Outcomes and their Determinants in Sudden Cardiac Arrest

Population health approaches to improve clinical outcomes

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Outcomes and determinants in patients with sudden cardiac arrest
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OUTCOMES AND THEIR DETERMINANTS IN PATIENTS WITH SUDDEN CARDIAC ARREST

Gevolgen en determinanten van plotselinge hartstilstand

(met een samenvatting in het Nederlands)

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Chapter 1

General Introduction

Andrew Fu Wah Ho

Out-of-hospital cardiac arrest as a unique medical emergency

Sudden cardiac arrest is the abrupt loss of functional mechanical cardiac function resulting in the absence of systemic circulation.[1] Out-of-hospital cardiac arrest (OHCA) is when this occurs outside of the hospital setting. Although an estimated 70% of cases are due to ischemic heart disease, non-cardiac and non-ischemic cardiac etiologies are not uncommonly encountered.[2] Non-cardiac etiologies of OHCA include asphyxia, trauma, pulmonary embolism, and accidental hypothermia. OHCA is the most time-critical and the most catastrophic medical emergency. Inevitably fatal if left untreated, every second of delay in treatment prolongs anoxic injury to vital organs, and accordingly, a drastic reduction in the chance of survival. The unpredictable onset and time-sensitive nature of OHCA makes it a uniquely challenging disease both to treat and to study.[3] Despite a long history of trying to improve how we manage OHCA, survival remains dismally low.[4] Only over the past decade have we begun to see meaningful improvements in prognosis and neurological outcomes.[5] A comprehensive understanding of clinical outcomes and their determinants in these patients is critically needed to formulate effective strategies to improve outcomes.

Out-of-hospital cardiac arrest as a major public health concern

OHCA exerts a tremendous disease burden in our society, although its quantification is challenging due to variations in case definition and unavailability of high-quality epidemiological data. The incidence rate of adult OHCA attended by Emergency Medical Services (EMS), pooled from global data, was estimated at 83.7 per 100,000 person-years.[4] Another study has estimated that globally, only 8.0% of all OHCA occurring in 2000-2009, and 13.3% of those occurring in 2010-2019, survived to hospital discharge.[5] Yet other studies have found varying degrees of post-acute sequelae amongst survivors of OHCA, such as in terms of physical disability, cognition, return to work, mental illnesses and caregiver burden.[6] More recently, the maturation of resuscitation registries allowed investigators to employ disease burden metrics (specifically, disability-adjusted life years, DALYs) that more soundly incorporated both mortality and morbidity, as well as allow comparisons with other diseases. Unsurprisingly, in one of the few such attempts, adult nontraumatic OHCA ranked third in the United States for highest disease burden measured by DALYs, behind only ischemic heart disease and low back and neck pain.[7] This study estimated that OHCA was responsible for 1,194,993 DALYs (1,194,069 years of life lost and 924 years lived with disability) in the year 2016 in the United States.

Current concepts in out-of-hospital cardiac arrest research

A number of conceptual theories, models and framework are currently in use, with varying effectiveness, to organize interrelated concepts in OHCA. By organizing concepts and illustrating relationships between them, they lend structural aid to enable researchers, clinicians, and policymakers to explain phenomenon, set agenda, design interventions, and plan evaluation. Some frameworks and models have developed iteratively amidst evolving knowledge and priorities, while others have developed independently. Some of the more important ones are summarized below in order to illustrate current concepts and historical shifts in thinking within the field.

Figure 1. The Chain of Survival. *Taken from https://cpr.heart.org/en/resources/cpr-facts-and-stats/out-of-hospital-chain-of-survival*

Among the earliest of these, one still relevant today, is the Chain of Survival which gained traction in the early 2000s. Like how a chain is only as strong as its weakest link, the Chain of Survival describes a chain of events that must occur quickly and seamlessly to enable a patient to survive an OHCA. Originally comprising four links (early recognition and activation of EMS, early cardiopulmonary resuscitation [CPR], early defibrillation, and early advanced life support)[8], additional links have more recently been proposed with varying degrees of adoption. These include post-cardiac arrest care[9], and recovery[10], and they reflect an evolving state of knowledge and priorities among experts in this field. The first important observation is that the first three links are performed by bystanders (usually lay persons). Without early recognition and bystander CPR, subsequent links delivered by health professionals are often futile. Hence, in no other medical situation is there such a vital reliance on the community. The second important observation is that in order to enable a patient to survive OHCA, the entire emergency care system needs to function cohesively. The latest iteration of the Chain of Survival is shown in Figure 1.

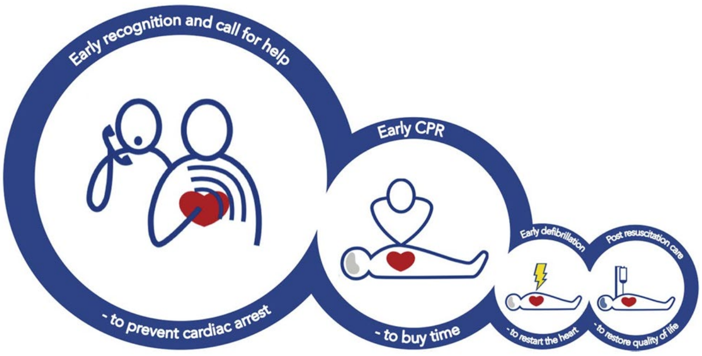

Figure 2. Deakin's modified Chain of Survival. The relative areas of the circles reflect how the contribution of each of the links diminishes quickly as patients succumb at each stage and the attrition rate results in decreasing numbers of patients that may benefit from the next stage. *Figure taken from Deakin CD. The chain of survival: Not all links are equal. Resuscitation. 2018;126:80-82.*

Recognizing that the original Chain of Survival does not convey the relative importance of each key stage of resuscitation, Deakins proposed a modification of the Chain of Survival (Figure 2).[11] By using circles of different sizes to represent different numbers of patients that may benefit from each stage of resuscitation, the potential impact of each stage is illustrated. This forms a more accurate reflection in that the contribution of each of the links diminishes quickly as patients succumb at each stage and the attrition rate results in rapidly decreasing numbers of patients that may benefit from the next stage. Put another way, a subsequent link is only useful if the preceding link was performed successfully. Taking the initial link (early recognition and activation of EMS) as the starting point with a ratio of 1.0, the percentage of patients progressing to each subsequent link was used to construct a chain where the area of each circle indicates the percentage of patients reaching each link. The result of this weighted approach was a framework that reflects the relative potential benefit of allocating resources to each link. This presents a useful aid to clinicians, scientists and policymakers who need to allocate scarce resources to competing priorities. Clearly, focusing on community response appears to be a sensible strategy to impact OHCA survival as it increases the base of patients who have any chance of benefitting from the subsequent ambulance and hospital interventions. While a significant improvement, an important limitation of this modified framework is that the weighting is based only on number of patients rather than "room for improvement". Both are relevant if one were to make a rational judgment on potential impact.

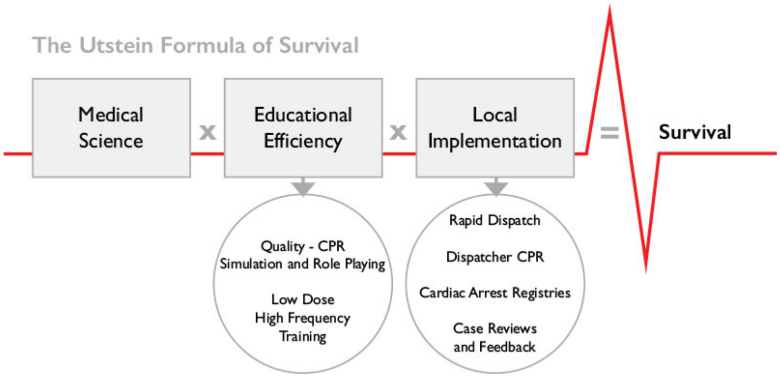

Figure 3. Utstein Formula for Survival. *Figure taken from Acting on the Call. 2018 Update from the Global Resuscitation Alliance Including 27 Case Reports. Global Resuscitation Alliance 2018.*

In response to the observation of substantial disparity between communities in how scientific advances have been successfully implemented to impact outcomes, the Utstein Formula for Survival has been adopted by the Global Resuscitation Alliance group (Figure 3). This theory asserts that medical science alone cannot achieve population impact, but rather, the formula to increase survival involves three complementary factors: guideline quality (science), efficient knowledge transfer, and effective local implementation.[12] This theory presents a much-needed reminder to stakeholders that scientific evidence does not directly improve survival, but require deliberate attention to translation. This ought to be deliberately reflected in agenda-setting and resource allocation. The limitation to this theory is that the three factors need not necessarily be placed in silos, and are in fact impossible to disentangle sometimes. Examples of these situations include how pragmatic trials do account for real-world effectiveness, and how implementation strategies can be scientifically approached as evident in the emerging field of Implementation Science.

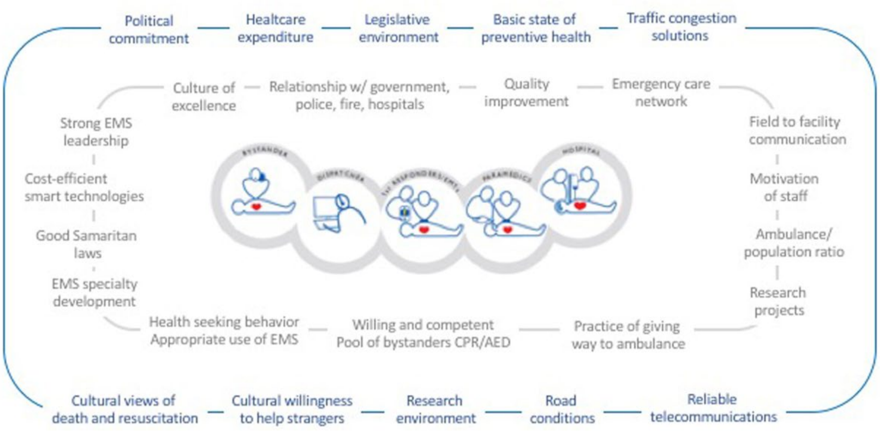

Figure 4. Modified Frame of Survival. *Taken from Nadarajan GD, Tiah L, Ho AFW, et al. Global resuscitation alliance Utstein recommendations for developing emergency care systems to improve cardiac arrest survival. Resuscitation. 2018;132:85-89.*

More recently, there is a recognition that the Chain of Survival, while incorporating key stages of a patient's resuscitation, omits higher-level factors pertinent from a health systems perspective. These interpersonal, organizational, community and policy factors are not captured in the Chain of Survival. The Modified Frame of Survival, codified through a modified Delphi process, identified a number of factors that influenced the overall effectiveness of a health system in providing good outcomes in OHCA (Figure 4).[13] These are arranged in two concentric circles, with an "inner frame" comprising factors (such as quality improvement programs) that are within the traditional sphere of influence of EMS, and an "outer frame" that comprise factors (such as traffic congestion solutions) that are traditionally less readily modifiable. These factors are highly pertinent because the dependence on the community and the entire emergency care system brings with it the baggage of cultural norms and diversity in attitudes and infrastructure. This framework is useful in helping health systems to identify areas of improvement and prioritize change efforts. However, the main limitation of this framework is that some concepts are included based on expert-consensus rather than scientific evidence.

Current obstacles to improving outcomes

Some current obstacles to improving outcomes in OHCA are presented below, of which most are addressed in the subsequent chapters of this thesis.

1. Despite improvements in bystander CPR rates over time, most OHCA patients still do not receive bystander CPR. Even in countries with a comprehensive program, rates of bystander CPR can remain low.[14] There remains a critical need to understand the determinants of bystander CPR, and apply this knowledge to design targeted and effective strategies to increase bystander CPR. Innovative solutions are needed to engage the community and these may leverage technologies such as mobile phone applications and artificial intelligence. Crucially, the effectiveness of these solutions within the local population, as well as applicability to other populations, need to be robustly evaluated.
2. We currently lack a sound understanding of long-term outcomes after OHCA.[10] It was only in 2020 that the American Heart Association added the recovery phase as the sixth link in the Chain of Survival. The world is currently lacking in data infrastructure, taxonomy, and instruments to describe these outcomes. Consequently, critical knowledge gaps exist regarding what happens to patients discharged alive from hospitals after OHCA, including survival duration, return to work, recurrence and quality of life. Data on these patient-oriented outcomes are urgently needed to evaluate interventions, prognosticate, and intervene to target quality survivorship.
3. Randomized controlled trial (RCT) methodology have limited usefulness in testing many interventions for OHCA.[15] The unpredictable and highly time-sensitive nature, and often chaotic pre-hospital setting, of OHCA makes it difficult to execute RCTs. Furthermore, many promising interventions are not drug or device-related, but rather, systems and policy interventions that lend better to be tested by non-RCT designs such as quasi-experimental designs, cohort studies, and simulation modelling. There is a need to effectively employ these techniques for causal inference to inform us about interventions.
4. Emerging environmental risk factors for developing OHCA needs to be elucidated. These include climate change and environmental pollution, which are gaining relevance amidst rapid urbanization. We need high quality epidemiological evidence on the impact of the environment on catastrophic health events to enable evidence-based health policy and rational advocacy.
5. There exists huge geographical variation in OHCA outcomes, with much of the variation due to differences in health system characteristics (relating to community response, EMS and hospital organization), rather than patient characteristics.[16] This indicates that tremendous opportunities exist to improve outcomes and reduce disparities by targeting interventions at a systems level to achieve population impact.
6. Recent data have cast increasing attention to the presence of disparities in OHCA care received on account of gender, ethnicity, and socioeconomic position. Addressing these disparities requires a deep understanding of the underlying factors, and targeted interventions to reduce inequities.
7. There remains a clinical challenge to accurately risk stratify the large volumes of patients presenting to Emergency Departments with chest pain. Current risk stratification tools provide some ability to do this but are currently imperfect, with occasional patients initially risk stratified as low-risk but going on to develop major adverse events such as OHCA. Improving the accuracy of risk stratification of these patients is needed to both allow safe discharge of low-risk patients, and to reduce unnecessary admissions and testing.

Outline of the thesis

This thesis describes a series of academic pursuits aimed at improving OHCA outcomes. It comprises an introduction, a textbook chapter, as well as original investigations that address current issues in improving OHCA outcomes. These investigations employ a number of study designs to interrogate interrelated topics surrounding risk factors, prognostication and treatment of OHCA.

Chapter 1 is an introductory overview of current issues in the field and summarizes the motivation for the thesis. Next, **Chapter 2** is a textbook chapter that teaches the reader to design interventional studies other than RCTs.[17] In order to illustrate different study designs used in pre-hospital medicine, a number of examples were drawn from OHCA research. **Chapters 3 and 4** consist of two studies relating to long-term outcomes amongst OHCA patients who survived the initial event. The first investigation is a systematic review and meta-analysis of previous literature that followed up OHCA patients for at least 12 months, which provided pooled estimates for long-term survival and their correlates.[18] The second investigation was an open cohort study of 802 OHCA patients in Singapore who survived to hospital discharge, following them up for up to ten years and describing their survival time, cause of death and DALYs.[19] **Chapter 5** explores another dimension in the long-term outcomes of OHCA patients – that is, recurrence. This is a systematic review and meta-analysis that estimated the prevalence and risk factors of having recurrences of OHCA amongst OHCA survivors.[20] **Chapters 6 and 7** consist of two published studies investigating ambient air quality as a risk factor for OHCA. The first was a case-crossover study that showed that air quality measured by Pollutant Standards Index (PSI) was associated with increased risk of OHCA.[21] This finding begged the research question of which exact constituent pollutant was driving the association. Accordingly, the second study was a time series study that shows the effects of individual pollutants.[22] Both studies attracted media attention from international news agency, including the British Broadcasting Corporation and the Cable News Network as they joined a small body of work that described the health impacts in the context of the geopolitically contentious Southeast Asian Haze Problem. Next, **Chapters 8, 9 and 10** hone in on the crucial matter of bystander CPR which is the largest modifiable determinant of OHCA survival. The first study is a cohort study that discovered that the socioeconomic position of the residential area was associated with the chance that a patient received bystander CPR.[23] The second study was a cohort study that evaluated a series of bystander-focused public health interventions and found some of these to be associated with increased bystander CPR rates.[24] The third study casts a wider, global perspective and uses meta-analysis to provide pooled estimates of the proportion of general populations trained to provide bystander CPR and defibrillation, and examined variations based on geographical region, regional income and education level.[25] **Chapter 11** is a descriptive study of OHCA outcomes and processes in Singapore during the period 2011-2016.[26] It discussed trends and how they were temporally associated with a medley of community and pre-hospital interventions encapsulated within a national pre-hospital strategy (National 5-Year Plan for Prehospital Emergency Care). Finally, **Chapter 12** addresses the challenging task of risk-stratifying patients who present with low-risk chest pain. Despite recent advances in prognostication tools, some patients with chest pain deemed to be low-risk and hence discharged from Emergency Departments do go on to develop major adverse events such as OHCA. Using a multi-center cohort of Dutch and Singapore Emergency Department patients, we examined the extent of the problem and specifically characterized patients who were missed by HEART score.

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Chapter 2

Experimental Studies Other than Randomised Controlled Trials.

Ho AFW, Blewer AL, Ong M.

In: Introducing, Designing and Conducting Research for Paramedics. 1st ed. Elsevier Health Sciences; 2022:107-111.

Learning Objectives

1. Describe experimental clinical designs other than Randomized Controlled Trials
2. Give examples of quasi-experimental and natural experiments
3. Recognize situations and scenarios where these designs are advantageous over RCT
4. Describe the limitations of these designs as compared to RCT

The need for experimental studies other than RCTs

Randomised controlled trials (RCT) are considered the gold standard of clinical research design, as they provide the highest internal validity for addressing questions of efficacy and effectiveness in healthcare, be it of a diagnostic tool, treatment, clinical pathway, strategy or policy. The random assignment in RCTs is key to the design strength. Without it, one cannot be certain that the difference in outcome between treatment arms is solely the effect of different treatment, or is distorted by confounders. However, a RCT is not always the best 'real-world' strategy, due to practical and ethical difficulties (Nichol & Huszti, 2007).[1] As these situations are common in pre-hospital research (Table 1), pre-hospital researchers should be aware of design techniques to handle such situations.

Table 1. *Potential barriers to the conduct of rigorous randomised controlled trials in the pre-hospital setting*

Barriers
Lack of established clinical trial research infrastructure
Lack of pilot trial data to robustly guide design and sample size calculations
Prior understanding of the risk/benefit of the intervention and ethical considerations for assigning treatment
Difficulty obtaining valid consent from severely ill patients e.g. unconscious, agitated
Difficulty obtaining valid consent due to time and space constraints
Some health systems require a physician to be present to obtain consent
Consent process may delay time-critical interventions
Trial procedures encumber routine care which is already complex
Chaotic pre-hospital environment

Need for large sample sizes as randomisation is often at cluster level
Lack of access to meaningful in-hospital outcome data

When RCTs are not feasible, investigators can adopt several alternative designs to address their research questions. First, they can modify the RCT design (see below) to circumvent these limitations while preserving randomised assignment. Secondly, they can use quasi-experimental designs, which are more commonly done. Thirdly, where possible—and this is rare—they can take advantage of natural experiments. This chapter will be structured according to these 3 options, which are summarized in Table 2. These are not short-cuts for a well-designed RCT, which is rightfully the default design to answer interventional questions. While alternative methods can occasionally achieve high enough internal validity to be believable, many times they do not and become wasteful when a RCT is still needed. Therefore, the decision to deviate from a RCT design should be a deliberate one stemming from a pressing need to answer a research question when a RCT is impossible.

***Table 2**. Differences between randomised controlled trials, quasi-experiments and natural experiments*

	Randomised controlled trial	**Quasi-experiment**	**Natural experiment**
Random assignment to treatment (A)	Yes. Researcher randomly assigns subjects to treatment groups (e.g. flipping a coin)	No. Researcher uses a non-random method to assign subjects to treatment groups (e.g. before-after, odd-even day, need, merit, risk)	Often (e.g. in 2008, Oregon used a lottery to ration Medicaid program among low-income, uninsured adults)
Control over treatment by researchers? (B)	Yes	Yes	No. Typically assigned by an external process outside the control of researcher
True experiment (Requires both A & B)	Yes	No	No
Initiated by	Researcher	Researcher	Opportunistic
Strength of causal inference if designed and conducted well	Typically high	Typically medium	Typically high. Caution: the term “natural experiment” is sometimes used loosely. In these cases, causal inference can be much lower.
Example of designs	Clinical trial, community trial, pragmatic trial	Historical control, interrupted time series, simultaneous nonrandomised control	

Option 1: Modifications to the RCT design

Modifications can sometimes allow an RCT design where it is ordinarily not feasible. Here we give two examples.

Cohort multiple RCT (cmRCT): The cmRCT design (Relton et al., 2010) embeds a RCT into an existing cohort study.[2] Lengthy follow-up and high-quality outcome ascertainment are costly, but may already be done in existing registry studies. If the lack of funding or follow-up is the issue, the cmRCT allows for additional analyses at a lower cost. As an example, a trial investigating a new ambulance diversion policy for stroke could be designed with ambulances cluster-randomised to the new policy or current policy, and the outcome (such as timely receipt of thrombolysis or functional outcomes) ascertained using a national stroke registry. The key to implementing this is to be aware of existing data sources and collaborate with researchers who have access to them.

Modified Zelen's design: This is a double-consent design to work around slow recruitment due to eligible patients being uncertain about treatment allocation (Adamson et al., 2006).[3] Here, eligible patients are initially asked to consent only to randomization and follow-up, and then randomised. Only if randomised to experimental treatment, specific consent for treatment is taken. If the latter consent is declined, the subject is given standard treatment and still followed up. Hence, recruitment is hastened, non-compliance in the experimental arm is reduced, and there is less "Hawthorne effect" in the control group. The downside is that selection bias is introduced due to differential consent rate, and allocation concealment and blinding are violated.

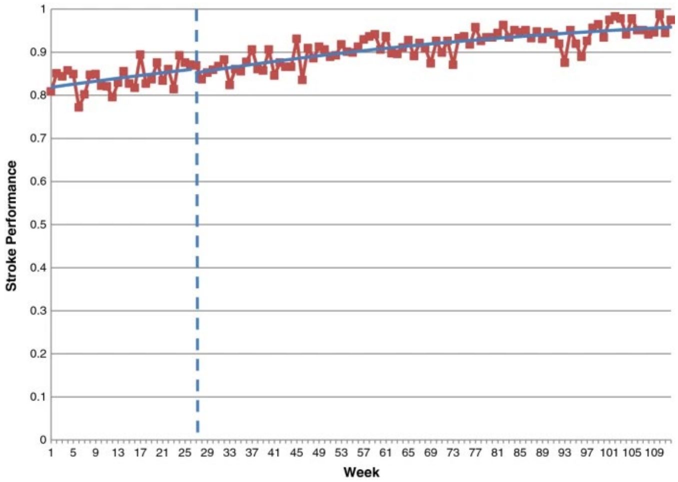
Option 2: Quasi-experimental designs

In these interventional studies, treatment assignment is non-random, but rather, assigned based on patient, clinician or researcher preference. They suffer from selection bias that needs to be controlled for in design and analysis. Quasi-experiments by definition require manipulation of the independent variable, but sometimes, the data is already collected and one attempts to make the best of observational data to obtain insights about an intervention.

Historical control, or "pretest-posttest", or "before-after" design: Here, the average outcome of interest in a population is measured once before, then once after a system-wide intervention is introduced. If the average posttest outcome is better than the average pretest outcome, then we might infer that the treatment was responsible for the improvement. While its simplicity is attractive, historical controls are ineffective—one cannot infer treatment effects with high certainty. We could be seeing a baseline improving trend unaffected (or even retarded) by the treatment. The 'improvement' could also be due to a particularly bad month "regressing to the mean". The improvement could also be a result of many things other than the treatment, that change over time (often termed "secular changes"), that influence the outcome, or the quality of the outcome data. Occasionally, a before-after design can be powerful given that 1) the improvement is drastic, 2) no alternative explanation can account for the improvement after careful consideration.

Interrupted time series: This extends the pretest-posttest design by taking multiple measurements over time before and after a system-wide intervention is introduced. If the intervention is effective, it should cause an "interruption" in the underlying trend. The advantage is clear when measurements are already collected routinely. However, it shares many limitations of the pretest-posttest design and is only marginally stronger causally. An example is a UK study evaluating a national Quality Improvement Collaborative (QIC) on improvement in the delivery rate of care bundles in acute myocardial infarction (AMI) and stroke patients. All English ambulance services were monitored between 2010-2012, during which a series of QI initiatives were implemented. In the first report of this study, the authors used a simple historical control approach and found that care bundle performance for stroke in England improved from 83 to 96%, and concluded that the "QIC led to significant improvements in ambulance stroke care" (Siriwardena et al., 2014).[4] However, the excitement was tempered when a second report which treated the data as an interrupted time series, found that the improvement was no more than a secular trend (i.e., the improvement observed would likely have been seen even if the QI program was not implemented). (Figure 1) (Taljaard et al., 2014).[5] These conflicting conclusions from the same data highlight the potential pitfall of quasi-experimental designs, where causal inferences are less robust.

Fig 1. *Using an interrupted time series approach to evaluate the effect of a national Quality Improvement Collaborative on improvement in the delivery rate of care bundles in and stroke patients.*



Simultaneous nonrandomised control: This method applies a treatment to one group, and compares its outcome improvement with a control group. There are many possible ways to select controls in a nonrandomised fashion. For example, one could assign treatment based on means, preference and risk. We can then compare the average change in outcome among different treatment groups, thereby inferring efficacy. These nonrandom assignment methods introduce both selection bias, and ascertainment bias (due to predictable and unmasked assignment). Statistical methods can reduce, but not eliminate these biases. An example is an EMS trial investigating endotracheal intubation (ETI) versus bag-valve-mask ventilation (BVM) in children (Gausche et al., 2000).[6] Here, Gausche et al ordered paramedics to use ETI on odd-days and BVM on even days (Figure 2). The study found no evidence for the benefit of endotracheal intubation in the out-of-hospital setting but did show a substantial increase in complications. Based on these findings, the Los Angeles and Orange County EMS agencies in California eliminated pediatric intubation from the scope of paramedic practice. In this case, selection bias is expected to be minimal as we do not expect patients to differ systematically on odd-days and even-days. However, the treatment and ascertainment biases from the loss of allocation concealment and blinding are limitations of the study.

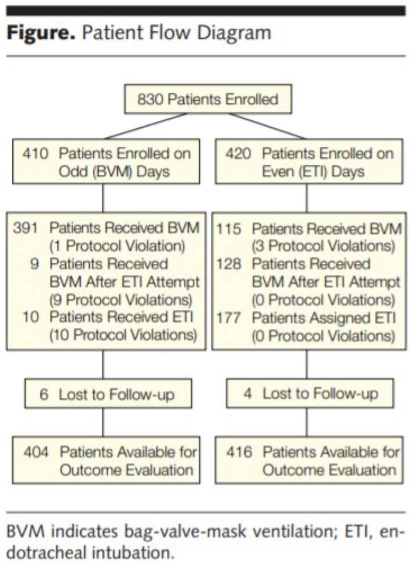


Fig 1. *Patient flow diagram used in a simultaneous nonrandomised control trial of endotracheal intubation versus bag-valve-mask ventilation.*

Statistical approaches: In these non-randomised designs (including observational designs), one could analyze the data such that randomization is mimicked. The common statistical techniques used to control for confounding are: regression modelling (isolate the effect of exposure of interest while holding all confounders constant), propensity score matching (compare only cases and controls that have a similar likelihood of receiving treatment), and instrumental variable analysis.

Option 3: Natural experiments

Natural experiments are "true" experiments. They feature randomised assignment, but unlike RCTs, the randomization occurs naturally, rather than being manipulated by investigators. Hence, they are *random* but not *controlled*. True natural experiments are rare (and indeed, the term is sometimes used loosely), and therefore its use is often opportunistic. Such natural experiments can provide robust causal inference at a fraction of the cost of a RCT, and should be leveraged when available. It requires the astute investigator to spot these opportunities and resourcefully capitalize on them.

Conclusion

In pre-hospital research, practical and ethical constraints sometimes necessitate interventional studies that are non-RCTs. Several alternatives are presented in this chapter. Their use needs to be coupled with a sound understanding of biases inherent in these designs, and their results are interpreted with caution. When used well, they can produce believable, practice-changing studies.

Review questions

1. Describe some experimental clinical designs other than Randomized Controlled Trials
2. Give an example of a well-conducted non-RCT that has impacted paramedicine practice.
3. List some situations and scenarios where these designs are advantageous over RCT
4. Describe the limitations of these designs as compared to RCT

Suggested further reading

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Chapter 3

Long-term outcomes after out-of-hospital cardiac arrest: a systematic review and meta-analysis.

Yip Han Chin, Clyve Yu Leon Yaow, Seth En Teoh, Mabel Zhi Qi Foo, Nan Luo, Nicholas Graves, Marcus Eng Hock Ong, Andrew Fu Wah Ho

Resuscitation. 2022 Feb;171:15-29

Abstract

Aims: Long term outcomes after out-of-hospital cardiac arrest (OHCA) are not well understood. This study aimed to evaluate the long-term (1-year and beyond) survival outcomes, including overall survival and survival with favorable neurological status and the quality-of-life (QOL) outcomes, among patients who survived the initial OHCA event (30 days or till hospital discharge).

Methods: Embase, Medline and PubMed were searched for primary studies (randomized controlled trials, cohort and cross-sectional studies) which reported the long-term survival outcomes of OHCA patients. Data abstraction and quality assessment was conducted, and survival at predetermined timepoints were assessed via single-arm meta-analyses of proportions, using generalized linear mixed models. Comparative meta-analyses were conducted using the Mantel-Haenszel Risk Ratio (RR) estimates, using the DerSimonian and Laird model.

Results: 67 studies were included, and among patients that survived to hospital discharge or 30-days, 77.3% (CI = 71.2–82.4), 69.6% (CI = 54.5– 70.3), 62.7% (CI = 54.5–70.3), 46.5% (CI = 32.0–61.6), and 20.8% (CI = 7.8–44.9) survived to 1-, 3-, 5-, 10- and 15-years respectively. Compared to Asia, the probability of 1-year survival was greater in Europe (RR = 2.1, CI = 1.8–2.3), North America (RR = 2.0, CI = 1.7–2.2) and Oceania (RR = 1.9, CI = 1.6–2.1). Males had a higher 1-year survival (RR:1.41, CI = 1.25–1.59), and patients with initial shockable rhythm had improved 1-year (RR = 3.07, CI = 1.78–5.30) and 3-year survival (RR = 1.45, CI = 1.19–1.77). OHCA occurring in residential locations had worse 1-year survival (RR = 0.42, CI = 0.25–0.73).

Conclusion: Our study found that up to 20.8% of OHCA patients survived to 15-years, and survival was lower in Asia compared to the other regions. Further analysis on the differences in survival between the regions are needed to direct future long-term treatment of OHCA patients.

Introduction

Out-of-hospital cardiac arrest (OHCA), or sudden cardiac arrest, is the most time-critical medical emergency. OHCA exerts a tremendous disease burden worldwide,[1,2] with global incidence estimated at 55 per 100,000 person-years.[3] With increasingly-sophisticated basic and advanced resuscitative interventions available in the community, pre-hospital and hospital settings, more patients who experience OHCAs are surviving the initial event.[4,5] There is tremendous scientific and public health interest in the long-term survivorship of OHCA patients, with unanswered questions on length and quality of survival, and their modifiable and non-modifiable determinants.

While the literature on OHCA is heavily reliant on proximal clinical outcomes, for example return of spontaneous circulation, 30-day survival and survival to discharge, long-term outcomes beyond one year are poorly understood. In the Utstein Resuscitation Registry Templates, which is the leading standardized reporting framework for resuscitation registries, "30-day survival or survival to discharge" was a core outcome, survival at 1-year was a supplemental outcome, and there were no requirements to capture outcomes at timepoints more distal than 1-year.[6,7] The static outcome of an OHCA patient at discharge does not take into account the natural history and progression of post-cardiac arrest patients,[8] and this is important to guide clinical follow-up and prognostication outcomes of communities with a sizable and growing cohorts of OHCA survivors.

Apart from the need to account for long-term quantitative outcomes after OHCA, also important to consider is the health-related quality of life (HRQoL) during these additional years. A systematic review by Haywood et al concluded a lack of conceptual and empirical HRQoL research in the OHCA population.[9] Stimulated by the recent inclusion of HRQoL measures as supplementary outcomes in the Utstein template, recent studies started to report HRQoL after OHCA.

This study aimed to evaluate the long-term outcomes (1-year and beyond) survival outcomes including overall survival and survival with favorable neurological status as well as the health-related quality-of-life (HRQoL) outcomes, among patients who survived the initial OHCA event; that is, survived to 30 days or hospital discharge.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The study protocol has been published in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021260955).

Search strategy

A systematic literature search was performed in the Medline, Embase and PubMed databases from inception to March 15, 2021 for articles that reported long-term outcomes of OHCA patients. The search strategy was developed in consultation with a medical information specialist (Medical Library, National University of Singapore). Key search terms such as "cardiac arrest", "survival", "mortality" and "quality of life" were used in the search strategy. The detailed search strategy is available in the supplementary materials. Content experts were consulted for additional references and references of relevant sources were hand-searched to identify additional relevant studies. Articles were viewed through Endnote X9 (Clarivate, Philadelphia, Pennsylvania) for article sieve.

Inclusion and exclusion criteria

The selection of articles for inclusion was conducted by four researchers (YHC, CYYL, SET, NC). Each article was reviewed by at least two researchers blinded to each others' decision. Disputes were resolved through consensus from the senior author (AFWH). The predefined criterion for inclusion were: (1) articles reporting long-term survival and outcomes of OHCA patients at any of: 1-, 3-, 5-, 10- and 15-year timepoints, (2) articles with subjects that were aged 16 years and above, (3) original articles (randomized controlled trials [RCT], case control studies, quasi-RCTs, cohort and cross-sectional studies) and (4) articles written or translated into the English language. The criterion for exclusion were: (1) studies for which data for OHCA patients could not be separated from studies that reported both OHCA and in-hospital cardiac arrest patients, and (2) studies examining OHCA in a selective subgroup of patients (i.e. liver failure and pregnant patients). To prevent the duplication of patient datasets analyzed, studies originating from the same center(s) during the same or overlapping time periods were collated, and only the most relevant (typically, most recent) study was included for analysis.

Data abstraction

Data were abstracted into an Excel spreadsheet (Microsoft Corp, New Mexico, United States). Each article was double-coded by either pair of researchers (YHC/CYYL or SET/NC), blinded within pairs. Disputes were resolved through consensus from the senior author (AFWH). Data abstracted included study characteristics (e.g. author name, year of publication, country or region), study population characteristics (e.g. sample size, ethnicity, age, country, comorbidities), emergency medical services (EMS) system characteristics (e.g. single or dual dispatch system), and OHCA event characteristics (e.g. location, initial rhythm, etiology, use of targeted temperature management (TTM), cause of death, survival at each predefined timepoints). Shockable rhythms were defined as ventricular fibrillation and pulseless ventricular tachycardia.[11] Receipt of TTM was defined in accordance with each individual included study. Etiologies were classified into: medical, traumatic, drug overdose, drowning, electrocution and asphyxial. Whenever relevant, data abstraction was organized in accordance with the Utstein style for reporting OHCA cases.[12] Survival outcomes included survival and survival with favorable neurological status at previously mentioned timepoints. Favorable neurological status was defined as having a Pittsburgh Cerebral Performance Category (CPC) of one (good recovery) or two (moderate disability);[13,14] or Overall Performance Category (OPC) of one (good capability) or two (moderate capability).[15]

For continuous variables, mean and standard deviation (SD) were abstracted. Where these data were unavailable, appropriate formulae were applied to transform the data from median and range or interquartile range to mean and SD.[16,17] For categorical variables, frequency and percentages were abstracted.

Statistical analysis
Data analyses were conducted using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed statistical significance was set at p-value 0.05. Two forms of meta-analyses were conducted: a single-arm meta-analysis of proportions and a comparative meta-analysis.

Firstly, single-arm meta-analyses of proportions were used to summarize survival and survival with favorable neurological outcomes at each predefined timepoint. Generalized linear mixed models have been found in recent simulation studies to be the more accurate transformation method for meta-analysis of single proportions compared to the more commonly used Freeman-Tukey double arcsine transformation.[18,19] Subgroup analyses were performed on the etiology of OHCA (first, non-traumatic, and thereafter, a further analysis of cardiac and non-cardiac etiologies) and type of study (RCT and Non-RCT studies). Additional analyses were performed based on the region of origin of the study populations, classified into Asia, Middle East, North America, Oceania, South America and others.[20,21] To estimate the effect of region on survival, a generalized linear model (Poisson family and logit link) was applied with inverse variance weightage risk ratios (RR).[22-24]

Secondly, comparative meta-analyses were performed to summarize survival outcomes between prespecified subgroups at the predetermined timepoints whenever possible. The subgroups were: (1) shockable vs non-shockable initial rhythm, (2) receipt of TTM vs none, (3) male vs female gender, (4) residential vs non-residential OHCAs. In the comparative meta-analysis, Mantel-Haenszel RR estimates with corresponding 95% confidence intervals (CI) were pooled using the DerSimonian and Laird model.[25]

For data that had fewer than ten data points, meta-analysis was considered to be inappropriate and they were instead systematically reported. Heterogeneity was quantified using the Cochran Q test and I^2 statistics. I^2 value thresholds of 25%, 50% and 75% signified low, moderate and high heterogeneity respectively.[26] All models were random effects regardless of heterogeneity measures. Assessment of publication bias was not conducted due to the lack of an appropriate tool for publication bias assessment in single-arm meta-analysis of proportions.[27]

Risk of bias assessment
The risk of bias assessment for observational studies was conducted using the Newcastle-Ottawa Scale (NOS),[28] and for non-randomized interventional studies, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used,[29] while the Cochrane's Risk of Bias 2 (RoB2) tool was used for randomized controlled trials (RCTs).[30] The NOS assesses each study in three domains: selection of the research population, comparability of the study groups and results. NOS scores 7 stars were considered high-quality. Next, the ROBINS-I tool assesses each study based on pre-interventional risk, interventional risk, and post intervention risk. The RoB2 tool assesses quality on 5 domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurements and reporting.[31]

Results

Literature retrieval and summary of included articles
The database search yielded 5,013 records, from which 2,766 duplicates were removed. Of the remaining 2,249 records, 1,986 were excluded on the basis of their titles and abstracts. 200 full-texts were reviewed, of which 65 articles were eligible. An additional two articles were identified from reviewing references of eligible articles. Therefore, 67 articles were included for analysis. The selection process and reasons for excluding articles were illustrated in the PRISMA flow diagram (Fig. 1).

A total of 115,909 OHCA patients were included across 67 studies. Mean age ranged from 57.6 to 78.5 years. There were four RCTs, 40 retrospective cohort studies and 23 prospective studies. There were two multinational studies, namely Nielsen et al,[32] which involved ten countries and Gueugniaud et al which involved two countries.[33] A summary table of the included articles is available in the supplementary materials.

