, methods of data extraction and quality assessment, and statistical analysis are described in detail. The second paper is a systematic review and meta-analysis. In this paper, the methods described in the protocol are applied to assess incidence rates; survival outcomes which include ROSC, event survival, survival to hospital discharge, long-term outcomes for survivors; and predictors of survival.

Manuscript 2. Emergency medical services and cardiac arrest from drug overdose: A protocol for a systematic review of incidence and survival outcomes

Emergency medical services and cardiac arrest from drug overdose: a protocol for a systematic review of incidence and survival outcomes

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Review question: The primary review question is: what is the global incidence rate of emergency medical services (EMS)-attended and EMS-treated out-of-hospital cardiac arrest (OHCA) precipitated by drug overdose in adults? The secondary review questions are: what proportion of adults with EMS-treated overdose OHCA: i) survived to hospital discharge or 30 days, ii) survived with intact neurological function at hospital discharge (i.e. Cerebral Performance Category or modified Rankin Scale ≤ 2), iii) achieved prehospital return of spontaneous circulation, iv) survived to hospital, and v) survived to 12 months?

Keywords Cardiopulmonary resuscitation; drug; out-of-hospital cardiac arrest; overdose; substance

JBI Database System Rev Implement Rep 2019; 17(4):500–506.

Introduction

Drug overdose poses a significant public health problem worldwide and accounts for thousands of deaths each year.[1,2] Between 2004 and 2014, drug overdose caused nearly half a million deaths in the United States.[1] In 2016, as many as 100,000 people older than 15 years died from drug overdose globally,[1] and opioid overdose alone was responsible for about 70% of these deaths.[2] Although the incidence of drug overdose has remained stable in the past few years, deaths from drug overdose have not reduced and continue to be a significant public health issue.[1]

Out-of-hospital cardiac arrest (OHCA) is a common pathophysiological mechanism of death following drug overdose and is relatively common among young adults.[3-8] In a study conducted in London, United Kingdom, drug overdose accounted for 34% of OHCA cases and was concentrated among adults between the ages of 18 to 35 years.[8] Similarly, drug overdose was the most common cause of OHCA (33.5%) in young adults aged 16 to 39 years in Melbourne, Australia.[7]

There is growing evidence that the incidence of OHCA precipitated by drug overdose is increasing in developed countries.[5,6,9] In Ontario, Canada, the incidence of drug-overdose OHCA increased 9% between 2007 and 2013, and the number of deaths from drug overdose nearly tripled from 1.3 to 3.3 cases per 1000 people between 1992 and 2010.[6] In 2011, approximately 8% of OHCAs in Pittsburgh, United States, were due to drug overdose, which is a three-fold increase from 1999.[9] The widespread use of prescribed and recreational drugs is thought to be the key contributing factor to the increase in drug overdose OHCA.[4-6]

Emergency medical services (EMS) are often the first point of contact for most drug overdose-related events and can make a significant difference in reducing the burden of disease and illness from OHCA.[3-6] A number of well-developed EMS systems have demonstrated that targeted improvements to the chain of survival, which focus on the early delivery of cardiopulmonary resuscitation (CPR) and defibrillation by members of the community, can yield substantial increases in the survival rate after OHCA.[10-15] For example, in the United States,

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neurologically intact survival following OHCA of presumed cardiac etiology increased by 45% between 2005 and 2012.[10] Similarly, there was a 53% increase in neurologically favorable survival in a nationwide study conducted in Japan between 2005 and 2009.[11] However, much of the growth in survival following OHCA has occurred in populations with presumed cardiac etiology or initial shockable arrest rhythms, and these patients typically benefit from the early application of interventions such as bystander CPR and defibrillation.[10-12,15]

In comparison to OHCA of presumed cardiac etiology, cases of drug-overdose OHCA are usually unwitnessed and often present with asystole.[3-6,16] As a result, it is unclear whether existing initiatives to tackle the low rate of survival from OHCA are useful in populations with non-cardiac etiologies, such as drug overdose. In addition, comparatively little is known about the global incidence and outcomes of drug-related OHCA. The lack of synthesized data can contribute to delays in the development of novel treatment interventions or preventive strategies, which can help minimize the burden of these events in the community.

A systematic review from 2010 examined the global incidence and outcomes of OHCA but focused mainly on cases with presumed cardiac etiologies.[17] The review found that the global incidence of EMS-attended OHCA (i.e. all patients with OHCA attended by EMS irrespective of whether treatment was provided) was 83.7 cases per 100,000 person-years. The incidence of EMS-treated OHCA (i.e. patients receiving any attempt at resuscitation) was 34.7 per 100,000 person-years, and the rate of survival to hospital discharge was 7.1%. A preliminary literature search has been conducted through the Cochrane Database of Systematic Reviews, *JBI Database of Systematic Reviews and Implementation Reports*, and the databases of PROSPERO, MEDLINE and Embase, and found no systematic review, protocol or title published or underway on this topic. To date, studies investigating overdose OHCA have not been systematically assessed. Therefore, we aimed to systematically review the literature on the incidence and outcomes of adult OHCA precipitated by drug overdose. The findings of this review may help inform public health initiatives in the development of novel prevention and treatment strategies.

Inclusion criteria

Participants

This review will consider studies, conducted worldwide, that include adult patients aged $\geq$ 15 years who are attended and/or treated by EMS for drug overdose. EMS-attended OHCA refers to all cases of OHCA attended by the EMS, irrespective of whether treatment has been provided. EMS-treated cases refer to the sub-group of EMS-attended OHCA who receive any attempt at resuscitation. Studies assessing only the pediatric population (aged $<$15 years) will be excluded.

Condition

Internationally agreed definitions for OHCA and drug-overdose OHCA have been reported.[18] OHCA is defined as "the absence of signs of circulation irrespective of whether the assessment was made by EMS or bystander".[18(p.1288)] OHCA precipitated by drug overdose is defined as "evidence that cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol".[18(p.1290)] This review will consider studies of drug overdose OHCA that are aligned with these definitions. Studies that have not clearly defined overdose but have used the terms "drug-related", "overdose", "poisoning" or "intoxication" as the cause of OHCA will be included. As the primary outcome of the study is to pool the global incidence and outcomes of an undifferentiated population of drug-related OHCA, we will exclude studies of selected or isolated cases of drug overdose (e.g. tricyclic antidepressant overdose or opioid overdose) or chemical poisoning (e.g. organophosphate or carbon monoxide poisoning), which could introduce heterogeneity.

Context

We will include studies involving cardiac arrest populations in out-of-hospital settings. Studies of in-hospital cardiac arrest will be excluded.

Outcomes

The main outcome of this review is the pooled incidences rate of EMS-attended and EMS-treated OHCA cases per 100,000 people. Secondary outcomes include the pooled proportion of survivors to hospital discharge or 30 days, survivors with intact neurological function at hospital discharge, patients achieving return of spontaneous circulation, patients surviving to hospital, and patients surviving to 12 months.

Types of studies

This review will consider interventional studies including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. In addition, both descriptive and analytical observational studies including retrospective and prospective cohort studies will be considered for inclusion. Studies published after January 1990 will be included; however, if a study collected data before 1990 but was published after 1990, it will be excluded. During 1990, the Utstein template for unified terms and definitions of OHCA was developed and implemented by many cardiac arrest registries.[19] Our aim is to find studies with rigorous reporting and less heterogeneity so that we can have accurate estimates and summaries. Study designs that cannot be used to pool the incidence rates of EMS-attended and EMS-treated cases, including non-consecutive case series and case reports, will be excluded. Editorial letters will also be excluded.

Methods

We will use the Joanna Briggs Institute (JBI) methodology for systematic reviews of prevalence and incidence.[20] The title of this review has been registered with JBI.

Search strategy

The search strategy aims to find published studies and unpublished studies written in English. We will use a three-step search strategy in this review. First, we will search MEDLINE and Embase using keywords specific for the topic (heart attack, cardiac arrest, cardiopulmonary resuscitation, drug overdose, substance abuse) (Appendix I). We will analyze text words contained in the titles and abstracts, and the index terms used to describe the topic. Second, we will search MEDLINE, Embase, Emcare, all EBM reviews (ACP Journal Club, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and National Health Service Economic Evaluation Database), and CINAHL using all relevant keywords and index terms. Third, we will identify relevant articles that are eligible for final inclusion and critical appraisal, and review their reference lists for potential studies that may have been missed in the initial search. The search for unpublished studies will include CORE, MedNar, Trove and the Resuscitation Outcomes Consortium.

Study selection

Studies will be collated and uploaded using EndNote X7 (Clarivate Analytics, PA, USA), and duplicates will be removed. Two reviewers will independently review the titles and abstracts of all articles for relevant eligibility criteria. Discrepancies in included articles between reviewers will be resolved through mutual consensus. If not resolved, a third reviewer will make the final decision. A PRISMA flow chart will display the process of data search and inclusion.[21]

Assessment of methodological quality

Studies that will be considered for the review will be assessed by two independent reviewers. The JBI critical appraisal tools for studies reporting incidence data will be utilized and will be selected based on the type of study design.[22] The reviewers will resolve any disagreements through consensus. If disagreements are not resolved, the consensus of a third reviewer will be sought. All studies, regardless of their methodological quality, will undergo data extraction and synthesis where possible.

Data extraction

We will develop a standardized data extraction form using Microsoft Excel (2013). This form is modified from the standardized data extraction tool for systematic reviews of prevalence and incidence developed by JBI.[22] Main components of the form will include citation details, study details, demographics and clinical characteristics, and survival outcomes (Appendix II). The citation details include author(s) name, year of publication and aims. The study details include settings, study design and duration, total population and how overdose OHCA was defined. The patients' demographics and clinical characteristics include the number of EMS-attended and EMS-treated cases, mean age, sex, and the percentage of cardiac arrest incidents that were witnessed by a bystander, received any attempt at CPR by a member of the public (i.e. bystander CPR), occurred in private residence and presented with shockable arrest rhythm. The survival outcomes include all outcomes that are described in the review questions. Two reviewers will extract data independently. Differences in data extraction will be resolved by discussion or a third opinion. If there are missing data, we will contact the main author for more clarification.

Data synthesis

Quantitative data will be analyzed in STATA 15.0 (Stata Corp LLC, Texas, USA) for statistical meta-analysis using random-effects model because we assume that the true incidence and survival outcome estimates vary across studies. All results will undergo double data entry. First, the incidence rate for EMS-attended and EMS-treated drug-overdose OHCA will be calculated as the number of new cases divided by the average of the total population during that same period (person-years) multiplied by 100,000. The 95% confidence intervals (CI) will be calculated using the Poisson distribution.[23] The DerSimonian and Laird method will be computed to pool incidence rates, with the estimate of heterogeneity taken from the inverse variance. Second, the proportions of survival outcomes will be calculated as the number of cases in each outcome divided by the EMS-treated cases. Because the proportions of survival outcomes in OHCA studies are below 0.5 and close to 0,[24] we will enable the Freeman-Tuckey double arcsine transformation and use the score 95% CI for individual study.[25]

Third, subgroup analysis by study region and case definition (i.e. aligned with Utstein definition and not aligned with Utstein definition) will be conducted if sufficient data are available to explore sources of heterogeneity. Fourth, meta-regression will, where possible, be conducted using the random-effects model to assess if the rates of witnessed arrest status, bystander CPR and initial shockable arrest rhythm can explain any of the heterogeneity in survival proportions across studies. Heterogeneity will be assessed statistically using the standard Chi-square and I^2 square tests. The I^2 values of 25%, 50% and 75% will indicate low, moderate and high heterogeneity, respectively.[26] The *P* value of < 0.10 will indicate significant heterogeneity. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

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Appendix I: Search strategy

MEDLINE

Number	Search	Results
1	cardiac arrest.ti.	10,771
2	exp Heart Arrest/	43,083
3	exp Resuscitation/	87,315
4	exp Cardiopulmonary Resuscitation/	15,171
5	resuscitat$.ti.	21,973
6	CPR.ti.	2119
7	drug$.ti.	334,496
8	overdose$.ti.	5861
9	over-dose$.ti.	13
10	substance$.ti.	60,922
11	poison$.ti.	48,426
12	exp Drug Overdose/	9696
13	1 or 2 or 3 or 4 or 5 or 6	119,478
14	7 or 8 or 9 or 10 or 11 or 12	440,042
15	13 and 14	2020
16	limit 15 to (humans and yr = "1990 -Current")	1213
Total		1213

Embase

Number	Search	Results
1	cardiac arrest.ti.	17,170
2	exp Heart Arrest/	77,530
3	exp Resuscitation/	101,082
4	resuscitat$.ti.	28,427
5	CPR.ti.	3300
6	drug$.ti.	490,049
7	overdose$.ti.	7986
8	over-dose$.ti.	22
9	substance$.ti.	76,664
10	poison$.ti.	58,645
11	exp Drug Overdose/	20,992
12	1 or 2 or 3 or 4 or 5	156,827
13	6 or 7 or 8 or 9 or 10 or 11	640,446
14	12 and 13	3590
15	limit 14 to humans	2919
16	limit 15 to yr = "1990 -Current"	2580
Total		2580

Appendix II: Modified data extraction form

Citation details	
Author(s)	
Journal	
Year of publication	
Aims	
Study details	
Study design	
Country	
Year/timeframe for data collection	
Total population	
Overdose out-of-hospital cardiac arrest definition	
Demographics and clinical characteristics	
EMS-attended n	
EMS-treated n	
Mean age	
Sex %	
Witness status %	
Bystander cardiopulmonary resuscitation %	
Arrest location %	
Initial shockable rhythm %	
Outcomes	
Survived to hospital discharge n	
Survived with intact neurological function n	
Achieved return of spontaneous circulation n	
Survived to hospital n	
Survived to 12-months n	

Manuscript 3. Incidence and outcomes of OHCA precipitated by drug overdose: A systematic review and meta-analysis

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Resuscitation

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Review

The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: A systematic review and meta-analysis

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Abstract

Background: Out-of-hospital cardiac arrests (OHCA) precipitated by drug overdose (OD) are becoming an increasing public health problem in developed countries. Empirical data on the global incidence and outcomes are needed to guide preventive and treatment strategies.

Methods: We conducted a systematic review using MEDLINE, Embase, Emcare, All EBM Reviews and CINAHL to identify observational or interventional studies reporting the incidence or outcomes of adult OHCA precipitated by drug OD between 1990 and 2018. Pooled incidence rates per 100,000 person-years and survival outcomes were summarised using random-effects models.

Results: Twelve articles met the eligibility criteria, of which six were from North America, four from Europe and two from Asia. Only two studies reported the incidence of EMS-attended cases. The pooled incidence of EMS-treated OHCA was 1.4 cases per 100,000 person-years. The pooled rate of survival to hospital discharge and survival with favourable neurological outcome was 9% (95% CI: 6%, 12%; $I^2 = 90\%$; $p < 0.001$) and 6% (95% CI: 2%, 13%; $I^2 = 81\%$; $p < 0.001$), respectively. The pooled rate of return of spontaneous circulation was 25% (95% CI: 11%, 41%; $I^2 = 97\%$; $p < 0.001$). Drug OD OHCA was associated with an improvement in the odds of survival to hospital discharge (pooled odds ratio 2.2, 95% CI: 1.7, 2.7; $I^2 = 0\%$; $p = 0.45$).

Conclusion: The incidence and survival outcomes of drug OD OHCA varies substantially across regions. Effective strategies designed to reduce incidence and improve survival outcomes are needed.

Keywords: Out-of-hospital cardiac arrest, Drug overdose, Emergency medical services, Cardiopulmonary resuscitation

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Introduction

Drug overdose (OD) poses a significant public health problem worldwide and accounts for thousands of deaths each year.[1,2] In 2016, as many as 100,000 adults died from drug OD globally,[1] and opioid OD alone was responsible for about 70% of these deaths.[2] A leading mechanism of death in drug OD is cardiopulmonary arrest occurring before arrival at hospital,[3] which has been estimated to affect as many as 500,000 people in the USA between 2004 and 2014.[2] Out-of-hospital cardiac arrest (OHCA) precipitated by drug OD accounts for as many as one third of all OHCA events, and is particularly prevalent among young adults.[4,5]

Emergency medical services (EMS) are often the first point of contact for most drug OD-related events, and can contribute to reducing the burden of disease from OHCA.[3,6–8] Unfortunately, much of the improvement in survival following OHCA has occurred in populations with presumed cardiac aetiology or initial shockable arrests, who benefit from the early application of life-saving interventions such as cardiopulmonary resuscitation (CPR) and defibrillation.[9–14] In comparison, drug-related OHCA are usually unwitnessed and often present in asystole.[3,7,15] As such, it is unclear if community-based initiatives to increase rates of bystander CPR and defibrillation can help yield additional survivors.

Unlike OHCA precipitated by presumed cardiac aetiology, comparatively little is known about the global incidence and outcomes of drug-related OHCA. The lack of synthesised data on the problem can contribute to delays in the development of novel treatment interventions or preventive strategies which can help minimise the burden of these events in the community. In this study, we aimed to systematically review the literature on the incidence and outcomes of adult OHCA precipitated by drug OD.