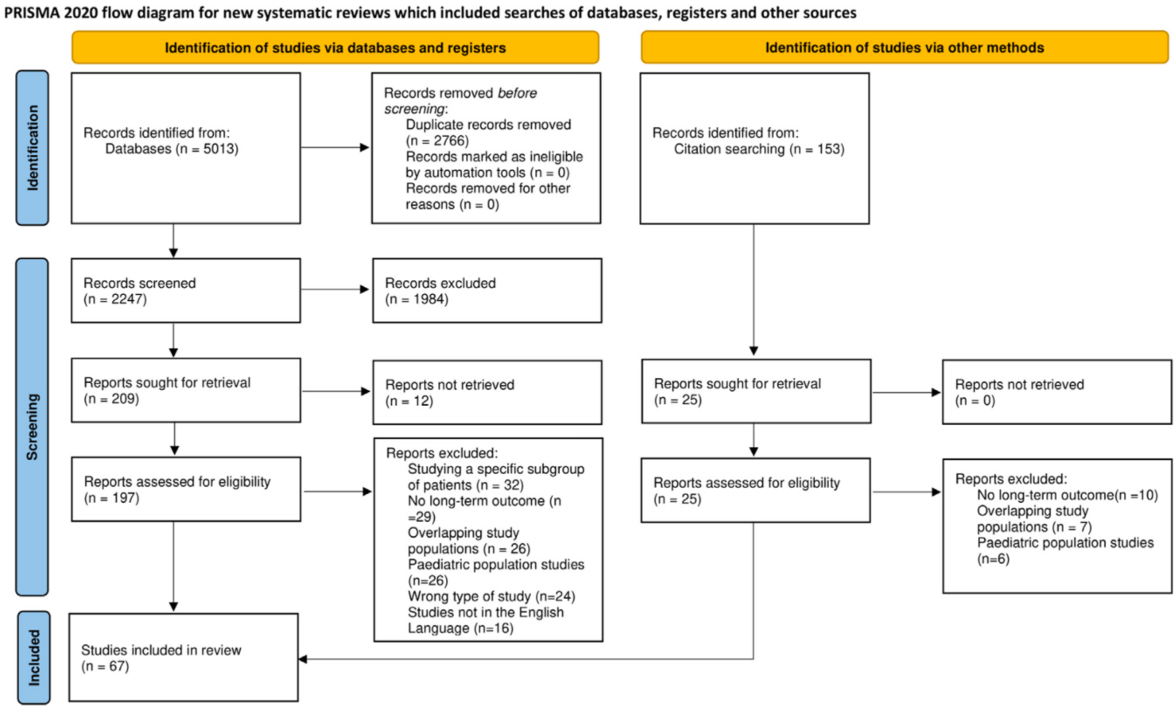

Fig. 1 *– PRISMA flowchart.*

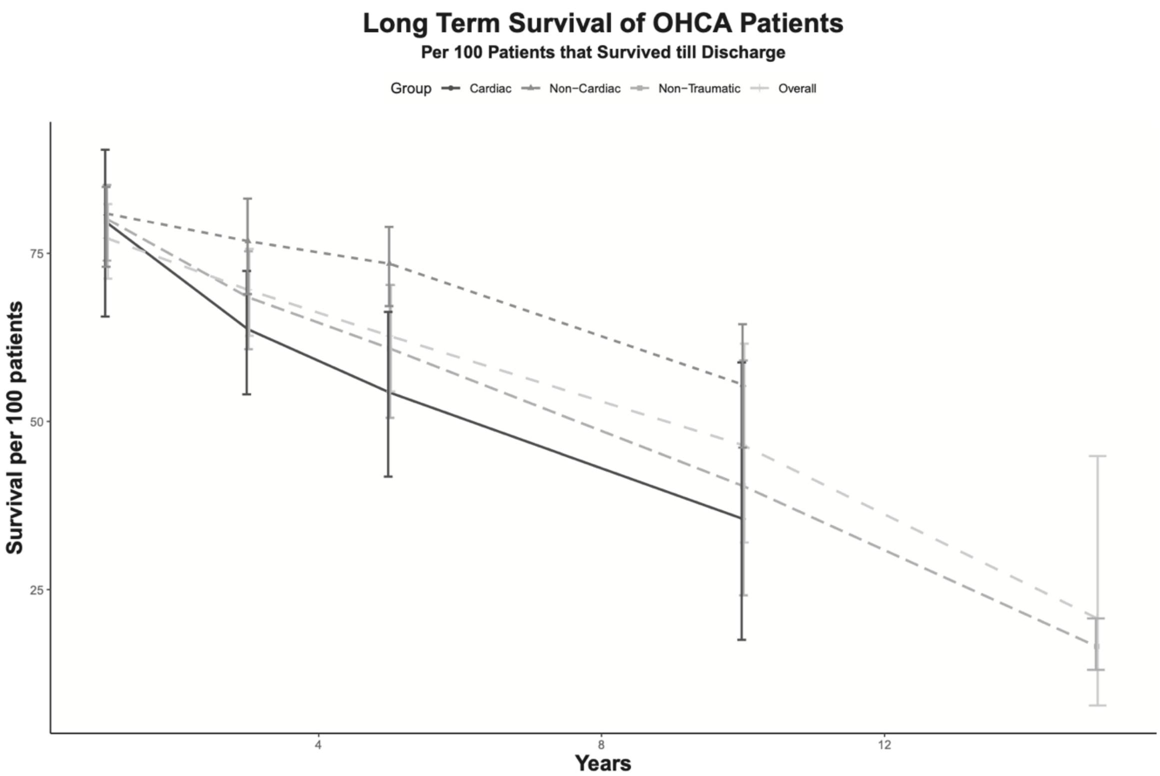

Fig. 2 *– Survival rates of OHCA patients for the Overall population, Non-traumatic Causes of OHCA, Cardiac causes of OHCA and Non-Cardiac causes of OHCA.*

In terms of the country of origin of study populations, the United States (n = 11) contributed the most studies,[34- 44] while there were six each from Japan[45- 50] and Norway;[32,51- 55] five each from Australia[32,56-59] and France[33,60- 63]; four each from Denmark,[32,64-66] Finland,[67- 70] Germany,[71- 74] the Netherlands[32, 75-77] and the UK[32, 78- 80]; three each from the Czech Republic,[32,81,82] Italy[32,83-84] and Sweden[32,85,86]; two each from Israel[87-88], Slovenia[89,90] and Switzerland;[32,91] and one each from Austria,[92] Canada,[93] China,[94] Estonia,[95] Scotland,[96] Serbia[97] and South Korea.[98] Therefore, in terms of regions, there were 40 from Europe, 12 from North America, seven from Asia, four from Oceania and two from the Middle East.

All included RCTs were classified to be of low-to-moderate risk of bias, interventional studies as assessed by ROBINS-I tool were found to be of low to moderate risk of bias, and all included observational studies were classified to be of moderate to high quality. The detailed risk of bias assessment results were available as supplementary material.

Table 1 – Summary of Meta-analysis Findings.

Analysis	Studies	Total number of OHCA Patients at risk*	Events occurred^	I^2	Survival (95 %CI)
1 year survival					
Overall	**61**	**38,016**	**25,144**	**99.4%**	**77.3 (CI:71.2–82.4)**
Type of Study					
Non-RCT	57	36,720	24,025	99.4%	76.4 (CI:69.9–81.9)
RCT	4	1296	1119	94.6%	86.6 (CI: 76.4–92.8)
Aetiology					
Non-traumatic	41	19,106	12,688	99.2%	80.2 (CI:73.9–85.2)
Cardiac	29	13,473	8620	99.1%	79.6 (CI:65.6–90.5)
Non-Cardiac	12	4762	3275	99.3%	81.0 (CI:73.0–84.9)
3-year survival					
Overall	**22**	**13,232**	**9798**	**96.6%**	**69.6 (CI:62.7–75.7)**
Aetiology					
Non-traumatic	15	8180	5815	96.5%	68.5 (CI:60.7–75.3)
Cardiac	10	4167	2643	92.4%	63.7 (CI:54.0–72.4)
Non-Cardiac	5	4013	3172	93.4%	76.8 (CI:68.9–83.2)
5-year survival					
Overall	**20**	**11,929**	**7949**	**98.3%**	**62.7 (CI:54.5–70.3)**
Aetiology					
Non-traumatic	13	6575	3965	97.0%	60.9 (CI:50.6–70.3)
Cardiac	9	4024	2127	93.5%	54.3 (CI:41.8–66.3)
Non-Cardiac	4	2551	1838	94.9%	73.5 (CI:67.2–78.9)
10-year survival					
Overall	**11**	**8488**	**4511**	**99.0%**	**46.5 (CI:32.0–61.6)**
Aetiology					
Non-traumatic	8	4524	1789	97.7%	40.4 (CI:24.2–59.1)
Cardiac	6	3057	1009	96.0%	35.5 (CI:17.5–58.8)
Non-Cardiac	2	1467	780	95.5%	55.5 (CI:46.1–64.5)
15-year survival					
Overall	**4**	**4499**	**2313**	**99.5%**	**20.8 (CI:7.8–44.9)**
Aetiology					
Non-traumatic	2	895	153	73.0%	16.5 (CI:13.1–20.7)
Cardiac	2	895	153	73.0%	16.5 (CI:13.1–20.7)
Favourable Neurological outcomes					
At 1 year	16	6534	2837	99.0%	83.3 (CI:71.2–91.0)
Type of Study					
RCT	1	446	402	-	90.1 (CI:87.0–92.6)
Non-RCT	15	6088	2435	98.7%	82.8 (CI:69.5–91.1)
Aetiology					
Non-Traumatic	8	651	534	93.0%	84.3 (CI:67.7–93.3)
Cardiac	5	361	275	94.0%	79.1 (CI:54.7–92.2)
Non-Cardiac	3	290	259	93.2%	90.5 (CI:69.4–97.6)

CI – Confidence intervals; RCT – Randomized controlled trials.

* Refers to the total number of out of hospital cardiac arrest patients surviving to discharge or 30 days for survival, or total number of out of hospital cardiac arrest patients who survived to 1 year for favourable neurological outcomes.

^ Refers to the number of out of hospital cardiac arrest patients surviving to 1-, 3-, 5-, 10-, 15- years for survival, and number of patients with favourable neurological outcomes.

Table 2 – Health Related Quality of Life outcomes reported in the 6 included articles.

Author(s)	Year	Scales used	Further explanations	Summary estimates
Comparative HRQoL analysis (Long-term OHCA survivors vs General population)				
Reinhard et al.	2009	HRQoL analysis (>One-year post-arrest) RAND SF-36	*RAND SF-36* – After > 1 year of resuscitation from OHCA – Physical functioning, physical role functioning, emotional role functioning, social functioning, general health significantly worse than general population – No significant difference found in mental health, vitality, or bodily pain.	*RAND SF-36* – Significantly worse than general population in: – Physical functioning ($p < 0.001$) – Physical role functioning ($p = 0.001$) – Emotional role functioning ($p < 0.001$) – Social functioning ($p = 0.001$) – General health ($p < 0.001$) – No significant difference in – Mental health ($p = 0.279$) – Vitality ($p = 0.284$) – Bodily pain($p = 0.093$)
Smith et al.	2015	HRQoL analysis (One-year post-arrest) EuroQol EQ-5D – EuroQol EQ-5D Visual Analogue Scale – SF-12 o MCS score o PCS score	*EuroQol EQ-5D* – One-third of responders reported no problem in all 5 domains assessed via the EQ-5D (37.7%) – Comparable mean EQ-5D index as compared to UK normalised EQ-5D indexVisual Analogue Scale – Compared to pre-arrest – 55.7% reported a decrease in HRQoL – 24.5% reported to have no change HRQoL – 19.8% reported an increased HRQoL SF-12 MCS score – No significant differences compared to the Australian population. SF-12 PCS score – No significant differences compared to the Australian population. (mean difference) – Significantly lower PCS compared to Australian population (standardized mean difference)	*EuroQol EQ-5D* – Mean EQ-5D index score – Survivors vs age- and sex-adjusted UK norm – 0.82 ± 0.19 vs 0.81 ± 0.34SF-12 MCS score – Survivors vs Australian population – 53.0 ± 10.2 vs 53.1 ± 21.8 SF-12 PCS score – Survivors vs Australian population – 46.1 ± 11.2 vs 46.8 ± 19.2 – SMD = -0.114, 95 %CI = -0.206 to −0.022
Tiainen et al.	2018	HRQoL analysis (One-year post-arrest) EuroQol EQ-5D	HRQoL Analysis*EuroQol EQ-5D* – Comparable EQ-5D index as compared to age- and sex-matched Finnish general population EQ-5D indexEuroQol EQ-VAS – EQ-VAS value of the respondents was higher as compared to age- and sex-matched Finnish general population EQ-VAS value	*EuroQol EQ-5D* – Survivors vs Australian population – Median 1.000 (IQR 0.690–1.000, mean 0.822) vs median 0.859 (IQR 0.826–0.882, mean 0.853) ($p = 0.18$) EuroQol EQ-VAS – Survivors vs Australian population – Median 80 (IQR 70–90, mean 77.8) vs median 69.5 (IQR 56.1–87.3, mean 72.1) ($p < 0.001$).

Table 2 (continued)

Author(s)	Year	Scales used	Further explanations	Summary estimates
Bunch et al.	2003	HRQoL analysis (Mean Follow up 4.8 ± 3.0 post-arrest) – RAND SF-36 – MFQ scales	*MFQ*T OHCA outcomes were found to be generally better outcomes as compared to the general populationSF-36: – Overall PCS and MCS scores were comparable to the general population. – Vitality was worse compared to control – However, the normalized score was 45 ± 11.1, a value that crosses the normal value in the control population.	*MFQ:* – Frequency of forgetting: – 144.2 ± 37.4 vs 168.1 ± 27.3(P < 0.001) – Retrospective function score: – 18.4 ± 6.8 vs 18.7 ± 5.0 (P = 0.74) – Seriousness of forgetting score: – 84.8 ± 26.7 vs 95.2 ± 19.7 (P = 0.004) SF-35: – PCS (0.31) and MCS score (P = 0.19) – Vitality (P = 0.01) – But normalised score crosses the normal value in control
Non-comparative HRQoL analysis of OHCA survivors				
Kuilman et al.	1999	HRQoL analysis (Up to 8 years post-arrest) – EuroQol EQ-5D – Visual analogue scale	No significant differences found between the four groups of patients who were resuscitated in the period.	(P = 0.12)
Harve et al.	2007	HRQoL analysis (Up to 15 years post-arrest) – Detailed neuropsychological assessment by neuropsychologist and neurologist. – Questionnaire – Satisfactory score: At least 80% of the maximum score – Seven domains of life analysed: overall quality of life, activities of daily living, hobbies, family, marital, sexual and social life.	Neuropsychological status – 7 patients were normal. – 4 patients had mild neurological issues.HRQoL analysis – 1-year: 3 out of 9 patients considered themselves to have satisfied levels of HRQoL – 15-year: 7 out of 7 patients considered themselves to have satisfied HRQoL, 1 had significant decrease in HRQoL due to passing of loved one – Generally found better HRQoL at 15-years than at 1-year	-

Health-related Quality of Life (HRQoL); Mental Component Summary (MCS); Mood and Feelings Questionnaire (MFQ); Out-of-hospital cardiac arrest (OHCA); Physical Component Summary (PCS); Quality of Life (QoL); Short-Form 36-item Health Survey (SF-36); Standardized Mean Difference (SMD).

Survival at 1-, 3-, 5-, 10- and 15-year timepoints

Pooled analysis revealed that among patients that had survived to hospital discharge or 30-day, 77.3% (61 studies, CI = 71.2–82.4, I^2 = 99.4%), 69.6% (22 studies, CI = 62.7–75.7, I^2 = 96.6%), 62.7% (20 studies, CI = 54.5–70.3, I^2 = 98.3%), 46.5% (11 studies, CI = 32.0–61.6, I^2 = 99.0%) and 20.8% (4 studies, CI = 7.8–44.9, I^2 = 99.5%) survived to 1-year, 3-year, 5-year, 10-year and 15-year respectively (Fig. 2). A summary of the full analysis can be found in Table 1. A subgroup analysis found non-RCT studies and RCT studies had a similar 1-year survival (p = 0.08) of 76.4% (57 studies, CI = 69.9–81.9, I2 = 99.4%) and 86.6% (4 studies, CI = 76.4–92.8, I2 = 94.6%), respectively.

Further analysis by the etiology of OHCA revealed that non-traumatic causes had a slightly higher survival of 80.2% (41 studies, CI = 73.9–85.2, I^2 = 99.2%) at 1-year, and lower survival for the other timepoints (3-, 5-, 10-, 15-year). Further division of non-traumatic cases into non-cardiac and cardiac etiology subgroups found that while both subgroups had similar 1-year survival, the two groups diverged beyond one year, with non-cardiac etiologies having higher survival at all timepoints, ranging between 76.8% (5 studies, CI = 68. 9–83.2, I^2 = 93.4%) at 3-year to 55.5% (2 studies, CI = 46.1–64.5, I^2 = 95.5%) at 10-year, compared to that of cardiac etiologies which ranged between 63.7% (10 studies, CI = 54.0–72.4, I^2 = 92.4%) at 3-year, to 16.5% (2 studies, CI = 13.1–20.7, I^2 = 73.0%) at 15-year (Table 1, Fig. 2).

Survival with favorable neurological outcomes

Pooled analysis at 1-year found that out of 6534 patients who survived to 1-year, 83.3% of the patients (16 studies, CI = 71.2–91.0, I^2 = 99.0%, Table 1) had favorable neurological outcomes. Subgroup analysis by the etiology of OHCA and by type of study found no significant differences (p = 0.602 and p = 0.121) (Table 1). For timepoints more distal than 1-year, there were insufficient studies reporting these outcomes to be pooled.

Health-related quality of life outcomes

6 articles reported the HRQoL outcomes of OHCA patients. Four studies were comparative studies,[40,59,69,95] which compared the HRQoL of the long-term survivors of OHCA to the general population, while two studies were non-comparative.[67,75] Four instruments were used in the studies; the Mood and Feelings Questionnaire (MFQ), the Short-Form 36-item Health Survey (SF-36) and the Short-Form 12-item version (SF-12), and the EuroQol EQ-5D. In terms of the follow-up time, 3 studies examined their patients 1-year post arrest,[59,69,95] one had a mean follow up of 4.8 years,[40] one followed their patients up till 8 years[75] and one examined their patients up to 15 years post-arrest.[67] Due to the heterogeneity and the small number of studies examining the HRQoL outcomes, a meta-analysis was not performed, and a systematic reporting of data was done instead. The HRQoL outcomes were summarized in Table 2.

Of the four comparative studies, three found that long term survivors of OHCA had comparable overall HRQoL outcomes as compared to the general population.[40,59,69] Smith et al.,[59] using EuroQol EQ-5D and SF-12 scales, and Tiainen et al,[69] using the EuroQol EQ-5D scale (p = 0.18), found no significant differences at 1-year timepoint (Table 2). Tianen et al also found that, using the HRQoL-VAS scoring, OHCA patients had better perception of HRQoL compared to the general population. Next, Bunch et al found no differences in the physical component summary (PCS) (P = 0.31) and mental component summary (MCS score) (P = 0.19) when analysed over a mean follow-up time of 4.8 ± 3.0 years.[40] However, Reinhard et al(SF-36 score) and Smith et al. found that OHCA patients had poorer HRQoL outcomes compared to the general population, with Smith et al. (SF-12) noting that OHCA patients had poorer PCS scores compared to the general population when measured using standardized mean differences.

Looking at the specific components of the HRQoL scores, other than Tiainen et al, the 3 other studies reported that OHCA patients had significantly poorer outcomes in some components compared to the general population. When analysing the HRQoL at one-year, Reinhard et al. (SF-36 score) found that the patients' quality of life was significantly worse than the general population in the categories of physical functioning, physical role functioning, emotional role functioning, social functioning and general health (Table 2). Lastly, Bunch et al. found that patients had poorer vitality scores (P = 0.01) compared to the general population when analysed over a mean follow-up time of 4.8 ± 3.0 years.

Table 3 – Comparative Meta-analysis Results.

Comparative	Studies	I^2	RR (95 %CI)	P-Value
Shockable vs non-shockable				
1-year survival	11	95.5	3.07 (CI:1.78–5.30)	**0.001**
3-year survival	3	29.2	1.45 (CI:1.19–1.77)	**0.015**
5-year survival	3	80.0	1.43 (CI:0.90–2.27)	0.080
TTM vs No TTM				
1-year survival	4	94.6	1.25 (CI:0.66–2.37)	0.342
Type of study				0.281
RCT	1	-	1.03 (CI:0.96–1.11)	0.419
Non-RCT	3	96.7	1.40 (CI:0.41–4.78)	0.356
Male vs Female				
1-year survival	7	2.9	1.41 (CI:1.25–1.59)	**<0.001**
3-year survival	2	0.0	1.31 (CI:0.35–4.88)	0.236
Residential vs non-residential location of arrest				
1-year survival	6	86.1	0.42 (CI:0.25–0.73)	**0.009**
3-year survival	2	84.3	0.33 (CI:0.00–77.55)	0.236

P < 0.05 is taken as statistically significant results. TTM – Targeted temperature monitoring; RR – Risk Ratio.

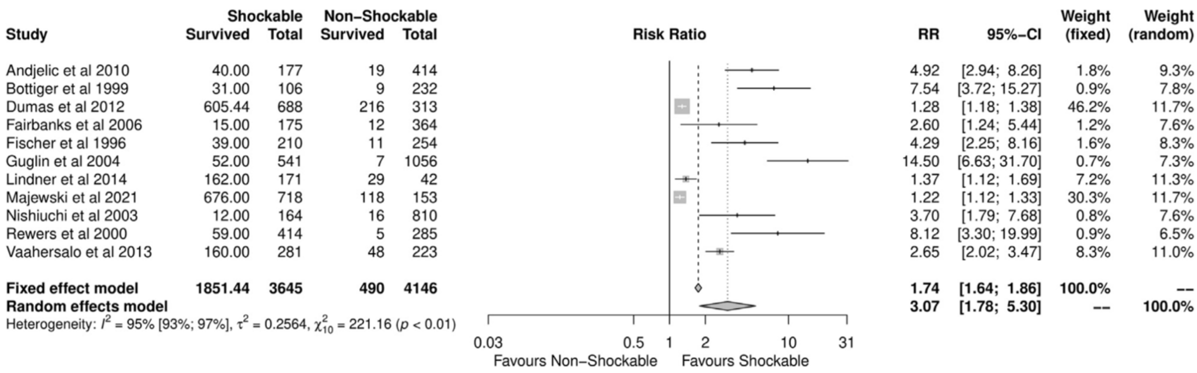

Fig. 3 *– Forest Plot of the Risk Ratio for the 1-year Survival of Shockable vs Non-shockable Causes of OHCA patients.*

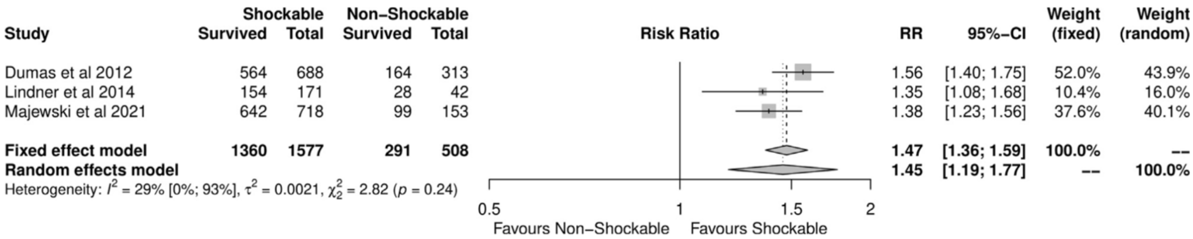

Fig. 4 *– Forest Plot of the Risk Ratio for the 3-year Survival of Shockable vs Non-shockable Causes of OHCA patients.*

Of the non-comparative studies, both found that patients generally had "satisfactory" levels of HRQoL,[67,75] and Harve et al found that patients generally found that their HRQoL at 15 years were better than that at one-year.[67]

Comparative meta-analysis of prespecified subgroups

A summary of the comparative meta-analysis can be found in Table 3. In terms of initial rhythm, compared to patients with non-shockable rhythms, those with shockable rhythms had 3.1 times (11 studies, CI = 1.8–5.3, I^2 = 95.5%, p = 0.001, Fig. 3) the probability (RR) of 1-year survival and 1.5 times

(3 studies, CI = 1.2–1.8, $I^2 = 29.2\%$, $p = 0.015$, Fig. 4) the probability of 3-year survival as compared to non-shockable patients. Analysis at the 5-year timepoint found no significant difference in survival between patients with shockable and non-shockable rhythms (3 studies, $p = 0.08$).

In terms of gender, male patients had 1.4 times (7 studies, CI = 1.3–1.6, $I^2 = 2.9\%$, $p < 0.001$) the probability of 1-year survival as compared to female patients. Analysis at the 3-year timepoint found no significant differences between genders (2 studies, $p = 0.236$).

In terms of location of arrest, patients that had residential OHCA had 0.4 times (6 studies, CI = 0.3–0.7, $I^2 = 86.1\%$, $p = 0.009$, Table 3) the probability of 1-year survival as compared to patients that had OHCA out of their homes. Analysis of the probability of survival at the 3-year timepoint found no significant differences (2 studies, $p = 0.236$). In terms of TTM, patients with TTM and patients without TTM had no significant differences in the probability of 1-year survival (4 studies, $p = 0.342$). When analysed by type of study, no significant differences were noted for both RCT and non-RCT studies (Table 3).

Influence of region on long-term OHCA outcomes

In terms of the effect of regions on the long-term survival of OHCA patients, our analysis found that at the 1-year timepoint Asian studies had the lowest 1-year survival at (63.5%, 5 studies, CI = 16.1–94.0, $I^2 = 99.6\%$), followed by the Middle East (77.5%, 2 studies, CI = 25. 4–97.2, $I^2 = 97.2\%$), North America (77.5%, 12 studies, CI = 69.4– 83.9, $I^2 = 92.3\%$), Europe (79.0%, 39 studies, CI = 72.8–84.1, $I^2 = 98.7\%$) then Oceania (79.1%, 3 studies, CI = 40.7–95.4, $I^2 = 99.9\%$). On estimating the RR by region, when compared to Asian studies (supplemental Table 2), there was a higher probability of 1-year survival in Europe (RR = 2.1, CI = 1.8–2.3, $p < 0.001$), North America (RR = 2.0, CI = 1.7–2.2, $p < 0.001$) and Oceania (RR = 1.9,CI = 1.6–2.1, $p < 0.001$). No statistical significance was found for the Middle East (RR = 2.0, CI = 1.6–2.6, $p = 0.113$).

At the 3-year timepoint, studies originating from the Middle East had the lowest survival (30.8%, 1 study, CI = 19.8–44.5), followed by Asian studies (57.1%, 1 study, CI = 46.4–67.3), Europe (69.9%, 13 studies, CI = 61.5–77.2, $I^2 = 94.8\%$), North America (70.2%, 5 studies, CI = 58.5–79.8, $I^2 = 97.2\%$) then lastly, Oceania (82.8%, 2 studies, CI = 79.4–85.7, $I^2 = 89.3\%$). Compared to Asian studies, no significant differences in risk of survival were noted for all countries at 3-year (supplemental Table 2).

Survival with favourable neurological outcomes

At 1-year timepoint, Asian studies had the lowest proportion of survivors with favorable neurological outcomes (42.1%, 4 studies, CI = 24.6–61.7, $I^2 = 99.0\%$), followed by Middle Eastern studies (73.3%, 1 study, CI = 55.0–86.1), North America (90.1%, 1 study, CI = 87.0–92.6) then Europe (91.1%, 13 studies, CI = 87.1–93.9, $I^2 = 67.0\%$).

Table 4 – Influence of Region on Survival and Neurological outcomes.

Analysis	Studies	Total	Events	I^2	Survival per 100 patients (95 %CI)
1 year survival	**61**	**38,016**	**25,144**	**99.40%**	**77.27 (CI:71.23–82.36)**
Oceania	3	8713	5340	99.90%	79.11 (CI:40.73–95.43)
Asia	5	5275	680	99.60%	63.50 (CI:16.11–94.04)
Europe	39	18,621	14,796	98.70%	79.00 (CI:72.77–84.12)
Middle East	2	144	108	97.20%	77.45 (CI:25.39–97.19)
North America	12	5263	4220	92.30%	77.49 (CI:69.44–83.92)
3-year survival	**22**	**13,232**	**9798**	**96.60%**	**69.58 (CI:62.74–75.66)**
Oceania	2	4320	3525	89.30%	82.76 (CI:79.36–85.70)
Asia	1	84	48	-	57.14 (CI:46.40–67.26)
Europe	13	4365	3120	94.80%	69.93 (CI:61.54–77.17)
Middle East	1	52	16	-	30.77 (CI:19.78–44.47)
North America	5	4411	3089	97.20%	70.24 (CI:58.47–79.82)
Neurological outcomes					
Favourable Neurological Outcomes at 1 year	**16**	**6534**	**2837**	**99.00%**	**83.33 (CI:71.23–90.99)**
Oceania	-	-	-	-	-
Asia	4	1330	4868	99.0%	42.07 (CI:24.63–61.74)
Europe	13	1083	1190	67.0%	91.10 (CI:87.12–93.94)
Middle East	1	22	30	-	73.33 (CI:55.04–86.07)
North America	1	402	446	-	90.13 (CI:87.00–92.58)

Discussion

This systematic review and meta-analysis reveals the long-term quantitative and qualitative outcomes of OHCA patients. To our knowledge, this is the first meta-analysis to analyze outcomes up to 15-years post-discharge. The main findings were: pooled survival at 1-, 3-, 5-, 10-, 15-year was 77.3%, 69.6%, 62.7%, 46.5% and 20.8% respectively, with no differences noted when comparing between RCT and non-RCT studies; with increasingly long timepoints there was reduced survival, fewer studies and greater statistical uncertainty; a large proportion of 1-year survivors of OHCA (83.3%) had favorable neurological outcomes; HRQoL for survivors was comparable to the general population; OHCA patients of Oceania, Europe and North America studies had between 1.9–2.1 RR of survival as compared to Asian studies. Further subgroup analyses found minimal differences in survival. A large proportion of OHCA survivors (83.3%) also had relatively favorable neurological outcomes and had good QoL outcomes 1-year after discharge.

When comparing the survival of patients by continent, Asian and Middle Eastern studies generally had poorer 1- and 3-year survival rates, as compared to studies from Europe, North America, and Oceania (Table 4). Examining the RR, studies from all other regions had 1.9–2.1 increased probability of survival compared to Asian studies. Reasons for this difference in survival may be due to differences in etiologies of OHCA, EMS response times, and bystander CPR rates.[99] Disparities were also noted for neurological outcomes, with Asian countries having lower proportions of patients with favorable neurological outcomes compared to Europe and North American studies. This could be due to variations in the practices of withdrawal of life sustaining treatment (WLST). Asian countries have been cited to not have the practice of WLST, and they would have a larger cohort of patients being discharged with more complications and less favourable neurological outcomes.[100] However, there are marked variations in this practice, and studies on the trend of WLST remains inconclusive,[100, 101,102] thus more studies should be conducted to analyse these findings. Next, studies have reported that the thresholds of EMS protocols for initiating resuscitation were lower in Asian countries,[3,103] potentially contributing to this disparity of findings.

Another reason for these differences may be due to the lack of studies outside the sphere of North America, Europe, and Oceania. Similar to the findings of previous studies such as Berdowski et al. and Paratz et al.,[3,104] our study had only 5 studies from Asia, and 2 from the Middle East in our analysis by region. Paratz et al. found that global coverage of cardiac arrest or sudden cardiac deaths were biased towards well-developed regions (North America, Europe and Australia).[104] They found that within the Asian continent, only three countries (Japan, Korea, and Taiwan) had well established registries. Similar situations were also found in other regions such as the Middle East (Qatar, Lebanon, and Egypt) and South America (Brazil). Furthermore, there were no existing registries in Africa, less the Pan-Africa SCD study, which is still awaiting approval and funding.[105] Data from underrepresented regions are crucial to better understand the global burden and long-term outcomes of OHCA patients.

Our comparative meta-analysis found that in general, patients who were male, had a shockable rhythm, and had non-residential OHCA, had better survival as compared to their respective counterparts. This is in line with previous studies, which reported similar results.[61,106,107] Females were noted to have poorer overall discharge survival and survival to 1-year.[106, 107] However, previous studies have noted that female patients usually have heart disease at an older age as compared to males, which may have confounded the results. Another comparison was the use of TTM in OHCA patients, which our study found no significant differences compared to normothermia. The data on the effect of TTM on long-term survival is mixed. Previous studies have concluded that it improves neurological outcomes and long-term survival,[108] and the current American Heart Association (AHA) 2020 Guidelines advocates the use of therapeutic hypothermia or TTM for CA patients.[109] However, recent studies such as those conducted by Bhattacharjee et al. found that it did not significantly affect long-term outcomes and survival,[110] but may potentially lead to an increased risk for pneumonia and sepsis,[88,111] as well as other complications such as hypokalemia and cardiac arrhythmias. Thus, further studies examining the effectiveness of TTM on the long-term survival of OHCA patients are needed. Our paper also found that the long-term HRQoL of patients were comparable, although slightly worse in some specific domains, to the general population (Table 3). In addition, a high proportion of survivors at 1-year had favorable neurological outcomes. This suggests that patients who survive to 1-year usually have favorable HRQoL and morbidity outcomes, in concordance with Green et al.[112] However, these results may be attributed to 'survivor effect' and self-selection bias. Responders to HRQoL studies are likely to have better neurological, cognitive and/or HRQoL outcomes than those who did not.[9,112] Hence, these findings may not be truly reflective of the HRQoL in the long-term survivors of OHCA.[4] Additionally, our findings should be interpreted with caution as HRQoL is a complex topic and requires a more robust and in-depth study into it, which our study could not do. Future studies exploring this topic should be conducted as HRQoL is an important part of the long-term outcomes of OHCA patients.

Like in previous reviews, we have also found that a variety of scales were used to assess the patients' HRQoL,[9] which limits the ability of clinicians to compare between the different studies.[112] Non-comparative data of unverified HRQoL scores are difficult to interpret, as they lack the robustness of comparative validated scores. While comparative studies provided statistically interpretable HRQoL results, many of them did not reported the numerical values of the HRQoL scores, which precludes the possibility of meta-analysis or the assessment of their clinical significance by comparison with the minimally important differences (MID) of the HRQoL scores.[113] Thus, there is a need to identify and develop a standardized method of reporting and comparing the HRQoL of OHCA patients to allow for better comparisons between studies and populations. This would enable statistical analysis of HRQoL data in OHCA in the future.

Strengths and limitations

Our study has several strengths and limitations. Firstly, to our best knowledge, this is the most extensive meta-analysis and systematic review summarizing the long-term outcomes of OHCA patients. Next, we conducted multiple subgroup analysis to analyze the possible differences between the various types of cardiac arrest. Lastly, this study highlights the differences in survival from studies originating from different regions, which might provide further explanations towards the heterogeneity of the long-term outcomes of OHCA patients. However, this meta-analysis concedes some limitations. Firstly, our paper found substantial heterogeneity in most of our analysis ($I^2 > 75\%$), however, the I^2 can be influenced by sample sizes and thus can be misleading[114,115] with many single-arm meta-analyses of large sample sizes depicting substantial heterogeneity of more than 90%.[116] There is also a lack of representation of articles from the Asian, African, South American, and Middle East regions. Additionally, only articles written in or translated into the English language were included in this paper, which further limits the generalizability of the paper. Next, there were few articles analyzed in our comparative meta-analysis, subtypes of causes of cardiac arrest, which may limit the generalizability of our findings, and increase bias to these analyses. For outcomes on the disposition of OHCA patients post-cardiac arrest, we were unable to analyze a myriad of other scores such as the Glasgow outcome scale (GOSE) and pre-event independence, due to the paucity of data reported. Analysis of publication bias was also not done due to the lack of appropriate methods of assessment in single-arm meta-analysis.[27] Lastly, there was a lack of studies analyzing the long-term outcomes of trauma patients, and we were unable to have a detailed analysis on this subgroup of OHCA patients.

Conclusion

Our study found that the overall survival of OHCA patients that survived to discharge were 77.3%, 69.6%, 62.7%, 46.5% and 20.8% at 1-, 3-, 5-, 10- and 15-year timepoints respectively. We found that survival and favorable neurological outcomes were lower in Asian and Middle Eastern countries as compared to Europe and North American countries. Males, cardiac causes of OHCA, shockable rhythm, and out-of-home cardiac arrests had better survival rates. Further analysis on the differences in survival between the regions on the long-term outcomes of OHCA patients are needed to better direct future breakthroughs in the long-term treatment of OHCA patients.

Declaration of Competing Interest

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

CRediT authorship contribution statement

Yip Han Chin: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Clyve Yu Leon Yaow: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Seth En Teoh: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Nan Luo: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. Nicholas Graves: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. Marcus Eng Hock Ong: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. Andrew Fu Wah Ho: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi. org/10.1016/j.resuscitation.2021.12.026.

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Chapter 4

Long term survival and disease burden from out-of-hospital cardiac arrest in Singapore: a population-based cohort study

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Summary

Background: Understanding the long-term outcomes and disability-adjusted life years (DALY) after out-of-hospital cardiac arrest (OHCA) is important to understand the overall health and disease burden of OHCA respectively, but data in Asia remains limited. We aimed to quantify long-term survival and the annual disease burden of OHCA within a national multi-ethnic Asian cohort.

Methods: We conducted an open cohort study linking the Singapore Pan-Asian Resuscitation Outcomes Study (PAROS) and the Singapore Registry of Births and Deaths from 2010 to 2019. We performed Cox regression, constructed Kaplan–Meier curves, and calculated DALYs and standardised mortality ratios (SMR) for each year of follow-up.

Results: We analysed 802 cases. The mean age was 56.0 (SD 17.8). Most were male (631 cases, 78,7%) and of Chinese ethnicity (552 cases, 68.8%). At one year, the SMR was 14.9 (95% CI:12.5–17.8), decreasing to 1.2 (95% CI:0.7–1.8) at three years, and 0.4 (95% CI:0.2–0.8) at five years. Age at arrest (HR:1.03, 95% CI:1.02–1.04, $p < 0.001$), shockable presenting rhythm (HR:0.75, 95% CI:0.52–0.93, $p = 0.015$) and CPC category (HR:4.62, 95% CI:3.17–6.75, $p < 0.001$) were independently associated with mortality. Annual DALYs due to OHCA varied from 304.1 in 2010 to 849.7 in 2015, then 547.1 in 2018. Mean DALYs decreased from 12.162 in 2010 to 3.599 in 2018.

Conclusions: OHCA survivors had an increased mortality rate for the first three years which subsequently normalised compared to that of the general population. Annual OHCA disease burden in DALY trended downwards from 2010 to 2018. Improved surveillance and OHCA treatment strategies may improve long-term survivorship and decrease its global burden.

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Research in context

Evidence before this study

Before embarking on this study, we performed a literature review in the Medline and Embase databases. We used key search terms including "cardiac arrest", "heart arrest", "survival", and "mortality" to retrieve studies from inception of each database until December 31, 2021. The majority of studies addressed short-term survival post-OHCA, including survival until 30 days after OHCA or hospital discharge. However, there has been a growing focus on long-term OHCA survivorship and outcomes from multiple domains, such as long-term survival, complications, and quality-of-life among the group of OHCA patients who survive beyond 30 days after OHCA or hospital discharge. Recent international studies in Italy and Australia based on cardiac arrest registries with regional coverage have shed light on this area of research, but results varied with a standardised mortality ratio (SMR) 23 times and five times that of the general population in the former and latter studies respectively. A recent systematic review conducted in 2021 revealed that 20.8% of long-term OHCA survivors were alive at 15 years of follow-up, with lower survival in Asia compared to other regions. There were no studies which measured disability-adjusted life years (DALYs) among post-OHCA survivors in the Asian context. As a whole, data in the Asian context appeared limited.