Materials and methods

This systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of prevalence and incidence.[16] The systematic review protocol was registered prior to commencement of the study (reference number: JBISRIR-2017-003738).

Search strategy

A systematic review of the literature was conducted to identify published and unpublished studies written in English. Two reviewers independently (SA and ZN) performed a three-step search strategy to capture published studies. First, an initial MEDLINE and Embase search using topic-related keywords (e.g. cardiac arrest/CPR and drug overdose/substance abuse) was conducted to analyse text words and index terms contained within the titles and abstracts. Second, an optimised search strategy containing the index terms and relevant keywords identified in step one was applied to a broader database search using MEDLINE, Embase, Emcare, All EBM Reviews (ACP Journal Club, Cochrane Central Register of Controlled Trial, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and National Health Service Economic Evaluation), and CINAHL (Table S1 in the supplementary appendix). Third, the reference lists of the eligible articles were reviewed for potential studies that may have been missed. All studies published on or after January 1990 and May 2018 were considered for the review. We chose 1990 as the start of our inclusion period, aligned to the publication of the original Utstein template which sought to reduce variability in the reporting of OHCA definitions.[17] In addition, we searched CORE, MedNar, Trove and Resuscitation Outcomes Consortium for possible grey literature meeting eligibility criteria.

Study selection and eligibility

The titles and abstracts of relevant studies were appraised for eligibility by two authors (SA and ZN) independently. Studies were eligible for inclusion if they reported adults aged greater than 15 years who were attended by EMS for an OHCA precipitated by a drug OD. Cardiac arrest was defined as "the absence of signs of circulation irrespective of whether the assessment was made by a bystander or EMS personnel".[18] Cardiac arrests precipitated by drug OD were defined as "evidence that cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol".[18] Cohort observational studies and interventional studies were included. As the main outcome of this review is to pool the global incidence and outcomes of undifferentiated population of drug-related OHCA, we excluded studies of OHCA caused by isolated drug OD (e.g. tricyclic antidepressants or opioids) or chemical poisoning (e.g. organophosphate or carbon monoxide) which could introduce heterogeneity. Studies describing other populations of sudden cardiac arrest patients were also excluded (e.g. in-hospital cardiac arrests). Finally, studies where incidence could not be derived such as case control, cross sectional studies, case series, case reports, editorials, letters, comments, news, notes and reviews were also excluded. Discrepancies were resolved through discussion between the two authors.

Outcomes

The main outcomes of the review were the pooled incidence of EMS-attended and EMS-treated drug OD OHCA per 100,000 person-years and the pooled proportion of survivors to hospital discharge or 30 days. Secondary outcomes included the pooled proportion of patients who survived with intact neurological function at hospital discharge, achieved prehospital return of spontaneous circulation (ROSC), survived to hospital, and survived to 12 months. In a subgroup of included studies, we also pooled the adjusted odds ratios (AOR) of the effect of drug OD on survival to hospital discharge.

Data extraction

A data extraction form was developed and modified from the JBI.[19] Main components of the form included author(s) name, year of publication, aims, settings, study design and duration, EMS serviceable population, drug OD OHCA definition, mean age, sex, witness status, bystander CPR, arrest location, initial shockable rhythm, naloxone administration, the number of EMS-attended and EMS-treated cases, and survival outcomes. Survival outcomes were extracted as the proportion of EMS treated patients. If odds ratios for the effect of drug OD on survival were reported, we extracted the odds ratio which adjusted for the largest number of confounders. Two reviewers extracted data independently (SA and ZN). Differences in data extraction were resolved through discussion. The authors of two studies were also contacted to confirm the definition of drug OD OHCA,[20,21] and obtain information relating to the study setting and serviceable population.[20]

Quality assessment

The Joanna Briggs Institute critical appraisal tool for studies reporting prevalence and incidence data were used to assess the quality of the included studies.[19] Each reviewer (SA and ZN) critically appraised study quality independently by answering yes, no, unclear or not applicable to nine questions. Discrepancies were resolved through consensus.

Data synthesis and meta-analysis

The population published in the articles was corrected for the mid-point census population at the time of study (for North American areas, https://factfinder.census.gov/ and http://www12.statcan.gc.ca/; for European areas, http://epp.eurostat.ec.europa.eu/; for Asian areas, http://www.e-stat.go.jp/). Incidence rates of EMS-attended and EMS-treated drug OD OHCA were calculated as the number of cases during a study period divided by the total population at-risk during the same period, per 100,000 person-years. Ninety five percent confidence intervals (95% CI) were calculated assuming a Poisson distribution.[22] The DerSimonian and Laird method was used to pool incidence rates, with the estimates of heterogeneity taken from the inverse variance fixed-effect model. Since the proportions of survival outcomes were below 0.5 and close to 0, the Freeman-Tuckey double arcsine transformation was computed to estimate the proportions and the Wald 95% CI.[23] The AOR for the effect of drug OD on survival to hospital discharge in OHCA cases was computed using the DerSimonian and Laird random-effects model, as above.

Subgroup analysis by study regions and case definition (i.e. aligned with Utstein definition and not aligned with Utstein definition) was used to explore potential sources of heterogeneity. Where appropriate, we also conducted sensitivity analyses by excluding outlying observations which differed significantly in population characteristics. Heterogeneity was assessed statistically using I^2 tests. The I^2 values of 25%, 50%, and 75% indicate low, moderate and high heterogeneity, respectively.[24] All statistical analyses were undertaken using STATA 15.0 (Statacorp, College Station, Texas, USA).

Results

Study selection

Our search for published studies yielded 5575 citations. After removing duplicates (n = 1894), irrelevant study designs (n = 744) and those that did not meet our eligibility criteria (n = 2914), 23 articles underwent full text review. Eight articles met the inclusion criteria, and an additional four articles were identified from reference lists. The total studies included in the quantitative data synthesis was 12 (Fig. 1).

Study characteristics

Study characteristics are presented in Table 1. Fifty percent of the pooled population were from North America, 33% from Europe, and 17% from Asia. The total serviceable population was 102.6 million. All studies were of retrospective cohort design. Two studies reported the incidence of EMS-attended cases and all studies reported the incidence of EMS-treated cases. Age was reported in seven studies, with a mean age ranging between 36 and 50 years. Sex was reported in seven studies, with a percentage of males varying between 63% and 73%. The study by Kitamura et al. from Osaka, Japan had the lowest rates of witnessed arrest, bystander CPR and initial shockable rhythms with a rate of 5%, 18% and 1%, respectively. Eleven studies reported the percentage of patients who survived to hospital discharge with the highest observed in Pittsburgh, USA (19%) and the lowest in Korea (3%).

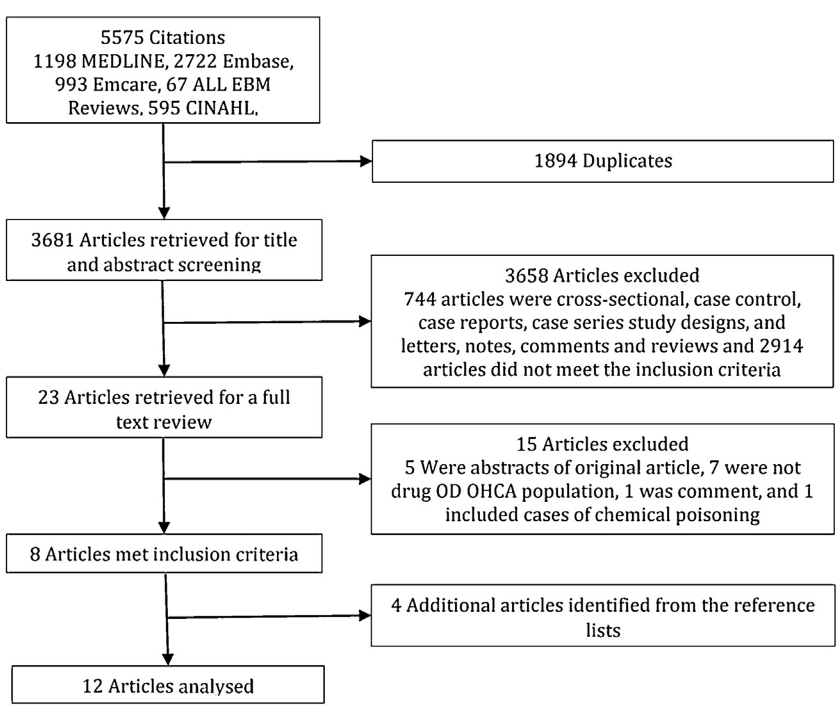

Fig. 1 – Literature search results.

Table 1 – Demographics and clinical characteristics.

Study	Year	Setting	Study time span (years)	Serviceable population[a]	Incidence per 100,000 person-years		Mean age	Male %	Witness %	Bystander CPR%	Initial shockable rhythm%	Discharged alive%
					EMS-attended	EMS-treated						
		Europe										
Kuisma[21]	1997	Helsinki, Finland	2	525,000	–	2.6	–	–	–	–	–	19
Engdahl[51]	2003	Goteborg, Sweden	20	443,000	–	2.0	42	69	24	31	5	3
Jabre[21]	2015	Ile De France, France	3	8,000,000	0.4	0.3	–	–	–	–	–	11
Claesson[15]	2017	Sweden	22	8,941,000	–	0.7	36	67	35	56	17	10
		North America										
Paredes[7]	2004	King County, WA	1	2,000,000	8.5	4.3	40.4	73	14	24	6	13
Hess[52]	2007	Olmsted County, MN	11	124,000	–	0.7	–	–	–	–	–	11
Koller[6]	2014	Pittsburgh, PA	5	935,000	–	3.9	44.8	65	55	48	16	19
Agy[53]	2015	Salt Lake County, UT	6.3	1,017,000	–	1.5	–	–	–	–	9	–
Salcido[8]	2016	Birmingham, AL; Dallas, TX; Milwaukee, WI; Pittsburgh, PA; Portland, OR; San Diego, CA; Seattle, WA; Toronto, ON; Vancouver, BC; Ottawa, ON	4	18,530,000	–	1.8	41	66	31	37	8	13
Orkin[3]	2017	Southern Ontario, ON	7	6,300,000	–	0.9	42.7	66	28	33	8	10
		Asia										
RO[54]	2012	Korea	3	48,600,000	–	0.5	–	–	–	–	–	22
Kitamura[25]	2014	Osaka, Japan	7	7,212,000	–	0.4	49.9	63	5	18	1	4

EMS indicates emergency medical services; CPR indicates cardiopulmonary resuscitation.
[a] Serviceable population is corrected for the mid-point census population at the time of the study.

Quality assessment

Table S2 in the Supplementary Appendix shows the results of the quality assessment for the included studies. The sample frame to address the target population was appropriate in three studies. The study participants were randomly sampled in 10 studies. The majority of studies had adequate sample size. Most studies described the setting where participants were recruited from, but only four studies clearly defined the participants according to Utstein template.[3,7,15,21] Missing data were less than 5% in 10 studies indicating sufficient coverage for data analysis. The methods used to identify the condition was valid in six studies and was not valid or unclear in the remaining studies. The condition was measured in a standard and reliable way for all participants in five studies. The analytical techniques were appropriate in all studies, and the response rates were appropriate in 10 studies. All studies were included in the quantitative synthesis, and subgroup analysis by case definition was considered.

Incidence

The incidence of EMS-attended drug OD OHCA was only reported in two studies which precluded meta-analysis. Fig. 2 shows that the pooled incidence of EMS-treated cases was 1.4 cases per 100,000 person-years (95% CI: 1.1, 1.6; $I^2 = 99\%$; $p < 0.001$). Subgroup analysis was conducted to explore heterogeneity by region. The incidence rate was 2.0 cases per 100,000 person-years (95% CI: 1.4, 2.7) in North America, 1.2 cases per 100,000 person-years (95% CI: 0.7, 1.6) in Europe, and 0.4 cases per 100,000 person-years (95% CI: 0.3, 0.5) in Asia. The test for heterogeneity between the groups was significant ($p < 0.001$).

Survival to hospital discharge

Fig. 3 shows that the pooled rate of survival to hospital discharge was 9% (95% CI: 6%, 12%; $I^2 = 90\%$; $p < 0.001$). In the subgroup analysis, studies that were aligned with the Utstein definition of drug OD had no evidence of heterogeneity and the pooled rate of survival was 10% (95% CI: 8%, 11%, $I^2 = 0.0\%$; $p = 0.39$). In comparison, studies that were not aligned with Utstein definitions had evidence of heterogeneity and the pooled rate was 8% (95% CI: 3%, 13%; $I^2 = 94\%$, $p < 0.001$). Fig. 4 shows that the pooled AOR for the effect of drug OD on survival to hospital discharge was 2.2 (95% CI: 1.7, 2.7; $I^2 = 0\%$; $p = 0.45$).

Secondary outcomes

No study reported on the rate of 12-month survival and only one study reported survival to hospital. The rates of patients who were discharged from the hospital with intact neurological function and who achieved ROSC varied substantially. The pooled rates were 6% (95% CI: 2%, 13%; $I^2 = 81\%$; $p < 0.001$) and 25% (95% CI: 11%, 41%; $I^2 = 97\%$; $p < 0.001$) respectively. In the sensitivity analysis, excluding one study which differed markedly with respect to clinical characteristics,[25] the pooled rate were 9% (95% CI: 6%, 13%; $I^2 = 0.0\%$, $p = 0.52$) and 33% (95% CI: 27%, 38%; $I^2 = 59\%$; $p = 0.06$), respectively.

Discussion

In this meta-analysis of 12 studies, the pooled incidence rate of EMS-treated drug OD OHCA was 1.4 per 100,000 person-years. The

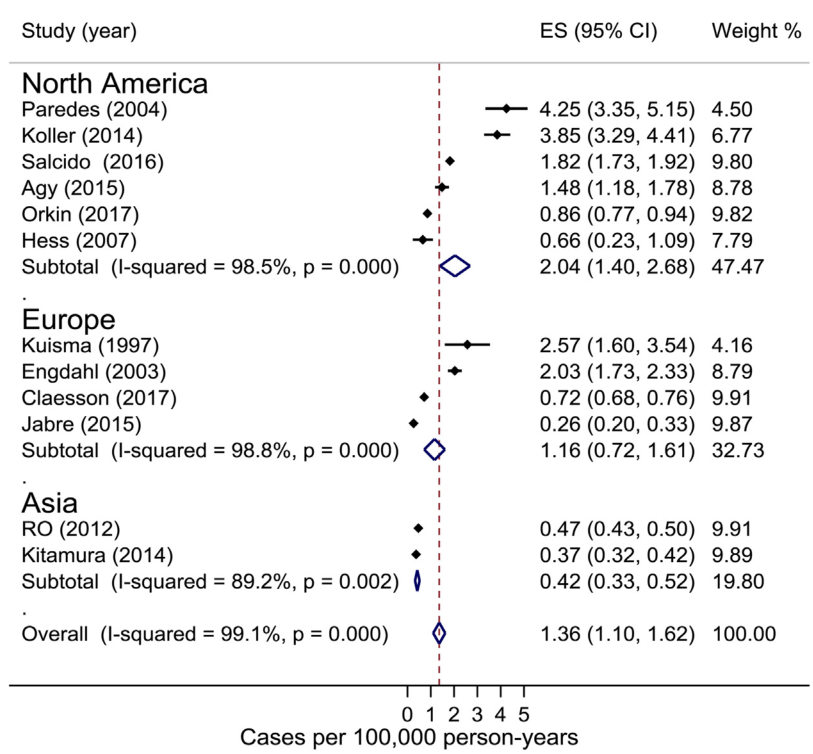

Fig. 2 – Incidence rate of EMS-treated cases per 100,000 person-years.

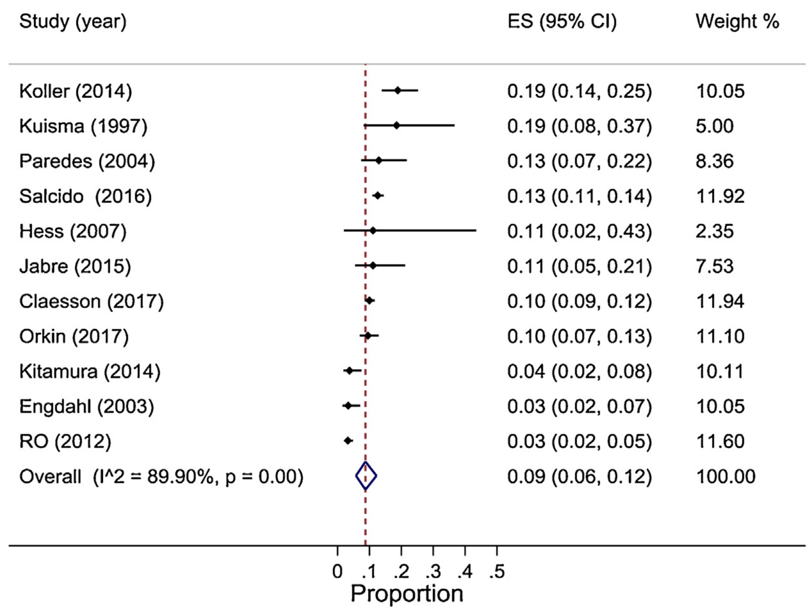

Fig. 3 – Pooled rate of survival to hospital discharge.