Added value of this study

Our study aimed to quantify the annual burden of OHCA estimated using DALYs after OHCA in the Asian context, as well as to describe long-term survival and factors associated with survival among OHCA survivors up to 10 years of follow-up. Our study linked the Singapore data from the Pan-Asian Resuscitation Outcomes Study, an international, multicentre, cardiac arrest registry which has complete national coverage in Singapore, to the national death registry. This allowed us to estimate the SMR for long-term OHCA survivors and calculate disease burden in terms of DALYs using a nationally representative sample which had comprehensive case capture. Our key findings were that (a) long-term survivorship of the OHCA cohort decreased through the follow-up period, (b) SMR decreased from the first to the fifth year of follow-up, and (c) total DALY attributable to long-term OHCA survivors varied although mean DALY decreased from 2010 to 2018. Our study is the first national Asian study to quantify long-term survival and disease burden of long-term OHCA survivors, to our knowledge, and thus represents an important contribution to current evidence.

Implications of all the available evidence

Taken together with existing evidence, our study suggests that adult OHCA continues to exert a large burden of disease, warranting an increased focus on OHCA with regard to public health policy. The available evidence suggests that SMR among OHCA survivors is the highest in the early years post-OHCA and eventually normalises to that of the general population. Furthermore, our study revealed a decreasing trend in DALYs despite contrary evidence from international studies, with these observed differences likely due to differences in surveillance or treatment strategies, ranging from community interventions to post-resuscitation care. Based on these findings, public health policy should pay close attention to OHCA survivors during the initial follow-up period, when they seem to be most vulnerable. Furthermore, additional data is urgently needed to investigate how and why the disease burden and long-term survival of OHCA varies, in order to guide research into treatment strategies for OHCA aimed at the various predictors of long-term survival, such as interventions to improve short-term neurological outcomes, which was a significant predictor of survival in our study.

Introduction

Out-of-hospital cardiac arrest (OHCA), or sudden cardiac arrest, is one of the leading causes of mortality worldwide.[1,2] The global incidence of emergency medical services (EMS)-treated OHCA may range from 30 to 97.1 per 100,000 population among which the percentage surviving to discharge is an estimated 8.6%–9.9%.[1–7] In Singapore, the age-adjusted incidence of OHCA was approximately 50.0 per 100,000 person-years and increased between 2011 and 2016, with survival rates of approximately 1.0–3.0% in the same period.[4,8] OHCA thus poses a large health burden both locally and internationally.

OHCA is defined as the loss of functional cardiac mechanical activity in association with an absence of systemic circulation, occurring outside of a hospital setting.[1] Extensive research has been conducted on factors associated with short-term survival following OHCA.[9–11] Recently, however, increased focus has been placed on the long-term outcomes of OHCA,[12–14] including long-term survival and health-related quality of life during the additional years of life lived,[12,15–17] which help evaluate the natural history and long-term impact of OHCA on the health burden of society.[12,18,19] To quantify both the fatal and non-fatal disease burden of OHCA, several recent articles had applied the concept of disability-adjusted life years (DALYs) to OHCA.[19–21] The DALY of a case is defined as the sum of the number of years of life lost (YLL) and the number of years lived with disability (YLD).[22] Thus, one DALY is equal to one year of healthy life lost. The estimated annual DALYs after adult nontraumatic EMS-treated OHCA in the United States was 4,354,192 in 2016, with a rate of 1347 OHCA DALYs per 100,000 population (third highest cause of DALYs in the US).[21]

To our knowledge, data on the long-term outcomes of OHCA in Asia has been limited[12] with no reports on DALYs after OHCA in Asia. We aimed to quantify the annual disease burden of OHCA estimated using DALYs in a national multi-ethnic Asian cohort and describe factors associated with long-term survival (up to 10 years follow up).

Methods

Study design

We conducted an open cohort study through the linkage of two national datasets, the Singapore data from the Pan-Asian Resuscitation Outcomes Study (PAROS),[23] and the Singapore Registry of Births and Deaths (henceforth, the "death registry")[24] from 2010 to 2019. PAROS is an international, multicentre, prospective registry of OHCA in nine countries across the Asia–Pacific region established in 2009.[23] PAROS is based on Utstein-style recommendations[25] and has a data dictionary and taxonomy aligned with the Cardiac Arrest Registry to Improve Survival (CARES).[26] The death registry is maintained by the Ministry of Home Affairs Immigration and Checkpoints Authority and includes data on the cause and date of death of all Singaporeans and permanent residents residing in Singapore.[24] We then linked the PAROS data with the death registry to determine the survival status and duration of the OHCA survivors after OHCA. Data linkage was performed using the National Registration Identity Card (NRIC) numbers of each case, which is the unique national identification number in Singapore. There is legislative requirement to report death certifications according to the Registration of Births and Deaths Act of 1937, therefore ensuring complete and accurate ascertainment of nation-wide long-term mortality outcomes among OHCA cases.

Setting

This study was conducted in Singapore, an urbanized, multi-ethnic, densely populated island city-state located in Southeast Asia with a population of 5.7 million over a land area of 725.7 km^2 (population density of 7810 per km^2).[27] The Singapore Civil Defence Force (SCDF) provides nationwide EMS in Singapore and is a fire-based system activated by a centralized "995" dispatch system.[22,28] All ambulances have mechanical CPR devices, and all ambulance personnel are proficient in basic life support skills and can administer automated external defibrillators.[28] Patients experiencing OHCA in Singapore typically receive treatment at the scene and are then transported to the hospital by EMS after a brief period of resuscitation, usually with ongoing CPR.[4] In recent years, several new prehospital interventions have also been developed in Singapore and detailed description regarding EMS management of OHCA in Singapore can be found in a previous paper.[29]

Study population and data collection

We included all cases with OHCA in the PAROS dataset (Singapore participants) in this study, defined as any OHCA conveyed by EMS or presenting at emergency departments, as confirmed by the absence of pulse, unresponsiveness, and apnea.[23] As this study investigated the long-term outcomes of OHCA, we excluded all cases that demised within 30 days of the date of OHCA. We also excluded foreigners who had no follow-up data and hence no death information after linkage with the Singapore Death Registry, as they may have left the country. The date of OHCA was taken as the event date and the registry data were subject to annual audits for accuracy and inter-rater reliability. Outlier and illogical data were flagged and reviewed for final consensus among the registry coordinators. The study was approved by the Centralised Institutional Review Board (CIRB ref: 2018/2937) and qualified for exemption from full review as it analyzed de-identified data, with the Ministry of Health's Unit for Prehospital Emergency Care acting as a trusted third party.

Data collected from linkage of the two national databases included case demographics (age, sex, race), details of OHCA, initiation of targeted temperature management, and date and cause of death. Details of OHCA included the presenting rhythm (categorised as shockable, non-shockable, and unknown rhythm), the presence of a witness during the OHCA, the provision of bystander CPR, EMS response time (defined as time the call was received at dispatch to the time the ambulance arrived on scene and dichotomised to greater than 8 min and lesser than or equal to 8 min) and Cerebral Performance Category (CPC) categorised to CPC grades 1 and 2 versus CPC grades 3 and 4.

The primary outcome of interest was duration of survival after OHCA and was computed as the time from 30 days after the date of OHCA to the date of death as documented by the Singapore death registry. For the time-to-event analysis, the date of censoring was taken as the 30th of June 2020. The cause of death was determined from the death registry and was collected based on ICD 9 and ICD 10 codes reported by Singapore registered medical practitioners who announced the patient's death. ICD 9 and ICD 10 codes were harmonised using an open-source R package, icdcoder.[30]

Statistical analyses

Baseline characteristics were presented as frequencies and proportions for categorical variables, and median (interquartile range) or mean (standard deviation) for continuous variables, as appropriate for the distribution of the data. In accordance with previous literature,[31] we used a transport time of 8 min to dichotomise the cohort of OHCA survivors into two groups of similar size. Hypothesis testing was conducted using the Pearson Chi-squared test and the independent student t-test to compare baseline characteristics by death status at one year follow up.

To investigate the long-term survival of patients with OHCA, we conducted survival analyses and computed Cox proportion regression models to identify factors that were significantly and independently associated with survival. Covariates included in the cox-proportional models were demographics (age, sex, and race), details of OHCA (presenting rhythm, witnessed arrest, bystander CPR, EMS response time, and CPC category), and the initiation of targeted temperature management. In previous years, the median EMS response time in Singapore was found to be close to 8 min,[4,29] with both local studies[29] and international studies[31] using the 8-min timepoint as a natural cut-off, hence we chose to use the 8-min timepoint as a cut-off here. The proportional hazards assumption was assessed. Missing data within variables was kept as a separate category to preserve the overall sample size. Kaplan–Meier survival curves were constructed for the overall population, and by key characteristics. The proportion surviving (and 95% CI) was calculated annually for up to eight years post-OHCA.

For the final model, we started with the most significant covariate identified on univariate analysis and used the likelihood ratio to assess whether inclusion of the next most significant variable would improve the fit of the model. This was done sequentially until all variables had been assessed. Interaction effects were also assessed for the variables in the multivariate model. A stratified analysis was performed by CPC category as we found significant interaction effects. Kaplan–Meier survival curves were constructed for the overall population, and by key characteristics. The proportion surviving (and 95% CI) was calculated for up to eight years post-OHCA.

We calculated the standardised mortality ratio (SMR) for each year of follow up (computed as the ratio of the observed number of deaths divided by the expected number of deaths). The expected number of deaths was defined as the age and sex indirect standardised, with the expected death rates at each year of OHCA and follow up year calculated from the Complete Life Table for Singapore Residents 2019.32 The top 10 causes of death categorized by ICD10 categories were tabulated.

To quantify the annual disease burden of OHCA in Singapore, the DALY following OHCA was calculated as follows: for each death, the YLL was calculated from the remaining standard life expectancy at the age of death, stratified by gender, while the YLD was calculated by assigning a disability weight (DW) based on their CPC score.[19] Further details may be found in the Supplementary material Appendix S1. The DALY was a summation of YLL and YLD.[20] The sum and average DALY, along with YLL and YLD was calculated annually from 2010 to 2018. The level of significance was set at 5% and the analysis was performed using Stata V16 (Stata Corp, College Station, Tx, USA).

Results

We included 802 cases in the analysis. 17,473 cases were excluded because they died within 30 days of OHCA, and 41 cases were excluded because these were foreigners with no cause of death or death date. The detailed population flowchart may be found in Supplementary Fig. S1. 126 cases had demised at one-year follow up. The mean age of the cohort was 56.0 (SD 17.8) and majority of the cohort was male (631 cases, 78.7%) and of Chinese ethnicity (552 cases, 68.8%). OHCA survivors who died at one year of follow up had significantly older age, a lower proportion of shockable presenting rhythm, and higher CPC category at baseline (Table 1). All survival estimates refer to survival among patients surviving to 30 days after OHCA, therefore fulfilling the inclusion criteria.

Factor	Whole Cohort (%)	Alive at 1 Year (%)	Died at 1 Year (%)	p-Value[a]
Total N	802	676	126	
Gender				0.054
Male	631 (78.7%)	540 (79.9%)	91 (72.2%)	
Female	171 (21.3%)	136 (20.1%)	35 (27.8%)	
Age, mean (SD)	56.0 (17.8)	54.4 (17.5)	64.9 (16.7)	<0.001*
Race				0.99
Chinese	552 (68.8%)	455 (67.3%)	97 (77.0%)	
Malay	96 (12.0%)	83 (12.3%)	13 (10.3%)	
Indian	114 (14.2%)	100 (14.8%)	14 (11.1%)	
Other	40 (5.0%)	38 (5.6%)	2 (1.6%)	
Bystander CPR				0.39
No	316 (39.4%)	262 (38.8%)	54 (42.9%)	
Yes	486 (60.6%)	414 (61.2%)	72 (57.1%)	
Arrest witnessed				0.35
No	136 (17.0%)	111 (16.4%)	25 (19.8%)	
Yes	666 (83.0%)	565 (83.6%)	101 (80.2%)	
Hypothermia therapy initiated				0.42
No	554 (69.2%)	463 (68.6%)	91 (72.2%)	
Yes	247 (30.8%)	212 (31.4%)	35 (27.8%)	
EMS ambulance response time				0.59
≤8 min	381 (47.5%)	319 (47.2%)	62 (49.2%)	
>8 min	393 (49.0%)	335 (49.6%)	58 (46.0%)	
Missing	28 (3.5%)	22 (3.3%)	6 (4.8%)	
Shockable first arrest rhythm				<0.001*
Non-shockable	167 (20.8%)	121 (17.9%)	46 (36.5%)	
Shockable	577 (71.9%)	503 (74.4%)	74 (58.7%)	
Unknown	58 (7.2%)	52 (7.7%)	6 (4.8%)	
Cerebral performance category				
Grouped				<0.001*
1-2	540 (67.5%)	500 (74.2%)	40 (31.7%)	
3-4	257 (32.1%)	171 (25.4%)	86 (68.3%)	
Missing	3 (0.4%)	3 (0.4%)	0 (0.0%)	

OHCA: Out-of-hospital cardiac arrest; SD: Standard deviation; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical services. *p value < 0.05.[a]Test comparing alive and deceased at 1 year.

***Table 1*: Baseline demographics and clinical characteristics of the OHCA cohort stratified by mortality at one year follow up.**

In the univariate cox proportional hazards model, age at arrest (HR 1.04, 95% CI: 1.03–1.05, p < 0.001), female sex (HR 1.35, 95% CI: 1.01–1.81, p = 0.046), and CPC category 3-4 (HR 4.20, 95% CI: 3.23–5.46, p < 0.001) were found to be significantly associated with mortality while shockable presenting rhythm (HR 0.44, 95% CI: 0.33–0.58, p < 0.001) and 'other' race (HR 0.26, 95% CI: 0.10–0.69, p < 0.007) were significantly associated with survival (Table 2). Fig. 1A shows the overall survival curve, and Fig. 1B and C shows the curves for subgroups by CPC category and shockable rhythm.

In the multivariate cox proportional hazards model age at arrest (HR 1.03, 95% CI: 1.02–1.04, p < 0.001) and CPC category 3-4 (HR 4.62, 95% CI: 3.17–6.75, p < 0.001) were independently associated with mortality while shockable presenting rhythm (HR 0.75, 95% CI: 0.52–0.93, p = 0.015) was significantly associated with survival (Table 2). We found a significant interaction effect between CPC category and age (p < 0.001), as well as CPC category and a shockable first rhythm (p < 0.001) in a stratified analysis (Supplementary Table S1). Amongst those with CPC grades 1-2, age had a stronger effect on mortality (HR 1.05, 95% CI: 1.03–1.07) as compared to those with CPC grades 3-4 (HR 1.02, 95% CI: 1.01–1.03). In addition, amongst those with CPC grades 1-2, a shockable first rhythm had a significant protective effect (HR 0.36, 95% CI: 0.23–0.58) compared to those with CPC grades 3-4 (HR 1.02, 95% CI: 0.72–1.45).

The long-term survivorship of OHCA was reported for each year of follow up (Table 3). The proportion surviving at one year of follow up was 0.84 (95% CI: 0.81–0.87), at five years of follow up was 0.68

(95% CI 0.65–0.72), and at ten years of follow up was 0.62 (95% CI 0.57–0.67). The top three causes of death after OHCA based on ICD10 categories were pneumonia, chronic ischemic heart disease, and acute myocardial infarction (Supplementary Table S2). The age-sex SMR of the OHCA cohort compared to the standard Singapore population was shown in Fig. 2. At one year of follow up, the SMR was 14.9 (95% CI: 12.5–17.8) and this decreased to 1.2 (95% CI: 0.7–1.8) at three years follow up, and 0.4 (95% CI: 0.2–0.8) at five years follow up.

The annual disease burden of long-term OHCA survivors in Singapore measured using DALYs were reported from 2010 to 2018 in Table 4. The total YLL increased from 303.1 in 2010 to 844.2 in 2015, followed by decreasing to 538.5 in 2018. The total YLD increased from 1.0 in 2010 to 8.6 in 2018. The total DALY increased from 304.1 in 2010 to 849.7 in 2015, followed by decreasing to 547.1 in 2018, while mean DALY decreased from 12.162 in 2010 to 3.599 in 2018 among long-term OHCA survivors.

Covariate	Univariate analysis			Adjusted analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Gender						
Male	Reference					
Female	1.35	1.01–1.81	0.046*			
Age, every year increase	1.04	1.03–1.05	<0.001*	1.03	1.02–1.04	<0.001*
Race						
Chinese	Reference					
Malay	0.68	0.43–1.05	0.085			
Indian	0.90	0.62–1.31	0.589			
Other	0.26	0.10–0.69	0.007*			
Bystander CPR						
No	Reference					
Yes	0.89	0.68–1.15	0.362			
Arrest witnessed						
No	Reference					
Yes	0.96	0.68–1.34	0.793			
Hypothermia therapy initiated						
No	Reference					
Yes	0.90	0.68–1.20	0.482			
EMS ambulance response time						
≤8 min	Reference					
>8 min	0.95	0.73–1.24	0.713			
Shockable first arrest rhythm						
Non-shockable	Reference			Reference		
Shockable	0.44	0.33–0.58	<0.001*	0.70	0.52–0.93	0.015*
Unknown	0.40	0.22–0.73	0.003*	0.45	0.24–0.82	0.010*
Cerebral Performance Category						
1-2	Reference			Reference		
3-4	4.20	3.23–5.46	<0.001*	4.62	3.17–6.75	<0.001*

HR: Hazard ratio; 95% CI: 95% confidence interval; CPR: Cardiopulmonary resuscitation; EMS: Emergency medical services. *p value < 0.05.

***Table 2:* Demographic and clinical factors associated with survival on Cox-proportional hazards models.**

Discussion

We investigated the long-term survival of a large national Asian cohort who survived to 30 days after OHCA. The key findings of this study were that (a) long-term survivorship of the OHCA cohort decreased from 0.84 at one year of follow up to 0.62 at 10 years of follow up, (b) SMR decreased from 14.9 at one year of follow up to 1.2 and 0.4 and three and five years of follow up respectively, and (c) total DALY attributable to long-term OHCA survivors varied from 304.1 in 2010 to 849.7 in 2015 and finally to 547.1 in 2018, although mean DALY decreased from 12.2 in 2010 to 3.6 in 2018. To our knowledge, this is the first national Asian study to quantify the annual disease burden of OHCA over time using DALY and to describe the long-term survival of OHCA patients for up to 10 years, hence representing a significant contribution to the growing body of literature on the public health burden and long-term outcomes of OHCA.

In the Singapore Burden of Disease Study,[33] cardiovascular diseases including OHCA were the leading cause of DALY, largely driven by YLL. However, the overall decrease in the mean DALY from 2010 to 2018 in our study suggests that the long-term burden per OHCA patient has improved in Singapore over time, whereas international data revealed an increasing burden of disease due to OHCA from 2013 to 2018 (possibly because of more precise national OHCA surveillance in the later years).[20] This result from a cohort of initial OHCA survivors in a small city-state may have been influenced by nation-wide improvements to OHCA interventions,[34] ranging from community interventions such as the MyResponder phone application to improve rates of bystander CPR and AED use[35] to post-resuscitation interventions including coronary angiography (CAG) with percutaneous coronary intervention (PCI)[36] and targeted temperature management (TTM).[37–39] Although bystander CPR was not significantly associated with long-term survival in this study, the sum effect of these interventions may have improved short-term neurological outcomes, which was significantly associated with long-term survival here and elsewhere.[40] Yet, this encouraging result should not imply that OHCA has a decreasing public health burden, since total DALY may increase in the future considering Singapore's aging population and the association between older age and mortality.

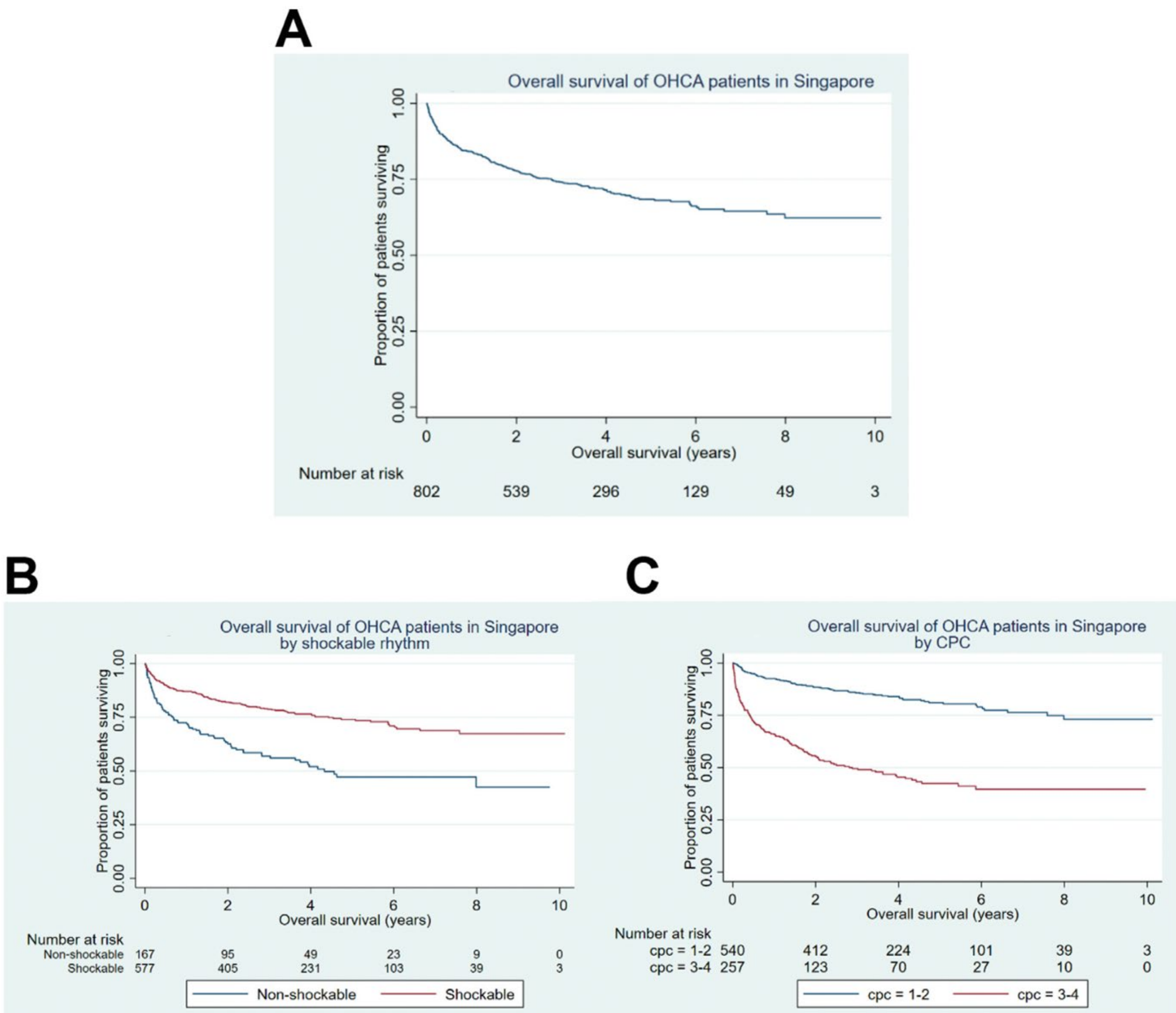

Fig. 1: Overall survival of out-of-hospital cardiac arrest patients in Singapore, in total (A), by shockable rhythm (B), and by Cerebral Performance Category (C).

Follow-up year	Population at risk	Deaths	Proportion surviving	95% CI	
1	675	127	0.84	0.81	0.87
2	539	50	0.78	0.75	0.80
3	414	23	0.74	0.71	0.77
4	296	13	0.71	0.68	0.75
5	196	11	0.68	0.65	0.72
6	129	5	0.66	0.62	0.70
7	89	3	0.65	0.60	0.69
8	49	2	0.62	0.57	0.67
9	26	0	0.62	0.57	0.67
10	3	0	0.62	0.57	0.67

95% CI: 95% confidence interval.

***Table 3*: Survival by follow-up period of the out-of-hospital cardiac arrest cohort.**

Our results further add to a body of knowledge about long-term OHCA survival contributed to by various international studies. A cohort of 3449 OHCA survivors in Victoria, Australia, had a 10-year absolute survival of 70% and an SMR that approached that of the general population after 5 years of follow-up.[16] A study by Baldi et al. based in Lombardia, Italy, demonstrated a SMR which decreased from 23 (95% CI: 16.8–30.2) to 2.6 (95% CI: 1.03–4.8) from the first to fifth year of follow up using an approach to SMR analysis similar in concept to our approach.[41] Lastly, a recent South Korean study also showed an all-cause mortality of 35.2% after 1 year of follow up and 62.7% after 5 years of follow up, suggesting that more than half of long-term survivors who died met their demise in the first year.[42] These results support the hypothesis that mortality in initial OHCA survivors is greatest during the immediate period after OHCA with increased mortality up to 15-fold higher than the general population. This improves in the later years,[43] suggesting that the longer patients survive beyond the initial 5 years after OHCA, the more likely they are to experience a life-span comparable to an age and sex-matched general population.[2,18,39] Our findings that age at arrest, non-shockable presenting rhythm, and CPC category 3-4 were independently associated with higher risk of mortality are largely consistent with other studies worldwide.[44,45] It has been previously hypothesised that traditional factors such as witnessed arrest, bystander CPR, and EMS response time influence long-term survival to a lesser degree than short-term survival.[16] As Singapore is a small, developed, and densely populated city-state with a mature healthcare system,[46] geographical factors in our study related to location of arrest and access to PCI-capable hospitals were also less of a concern compared to other countries.[1,16] Lastly, we identified CPC grade to be an effect modifier of the association between age or shockable first rhythm and mortality. Our results suggest that older age and non-shockable first rhythm had stronger effects on mortality in OHCA survivors with CPC grades 1-2 as compared to those with CPC grades 3-4. Hence, in patients with CPC grades 3-4, poor neurological recovery may be the most important predictive factor for mortality in the long-term.[16,47]

The importance of short-term good neurological outcome to long-term survival implies that interventions to improve short-term neurological outcomes such as CAG, PCI, intensive care, and other post-resuscitation care strategies may in turn improve longer term outcomes. More data about the long-term complications of OHCA, such as acute myocardial infarction (which was the third-most common cause of mortality in this study) or recurrent cardiac arrest, are needed to guide the long-term management of OHCA survivors.[48] This is also the case in Singapore, especially since our current findings are closely linked to future translational work and are part of an ongoing internal conversation exploring the long-term quality of life among OHCA survivors. Further research into these gaps will be important to elucidate the reasons behind changes in the burden of OHCA over the years, thereby guiding potential public health policies, although much remains unknown about the global burden of OHCA survivors in terms of DALY and what may ease this burden in the future.

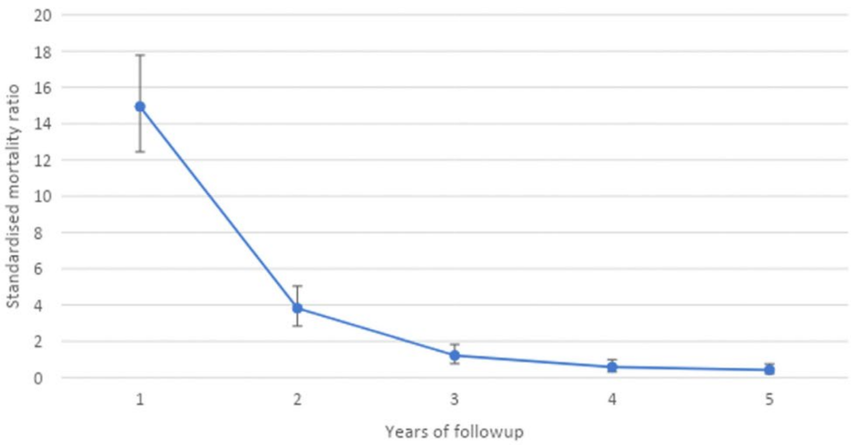

Fig. 2: **Yearly standardised mortality ratios (95% confidence interval) of out-of-hospital cardiac arrest patients in relation to the standard Singapore population in 2019.**

Fig. 2: Yearly standardised mortality ratios (95% confidence interval) of out-of-hospital cardiac arrest patients in relation to the standard Singapore population in 2019.

Year	Total YLL	Total YLD	Total DALY	YLL		YLD		DALY	
				Mean	95% CI	Mean	95% CI	Mean	95% CI
2010	303.1	1.0	304.1	27.6	16.4–38.7	0.07	0.05–0.09	12.2	4.9–19.4
2011	310.2	1.8	312.0	22.2	15.7–28.6	0.07	0.06–0.09	8.0	3.9–12.1
2012	371.4	1.8	373.2	18.6	15.1–22.1	0.06	0.05–0.08	7.8	4.8–10.8
2013	550.8	2.9	553.7	19.7	13.8–25.5	0.08	0.06–0.09	8.4	5.0–11.8
2014	624.8	2.8	627.6	21.5	17.8–25.3	0.06	0.05–0.07	8.0	5.3–10.8
2015	844.2	5.5	849.7	22.2	17.1–27.3	0.07	0.06–0.08	7.5	4.9–10.1
2016	731.6	7.7	739.3	18.8	14.7–22.8	0.07	0.06–0.07	4.8	3.2–6.4
2017	685.3	6.0	691.3	23.6	18.4–28.9	0.06	0.06–0.07	5.6	3.5–7.8
2018	538.5	8.6	547.1	20.7	16.3–25.2	0.07	0.06–0.07	3.6	2.2–5.0

YLL: Years of life lost; YLD: Years of healthy life lost due to disability; DALY: Disability-adjusted life years; 95% CI: 95% confidence intervals.

Table 4: **Disability-adjusted life years lost for the out-of-hospital cardiac arrest cohort from 2010 to 2018.**

Strengths and limitations

Our study is the first population-based Asian study to quantify the long-term survivorship of OHCA and the national disease burden exerted by this cohort of OHCA survivors. The strengths of our study include a nationally representative cohort of patients with comprehensive case capture via the linkage of two national cohorts using a national identification number, and the prospective ascertainment of exposure, outcomes and follow up time in the cohort. Our study is based on the PAROS registry, which has population-level coverage, and in fact has complete national coverage because Singapore is an island city-state with few patients spilling over to non-surveilled healthcare systems and every hospital, as well as the sole emergency ambulance service, contributes data fully to PAROS. However, we were not able to capture quality-of-life outcomes among long-term OHCA survivors, which are important but often overlooked by resuscitation studies. Furthermore, another limitation was the relatively smaller cohort size of our study. This may have led to less stable weight calculations and larger fluctuations in annual trends for our reported outcomes, although we encourage readers to interpret the estimates in context of the 95% confidence intervals, which we have reported in the manuscript. Our study was also limited by the exclusion of foreigners treated in Singapore that had no date of death recorded or whose deaths were not captured as they were overseas, and by the exclusion of cases with 2nd episode cardiac arrest. The choice of DW to calculate the YLD for individual patients also influenced our study findings, although this choice was made to improve comparability of results and reflects current understanding of how cardiac arrest impacts long-term quality of life. The observational design of this study implies our results are limited to observed associations and cannot establish a causal link between covariates and outcomes. Furthermore, our results are vulnerable to confounding, although efforts to minimise these effects were made through our adjusted analyses.

Conclusion

Adult OHCA has a large burden of disease and should be a focus of public health policy. In this national study, initial survivors of OHCA had an increased mortality rate compared to the general population for the first three years, but subsequently normalised to that of the general population, while the annual disease burden of OHCA quantified using DALYs showed decreasing trends from 2010 to 2018. Further improvements in the surveillance and OHCA treatment strategies are needed to improve long-term survivorship and to decrease the global burden of OHCA.

Contributors

AFWH, MJRL, and MEHO were involved in conceptualisation. AFWH, MJRL, AE, PPP, and MEHO were involved in data collection. AFWH, MJRL, NG, and AE were involved in data analysis. AFWH, MJRL, JWY, AB, and NG were involved in manuscript drafting. AFWH, MJRL, JWY, AB, NG, PPP, and LT were involved in manuscript review.

Data sharing statement

The data that support the findings of this study are available from the PAROS investigators and National Registry of Diseases Office. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the PAROS investigators and National Registry of Diseases Office.

Ethics approval and consent to participate

The study was approved by the Centralised Institutional Review Board (CIRB ref: 2018/2937) and qualified for exemption from full review as it analyzed de-identified data, with the Ministry of Health's Unit for Pre-hospital Emergency Care acting as a trusted third party.

Declaration of interests

MEH Ong reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices; grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation program to their Community CPR Training Centre Research Program in Norway. PP Pek reports previous accommodation for participation in Research Masterclass Laerdal. A Blewer reports previous involvement with the National Heart, Lung, and Blood Institute and Eunice Kennedy Shriver National Institute of Child Health and Human Development and Laerdal Foundation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi. org/10.1016/j.lanwpc.2022.100672.

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Chapter 5

Long term risk of recurrence among survivors of sudden cardiac arrest: A systematic review and meta-analysis

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Abstract

Aims: With a growing number of survivors of sudden cardiac arrest globally, their natural disease progression is of interest. This systematic review and meta-analysis aimed to determine the risk of recurrence after sudden cardiac arrest and its associated risk factors.

Methods: Medline, Embase, Cochrane Library and Scopus were searched from inception to October 2021. Studies involving survivors of an out-of hospital sudden cardiac arrest event of any non-traumatic aetiology were included. Meta-analyses of proportions using the random-effects model estimated the primary outcome of first recurrent sudden cardiac arrest incidence as well as secondary outcomes including cumulative incidence of recurrence at 1-year and incidence of second recurrence among survivors of first recurrence. A recurrent episode was defined as a sudden cardiac arrest that occurs 28 or more days after the index event. Subgroup and meta-regression analyses were conducted for predetermined variables. The Newcastle-Ottawa Scale was used to assess risk of bias for most studies.

Results: 35 studies of moderate to high quality comprising a total of 7186 survivors were analysed. The pooled incidence of first recurrence was 15.24% (32 studies; 95%CI, 11.01–19.95; mean follow-up time, 41.3 ± 29.3 months) and second recurrence was 35.03% (3 studies; 95%CI, 19.65– 51.93; mean follow-up time, 161.1 ± 54.3 months). At 1-year, incidence of recurrence was 10.62% (3 studies; 95%CI, 0.25–30.42). Subgroup analyses found no significant difference ($p = 0.204$) between incidence of first recurrence published from 1975-1992 and 1993–2021, and between studies with mean follow-up time of <24 months, 24–48 months, and >48 months. On meta-regression, initial shockable rhythm increased incidence of first recurrence ($p = 0.01$).

Conclusion: 15.24% of sudden cardiac arrest survivors experienced a recurrence, and of these, 35.03% experienced a second recurrence. Most recurrences occurred in the first year. Initial shockable rhythm increased this risk. Despite the limitations of inter-study heterogeneity, these findings can still guide intervention and follow-up of sudden cardiac arrest survivors.

Introduction

Sudden cardiac arrest (SCA) is a major contributor to disease burden,[1] with a global incidence of 55 cases per 100,000 person-years.[2] Although few patients survive to hospital discharge (global rate of 8.8%),[3] those who do can have reasonably good prognosis in the longer term, with 78% alive at 1-year, 47% alive at 3 years and 21% alive at 10 years.[4] With improving initial survival-to-discharge rates in many communities,[2] increasing numbers of SCA patients are now surviving the initial event, and living in the community. There is hence tremendous scientific and public health interest in the long-term survivorship of SCA patients.[5,6] Unanswered questions that have now gained relevance include the risk of recurrent SCA events, so as to guide clinical follow up and interventions.

SCA survivors are generally considered to be at heightened risk for developing subsequent life-threatening ventricular arrhythmias,[7] ostensibly contributed by myocardial scar tissue formation, heart failure or untreated hereditary arrhythmogenic conditions. Yet little is known about how often SCA recurs or its risk factors. Most studies in the SCA literature have focused on proximal outcomes such as survival at 1-month, while longer-term complications are infrequently reported. While there have been several cohort studies investigating SCA recurrence, there is apparent variability in reported incidences. For example, Wilber et al. reported a 17% recurrence rate of SCA over a mean follow-up period of 33 months while Sager et al. reported a recurrence rate of 42% over a mean follow-up period of 16 months.[8,9]

Clarity on the risk of SCA recurrence and its risk factors can inform clinical follow-up and aid in the identification of high-risk patients for treatments such as implantable cardioverter-defibrillators (ICD), antiarrhythmic medications, catheter ablation and targeted training of patient's household members in Basic Life Support. This systematic review and meta-analysis therefore aimed to estimate the risk and determinants of recurrence amongst SCA survivors.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10,11] The study protocol had been published in the International Prospective Register of Systematic Reviews (PROSPERO CRD 42022291894). The data collected in this study are available upon reasonable request.

Search strategy

A systematic literature search was performed in Medline, Embase, the Cochrane Library and Scopus from inception through to October 22, 2021. The search strategy was developed in consultation with a medical information specialist (Medical Library, National University of Singapore). Search terms included the medical subject heading (MeSH) terms "out-of-hospital cardiac arrest" and "heart arrest" as well as keywords relating to "out of hospital", "cardiac arrest", "out-of-hospital cardiac arrest" and "recurrence", all of which were combined for the search strategy. The detailed search strategy is available in Data S1. Reference lists of relevant sources were hand-searched and enquiries made to the content experts for relevant studies. This process surfaced 1 article that was not captured by the search strategy. Abstracts retrieved from the electronic databases along with the single additional article were subsequently imported into EndNote X9 (Clarivate, Philadelphia, PA) for the removal of duplicates.

Study selection criteria

Article sieve was conducted using the web-based platform Rayyan QCRI by 3 authors (T.J.R.L, J.P, J.Y) according to predefined criteria.[12] Decisions made by the authors were blinded and any conflicts resolved through a group discussion. Articles were initially excluded based on their titles and abstracts prior to assessment of the remaining full texts.

Studies were eligible for inclusion if they met the following criteria: (1) patients selected for the study population had experienced an index SCA event of any non-traumatic aetiology and survived to hospital discharge; (2) reported outcomes pertaining to out-of-hospital recurrence of SCA; (3) involved human subjects; (4) original articles encompassing randomized controlled trials (RCTs), cohort and cross-sectional studies, as well as conference abstracts; (5) written in or translated to the English language. Studies were excluded if: (1) patients selected experienced an initial in-hospital cardiac arrest; (2) the recurrence of cardiac arrest prior to discharge or the recurrence of cardiac arrest within a hospital setting was the focus; (3) only recurrent cardiac arrest occurring less than 28 days from the previous cardiac arrest was examined; (4) the recurrent ventricular fibrillation (VF) or ventricular tachycardia (VT) was circumvented by the activation of an ICD or it is otherwise unclear if the recurrent VF occurrences were resolved by an ICD; (5) there was no primary data (meta-analyses, literature reviews, protocols, letters, commentaries, and editorials) or with a sample size of 5 or less. Studies reporting on similar cohorts within the same time-period were assessed to ensure no overlapping datasets were used.

Definition of SCA and recurrence

SCA was defined as the abrupt loss of functional cardiac mechanical activity in association with an absence of systemic circulation, occurring outside of a hospital setting.[13] As there has not been a consensus definition for the time frame in which a SCA event is considered a separate event (hence, "recurrent") from the index SCA, in this review, we followed the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) framework for episode management in reporting acute coronary events.[14] Using this approach, recurrent SCA was considered a separate event if it occurred 28 or more days after the index SCA event. This is important because it is common for patients to have several early recurrences immediately after resuscitation during the index hospital admission, but these are less relevant for the understanding of the long-term risk of recurrence.