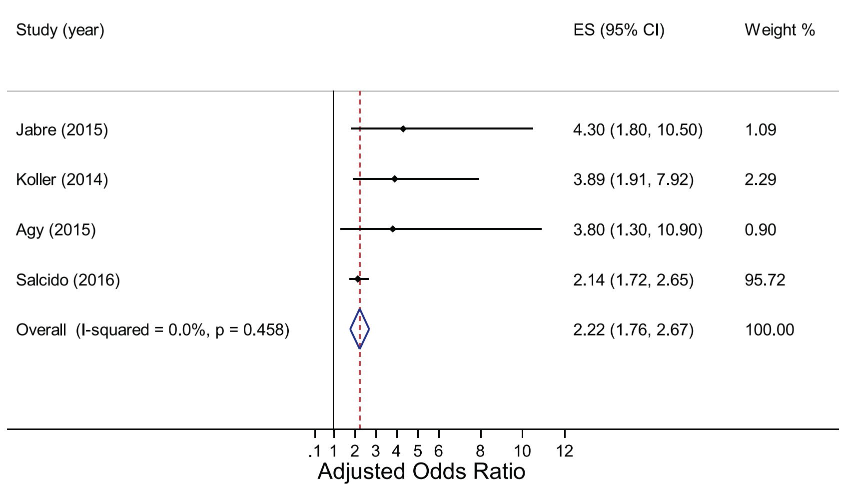

Fig. 4 – Pooled AOR of drug OD OHCA on survival to hospital discharge.

pooled rate of survival to hospital discharge and survival with intact neurological outcomes was 9% and 6%, respectively. Cases of drug OD OHCA were 120% more likely to survive to hospital discharge compared to cases of non-drug OD OHCA. Extrapolating these estimates would suggest that as many as 105,000 adults globally will receive an attempted resuscitation by EMS for a drug-related OHCA annually, of which approximately 9000 survive to hospital discharge.

However, our pooled estimates are derived from studies published across different time periods, and regions, and should therefore be interpreted with some caution. The global epidemic of drug-related OD has increased rapidly over the past decade,[26] and there is also evidence of an increasing temporal trend in the incidence of drug OD OHCA.[3] Therefore, it is possible that our findings may not be representative of the current burden of drug-related mortality in many communities. Although our review identified intercontinental differences in the incidence of drug OD OHCA, incidence also varied significantly within continents. The communities of Pittsburgh[6] and King County[7] reported rates of drug OD OHCA that were three to four times higher than other communities in North America. A myriad of sociological factors, and changes to the access of certain drugs, may be responsible for this variability.

For instance, death from prescription opioid OD is increasing disproportionately to illicit drugs in some communities,[27] and this may be related to local differences in the access to opioid prescriptions. While the rate of opioid prescription is associated with the rate of death from drug OD, these rates vary among communities.[28] For example, between 2013 and 2015, the rate of opioid prescription in Pennsylvania, US was 14% higher than the average national rate.[29] In 2016, the incidence of drug-related deaths was also 39% higher than the national rate.[29] In addition, the 2017 Narcotic Drugs report indicated that the US population had the highest standard daily doses of opioid worldwide, and was four, six, and eighteen times higher than Sweden, France and Korea, respectively.[30] The standard daily doses of opioid also varied considerably between Canada and US,[30] a finding which could explain the variability across North American sites.

Variation in EMS activation could also influence the incidence and outcomes of drug OD OHCA. Disparities in seeking medical aid by drug users varies between 13% and 68%.[31] The most common reason for this variation is related to fear of legal prosecution perceived by the drug users or witnesses.[32] Although Good Samaritan laws provide immunity from legal prosecution, the dissemination of this law varies across our studied regions. For instance, the law was enacted in 2008 in South Korea, while Washington, US, enacted the law in 1975.[33,34] The degree to which an individual is protected from legal liability in drug related events also varies between communities. For instance, people seeking medical aid in drug-related events are not prosecuted for possession of a controlled substance in Washington, US,[35] but may be charged in Minnesota, US.[36] These differences could result in either a reluctance or delay in accessing EMS for drug-related events.

Although pooled survival from drug OD OHCA was 9% in our review, there was strong evidence of heterogeneity across regions (ranging from 3% to 19%). This variation could be explained, in part, by differences in case definition and predictors of survival such as the rates of witnessed arrest, bystander CPR, and initial shockable rhythms.[37,38] For instance, the study from Pittsburgh, US,[6] reported high rates of initial shockable rhythms (16%), bystander witness status (55%) and survival to hospital discharge (19%). In addition, our subgroup analysis of studies aligned with the Utstein definition of drug OD showed less evidence of statistical heterogeneity. Importantly, there is evidence that variation in survival outcomes from one community to another is likely despite adjustment for Utstein variables.[39]

Although we observed low rates of bystander CPR and initial shockable rhythms across most studies, our review does suggest that drug OD OHCA is associated with improved odds of survival. The causative pathophysiological mechanisms in many of these arrests includes hypoxia and circulatory collapse.[40] It is therefore plausible that timely EMS treatment including adequate ventilation, chest compressions and inotropic support could help to increase ROSC and survival in these patients. Variation in the quality of CPR and delays in EMS access could therefore explain the variation in survival observed among our included studies,[41,42] and be an important factor in the improvement of outcomes in this population.

The variability in survival across regions offers potential opportunities for public health interventions. While initial shockable rhythm is one of the major determinant of survival, increasing the rate of bystander application of automated external defibrillator could increase survival.[43,44] However, this may appear implausible in population with drug OD OHCA whose arrests are typically unwitnessed and of private arrest location.[45] Alternatively, increasing the rate of bystander CPR could extend time to defibrillation by EMS.[45] Unfortunately, there is evidence that the rate of bystander CPR is significantly lower in drug OD OHCAs compared to non-OD OHCAs.[3,46,47] Evidence suggests that family members and friends are reluctant to perform CPR as a result of panic and fear of causing harm and failure.[26] Focused CPR-training programs for potential rescuers may increase the rate of CPR and subsequently improve survival.

There are opportunities for public health initiatives to prevent death and reduce the incidence of drug OD OHCA. Most drug-related events occur in private residences and many of these are witnessed by individuals who are known to the drug user, such as friends and family members.[2] As opioids are a leading cause of drug-related events,[48] community engagement in naloxone administration may help to prevent cardiorespiratory arrest.[2] However, this relies on witnesses who are not also compromised by drugs to be available and willing to administer naloxone. The Wales government in 2010 has launched take home-naloxone program for opiate users to reduce the annual incidence of drug-related deaths which was 85 in previous years.[49] After one year of program assessment, the annual incidence of drug-related deaths was reduced to 68, a reduction of 18%.[49]

Similarly, there was an 18% reduction of drug-related deaths in communities who had access to naloxone and were trained in naloxone administration compared to those who had not, as demonstrated by a study conducted in Massachusetts, US.[50] Unfortunately, community access to naloxone in many countries is by physician prescription, and some countries also lack the availability of naloxone in medical settings.[2] Broader access to naloxone and targeted training programs for at-risk communities may help reduce the incidence of drug-related deaths.

Limitations

This review has a number of limitations. First, all studies were observational in design which suffer from inherent methodological limitations. Second, although incidence and survival estimates were pooled from a handful of communities, no estimates were found from regions such as Australia, the United Kingdom. Africa and South America. As such, our estimates may not be globally representative. Third, it is difficult to ascertain whether all patients were in cardiac arrest at the time the resuscitation began, and this may lead to differences in case capture across studies. Fourth, many studies did not include patients who did not undergo an EMS attempted resuscitation, and thus we were not able to estimate the incidence of EMS-attended cases. Fifth, few studies reported the clinical predictors of survival such as witnessed status, bystander CPR and initial shockable rhythm, and we were unable to statistically assess their effect on survival outcomes. Finally, the odds ratios for the effect of drug OD OHCA on survival to hospital discharge were taken from different studies, and some of the confounders considered for adjustment in these studies varied.

Conclusion

The findings from this meta-analysis provide a benchmark to evaluate the future preventive and treatment strategies for drug-related OHCA. Globally, as many as 105,000 adults annually will be treated by EMS for drug-related OHCA, of which 9000 survive to hospital discharge. These global estimates should be interpreted with caution, as these pooled estimates are derived from select communities and may not reflect existing temporal trends in drug-related OHCA. Effective strategies designed to reduce the incidence rate and improve survival outcomes are needed. This includes more research with comprehensive data reporting to enable precise measurement of the disease burden and to assess the value of treatment interventions. Broader access to naloxone and CPR training programs for communities at-risk may also be effective in preventing OHCA.

Conflict of interest

None to declare.

Source of funding

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.12.020.

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Manuscript 3 Appendix. Supplementary Data

Appendix:

Table S1. Keywords and index terms used across all databases.

No	Keywords/index terms for Embase,MEDLINE,Emcare & All EBM	Embase	MEDLINE	Emcare	All EBM	Key-words/index terms for CINAHL	CINAHL
1	cardiac arrest.ti.	18500	11026	6973	986	(MH "Heart Arrest+")	16056
2	exp Heart Arrest/	82556	42739	27267	1444	(MH "Resuscitation+")	36913
3	exp Resuscitation/	104557	86633	35100	4419	(MH "Resuscitation, Cardiopulmonary+")	11844
4	exp Cardiopulmonary Resuscitation/	104557	15572	35100	900	TI resuscitat*	9543
5	resuscitat$.ti.	29379	21936	10564	1650	TI CPR	2121
6	CPR.ti.	3483	2141	1340	343	TI drug*	76066
7	drug$.ti.	503039	331257	74040	19692	TI overdose*	2494
8	overdose$.ti.	8304	5836	2336	126	TI over-dose*	10
9	over-dose$.ti.	25	11	3	282	TI substance*	14305
10	substance$.ti.	78180	59442	16057	2437	TI poison*	4902
11	poison$.ti.	59262	46584	5114	456	(MH "Overdose")	4787
12	exp Drug Overdose/	22349	9694	5952	90	TI "drug overdose"	182
13	1 or 2 or 3 or 4 or 5 or 6	163887	118136	51842	6887	TI "cardiac arrest"	6427
14	7 or 8 or 9 or 10 or 11 or 12	656646	443447	99880	22902	S1 OR S2 OR S3 OR S4 OR S5 OR S13	50779
15	13 and 14	3744	1979	1115	70	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	99001
16	limit 16 to year="1990 -Current"	2722	1198	993	67	S14 AND S15	595
Total		**2722**	**1198**	**993**	**67**		**595**

Table S2: Methodological quality assessment.

No	Question	Study											
		Kuisma[21]	Engdahl[51]	Jabre[20]	Claesson[15]	Paredes[7]	Hess[52]	Koller[6]	Agy[53]	Salcido[8]	Orkin[3]	RO[54]	Kitamura[25]
1	Was the sample frame appropriate to address the target population?	N	N	N	Y	Y	N	N	U	N	Y	N	N
2	Were study participants sampled in an appropriate way?	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y
3	Was the sample size adequate?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
4	Were the study subjects and the setting described in detail?	Y	N	N	Y	Y	N	N	N	N	Y	N	N
5	Was the data analysis conducted with sufficient coverage of the identified sample?	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y
6	Were valid methods used for the identification of the condition?	Y	Y	U	N	Y	U	N	Y	Y	Y	N	N
7	Was the condition measured in a standard, reliable way for all participants?	Y	Y	U	N	Y	U	Y	U	N	Y	N	N
8	Was there appropriate statistical analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y
Decision to include in the review		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Decision to include in the meta-analysis		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y indicates yes; N indicates no; U indicates unclear.

Summary of findings

Every year, more than 100,000 cases of drug overdose OHCA are expected to be treated by EMS worldwide of which 9.0% survive to hospital discharge, and 6.0% survive with intact neurological function at hospital discharge. Also, survival to hospital discharge was twice as likely in drug overdose OHCA cases compared to that in non-drug overdose cases. Notably, there was a 16-fold variation in the incidence of EMS-treated cases across the studied regions and 6-fold variation in survival. Incidence variations could partly be explained by differences in access to opioid prescriptions and health-seeking behaviour. In addition, differences in case definitions and rates of witnessed arrest, bystander CPR and shockable rhythms could explain variations in survival.

Chapter 3. Epidemiology and outcomes of drug overdose OHCA in Victoria, Australia

Background

In the previous chapter, it was shown that drug overdose OHCA is a worsening public health problem with a pooled rate of survival to hospital discharge of only 9.0%. While temporal changes in the rate of bystander CPR and defibrillation are associated with improved survival in OHCA of presumed cardiac aetiology,[10, 11, 13, 14] it is not clear if these time-sensitive interventions can yield additional survivors from drug overdose OHCA. Also, although 6.0% of cases are discharged alive with intact neurological function at hospital discharge, the long-term functional recovery and HRQoL outcomes for survivors are unknown. Survivors may experience poor long-term outcomes given the vast majority of cases are found in initial non-shockable rhythms.

Aims

The aim of this chapter, which consists of a published paper, was to describe the long-term epidemiology and outcomes of drug overdose OHCA. Functional recovery and HRQoL outcomes at 12-month follow-up will be summarised, and predictors of survival to hospital discharge will be assessed.

Manuscript 4. Long-term trends in the epidemiology of OHCA precipitated by suspected drug overdose

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Clinical paper

Long-term trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose

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Abstract

Background: Little is known about the long-term trends in the incidence and outcomes of drug overdose out-of-hospital cardiac arrests (OHCA).

Method: Between 2000 and 2017, we retrospectively reviewed drug overdose OHCAs from the Victorian Ambulance Cardiac Arrest Registry. Incidence was assessed using linear regression, and the baseline characteristics and survival outcomes were assessed using nonparametric test for trend. Arrest factors associated with survival to hospital discharge were assessed using logistic regression. The 12-month functional recovery and health related quality of life for survivors was summarised using descriptive statistics.

Results: The incidence of emergency medical services (EMS)-attended and EMS-treated cases was 5.8 and 2.0 per 100,000 person-years, respectively, with no significant changes in trend over time. Return of spontaneous circulation increased from 23% to 34% (p for trend = 0.001), event survival increased from 23% to 30% (p for trend = 0.007), and survival to hospital discharge increased from 4% to 13% (p for trend = 0.03). Age, arrest witnessed by bystander or EMS, initial shockable rhythm or pulseless electrical activity, intubation, epinephrine and sodium bicarbonate administration were independently associated with survival. The adjusted-temporal trend for survival was not significant (per year increase; OR 1.02, 95% CI: 0.98, 1.07; p = 0.244). Of the 12-month survivors, 50% of the responders reported good functional recovery, and few reported severe problems with mobility, self-care, daily activity, pain, and anxiety/depression.

Conclusion: Although the incidence of drug overdose OHCA remained unchanged between 2000 and 2017, the rates of survival have significantly improved.

Keywords: Out-of-hospital cardiac arrest, Drug overdose, Cardiopulmonary resuscitation, Emergency medical services, Quality of life

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major health issue affecting millions of people each year.[1] A number of studies demonstrated that early initiation of cardiopulmonary resuscitation (CPR) and defibrillation by members of the community can increase survival rates.[2–4] However, much of the improvement in survival occurred in OHCA patients precipitated by presumed cardiac aetiology or initial shockable arrest rhythms.[2–4] In comparison, OHCA precipitated by non-cardiac

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aetiologies less frequently arrest into shockable rhythms,[5,6] and long-term trends in outcomes are less often described.

OHCA precipitated by suspected drug overdose is a distinct subset of non-cardiac aetiologies which commonly involve middle aged males.[7,8] They are typically unwitnessed, occur in a private locations, are less likely to receive bystander CPR, and rarely present with initial shockable arrest rhythms.[9] As such, survival to hospital discharge outcomes have been reported as low as 3%.[10] Relatively little is known about the long-term trends in the incidence, epidemiology, and survival outcomes of OHCA precipitated by drug overdose. The long-term functional recovery and health-related quality-of-life (HRQoL) outcomes of survivors is also not well understood.

In this study, we describe long-term trends in the incidence, epidemiology, and survival outcomes after drug overdose OHCA, and examine factors related to survival. Additionally, the 12-month functional recovery and HRQoL outcomes of survivors arresting between 2010 and 2016 were also examined.

Methods

Study design

This is a retrospective study of OHCA cases precipitated by presumed drug overdose from the Victorian Ambulance Cardiac Arrest Registry (VACAR). All adult (aged $\geq$ 16 years) emergency medical service (EMS)-attended cases between 1st January 2000 and 31st December 2017 were included. The VACAR is a quality assurance initiative approved by the Victorian Government Department of Health and Human Research Ethics Committee. This study has ethics approval from the Monash University Human Research Ethics Committee (Project number: 9600).

Setting

The population in the state of Victoria is approximately 6.3 million.[11] The state provides EMS using a single provider, Ambulance Victoria. The EMS system consists of advanced life support and mobile intensive care paramedics who respond simultaneously to suspected OHCA events identified in the emergency call. Additionally, firefighters and community volunteers with basic life support training respond to OHCA cases in select areas throughout the state. Paramedics' clinical practice guidelines follow the recommendations of the Australian and New Zealand Council on Resuscitation (http://www.resus.org.au). Cardiac arrest patients who achieve return of spontaneous circulation (ROSC) in the field are transported to the closest appropriate hospital.

Data sources and definitions

Since 1999, the VACAR maintains a record of all EMS-attended OHCAs in the state of Victoria, Australia. The registry collects data variables according to the Utstein template,[12] and includes operational data, arrest features, patient demographics, treatment interventions, and outcomes. The VACAR also captures and stores all paper-based and electronic patient care records completed by paramedics.[13] A central electronic database identifies and stores potential cardiac arrest cases using a sensitive search criteria. Hospital outcomes for the majority of transported patients are obtained from the hospital medical records and cross-matched against death records from the Victorian Registry of Births, Deaths and Marriages. Cardiac arrest aetiology is presumed to be of cardiac cause unless there is an obvious precipitator (e.g. drowning, trauma). Cases precipitated by suspected drug overdose are defined as evidence that the cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol.[14]

Since 1st January 2010, the VACAR conducts a structured telephone interview with survivors at 12-month post arrest to assess functional recovery and HRQoL. The interview process and the instruments used are described in detail previously.[15] Functional recovery is assessed using the Glasgow Outcome Scale-Extended (GOSE) which is an eight-point scale ranging from 1 (death) to 8 (upper good recovery).[16] HRQoL is assessed using the Twelve-Item Short Form (SF-12) health survey which summarises mental and physical health based on a weighted score ranging from zero to 100.[17] Scores of $\geq$50 indicate no disability, 40–49 indicate mild disability, 30–39 indicate moderate disability, and $\leq$29 indicate severe disability.[17] Proxy responses for SF-12 are not considered valid.[15] In addition, the interview also administers the EuroQoL-5-3 L (EQ-5D) health survey which provides a single index score ranging from $-$0.594 to 1.0 for HRQoL according to five domains (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression).[18] Patients can also self-rate their health status using a verbal analogue scale (VAS), where 0 indicates the worst imaginable health state and 100 indicates the best imaginable health state.[18]

Outcomes

The primary outcome of the study was survival to hospital discharge. The secondary outcomes included ROSC, event survival, and 12-month functional recovery and HRQoL for survivors using the GOSE, SF-12, and EQ-5D.

Statistical analysis

The crude incidence rate of EMS-attended and EMS-treated cases were calculated using population estimates for people aged $\geq$16 years obtained from the Australian Bureau of Statistics.[19] Age-adjusted incidence rates were also calculated using the 2001 Australian standard population.[19] Trends in incidence rates over the study period were assessed using linear regression. Baseline characteristics and survival outcomes were reported using descriptive statistics and stratified by study year (2000–2003, 2004–2008, 2009–2013, and 2014–2017). Trends over time in baseline characteristics were assessed using a non-parametric test for trend.[20]

We constructed a multivariable logistic regression model to assess factors associated with survival to hospital discharge. The variables included were: age, sex, witness status, initial arrest rhythm, arrest location, bystander CPR, intubation attempt, administration of epinephrine and sodium bicarbonate, and EMS response time. A variable denoting consecutive calendar years in the study was also included in the model to assess whether survival trends were changing independent of other arrest characteristics. Relevant interactions between arrest characteristics were also tested in the model. Effect sizes were expressed as odds ratios (ORs) with 95% confidence intervals (CI).

The 12-month outcomes were summarised using descriptive statistics. The SF-12 scores of the 12-month survivors were compared with the Australian norms by standardising the SF-12 scores of the Australian population to the distribution of the 12-month survivors.[21]

We computed the standardised mean difference (SMD) of the SF-12 scores by subtracting the mean score of the age- and sex-adjusted Australian population from the mean score of the 12-month survivors and dividing by the pooled standard deviation of both population.[22] The SMD value is used to quantify the degree to which SF-12 scores of the 12-month survivors deviate from the population norm, with a value of >0.8 considered large.[22] STATA statistical software version 15.0 (Statacorp, College Station, Texas, USA) was used to analyse the data. A two-tailed p value of less than 0.05 was considered statistically significant.

Results

During the 18-year study period, EMS attended 4523 cases of adult drug overdose OHCA, of which 1545 (34%) cases received an attempt at resuscitation by EMS (Fig. S1).

Trends in incidence

Fig. 1 shows the crude incidence rate of drug overdose OHCA over the study period. The crude incidence rate of EMS-attended and EMS-treated cases was 5.8 and 2.0 events per 100,000 person-years, respectively. There was no significant change in the incidence of EMS-attended and EMS-treated drug overdose OHCA over time (p for trend = 0.17 and 0.21, respectively). The age-adjusted incidence rate of EMS-attended and EMS-treated cases was 6.0 and 2.1 events per 100,000 person-years, respectively (Fig. S2), with no significant changes in trend over time (p for trend = 0.26 and 0.15, respectively).

Trends in baseline characteristics

Table 1 shows the baseline characteristics of EMS-treated cases across year groups. The overall mean age was 37.4 years, 72% were male and 76% were unwitnessed. The mean age increased from 32.9 years in 2000–2003 to 40.6 years in 2014–2017 (p trend <0.001). The majority of cardiac arrests occurred in private residences (77%), increasing from 69% in 2000–2003 to 80% in 2014–2017 (p for trend = 0.001). Few cases presented with initial shockable rhythms (6%) and less than half received bystander CPR (44%). However, the proportion of bystander CPR increased from 27% in 2000–2003 to 59% in 2014–2017 (p trend <0.001). The median EMS response time was 7.2 min, increasing from 7.0 to 7.3 min between 2000–2003 and 2014–2017 (p trend <0.001). Rates of EMS interventions, such as endotracheal intubation, epinephrine and sodium bicarbonate administration, all declined over the study period. Table S1 in the supplementary appendix shows the baseline characteristics of drug overdose OHCA attended by EMS over time.

Trends in survival outcomes

Fig. 2 shows the survival outcomes of drug overdose OHCA treated by EMS over the study period. The overall proportion of patients who achieved ROSC was 33%, increasing from 23% in 2000 to 34% in 2017 (p for trend = 0.001). Overall event survival was 31%, increasing from 23% in 2000 to 30% in 2017 (p for trend = 0.007). Overall survival to hospital discharge was 9%, improving from 4% in 2000 to 13% in 2017 (p for trend = 0.03).

Predictors of survival to hospital discharge

The results of the multivariable logistic regression model of survival to hospital discharge are shown in Table 2. The following variables were independent predictors of survival: age (per year increase; OR 0.97, 95% CI: 0.95, 0.99; p < 0.002), witnessed by bystander (OR 2.95, 95% CI: 1.77, 4.94; p < 0.001) or EMS witnessed (OR 4.32, 95% CI: 2.20, 8.46; p < 0.001), initial shockable rhythm (OR 10.08, 95% CI: 5.01, 20.29; p < 0.001) or initial pulseless electrical activity (PEA) (OR 9.00, 95% CI: 5.51, 14.67; p < 0.001), attempted intubation (OR 1.91, 95% CI:1.04, 3.49; p = 0.04), epinephrine administration (OR 0.39, 95% CI: 0.22, 0.70; p = 0.002), and sodium bicarbonate administration (OR 0.16, 95% CI: 0.08, 0.31; p < 0.001). Male gender, location of arrest, bystander CPR, EMS response time were not significantly associated with survival. Furthermore, the temporal trend for survival was not significant after adjustment for arrest factors (per year increase; OR 1.02, 95% CI: 0.98, 1.07; p = 0.244).

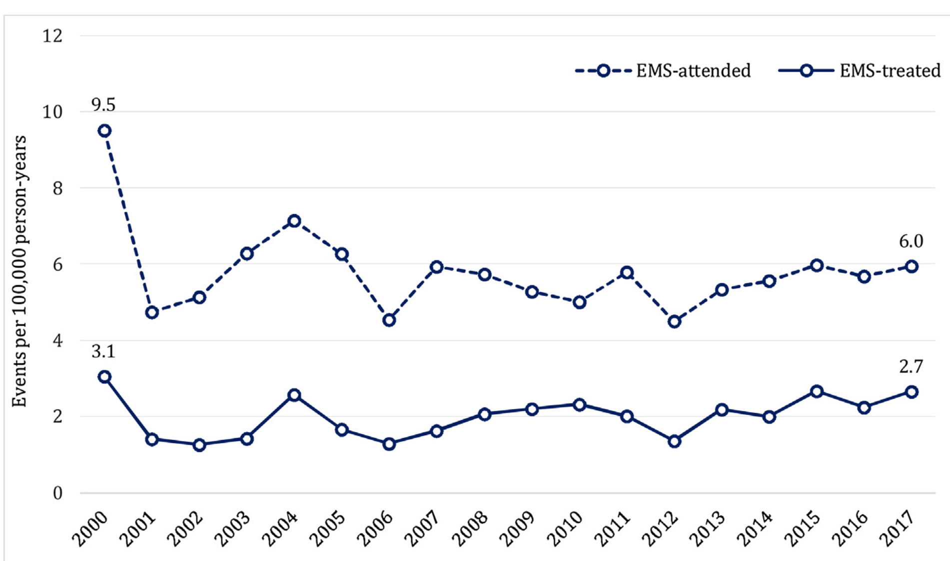

Fig. 1 – Crude incidence rate of EMS-attended and EMS-treated cases over time.

Table 1 – Characteristics of EMS-treated cases stratified by study year.

Variable	Overall n = 1545	2000–2003 n = 270	2004–2008 n = 368	2009–2013 n = 445	2014–2017 n = 462	p-Value for trend	Missing n (%)
Age in years, mean (SD)	37.4 (12.3)	32.9 (11.8)	35.8 (12.2)	38.0 (12.3)	40.6 (11.8)	<0.001	13 (0.8%)
Male, n (%)	1106 (71.6)	204 (75.6)	258 (70.1)	308 (69.2)	336 (72.7)	0.692	0
Witnessed status n, (%)							17 (1.1%)
Not witnessed	1161 (76.0)	199 (76.3)	277 (75.7)	350 (79.4)	335 (72.8)	0.262	
Bystander witnessed	249 (16.3)	45 (17.2)	67 (18.3)	57 (12.9)	80 (17.4)	0.778	
EMS witnessed	118 (7.7)	17 (6.5)	22 (6.0)	34 (7.7)	45 (9.8)	0.029	
Location of arrest, n (%)							0
Private location	1190 (77.0)	185 (68.5)	284 (77.2)	352 (79.1)	369 (79.9)	0.001	
Public location	305 (19.7)	77 (28.5)	74 (20.1)	79 (17.8)	75 (16.2)	<0.001	
Other	50 (3.2)	8 (3.0)	10 (2.7)	14 (3.2)	18 (3.9)	0.622	
First documented rhythm, n (%)							15 (1.0%)
VF/VT	93 (6.1)	19 (7.2)	29 (8.0)	26 (5.9)	19 (4.1)	0.068	
PEA	283 (18.5)	36 (13.6)	65 (17.9)	76 (17.1)	106 (23.1)	0.001	
Asystole	1154 (75.4)	209 (79.2)	269 (74.1)	342 (77.0)	334 (72.8)	0.064	
Bystander CPR, n (%)	680 (44.0)	72 (26.7)	101 (27.5)	233 (52.4)	274 (59.3)	<0.001	0
Intubation attempted, n (%)	1033 (66.9)	200 (74.1)	262 (71.2)	318 (71.5)	253 (54.8)	<0.001	0
Laryngeal Mask Airway, n (%)	321 (20.8)	16 (5.9)	32 (8.7)	32 (7.2)	241 (52.2)	<0.001	0
Epinephrine, n (%)	1056 (68.4)	194 (71.9)	259 (70.4)	313 (70.3)	290 (62.8)	0.008	0
Sodium bicarbonate, n (%)	568 (36.8)	143 (53.0)	149 (40.5)	171 (38.4)	105 (22.7)	<0.001	0
EMS response time, median (IQR)	7.2 (5.9, 9.8)	7.0 (5.0, 8.0)	7.0 (6.0, 9.0)	7.8 (6.0, 10.6)	7.3 (5.7, 10.1)	<0.001	5 (0.3%)
Scene outcome, n (%)							4 (0.3%)
Died at scene	991 (64.3)	175 (64.8)	243 (66.2)	275 (61.8)	298 (64.9)	0.512	
Transported with ongoing CPR	96 (6.2)	39 (14.4)	24 (6.5)	18 (4.0)	15 (3.3)	<0.001	
Transported with ROSC	454 (29.5)	56 (20.7)	100 (27.3)	152 (34.2)	146 (31.8)	<0.001	
ROSC at any time, n (%)	516 (33.4)	69 (25.6)	116 (31.5)	165 (37.1)	166 (35.9)	0.001	0
Event survival, n (%)	470 (30.7)	66 (24.8)	102 (28.1)	154 (34.6)	148 (32.2)	0.007	12 (0.8%)
Discharged alive, n (%)	133 (8.8)	18 (6.8)	31 (8.6)	33 (7.5)	51 (11.2)	0.029	26 (1.7%)

Abbreviations: SD standard deviation; VF/VT ventricular fibrillation/ventricular tachycardia; PEA pulseless electrical activity; CPR cardiopulmonary resuscitation; EMS emergency medical services; IQR interquartile range; ROSC return of spontaneous circulation.

12-month functional recovery and quality of life outcomes

Functional recovery and HRQoL outcomes were available for patients who arrested between 1st January 2010 and 31st December 2016 (Fig. S3). The number of EMS-treated cases was 682 (44% of the overall sample), of whom 60 survived to hospital discharge. Of those, eight patients died during the 12-month follow-up period leaving 52 patients for the 12-month telephone interview. A total of 26 patients responded (21 patients and five proxies) with a response rate of 50%. The majority of non-responders were lost to follow-up (n = 20), three refused to participate, and three were not appropriate for the 12-month follow-up. There was no significant differences in the baseline and arrest characteristics of responders and non-responders (Table S2).

The long-term functional recovery and HRQoL outcomes are shown in Table 3. At 12-month, 13 (50%) respondents reported good functional recovery, nine (35%) reported moderate functional recovery, and four (15%) reported severe disabilities. The median SF-12 mental and physical component scores were 52.5 (IQR 39.0, 57.0) and 41.5 (IQR 28.0, 57.0), respectively. When compared to the Australian norm, the mental component score did not differ (SMD −0.63; 95% CI: −1.35 to 0.09), however; the physical component score differed significantly (SMD − 1.04; 95% CI: −1.76 to −0.32). The median EQ-5D index score was 0.85 (IQR 0.59, 1), and median VAS was 70 (IQR 50, 80). Fig. 3 shows the proportion of 12 month survivors reporting problems across the five EQ-5D health domains. Few responders indicated that they have severe problems with mobility (n = 1), activity (n = 3), pain (n = 5), or anxiety/depression (n = 4).

Discussion

The findings from this study show that the incidence of OHCA due to suspected drug overdose in Victoria, Australia, remained unchanged over an 18-year period. Unadjusted survival rates improved substantially over time, with a three-fold increase in survival to hospital discharge between 2000 and 2017. Of the survivors to hospital discharge, 87% were alive at 12-months post-arrest. Among the patients who responded to the 12-month follow-up, 50% reported good functional recovery (GOSE ≥7). Although the majority of patients reported good HRQoL according to the EQ-5D, the proportion of survivors who reported some or severe problems with mobility, self-care, activity, pain and anxiety/depression ranges between 15% and 48%.

National figures from Australia show that drug-related deaths have increased over the last two decades, driven largely by heroin overdose in the late 1990s and pharmaceutical overdose involving codeine, oxycodone and fentanyl since 2001.[23,24] However, our findings show

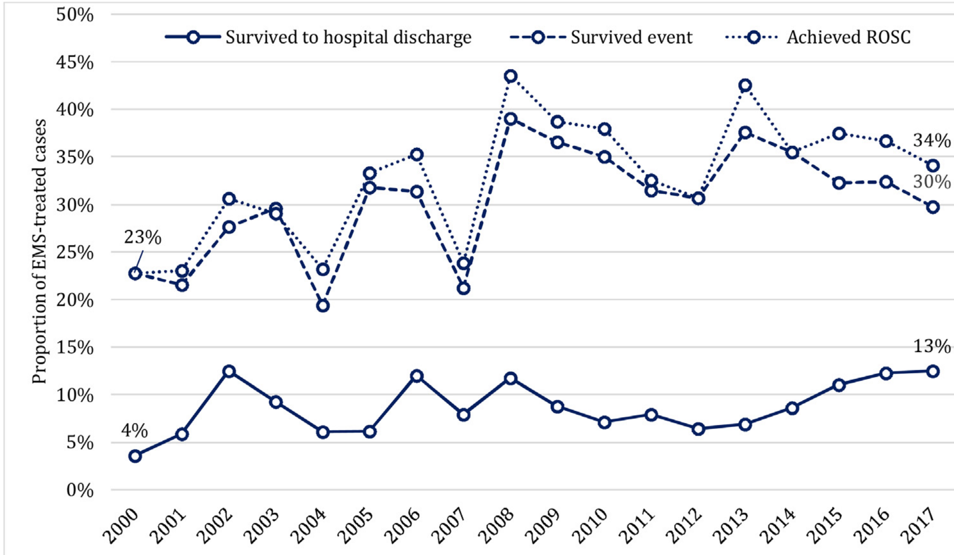

Fig. 2 – Long-term trends in the proportion of patients surviving to hospital discharge, surviving the event, and achieving prehospital ROSC.

that the incidence of drug overdose OHCA remained unchanged since 2000. The reduction in the incidence of drug overdose OHCA between 2000 and 2001 in our study could be explained by the national reduction in heroin supply between 1999 and 2001.[25] A number of other factors may also explain differences in the long-term incidence of drug-related deaths and drug-related OHCAs. For instance, national mortality figures include data from in-hospital and out-of-hospital settings, include deaths of overseas citizens, and the cause of death in these figures is mostly determined by a medical practitioner or a coroner.[23,24]Our study is limited to drug overdose OHCA, and the cause of cardiac arrest is presumed for all OHCA as autopsy findings are not routinely collected by the registry. It is possible that cases without clear evidence of drug-use could be misclassified (particularly pharmaceutical overdoses, which may be more difficult to identify in the field). For example, an autopsy study from San Francisco, United States, found that 14% of OHCA of presumed cardiac aetiology were in fact precipitated by drug overdose.[26]

Table 2 – Adjusted odds ratio (95% CI) for survival to hospital discharge.