Data extraction and quality assessment

3 authors (T.J.R.L, J.E.P, J.Y) independently extracted data on general study information (author, year of publication, country), baseline demographic and clinical characteristics (age, gender, comorbidities, follow-up duration, aetiology and initial rhythm of index cardiac arrest, electrophysiological testing results), interventions (antiarrhythmic regimen, number of patients receiving ICDs) as well as outcomes of interest. The primary outcome was the incidence of first recurrent SCA during follow-up, while secondary outcomes collected were cumulative incidence of recurrent SCA at 1-year as well as incidence of second recurrent SCA occurrence among survivors of first recurrent SCA. Any proportion or incidence data compatible with the outcome domains from each study were extracted. There was no restriction on the follow up length, but the recurrent SCA events must occur a minimum of 28 days after the index SCA. All articles were triple coded into a standardised data collection form with blinding between the coders. Conflicts were arbitrated through a group discussion including the senior author (A.F.W.H). Any missing or ambiguous data were clarified through email correspondence with the authors.

Mean and standard deviation (SD) values were abstracted for continuous variables while percentages and frequencies were abstracted for categorical variables. When mean and SD data were not available, the reported values were transformed using appropriate formulae.[15,16] For quality assessments, the Newcastle-Ottawa Scale (NOS)[17] for cohort studies and National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool for RCT were used.[18] Studies with an NOS score of 7 or more were considered high quality.

Statistical analysis

Meta-analyses of proportions were conducted for the primary outcome of incidence of recurrence during follow-up, as well as the secondary outcomes of cumulative incidence of recurrence at 1-year and incidence of second recurrence occurrence among survivors of a first recurrence.

Data analyses were performed using the meta 4.18–0 and meta-for 2.4–0 packages with R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Data were transformed using the Freeman-Tukey double arcsine method, and pooled through an inverse variance method, before back-transformation into normalized proportions. The DerSimmonian-Laird estimator was used as our between-study variance estimator, and random-effects models were employed due to anticipated clinical heterogeneity. Results were then presented in forest plots, with outcomes reported as proportions with 95% confidence intervals (95% CI).

Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistic. In Cochran's Q test, significant heterogeneity of intervention was represented by p value <0.1. For I^2 statistics, a value of more than 50% represented substantial statistical heterogeneity. Whenever there was substantial statistical heterogeneity, we evaluated for outliers by performing a set of case deletion diagnostics to identify influential studies and subsequent leave-one-out sensitivity analyses.

To account for possible moderators that might contribute to statistical heterogeneity, univariate meta-regression (via mixed-effects models) and subgroup analyses were performed for outcomes with high statistical heterogeneity and sufficient data points. For subgroup analysis, studies were first categorised according to their publication date, with the year 1993 chosen as the point of comparison. 3rd generation ICDs were released that year with vastly improved functionalities which were expected to have a major impact on reducing cardiac arrest occurrence.[19] Studies were also sorted according to their follow up periods with cut-offs at 24 and 48 months used to form 3 subgroups. Meta-regression was performed to establish the relationship between demographic (age, male gender, follow-up time) and clinical covariates (history of coronary artery disease and heart failure at baseline, left ventricular ejection fraction at baseline, index SCA associated with acute myocardial infarction, initial shockable rhythm, inducible rhythm at electrophysiological testing) with the primary outcome of first recurrent SCA incidence.

Lastly, publication bias was evaluated via visual evaluation of funnel plots and Egger's regression for outcomes with at least 10 data points.

Notable differences from PROSPERO-registered methodology

Following article selection, a few changes were made to the methodology. Several studies reported on patients with recurrent VF or VT events that were completely resolved by an ICD and did not progress further to cardiac arrest. The exclusion criteria was thus updated to preclude such studies from meta-analysis. It was originally planned for survival outcomes, such as time-to-event data, to be analysed. However, few papers reported it and hence it was not investigated. For the same reason, other complications arising from recurrent SCA were not analysed.

Results

Characteristics of included studies and baseline clinical data

3143 studies were identified from the database search, comprising 1943 unique studies after 1200 duplicates were removed. 1831 studies were excluded following the title and abstract screen leaving 112 articles for full text evaluation. Ultimately, 35 studies were included for analysis.[7,8,20–52] A single additional article was identified from the reference lists of relevant articles and included for evaluation, but was subsequently excluded following full text review. The PRISMA flow diagram (Fig. 1) details the study selection process and reasons for exclusion of 78 articles.

The 35 articles comprised 34 cohort studies and a single RCT. They originated from the following countries: Australia (n = 1), South Korea (n = 1), Spain (n = 1), Sweden (n = 1), France (n = 2), Netherlands (n = 2) and the United States of America (n = 27). In total, there were 15,380 patients with an index SCA, of which 7186 survivors were included for analysis of the primary outcome. The mean age ranged from 26.43 years to 66 years while the average follow-up period ranged from 14.9 months to 15 years. Clinical management was guided by the patient's underlying pathology and outcome of electro-physiological testing. Most of these interventions would be considered conventional and in line with existing guidelines at the time of publication.

All observational studies achieved a moderate- or high-quality score of between 6 and 9 on the Newcastle-Ottawa Quality Assessment Form. Key study characteristics, quality assessments, patient demographics, and clinical variables of the patient population are detailed in Table 1.

Incidence of SCA recurrence

Analysis of the proportion of SCA survivors experiencing a first recurrence revealed a pooled incidence of 15.24% (32 studies; 95% CI, 11.01–19.95; Fig. 2) within a mean follow up time of 41.3 ± 29.3 months from index SCA. The pooled incidence of second recurrence among survivors of a first recurrence was estimated to be 35.03% (3 studies; 95% CI, 19.65–51.93; Fig. 3) within a mean follow up time of 161.1 ± 54.3 months from index SCA. The cumulative incidence of first recurrence among survivors at the 1-year timepoint was calculated to be 10.62% (3 studies; 95% CI, 0.25–30.42; Fig. 4). Sager et al. reported the incidence of recurrent SCA at the 3-year timepoint to be 55%,[9] Kudenchuk et al reported the incidence at the 5 year timepoint to be 16.279%,[38] while Nehme et al reported the incidence at the 5 year and 10 year timepoint to be 6.0% and 8.4% respectively.[49] Pooled analysis of the incidence of first SCA recurrence at the 3-year, 5-year, 10-year, and other fixed long term timepoints was not possible due to an insufficient number of studies. All meta-analysis results are reported in Table 2.

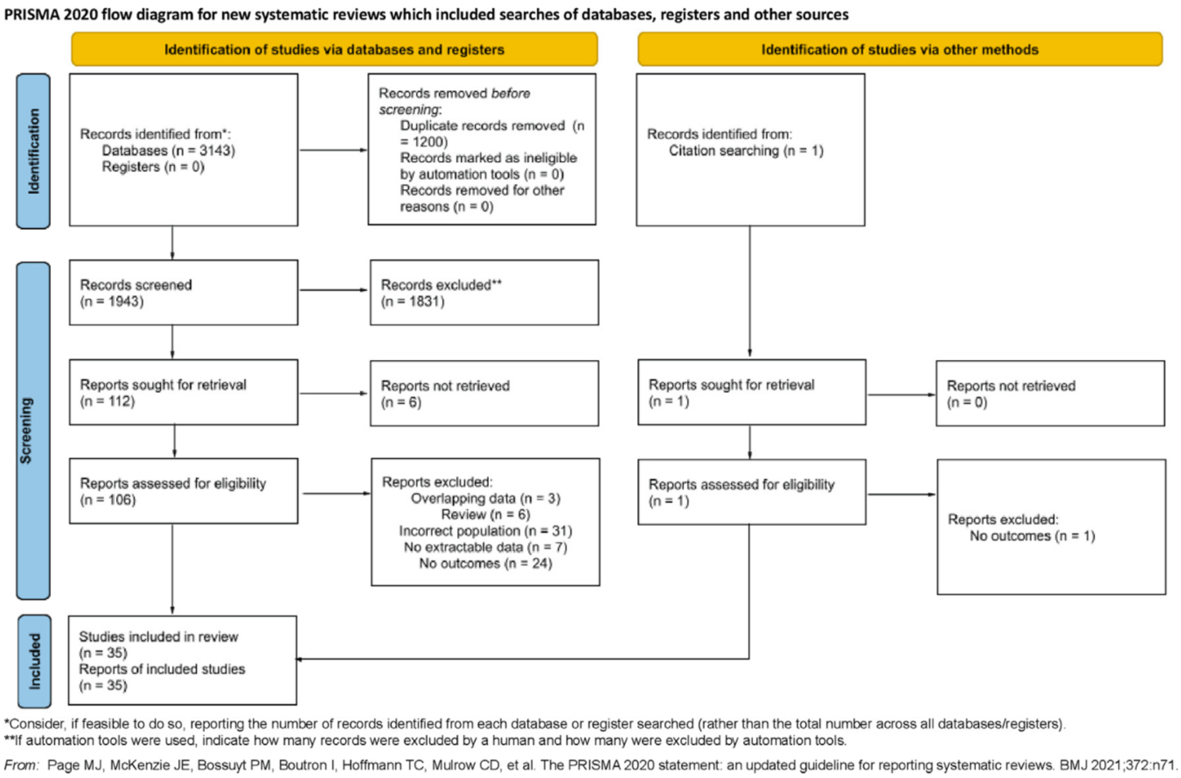

Fig. 1 – PRISMA flow diagram.

Subgroup analyses

The pooled incidence of first recurrent SCA for studies published between 1975–1992 and 1993–2021 was 17.09% (22 studies; 95% CI, 12.47–22.19) and 12.76% (10 studies; 95% CI, 7.50–19.04) respectively with no significant difference between subgroups (p = 0.204; Fig. 5). The pooled incidence of first SCA recurrence for studies with a mean follow-up time of <24 months was 12.92% (10 studies; 95% CI, 5.50–22.40), for studies with a mean follow-up time of 24–48 months was 16.40% (8 studies; 95% CI, 7.65– 27.25), and for the remaining studies with a mean follow-up time of >48 months was 17.11% (8 studies; 95% CI, 8.58–27.59) with no significant difference between subgroups (p = 0.824, Fig. 6).

Meta-regression

On meta-regression, only the proportion of shockable rhythm in the study population was found to have a significant effect on the incidence of recurrent SCA (b, 1.16; 95% CI, 0.231 to 2.09; p = 0.014). Further analyses found no significant effect for the moderators of age, male gender, mean follow-up time, association with acute myocardial infarction, history of coronary artery disease or heart failure at baseline, inducible rhythm at electrophysiological testing and left ventricular ejection fraction on the incidence of recurrent SCA. The regression data is reported in Table 3.

Sensitivity analysis

On leave-one-out analysis, the revised estimates were as follows: proportion of first SCA recurrence after excluding Caro et al was 16.04% (95% CI 11.67–20.89; $I^2 = 94\%$) while the proportion of SCA recurrence at 1-year timepoint after excluding Sager et al and Nehme et al was 4.41% (95% CI 0.02–13.76; $I^2 = 80\%$) and 18.27% (95% CI 2.24–43.10; $I^2 = 79\%$) respectively.[9,49,50] Using a threshold of 10% change in magnitude, there was no material change in magnitude for the outcomes of incidence of first recurrence and proportion of recurrence at 1-year. Leave-one-out analysis results are shown in Figs. S1–S5, while Baujat plots are shown in Figs. S6 and S7.

Publication bias

The funnel plot generated for the most reported primary outcome on incidence of first OHCA recurrence was visually symmetrical in appearance (Fig. S8). Coupled with the non-significant Egger's regression test ($p = 0.1636$; Table S1), this suggests the absence of publication bias.

Discussion

This systematic review and meta-analysis revealed several important findings. We found that 15.24% of SCA survivors experienced a recurrence after a pooled mean follow up time of 41.3 ± 29.3 months. Among the survivors of first SCA recurrence, 35.03% experienced a second recurrence after a pooled mean follow up time of 161.078 ± 54.341 months after index SCA. Most recurrences occurred in the first year, and initial shockable rhythm increased this risk. To the best of our knowledge, this is the first and only systematic review on this topic.

The long-term survivorship of SCA survivors is of increasing scientific and public health interest.[5,6] Among the multiple dimensions of survivorship, including return to work, health related quality of life and survival duration,[4,53] a facet that is highly relevant to patients, their caregivers as well as clinicians is that of recurrence. Understanding the probability of recurrence and its risk factors is important for optimisation of post-cardiac arrest care and surveillance, yet it remains poorly studied. Our current study synthesises the available literature and provides useful insights.

Firstly, we confirmed the conventional wisdom (but one without clear evidence) that SCA survivors are at an increased risk of SCA compared to the general population, as well as provided estimates of this risk. In contrast to the general population, which has an incidence of SCA that is much lower at 55 cases per 100,000 population (0.055%) in 1 year,[3] the pooled incidence of 15.24% over 3.5 years found in our study represents a markedly increased risk. This presents a tremendous opportunity for interventions to reduce the risk of SCA amongst these high-risk patients. In addition, regression analysis showed that recurrence is significantly more common amongst patients who sustained an index SCA with initial shockable rhythm. These highlight the potentially crucial role of routine electrophysiological testing for SCA survivors in risk stratification as well as identifying appropriate therapeutic interventions such as antiarrhythmic drugs, catheter ablation and device implantation to manage their elevated risks of SCA recurrence. The scientific community must learn how to better utilise these tools to manage the risk of recurrence amongst SCA survivors. In the meantime, it is imperative to equip these patients with the best chances of surviving the next SCA through careful education of patients and their household members, including on bystander cardiopulmonary resuscitation and automated external defibrillation. Finally, these estimates allow clinicians to appropriately counsel patients on their risk based on evidence.

The second major finding was that the 1-year pooled cumulative incidence was 10.62%. Given that the pooled incidence of recurrence was 15.24% over 3.5 years of follow up, it follows that up to two-thirds of recurrent events occurred in the first year. This finding corroborates the results from the Melbourne cohort study which found that the greatest risk of death after surviving SCA occurred in the first year (Standardized Mortality Ratio of 5.6), before declining rapidly in the second year onwards.[54] This supports early intensive follow-up efforts following the index SCA for the best chances of improving the long-term prognosis of the patient.

Table 1 – Study Details, Baseline Demographic and Clinical Characteristics.								
Author	Year	Country	Study Design	No. of patients[¶]	Age (years), Mean (SD)	Male gender (%)	Follow-up length	Quality Assessment[*,#]
Cobb et al.[20]	1975	USA	Cohort study	234	59.8	78	Mean: 437 days	7
Schaffer et al.[21]	1975	USA	Cohort study	234	–	–	Mean: 71 weeks	7
Weaver et al.[22]	1976	USA	Cohort study	64	55 (8)	–	Mean: 20.4 months	7
Ritchie et al.[23]	1979	USA	Cohort study	11	64.1 (10.8)	73	Range: 5–21 months	6
Weaver et al.[24]	1982	USA	Cohort study	144	61.1 (10.3)	81.25	Mean: 31.7 months (SD: 16.2 months)	7
Morady et al.[25]	1983	USA	Cohort study	45	56 (16)	86.67	Mean: 18 months (SD: 12 months)	7
Ruskin et al.[26]	1983	USA	Cohort study	73	–	–	Mean: 22 months	6
Ruskin et al.[27]	1983	USA	Cohort study	6	60.2 (11.8)	66.67	Mean: 32 months	6
Morady et al.[28]	1984	USA	Cohort study	19	59.3 (12.22)	84.21	Mean: 23.9 months (SD: 15.2 months)	6
Chadda et al.[29]	1986	USA	Cohort study	47	62.7 (13.3)	74.47	Mean: 14.9 months (SD: 8.1 months)	6
Hallstrom et al.[30]	1986	USA	Cohort study	310	56	80	Mean: 47.5 months	9
Jakobsson et al.[31]	1987	Sweden	Cohort study	11	65 (14)	81.82	Mean: 6 months	7
McLaran et al.[32]	1987	USA	Cohort study	59	52 (17.0)	61.02	–	8
Bhandari et al.[33]	1988	USA	Cohort study	9	43 (15)	33.33	Mean: 20.4 months (SD: 11.4 months)	6
Milner et al.[34]	1988	USA	Cohort study	10	55.2 (13.7)	50	Mean: 16.1 months (SD: 8.6 months)	6
Wilber et al.[8]	1988	USA	Cohort study	166	56 (14)	77.16	Mean: 32.8 months (SD: 14.5 months)	9
Furukawa et al.[7]	1989	USA	Cohort study	101	66 (10)	83.17	Mean: 27 months (SD: 17 months)	8
Hays et al.[35]	1989	USA	Cohort study	6	48.5 (19.5)	50	Mean: 40 months (SD: 9.7 months)	6
Poole et al.[36]	1990	USA	Cohort study	205	–	–	Mean: 30 months (SD: 15 months)	8
Sager et al.[37]	1990	USA	Cohort study	26	54 (13)	46.20	Mean: 16 months	7
Kudenchuk et al.[38]	1991	USA	Cohort study	43	47 (13)	76.70	Mean: 86 months (SD: 54 months)	8
Every et al.[39]	1992	USA	Cohort study	265	60.5 (10.5)	85.66	Mean: 4.9 years (SD: 3.7 years)	9
CASCADE investigators[40]	1993	USA	RCT	228	62 (10)	89	Mean: 6 years	8
Crandall et al.[41]	1993	USA	Cohort study	95	59 (11)	76	–	8
Powell et al.[42]	1993	USA	Cohort study	181	57 (14.0)	78	Mean: 49.2 months (SD: 39.1 months)	8
Remme et al.[43]	2001	Netherlands	Cohort study	14	26.4 (11.4)	71.43	Mean: 77 months (SD: 41 months)	7
Meune et al.[44]	2003	France	Cohort study	10	–	–	Mean: 55 months (SD: 27 months)	6
Borger et al.[45]	2004	Netherlands	Cohort study	116	–	–	Mean: 30 months (SD: 20 months)	6
Havmoeller et al.[46]	2012	USA	Cohort study	–[†]	–	–	–	6
Madhavan et al.[47]	2012	USA	Cohort study	68	64 (11)	82	Mean: 4.4 years (SD: 4.8 years)	8
Lee et al.[48]	2017	Korea	Cohort	74	51.5 (9.9)	70.27	Median: 3.9 years	8

Table 1 (continued)								
Author	Year	Country	Study Design	No. of patients[¶]	Age (years), Mean (SD)	Male gender (%)	Follow-up length	Quality Assessment[*,#]
			study					
Nehme *et al.*[49]	2017	Australia	Cohort study	3581	62.5 (3.7)	75.30	Mean: 15 years	8
Caro *et al.*[50]	2019	Spain	Cohort study	201	57.6 (14.2)	83.60	Median: 40.3 months	6
Conte *et al.*[51]	2019	International	Cohort study	19	–	–	Median: 63 months (IQR: 25–110 months)	8
Held *et al.*[52]	2021	USA	Cohort study	711	–	–	–	7

IQR, interquartile range; RCT, randomised controlled trial; SD, standard deviation.

– Data not available.

* Newcastle-Ottawa Scale (NOS) for non-randomized cohort and case-control studies in meta-analysis (0–3: high risk of bias; 4–6: moderate risk of bias; 7–9: low risk of bias).

National Heart, Lung and Blood Institute (NHLBI) scale for reporting randomised control trials (0: very poor – 5: rigorous).

¶ Includes only the patient population from which usable data was extracted. This comprises of patients who survived to discharge and were followed up for recurrent sudden cardiac arrest.

† Number of survivors to discharge after index sudden cardiac arrest event was not reported.

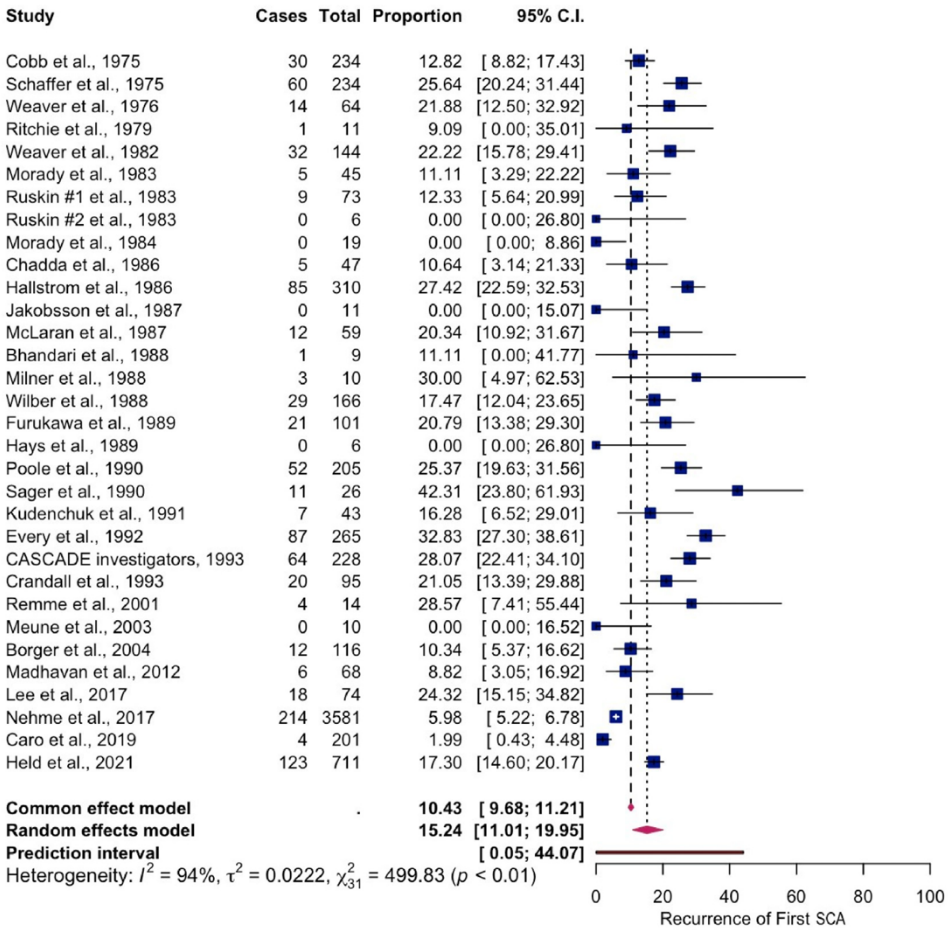

Fig. 2 – Forest plot for unadjusted meta-analyses of the incidence of first recurrent SCA among survivors to hospital discharge of an initial SCA event.

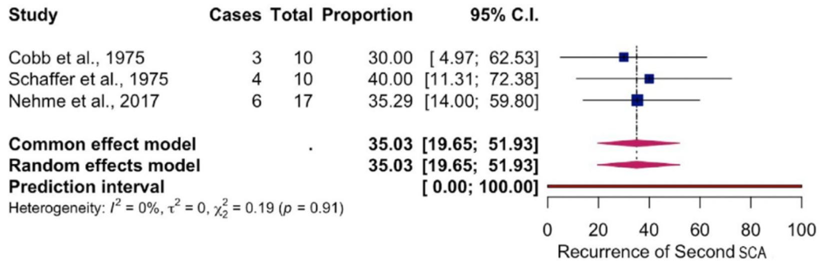

Fig. 3 – Forest plot for unadjusted meta-analyses of the incidence of second recurrent SCA among survivors to discharge of a first SCA recurrence.

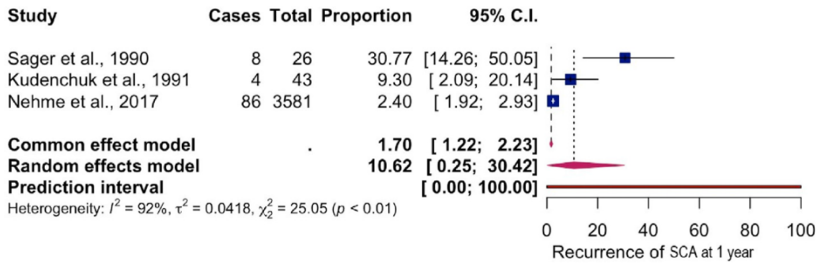

Fig. 4 – Forest plot for unadjusted meta-analyses of the incidence of first recurrent SCA at 1-year timepoint.

Table 2 – Summary of Meta-analysis Results.

Outcome	Studies	Total	Cases	Proportion (95% CI)	*p* value	I^2, %
First SCA recurrence among survivors to discharge of an initial SCA event						
Overall	32	7,186	929	15.24 (CI: 11.01–19.95)	<0.01*	94
Subgroup analysis (Publication year)	32	7,186	929		0.204†	
1975–1992	22	2088	464	17.09 (CI: 12.47–22.19)	<0.01*	74
1993–2021	10	5098	465	12.76 (CI: 7.50–19.04)	<0.01*	95
Subgroup analysis (Mean follow-up)	26	6,035	751		0.824†	
Follow-up < 24 months	10	538	78	12.92 (CI: 5.50–22.40)	<0.01*	65
Follow-up 24–48 months	8	1054	231	16.40 (CI: 7.65–27.25)	<0.01*	71
Follow-up > 48 months	8	4443	442	17.11 (CI: 8.58–27.59)	<0.01*	97
Second SCA recurrence among survivors to discharge of a first SCA recurrence						
Overall	3	37	13	35.03 (CI: 19.65–51.93)	0.91	0
SCA recurrence at 1 year						
Overall	3	3650	98	10.62 (CI: 0.25–30.42)	<0.01*	92

CI, confidence interval; SCA, sudden cardiac arrest.

* $P < 0.05$.

† Test of subgroup differences.

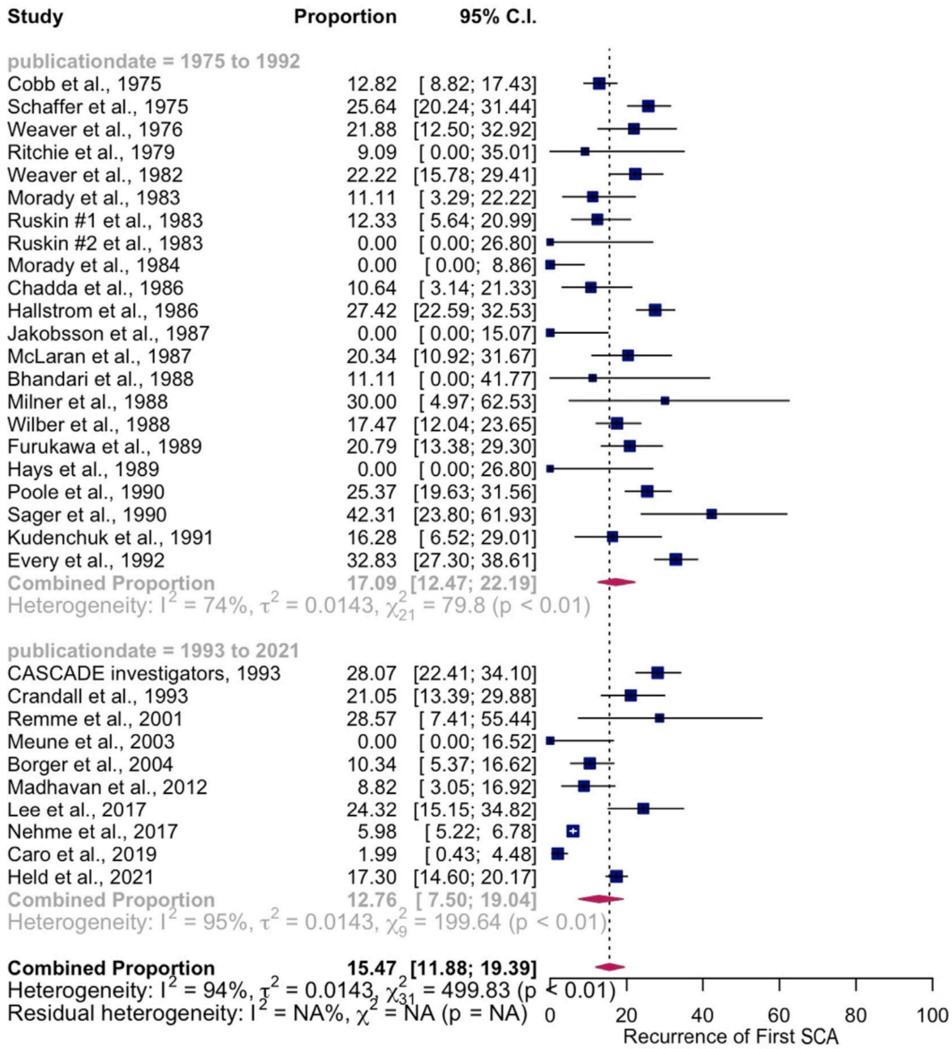

Fig. 5 – Subgroup analysis for the outcome of first recurrent SCA incidence based on date of publication, with 1993 chosen as the comparison year.

Lastly, meta-regression showed that an initial shockable rhythm increases the risk of SCA recurrence. This is an interesting revelation considering that initial shockable rhythm has usually been strongly associated with improved outcomes both in the short and long term.[4,55] This suggests that the relatively good prognosis of shockable relative to non-shockable SCA should not be a reason for complacency, but rather, taken as an impetus to search for and treat a modifiable cause of arrhythmia. A subset of shockable rhythms has been linked with structural cardiac pathologies,[56] which are often progressive and chronic with high rates of SCA as a complication if left untreated.[57] Therefore, survivors of SCA presenting with initial shockable rhythms may benefit from close follow up with early diagnosis and treatment of structural heart diseases, such as with the use of ICDs. This is in keeping with current cardiac arrest guidelines that recommend implantation of ICDs for secondary long-term prevention of sudden cardiac death in patients with structural heart problems such as ischemic heart disease and non-ischemic cardiomyopathy.[58].

To verify and reinforce the findings in this study, we recommend that more high-quality cohort studies with a primary focus on SCA recurrence utilising a probability-based sampling approach be conducted. In these studies, investigators should consider reporting the incidence of SCA recurrence at fixed timepoints.

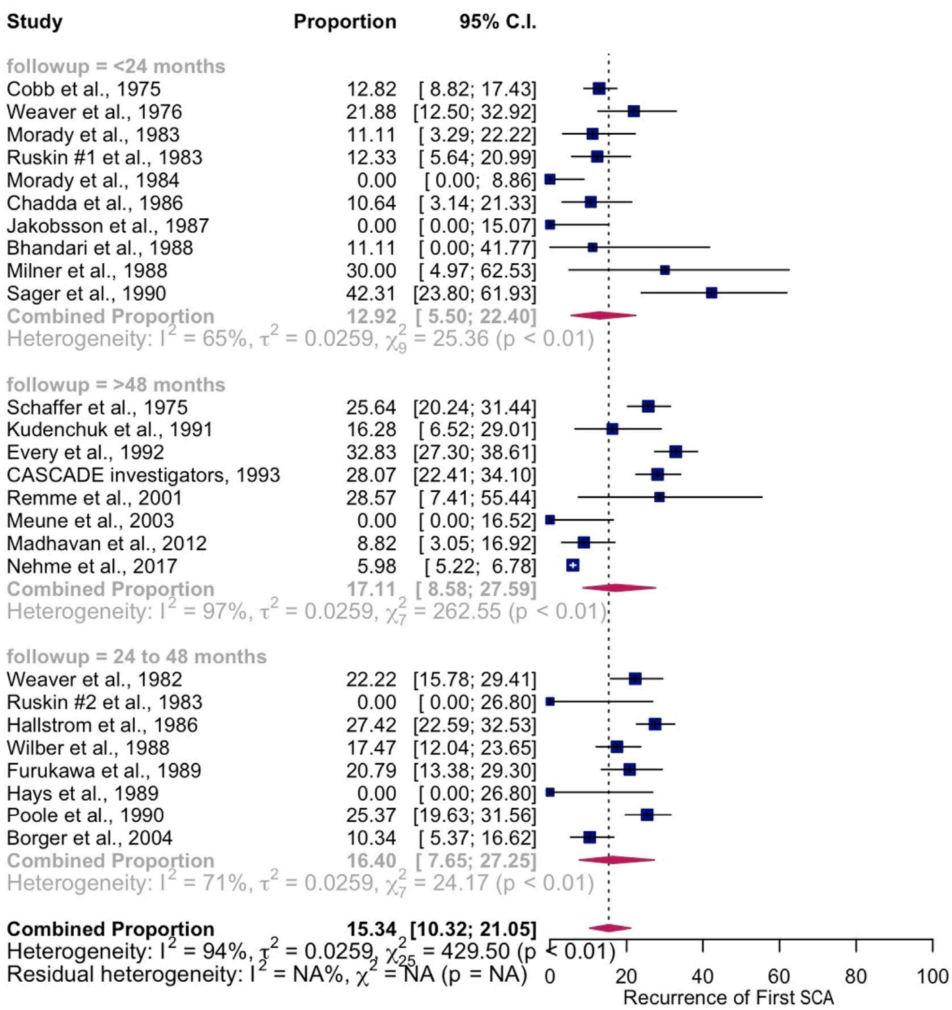

Fig. 6 – Subgroup analysis for the outcome of first recurrent SCA incidence based on length of follow up time (≤24 months, 24–48 months, ≥48 months).

Table 3 – Summary of Meta-Regression Analyses for SCA Recurrence according to Demographic and Clinical Factors.

Outcome	Factor	No. of papers	Coefficient (β)	CI	SE	*P* value
SCA first recurrence	Age	26	−0.0053	−0.0145 to 0.0039	0.0047	0.260
	Male gender	25	−0.2455	−0.8291 to 0.3381	0.2978	0.410
	Mean follow-up	26	−0.0004	−0.0018 to 0.0010	0.0007	0.616
	Index SCA associated with acute myocardial infarction	18	−0.1007	−0.3154 to 0.1141	0.1096	0.358
	Hx of coronary artery disease at baseline	13	0.0353	−0.2992 to 0.3698	0.1707	0.836
	Hx of heart failure at baseline	14	0.4461	−0.1179 to 1.0101	0.2878	0.121
	Left ventricular ejection fraction	15	−0.2672	−1.2852 to 0.7508	0.5194	0.607
	Initial shockable rhythm	17	1.1586	0.2308–2.0865	0.4734	0.014*
	Inducible rhythm at EPS/PVS testing	14	−0.0090	−0.2141 to 0.1961	0.1046	0.932

CI, confidence interval; EPS, electrophysiological; Hx, history; SCA, sudden cardiac arrest; PVS, programmed ventricular stimulation; SE, standard error.
* $P < 0.05$.

Strengths and limitations

To the best of our knowledge, this is the first systematic review conducted to estimate the risk of SCA recurrence. The analysis included a sizable sample of 35 studies, and our results were invariant to sensitivity and leave one out analyses.

Several limitations in our study were identified. First, differences in baseline demographic and clinical variables between study populations contributed to significant heterogeneity across studies. They include regional variability in demographics and culture, disparities in socioeconomic status, healthcare access and quality of care. These differences are likely to exist even between different regions within the same country, for example in the USA,[59] where the majority of our included studies took place. Furthermore, there was marked variation in follow up lengths and a lack of standardised reporting at fixed time-points in most studies. A few studies also restricted their study population to those with specific aetiologies or cardiac conditions, such as focusing only on patients with coronary artery disease.[22–24,32] Despite this, the aforementioned sensitivity and leave one out analysis failed to find any major outliers that could account for most of the heterogeneity. Additionally, outcomes on incidence of second SCA recurrence and first SCA recurrence at the 1-year timepoint were not commonly reported, with only 3 studies reporting each. The lack of statistical power resulted in relatively imprecise estimates (wide confidence intervals). Finally, North America was heavily represented in the included studies, limiting the generalizability to other regions of the world. This is particularly true for South American which was not presented at all, and Asia which only produced one study.

Conclusion

15.24% of SCA survivors experienced a recurrence, and of these, 35.03% experienced a second recurrence. Most recurrences occurred in the first year. Initial shockable rhythm increased this risk. These findings describe the natural progression of SCA survivors and guide intervention and follow-up of SCA survivors.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/coi_disclosure.pdf and declare: MEHO reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices and an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices. JTG reports travel cost reimbursement from ZOLL, Corpuls, BARD and Fresenius. AFWH was supported by the Estate of Tan Sri Khoo Teck Puat (Khoo Clinical Scholars Programme), Khoo Pilot Award (KP/2019/0034), Duke-NUS Medical School and National Medical Research Council (NMRC/CS_Seedfd/012/2018). The funders had no influence on the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT authorship contribution statement

Timothy Jia Rong Lam: Data curation, Methodology, Writing – original draft. Jacqueline Yang: Data curation, Writing – original draft. Jane Elizabeth Poh: Data curation, Writing – original draft. Marcus Eng Hock Ong: Writing - review & editing. Nan Liu: Formal analysis. Jun Wei Yeo: Conceptualisation, Supervision, Writing - review & editing. Jan-Thorsten Gräsner: Writing - review & editing. Yoshio Masuda: Formal analysis, Writing – original draft. Andrew Fu Wah Ho: Conceptualisation, Formal analysis, Supervision, Writing - review & editing.

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Data sharing

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval and patient consent

Ethical approval and patient consent for this systematic review and meta-analysis was not required.

Dissemination to participants and related patient and public communities

Results will be disseminated through social media platforms such as LinkedIn and featured at international conferences such as EMS Scotland.

Author contributions

JWY and AFWH conceived and designed the project. TJRL, JY and JEP selected the studies and acquired the data under supervision from JWY and AFWH. Interpretation of data was done by AFWH, YM and NL. TJRL, JY, JEP and YM drafted the article which was critically revised by AFWH, JWY, JTG and MEHO. The final manuscript was approved by all authors. TJRL and AFWH are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Systematic Review Registration

PROSPERO CRD42022291894.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi. org/10.1016/j.resuscitation.2022.04.027.

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Chapter 6

Health impacts of the Southeast Asian haze problem - A time-stratified case crossover study of the relationship between ambient air pollution and sudden cardiac deaths in Singapore

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Abstract

Objectives: To investigate the association between air pollution and out-of-hospital cardiac arrest (OHCA) incidence in Singapore.

Design: A time-stratified case-crossover design study.

Setting: OHCA incidences of all etiology in Singapore.

Participants: 8589 OHCA incidences reported to Pan-Asian Resuscitation Outcomes Study (PAROS) registry in Singapore between 2010 and 2015.

Main outcome measures: A conditional Poisson regression model was applied to daily OHCA incidence that included potential confounders such as daily temperature, rainfall, wind speed, Pollutant Standards Index (PSI) and age. All models were adjusted for over-dispersion, autocorrelation and population at risk. We assessed the relationship with OHCA incidence and PSI in the entire cohort and in predetermined subgroups of demographic and clinical characteristics.

Results: 334 out of 8589 (3.89%) cases survived. Moderate (Risk ratio/RR = 1.1, 95% CI = 1.07–1.15) and unhealthy (RR =1.37, 95% CI = 1.2–1.56) levels of PSI showed significant association with increased OHCA occurrence. Sub-group analysis based on individual demographic and clinical features showed generally significant association between OHCA incidence and moderate/unhealthy PSI, except in age <65, Malay and other ethnicity, traumatic arrests and history of heart disease and diabetes. The association was most pronounced among cases age >65, male, Indian and non-traumatic. Each increment of 30 unit in PSI on the same day and previous 1–5 days was significantly associated with 5.8–8.1% increased risk of OHCA (p <0.001).

Conclusions: We found a transient effect of short-term air pollution on OHCA incidence after adjusting for meteorological indicators and individual characteristics. These finding have public health implications for prevention of OHCA and emergency health services during haze.

What is already known on this subject?