Predictors	OR (95% CI)	p-Value
Age	0.97 (0.95, 0.99)	0.002
Male gender	0.86 (0.55, 1.34)	0.516
Witnessed arrest		
Not witnessed	Reference	
Public witnessed	2.95 (1.77, 4.94)	<0.001
EMS witnessed	4.32 (2.20, 8.46)	<0.001
Initial monitored rhythm		
Asystole	Reference	
VF/VT	10.08 (5.01, 20.29)	<0.001
PEA	9.00 (5.51, 14.67)	<0.001
Location of arrest		
Private residence	Reference	
Public location	0.92 (0.52, 1.58)	0.756
Other	1.08 (0.37, 3.10)	0.883
Bystander CPR	0.67 (0.41, 1.11)	0.128
Intubation attempted	1.91 (1.04, 3.49)	0.036
Epinephrine	0.39 (0.22, 0.70)	0.002
Sodium bicarbonate	0.16 (0.08, 0.31)	<0.001
EMS response time	0.98 (0.96, 1.01)	0.265
Year	1.02 (0.98, 1.07)	0.244

Abbreviations: OR, odds ratio; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activityCPR, cardiopulmonary resuscitation; EMS, emergency medical services.

Our study suggests that survival outcomes improved substantially over time. The increased rate of EMS witnessed arrests and an increase in the proportion of patients presenting with initial PEA may have contributed to this improvement. A study from British Colombia, Canada showed that EMS witnessed arrests increased significantly over a 10-year period and this was associated with improved survival to hospital discharge.[27] Additionally, a 26-year study from the Swedish OHCA registry showed that the proportion of initial PEA doubled between 1990 and 2016, and this led to a five-fold increase in 30-day survival.[28] An increase in both initial PEA and EMS witnessed arrests may indicate that bystanders are acting sooner to activate EMS following a drug-related event. Evidence from Victoria, Australia and elsewhere suggests that overdose response training programs enabled drug users and/or their peers to recognise drug-related events and activate EMS early.[29,30]

Although bystander CPR is a strong predictor of survival from OHCA,[2–4] it was not associated with improved survival to hospital discharge in our study population. The low rate of initial shockable rhythms in our cohort (6%) may have attenuated the impact of bystander CPR in our population. A number of studies demonstrated that the benefit of bystander CPR is diminished when the initial arrest rhythm is non-shockable.[31,32] However, there is evidence that the benefit of bystander CPR extends beyond short-term survival.[33,34] A national study from Denmark found that OHCA survivors who received bystander CPR were at lower risk of anoxic brain injury at one-year compared to those who did not.[33] Additionally, the effect of bystander CPR on five-year survival was 26% higher than the effect of bystander CPR on survival to hospital discharge in a

Table 3 – 12-month outcomes according to GOSE, SF-12 and EQ-5D.

12-month outcomes	Overall	Patients (n = 21)	Proxy (n = 5)
GOSE, n (%)			
Upper good recovery	7 (26.9)	6 (85.7)	1 (14.3)
Lower good recovery	6 (23.1)	6 (100)	0
Upper moderate recovery	4 (15.4)	3 (75)	1 (25)
Lower moderate recovery	5 (19.2)	4 (80)	1 (20)
Upper severe disability	0	0	0
Lower severe disability	4 (15.4)	2 (50)	2 (50)
Vegetative state	0	0	0
SF-12[a], median (IQR)			
Mental Component Score	52.5 (39.0, 57.0)	52.5 (39.0, 57.0)	–
Physical Component Score	41.5 (28.0, 57.0)	41.5 (28.0, 57.0)	–
EQ-5D, median (IQR)			
Index score[b]	0.85 (0.59, 1.0)	0.84 (0.64, 1.0)	0.76 (0.41, 0.85)
VAS[c]	70.0 (50.0, 80.0)	70 (50.0, 80.0)	67.5 (50.0, 82.5)

Abbreviations: GOSE, Glasgow Outcome Scale Extended; SF-12, Twelve-item short form health survey; IQR, interquartile range; EQ-5D, EuroQoL-5-3L Dimension, VAS, visual analogue scale.
[a] Includes patient responders only with three missing values.
[b] One missing value.
[c] Four missing values.

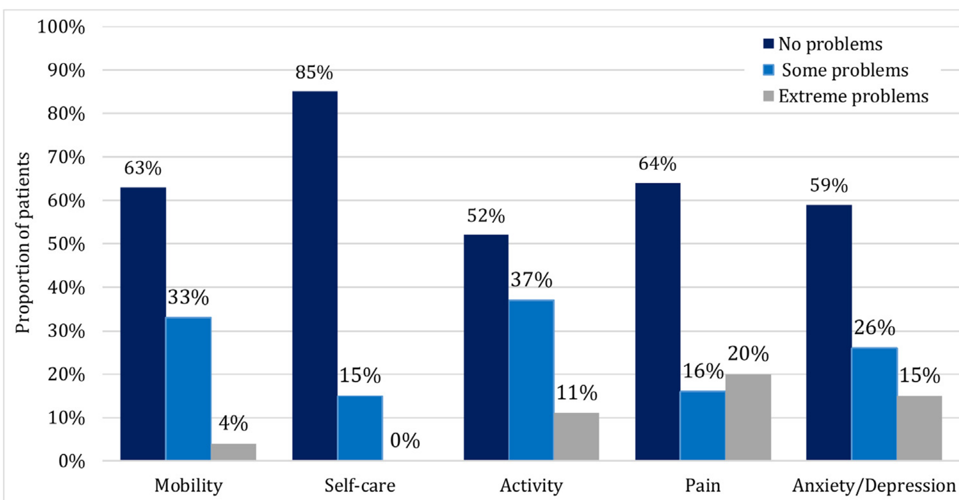

Fig. 3 – The proportion of 12 month survivors reporting problems across the five EQ-5D health domains (n = 26).

group of OHCA survivors from King County, United States.[34] Unfortunately, the impact of arrest factors were assessed at single point in time in our study, and we were unable to assess its impact on longer-term patient outcomes.

The majority of patients who survived to hospital discharge were alive at 12-month post-arrest (87%), and the majority of 12-month survivors reported good HRQoL outcomes. Our findings are similar to a previous study examining the functional outcome and HRQoL of 12-month survivors of OHCA, which showed that 92% survived to 12 months and 56% reported good functional recovery according to the GOSE.[15] However, the majority of the population in this study involved OHCA of presumed cardiac aetiology, and to date no studies have reported the long-term outcomes of survivors of OHCA precipitated by drug overdose.[9]

A number of opportunities exist to reduce the incidence of drug-related events and improve survival. As recognition of OHCA remains the main barrier to activating EMS and initiating CPR and defibrillation,[35] medically-supervised facilities could offer a safe environment for drug users without the concern of legal prosecution. In a recent systematic review, supervised injecting facilities were associated with a 35% reduction in mortality among drug users.[36] In addition, overdose response training programs could empower at risk populations to recognise the signs of drug overdose OHCA and respond appropriately by activating EMS and initiating CPR. Moreover, dispatcher-assisted CPR protocols could also help to increase bystander CPR in this population. Studies from Korea and the United States found that telephone-assisted CPR was associated with increased bystander CPR and improved survival in OHCA patients.[37,38]

Limitations

Our study has a number of limitations. First, our study is retrospective in nature and carries inherent limitations in its study design. Second, the

VACAR does not record information relating to the type of drug involved in OHCA events. Due to the nature of these events, it is possible that the drug/s involved in the incident were unknown to paramedics at the time of assessment. It is also possible that cases of drug overdose OHCA were misclassified by paramedics, either due to misinformation from bystander or the presence of drugs/alcohol on scene which may be independent of the cause of arrest. Third, due to the low response rate among survivors at 12-month follow-up, it is possible that non-responders experienced poorer functional outcomes and HRQoL and this would bias our findings. Fourth, despite our adjustment for key confounding variables, unmeasured confounding from patient comorbidity and post-cardiac arrest care may also influence survival outcomes. Finally, due the small sample of survivors, we were unable to assess HRQoL outcomes over time, or in multivariable models.

Conclusion

In our region, the incidence of drug overdose OHCA remained unchanged over an 18-year period. Despite this, the unadjusted rate of survival to hospital discharge improved over time and were mainly explained by an increase in EMS witnessed arrests and patients presenting with initial PEA. The majority of survivors who responded to the 12-month follow-up, reported good functional recovery and HRQoL. Opportunities to prevent the incidence of drug overdose OHCA and improve survival include supervised injecting facilities, overdose response training programs, and telephone-assisted CPR.

Conflict of interest

No conflict of interest.

Source of funding

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.08.036.

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Manuscript 4 Appendix. Supplementary Data

Supplementary appendix

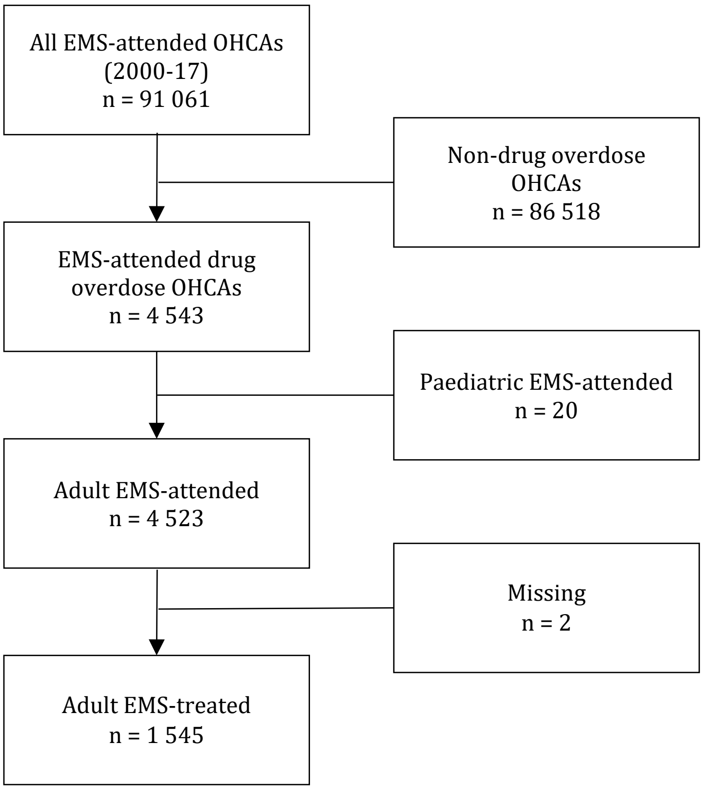


Figure S1. Flow diagram of the included patients.

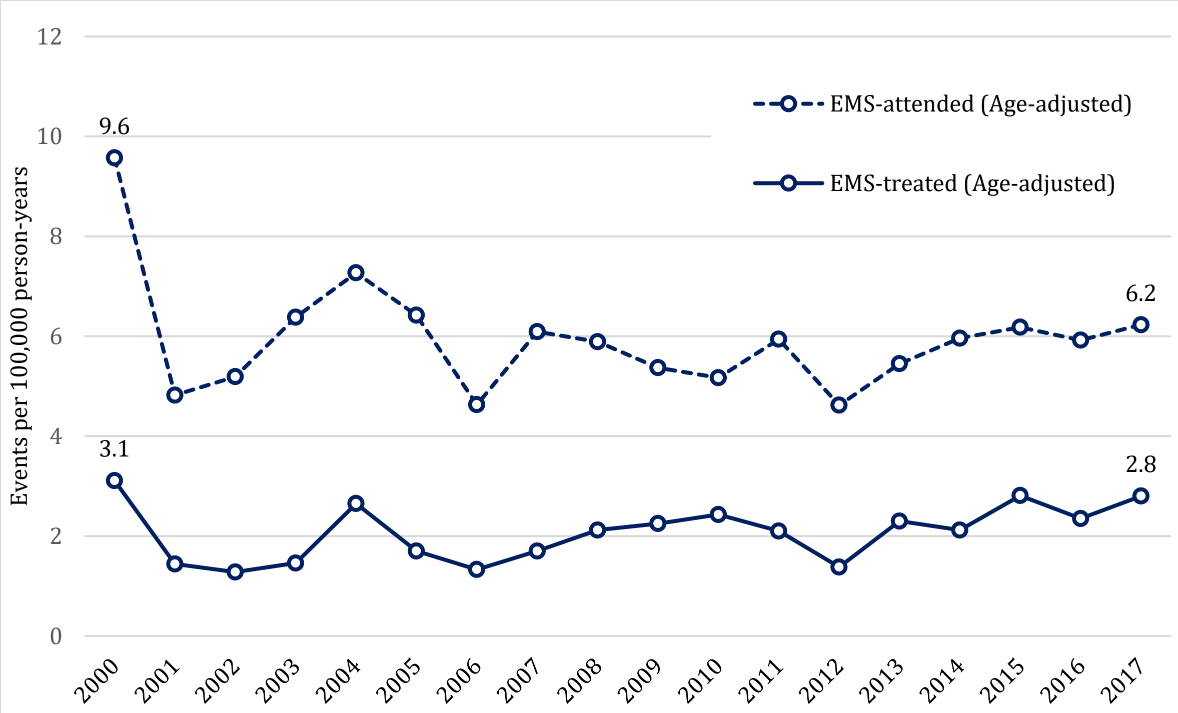


Figure S2. Age-adjusted incidence rate of EMS-attended and EMS-treated cases over time.

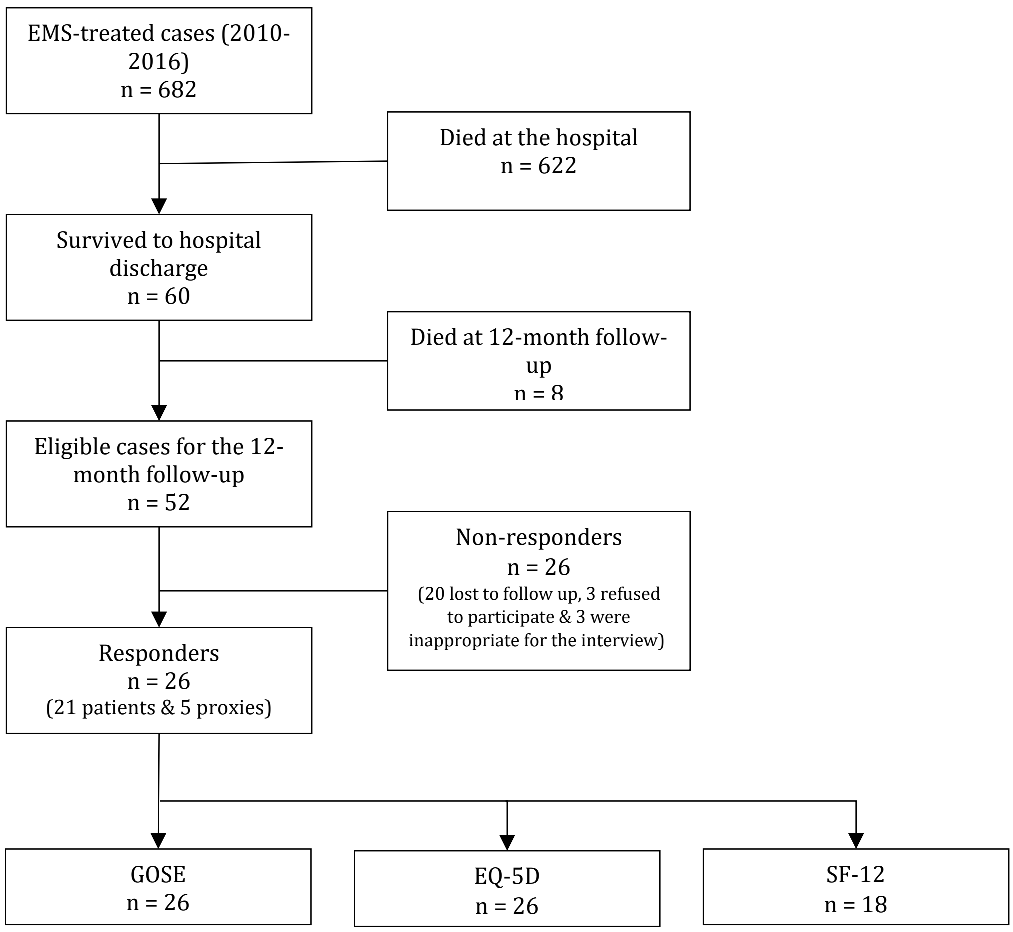


Figure S3. Flow diagram of the included patients for the structured telephone interview.

Table S1. Characteristics of EMS-attended cases stratified by study year.

Variable	Overall n=4523	2000-03 n=1001	2004-08 n=1223	2009-13 n=1171	2014-17 n=1128	P-value for trend	Missing n (%)
Age in years, mean (SD)	39.9 (14.1)	35.5 (12.9)	38.6 (13.7)	41.6 (14.5)	43.5 (14.0)	<0.001	145 (3.2%)
Male, n (%)	3236 (71.8)	745 (75.2)	862 (70.7)	819 (69.9)	810 (71.8)	0.129	13 (0.3%)
Witnessed status n, (%)							30 (0.7%)
Not witnessed	4096 (91.2)	916 (92.9)	1122 (91.9))	1069 (91.8)	989 (88.2)	<0.001	
Bystander witnessed	274 (6.1)	52 (5.3)	76 (6.2)	60 (5.2)	86 (7.7)	0.064	
EMS witnessed	123 (2.7)	18 (1.8)	23 (1.9)	36 (3.1)	46 (4.1)	<0.001	
Location of arrest, n (%)							1 (0.0%)
Private location	3354 (74.2)	667 (66.7)	872 (71.3)	898 (76.7)	917 (81.3)	<0.001	
Public location	1016 (22.5)	310 (31.0)	315 (25.8)	226 (19.3)	165 (14.6)	<0.001	
Other	152 (3.4)	23 (2.3)	36 (2.9)	47 (4.0)	46 (4.1)	0.009	
First documented rhythm, n (%)							16 (0.4%)
VF/VT	93 (2.1)	19 (1.9)	29 (2.4)	26 (2.2)	19 (1.7)	0.772	
PEA	286 (6.4)	37 (3.7)	65 (5.3)	78 (6.7)	106 (9.4)	<0.001	
Asystole	4128 (91.6)	938 (94.4)	1124 (92.3)	1066 (91.1)	1000 (88.9)	<0.001	
Bystander CPR, n (%)	944 (20.9)	111 (11.1)	147 (12.0)	330 (28.2)	356 (31.6)	<0.001	0
EMS response time, median (IQR)	7.6 (6.0, 10.6)	7.0 (5.0, 9.0)	7.4 (6.0, 10.0)	8.0 (6.1, 11.6)	7.8 (6.0, 11.3)	<0.001	50 (1.1%)

Abbreviations: SD, standard deviation; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range.

Table S2. Characteristics of responders and non-responders of the 12-month interview.

Variable	Responders (n = 26)	Non-responders (n = 26)	p-value
Age in years, mean (SD)	38.5 (13.3)	36.5 (12.6)	0.571
Male, n (%)	19 (70.4)	15 (57.7)	0.336
Witnessed status n, (%)			
Not witnessed	14 (56.0)	14 (53.9)	0.877
Bystander witnessed	6 (24.0)	5 (19.2)	0.679
EMS witnessed	5 (20.0)	7 (26.9)	0.560
Location of arrest, n (%)			
Private location	21 (77.8)	19 (73.0)	0.691
Public location	4 (14.8)	6 (23.1)	0.442
Other	2 (7.4)	1 (3.9)	0.575
First documented rhythm, n (%)			
VF/VT	4 (14.8)	3 (11.5)	0.725
PEA	19 (70.4)	17 (65.4)	0.697
Asystole	4 (14.8)	6 (23.1)	0.442
Bystander CPR, n (%)	13 (48.2)	9 (34.6)	0.318
EMS response time, median (IQR)	7.8 (6.9, 11.7)	9.0 (5.9, 11.3)	0.313

Abbreviations: SD, standard deviation; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range.

Summary of findings

Between 2000-03 and 2014-17, the rate of ROSC increased from 20.7% to 31.8%, event survival increased from 24.8% to 32.2%, and survival to hospital discharge increased from 6.8% to 11.2%. Despite significant improvements in the rate of bystander over the study period, bystander CPR was not associated with survival to hospital discharge. However, improvement in survival could be explained by witnessed arrest and PEA, which have increased over the 18 years. Of the survivors to hospital discharge between 2010 and 2017 (n = 60), 86.6% survive to 12-months. Of those who participated at 12-month follow-up (n = 26), 50% reported good functional outcomes according to the GOSE, and 52.0% to 85.0% reported no problems with mobility, self-care, daily activity, pain, and anxiety/depression according to the EQ-5D-3L.

Chapter 4. Epidemiology and outcomes of hanging-related OHCA in Victoria, Australia

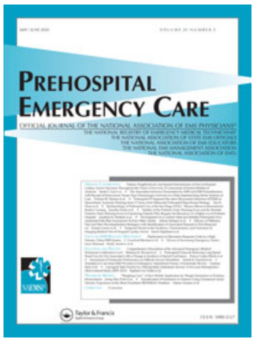
Background

In the previous chapter, it was shown that the majority of survivors from drug overdose OHCA reported good functional recovery and HRQoL at 12-month follow-up. In this population, chapter two showed that the pooled survival with intact neurological function at hospital discharge was 6.0%, a finding which could explain the good long-term functional recovery and HRQoL outcomes. However, survival with intact neurological function was < 1.0% in some non-cardiac OHCAs such as that precipitated by hanging.[9, 23] While resuscitation efforts could improve short- and long-term outcomes in drug overdose OHCA, the benefit of these efforts in hanging-related cases is not clear.

Aims

This chapter comprises a published paper that aimed to assess temporal trends in the incidence, characteristics, and survival of hanging-related OHCA across the overall population and by age groups. Functional recovery and HRQoL outcomes will also be described. In addition, predictors of survival and an EMS attempted resuscitation was examined.

Manuscript 5. Temporal trends in the incidence, characteristics, and outcomes of hanging-related OHCA



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Temporal Trends in the Incidence, Characteristics, and Outcomes of Hanging-Related Out-of-Hospital Cardiac Arrest

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Abstract

Aim: The aim of this study was to describe temporal trends in the incidence, characteristics, and outcomes of hanging-related out-of-hospital cardiac arrest (OHCA). **Method**: A retrospective study of all hanging-related OHCA in Victoria, Australia, between 2000 and 2017 was conducted. Trends in incidence, characteristics, and outcomes were assessed using linear regression and a non-parametric test for trend, as appropriate. Predictors of survival to hospital discharge were identified using multivariable logistic regression. **Results**: Between 2000 and 2017, emergency medical services (EMS)-attended 3,891 cases of hanging-related OHCA, of which 876 cases (23%) received an attempted resuscitation. The overall incidence rate of EMS-attended cases was 3.8 cases per 100,000 person-years increasing from 2.3 cases per 100,000 person-years in 2000 to 4.7 cases in 2017 (p for trend <0.001). Incidence rates increased approximately two-fold in young adults (18–44 years) and three-fold in middle aged adults (45–64 years). Despite improvement in the rate of bystander cardiopulmonary resuscitation (from 49% in 2000–2005 to 75% in 2012–2017), the survival to hospital discharge rate remained unchanged (3% overall). Among adult survivors with 12-month follow-up (n = 10), five patients responded to telephone interviews. Of those, three (60%) reported severe functional disability. Five patients responded to telephone interviews, of which 3 patients reported severe functional disability. An initial shockable rhythm (OR 23.17, 95% CI: 5.75, 93.36) or pulseless electrical activity (OR 13.14, 95% CI: 4.79, 36.03) were associated with survival. **Conclusion**: The incidence of hanging-related OHCA doubled over the 18 year period with no change to survival rates. New preventative strategies are needed to reduce the community burden of these events. **Key words:** out-of-hospital cardiac arrest; hanging; cardiopulmonary resuscitation; emergency medical services; quality of life

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Introduction

Suicide is the second leading cause of death in young adults and accounts for approximately 800,000 deaths each year worldwide (1). While restricting access to potentially lethal means has reduced deaths from some suicidal methods such as firearms and pesticide poisoning (2), suicide from hanging in some regions has increased in recent years (3–5). Suicide from hanging is characterized by cerebral hypoxia and neuronal cell death secondary to asphyxiation (6). Although survival rates following hanging have been estimated at around 30%, survival rates are lower when hanging results in out-of-hospital cardiac arrest (OHCA) (7).

The literature on the incidence and survival outcomes following hanging-related OHCA varies across regions (8–12). For example, the incidence of hanging-related OHCA in Japan is four-fold higher than that reported in France (9, 11). Additionally, survival rates have been reported as 2% in France compared to 10% in South Korea (9, 12). It is unclear if variation in the incidence and outcomes of hanging-related OHCA are related to differences in preventive or treatment approaches in each region, including improvements in systems-based factors such as bystander cardiopulmonary resuscitation (CPR). To date, no study has assessed temporal trends in the incidence, characteristics and outcomes of hanging-related OHCA. In addition, the long-term health related quality of life (HRQoL) and functional outcomes for survivors have not been examined.

This study aimed to assess temporal trends in the incidence, characteristics, and survival outcomes of hanging-related OHCAs. In addition, we aimed to examine the 12-month HRQoL outcomes for adult survivors and identify predictors of survival to hospital discharge and an emergency medical services (EMS) attempted resuscitation.

METHOD

Study Design

A retrospective case review of hanging-related OHCA from the Victorian Ambulance Cardiac Arrest Registry (VACAR) was performed. All cases who were attended by EMS between January 1, 2000 and December 31, 2017 were included. The collection of VACAR data has been considered a quality assurance project by the Victorian Government Department of Health Human Research Ethics Committee. The conduct of this retrospective study has been approved by the Monash University Human Research Ethics Committee (Project number: 9600).

Setting

Ambulance Victoria provides EMS in the state of Victoria, Australia, servicing approximately 6.3 million people (13). Paramedics with advanced life support and intensive care training co-respond to cases of suspected cardiac arrest in the emergency call. In addition, firefighters and community volunteers with basic life support training respond to cardiac arrest cases in select areas across the state. The treatment protocols for cardiac arrest follow the guidelines of Australian and New Zealand Council on Resuscitation (http://www.resus.org.au). Paramedics are authorized to withhold resuscitation in the field in adults with cardiac arrest if signs of obvious death are present, or initial asystole is present and the time between collapse and EMS arrival is more than 10 minutes (14). Patients who achieve return of spontaneous circulation (ROSC) in the field are transported to either the closest emergency care facility or, if spinal cord injury is suspected, to the highest level major trauma service within 45 minutes travel time.

Data Source and Definitions

Since 1999, the VACAR has recorded operational and clinical details of all EMS-attended OHCA cases in Victoria, Australia. Data sources and definitions have been described in detail elsewhere (15). Briefly, all paper-based and electronic patient treatment records completed by paramedics in the field are captured and stored in the registry. Potential cardiac arrest cases are identified through a highly sensitive search of patient care records, which then undergo manual review by registry staff for relevant eligibility criteria. The Utstein template is used to define elements of OHCA including patient and arrest characteristics, treatment interventions, and survival outcomes (16). Survival outcomes of transported cases are obtained from hospital medical records and validated against death records from the Victorian Registry of Births, Deaths, and Marriages. Cardiac arrest is defined as the absence of signs of circulation at any point during assessment by EMS. Hanging-related OHCA is determined by paramedics and documented on the prehospital patient care record.

Commencing January 1, 2010, the registry also conducts a follow-up interview with 12-month adult (>17 years) survivors to assess functional recovery and HRQoL outcomes. The follow-up interview has been described elsewhere (17). Briefly, a trained researcher contacts patients who are determined to be alive at 12-month follow up. Then, a structured interview is conducted with the patient or a proxy using the following health survey tools: Glasgow Outcomes Scale-Extended (GOSE) and EuroQol-5D-3L (EQ-5D) (17).

Statistical Analysis

Population estimates from the Australian Bureau of Statistics were used to calculate the crude incidence rate of hanging-related OHCA in EMS-attended and EMS-treated populations (13). The 2001 Australian standard population was used to calculate age-adjusted incidence rates (18). Linear regression was used to assess trends in incidence rates over the study period and to assess incidence rates across age groups (children [≤17 years], young adults [18–44 years], middle aged adults [45–64 years], and older adults [≥65 years]). For the baseline characteristics, we used mean and standard deviation (SD) or median and interquartile range (IQR) to summarize continuous variables and counts and proportions were used to summarize categorical variables. Differences in baseline characteristics and survival outcomes across age groups were assessed using chi-square test and ANOVA, as appropriate.

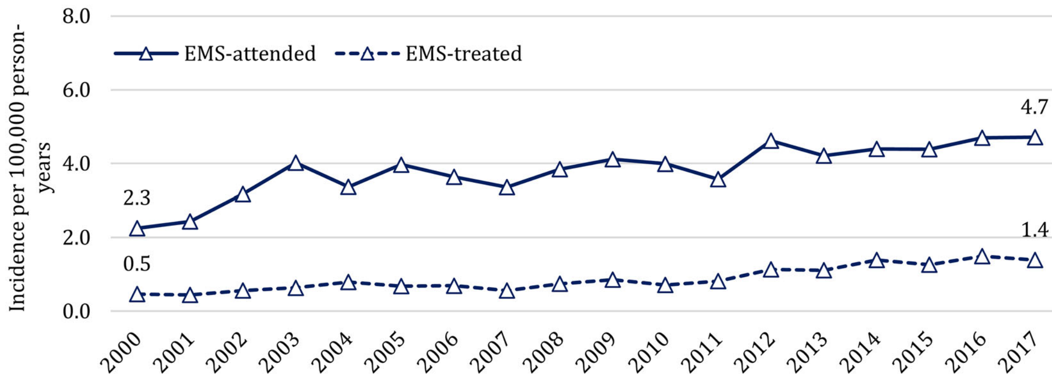

FIGURE 1. Overall crude incidence rate of emergency medical services (EMS)-attended and EMS-treated cases over the study period.

Trends in baseline characteristics and survival outcomes across study years (2000–2005, 2006–2011, and 2012–2017) were assessed using a non-parametric test for trend (19).

Multivariable logistic regression was used to assess predictors of survival to hospital discharge and an EMS decision to attempt resuscitation. The predictors assessed in the model include the following: age group, sex, witness status, first documented arrest rhythm, location of arrest, bystander CPR, EMS response time, and study year. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were used to report results. The 12-month functional recovery and HRQoL outcomes were also summarized using descriptive statistics as previously stated. A two-tailed p value of less than 0.05 was considered statistically significant. STATA statistical software version 15.0 (Statacorp, College Station, Texas, USA) was used to analyze data.

RESULTS

Between 2000 and 2017, EMS-attended 3,891 cases of hanging-related OHCA, of which 876 cases (23%) received an attempted resuscitation by EMS. The proportion of EMS treated cases increased from 20% in 2000 to 29% in 2017 (p for trend <0.001).

Trends in Incidence Rates

The incidence rates of EMS-attended and EMS-treated cases over the study period are shown in Figure 1. The overall incidence rate of EMS-attended cases was 3.8 cases per 100,000 person-years, increasing from 2.3 cases per 100,000 person-years in 2000 to 4.7 cases per 100,000 person-years in 2017 (p for trend <0.001). The overall incidence rate of EMS-treated cases was 0.9 cases per 100,000 person-years, increasing from 0.5 cases per 100,000 person-years in 2000 to 1.4 cases per 100,000 person-years in 2017 (p for trend <0.001). Crude incidence rates were similar to age-adjusted incidence rates (Figure S1).

Figure 2 shows trends in incidence rates of EMS-attended and EMS-treated cases across age groups. Incidence rates nearly doubled in young adults (18–44 years) and tripled in middle aged adults (45–64 years) (p for trend <0.001 for both).

Trends in Characteristics and Survival Outcomes

Population characteristics and survival outcomes of EMS-treated cases are presented in Table 1. Overall, the mean age was 38.0 years with no significant changes over time. Overall, 3% were witnessed by bystander or EMS, decreasing from 6% in 2000–2005 to 3% in 2012–2017. The majority of patients presented with initial asystole (81%). The rate of bystander CPR increased from 49% in 2000–2005 to 75% in 2012–2017. EMS interventions including intubation attempt and epinephrine and sodium bicarbonate administration significantly declined over time. There were no significant changes in outcomes over the period. Overall, 29% achieved prehospital ROSC, 27% survived the event, and 3% were discharged alive.

Table 2 presents differences in characteristics and survival outcomes of EMS-treated cases across age groups. Older adults (≥65 years) were more likely to be males and have a shorter EMS response time, and were less likely to receive bystander CPR, be intubated, and receive epinephrine compared to other age groups.