- Impact of air pollution on respiratory morbidities has been well established but the health impact on cardiovascular disease, specifically out-of-hospital cardiac arrest (OHCA), has recently gained recognition.
- Transboundary haze which occurs in Southeast Asia due to forest fires has posed numerous environmental health problem.
- Understanding the relationship between ambient air pollution due to transboundary haze in Southeast Asia and OHCA is of great public health interest.

What this study adds?

- Our study found that exposure to higher Pollutant Standards Index was associated with an increased short-intermediate term risk of having OHCA in Singapore, especially for cases who were over age 65, male, Indian ethnicity, and occurring in inter-monsoon periods.
- This is the first study linking the Southeast Asian haze to cardiovascular outcomes to our knowledge, and these results may have public health implications for the region.

1. Introduction

Transboundary haze in Southeast Asia due to forest fires is a major environmental health problem, exacting a large economic and health toll on the region. Cardiovascular disease (CVD) is the leading cause of death worldwide according to the World Health Organization [1]. Out-of-hospital cardiac arrest (OHCA), or sudden cardiac death, is the most disastrous presentation of cardiovascular disease and imposes heavy burden worldwide in terms of premature death or disability [2]. Understanding the relationship between ambient air pollution and OHCA is of great public health interest.

The impact of air pollution on all-cause mortality is well established [3], and was estimated to have caused three million premature deaths globally in 2012 alone [4]. While health impacts on respiratory morbidity is intuitive and well-understood [5], air pollution as an important determinant of CVD has recently gained recognition. A 2010 update to a scientific statement from the American Heart Association concluded that the evidence for association of particulate matter (PM) exposure was moderate for heart failure and stroke, and inconclusive for arrhythmia and cardiac arrest [6]. Indeed, associations of air pollution with OHCA have been observed in Rome, Italy [7], Victoria, Australia [8] and Indianapolis, Indiana [9] but not in Seattle, Washington [10,11] or Stockholm, Sweden [12]. These mixed findings may reflect different PM composition from different sources or variations in methodology. A 2016 meta-analysis of 20 studies found an overall significant association, with pooled risk ratios of individual pollutants ranging from 1.02 to 1.04 [13].

Singapore is a small, densely populated island city-state situated in the Southeast Asian (SEA) region, and experiences recurrent large-scale transboundary haze caused by industrial scale slash-and-burn agricultural practices in neighboring countries. It is hence susceptible to wide day-to-day fluctuations in ambient air pollutant levels over decades. Singapore also has robust disease surveillance capabilities for conditions such as OHCA. These characteristics make Singapore an optimal natural population laboratory to study short-intermediate term health impacts arising from the SEA haze problem.

The objective of this study is to investigate the association between ambient air pollution and OHCA occurrence using a time-stratified case-crossover design while adjusting for other meteorological parameters such as ambient temperature and rainfall and individual characteristics. It is hypothesized that exposure to increased Pollutant Standards Index (PSI) is associated with increase in number of OHCA cases. Other research questions are whether the effect is highest on same day of exposure or after lagged terms of a few days, and whether the risk is different in various subgroups. Findings may inform public health policies relating to measures to reduce air pollutants as well as those to mitigate their effect on susceptible subgroups of the population.

2. Materials and methods

2.1. Setting

Singapore is an urbanized island city-state situated at the southernmost tip of continental Asia and peninsula Malaysia with a population of 5.5 million over a land area of 719.1 km^2 [14]. Singapore has a gross domestic product of 295.7 billion dollars [15] and a life expectancy of 82.1 years. Singapore has a mixed health-care system [16], where the public healthcare system is funded through a system of compulsory savings, subsidies, and price controls [17]. There are an estimated 2000–2300 OHCA cases in Singapore per year (unpublished internal data from Singapore Civil Defence Force). Survival to hospital discharge rate for OHCA cases in Singapore was around 2–3% between 2010 and 2012 [18]. Singapore is 1.5 degrees north of the equator, with a climate that is classified as tropical rainforest climate (Köppen-Geiger classification system). As a result of its geographical location and maritime exposure, its climate is characterized by uniform temperature and pressure, high humidity, abundant rainfall and no true distinct seasons.

2.2. Southeast Asian haze situation

The SEA haze situation describes a series of large-scale air pollution episodes that occurs regularly, and has been recorded since 1972 [19]. These haze events have caused adverse health and economic impact, notably in Indonesia, Singapore [20] and Malaysia. The haze has been attributed to forest fires due to illegal industrial-scale slash-and-burn agricultural practices in the region, such as from the Indonesian islands of Sumatra and Borneo [21]. Clearing peatlands using fire, while illegal, is attractive to businesses because it is faster and cheaper compared to using machinery [21].

The haze situation exacerbates recurrently in Singapore, usually coinciding with the dry season from July to September, which is also when the southwest monsoon operates, which shifts haze towards

Singapore.

This transboundary haze has been implicated in damages amounting to an estimated of US$ 4.5 billion for the fire episodes in 1997 alone, due to long-term health damage, reduced crop yield, reduced visibility, preventive expenditures, accidents, loss of life, evacuations, and the loss of confidence of foreign investors [22]. Following severe land and forest fires in 1997–1998, member states of the Association of Southeast Asian Nations (ASEAN) signed the ASEAN Agreement on Transboundary Haze Pollution (AATHP) in 2002 to monitor, prevent and mitigate land and forest fires to control transboundary haze pollution through concerted national efforts and international cooperation.

2.3. Study population and outcome data – the Pan-Asian Resuscitation Outcomes Study

We performed a time-stratified case-crossover design on all reported OHCA cases to PAROS registry from 2010 to 2015 (2015 was partial data) in Singapore. The primary outcome variable is the occurrence of an OHCA. National OHCA data was obtained for the whole of Singapore, from the Pan-Asian Resuscitation Outcomes Study (PAROS). PAROS is a prospectively collected, multi-center registry to provide baseline information on OHCA epidemiology, management and outcomes. Data definitions follow the Utstein recommendations [23] and collaboration with the Cardiac Arrest Registry to Enhance Survival (CARES) [24] in the United States enabled the development of a common taxonomy and data dictionary to allow valid comparisons with global data [25]. Data was extracted from emergency dispatch records, ambulance patient case notes, and emergency department (ED) and in-hospital records. We included OHCA of all etiology brought in by EMS or presenting at EDs, as confirmed by the absence of pulse, unresponsiveness and apnea.

2.4. Environmental data

The primary exposure variable was 24-hour average Pollutant Standards Index (PSI). PSI is an air quality index, which is used to indicate the level of pollutants in the air. This was based on a scale devised by the United States Environmental Protection Agency to provide a way for news agencies to report daily air quality. PSI has been used in several countries including the United States, Brunei Darussalam and Singapore. In Singapore, the National Environment Agency (NEA) classifies 24-hour PSI into ranges of good (0–50), moderate (51–100), unhealthy (101−200), very unhealthy (201−300) and hazardous (N300) [26].

PSI is computed based on six air pollutants: fine particulate matter with aerodynamic diameter smaller than 2.5 µm ($PM_{2.5}$), PM_{10}, sulphur dioxide (SO_2), carbon monoxide (CO), ozone (O_3) and nitrogen dioxide (NO_2). For each pollutant, a sub-index is calculated from a segmented linear function that transforms ambient concentrations onto a scale extending from 0 through 500 [27]. PSI is then computed to be the maximum of the six sub-indices. $PM_{2.5}$ is the major pollutant released by forest fires [28], and the World Health Organization guideline level for 24-hour mean $PM_{2.5}$ is 25 $\mu g/m^3$ [4].

In Singapore, ambient pollutant levels are continuously monitored at 22 telemetric air quality monitoring stations across the island [29]. Exposure data were retrieved from local government websites. The data were those that are made publicly available by the government agencies, but required the authors to write a script to aggregate the data in a spreadsheet format. Historical 24-hour PSI data was obtained from www.haze.gov.sg which is maintained by the NEA. Other historical environmental parameters were obtained from www.weather.gov.sg which is maintained by the Meteorological Service Singapore, and included total daily rainfall, daily highest rainfall (over 30-, 60- and 120-minute intervals), daily temperature (mean, maximum, minimum) and daily wind speed (mean, maximum).

2.5. Ethics approval

The Centralised Institutional Review Board and Domain Specific Review Boards granted approval for this study with a waiver of informed consent.

2.6. Statistical analysis

Data entry was performed using a spreadsheet application (Excel 2003, Microsoft Corp., Redmond, WA) and data analysis using Stata version 14 (StataCorp, College Station, TX) [30]. Categorical and continuous data were presented as frequency with percentage and median with interquartile range (IQR), respectively. Statistical significance was set at p b 0.05. In the sub-group analysis, Bonferroni correction was applied to all p values (p = 0.002) for 26 subgroup analyses, which were determined *a priori.*

This study used a time-stratified design to control for time trend and other short-term varying confounders like seasonality since it compares exposure levels between same weekdays within each month of each year [31]. Exposure on days was compared with the control days on which exposure did not occur. Control days were chosen on the same day of the week earlier and later in the same month in the same year. Daily OHCA counts approximately follow Poisson distribution.

We fitted a conditional Poisson regression model to daily OHCA incidence that included potential confounders such as daily temperature, rainfall, wind speed, PSI, age, gender and cause of arrest. Based on NEA's recommended range, PSI was categorized into three categories: good, moderate and unhealthy, with cutoffs previously stated. We assessed the relationship with OHCA incidence and PSI after adjusting for temperature, rainfall, wind speed indicators and individual characteristics. All models were adjusted for over-dispersion, autocorrelation and population at risk.

We also investigated percent excess risk of OHCA associated with 30 unit increase in PSI values on the day of incidence (lag 0 day) and 1 to 5 day before the incidence (lag 1, 2, 3, 4, 5). The results were presented as risk ratio (RR) and 95% confidence interval (CI) for PSI range and percent excess risk in OHCA per 30 unit increase in PSI values using the formula (Risk Ratio − 1) ∗ 100.

2.7. Patient involvement

There were no patients' involvement or interaction during the study period.

3. Results

3.1. Study population

There were 8589 OHCA cases during the study period. There were yearly increases from 1081 cases in 2010, 1376 cases in 2011, 1440 cases in 2012, 1734 cases in 2013, to 2034 cases in 2014. 65.2% were male and the median age was 66 years (IQR 54–78). 97.0% of the cases were non-trauma in etiology and 18.2% had a shockable initial rhythm (pulseless ventricular tachycardia or ventricular fibrillation). The characteristics of included cases are further described in Table 1.

3.2. Description of exposure data

During the study period, mean 24-hour PSI was 36 (standard deviation, SD 15.5) with an interquartile range of 25.5–44.2. The maximum PSI was 197.6.

Mean total daily rainfall was 5.8 mm (SD 13.8) with an interquartile range of 0–4.4 mm. Mean temperature was 27.7 °C (SD 1.1), with an interquartile range of 27–28.6 °C. Mean wind speed was 8.4 km/h (SD 2.7), with an interquartile range of 6.3–10.2 km/h.

3.3. Association of Pollutant Standards Index with occurrence of out-of-hospital cardiac arrest

Fig. 1 shows the distribution of daily OHCA incidence with daily measures of 24-hour PSI (smoothing of data included two lagged terms, two forward terms, and the current observation in the time-series moving average filter).

Table 1
Demographic and clinical characteristics of out-of-hospital cardiac arrest cases.

	N = 8589 (%)
Male gender	5596 (65.15)
Age, median (IQR)	66 (54–78)
Year of occurrence	
2010	1081 (12.59)
2011	1376 (16.02)
2012	1440 (16.77)
2013	1734 (20.19)
2014	2034 (23.68)
2015	924 (10.76)
Cause of arrest	
Trauma	262 (3.05)
Non-trauma	8325 (96.95)
Presumed cardiac etiology	6029 (70.19)
Respiratory etiology	535 (6.23)
Race	
Chinese	5817 (67.73)
Indian	909 (10.58)
Malay	1357 (15.8)
Others	506 (5.89)
Shockable rhythm	1536 (18.21)
Non-shockable rhythm	6901 (81.79)
Witnessed	5084 (59.19)
Not witnessed	3505 (40.81)
History of heart disease	3126 (39.42)
History of diabetes mellitus	2716 (34.25)
History of hypertension	4490 (56.62)
History of hyperlipidemia	2969 (37.44)
History of stroke	1068 (13.47)
History of any medical disease	6870 (86.63)
Survived to hospital admission	1515 (17.64)
ROSC at scene or ED	2797 (32.56)
Survival to hospital discharge or alive at 30 days	334 (3.89)
Favorable neurological status CPC(1/2)	206 (2.4)
Monsoon seasons	
Northeast monsoon season (December to early March)	2604 (30.07)
Inter-monsoon period (late March to May)	2029 (23.43)
Southwest monsoon season (June to September)	2757 (31.84)
Inter-monsoon period (October to November)	1270 (14.67)

IQR, interquartile range; ROSC, return of spontaneous circulation; ED, emergency department; CPC, cerebral performance score.

After adjusting for temperature, rainfall, wind speed and individual characteristics, moderate and unhealthy levels of PSI showed significant association with increased OHCA risk (RR 1.11, 95% CI 1.07–1.15) and (RR 1.37, 95% CI 1.2–1.56) respectively (Table 2).

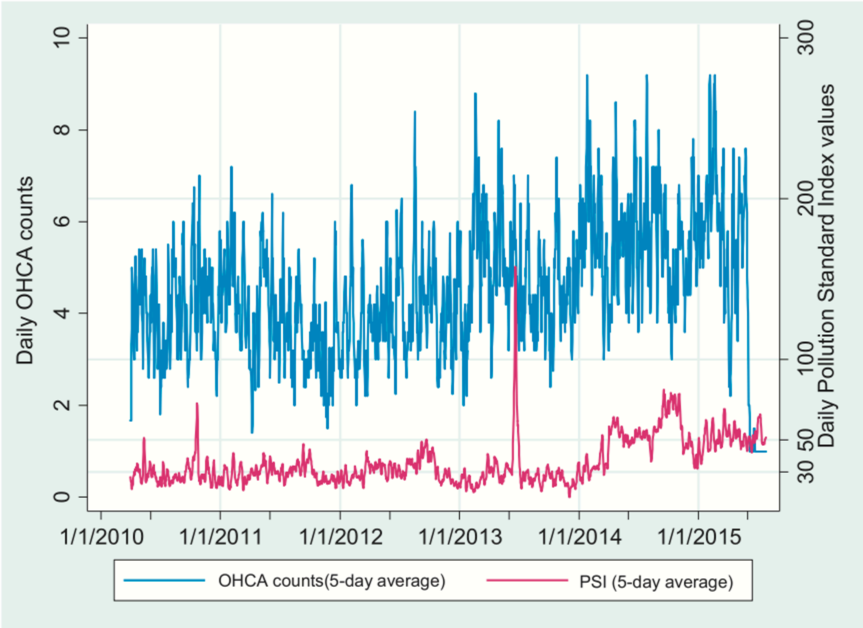

Fig. 1. Distribution of daily OHCA incidence with daily measures of 24-hour Pollutant Standards Index (smoothing of data included two lagged terms, two forward terms, and the current observation in the time-series moving average filter).

3.4. Subgroup analyses

Sub-group analysis based on individual demographic and clinical characteristics and seasons generally showed positive association between OHCA incidence and moderate and unhealthy ranges of PSI (Table 2). The associations were significant for moderate level PSI and OHCA for all subgroups by demographics and clinical features (all $p < 0.002$). The associations were mostly significantly for unhealthy level PSI and OHCA for subgroups by demographics and clinical features except in age b65 (RR 1.29, 95% CI 1.06–1.58, p = 0.012), Malay ethnicity (RR 1.39, 95% CI 1.08–1.8, p = 0.012), “others” ethnicity (RR 1.18, 95% CI 0.77–1.82, p = 0.437), traumatic arrests (RR 1.32, 95% CI 0.65–2.67, p = 0.447), history of heart disease (RR 1.3, 95% CI 1.03–1.63, p = 0.025), history of diabetes mellitus (RR 1.38, 95% CI 1.1–1.74, p = 0.005), history of stroke, non-cardiac etiology and respiratory etiology.

3.5. Excess risk at different lag terms

In addition, after adjusting for temperature, rainfall and wind speed, each 30 unit increment in PSI values on the same day (lag 0) and previous 1 day up until 5 days (Lag 1–5, not cumulative) was significantly associated with increased risk of OHCA incidence (Table 3). The excess risk for same day exposure was 8.15% (95% CI 5.41%–10.96%), and for lag 1–5 were 7.77% (95% CI 5.01%–10.6%), 5.86% (95% CI 3.21%–8.59%), 7.29% (95% CI 4.5%–10.16%), 5.96% (95% CI 3.13%–8.88%), 6.57% (95% CI 3.76%–9.46%) and respectively (all p b 0.001).

4. Discussion

This study reveals that during the study period, exposure to higher PSI was associated with an increased short-intermediate term risk of having OHCA in Singapore. The effect of association was more pronounced on the same day exposure to PSI than previous few days' exposure. This is, to our knowledge, the first study linking the Southeast Asian haze to cardiovascular outcomes.

Table 2
Association between OHCA occurrence and 24-hour Pollutant Standards Index.

PSI range	Good (0–50) n = 6902 (79.7%)	Moderate (51–100) n = 1706 (19.7%)		Unhealthy (101≥) n = 52 (0.6%)	
		RR (95% CI)	p value	RR (95% CI)	p value
Entire cohort	Reference	1.11 (1.07–1.15)	<0.001*	1.37 (1.2–1.56)	<0.001*
Subgroups by demographics					
Age					
Age < 65	Reference	1.14 (1.09–1.19)	<0.001*	1.29 (1.06–1.58)	0.012
Age 65 and above	Reference	1.15 (1.11–1.2)	<0.001*	1.44 (1.22–1.69)	<0.001*
Gender					
Female	Reference	1.13 (1.08–1.19)	<0.001*	1.39 (1.17–1.66)	<0.001*
Male	Reference	1.16 (1.11–1.21)	<0.001*	1.38 (1.15–1.66)	0.001*
Cause of arrest	Reference				
Trauma	Reference	1.18 (1.04–1.33)	0.008	1.32 (0.65–2.67)	0.447
Non-trauma	Reference	1.11 (1.08–1.15)	<0.001*	1.37 (1.2–1.57)	<0.001*
Presumed cardiac etiology					
Yes	Reference	1.14 (1.09–1.18)	<0.001*	1.36 (1.17–1.59)	<0.001*
No	Reference	1.15 (1.1–1.21)	<0.001*	1.36 (1.08–1.7)	0.008
Respiratory etiology					
Yes	Reference	1.23 (1.11–1.35)	<0.001*	0.87 (0.36–2.11)	0.761
No	Reference	1.11 (1.08–1.15)	<0.001*	1.37 (1.2–1.56)	<0.001*
Race	Reference				
Chinese	Reference	1.15 (1.11–1.2)	<0.001*	1.34 (1.15–1.58)	<0.001*
Indian	Reference	1.18 (1.1–1.26)	<0.001*	1.68 (1.25–2.26)	0.001*
Malay	Reference	1.19 (1.12–1.26)	<0.001*	1.39 (1.08–1.8)	0.012
Others	Reference	1.18 (1.07–1.29)	0.001*	1.18 (0.77–1.82)	0.437
Subgroups by clinical features					
History of heart disease					
Yes	Reference	1.15 (1.1–1.21)	<0.001*	1.3 (1.03–1.63)	0.025
No	Reference	1.14 (1.1–1.19)	<0.001*	1.49 (1.27–1.74)	<0.001*
History of diabetes mellitus					
Yes	Reference	1.17 (1.11–1.23)	<0.001*	1.38 (1.1–1.74)	0.005
No	Reference	1.14 (1.1–1.19)	<0.001*	1.44 (1.23–1.7)	<0.001*
History of hypertension					
Yes	Reference	1.14 (1.1–1.19)	<0.001*	1.35 (1.14–1.6)	0.001*
No	Reference	1.16 (1.1–1.21)	<0.001*	1.5 (1.23–1.83)	<0.001*
History of hyperlipidemia					
Yes	Reference	1.15 (1.1–1.21)	<0.001*	1.49 (1.2–1.84)	<0.001*
No	Reference	1.15 (1.1–1.19)	<0.001*	1.38 (1.16–1.63)	<0.001*
History of stroke					
Yes	Reference	1.19 (1.12–1.27)	<0.001*	1.55 (1.16–2.07)	0.003
No	Reference	1.12 (1.08–1.16)	<0.001*	1.38 (1.19–1.6)	<0.001*
History of any medical disease					
Yes	Reference	1.13 (1.09–1.17)	<0.001*	1.37 (1.18–1.59)	<0.001*
No	Reference	1.17 (1.09–1.25)	<0.001*	1.65 (1.27–2.14)	<0.001*
Monsoon seasons					
Northeast Monsoon Season (December-early March)	Reference	1.04 (0.98–1.12)	0.191	NA	
Inter-monsoon Period (Late March–May)	Reference	1.15 (1.08–1.22)	<0.001*	NA	
Southwest Monsoon Season (June–September)	Reference	1.12 (1.05–1.18)	<0.001*	1.1 (0.93–1.31)	0.257
Inter-monsoon Period (October–November)	Reference	1.13 (1.03–1.25)	0.012	2.08 (1.64–2.63)	<0.001*

Adjusted for temperature, rainfall, wind speed, age, gender, cause of arrest.
* p value < α, where α = 0.05 for main comparison of entire cohort, and α = 0.002 for subgroups (each subgroup tested at Bonferroni adjusted α = 0.002).

Table 3
Estimated percent excess risk of out-of-hospital cardiac arrest per 30 unit increment in 24-hour Pollutant Standards Index at different lag terms.

Lag terms, days	% Excess risk (95% CI)[a]	p value
Lag 0	8.15 (5.41–10.96)	<0.001*
Lag 1	7.77 (5.01–10.6)	<0.001*
Lag 2	5.86 (3.21–8.59)	<0.001*
Lag 3	7.29 (4.5–10.16)	<0.001*
Lag 4	5.96 (3.13–8.88)	<0.001*
Lag 5	6.57 (3.76–9.46)	<0.001*

Lag 0, same day exposure; Lag 1 to 5, exposure at 1 to 5 days prior respectively.
[a] Adjusted for temperature, rainfall, wind speed, age, gender, cause of arrest.
* $p < 0.05$.

The finding of a significant association of exposure to air pollution and occurrence of OHCA is consistent with previous studies. A limited number of studies to date have investigated the effect of air pollution on OHCA and fewer still specifically for forest fires. Evidence from the forest fires predominantly origin from Australia [8,32], and in a study of the 2006–2007 Victoria wildfire season, a 4.25 μg/m^3 increase in $PM_{2.5}$ was associated with 3.75% increased risk of OHCA in Melbourne, Australia due to smoke from the forest fires [32].

One finding is that the association between unhealthy PSI and OHCA was not significant in cases where age <65. This could be related to the known phenomenon that cardiac arrest in younger people are often due to non-thrombotic causes (for example, cardiomyopathies, congenital heart defects and hereditary arrhythmogenic conditions) [33], and these etiologies interact diffearently with exposure to air pollution. The lack of significant association in traumatic arrests could similarly be explained by alternative mechanistic etiologies. Unlike at least four studies that found sex-specific observations, specifically that men showed a significantly stronger association between $PM_{2.5}$ and OHCA [32,34–36], our study did not identify such sex-specific susceptibility.

4.1. Strengths and limitations

A strength of this study lies in the high-quality disease data, which is gleaned from a prospective registry. The registry captures cases comprehensively from ambulance and all major general hospitals in Singapore, and is advantageous over studies using only hospital data which likely underestimates incidence as the more severe OHCA cases may have died at scene and not conveyed to the hospital. The registry also provided individual data on demographics and risk factors, allowing us to study susceptible subgroups. Also, we used exposure data that is directly measured by stations in various regions of Singapore, and negates the need to extrapolate via modelling to rural areas with no monitoring facilities which may need to inaccuracy. Also, compared to studies which centered on a single major haze event, such as the severe forest fire southeast of Australia of 2006–2007 [8,32], our study period included a succession of wide fluctuations corresponding to exacerbations of the Southeast Asian haze situation over half a decade. Additionally, conditional Poisson regression model used in this study has accounted for overdispersion and autocorrelation in the counts data and varying population-at-risk over time in the denominator to provide more accurate estimates [31].

With regards to underlying mechanism of this association, this study provides the basis to interrogate the relationship further through bio-marker and radiological studies. Current theories include particulate matter-induced endothelial dysfunction and vasoconstriction, increased mean arterial pressure, coagulation changes, systemic inflammatory and oxidative stress responses, autonomic imbalance and arrhythmias, and the progression of atherosclerosis [37–41]. Our findings of increased susceptibility at the older age group, non-traumatic causes and in particular, no traditional risk factors of heart disease and diabetes mellitus narrows, which are not investigated in many related studies, give insight to mechanistic postulations. That a significant association was found for both respiratory and cardiac etiology subgroups is interesting, as the two groups tend to have different pathophysiological mechanisms, and lends weight to the hypothesis that the role of air pollution in cardiovascular diseases are distinct from that of respiratory diseases.

This study suffers from several limitations. First, this is an ecological study, and while an association between PSI and OHCA was demonstrated, it does not permit conclusions of causation. While several criteria for causation are demonstrated in this study in the form of plausibility, temporality and biological gradient, there are likely to be important risk-modifying factors that we were unable to measure and account for.

Secondly, the study design did not permit controlling for time-variant variables such as behavioral changes related to weather, as people may take differential approaches to mitigation. For example, while the elderly can mitigate the haze by staying at home, those who had to work outdoors during the haze period have no such recourse. Also, those with higher socio-economic status may have access to air-conditioning and respirator masks which may modify their risks to the same exposure.

Thirdly, while Singapore's small land area produces relatively little regional variation in environmental parameters, differences in these parameters at the geographical ends of the island may result in misclassification of exposure category. This study used the average of the several PSI measurement locations to give a daily national average. Further studies could benefit from geospatial techniques to fine-tune the analysis by matching OHCA incident location with the nearest PSI measurement location. Fourthly, PSI (a composite air quality index) was studied instead of the levels of individual pollutants as in other studies due to unavailability of data. This means that we are unable to identify the relative excess risk imposed by each type of pollutant. On the flip side, PSI is an easily recognizable indicator for the public to understand, monitor and interpret. The findings of this study are hence much more easily applied towards health education of the public and to calibrate as public policy. Previous studies have found $PM_{2.5}$ to have the highest excess risk for OHCA [32], while for O_3 the studies were non-conclusive as to the presence of an association. This means that our study may underestimate the effect size, as it can be diluted by the use of a composite index. However, PSI is arguably a better real-world representation of air pollution and studies based on such an index would better inform health policies as each pollutant does not appear in isolation outside of experimental settings.

These results are timely in the context of a particularly bad haze episode in 2015, which was unusually prolonged due to drier conditions caused by the El Nino effect. This episode was considered among the most severe on record [42] and resulted in six Indonesian provinces declaring states of emergency, school closures and sports meets disruptions in Indonesia, Malaysia and Singapore.

Millions of people worldwide are exposed to seasonal high levels of air pollution from forest fires, which is a modifiable risk factor, making it a formidable public health concern. Even though effect estimates of air pollution on diseases may be small, the ubiquitous and involuntary exposure of the entire population greatly magnifies the health burden. In 2014, an estimated 92% of the world's population was living in places where the WHO air pollution guideline levels were not met [4]. Forest fires are predicted to increase in frequency, duration and severity owing to climate changes [43–46]. There is a need for epidemiologic studies to understand the health impact of forest fires, as a distinct source of pollutants with distinct composition and other characteristics.

The first public health implication from these results is that this study adds a Southeast Asian context to the large body of evidence on the general and specific health hazards of exposure of air pollutants, which as a whole, presents a compelling argument for concerted national efforts and intensified international cooperation to develop sustainable programs to tackle the haze problem. Also, the ability to quantify the impact helps policy makers to decide on the resourcing that should be devoted to mitigate this problem.

Further, the data aids in the formulation of health policy to mitigate health effects from exposure to air pollution at various levels. Interventions in this area include health advisories from the government agencies, city planning and building design from the urban development perspective, emergency medical resources deployment, public face-mask distribution programs as well as training policies for schools and military training institutes. Just as important as it is to target people with chronic respiratory conditions like asthma, people with known or risk factors of cardiovascular diseases should also be a primary target for preventive intervention. In our study, we have identified that the association was most pronounced among cases who were over age 65, male, Indian ethnicity, and occurring in inter-monsoon periods. This provides an action point for health policies.

5. Conclusion

During the study period, exposure to higher PSI was associated with an increased short-intermediate term risk of having OHCA in Singapore. This is, to our knowledge, the first study linking the Southeast Asian haze to cardiovascular outcomes. These results may have public health implications for the region.

Competing interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. A/Prof Ong has licensing agreement and patent filing (Application no: 13/047,348) pending with ZOLL Medical Corporation for a study titled 'Method of predicting acute cardiopulmonary events and survivability of a patient'.

All other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Singapore PAROS Investigators

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Chapter 7

Air quality and the risk of out-of-hospital cardiac arrest in Singapore (PAROS): a time series analysis

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Summary

Background Previous studies have reported positive associations between out-of-hospital cardiac arrest (OHCA) and air pollutant concentrations, but there are inconsistencies across studies. We aimed to investigate the association between pollutant concentrations and the risk of OHCA in Singapore.

Methods We did a time series analysis of all cases of OHCA in Singapore reported between July 1, 2010, and Dec 31, 2018, to the Pan-Asian Resuscitation Outcomes Study (PAROS), a prospective, population-based registry. Using multivariable fractional polynomial modelling, we investigated the immediate (day 0) and lagged (up to 5 days after exposure) association between 10 μg/m³ increases in concentrations of particulate matter with a diameter of 2·5 μm or smaller (PM2·5), particulate matter with a diameter of 10 μm or smaller (PM10), ozone (O3), nitrogen dioxide (NO2), and sulphur dioxide (SO2) and 1 mg/m³ increase in carbon monoxide (CO) and relative risk (RR) of OHCA.

Findings We extracted data for 18 131 cases of OHCA. The median age of this cohort of cases was 65 years (IQR 56–80), 6484 (35·8%) were female, 11 647 (64·2%) were male, 12 270 (67·7%) were Chinese, 2873 (15·8%) were Malay, and 2010 (11·1%) were Indian. Every 10 μg/m³ increase in PM2·5 was associated with increased risk of OHCA (RR 1·022 [95% 1·002–1·043]) over the next 2 days, which decreased over the subsequent 3 days (3–5 days after exposure; 0·976 [0·955–0·998]). For PM10, O3, NO2, and SO2, we did not observe any associations between increased concentration and risk of OHCA on day 0 or cumulative risk over time (ie, at 0–1 days, 0–2 days, 0–3 days, 0–4 days, 0–5 days, and 3–5 days after exposure). For CO, we observed a cumulative decreased risk of OHCA across 0–5 days after exposure (0·876 [0·770–0·997]) and at days 3–5 after exposure (0·810 [0·690–0·949]). We observed effect modification of the association between increasing PM2·5 concentration and OHCA 0–2 days after exposure by cardiac arrest rhythm (non-shockable 1·027 [1·004–1·050] vs shockable 1·002 [0·956–1·051]) and location of OHCA (at home: 1·033 [1·008–1·057] vs not at home 0·955 [0·957–1·035]). In hypothetical modelling, the number of OHCA events associated with PM2·5 could be reduced by 8% with a 1 μg/m³ decrease in PM2·5 concentrations and by 30% with a 3 μg/m³ decrease in PM2·5 concentrations.

Interpretation Increases in PM2·5 concentration were associated with an initial increased risk of OHCA and a subsequent reduced risk from 3–5 days after exposure, suggesting a short-term harvesting effect. A decrease in PM2·5 concentrations could reduce population demand for emergency health services.

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Research in context

Evidence before this study

Epidemiological studies have found that increasing air pollution might be associated with increased risk of out-of-hospital cardiac arrest (OHCA), with strongest evidence for particulate matter with a diameter of 2·5 μm or smaller ($PM_{2·5}$) concentrations. We searched PubMed and Google Scholar for articles published from database inception up to Oct 21, 2021, using the keywords and medical subject heading terms "air pollution", "air pollutant", "cardiac arrest", "OHCA", and "out of hospital cardiac arrest". We identified 45 studies, which included population-based cohorts and meta-analyses.

We found that the results on the association of air pollutants and OHCA were inconsistent, especially at concentration levels below the WHO air quality guideline values. Studies were often limited by the sample size and quality of clinical, meteorological, and air quality data available.

Added value of the study

To our knowledge, this is the first time series analysis of high-quality data from the Pan-Asian Resuscitation Outcomes Study (a prospective, population-based registry that captures data from ambulance services and hospitals) and robust air quality surveillance data from the National Environment Agency Singapore. We observed a potential harvesting effect associated with $PM_{2·5}$, with an initial increase in risk of OHCA and subsequent reduced risk with increases in $PM_{2·5}$ concentration over the 5 days after initial exposure. Using hypothetical scenarios, we estimated that the number of

OHCA events associated with $PM_{2.5}$ could be reduced by 8% with a 1 μg/m³ decrease and by 30% with a 3 μg/m³ decrease in $PM_{2.5}$ concentrations, which would reduce levels to below the WHO air quality guideline values.

Implications of all the available evidence

Air pollutants, such as $PM_{2.5}$, are significantly associated with OHCA events, possibly by triggering events in susceptible individuals. Public health strategies to reduce $PM_{2.5}$ concentrations might lead to a decrease in the population burden of cardiac arrests that occur out of hospital and reduce the demand for $PM_{2.5}$-attributable emergency health services.

Introduction

Out-of-hospital cardiac arrest (OHCA) is the most severe presentation of cardiovascular diseases, with an incidence of 84 cases per 100 000 persons-years and a survival rate of less than 10%.[1] Because of the considerable disease burden of OHCA, understanding and reducing the contributors to cardiovascular diseases and OHCA is important. Air pollution is one of the major modifiable causes of disease, accounting for approximately 4·2 million all-age all-cause deaths in 2015 globally.[2] One of the most studied air pollutants is particulate matter (PM), including those with a median aerodynamic diameter of 2·5 μm or less ($PM_{2.5}$) and of 10 μm or less (PM_{10}). Exposure to $PM_{2.5}$ is a major recognised cardiovascular risk factor, such that the Lancet Commission on Pollution and Health highlighted air quality action plans to address cardiovascular diseases.[3]

Short-term increases in concentrations of $PM_{2.5}$ and PM_{10} have been associated with acute myocardial infarction, stroke, and death due to cardiovascular diseases.[4] The WHO air quality guideline values were lowered in 2021, from a target annual $PM_{2.5}$ concentration of 10 μg/m³ to 5 μg/m³, and from a target annual PM_{10} concentration of 20 μg/m³ to 15 μg/m³, because of new evidence of adverse health outcomes at lower concentration levels than previous thought.[5] Studies investigating the correlation between risk of OHCA and the concentration of air pollutants have reported inconsistent results, especially at pollution concentrations below the WHO air quality guideline values. $PM_{2.5}$ has been found to be associated with OHCA in cities such as New York (NY, USA), Houston (TX, USA), and Melbourne (VIC, Australia), but not in areas with lower concentrations of pollutants, such as Denmark and Seattle (WA, USA).[6] Findings from studies on other pollutants such as nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) have equally been mixed.[6,7] For example, a systematic review done in 2017 found that NO_2 and O_3 were associated with increased risk of OHCA,[8] whereas some nationwide studies have found no significant associations.[6,7] Additional research is needed to clarify whether there is an association between ambient air pollutants and risk of OHCA.

Singapore has variations in air quality that are contributed to by both local and non-local sources of emissions, including regional land fires.[9] The resultant variation in air quality, in addition to Singapore's robust surveillance, provide optimal real-world data for assessing its effect on population health.[9] We aimed to investigate the association between air pollutant concentrations and risk of OHCA in Singapore.

Methods

Study design and population

In this time series analysis, we used data from the Pan-Asian Resuscitation Outcomes Study (PAROS) to assess the association between air pollutants and risk of OHCA in Singapore. The PAROS is an ongoing, prospective, population-based registry designed to provide data on the epidemiology, management, and outcomes of OHCA in nine countries across the Asia-Pacific region—namely Japan, South Korea, Taiwan, Australia, Malaysia, Singapore, Thailand, Türkiye, and the United Arab Emirates.[10]

Singapore is an urban city-state with a tropical climate characterised by warm temperatures, high humidity, and abundant rainfall. Its major sources of air pollution include motor vehicle, industrial, and maritime emissions, and episodic transboundary pollution from wildfires and land-clearing activities in the wider southeast Asian region.[11] In 2018, the crude incidence of OHCA in Singapore was 52·7 per 100 000 population, and the age-standardised rate was 42·2 cases per 100 000 population.[12]

We collected data on all cases of OHCA in Singapore that were reported to PAROS between July 1, 2010, and Dec 31, 2018. All OHCA cases were attended by the national emergency ambulance service, and all public hospital OHCA data are reported to PAROS. Data were extracted from emergency dispatch records, ambulance case notes, and hospital records. Cases of OHCA were defined according to the Utstein recommendations.[13] We included OHCAs of all causes in this study.

The Centralised Institutional Review Board and the Domain Specific Review Board granted approval for our study with a waiver of patient consent (reference 2017/2380).

Air quality data

We obtained the concentrations of six air pollutants ($PM_{2·5}$, PM_{10}, O_3, NO_2, CO, and SO_2) from June 1, 2010, to Dec 31, 2018, from the National Environment Agency (NEA) Singapore. The NEA collects ambient pollutant concentrations via 22 remote stations, and data on temperature, humidity, and rainfall via 11 weather stations across Singapore. The approximate locations of the remote air quality stations are shown in the appendix (p 3), in addition to mobile telemetric monitoring stations that travel across the city-state.

Statistical analysis

We averaged the daily measurements of pollutant concentrations, temperature, humidity, and rainfall across air quality monitoring and weather stations to derive daily national mean (SD) measures. We then linked the environmental exposures to nationally reported OHCA events on a daily timescale to form the dataset used in our analysis. We analysed OHCA events by case, rather than by individual, such that the same individual might be included multiple times if they had multiple events during the study period.

We report demographic variables as frequencies and percentages and air quality variables as medians and IQRs. We developed the core model using generalised Poisson regression and we adjusted the long-term trend using linear and quadratic terms together with trigonometric functions for periodic patterns. We used multivariable fractional polynomial modelling to explore the linearity of the temperature effect using the R function mfp. For example,

$$\begin{aligned}\log(E[\text{cardiac\_arrest}_t])=\alpha &+\sin(2k\pi t/365)\\ &+\cos(2k\pi t/365)\\ &+fp(\text{temp}_t)+fp(\text{temp}_{t-1})\\ &+fp(\text{temp}_{t-2})\end{aligned} \quad (1)$$

where *E* denotes cardiac arrest event, *t* denotes the day, *fp* denotes the fractional polynomial, and *k* is equal to 1, 2, 3, 4, or 6 to denote the cycles of 12, 6, 4, 3, and 2 months, respectively.

We examined the same-day (lag 0 days) and delayed effects (up to 5 days after exposure) of each air pollutant for an association with OHCA incidence.[7] A lag of up to 5 days was selected because this was commonly adopted in previous studies[8], and across ten US cities the estimated effect of air pollution and daily deaths did not reach zero until 5 days after exposure, which might be due to the distribution of sensitivities to air pollution in the general population.[14] We assessed the independent immediate and lag-specific effects of each air pollutant and their cumulative effects on risk of OHCA using the core model. The daily number of OHCA cases was the dependent variable. We reported the cumulative and adjusted relative risk (RR) and 95% CI, for every 10 $\mu g/m^3$ increase in the concentration of $PM_{2·5}$, PM_{10}, O_3, NO_2 and SO_2, and every 1·0 mg/m^3 increase in CO concentration, adjusted for daily mean temperature, daily relative humidity, and daily total rainfall.