Functional Recovery and HRQoL Outcomes at 12-Month

Between January 1, 2010 and December 31, 2017, EMS treated 508 hanging-related OHCA patients (>17 years of age) of whom 14 (3%) survived to hospital discharge and 10 (2%) survived to 12-months.

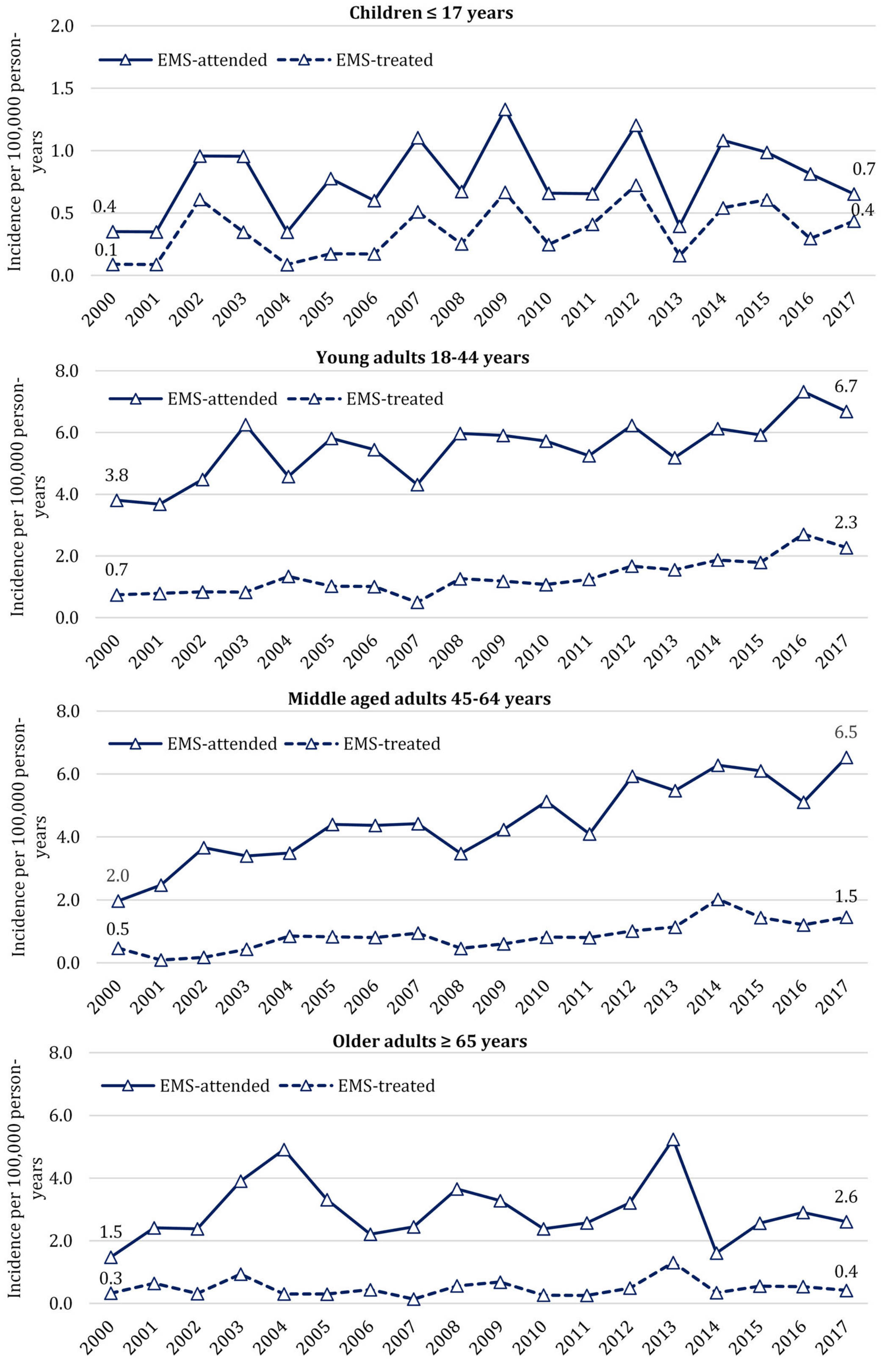

FIGURE 2. Tends in incidence rates of emergency medical services (EMS)-attended and EMS-treated cases across age groups.

Of those who were alive, 5 responded to the 12-month follow-up interview (2 patients and 3 proxies). Three (60%) of the survivors reported lower severe disability (GOSE = 3). According to EQ-5D, the median index score was 0.70 and visual analog scale was 67.5. Three (60%) of the survivors also

TABLE 1. Trends in characteristics and survival outcomes of EMS-treated cases over the study period

Variable	Overall (*n* = 876)	2000–2005 (*n* = 174)	2006–2011 (*n* = 235)	2012–2017 (*n* = 467)	*P*-value	Missing, *n* (%)
Mean age (SD)	38.0 (16.7)	36.7 (17.7)	37.6 (17.2)	38.6 (16.1)	0.239	3 (0.3)
Male, *n* (%)	653 (74.5)	120 (69.0)	174 (74.0)	76 (76.9)	0.004	0
Witnessed arrest, *n* (%)	30 (3.4)	10 (5.8)	8 (3.4)	12 (2.6)	0.027	0
Arrest in public location, *n* (%)	84 (9.6)	14 (8.1)	27 (11.5)	43 (9.6)	0.738	0
First documented rhythm, *n* (%)						4 (0.5)
VF/VT	26 (3.0)	3 (1.7)	9 (3.9)	14 (3.0)	0.761	
PEA	136 (15.6)	28 (16.2)	31 (13.3)	77 (16.5)	0.583	
Asystole	710 (81.4)	142 (82.1)	193 (82.8)	375 (80.5)	0.705	
Received bystander CPR, *n* (%)	567 (64.7)	85 (48.9)	133 (56.6)	349 (74.7)	<0.001	0
Endotracheal intubation attempted, *n* (%)	472 (53.9)	100 (57.5)	149 (63.4)	223 (47.8)	0.001	0
Epinephrine, *n* (%)	517 (59.0)	114 (65.5)	150 (63.8)	253 (54.2)	0.005	0
Sodium bicarbonate,* *n* (%)	251 (28.7)	75 (43.1)	82 (34.9)	94 (20.1)	<0.001	0
EMS response time, median (IQR)	7.6 (5.8, 9.1)	7.0 (5.0, 8.0)	7.5 (6.0, 9.7)	7.4 (5.8, 9.2)	0.037	3 (0.3)
Scene outcome, *n* (%)						0
Died at scene	604 (68.8)	115 (66.1)	155 (66.0)	334 (71.5)	0.074	
Transported with ongoing CPR	43 (4.9)	26 (14.9)	9 (3.8)	8 (1.7)	<0.001	
Transported with ROSC	229 (26.1)	33 (19.0)	71 (30.2)	125 (26.8)	0.153	
ROSC at any time, *n* (%)	252 (28.8)	43 (24.7)	75 (31.9)	134 (28.7)	0.646	0
Event survival, *n* (%)	237 (27.2)	42 (24.3)	70 (30.2)	125 (26.8)	0.899	4 (0.5)
Discharged alive, *n* (%)	25 (2.9)	3 (1.8)	9 (3.9)	13 (2.8)	0.756	6 (0.7)

*Sodium bicarbonate was removed from cardiac arrest treatment guidelines in 2016.
SD = standard deviation; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; IQR = interquartile range; ROSC = return of spontaneous circulation.

reported some or extreme problems in mobility and self-care, and 4 (80%) reported some or extreme problems in usual activity and anxiety/depression according to EQ-5D.

Predictors of Survival to Hospital Discharge

Multivariable logistic regression of survival to hospital discharge is presented in Table 3. An initial shockable rhythm (OR 23.17, 95% CI: 5.75, 93.36; $p < 0.001$) or pulseless electrical activity (OR 13.14, 95% CI: 4.79, 36.03; $p < 0.001$) were the only predictors significantly associated with survival to hospital discharge.

Factors Influencing EMS Decision to Attempt Resuscitation

Multivariable logistic regression of an EMS attempted resuscitation is presented in Table 4. The following factors were associated with an EMS decision to attempt resuscitation: young adults [18–44 years] (OR 0.53, 95% CI: 0.34, 0.82; $p = 0.004$), middle aged adults [45–64 years] (OR 0.45, 95% CI: 0.29, 0.72; $p = 0.001$), older adults [≥ 65 years] (OR 0.35, 95% CI: 0.21, 0.61; $p < 0.001$), witnessed arrest (OR 3.98, 95% CI: 1.36, 11.60; $p = 0.012$), initial PEA (OR 385.38, 95% CI: 52.82, 2811.60; $p < 0.001$), bystander CPR (OR 17.54, 95% CI: 14.22, 21.63; $p < 0.001$), and EMS response time (OR 0.95, 95% CI: 0.94, 0.97; $p < 0.001$). All patients with an initial shockable rhythm received an attempted resuscitation; as a result, this variable was omitted from the model.

DISCUSSION

In this 18-year case review, the overall incidence rate of hanging-related OHCA doubled between 2000 and 2017 in Victoria, Australia. Although incidence rates remained stable in children (≤ 17 years) and older adults (≥ 65 years), incidence rates increased approximately two-fold in young adults (18–44 years) and three-fold in middle aged adults (45–64 years). Despite substantial increases in bystander CPR over the study period, survival outcomes did not significantly change over time with an overall rate of survival to hospital discharge of 3%. Of the responders to the 12-month follow-up, most survivors reported lower severe disability according to the GOSE. In our multivariate analysis, only initial shockable or initial PEAs were associated with survival to hospital discharge.

The increase in incidence of hanging-related OHCA in our study was driven largely by events occurring in young to middle adulthood. In Australia, hanging is the leading cause of suicide (5). A report from the Australian Institute of Health and Welfare shows that suicidal death from hanging increased by more than 80% between 1990 and 2010, and this was driven largely by an increase in cases in middle adulthood (20). Similarly, hanging is the

TABLE 2. Difference in characteristics and outcomes of EMS-treated cases across age groups ($n = 873$)

Variable	Children ≤17 years ($n = 79$)	Young adults 18–44 years ($n = 516$)	Middle aged adults 45–64 years ($n = 211$)	Older adults ≥65 years ($n = 67$)	*P*-value	Missing *n* (%)
Male, *n* (%)	51 (64.6)	375 (72.7)	168 (79.6)	57 (85.1)	0.008	0
Witnessed arrest, *n* (%)	5 (6.3)	20 (3.9)	3 (1.4)	2 (3.0)	0.178	0
Arrest in public location, *n* (%)	5 (6.3)	47 (9.1)	20 (9.5)	11 (16.4)	0.192	0
First documented rhythm, *n* (%)						4 (0.5)
VF/VT	2 (2.5)	15 (2.9)	4 (1.9)	5 (7.5)	0.138	
PEA	12 (15.2)	84 (16.3)	28 (13.4)	11 (16.4)	0.794	
Asystole	65 (82.3)	415 (80.7)	177 (84.7)	51 (76.1)	0.404	
Received bystander CPR, *n* (%)	58 (73.4)	338 (65.5)	135 (64.0)	35 (52.2)	0.061	0
Endotracheal intubation attempted, *n* (%)	62 (78.5)	288 (55.8)	97 (46.0)	25 (37.3)	<0.001	0
Epinephrine, *n* (%)	66 (83.5)	312 (60.5)	111 (52.6)	28 (41.8)	<0.001	0
Sodium bicarbonate, *n* (%)	33 (41.8)	152 (29.5)	49 (23.2)	17 (25.4)	0.017	0
EMS response time, media *n* (IQR)	7.6 (6.2, 11.0)	7.1 (5.9, 9.0)	7.5 (5.8, 9.0)	6.9 (5.6, 10.0)	0.040	3 (0.3)
Scene outcome, *n* (%)						0
Died at scene	49 (62.0)	346 (67.1)	153 (72.5)	53 (79.1)	0.069	
Transported with ongoing CPR	14 (17.7)	24 (4.7)	4 (1.9)	1 (1.5)	<0.001	
Transported with ROSC	16 (20.3)	146 (28.3)	54 (25.6)	13 (19.4)	0.235	
ROSC at any time, *n* (%)	21 (26.6)	160 (31.0)	56 (26.5)	15 (22.4)	0.351	0
Event survival, *n* (%)	19 (24.7)	150 (29.1)	55 (26.2)	13 (19.7)	0.371	4 (0.5)
Discharged alive, *n* (%)	3 (3.8)	16 (3.1)	5 (2.4)	1 (1.5)	0.804	6 (0.7)

SD = standard deviation; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; IQR = interquartile range; ROSC = return of spontaneous circulation.

second leading cause of suicide in the United States, and the incidence is also increasing over time (21). A report from the United States Center for Disease Control and Prevention shows a 52% increase in death from suicidal hanging between 2000 and 2010, and this was mainly due to an increase in cases involving middle aged adults (22). Similarly, a recent report from Japan shows that suicide by hanging increased by 60% between 1979 and 2016 and remained the primary method of suicide (23).

Although the rate of bystander CPR in our cohort reached 75% by 2012–2017, survival outcomes remained unchanged over the study period. Bystander CPR alone does not necessarily improve survival (24, 25). A growing body of literature suggests that bystander CPR could be futile in several subgroups of OHCA, including unwitnessed arrests and initial non-shockable arrests (26–28). It is possible that the value of bystander CPR in our cohort was diminished by the high rate of patients who were unwitnessed and presented with initial non-shockable arrest rhythms (>93%). It is also possible that rescue breathing may have not been considered when CPR was administered by bystanders in our population. Animal studies suggest that bystander CPR with rescue breathing is associated with better survival outcomes compared to compression-only CPR in cardiac arrests precipitated by asphyxia (29, 30).

Our study suggests that hanging-related OHCA is a lethal event with a low rate of survival (3%). Similarly, the rate of survival to hospital discharge

Table 3. Adjusted odds ratio of survival to hospital discharge

Predictor	OR (95% CI)	*P*-value
Age group		
Children ≤ 17 years	Reference	
Young adults 18–44 years	0.67 (0.17, 2.61)	0.567
Middle age adults 45–64 years	0.50 (0.05, 3.27)	0.409
Older adults ≥ 65 years	0.25 (0.02, 2.80)	0.263
Male gender	0.87 (0.32, 2.42)	0.802
Witnessed arrest	1.20 (0.24, 6.99)	0.819
First documented rhythm		
Asystole	Reference	
VF/VT	23.17 (5.75, 93.36)	<0.001
PEA	13.14 (4.79, 36.02)	<0.001
Public location	0.78 (0.16, 3.68)	0.763
Bystander CPR	0.91 (0.33, 2.41)	0.844
EMS response time	0.91 (0.79, 1.03)	0.155
Year	1.00 (0.91, 1.10)	0.914

OR = odds ratio; CI = confidence intervals; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity; CPR = cardiopulmonary resuscitation; EMS = emergency medical services.

Table 4. Adjusted odds ratio of EMS decision to resuscitate

Predictor	OR (95% CI)	*P*-value
Age group		
Children ≤ 17 years	Reference	
Young adults 18–44 years	0.53 (0.34, 0.82)	0.004
Middle age adults 45–64 years	0.45 (0.29, 0.72)	0.001
Older adults ≥ 65 years	0.35 (0.21, 0.61)	<0.001
Male gender	0.89 (0.70, 1.14)	0.356
Witnessed arrest	3.98 (1.36, 11.60)	0.012
First documented rhythm		
Asystole	Reference	
VF/VT*	1	–
PEA	385.38 (52.82, 2811.60)	<0.001
Public location	0.77 (0.55, 1.07)	0.122
Bystander CPR	17.54 (14.22, 21.63)	<0.001
EMS response time	0.95 (0.94, 0.97)	<0.001
Year	1.01 (0.99, 1.03)	0.165

* Fell out of the model due to perfect collinearity.
OR = odds ratio; CI = confidence intervals; VF/VT = ventricular fibrillation/ventricular tachycardia; PEA = pulseless electrical activity; CPR = cardiopulmonary resuscitation; EMS = emergency medical services.

in a group of hanging-related OHCAs from France was 2%, and 4% in Osaka, Japan (9, 11). In contrast, the rate of survival was 10% in a small case series of hanging-related OHCAs from Seoul, South Korea ($n = 52$) (12). However, the population included in this study was from a single tertiary hospital and included patients who survived to hospital admission. In that study, all survivors were discharged in a persistent vegetative state. Our study also suggests that the long-term functional outcomes of survivors are poor, assuming that patients who were lost to follow-up at 12 months also experienced poor functional outcomes (17). This may be due to the high rate of initial non-shockable arrest rhythms (97%) in our cohort.

While suicide prevention is considered a high priority by many developed countries such as the United Kingdom, Japan, and Australia, suicide prevention initiatives in these countries focus on reducing access to lethal means (31). This approach is likely to prevent suicide from firearms, poisoning, and common sites for suicide by jumping such as bridges, subways, and buildings (2, 32). However, these methods combined account for 50% of suicides, while suicidal hanging alone accounts for a further 50%. Unfortunately, no specific approach to date is available to minimize community access to the means of hanging (2, 7, 32). In addition, some common preventative initiatives have not necessarily been demonstrated to reduce suicide rates from hanging (2, 32). These include public awareness campaigns on suicide, suicide training programs for gatekeepers (e.g., school teachers and community leaders), media reporting on suicide, and internet or telephone support (2).