We also explored the association between $PM_{2.5}$ and risk of OHCA in the subgroups of age (<65 and ≥65 years), arrest rhythm (non-shockable and shockable; shockable rhythms include ventricular tachycardia and ventricular fibrillation, and non-shockable rhythms include asystole and pulseless electrical activity), and location of arrest (at home and not at home) concentration. We determined that effect modification from these factors was present if a significant association between an air pollutant concentration and risk of OHCA was found in one subgroup but not the other. Additionally, we did a stratified analysis by sex to explore any sex differences in risk of OHCA with increasing $PM_{2.5}$.

To established how reduction in air pollutant concentrations would reduce the number of the OHCA events, we did a prespecified analysis using equation 2 to estimate the attributable fraction and equation 3 estimate the absolute number of OHCA events associated with a 10 μg/m³ increase in the concentration of $PM_{2.5}$ on the present day.

$$AF_d = \frac{RR_d - 1}{RR_d} \quad (2)$$

$$AN_d = AF_d \times N_d \quad (3)$$

AF_d refers to the attributable fraction for the air pollutant of interest on the day d, N_d refers to the number of OHCA on day d, RR_d refers to the cumulative RR corresponding to the increase in concentration of the air pollutant of interest, for which the reference value is the lowest observed concentration in our study period, and AN_d refers to the absolute number of OHCA events on the day of interest. To obtain the air pollutant-specific total attributable fraction for the study, we took the sum of its immediate and lagged contributions from all days of the study and divided it by the total number of cases of OHCA reported. We used the 95% CIs for the RRs to calculate the 95% CIs for the attributable fractions.

We then assumed two hypothetical scenarios in which the $PM_{2.5}$ concentrations on each day were reduced by 1 μg/m³ and 3 μg/m³ and calculated the corresponding change in the number of OHCA events. We only did the attributable burden analysis for $PM_{2.5}$ because this is the pollutant of greatest concern internationally and is often selected as an overall indicator of the health risks from the overall mix of pollutants.

We did all analyses using R (version 4.04), and we considered p values of less than 0·05 to be significant.

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Results

There were 18 131 cases of OHCA in Singapore during the study period. 35 people had more than one OHCA event and were included in our analysis for each event. The mean number of daily cases was 5·8 (SD 3·0). The median age at the time of OHCA was 65 years (IQR 56–80) and 6484 (35·8%) patients were female, 11 647 (64·2%) were male, 12 270 (67·7%) were Chinese, 2873 (15·8%) were Malay, and 2010 (11·1%) were Indian (table 1). The most common medical comorbidities were hypertension, hyperlipidaemia, heart diseases, and diabetes (table 1). The most common first arrest rhythm was shockable (i.e., pulseless ventricular tachycardia, or ventricular fibrillation). Most OHCA events occurred at home, with the other events occurring at a public or commercial building, on a street or highway, or at other locations (table 1).

	Cases of OHCA (N=18 131)
Age, years	
Median	65 (56–80)
0–64	7683 (42·4%)
≥65	10 448 (57·6%)
Sex	
Female	6484 (35·8%)
Male	11 647 (64·2%)
Ethnicity	
Chinese	12 270 (67·7%)
Malay	2873 (15·8%)
Indian	2010 (11·1%)
Other	978 (5·4%)
Location of cardiac arrest	
Home residence	13 051 (72·0%)
Public or commercial building	1261 (7·0%)
Street or highway	783 (4·3%)
Other	3036 (16·7%)
Transportation to hospital	
Emergency medical services	17 881 (98·6%)
Other	250 (1·4%)
Previous medical condition	
Hypertension	8534 (47·1%)
Hyperlipidaemia	6024 (33·2%)
Heart disease	5694 (31·4%)
Diabetes	5159 (28·5%)
Renal disease	2115 (11·7%)
Stroke	2053 (11·3%)
Respiratory disease	1891 (10·4%)
Cancer	1592 (8·8%)
Other	7361 (40·6%)
First arrest rhythm	
Asystole	9004 (49·7%)
Pulseless electrical activity	5051 (27·9%)
Ventricular fibrillation or ventricular tachycardia	2622 (14·4%)
Other	1454 (8·0%)

Data are n (%) or median (IQR). The study population comprised the cases of OHCA recorded during the study period, rather than the individuals who had OHCA, such that an individual might be included multiple times if they had multiple instances of OHCA. OHCA=out-of-hospital cardiac arrest.

Table 1: **Demographics and clinical characteristics of study population**

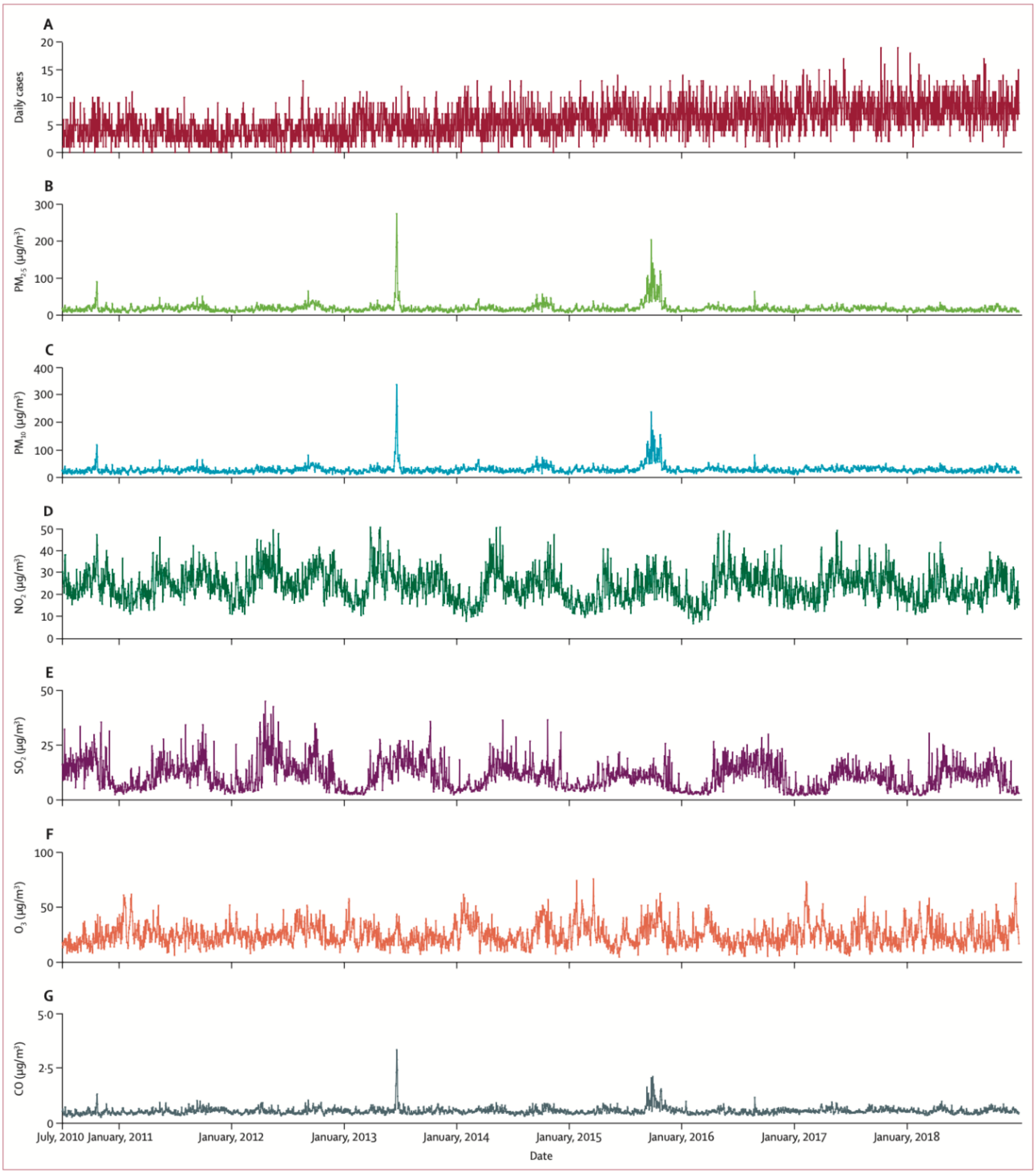
Across the study period, the mean daily temperature was 27·8°C (SD 1·1), and the mean relative humidity was 79·6% (SD 5·4). The median daily concentration of $PM_{2·5}$ was 15·9 μg/m³ (IQR 12·6–20·4), PM_{10} was 27·4 μg/m³ (22·8–33·4), O_3 was 23·2 μg/m³ (17·9–30·8), NO_2 was 23·6 μg/m³ (19·1–28·9), CO was 0·53 mg/m³ (0·46–0·61), and SO_2 was 10·4 μg/m³ (5·8–14·9). The distributions of the daily concentrations of the six air pollutants were positively skewed (appendix p 1). There were two major peaks in concentrations of $PM_{2·5}$, PM_{10}, and CO between June and July, 2013, and between September and October, 2015, corresponding to the 2013 and 2015 southeast Asian haze events (figure).

Increases in $PM_{2.5}$, PM_{10}, O_3, NO_2, CO, and SO_2 were not significantly associated with risk of OHCA on the same day (i.e., 0 days of lag; table 2). Every 10 μg/m³ increase in $PM_{2.5}$ was associated with a cumulative increased risk of OHCA 0–2 days after exposure, and decreased risk over the next 3 days (3–5 days after exposure; table 2). An increase in CO of 1·0 mg/m³ was associated with a significant cumulative decrease in risk of OHCA between days 0 and 5 and between days 3 and 5 after exposure. The increases in the concentrations of PM_{10}, O_3, NO_2, and SO_2 were not associated with immediate or cumulative risk of OHCA up to 5 days.

We did a subgroup analysis of risk of OHCA with increasing $PM_{2.5}$ concentration in patients with shockable and non-shockable rhythms (table 3). In patients with non-shockable OHCA, each 10 μg/m³ increase in $PM_{2.5}$ was associated with an increased cumulative risk of OHCA in the next 2 days, and a decreased cumulative risk in the subsequent 3 days, but no such associations were seen for those with shockable arrest rhythms. In the subgroup analysis by age group, increasing $PM_{2.5}$ concentration was not associated with increased cumulative risk of OHCA but was associated with decreased cumulative risk of OHCA after 3–5 days, and only in those aged 65 years and older (table 3). In the subgroup analysis by location of OHCA, we found an increased cumulative risk of OHCA with increasing $PM_{2.5}$ in individuals who had an at-home OHCA 0–2 days after exposure, and a subsequent cumulative decrease in risk 3–5 days after exposure (table 3). We found no associations between $PM_{2.5}$ and OHCA events that did not occur at home.

In the exploratory sex-stratified analysis, we did not observe any evidence that sex affected the association between increasing $PM_{2.5}$ and risk of OHCA (appendix p 2). An increase in $PM_{2.5}$ concentration on day 0 was associated with a cumulative increase in the risk of OHCA in male individuals up to 2 days later (RR 1·034 [95% CI 1·009–1·061]) and in female individuals up to 3 days later (1·041 [1·007–1·077]). For both sexes, we observed a similar cumulative decrease in the risk of $PM_{2.5}$-attributable OHCA risk subsequent to the initial increase in risk (RR for male individuals 3–5 days after exposure 0·963 [95% CI 0·937–0·989] and RR for female individuals 4–5 days after exposure 0·958 [95% CI 0·924–0·993]; appendix p 2).

Figure: Daily air pollutant concentrations and cases of out-of-hospital cardiac arrest in Singapore, from June 1, 2010, to Dec 31, 2018 Daily cases of out-of-hospital cardiac arrest (A) and concentrations of particulate matter with a diameter of 2·5 µm or smaller (PM2·5; B), particulate matter with a diameter of 10 µm or smaller (PM10; C), nitrogen dioxide (NO2; D), sulphur dioxide (SO2; E), ozone (O3; F), and carbon monoxide (CO; G).



	Day of exposure	0–1 days after exposure	0–2 days after exposure	0–3 days after exposure	0–4 days after exposure	0–5 days after exposure	3–5 days after exposure
$PM_{2·5}$	1·007 (0·988–1·027; p=0·48)	1·006 (0·986–1·026; p=0·58)	1·022 (1·002–1·043; p=0·034)	1·011 (0·990–1·032; p=0·32)	0·999 (0·977–1·021; p=0·90)	0·998 (0·984–1·012; p=0·78)	0·976 (0·955–0·998; p=0·029)
PM_{10}	1·002 (0·986–1·018; p=0·79)	1·003 (0·987–1·020; p=0·71)	1·015 (0·998–1·032; p=0·077)	1·009 (0·992–1·027; p=0·29)	0·997 (0·980–1·015; p=0·75)	1·000 (0·988–1·011; p=0·96)	0·985 (0·968–1·002; p=0·084)
O_3	1·002 (0·980–1·025; p=0·83)	1·014 (0·990–1·039; p=0·24)	1·020 (0·995–1·046; p=0·11)	0·991 (0·967–1·016; p=0·48)	1·009 (0·983–1·035; p=0·50)	1·005 (0·985–1·026; p=0·62)	0·985 (0·961–1·010; p=0·24)
NO_2	0·987 (0·956–1·020; p=0·44)	0·980 (0·947–1·015; p=0·27)	0·973 (0·938–1·011; p=0·16)	1·002 (0·964–1·042; p=0·90)	0·967 (0·929–1·008; p=0·11)	0·964 (0·930–1·000; p=0·050)	0·991 (0·955–1·028; p=0·62)
CO	0·949 (0·822–1·096; p=0·48)	0·964 (0·831–1·119; p=0·63)	1·082 (0·928–1·262; p=0·32)	0·978 (0·834–1·147; p=0·79)	0·918 (0·779–1·082; p=0·31)	0·876 (0·770–0·997; p=0·044)	0·810 (0·690–0·949; p=0·0092)
SO_2	1·002 (0·965–1·041; p=0·91)	0·977 (0·935–1·021; p=0·30)	1·008 (0·961–1·056; p=0·75)	1·000 (0·951–1·052; p=0·99)	1·021 (0·970–1·076; p=0·43)	0·975 (0·928–1·024; p=0·32)	0·968 (0·923–1·015; p=0·17)

Data are relative risks, adjusted for daily mean temperature, daily relative humidity, and daily total rainfall, and p values were calculated using generalised Poisson regression. $PM_{2·5}$=particulate matter with a diameter of 2·5 μm or smaller. PM_{10}=particulate matter with a diameter of 10 μm or smaller. O_3=ozone. NO_2=nitrogen dioxide. CO=carbon monoxide. SO_2=sulphur dioxide.

***Table 2:* Summary relative risk of out-of-hospital cardiac arrest for every increase of 10 μg/m³ of $PM_{2·5}$, PM_{10}, O_3, NO_2, and SO_2 and 1 mg/m³ of CO concentration on cumulative days after exposure**

	Day 0	0–1 days after exposure	0–2 days after exposure	0–3 days after exposure	0–4 days after exposure	0–5 days after exposure	3–5 days after exposure
Arrest rhythm							
Shockable	1·028 (0·986–1·073; p=0·20)	1·007 (0·963–1·053; p=0·76)	1·002 (0·956–1·051; p=0·93)	0·990 (0·944–1·039; p=0·69)	0·990 (0·943–1·041; p=0·70)	0·979 (0·947–1·012; p=0·21)	0·977 (0·930–1·026; p=0·35)
Non-shockable	1·002 (0·980–1·024; p=0·88)	1·005 (0·983–1·028; p=0·66)	1·027 (1·004–1·050; p=0·020)	1·015 (0·992–1·039; p=0·20)	1·000 (0·976–1·025; p=1·00)	1·002 (0·987–1·018; p=0·77)	0·976 (0·953–1·000; p=0·047)
Age group, years							
0–64	1·015 (0·985–1·045; p=0·33)	0·991 (0·961–1·022; p=0·55)	1·023 (0·992–1·055; p=0·14)	1·009 (0·977–1·041; p=0·59)	1·001 (0·969–1·035; p=0·95)	1·010 (0·989–1·031; p=0·37)	0·987 (0·956–1·019; p=0·41)
≥65	1·002 (0·976–1·028; p=0·91)	1·017 (0·991–1·044; p=0·20)	1·022 (0·994–1·050; p=0·12)	1·012 (0·984–1·041; p=0·39)	0·996 (0·968–1·026; p=0·81)	0·988 (0·969–1·008; p=0·24)	0·968 (0·940–0·996; p=0·027)
Location of arrest							
At home	0·998 (0·975–1·021; p=0·86)	1·007 (0·984–1·031; p=0·53)	1·033 (1·008–1·057; p=0·0082)	1·016 (0·991–1·041; p=0·22)	0·991 (0·966–1·017; p=0·51)	0·995 (0·978–1·012; p=0·53)	0·963 (0·939–0·988; p=0·0045)
Not at home	1·030 (0·994–1·068; p=0·10)	1·000 (0·964–1·039; p=0·98)	0·995 (0·957–1·035; p=0·82)	0·997 (0·959–1·038; p=0·89)	1·013 (0·973–1·055; p=0·53)	1·003 (0·977–1·031; p=0·80)	1·008 (0·970–1·048; p=0·69)

Data are relative risks, adjusted for daily mean temperature, daily relative humidity, and daily total rainfall, and p values were calculated using generalised Poisson regression. $PM_{2·5}$=particulate matter with a diameter of 2·5 μm or smaller.

***Table 3:* Stratified reactive risk analysis of the association between cumulative risk of out-of-hospital cardiac arrest and 10 μg/m³ increase in $PM_{2·5}$ concentration**

Using the lowest $PM_{2·5}$ reference value of 5·69 μg/m³ observed over the study period, we estimated that 492 (95% CI 43–919) OHCA events on day 0 and the subsequent 2 days (0–2 days after exposure) were attributable to an increase in $PM_{2·5}$ concentration on day 0. Assuming that the $PM_{2·5}$ reference value remained constant, a hypothetical 1 μg/m³ decrease in $PM_{2·5}$ concentrations could result in an 8% reduction in the number of OHCA events, and a 3 μg/m³ decrease n $PM_{2·5}$ concentration could result in a 30% reduction in the number of events (table 4).

Discussion

In this time series analysis, we found that increasing $PM_{2\cdot5}$ concentrations were associated with an immediate increased risk of OHCA over the first 2 days after exposure and a subsequent cumulative decrease in risk 3–5 days after exposure. The association between $PM_{2\cdot5}$ concentration and risk of OHCA was affected by the type of arrest rhythm and the location of the arrest event.

Previous studies have found that $PM_{2\cdot5}$ concentrations are more strongly associated with OHCA than CO, SO_2, O_3, and NO_2 concentrations and had the highest population attributable fraction.[7,8] A systematic review of 15 studies found that a short term (0–6 days before the OHCA event) 10 µg/m³ increase in $PM_{2\cdot5}$ concentration was associated with 4·1% increase in risk of OHCA.[8] We found that increases in $PM_{2\cdot5}$ concentration increased the risk of OHCA in the first 2 days after exposure, but decreased the risk on days 3–5. One possible explanation is a harvesting effect, such that an increase in $PM_{2\cdot5}$ concentration triggered earlier OHCA in those who had compromised health and who would probably have had a cardiac arrest subsequently. After this initial harvesting effect within the first few days of exposure, the number of cases of OHCA might decrease because the population who are susceptible has decreased. Similarly, another study in Nanjing, China, found that the association between $PM_{2\cdot5}$ concentration and overall or cardiovascular mortality was initially positive at 0–1 day after exposure but negative 2 days after exposure.[15] Over cumulative lag periods of 0–15 days and 0–30 days, increase in $PM_{2\cdot5}$ concentration was associated with increased cardiovascular death.[15] In seven major cities in South Korea, incidence of cardiovascular death associated with PM_{10} increased 0–1 days after exposure, but within 28 days of exposure increased PM_{10} was associated with reduced incidence of cardiovascular death.[16] However, at 0–45 days after exposure, increased PM_{10} concentration was again associated with increased incidence of cardiovascular death.[16] Taken together, PM might lead to an acute increase in OHCA in the first few days of exposure due to a harvesting effect, but in the medium and longer term might lead to a genuine increase in the incidence of OHCA. Further research is needed with longer lag durations to confirm this hypothesis.

Several pathophysiological mechanisms for the association between PM and OHCA have been suggested. PM might cause systemic inflammation, subsequently causing increased coagulation, platelet aggregation, and thrombus formation in the coronary arteries.[17] Furthermore, PM might lead to autonomic imbalance, which has been associated with increased risk of cardiac events, sustained ventricular tachycardia, and mortality.[18] The cause of OHCA is most often cardiac, of which ischaemic heart disease is the most common.[1] In an American Cancer Society study,[19] ischaemic cardiac events were found to account for the largest relative and absolute risk for mortality per 10 µm/m³ increase in $PM_{2\cdot5}$ concentration.

In particular, $PM_{2\cdot5}$ is more strongly associated with ST-elevation myocardial infarction (STEMI) than non-STEMI.[20] STEMI is caused by a complete occlusion of a coronary vessel, leading to larger infarct sizes than non-STEMI. $PM_{2\cdot5}$ might trigger STEMI through increased oxidative stress and inflammatory reactions, elevation of blood pressure due to endothelial dysfunction and autonomic dysfunction, and thrombosis caused by the hypercoagulable state.[20] The triggering of acute cardiac events by $PM_{2\cdot5}$ might be mediated through epigenetic changes, involving DNA methylation, histone acetylation modification, and chromosome remodelling,[21] which is a potential area for future research in air pollution and OHCA risk.

We found that $PM_{2\cdot5}$ was associated with risk of non-shockable arrest rhythm types of OHCA but not shockable arrest rhythm types. Shockable arrests are most commonly caused by ischaemic heart disease and acute myocardial infarction, while non-shockable rhythms are caused by the common reversible causes of cardiac arrest such as hypovolaemia, hypoxia, tamponade, tension pneumothorax, and late manifestations of ventricular tachycardia or ventricular fibrillation (together commonly known as the Hs and Ts). In a study by Rosenthal and colleagues[22] in Helsinki, Finland, $PM_{2\cdot5}$-associated OHCA was found to be mainly caused by acute myocardial infarction. In the initial phase of acute myocardial infarction, ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation occur due to ischaemia, causing acidosis and electrolyte imbalance in the myocardium. In acute myocardial infarction associated with $PM_{2.5}$, non-shockable OHCA might result from sustained ventricular tachycardia or ventricular fibrillation causing cessation of electrical and mechanical cardiac activity.

	$PM_{2.5}$ mean daily concentration, μg/m³	$PM_{2.5}$ attributable number of events	Change in number of events
Study observation	18·44	492 (43 to 919)	Ref
Hypothetical 1 μg/m³ decrease each day	17·44	453 (39 to 847)	–8%
Hypothetical 3 μg/m³ decrease each day	14·65	343 (30 to 640)	–30%

Data in parentheses are 95% CIs. $PM_{2.5}$=particulate matter with a diameter of 2·5 μm or smaller.

***Table 4:* Burden of $PM_{2.5}$ attributable out-of-hospital cardiac arrest events over the study period**

We found that $PM_{2.5}$ was associated with risk of non-shockable arrest rhythm types of OHCA but not shockable arrest rhythm types. Shockable arrests are most commonly caused by ischaemic heart disease and acute myocardial infarction, while non-shockable rhythms are caused by the common reversible causes of cardiac arrest such as hypovolaemia, hypoxia, tamponade, tension pneumothorax, and late manifestations of ventricular tachycardia or ventricular fibrillation (together commonly known as the Hs and Ts). In a study by Rosenthal and colleagues[22] in Helsinki, Finland, $PM_{2.5}$-associated OHCA was found to be mainly caused by acute myocardial infarction. In the initial phase of acute myocardial infarction, ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation occur due to ischaemia, causing acidosis and electrolyte imbalance in the myocardium. In acute myocardial infarction associated with $PM_{2.5}$, non-shockable OHCA might result from sustained ventricular tachycardia or ventricular fibrillation causing cessation of electrical and mechanical cardiac activity.

An initial non-shockable rhythm in OHCA caused by STEMI has been found to be associated with worse neurological outcomes and survival.[23] Possibly due to the systemic inflammation effect of PM, PM is also associated with lung inflammation and respiratory diseases, which are important non-cardiac causes of non-shockable OHCA.[24] Therefore, PM-associated OHCA might have poorer outcomes than OHCA due to other causes and should be prioritised in environmental and public health policies.

There is a paucity of published data on how the risk of OHCA associated with air pollution is altered by the location of the arrest event. In our dataset, 72% of OHCAs occurred at home, and such events have higher mortality than OHCAs that occur at other locations do,[25] and might comprise a more vulnerable population because individuals with lower physiological reserve and exercise tolerance are more likely to stay at home. In our stratified analyses, we found that increasing $PM_{2.5}$ concentration was associated with OHCA at home 0–2 days after exposure, and so, considering that people at home might be more vulnerable, this increasing risk might further increase the risk of poor OHCA outcomes.

Hence, public education on cardiopulmonary resuscitation (known as CPR) might be of importance in improving the outcomes of OHCA in residential areas with high $PM_{2.5}$ concentrations. Indoor filtration devices might also have cardiovascular benefits, and a meta-analysis of 14 randomised controlled trials showed that systolic blood pressure, pulse pressure, reactive hyperaemia index, and inflammatory markers improved with indoor air purification.[26] However, the effect of air filtration devices on OHCA requires further study.

We did not have sufficient evidence to suggest effect modification by age. Although increasing $PM_{2.5}$

concentration was significantly associated with lower cumulative risk of OHCA 3–5 days after exposure in those aged 65 years and older, the cumulative risk of OHCA 0–2 days after exposure did not differ significantly in either subgroup (<65 or ≥65 years). The reduction in risk of OHCA 3–5 days after exposure in those aged 65 years and older might be due to an increased harvesting effect in the older age group. In Japan, a short-term effect of an increase in $PM_{2·5}$ concentration up to 3 days before the cardiac arrest was associated with cardiac OHCA in individuals aged 65 years and older, but not in those who were younger than 65 years.[7] Similarly, in Houston (TX, USA), increasing $PM_{2·5}$ concentration had a greater effect on risk of OHCA in patients younger than 65 years than those aged 65 years and older,[27] but more studies are warranted.

A meta-analysis of 11 studies with a median or mean range of CO concentrations from 0·14 to 2·14 mg/m³ showed no significant association with OHCA.[8] In our study, we found a negative association between increasing concentrations of CO at 0–5 days and 3–5 days after exposure and risk of OHCA, which differed from findings in a previous meta-analysis.[8] This difference in findings might be due to a more pronounced harvesting effect in our study than in other studies, because CO 0–2 days after exposure was associated with a positive trend in risk of OHCA, which did not reach statistical significance. Further studies are required to ascertain the biological mechanisms through which CO affects risk of OHCA.

Each life saved from an OHCA event might on average reduce 18·1 disability-adjusted life years, defined as the sum of years of life lost and years lived with disability.[28] We found that a 1 μg/m³ decrease in mean daily $PM_{2·5}$ concentrations could potentially reduce the number of acute OHCA events (ie, occuring within 0–2 days) by 8%. A decrease of 3 μg/m³ in mean daily $PM_{2·5}$ concentrations, which would effectively put the mean concentrations below the 2021 WHO air quality guidance value of 15 μg/m³, could potentially reduce the number of OHCA events by 30%. On days with high concentrations of $PM_{2·5}$, individuals at high baseline risk of OHCA might be particularly susceptible to $PM_{2·5}$-associated OHCA, and so using remote cardiac telemonitoring to assist with the detection and subsequent management of OHCA would be particularly helpful, and is in development for such situations.[29] Improvements in air quality have good potential to reduce the risk of OHCA and consequently reduce $PM_{2·5}$-attributable population demand for emergency health services.

Our study has several strengths. We used high quality disease data from a prospective, population-based, nationwide database. This database captured OHCA events from the ambulance services in addition to hospital cases; therefore, we were able to capture cardiac arrest events in patients who might have died at the scene who might have been missed in hospital-based studies. Additionally, the quality of the air quality data is also high because of robust surveillance around the island. The concentrations of air pollution is generally comparable with European and North American cities, which might aid the generalisability of our results to these regions.[30]

However, this might also cause statistical limitations because of the relatively large increments of air pollutant concentration used in this study, which we selected to allow comparisons with previous literature. Our study also has several limitations. First, the average pollutant concentration across all the stations might not accurately reflect individual exposures, because pollutant concentrations might vary by proximity to the air pollutant measurement station and might not be the same indoors because of additional emission sources or behaviours such as mask wearing or using air filtration devices. Concentrations of air pollutants might also vary with vertical height, which could affect individual exposure because high-rise residences are common in Singapore. There is scope in future studies with more detailed exposure modelling to account for spatial heterogeneity. Second, this is an observational ecological study, and therefore our findings are not generalisable at an individual level. Third, our results might be biased by unmeasured confounders, such as time of OHCA, socioeconomic status, and comorbidities. We analysed the daily counts of OHCA events and rather than individuals who had events because it is unlikely that more than one event for a single individual would occur on the same day, because the individual would either die or be admitted to hospital. Fourth, the air pollutants we considered in our study might not completely reflect the range of other air pollutants that exist concurrently and that might also have contributed to OHCA. However, the air pollutants we included might still be relied on as proxies of the air quality variations on OHCA risk. Finally, potential colinearity of coexposures, such as between copollutants and meteorological factors, can restrict the ability of statistical models to identify the independent effects of each factor. In this regard, this study should be considered in the context of the international literature where other studies have been conducted in settings with a different mix of coexposures.

In summary, increases in $PM_{2·5}$ concentration were associated with a short-term increases in cumulative risk of OHCA at days 0–2 after exposure, and a reduced cumulative risk at days 3–5 after exposure, which suggests a short-term harvesting effect. $PM_{2·5}$ concentrations might be associated with non-shockable OHCA at home and, therefore, might increase the risk of OHCA with poor outcomes. Improvements in $PM_{2·5}$ concentrations might lead to a decrease in the population burden of OHCA and reduce the demand for $PM_{2·5}$-attributable emergency health services.

Contributors

AFWH contributed to study conceptualisation, methods, investigation, collecting resources, and writing, reviewing, and editing the manuscript. JSYH contributed to investigation, data curation, and writing the original draft of the manuscript. BY-QT contributed to investigation, collecting resources, and writing, reviewing, and editing the manuscript. SES contributed to the formal analysis and writing, reviewing, and editing of the manuscript. JWY, C-HS, and MW contributed to investigation, validation, data curation, and writing, reviewing, and editing of the manuscript. JA contributed to study supervision, investigation, and writing, reviewing, and editing of the manuscript. HZ contributed to the formal analysis, designing of figures, and writing, reviewing, and editing of the manuscript. GM, WWST, and WJS contributed to investigation, data curation, and writing, reviewing, and editing of the manuscript. MEHO contributed to study supervision, conceptualisation, method, data curation, and writing, reviewing, and editing of the manuscript. JA, HZ, SES, and WTWS accessed and verified the underlying study data. AFWH, JA, WJS, HZ, and MEHO had final responsibility for the decision to submit for publication and all authors had full access to all the data in the study.

Declaration of interests

MEHO reports funding from the Zoll Medical Corporation for a study involving mechanical cardiopulmonary resuscitation devices; grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation programme to their Community CPR Training Centre Research Program in Norway. All other authors declare no competing interests.

Data sharing

Data used in this study are available upon reasonable request to the PAROS registry and NEA, Singapore.

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Chapter 8

The Effect of Building-Level Socioeconomic Status on Bystander Cardiopulmonary Resuscitation: A Retrospective Cohort Study

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Abstract

Objective: Understanding the social determinants of bystander cardiopulmonary resuscitation (CPR) receipt can inform the design of public health interventions to increase bystander CPR. The association of socioeconomic status with bystander CPR is generally poorly understood. We evaluated the relationship between socioeconomic status and bystander CPR in cases of out-of-hospital cardiac arrest (OHCA). Methods: This was a retrospective cohort study based on the Singapore cohort of the Pan-Asian Resuscitation Outcomes Study registry between 2010 and 2018. We categorized patients into low, medium, and high Singapore Housing Index (SHI) levels—a building-level index of socioeconomic status. The primary outcome was receipt of bystander CPR. The secondary outcomes were prehospital return of spontaneous circulation and survival to discharge.

Results: A total of 12,730 OHCA cases were included, the median age was 71years, and 58.9% were male. The bystander CPR rate was 56.7%. Compared to patients in the low SHI category, those in the medium and high SHI categories were more likely to receive bystander CPR (medium SHI: adjusted odds ratio [aOR] 1.48, 95% CI 1.30–1.69; high SHI: aOR 1.93, 95% CI 1.67–2.24). High SHI patients had higher survival compared to low SHI patients on unadjusted analysis (OR 1.79, 95% CI 1.08–2.96), but not adjusted analysis (adjusted for age, sex, race, witness status, arrest time, past medical history of cancer, and first arrest rhythm). When comparing high with low SHI, females had larger increases in bystander CPR rates than males.

Conclusions: Lower building-level socioeconomic status was independently associated with lower rate of bystander CPR, and females were more susceptible to the effect of low socioeconomic status on lower rate of bystander CPR.

Introduction

Out-of-hospital cardiac arrest (OHCA), defined as the cessation of cardiac mechanical activity as indicated by the absence of signs of circulation outside of the hospital setting, is a major public health concern. The global incidence of OHCA cases is estimated at 84 per 100,000 person-years (1). Despite advancements in resuscitation care, outcomes have remained poor, with a survival to hospital discharge rate of 8.8% (2). Hence it is important to understand and address factors affecting OHCA survival (1).

Survival after OHCA is contingent on the "chain of survival"—the rapid and seamless delivery of a series of rescuer actions (3), of which early cardiopulmonary resuscitation (CPR) has the largest survival benefit (4,5). Bystander CPR, defined as CPR performed by a layperson who is not part of the emergency medical services (EMS) system, increases survival by nearly three-fold, and is associated with lower risks of brain damage (6,7). Unfortunately, it has been estimated that patients with OHCA receive bystander CPR less than one-third of the time, despite being witnessed by bystanders in more than half of cases (6). Hence, it is imperative to understand the determinants of bystander CPR and inform the design and implementation of public health programs to increase bystander CPR rates (8,9).

A recent article by Khanji et al. highlighted the potential health care inequalities in the delivery of bystander CPR and training the public (10). Systematic reviews have shown that low socioeconomic status (SES) was associated with reduced provision of bystander CPR (11,12). However, this conclusion relied on studies whose internal validity was limited from using area-level SES measures, often categorizing the area by census tract level or district level data based on educational status, residential neighborhood, income, racial segregation, or enrollment in insurance programs. This approach can be susceptible to the ecological fallacy where the individual SES is assumed to be the same as the area SES. Furthermore, none of the studies reported associations based on age or sex (12), which remains a significant knowledge gap as previous studies have suggested that older women have lower chances of receiving bystander CPR and lower probability of survival (13).

We aimed to evaluate relationship between SES and bystander CPR receipt using a building-level SES marker, the Singapore Housing Index (SHI) in Singapore (14), with pre-defined subgroups including sex and age. We hypothesized that higher building-level SES would be associated with a higher likelihood of receiving bystander CPR.

Methods

Setting

Singapore is a multi-ethnic city-state in Southeast Asia, comprising an area of 728.1 square kilometers with a population of 5.68 million in 2020. The average monthly income per household member is shown in Supplementary Table 1 (15). Approximately 96% of Singapore's resident households reside in high-rise apartments, with 80% residing in flats designed and built by the Housing and Development Board (HDB) (16). In Singapore, 31.4% of the population has been trained in CPR, and 10.7% has been trained in automated external defibrillation (AED) (17). The age-standardized survival was 12.0% in 2016, with 56.3% of all OHCA cases receiving bystander CPR in the same year (18).

Study Population and Outcomes Data

This was a secondary analysis of the Singapore data from the Pan-Asian Resuscitation Outcomes Study (PAROS) between 2010–2018. PAROS is an ongoing long-term prospective registry for OHCA in the Asia-Pacific region, designed to provide baseline information on OHCA epidemiology, recording data in accordance with Utstein recommendations for data definitions and extraction methods. All OHCA cases (as confirmed by the absence of pulse, unresponsiveness, and apnoea), which presented to the emergency department (ED) or were attended to by EMS, were included in the registry. Only patients with valid locally registered residential addresses, and OHCA cases that occurred at the patient's residence were included. OHCA cases that were witnessed by EMS (which precluded bystander CPR) were excluded. Patient-level data on the demographics, comorbidities, and care process characteristics were obtained from PAROS. Data required to generate the SHI (i.e. National Registration Identification Card [NRIC] number, residential address, and postal code) were also collected.

The primary outcome was receipt of bystander CPR. The secondary outcomes were any return of spontaneous circulation (ROSC) and survival to hospital discharge, defined as survival to 30days or hospital discharge, whichever occurred first.

Socioeconomic Status Measure: The Singapore Housing Index

The SHI, first implemented by Wong et al., was adopted as a marker of SES for our study (19). The SHI, which appraises a residential property value on an ordinal scale of 1 to 7 (low to high), is a building-level marker that has a robust association with income and residence value. The estimated average and median monthly household income from work among resident employed households by the type of dwelling, from the national data registry in 2020, is shown in Supplementary Table 2. The SHI has been applied in a variety of health settings in Singapore (19–25).

To obtain the updated SHI dataset, we followed the methodology described by Lim et al., which leveraged government open data sources (14). We first matched each patient by the NRIC to the latest known residential address on record. The six-digit postal code was then matched to either a specific HDB block, or a private apartment or landed property based on the master plan on land use from the Singapore Land Authority. Patients staying in public housing (a HDB block) were assigned an SHI value ranging from 1 to 6, derived by calculating the weighted average number of rooms per unit in the building. Non-subsidized private apartments and landed housing blocks were assigned SHI values of 6 and 7 respectively. We categorized patients into three ordinal SHI levels: low, medium, and high SHI (Supplementary Table 2) consistent with previous literature (19).

Statistical Analysis

We summarized continuous variables as median (interquartile range, IQR) and categorical variables as frequency (percentage). Analysis of variance and Kruskal-Wallis tests were performed for continuous variables and chi-square test for categorical variables. Multivariable logistic regression was performed with forward selection of incrementally added covariates (SHI, age, sex, race, witness status, arrest time, history of cancer, first arrest rhythm, and year of arrest) selected from literature review (26), in order to identify confounding relationships. We also analyzed SHI as a continuous variable. The design effect of the logistic regression models is shown in Supplementary Table 3. Sensitivity analysis excluding trauma patients was performed for primary and secondary outcomes. Subgroup analysis according to age (65 years), sex (female), witnessed arrest, daytime arrest (07:00 to 18:59), and arrests after year 2014, which was half-way within the study period, was performed. Odds ratios (OR) were calculated to determine the interaction effect of the variable on the association of bystander CPR with SHI, and OR >1.0 implied that patients with the variable of interest had a larger interaction effect on the relationship between bystander CPR and SHI. All analyses were performed using the SPSS Statistics version 25 (IBM Corporation, Armonk, NY). A two-sided *p*-value < 0.05 was considered statistically significant.

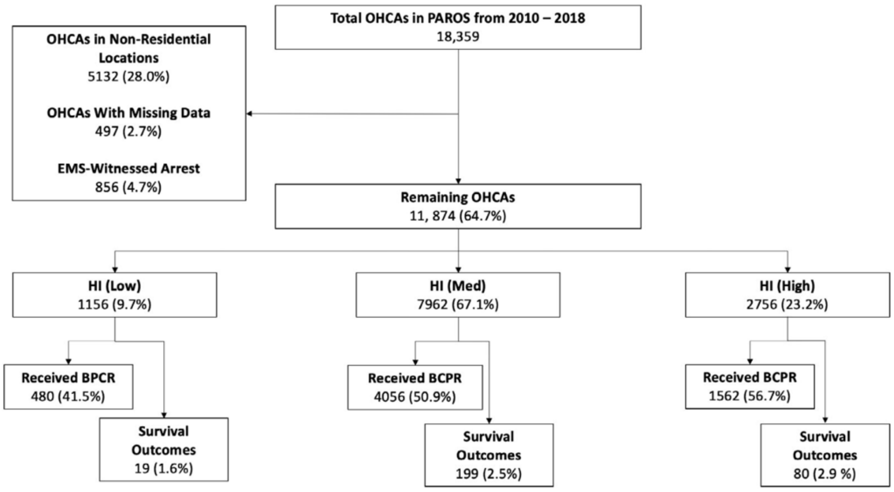

Figure 1. Case selection flowchart and outcome measures. PAROS—Pan-Asian Resuscitation Outcomes Study; OHCA—Out-of-hospital cardiac arrest; B-CPR—Bystander cardiopulmonary resuscitation; SHI—Singapore Housing Index.

Ethics Approval

The Centralized Institutional Review Board (2013/604/C) and Domain Specific Review Board (2013/00929) granted approval for this study with a waiver of patient informed consent.

Results

There were 18,359 OHCA patients during the study period; exclusions are shown in Figure 1. Out of the 11,874 included OHCA cases, 7,962 (67.1%) had medium SHI, 2,756 (23.2%) had high SHI, and 1,156 (9.7%) had low SHI. The median SHI was 4.19, the median age was 71 years (IQR 59–82), and 58.9% were male.

Baseline Characteristics Categorized by SHI

Among the three SHI strata, OHCA patients in the low SHI tier were the youngest (median age low SHI: 69 [IQR 56 – 80], medium SHI: 70 [IQR 59 – 81], high SHI: 74 [IQR 60 – 84] years, p<0.01). Those in the low SHI category were most likely male, and least likely to be of Chinese ethnicity, or have any medical co-morbidities (p<0.01) (Table 1). Those in the high SHI category had the longest EMS response times (p<0.01). There were no significant differences in the first arrest rhythm, and proportion of daytime arrest between SHI strata.

Primary Outcome

Overall, 6,098 patients (51.4%) received bystander CPR, and patients in the low SHI category were the least likely to receive bystander CPR (high SHI: 56.7% [1562 patients]; medium SHI 50.9% [4056 patients]; low SHI 41.5% [480 patients]; p patients] Table 1). Dispatcher-assisted CPR was the most common in low SHI (385 patients, 33.3%), compared to medium SHI (2594 patients, 32.6%) and high SHI (892 patients, 32.4%).

With reference to the low SHI category, patients in medium SHI category had significantly higher odds of BCPR (unadjusted OR 1.462, 95% CI 1.291-1.657, p<0.01), which remained significant after adjusting for age, sex, race, witness status, arrest time, presence of cancer, arrest rhythm and year of arrest (adjusted OR [aOR] 1.483, 95% CI 1.301-1.691, p<0.01) (Table 2). Similarly, patients in the high SHI category had higher odds of B-CPR compared to low SHI (OR 1.842, 95% CI 1.603-2.117, p<0.01; aOR 1.933, 95% CI 1.669-2.240, p<0.01). Modelling SHI as a continuous variable, every unit increase in SHI was associated with increased BCPR (OR 1.136, 95% CI 1.107-1.167, p<0.001; aOR 1.142, 95% CI 1.110-1.174, p<0.001) (Table 3).

Table 1. Patient characteristics by Singapore housing index categories.

Characteristics	All	Low SHI	Medium SHI	High SHI	*P*-value
Age, median (IQR) (years)	71 (59–82)	69 (56–80)	70 (59–81)	74 (60–84)	<0.01
Male (%)	6991 (58.9)	746 (64.5)	4688 (58.9)	1557 (56.5)	<0.01
Race					<0.01
Chinese (%)	8244 (69.4)	714 (61.8)	5522 (69.4)	2008 (72.9)	
Malay (%)	1926 (16.2)	278 (24.0)	1434 (18.0)	214 (7.8)	
Indian (%)	1201 (10.1)	125 (10.8)	759 (9.5)	317 (11.5)	
Others (%)	503 (4.2)	39 (3.4)	247 (3.1)	217 (7.9)	
Cause of arrest					<0.01
Trauma (%)	142 (1.2)	23 (2.0)	81 (1.0)	38 (1.4)	
Presumed cardiac etiology (%)	8060 (67.9)	819 (70.8)	5421 (68.1)	1820 (66.0)	
Drowning (%)	39 (0.3)	0 (0.0)	3 (0.0)	36 (1.3)	
Respiratory (%)	632 (5.3)	78 (6.7)	420 (5.3)	134 (4.9)	
Electrocution (%)	2 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	
Others (%)	2999 (25.3)	236 (20.4)	2035 (25.6)	728 (26.4)	
Medical History					
Previous co-morbidity (%)	10344 (87.1)	967 (83.7)	6973 (87.6)	2404 (87.2)	<0.01
Heart (%)	4556 (38.4)	429 (37.1)	3112 (39.1)	1015 (36.8)	0.188
Diabetes (%)	4224 (35.6)	386 (33.4)	2924 (36.7)	914 (33.2)	<0.01
Cancer (%)	1433 (12.1)	104 (9.0)	977 (12.3)	352 (12.8)	0.011
Hypertension (%)	6893 (58.1)	629 (54.4)	4717 (59.2)	1547 (56.1)	<0.01
Renal (%)	1816 (15.3)	164 (14.2)	1269 (15.9)	383 (13.9)	0.059
Respiratory (%)	1601 (13.5)	189 (16.3)	1097 (13.8)	315 (11.4)	<0.01
Hyperlipidemia (%)	4901 (41.3)	438 (37.9)	3408 (42.8)	1055 (38.3)	<0.01
Stroke (%)	1692 (14.2)	143 (12.4)	1149 (14.4)	400 (14.5)	0.157
HIV (%)	20 (0.2)	4 (0.3)	13 (0.2)	3 (0.1)	0.308
Other (%)	6151 (51.8)	590 (51.0)	4125 (51.8)	1436 (52.1)	0.505
Daytime arrest (%)	6794 (57.2)	649 (56.1)	4543 (57.1)	1602 (58.1)	0.458
EMS response intervals					
Call to arrival at scene, median (IQR) (mm: ss)	08:39 (06:46–11:04)	08:32 (06:42–11:05)	08:30 (06:41–10:51)	09:07 (07:10–11:42)	<0.01
Scene to patient's side, median (IQR) (mm: ss)	02:27 (01:29–03:37)	02:28 (01:28–03:35)	02:31 (01:34–03:39)	02:16 (01:16–03:29)	<0.01
Call to patient's side, median (IQR) (mm: ss)	11:11 (09:05–13:48)	11:09 (09:00–13:52)	11:04 (09:01–13:40)	11:31 (09:35–14:10)	<0.01
Received bystander CPR (%)	6098 (51.4)	480 (41.5)	4056 (50.9)	1562 (56.7)	<0.01
DA-CPR performed (%)	3871 (32.6)	385 (33.3)	2594 (32.6)	892 (32.4)	
Received bystander AED (%)	101 (0.9)	11 (1.0)	61 (0.8)	29 (1.1)	0.343
Arrest witnessed by bystander (%)	6189 (52.1)	570 (49.3)	4158 (52.2)	1461 (53.0)	0.102
First arrest rhythm					0.361
Asystole (%)	6877 (57.9)	671 (58.0)	4612 (57.9)	1594 (57.8)	
PEA (%)	3118 (26.3)	317 (27.4)	2081 (26.1)	720 (26.1)	
Unknown unshockable (%)	394 (3.3)	32 (2.8)	271 (3.4)	91 (3.3)	
Unknown shockable (%)	101 (0.9)	10 (0.9)	65 (0.8)	26 (0.9)	
VT (%)	31 (0.3)	4 (0.3)	18 (0.2)	9 (0.3)	
VF (%)	1301 (11.0)	119 (10.3)	887 (11.1)	295 (10.5)	
Unknown (%)	52 (0.4)	3 (0.3)	28 (0.4)	21 (0.8)	
Any ROSC (%)	3487 (29.4)	322 (27.9)	2340 (29.4)	825 (29.9)	0.426
Survival outcomes (%)	298 (2.5)	19 (1.6)	199 (2.5)	80 (2.9)	0.071

AED—automated external defibrillator; CPR—cardiopulmonary resuscitation; DA-CPR—dispatcher-assisted cardiopulmonary resuscitation; EMS—emergency medical services; SHI—Singapore Housing Index; HIV—Human Immunodeficiency Virus; IQR—interquartile range; PEA—pulseless electrical activity; ROSC—return of spontaneous circulation; VF—ventricular fibrillation; VT—ventricular tachycardia.

Secondary Outcomes

There were no significant differences in the proportion of ROSC either en-route or at ED across three categories of SHI (p=0.426) (Table 1). High SHI patients had higher 30-day survival compared to low SHI patients on unadjusted analysis (OR 1.789, 95% CI 1.080-2.964, p=0.024) but not adjusted analysis (aOR 1.629, 95% CI 0.946-2.805, p=0.079). Low SHI and medium SHI patients had no statically significant difference in survival (Table 2). As a continuous variable, SHI was significantly associated with increased 30-day survival on unadjusted analysis (OR 1.092, 95% CI 1.003-1.188, p=0.042), but not on adjusted analysis (aOR 1.041, 95% CI 0.949-1.141, p=0.395) (Table 3).

Subgroup Analysis

Females in the medium SHI tier were significantly more likely to receive BCPR (OR 1.407, 95% CI 1.082-1.828, p=0.011) than those in the low SHI tier (Table 4). Comparing medium SHI with low SHI, females demonstrated a larger association between bystander CPR rates and SHI compared to males (ratio of OR 1.47, 95% CI 1.12–1.93), which was also observed in the comparison between high SHI and low SHI (OR 1.37, 95% CI 1.01–1.85). There were no significant associations between SHI and bystander CPR in the subgroups age ≥65 years, witnessed arrest, daytime arrest, and arrests after 2014, and no interaction effects were observed.

Discussion

In this study, we found that low SHI was associated with the lowest odds of receiving bystander CPR, higher SHI was associated with higher 30-day survival on unadjusted analysis, and females were more susceptible to the effect of low SES on the rate of bystander CPR.

Low SES has been linked to reduced bystander CPR in OHCA, based on area-level SES studies (11). In a meta-analysis of 12 studies, the SES of the area in which OHCA occurred was associated with bystander CPR in 10 studies, but evidence on individual level SES was lacking (12). Area-level SES measures, often categorizing the area by census tract level or district level data (27–30), are susceptible to the ecological fallacy (i.e. inaccurately classifying individuals' exposure). For example, a spatial scan statistic showed clusters of a few kilometers radius with lower-than-expected bystander CPR rates compared to the rest of Houston, even after adjustments for individual-level characteristics (31). A building-level marker such as the SHI used in this study, being a small area measure, reduces misclassification compared to area-level markers (19). We found that low building-level SES as both a categorical and continuous variable remained significantly associated with lower odds of bystander CPR, suggesting that there is a robust relationship, and public CPR education and policies targeting low building-level SES may be more effective than those based on area-level SES.

The disparity in bystander CPR rates among low SES communities is likely multifactorial. A national population-based survey in Singapore demonstrated that the likelihood of an individual being trained in CPR was dependent on education and income levels (17). As those who are trained in CPR are more likely to perform bystander CPR (32), a lower rate of CPR training may contribute to lower bystander CPR rates. Discrimination and prejudice against patients of lower SES may contribute to the hesitancy for CPR delivery (33). In the landmark study by Sasson et al., Black and Hispanic patients were 30% less likely to received bystander CPR (28). We found that significantly fewer patients in the low SHI group were Chinese and more were Malay. However, after adjusting for race, the effect of SES on bystander CPR rates did not change significantly; therefore, race was unlikely to be a confounder in this group. Similarly, other studies on SES and clinical outcomes in cancer and falls found no significant effect of race on outcomes after adjusting for SES (22–24). Further studies are needed to understand the root causes behind the association of low SES and low bystander CPR levels.

Low SES is also consistently associated with reduced survival to discharge post-OHCA, suggesting that the lower rate of bystander CPR has implications on OHCA outcomes (11). OHCA in predominantly Black neighborhoods had the lowest rates of bystander CPR, AED use, and survival in one study (34). Interestingly, a meta-analysis of 13 studies found that survival was associated with individual-level SES of the patient but not the area-level SES of the patient (12). Smaller area-level SES may be more strongly associated with survival, as the aggregated education level of 1 km^2 grid cells in Stockholm was a strong predictor of 30-day survival after OHCA, on par with the effect of bystander CPR (35). We found that at a building level, OHCA patients at lower SHI tiers had similar survival, but our study was perhaps underpowered for this outcome.

Table 2. Unadjusted and adjusted odds ratios (OR) for receipt of bystander CPR and 30-day survival by SHI tiers.

Outcome	N (%) with outcome	Unadjusted OR	*P* value	95% CI	Adjusted OR	*P* value	95% CI
Bystander CPR[a]							
Low SHI	480 (41.5%)	Reference			Reference		
Medium SHI	4056 (50.9%)	1.462	**<0.01**	1.291–1.657	1.483	**<0.01**	1.301–1.691
High SHI	1562 (56.7%)	1.842	**<0.01**	1.603–2.117	1.933	**<0.01**	1.669–2.240
30-day survival[b]							
Low SHI	19 (1.6%)	Reference			Reference		
Medium SHI	199 (2.5%)	1.534	0.077	0.954–2.466	1.581	0.075	0.954–2.618
High SHI	80 (2.9%)	1.789	**0.024**	1.080–2.964	1.629	0.079	0.946–2.805

CI—confidence interval; CPR—cardiopulmonary resuscitation; SHI—Singapore Housing Index; OR—odds ratio.
[a]**Adjusted for covariates:** age, sex, race, witness status, arrest time, cancer, first arrest rhythm (shockable, non-shockable), year of arrest (before 2014, after 2014).
[b]**Adjusted for covariates:** age, sex, race, witness status, arrest time, cancer, first arrest rhythm (shockable, non-shockable), year of arrest (before 2014, after 2014), bystander CPR.

Table 3. Unadjusted and adjusted odds ratios (OR) for receipt of bystander CPR by SHI as continuous variable.

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Bystander CPR[a]				
SHI (Continuous)	1.136 (1.107–1.167)	**<0.001**	1.142 (1.110–1.174)	**<0.001**
30-day survival[b]				
SHI (Continuous)	1.092 (1.003–1.188)	**0.042**	1.041 (0.949–1.141)	0.395

CI—confidence interval; CPR—cardiopulmonary resuscitation; SHI—Singapore Housing Index; OR—odds ratio.
[a]**Adjusted for covariates:** age, sex, race, witness status, arrest time, cancer, first arrest rhythm (shockable, non-shockable), year of arrest (before 2014, after 2014).
[b]**Adjusted for covariates:** age, sex, race, witness status, arrest time, cancer, first arrest rhythm (shockable, non-shockable), year of arrest (before 2014, after 2014), bystander CPR.

In addition to lower rates of bystander CPR, other factors may contribute to the differential outcomes based on SES. For cardiac arrests in the inpatient setting, thus independent of bystander CPR, both high patient-level income and education were associated with increased survival with good neurological outcomes and 30-day survival in Sweden (33). In Korea, patients under Medical Aid were less likely to receive coronary reperfusion therapy or targeted temperature management post OHCA, and had worse neurological outcomes (36). Identification of the relative effects of prehospital factors and inpatient care on the association of SES with survival post-OHCA would allow targeted interventions to be made accordingly. As patients from low SHI were younger and had fewer co-morbidities in our study, we postulate that there could be an element of underdiagnosis of cardiovascular risk factors and co-morbidities, and lower engagement with health care. Further investigation is needed to characterize this and identify the possible effects on OHCA survival.

Age and sex may influence the rates of bystander CPR based on previous studies. Women, particularly those aged >55 years, had lower rates of survival post OHCA compared to men (OR 0.64), which was no longer significant after adjusting for prehospital Utstein factors, such as location of OHCA, initial rhythm, witness status, and bystander CPR (37). Women were significantly less likely to receive bystander CPR and AED shocks in North America (37). Similarly, the OPALS study based in Ontario found that lower rates of bystander CPR and shockable rhythms contributed to the lower probability of survival post-OHCA in women (13). Reasons proposed for the low bystander CPR rate in females include longer delay from OHCA onset to recognition by bystanders due to atypical presentations, or social factors such as women being more likely to live alone due to a longer life-expectancy than men (38).

The low bystander CPR rate in females may be an important factor in their low probability of OHCA survival, and sex may further compound the relationship between SES on bystander CPR rates. Recent systematic reviews did not find any studies reporting age and sex differences in SES trends on OHCA (12), although for coronary heart disease, stroke, and cardiovascular diseases, a meta-analysis found that there was significantly greater excess risk associated with low SES in women than men (39). Our study found that women showed a steeper decrease in bystander CPR rates associated with lower SHI than men. A national survey of members of the public found perceived fears of inappropriate touching, accusations of sexual assault, and causing injury as women are weak and frail to be reasons against performing CPR in women (40). These factors may play less of a role in OHCA cases in private residences, but other factors such as women being more likely to live alone or be the caregiver in a household may have an effect. Further research into the societal and cultural factors that may influence rates of bystander CPR is needed. One way of addressing this disparity may be to focus on recognizing OHCA and performing bystander CPR in women in community CPR education programs, to increase the confidence of the public on performing CPR in women, especially in areas with low SES.

Table 4. Interaction effect of bystander CPR by SHI as categorical variable.

Covariate	SHI category	N (%)	Unadjusted OR (95% CI)	*P* value	Ratio of OR (95% CI)	*P* value
Age ≥65	Low	676 (58.5%)	Reference		Reference	
	Medium	5028 (63.1%)	1.279 (0.992–1.649)	0.057	1.218 (0.934–1.589)	0.145
	High	1899 (68.9%)	1.205 (0.904–1.607)	0.204	1.179 (0.873–1.594)	0.283
Female	Low	410 (35.5%)	Reference		Reference	
	Medium	3274 (41.1%)	1.407 (1.082–1.828)	0.011	1.472 (1.120–1.935)	0.006
	High	1199 (43.5%)	1.320 (0.988–1.764)	0.060	1.370 (1.012–1.853)	0.041
Witnessed Arrest	Low	570 (49.3%)	Reference		Reference	
	Medium	4158 (52.2%)	1.109 (0.864–1.424)	0.416	1.123 (0.865–1.458)	0.383
	High	1461 (53.0%)	1.053 (0.797–1.392)	0.714	1.098 (0.821–1.469)	0.528
Daytime Arrest	Low	649 (56.1%)	Reference		Reference	
	Medium	4543 (57.1%)	1.017 (0.790–1.308)	0.897	0.919 (0.706–1.196)	0.531
	High	1602 (58.1%)	0.990 (0.748–1.311)	0.944	0.963 (0.718–1.292)	0.803
Arrests after 2014	Low	665 (57.5%)	Reference		Reference	
	Medium	4687 (58.9%)	1.065 (0.815–1.393)	0.643	1.070 (0.817–1.400)	0.624
	High	1611 (58.5%)	1.076 (0.800–1.448)	0.628	1.071 (0.795–1.444)	0.651

CI—confidence interval; CPR—cardiopulmonary resuscitation; SHI—Singapore Housing Index; OR—odds ratio.

Strengths and Limitations

A major strength of this study was the use of building-level SES measure, the SHI developed by Wong et al. (19), which was a good compromise between area-level data susceptible to ecological fallacy, and individual-level data, with loss of community-level factors such as benefits of living in a highly educated area (35). National patient-level data on OHCA in Singapore were extracted from a prospective database with cases captured from ambulance services and hospital cases, therefore providing reliable data on prehospital care such as bystander CPR, initial rhythm, and location of arrests. This study has several limitations. First, we did not have access to individual-level SES, and the ecological fallacy remained possible. Individual-level SES data (mainly income, education, and occupation) are especially difficult to obtain in Singapore's context as the collection and use of these sensitive data are impeded by increasing confidentiality issues and the associated legalities. Second, as this was a retrospective observational analysis, causality between low SES and low rates of bystander CPR cannot be conclusively inferred given possible residual confounding. For example, reliable data on the rates of smoking were not available, and cannot be excluded as a confounding factor between SES and survival. We also excluded cases of OHCA without a registered address, mostly due to inaccurate or missing recording rather than homelessness, as the rate of homeless in Singapore is very low (41). A quarter of the patients in this study had OHCA of unspecified causes (in the "other" category), which may have a different bystander CPR rate compared to medical causes of OHCA. Third, this study was likely underpowered in the analysis of survival post-OHCA, therefore concrete conclusions could not be made. Lastly, we did not investigate the effect of the SES of the bystander-on-bystander CPR or survival post-OHCA, and the SES of the bystander may not be the same as that of the patient, especially for daytime arrests.

Conclusions

In this study we found that lower building-level SES was independently associated with lower rate of bystander CPR. Higher SES was associated with higher 30-day survival on unadjusted analysis but not adjusted analysis, and this study may be under-powered for this outcome. Females were more susceptible to the effect of low SES on lower rate of bystander CPR, and community CPR training should focus on recognizing OHCA and performing bystander CPR on women in low SES communities. Public CPR education and policies targeting low building-level SES may be more effective than those based on area-level SES.

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Authors' Contributions

Andrew Ho: Conceptualization, methodology, investigation, resources, writing—review & editing Priscilla Ting, Jamie Ho: Investigation, data curation, formal analysis, writing—original draft Stephanie Fook-Chong: Investigation, data curation, formal analysis, writing—review & editing Nur Shahidah: Investigation, resources, writing—review & editing Pin Pin Pek, Nan Liu, Seth Teoh En: Investigation, validation, data curation, writing—review & editing Ching-Hui Sia, Daniel Lim: Investigation, data curation, writing—review & editing Shir Lynn Lim, Ting Hway Wong, Marcus Ong: Supervision, conceptualization, methodology, data curation, writing—review & editing

Disclosure Statement

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Chapter 9

Impact of bystander-focused public health interventions on cardiopulmonary resuscitation and survival: a cohort study

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Summary

Background: Bystander cardiopulmonary resuscitation (CPR) increases an individual's chance of survival from out-of-hospital cardiac arrest (OHCA), but the frequency of bystander CPR is low in many communities. We aimed to assess the cumulative effect of CPR-targeted public health interventions in Singapore, which were incrementally introduced between 2012 and 2016.

Methods: We did a secondary analysis of a prospective cohort study of adult, non-traumatic OHCAs, through the Singapore registry. National interventions introduced during this time included emergency services interventions, as well as dispatch-assisted CPR (introduced on July 1, 2012), a training programme for CPR and automated external defibrillators (April 1, 2014), and a first responder mobile application (myResponder; April 17, 2015). Using multilevel mixed-effects logistic regression, we modelled the likelihood of receiving bystander CPR with the increasing number of interventions, accounting for year as a random effect.

Findings: The Singapore registry contained 11 465 OHCA events between Jan 1, 2011, and Dec 31, 2016. Paediatric arrests, arrests witnessed by emergency medical services, and healthcare-facility arrests were excluded, and 6788 events were analysed. Bystander CPR was administered in 3248 (48%) of 6788 events. Compared with no intervention, likelihood of bystander CPR was not significantly altered by the addition of emergency medical services interventions (odds ratio [OR] 1·33 [95% CI 0·98–1·79]; p=0·065), but increased with implementation of dispatch-assisted CPR (3·72 [2·84–4·88]; p<0·0001), with addition of the CPR and automated external defibrillator training programme (6·16 [4·66–8·14]; p<0·0001), and with addition of the myResponder application (7·66 [5·85–10·03]; p<0·0001). Survival to hospital discharge increased after the addition of all interventions, compared with no intervention (OR 3·10 [95% CI 1·53–6·26]; p<0·0001).

Interpretation: National bystander-focused public health interventions were associated with an increased likelihood of bystander CPR, and an increased survival to hospital discharge. Understanding the combined impact of public health interventions might improve strategies to increase the likelihood of bystander CPR, and inform targeted initiatives to improve survival from OHCA.

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Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2010, and Oct 1, 2019, with the terms "cardiopulmonary resuscitation", "bystander", "CPR", "bystander CPR", "bystander cardiopulmonary resuscitation", "sudden cardiac arrest", "cardiac arrest", and "out of hospital cardiac arrest". We also cross-referenced this search with "dispatch-assisted CPR", "dispatch CPR", "telecommunicator CPR", "CPR training", "AED training", "resuscitation training", and "mobile phone technologies".

We reviewed the referenced lists of articles and selected those deemed most relevant. Bystander cardiopulmonary resuscitation (CPR) increases an individual's chance of survival from out-of-hospital cardiac arrest (OHCA), but the frequency of bystander CPR is low (approximately 40% likelihood) in many communities. Community-level, bystander-focused public health interventions might affect likelihood of bystander CPR and survival. Some analyses have examined the effect of individual interventions, but few studies have examined the combined effect of these interventions on bystander CPR and survival.

Added value of this study

We aimed to assess the cumulative effect of bystander-focused public health interventions on the likelihood of bystander CPR and subsequent survival to hospital discharge. We found that national bystander-focused public health interventions (dispatch-assisted CPR, CPR and automated external defibrillator training, and the myResponder mobile application) increased the likelihood of layperson bystander CPR. Additionally, these findings were associated with increased survival to hospital discharge. This study provides insight into ways to potentially increase bystander CPR and survival through community-level, bystander-focused public health interventions.

Implications of all the available evidence

These findings could help inform future public policy initiatives and considerations for allocating resources to increase the likelihood of receiving bystander CPR and improve outcomes from cardiac arrest.

Introduction

Bystander cardiopulmonary resuscitation (CPR) can double an individual's chance of survival from out-of-hospital cardiac arrest (OHCA), but bystander CPR frequency is low in many communities.[1,2] [3]The National Academy of Medicine and the International Liaison Committee on Resuscitation have highlighted increasing bystander CPR as a crucial international objective. [4,5] Few studies have examined the combined effect of bystander-focused public health interventions on bystander CPR frequency and subsequent survival.

Several studies have examined the large-scale impact of single, city-wide, public health interventions on bystander CPR. For example, in Phoenix, AZ, USA, implementation of a bundled dispatch-assisted CPR protocol conferred a 7% increase in bystander CPR frequency and subsequent survival also increased (odds ratio [OR] 1·64, 95% CI 1·61–2·30). [6,7] Furthermore, a Swedish study demonstrated an ecological correlation between mass CPR training and increased rates of bystander CPR before the arrival of emergency medical services. [3] Additionally, mobile-phone dispatching of layperson volunteers was shown to be associated with a significant increase in bystander CPR frequency in the population. [8] Although many of these studies have shown the independent impact of interventions on bystander CPR frequency, few studies have examined the cumulative impact of each additional intervention. This knowledge could help inform future public health planning and public policy initiatives surrounding OHCA, by helping to identify the core components necessary to improve bystander CPR frequency and survival, while simultaneously reducing the resources required.

Singapore has been collecting prospective nationwide OHCA data through the Pan-Asian Resuscitation Outcome Study (PAROS), and has implemented a series of public health interventions to increase bystander CPR frequency. We aimed to assess the cumulative effect of a bundle of public health interventions on bystander CPR and survival. We hypothesised that implementation of three interventions together: dispatch-assisted CPR, CPR and automated external defibrillator training, and a first responder mobile application (myResponder), would increase bystander CPR frequency by at least 100%.

Methods

Study design and setting

We did a secondary analysis of a prospective cohort registry study, examining differences in likelihood of bystander CPR and survival after the implementation of national bystander interventions in Singapore. Singapore is a single city-state island in southeast Asia and has a population of 5·7 million residents. The population is projected to continue to grow at a rate of 1·4% per year, and is comprised of a mixture of Chinese, Malay, Indian, and other ethnic populations. The population density is 55623 people per km^2.[9] The heterogeneity in ethnicities and density of Singapore's population allows for a unique, contained assessment of the effect of bystander public health interventions on outcomes after OHCA. The Centralised Institutional Review Board (2013/604/C) and the Domain Specific Review Board (2013/00929) granted approval for this study. For the primary PAROS study, each participating site obtained Institutional Review Board approval from their respective national board and met the criteria for minimal risk. As the data were de-identified, the SingHealth Institutional Review Board determined this study to be exempt from requirements for informed consent.

Data sources

We used de-identified registry data collected prospectively by PAROS in Singapore from Jan 1, 2011, to Dec 31, 2016. PAROS represents a clinical research network formed in 2010 by pre-hospital health-care providers and emergency care physicians conducting research in the Asia-Pacific region, with data from Japan, Malaysia, Singapore, South Korea, Taiwan, Thailand, and the United Arab Emirates.[10] [11] [12] Collected variables use the Utstein definitions for OHCA and include bystander CPR and other time-sensitive OHCA data elements.[13] Data from the emergency medical services system and hospital are linked and governed by the Unit for Prehospital Emergency Care, Ministry of Health for Singapore's national OHCA registry. De-identified data are then sent to the PAROS network, as Singapore is a participating site.[12] Data collected are entered into a secured online electronic data capture system developed with assistance from the US Center for Disease Control and the Cardiac Arrest Registry to Enhance Survival. All data entered into the data capture system are assigned a unique case number to ensure patient de-identification. Each participating site has their own local research coordinator who is responsible for ensuring data accuracy and completion. Additional quality assurance measures include a built-in validation rule that cross-checks data fields and flags missing fields to ensure accurate and complete data capture. The PAROS data administrator manages the online data entry system and performs additional data quality audits. In Singapore, OHCA data from seven participating tertiary hospitals (including one children's hospital) are collected prospectively by a research coordinator following similar data quality checks and verification. All OHCA patients transported by the national emergency medical services agency to the tertiary hospitals were included in the study. PAROS epidemiological data and in-hospital data have also been reported elsewhere. [14] [15] [16] [17] From 2011 to 2016 (the period of the study), Singapore did not have a termination of resuscitation rule; the termination of resuscitation protocol would allow paramedics to terminate ongoing resuscitation and pronounce the death at the scene if certain conditions were fulfilled.

Procedures

During the study period, various public health interventions to improve the effectiveness of CPR in OHCA were introduced across Singapore, including improved equipment in emergency response vehicles, protocols for dispatch-assisted bystander CPR, and community first responder training. We determined the date of implementation of each intervention, and approximated a 6-month run-in period to account for intervention dissemination (informed by the original report[18] of one of the interventions, dispatch-assisted CPR, in which greater than 50% of dispatch-assisted CPR calls correctly followed the new protocol by 6 months). The implementation information was gathered from the individuals and organisations that enacted the programmes nationwide. The comparison group was all cases that occurred prior to the intervention periods (pre-intervention category; from Jan 1, 2011, to Dec 31, 2011).

The first set of interventions (commenced Jan 1, 2012; run-in completed June 30, 2012) focused on emergency medical services, including providing emergency medical services access to mechanical CPR devices in ambulances, and the Firebiker scheme in which fire and rescue specialists trained in appropriate resuscitation techniques are dispatched on a motorcycle ahead of an ambulance.[19] Subsequently, on July 1, 2012 (run-in completed June 30, 2012), a centralised protocol for dispatch-assisted CPR was introduced throughout Singapore.[20] The protocol was adapted from that of the Arizona Department of Health Services,[21] and the dispatcher would use the compression-only protocol to guide the caller. An audit and review of 3371 OHCA events (35·9% of 9400 total cases) between July 1, 2012, and Dec 31, 2016, found that 2435 (72·2%) of patients in these 3371 cases were given dispatch-assisted CPR in compliance with the protocol.

After successful implementation of dispatch-assisted CPR, a community-based training programme for dispatch-assisted first responders was introduced in April 1, 2014 (run-in completed Oct 31, 2014), providing free training on CPR and automatic external defibrillators to school children and members of the general public. The dispatch-assisted first responder training programme focuses on training individuals to telephone the emergency services on 9-9-5, push hard and fast on the centre of the chest (compression-only CPR), and use an automatic external defibrillator. From April 1, 2014, to Dec 31, 2016, 41 021 individuals were trained through this programme; 36936 through at least 100 schools and 4085 in public settings including workplaces, offices, community centres, places of worship, and government buildings.

Finally, on April 17, 2015 (run-in completed Oct 16, 2015), Singapore supported the centralised availability of the myResponder mobile application, which crowdsources layperson responders with CPR and automatic external defibrillator training to respond to cardiac arrest events within 400 m of their location.[22] Layperson responders do not need to be certified in CPR and automatic external defibrillator use to enrol with myResponder. Additionally, the myResponder application has the ability to show nearby automatic external defibrillators upon acceptance of the case by responders. Since 2015, 12248 volunteers have enrolled in myResponder. On Oct 1, 2015, the myResponder application was extended to crowdsource Singapore Mass Rapid Transit taxi drivers (n=100) equipped with automatic external defibrillators, who previously had enrolled in the AEDonWheels programme. Taxi drivers were notified via myResponder to assist with suspected cardiac arrests within a 1·5 km radius of their location. For the purposes of this analysis, we compared events after each additional intervention to events in the pre-intervention period. In the sensitivity analysis, we combined events in the pre-intervention period with events after non-bystander, emergency medical services interventions (appendix p 1).[1]

Outcomes

Consistent with our prior work, we defined bystander CPR, our primary outcome, as delivery of CPR from a layperson bystander, excluding CPR from law enforcement or emergency medical services first responders.[23] Survival, our secondary outcome, was defined as survival to hospital discharge. This information was taken from the emergency medical services forms and verified by emergency medical services personnel. We excluded paediatric arrests (in individuals younger than 18 years of age), arrests witnessed by emergency medical services, and OHCA events from traumatic injury or non-cardiac causes. We also excluded arrest events that occurred in a residential institution (e.g., skilled nursing facility) or health-care centre. Patient ethnicity was modelled categorically; age was modelled as a continuous variable. Location of cardiac arrest was defined as residential (i.e., home) or non-residential (e.g., public building, place of recreation, or other public location). As bystander response to OHCA varies by location, examining variation by location was warranted.

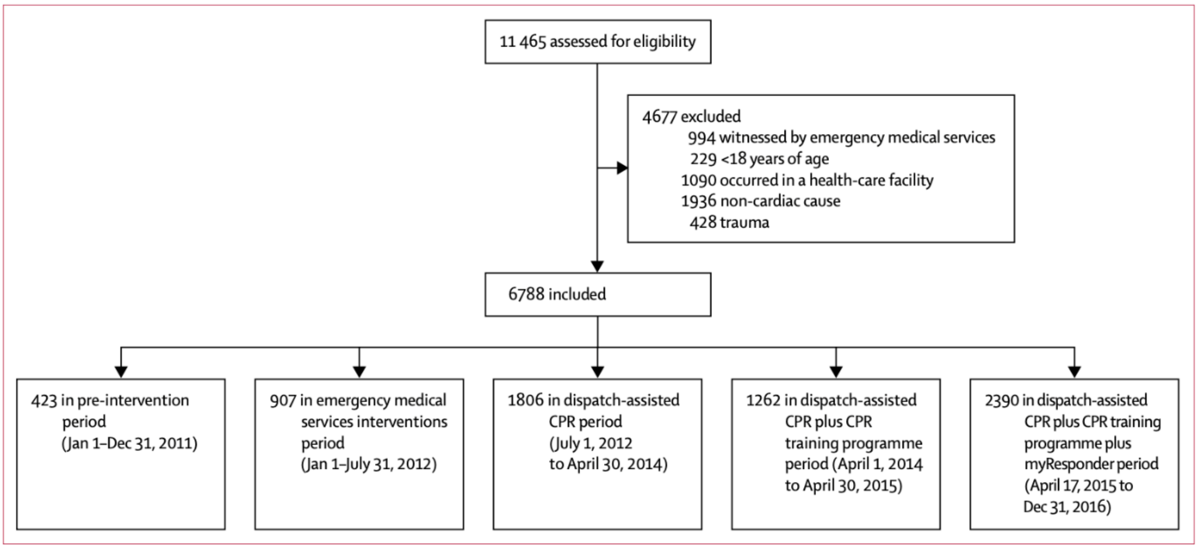

Figure 1: **Out-of-hospital cardiac arrests categorised by intervention period**
CPR=cardiopulmonary resuscitation.