In comparison, a number of preventative strategies have successfully been used to reduce the rates of attempted and actual suicide. As previous suicide attempts are a strong predictor for suicide (1), school-based intervention programs may help to reduce suicide attempts (33–35). A multicenter cluster-randomized control trial from ten European Union countries showed that a Mental Health Awareness Program reduced the incidence of suicide attempts and severe suicidal ideation at 12-month follow-up by 55% and 50%, respectively (34). This program aimed to enable students (aged between 14 and 16 years) to recognize mental health through interactive discussion and seek medical aid (36). Such a program may also help identify at-risk youth who are likely to develop persistent mental health disorders at lifetime (34). In addition, as nearly 50% of individuals who commit suicide sought medical aid one month before suicide (37, 38), primary care physician education programs that aim to improve the early recognition of depression and risk of suicide can reduce suicide rates by 22%–73% (32). Including such programs in suicide prevention strategies may contribute to reducing suicide rates by hanging.

Limitations

This study has potential limitations. As with any observational study, our study design suffers from inherit methodological limitations. The etiology of cardiac arrest was mainly determined by the EMS, and autopsy findings were not routinely collected by the VACAR to confirm the cause of cardiac arrest. The VACAR does not also collect in-hospital data that would enable us to distinguish between traumatic and asphyxial hanging. In addition, the time between cardiac arrest and the first initiation of bystander CPR is not captured by our registry given difficulties in validating this field. Importantly, the findings of our multivariable model for survival is likely to be impacted by the low number of survivors ($n = 25$). Similarly, there were only 10 survivors that were eligible for 12-month follow-up of which we had a 50% non-response rate.

CONCLUSION

Hanging-related OHCA is frequent event with a high rate of mortality. Despite improvements to bystander interventions, the case-fatality rate remained unchanged over an 18-year study period. Furthermore, the incidence has doubled between 2000 and 2017, and some patient groups have seen more than a three-fold increase in incidence rates over the study period. These findings suggest that new preventative strategies are needed to reduce the burden of these events in the community.

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Manuscript 5 Appendix. Supplementary Data

Temporal trends in the incidence, characteristics and outcomes of hanging-related out-of-hospital cardiac arrest

Supplementary file

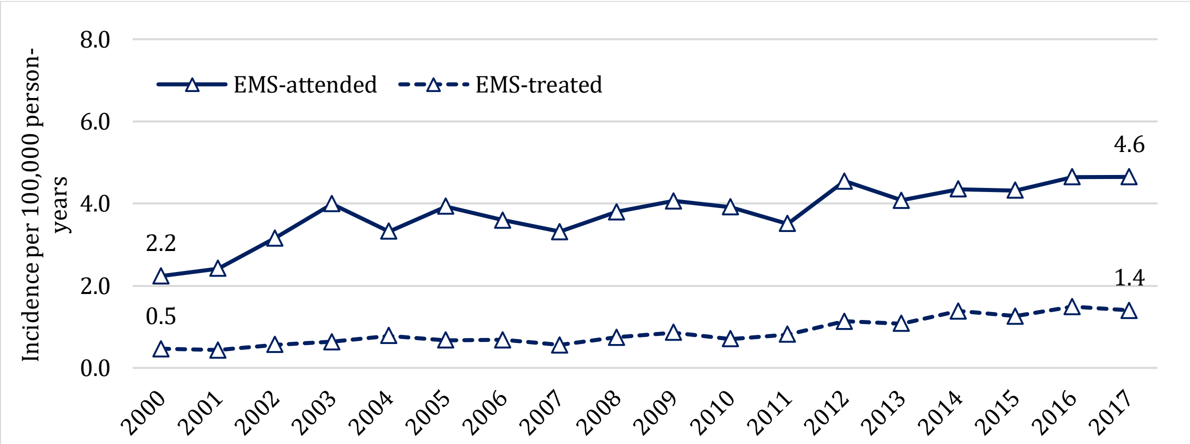

Figure S1. Age-adjusted incidence rate of EMS-attended and EMS-treated cases overtime.

Summary of findings

In Victoria, Australia, the incidence of hanging-related OHCA increased from 2.3 cases per 100,000 person-years in 2000 to 4.7 cases per 100,000 person-years in 2017. This increase is primarily driven by the increased incidence in young adults (18-44 years) which increased from 3.8 cases per 100,000 person-years in 2000 to 6.7 cases per 100,000 person-years in 2017 and in middle-aged adults (45-64 years) which increased from 2.0 cases per 100,000 person-years in 2000 to 6.5 cases per 100,000 person-years in 2017. Over the 18 years, survival outcomes remained unchanged with an overall rate of survival to hospital discharge of 2.9%. Also, survival outcomes did not differ across age groups. Bystander CPR was not associated with survival, but it was associated with an EMS attempted resuscitation. Patients who are found in VF/VT or PEA were more likely to survive to hospital discharge compared to that who are found in asystole. Of the 14 cases who survived to hospital discharge between 2010 and 2017, 10 (71.4%) survived at 12-months. Of those survivors who participated in the 12-month follow-up (n = 5), three reported lower severe disability according to the GOSE and problems with mobility, self-care, usual activity, pain, and anxiety/depression according to the EQ-5D-3L.

Chapter 5. General discussion of the main findings, and thesis implications and recommendations, and conclusion

General discussion

In Victoria, Australia, non-cardiac aetiologies accounted for 28.9% of OHCAs between 2000 and 2017. Of these cases, 91.7% were precipitated by trauma, terminal illness, drug overdose, hanging and respiratory causes. Moreover, the incidence increased by 1.6% per year, with an overall rate of 23.8 cases per 100,000 person-years. In some of the precipitating aetiologies, the incidence increased by ≥ 3.0% per year, such as that precipitated by medical exsanguination, respiratory, neurological and hanging. The adjusted rate of survival increased from 5.3% in 2000-05 to 7.4% in 2012-17 with an overall adjusted rate of 6.3%. This improvement in survival is driven by the increased rate of survival in PEA, which increased from 5.7% in 2000-05 to 14.2% in 2012-17. Relative to asystole, PEA was a predictor of survival in some non-cardiac aetiologies such as that precipitated by drug overdose and hanging. In drug overdose OHCA, the overall rate of survival was consistent with the pooled international rate of survival (9.0%), but this rate increased from 6.8% in 2000-03 to 11.2% in 2014-17 in Victoria, Australia. Conversely, the rate of survival remained unchanged at 2.8% in hanging-related OHCA over the 18-years. In both populations, bystander CPR was not associated with survival. Despite this, the majority of survivors from drug overdose OHCA reported good functional recovery and HRQoL at 12-month follow-up.

The proportion of non-cardiac aetiologies to OHCA in Victoria, Australia is similar to that reported in some regions. For example, OHCA precipitated by non-cardiac aetiologies was 34.1% in Helsinki, Finland, and 24.7% in Goteborg, Sweden.[21, 22] Since many untreated cases were excluded from these reports, it is difficult to compare the distribution of a precipitating aetiology in these regions with that in Victoria, Australia. Notably, while the incidence has changed over time in Victoria, Australia, similar changes have been reported in other regions. For example, in Osaka, Japan, the incidence increased from 12.4 cases per 100,000 population in 2005 to 13.3 cases in 2011.[9] Similarly, the incidence increased from 8.7 cases per 100,000 population to 11.6 cases between 2006 and 2010 in South Korea.[33] In Olmsted County, US, the incidence also increased from approximately 3.0 cases per 100,000 population in 1995 to 15.0 cases in 2005.[7] Despite these changes, the incidence rates reported in these regions do not reflect the burden of OHCA of non-cardiac aetiologies because a significant proportion of untreated cases were excluded (8.1%-47.9%). Unlike the findings reported in these regions, findings from this thesis reflect the burden of OHCA of non-cardiac aetiologies in Victoria, Australia.

In Victoria, Australia, the rate of survival to hospital discharge in the non-cardiac population increased modestly over time, and several factors could explain this. The rate of witnessed arrest, bystander CPR, and PEA increased by ≥ 60.0% over the 18 years. Witnessed arrest and PEA (relative to asystole) are directly associated with survival, and this was observed in drug overdose and hanging related OHCAs. Additionally, while bystander CPR was associated with an EMS attempted resuscitation, this could indirectly be associated with survival. It is possible that bystander CPR could prolong the presence of PEA on EMS arrival, which may have resulted in improved survival. Importantly, this incremental increase in survival is independent of other cardiac arrest characteristics. As demonstrated in the systematic review, drug overdose cases were twice as likely to survive to hospital discharge compared to non-drug overdose cases. This finding differs from that reported in Japan, Osaka.[9] In that study, the rate of survival did not improve over seven years, with an overall rate of 5.3%. However, our study spans a much broader period (2000-2017) in Victoria, Australia, compared to that in Osaka, Japan (2005-2011). As such, the effect of significant changes in resuscitation guidelines which have been introduced in 2010 such as compression-only CPR and dispatcher-assisted CPR may have been more influential in Victoria, Australia, compared to that in Osaka, Japan.[34] These changes could have translated into more bystander CPR engagement by the Victorian community and more resuscitation attempted by Victorian EMS, and these could have resulted in improved survival in the Victorian population.

While the majority of survivors from drug overdose OHCA reported good long-term outcomes, the majority of hanging-related OHCA survivors reported poor outcomes. Differences in short-term functional outcomes could explain this difference. In drug overdose, OHCA, data from the systematic review showed that 30-day survival with intact neurological function was 6.0%. In comparison, several reports showed that neurological function at hospital discharge from hanging-related OHCA was less than 1.0%.[9, 23] This difference in short-term prognosis could be related to differences in the time to initiating bystander CPR in cardiac arrest patients. In hanging-related OHCAs, it is difficult to perform immediate CPR in cases found suspended. As such, survivors from hanging-related OHCA may have sustained anoxic brain damage due to a delay in cerebral perfusion, and this may have resulted in poor long-term outcomes for survivors. However, these findings should be interpreted in the context of their limitation. In both populations, the number of survivors was small ($n \le 26$), and predictors associated with long-term outcomes for survivors were not assessed.

Implications and recommendations

Non-cardiac aetiologies could be the leading cause of OHCA in our region by 2052, and there is a need for more effective cause-specific measures to counteract this increase. For example, hanging-related OHCA is on the rise in our region, and mean restriction is considered the only effective prevention approach in suicide by hanging.[35] Although removing ligatures and suspension points can reduce suicidal death from hanging in institutional settings such as psychiatric units and prisons; this approach is unlikely to be successful in the general community because ligatures and suspension points are universally available. Despite this, it is possible to reduce the incidence of suicide by hanging or other lethal means in the general community if at-risk individuals are identified early by clinicians, given that 49.9% of people who die by suicide seek medical aid one month before death. This percentage could be as high as 82.7% within 12 months.[36] Clinicians in primary care settings are often the first point of contact in most suicidal cases and; therefore, have the potential to manage individuals at risk before they commit suicide.[36] However, identifying individuals at risk of suicide is challenging.

Individuals at risk of suicide could be those with undiagnosed mental disorders such as depression, bipolar, substance-related, psychotic and personality disorders.[37] Importantly, they could be those presenting with more than one risk factor in which multiple factors work together to cause intentionally fatal self-injury by hanging or other lethal means.[38] Unfortunately, there is no single prescribed approach to date that could help clinicians to detect individuals at risk of suicide. As such, there is a need for one that considers that risk assessment for suicide should not be isolated from a psychiatric assessment. The reason for this is that there is strong evidence from 27 psychological autopsy studies that 87.3% of suicidal deaths are related to mental disorders, and that half of these deaths can be explained by depressive and bipolar disorders.[39] Additionally, clinicians in primary care settings should receive ongoing training in mental health. Physicians trained in mental health can reduce the incidence of suicide by up to 73.0%.[40]

Similar to hanging-related OHCA, drug overdose is a significant precipitator of OHCA and is on the rise in our region if incidence cases between 2000 and 2001 were excluded. During this time, there was a rapid decline in drug-related death which was driven mainly by a reduction in heroin supply.[42] While restricting access to illicit drugs can reduce the incidence of drug-related mortality and morbidity; other approaches have the potential to minimise associated harm from substance abuse. This includes drug-addiction treatment programs, overdose-response training programs, public education programs on drugs, supervised injecting facilities, needle syringe programs, and take-home naloxone.[43-45] However, evidence from Australia and elsewhere suggests that misuse of pharmaceutical analgesics is an ongoing public health problem.[46] According to a coronial data from Australia, the incidence of drug-related death increased from 3.9 cases per 100,000 population in 2001 to 5.2 cases in 2012.[47] Much of this increase in fatality cases can be explained by pharmaceutical opioid-related death which increased from 2.2 cases per 100,000 population in 2001 to 3.6 cases in 2012. Increased prescription of opioid analgesics such as oxycodone, fentanyl, and methadone were related to these deaths. Unfortunately, opioid prescription is growing in Australia and worldwide,[46] and efforts are needed to restrict opioid prescription.

The rate of survival in OHCA of non-cardiac aetiologies is increasing in our region, and resuscitation efforts in this population are not necessarily futile. It is plausible that a coordinated system response from emergency dispatchers, bystanders, EMS personnel, and hospital providers are effective. However, there is some potential for improvements in this population, given that they often present with initial non-shockable rhythms. An example of this is the use of targeted temperature management (TTM) which could improve survival and long-term outcomes for survivors from OHCA of non-cardiac aetiologies. A recent randomised-control trial of cardiac arrest with initial non-shockable rhythms indicated that 90-days survival with good neurological outcomes was higher in patients who received TTM at 33°C (10.2%) compared to those who received normothermia (5.7%).[48] In that study, two-thirds of cardiac arrests were precipitated by non-cardiac aetiologies. Despite this, TTM in Australia is only recommended for cardiac arrests of presumed cardiac aetiology.[49]

The incidence of some OHCA of non-cardiac aetiologies is rapidly increasing in Victoria, Australia. This includes OHCA precipitated by non-traumatic exsanguination, respiratory and neurological causes. However, none of these aetiologies has been described in depth in the resuscitation literature. Unfortunately, it is not clear if these increases are related to changes in demographical profiles such as age, sex, and ethnicity, common comorbidities such as chronic obstructive pulmonary disease, asthma, and hypertension or emerging health conditions.[50, 51] It is also not clear if cases of these aetiologies respond well to common prehospital treatment interventions. This lack of understanding may lead to a delay in cause-specific prevention and treatment interventions or provision of unnecessary resuscitation attempts. As such, further investigation into the epidemiology and outcomes of OHCA from these aetiologies is also needed.

Conclusion

By 2052, non-cardiac aetiologies could be the major cause of OHCA in our region, and there is a need for more effective cause-specific prevention interventions to counteract the increase in incidence. Death from suicide by hanging is preventable if individuals at risk are identified early and treated with medication and psychotherapy. Similarly, death from drug overdose can be avoided if prevention strategies specifically target emerging patterns of substance abuse. In addition, survival in non-cardiac OHCA is improving in our region, and resuscitation efforts in some of this population are not necessarily futile such as that precipitated by drug overdose. However, there is potential for improvement. An example of this is the use of TTM, which could improve short- and long-term survival in this population whose initial rhythms are often non-shockable. Finally, the number of precipitating aetiologies are rapidly increasing such as that precipitated by medical exsanguination, respiratory and neurological causes, and research is needed to understand the epidemiology and outcomes of these aetiologies to avoid delays in prevention and treatment interventions.

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Appendices

1. Monash University Human Research Ethics Committee Approval

2. Ambulance Victoria Research Committee Approval

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number:	9600
Project Title:	Out-of-hospital cardiac arrest precipitated by non-cardiac causes: Epidemiology, outcomes, and long-term functional recovery
Chief Investigator:	Assoc Professor Brett Williams
Expiry Date:	28/06/2022

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data collection can occur at the specified organisation.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible for the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

CC: Mr Ziad Nehme, Dr Karen Smith, Mr Saeed Alqahtani

List of approved documents:

AmbulanceVictoria

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T 03 9840 3500

ABN 50 373 327 705 004

5 JULY 2017

File Ref: R17-008

Mr Saeed Alqahtani
Monash University

Dear Saeed,

Re: Research Proposal "R17-008: Out-of-hospital cardiac arrest precipitated by non-cardiac causes: epidemiology, outcomes, and long-term functional recovery" dated 31/05/2017.

I am pleased to inform you that Ambulance Victoria (AV) has approved participation in the above study, subject to Human Research Ethics Committee approval.

Note that any changes to the original application will require submission of a protocol amendment to the AV Research Committee for consideration. Please ensure that AV is informed of any protocol changes as soon as possible.

As a component of ongoing communication processes, AV requires annual progress reports and a final report on completion of the study. You will be emailed the progress report approximately four weeks prior to the due date. Progress reports are required to be submitted by email.

Yours sincerely,

KAREN SMITH
Manager Research & Evaluation
On behalf of the Research Committee
Ambulance Victoria