[1] See **Online** for appendix

	Overall (n=6788)	Pre-interventions (n=423)	Emergency medical services interventions (n=907)	Dispatch-assisted CPR (n=1806)	Dispatch-assisted CPR plus CPR training programme (n=1262)	Dispatch-assisted CPR plus CPR training programme plus myResponder (n=2390)
Bystander CPR						
No	3540 (52·2%)	344 (81·3%)	701 (77·3%)	1010 (55·9%)	551 (43·7%)	934 (39·1%)
Yes	3248 (47·8%)	79 (18·7%)	206 (22·7%)	796 (44·1%)	711 (56·3%)	1456 (60·9%)
Survival to hospital discharge						
No	6451 (95·0%)	402 (95·0%)	851 (93·8%)	1732 (95·9%)	1205 (95·5%)	2261 (94·6%)
Yes	297 (4·4%)	10 (2·4%)	27 (3·0%)	74 (4·1%)	57 (4·5%)	129 (5·4%)
Location of arrest						
Non-residential	1562 (23·0%)	93 (22·0%)	202 (22·3%)	450 (24·9%)	290 (23·0%)	527 (22·1%)
Residential	5226 (77·0%)	330 (78·0%)	705 (77·7%)	1356 (75·1%)	972 (77·0%)	1863 (77·9%)
Age, years (IQR)	67 (52–82)	65 (50–80)	66 (51–81)	67 (52–82)	67 (52–82)	68 (53–83)
Gender						
Male	4615 (68·0%)	285 (67·4%)	651 (71·8%)	1220 (67·6%)	860 (68·1%)	1599 (66·9%)
Female	2173 (32·0%)	138 (32·6%)	256 (28·2%)	586 (32·4%)	402 (31·9%)	791 (33·1%)
Ethnicity						
Chinese	4434 (65·3%)	266 (62·9%)	585 (64·5%)	1215 (67·3%)	821 (65·1%)	1547 (64·7%)
Indian	819 (12·1%)	57 (13·5%)	120 (13·2%)	182 (10·1%)	157 (12·4%)	303 (12·7%)
Malay	1129 (16·6%)	71 (16·8%)	131 (14·4%)	312 (17·3%)	213 (16·9%)	402 (16·8%)
Other	406 (6·0%)	29 (6·9%)	71 (7·8%)	97 (5·4%)	71 (5·6%)	138 (5·8%)
Receiving hospital						
A	557 (8·2%)	9 (2·1%)	28 (3·1%)	71 (3·9%)	61 (4·8%)	388 (16·2%)
B	1530 (22·5%)	112 (26·5%)	204 (22·5%)	402 (22·3%)	282 (22·3%)	530 (22·2%)
C	1154 (17·0%)	81 (19·1%)	188 (20·7%)	311 (17·2%)	205 (16·2%)	369 (15·4%)
D	1154 (17·0%)	98 (23·2%)	167 (18·4%)	373 (20·7%)	295 (23·4%)	221 (9·2%)
E	1709 (25·2%)	79 (18·7%)	230 (25%)	459 (25·4%)	299 (23·7%)	642 (26·9%)
F	684 (10·1%)	44 (10·4%)	90 (9·9%)	190 (10·5%)	120 (9·5%)	240 (10·0%)

(Table 1 continues on next page)

	Overall (n=6788)	Pre-interventions (n=423)	Emergency medical services interventions (n=907)	Dispatch-assisted CPR (n=1806)	Dispatch-assisted CPR plus CPR training programme (n=1262)	Dispatch-assisted CPR plus CPR training programme plus myResponder (n=2390)
(Continued from previous page)						
Time of day						
2300–0559 h	1316 (19·4%)	84 (19·9%)	167 (18·4%)	340 (18·8%)	267 (21·2%)	458 (19·2%)
0600–0859 h	982 (14·5%)	63 (14·9%)	129 (14·2%)	263 (14·6%)	166 (13·2%)	361 (15·1%)
0900–1559 h	2236 (32·9%)	132 (31·2%)	313 (34·5%)	581 (32·2%)	419 (33·2%)	791 (33·1%)
1600–1859 h	998 (14·7%)	60 (14·2%)	133 (14·7%)	270 (15·0%)	169 (13·4%)	366 (15·3%)
1900–2259 h	1220 (18·0%)	81 (19·1%)	159 (17·5%)	342 (18·9%)	234 (18·5%)	404 (16·9%)
Response time						
<8 min	2245 (33·1%)	192 (45·4%)	361 (39·8%)	602 (33·3%)	332 (26·3%)	758 (31·7%)
≥8 min	4543 (66·9%)	231 (54·6%)	546 (60·2%)	1204 (66·7%)	930 (73·7%)	1632 (68·3%)
ROSC						
No	4887 (72·0%)	327 (77·3%)	686 (75·6%)	1290 (71·4%)	877 (69·5%)	1707 (71·4%)
Yes	1679 (24·7%)	89 (21·0%)	200 (22·1%)	471 (26·1%)	349 (27·7%)	570 (23·8%)
Not applicable*	222 (3·3%)	7 (1·7%)	21 (2·3%)	45 (2·5%)	36 (2·9%)	113 (4·7%)
First arrest rhythm						
Asystole	3313 (48·9%)	239 (56·5%)	477 (52·6%)	904 (50·1%)	625 (49·5%)	1068 (44·7%)
PEA	1560 (23·0%)	86 (20·3%)	200 (22·1%)	392 (21·7%)	319 (25·3%)	563 (23·6%)
Unknown shockable or unshockable	483 (7·1%)	3 (0·7%)	14 (1·5%)	121 (6·7%)	47 (3·7%)	298 (12·5%)
VF or VT	1386 (20·4%)	92 (21·3%)	212 (23·4%)	382 (21·2%)	255 (20·2%)	445 (18·6%)
Not applicable*	42 (0·6%)	2 (0·5%)	1 (0·1%)	7 (0·4%)	16 (1·3%)	16 (0·7%)
Defibrillation						
No	4441 (65·4%)	304 (71·9%)	612 (67·5%)	1192 (66·0%)	795 (63·0%)	1538 (64·4%)
Yes	2301 (33·9%)	116 (27·4%)	291 (32·1%)	607 (33·6%)	451 (35·7%)	836 (35·0%)
Not applicable*	42 (0·6%)	2 (0·5%)	1 (0·1%)	7 (0·4%)	16 (1·3%)	16 (0·7%)
Year						
2011	914 (13·5%)	423 (100·0%)	491 (54·1%)	..	..	..
2012	876 (12·9%)	..	416 (45·9%)	460 (25·5%)	..	..
2013	1020 (15·0%)	..	..	1020 (56·5%)	..	..
2014	1208 (17·8%)	..	..	326 (18·1%)	882 (69·9%)	..
2015	1350 (19·9%)	..	..	..	380 (30·1%)	970 (40·6%)
2016	1420 (20·9%)	..	..	..	..	1420 (59·4%)

Data are n (%) unless otherwise stated. Missing data: survival to hospital discharge (n=40), time of day (n=36), first arrest rhythm (n=4), and defibrillation (n=4). Receiving hospital names are not disclosed. CPR=cardiopulmonary resuscitation. ROSC=return of spontaneous circulation. PEA=pulseless electrical activity. VF=ventricular fibrillation. VT=pulseless ventricular tachycardia. *Refers to arrest patients that were transported to the hospital by transport other than the emergency medical services, as this information is not provided in these cases.

Table 1: **Patient demographics**

Statistical analysis

There was minimal missing data for the primary outcome, secondary outcome, and independent variables of interest, thus we analysed the data in a complete case analysis, using STATA/SE 16.0. We initially examined the data using descriptive statistics and frequencies. Next, we fit a multilevel mixed-effects logistic regression model (command "melogit" in STATA) to assess the differences in likelihood of bystander CPR, and survival to hospital discharge, with increased public health intervention. We chose to model year as a random effect rather than a fixed effect, to allow for random heterogeneity within the year variable. Consistent with prior investigations, patient-level variables with a p value less than 0·15 for association in a univariate analysis were included in the final multivariable model, in addition to variables added on the basis of clinical significance. The final regression model for both the primary outcome of likelihood of receipt of bystander CPR and the secondary outcome of survival to hospital discharge included intervention (exposure); gender, age, ethnicity, and location of the patient; witness status; receiving hospital; response time; time of day; and year. We included receiving hospital as a fixed effect in the final regression equation. We examined likelihood of bystander CPR with increased intervention, stratified by residential and non-residential locations. To further examine our data, we used predictive margins, specifically the "margins" and "marginsplot" package in STATA to view the data and understand the likelihood of bystander CPR and survival with each additional intervention.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and senior author had full access to all of the data and had the final responsibility for the decision to submit for publication.

	Bystander CPR (n=6752)		Survival to hospital discharge (n=6715)	
	OR (95% CI)	p value	OR (95% CI)	p value
Pre-interventions	1·0	..	1·0	..
Emergency medical services interventions	1·33 (0·98–1·79)	0·065	1·62 (0·74–3·53)	0·22
Dispatch-assisted CPR	3·72 (2·84–4·88)	<0·0001	2·12 (1·04–4·33)	0·040
Dispatch-assisted CPR plus CPR training programme	6·16 (4·66–8·14)	<0·0001	2·50 (1·20–5·19)	0·014
Dispatch-assisted CPR plus CPR training programme plus myResponder	7·66 (5·85–10·03)	<0·0001	3·10 (1·53–6·26)	<0·0001

Models for bystander CPR and survival to hospital discharge were mixed-effects regressions controlling for age, gender, ethnicity, and location of the patient, witness status, receiving hospital, response time, and time of day. CPR=cardiopulmonary resuscitation. OR=odds ratio.

Table 2: **Likelihood of bystander CPR and survival to hospital discharge by number of public health interventions**

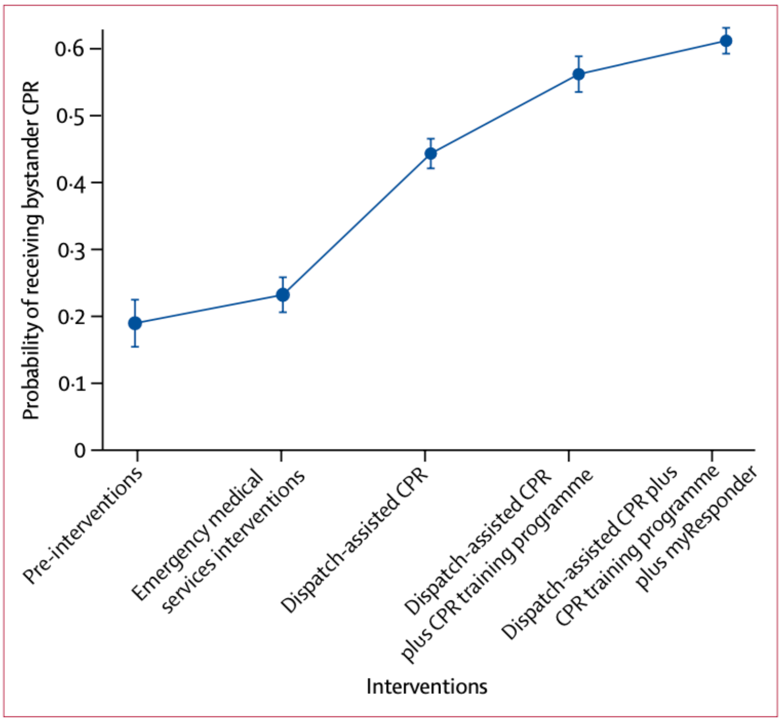

Figure 2: **Probability of bystander CPR by number of interventions**
CPR=cardiopulmonary resuscitation.

Results

From Jan 1, 2011, to Dec 31, 2016, the Singapore PAROS registry recorded 11 465 OHCA events.

After excluding paediatric arrests, arrests in health-care facilities, arrests witnessed by emergency medical services, and arrests of non-cardiac cause, 6788 events were analysed (figure 1, table 1).

Arrests during the period after implementation of interventions focused on emergency medical services were associated with a slight, non-significant increase in bystander CPR frequency compared with the pre-intervention period, from 18·7% (79 of 423 arrests) in the pre-intervention period to 22·7% (206 of 907 arrests) in the intervention period (OR 1·33 [95% CI 0·98–1·79]; p=0·065). Arrests in the period after implementation of dispatch-assisted CPR were associated with an increased likelihood of bystander CPR (44·1%; 796 of 1806 arrests) compared with arrests in the pre-intervention period (3·72 [2·84–4·88]; p<0·0001). The odds of receiving of bystander CPR increased again after the implementation of the dispatch-assisted first responder training programme (56·3%; 711 of 1262 arrests; OR 6·16 [4·66–8·14]; p<0·0001) and after the implementation of the myResponder application (60·9%; 1456 of 2390 arrests; 7·66 [5·85–10·03]; p<0·0001), compared with the pre-intervention period (table 2). The predicted probability of receiving bystander CPR increased with each added intervention (figure 2).

Dispatch-assisted CPR and subsequent interventions were associated with an increased likelihood of bystander CPR compared with the pre-intervention period in arrests that occurred in residential locations (n=5213, p<0·0001). Within residential locations, there was increased frequency of bystander CPR after implementation of dispatch-assisted CPR and the dispatch-assisted first responder training programme (OR 7·89 [95% CI 5·61–11·09]; p<0·0001), as well as after the addition of the myResponder application (9·90 [7·11–13·78]; p<0·0001), compared with the frequency in the pre-intervention period (table 3).

In non-residential locations, interventions were similarly associated with an increased likelihood of bystander CPR (n=1539, p<0·0001). Within non-residential locations, there was an increased frequency of bystander CPR after implementation of dispatch-assisted CPR (OR 2·37 [95% CI (1·42–-3·94]; p<0·0001), and after dispatch-assisted CPR, dispatch-assisted first responder training, and myResponder had all been implemented (3·80 [2·28–-6·34]; p<0·0001), compared with the frequency in the pre-intervention period (table 3).

Dispatch-assisted CPR and subsequent interventions were associated with an increase in survival to hospital discharge (p<0·0001;) figure 3). There were increased rates of survival to hospital discharge after the implementation of dispatch-assisted CPR (OR 2·12 [95% CI 1·04–4·33]; p=0·04), and after dispatch-assisted CPR, dispatch-assisted first responder training, and myResponder had all been implemented (3·10 [1·53–6·26]; p<0·0001), compared with rates in the pre-intervention period (table 2).

	Residential (n=5213)		Non-residential (n=1539)	
	OR (95 CI%)	p value	OR (95% CI)	p value
Pre-interventions	1·00	..	1·00	..
Emergency medical services interventions	1·37 (0·95–1·99)	0·091	1·35 (0·77–2·37)	0·29
Dispatch-assisted CPR	4·51 (3·23–6·30)	<0·0001	2·37 (1·42–3·94)	<0·0001
Dispatch-assisted CPR plus CPR training programme	7·89 (5·61–11·09)	<0·0001	3·29 (1·93–5·61)	<0·0001
Dispatch-assisted CPR plus CPR training programme plus myResponder	9·90 (7·11–13·78)	<0·0001	3·80 (2·28–6·34)	<0·0001

Multilevel mixed-effects logistic regression controlling for age, gender, and ethnicity of the patient, witness status, receiving hospital, response time, and time of day. CPR=cardiopulmonary resuscitation. OR=odds ratio.

Table 3: **Likelihood of bystander CPR by number of interventions, in residential and non-residential locations**

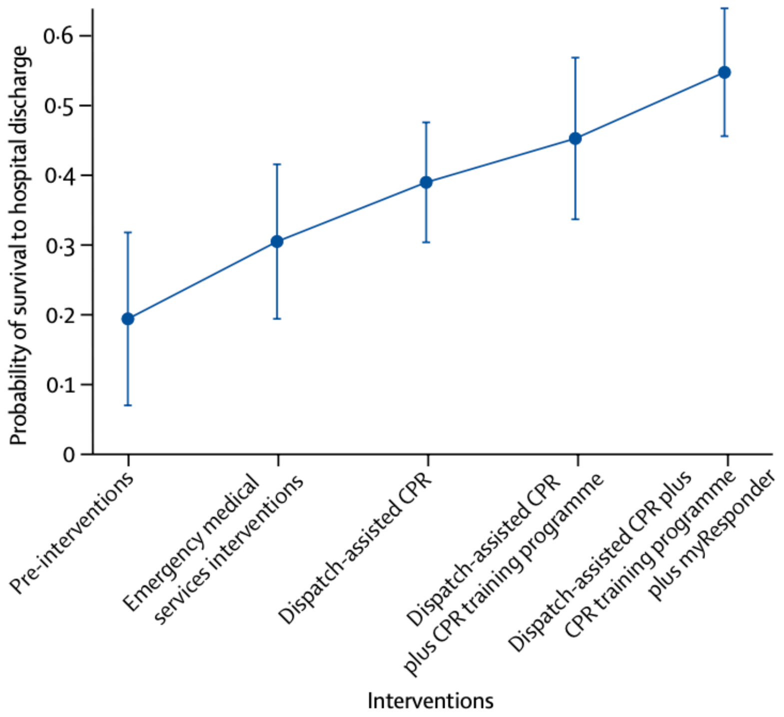

Figure 3: **Probability of survival to hospital discharge by number of interventions**
CPR=cardiopulmonary resuscitation.

Discussion

In Singapore, a bundle of three public health bystander-focused interventions was associated with increased bystander CPR frequency and increased survival to hospital discharge after OHCA, compared with the pre-intervention time period. It is important to note that while the emergency medical services-focused interventions were important to strengthen the pre-hospital infrastructure, the interventions themselves were not designed to target bystanders. As such, an investigation examining the effect of the bystander-focused interventions was warranted. Our findings could be considered when developing targeted community-wide training to improve bystander CPR and subsequent survival outcomes from OHCA.

Studies have demonstrated that dispatch-assisted CPR improves both layperson bystander CPR delivery, and survival, from OHCA. A recent prospective investigation demonstrated an increase in compressions started with community implementation of dispatch-assisted CPR (compressions started in 44% of arrests pre-intervention *vs* 53% post-intervention, p<0·0001).[7] Furthermore, a recent publication from Arizona, USA demonstrated that dispatch-assisted CPR was associated with improved survival compared with before the implementation of dispatch-assisted CPR (OR 1·64 [95% CI 1·61–2·30]).[6]

Prior studies in Singapore have focused on methods to improve dispatch-assisted CPR and examining barriers to this intervention.24 It is important to consider that dispatch-assisted CPR is centralised in Singapore, therefore there are robust quality and assurance measures to ensure adherence to the protocol and resuscitation process metrics. Additionally, Singapore continues to optimise the dispatch-assisted CPR protocol to improve outcomes and survival from OHCA. Future studies could consider taking aspects of the Singapore dispatch-assisted CPR protocol and implementing it in other locations, such as urban cities in the USA.

Recent publications have supported the notion of mandating CPR training in schools prior to high-school graduation in the USA.[25 26]A recent publication in the USA showed that mandated CPR training legislation was associated with an increased likelihood of CPR training.[27] Although studies suggest CPR training legislation could improve CPR frequency, prospective investigation in Denmark has identified challenges with the implementation of CPR training legislation.[28 29]

The Ministry of Education in Singapore requires that school-aged children are taught CPR in physical education classes. In addition to this requirement, Singapore offers free CPR and automatic external defibrillator training to schools, community-based groups, and workplaces through the dispatch-assisted first responder training programme. Providing free CPR training removes one of the known barriers to CPR training, specifically, cost and access to the course.[30] This study showed the impact of including dispatch-assisted CPR together with free CPR training. Future public health programming considerations might examine the cost-benefit analysis of such a centralised free CPR programme, and investigate whether the strategy is truly reaching the desired population.

Other studies have examined crowdsourcing bystander CPR response through mobile applications.[31 32] Specifically, Stockholm, Sweden has observed an increase in bystander CPR frequency and survival outcomes associated with these crowdsourcing mobile applications.[8] Other parts of the world are working to implement variations of a crowdsourcing bystander CPR mobile application for OHCA and have observed some challenges in implementation.[33]

Singapore's bystander crowdsourcing mobile application, myResponder, is offered to all citizens and is maintained centrally through the emergency medical services and dispatch centre. Furthermore, the application is linked to the centralised automatic external defibrillator registry, and is offered with the free CPR and automatic external defibrillator training, highlighting the importance of bundling the intervention for the general public. Future studies could consider ways to encourage individuals to maintain the application on their phones and encourage response in OHCA situations. Additionally, it might be important to consider the population density and cultural norms, and how these factors affect bystander response in OHCA situations.

Few studies have examined the bundling of public health interventions to improve bystander CPR response. Our findings are similar to those seen in a study in North Carolina, USA from 2010 to 2013, which examined the impact of a state-wide bystander and first responder education programme and found an increased likelihood of survival after implementation of the programme.[34] Similarly, a publication from Denmark reported wide-spread CPR training efforts from 2001 to 2010 and observed an increase in survival to hospital discharge and bystander CPR rates.[35] This study from Singapore provides a unique opportunity to examine the combined effects of three interventions on bystander CPR frequency and survival outcomes. Although we were unable to examine the individual effect of each intervention, the findings suggest the importance of bundling interventions, especially public health interventions, to improve outcomes for OHCA. It is possible that dispatch-assisted CPR and CPR training are dependent on each other in order to see a benefit.[36] Furthermore, our results could also show the effect of these bundled interventions on overall public knowledge and awareness. This study also highlights the importance of needing different bystander interventions to cover critical aspects of the chain of survival, specifically, chest compressions and defibrillation of a cardiac arrest victim. Future studies might consider the added effect of additional interventions on subsequent outcomes from OHCA in other locations.

There are several inherent limitations in this study. It was a retrospective analysis using a quality improvement database and only provides an estimation of the effects of interventions. The analysis lacks bystander CPR quality, thus we are unable to account for the role of CPR quality on improved OHCA outcomes. Furthermore, data collection through PAROS might directly affect the bystander CPR frequency and survival findings. Unfortunately, we are limited in our ability to measure the effect of PAROS on bystander CPR frequency and survival. Additionally, unmeasured confounders such as improved quality of emergency medical services CPR, in-hospital treatment, mechanical CPR transitions, and post-resuscitation care, could influence the results seen in by-stander CPR frequency and survival to hospital discharge. Our exposure is an ecological, estimated exposure, although we matched the data with individual-level data to create a semi-ecological study. By doing so, we were able to reduce the bias inherent in ecological, city-wide study designs, but acknowledge the limitations to causal inference. The nature of this analysis is dependent on the dates set for the interventions, for which we estimated a 6-month run-in period. This estimation might be partially confounded by unmeasured lagged effects and potential pre-intervention confounding. Lastly, the findings are reflective of the nation of Singapore, of which the demographics, centralised emergency medical services systems, and population size might not be generalisable to other locations. Despite this, the findings associated with these bystander-focused public health interventions are encouraging and could assist in generating ideas for many other populations. In conclusion, our study provides a unique perspective on the effect of public health interventions on the frequency of bystander CPR and survival from OHCA. The likelihood of a patient with OHCA receiving bystander CPR increased as the interventions were sequentially introduced, particularly in residential settings, and coincided with increased survival to hospital discharge. These findings could prove useful for future, targeted efforts to increase the use and effectiveness of bystander CPR, and improve survival after OHCA.

Contributors

ALB was responsible for study design, data analysis, data interpretation, and manuscript writing. AFWH was responsible for study design, data interpretation, and manuscript review. NS, AEW, and PPP was responsible for data collection, data analysis, and manuscript review. YYN, DRM, LT, MY-CC, BS-HL, SOC, LPT, JPHK, and SA were responsible for data collection, data interpretation, and manuscript review. TØ, HBB, and MEHO were responsible for study design, data interpretation, and manuscript review.

Declaration of interests

MEHO has licensing agreement and patent filing (application number 13/047,348) with ZOLL Medical Corporation for a study titled “Method of predicting acute cardiopulmonary events and survivability of a patient”, and is a scientific advisor to Global Healthcare.

All other authors declare no competing interests.

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Chapter 10

Global prevalence of basic life support training: A systematic review and meta-analysis

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Abstract

Background and Aims: Out-of-hospital cardiac arrest exerts a large disease burden, which may be mitigated by bystander cardiopulmonary resuscitation and automated external defibrillation. We aimed to estimate the global prevalence and distribution of bystander training among laypersons, which are poorly understood, and to identify their determinants.

Methods: We searched electronic databases for cross-sectional studies reporting the prevalence of bystander training from representative population samples. Pooled prevalence was calculated using random-effects models. Key outcome was cardiopulmonary resuscitation training (training within two-years and those who were ever trained). We explored determinants of interest using subgroup analysis and meta-regression. Results: 29 studies were included, representing 53,397 laypersons. Among national studies, the prevalence of cardiopulmonary resuscitation training within two-years and among those who were ever trained, and automated external defibrillator training was 10.02% (95% CI 6.60 -14.05), 42.04% (95% CI 30.98-53.28) and 21.08% (95%CI 10.16-34.66) respectively.

Subgroup analyses by continent revealed pooled prevalence estimates of 31.58% (95%CI 18.70–46.09), 58.78% (95%CI 42.41–74.21), 18.93 (95% CI 0.00–62.94), 64.97% (95%CI 64.00–65.93), and 50.56% (95%CI 47.57–53.54) in Asia, Europe, Middle East, North America, and Oceania respectively, with significant subgroup differences ($p < 0.01$). A country's income and cardiopulmonary resuscitation training (ever trained) ($p = 0.033$) were positively correlated. Similarly, this prevalence was higher among the highly educated ($p<0.00001$).

Conclusions: Large regional variation exists in data availability and bystander training prevalence. Socioeconomic status correlated with prevalence of bystander training, and regional disparities were apparent between continents. Bystander training should be promoted, particularly in Asia, Middle East, and low-income regions. Data availability should be encouraged from under-represented regions.

Keywords: Basic life support, Cardiopulmonary resuscitation, Life-saving skills, Training, meta-analysis

Introduction

Out-of-hospital cardiac arrest (OHCA) is the loss of functional cardiac mechanical activity in association with an absence of systemic circulation, occurring at a setting outside of the hospital.[1] OHCA is a common, time-critical disease and is a major cause of mortality and morbidity globally.[2] Despite advances in healthcare, mortality in OHCA remains high, with the pooled incidence of return of spontaneous circulation at 29.7%, and survival to admission at 22.0% for patients to whom cardiopulmonary resuscitation was initiated.[3] Observed variations in OHCA outcomes are multifactorial. Contributors to OHCA outcomes include factors such as local differences in the community aspects of the chain of survival[4–6] including early bystander cardiopulmonary resuscitation (CPR) and defibrillation with an automated external defibrillator (AED). A study done in Sweden has showed that survival rates are proportional to the rates of bystander CPR, which are linked to the percentage of the population who are CPR trained.[7] Bystander CPR and AED use are crucial determinants of patient outcomes,[8] and prior CPR or AED training is associated with performing bystander CPR and AED.[7,9,10]

However, the prevalence of the population trained in CPR or AED training is likely to vary by geographical region and has been reported to be as low as 2.4%.[11] Worldwide, efforts have been made to improve access to CPR or AED training by various organizations, such as the American Heart Association, the Red Cross societies and the Laerdal Foundation,[12] but little is known about the effectiveness of such measures and the factors that influence training uptake.[11] These may include strategies such as incorporating basic life support (BLS) training into educational curriculum in public schools and training BLS skills at community institutions such as religious institutions or sports clubs, among other interventions.[13] Beyond in-person courses, BLS training may be offered on online platforms as well, such as an interactive website by the Resuscitation Council UK. Data regarding the prevalence of CPR or AED training across the globe and which subpopulations have poorest access to BLS training is hence urgently needed to guide targeted public health and educational initiatives that promote BLS training among laypersons.

Although various communities have individually reported the prevalence of BLS training both at the national level and for school-going populations, there has been no previous systematic review done to consolidate these. Hence, we performed a systematic review and meta-analysis to investigate the global prevalence of CPR and AED training and their determinants.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[14] and the Joanna Briggs Institute Manual for Evidence Synthesis chapter on systematic reviews of prevalence and incidence.[15] The study protocol had been published in the International Prospective Register of Systematic Reviews (PROSPERO CRD: 42022300559).

Search strategy and study selection

We conducted a systematic literature search in Medline, Embase and Cochrane Library from database inception to March 2nd 2023. The search strategy was developed in consultation with a medical information specialist (Medical Library, National University of Singapore). The search terms included medical subject heading (MeSH) terms such as “Out-of-Hospital Cardiac Arrest”, “Cardiopulmonary Resuscitation”, “Automated External Defibrillator”, “Basic Life Support” and related synonyms. Google Scholar and the reference lists of relevant sources were hand-searched, and this process surfaced four more studies which were included in the final analysis.[16–18] Grey literature and non-English language articles were excluded. Abstracts retrieved from the search were imported into EndNote X9 (Clarivate, Philadelphia, PA) for the removal of duplicates.

Inclusion criteria

After deduplication of entries, three reviewers (TPN, SE, JT) independently screened all the abstracts using pre-defined inclusion and exclusion criteria. Article sieve was conducted using Google Sheets (Google LLC, Mountain View, CA). After identifying potentially relevant studies, the full-text articles were retrieved. Three reviewers (TPN, SE, JT) independently screened the full-texts and the reasons for exclusion were recorded. Discrepancies at any stage of the screening were resolved by discussion between the three reviewers and consensus with the senior author (AFWH).

The inclusion criteria were: (1) Studies with a primary or secondary aim of reporting the proportion of laypersons who have undergone CPR or AED training, (2) Studies representing a sample of a well-defined geographical population. We considered laypersons among the general population or school-going population (students enrolled in educational institutions). A small number of off-duty healthcare workers who were part of the sample may be included in this population. We did not consider self-reported knowledge on CPR or willingness to provide bystander CPR as an indication of CPR training, and likewise for AED training. Exclusion criteria were: (1) Studies with no numerical data, (2) Studies only including healthcare workers (3) Unpublished or unfinished studies, (4) Conference abstracts, (5) Articles with small sample sizes (n < 5), (6) Case reports or series, (7) Narrative reviews or systematic reviews (8) Non-English language studies.

Data extraction and outcomes

Data were extracted from the studies using a case record form by three independent investigators (TPN, SE, JT). The data extraction process was blinded, and discrepancies were resolved through discussion and consensus with the senior author (AFWH). In this study, the main variables of interest were the proportion of laypersons who had ever undergone CPR (CPR-E) or AED (AED-E) training and the proportion of laypersons who had valid CPR (CPR-V) or AED (AED-V) training, defined as possession of a valid certificate in AED and CPR administration within two years of training. We also extracted variables such as gender, age, location (population density, rural or metropolitan residents), educational level, occupation, socioeconomical status (SES), race, marital status, population who received AED and CPR training, training location, and whether the training was mandatory from the included studies.

Statistical analysis

Data analyses were performed using the meta 4.18–0 package in R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

We conducted a single-arm meta-analysis of proportions for the primary outcomes. Nationally representative studies were selected if they fit the had a study aim was to ascertain training prevalence in a particular geographic area with the largest possible sample size. Data was transformed using the Freeman-Tukey double arcsine method[19,20] to stabilise variance before the calculation of pooled prevalence estimates using Clopper-Pearson intervals. Random effects models were used given expected heterogeneity between communities studied and the restricted maximum likelihood estimator was applied for between-study variance. Statistical heterogeneity was evaluated through the I^2 statistic, s^2, and Cochran Q test values. I^2 values of 25%, 50%, and 75% were taken as thresholds for low, moderate, and high heterogeneity, respectively. We opted to use multiple measures of statistical heterogeneity because recent studies showed that in meta-analyses of prevalence (single-arm meta-analysis), I^2 alone is unreliable and may be misleading.[21] Comparative data exploring the effect of variables on CPR or AED training were extracted as crude odds ratios. Where possible, odds ratios were calculated using 2x2 contingency tables for binary variables of interest.

To further explore the heterogeneity between studies, we performed pre-defined subgroup analyses according to study-level variables including region (continent) and Gross National Income (GNI). Countries were categorised into subgroups based on their GNI per capita according to classification by the World Bank in the year 2021.[22,23] According to the World Bank, GNI per capita is defined as the gross national income divided by the midyear population, converted to United States Dollars at official exchange rates. We then performed univariate meta-regression to test *a priori* hypotheses that CPR or AED training would vary with the GNI per capita and mean age of study population. Finally, we performed conventional pairwise meta-analysis comparing the effects of binary variables (sex, education level, employment status) on CPR or AED training using Review Manager (RevMan 5.4, The Cochrane Collaboration). We used a Dersimonian-Laird random effects model and the Mantel-Haenszel method to pool the log odds ratios. Two-tailed statistical significance was set at $p < 0.05$. Quality assessment of the prevalence studies were assessed on 10 domains using the tool by Hoy et al.[24] A post-hoc analysis of studies which were identified to be of a low risk of bias was done. Publication bias was not assessed for pooled prevalence due to the lack of an appropriate test for single-arm meta-analysis of proportion,[25] whereas for comparative meta-analysis, a funnel plot was plotted and inspected for asymmetry whenever there are at least ten data-points.

Specific ethics review was not required for this review.

Results

Literature retrieval & summary of included studies

A total of 10,402 articles were retrieved from the initial search, of which 4,480 were duplicates. After the title and abstract sieve, the full texts of 209 articles were then evaluated for eligibility. 202 articles were excluded in the full text sieve. Finally, 29 studies qualified for synthesis,[12,17,18,26–50] with one study having two separate sample populations in China and India.[30] A total of 17 studies representing a national population, and two studies representing a school going population were analysed. A summary of the search strategy is illustrated in Fig. 1.

Four studies were conducted on populations in Australia,[12,28,44,51] three in Saudi Arabia,[50,52,53] two in China,[54,55] one with populations in China and India,[30] two in Hong Kong Special Administrative Region,[17,56] three in the United Kingdom,[35,49,57] two in USA,[11,43] two in Japan,[47,58] and one from each of the following countries: Canada,[59] Korea,[32] Ukraine,[60] Ireland,[48] Turkey,[61] Spain,[62] Sweden,[18] Slovenia,[37] Denmark,[74] and Singapore.[39]

There were no studies appraised to be of high risk of bias. Three studies had a moderate risk of bias, and 26 studies were low-risk. Among included studies, data was collected from 1998 to 2023. Studies included were cross-sectional studies which utilised probability or non-probability sampling methods. The characteristics of included studies can be found in supplementary material 1.

The total at-risk population from all included studies consisted of 53,397 laypersons.

Global prevalence of CPR training

A summary of pooled global prevalence results can be found in Table 1. The meta-regression and comparative analyses can be found in Table 2.

Prevalence of CPR-E training

18 studies reported the prevalence of CPR-E training among a total of 40,066 laypersons from a national population.[11,17,18,28,30,32,37,39,50,55,58–63] The pooled prevalence of CPR-E was 42.04% (95% confidence interval [95%CI] 30.98 to 53.28, Fig. 2) and when excluding 2 studies with a moderate risk of bias,[31,63] the pooled prevalence of CPR-E slightly decreased to 40.57% (95%CI 28.46 to 53.52, Fig. 2). Two studies reported the prevalence of CPR-E training among a total of 2,577 laypersons from a school-going population.[52,54] The pooled prevalence was 12.60% (95%CI 9.18 to 16.47, Fig. 2).

Subgroup analyses by GNI per capita (Fig. 3) revealed pooled prevalence of CPR-E estimates of 46.69% (95%CI 34.12 to 59.48), 40.13% (95%CI 25.88 to 55.29), and 3.00% (95%CI 2.35 to 3.72) for GNI per capita at high-, upper middle-, and lower middle-income levels respectively, with significant difference between the subgroups ($p < 0.01$).

Subgroup analyses by continent for CPR-E (Fig. 4) revealed pooled prevalence estimates of 64.97% (95%CI 64.00 to 65.93), 50.56% (95%CI 47.57 to 53.54), 31.58% (95%CI 18.70 to 46.09), 18.93 (95%CI 0.00 to 62.94), 58.78% (95%CI 42.41 to 74.21) for the continents of North America, Oceania, Asia, Middle East, and Europe respectively, with significant difference between them ($p < 0.01$).

Prevalence of CPR-V training

Six studies reported the prevalence of CPR-V training among a total of 20,540 laypersons from a national population.[11,17,28,39,58,60] The pooled prevalence was 10.02% (95% CI 6.60 to 14.05, Fig. 5) and when excluding 1 moderate-risk study the prevalence of CPR-V training was 11.14% (95% CI 7.51 to 15.39, Fig. 5). Only one study reported the prevalence of CPR-V training among a total of 1,407 laypersons from a school-going population.[54] The reported prevalence was 5.76% (95%CI 4.60 to 7.04, Fig. 5).

Subgroup analyses by GNI per capita revealed pooled prevalence estimates of 9.54% (95% CI 5.72 to 14.21) and 12.76% (95% CI 9.60 to 16.30) for GNI per capita at high and upper middle-income levels respectively, with no significant difference between the subgroups ($p = 0.54$).

Subgroup analyses by continent revealed pooled prevalence estimates of 8.04% (95% CI 5.13 to 11.52), 18.0% (95% CI 17.21 to 18.8), and 10.87% (95% CI 9.08 to 12.81) for the continents of Asia, North America, and Oceania respectively, with significant difference between the subgroups ($p < 0.01$).

Global prevalence of AED training

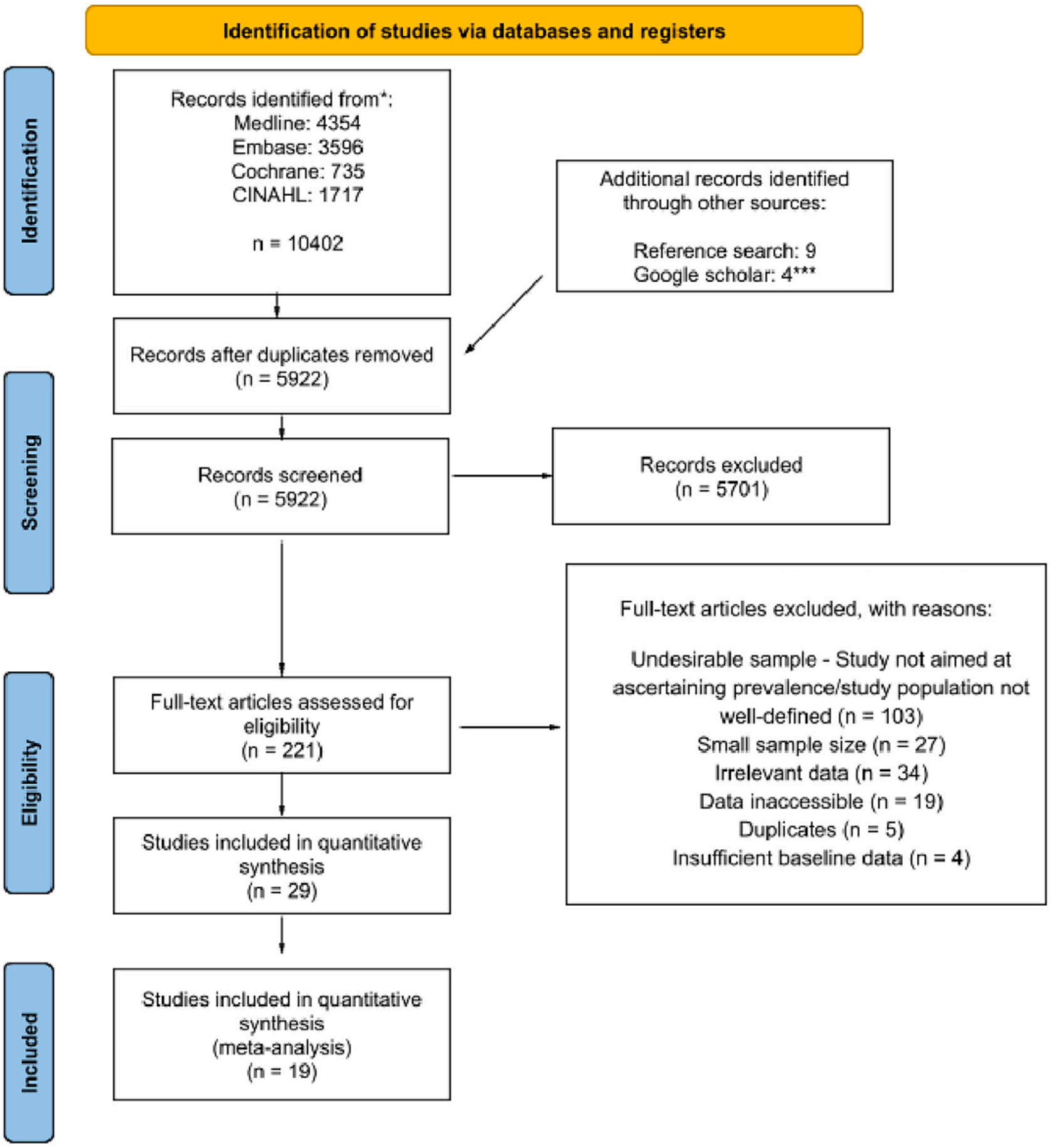
Prevalence of AED-E training

Six studies reported the prevalence of only AED-E training among a total of 13,305 laypersons from a national population.[32,39,47,55,63,74] The pooled prevalence was 21.08% (95% CI, 10.16 to 34.66) (Table 1). There were no studies which reported the prevalence of only AED-E training among laypersons from a school-going population.

Prevalence of AED-V training

One study from Singapore reported the prevalence of AED-V training among a total of 4,192 laypersons from a national population. The reported prevalence was 3.70% (95% CI, 3.15 to 4.29).[39] There were no studies which reported the prevalence of AED-V training among laypersons from a school-going population.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

*** Grabmayr 2022 identified on Google Scholar, not indexed in Medline, Embase, Cochrane and CINAHL at time of search

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Fig. 1 – PRISMA Flowchart.

Table 1 – Summary of Pooled Global Prevalence Results.

Pooled Global Prevalence	Ever Trained				Valid Training			
	Studies representing national population		Studies representing school population		Studies representing national population		Studies representing school population	
	# of Studies (n)	*% Prevalence (95% CI)*	*# of Studies (n)*	*% Prevalence (95% CI)*	*# of Studies (n)*	*% Prevalence (95% CI)*	*# of Studies (n)*	*% Prevalence (95% CI)*
Overall prevalence of CPR training (all studies)	18 (40,066)	42.04% (30.98–52.52)	2 (2577)	12.60% (9.18–16.47)	6 (21,947)	10.02% (6.60–14.05)	1 (1407)	5.76% (4.60–7.04)
Overall prevalence of CPR training (low-risk studies only)	16 (33,129)	40.57% (28.46–53.28)	2 (2577)	12.60% (9.18–16.47)	5 (17,094)	11.14% (7.51–15.39)	1 (1407)	5.76% (4.60–7.04)
Subgroup analyses								
GNI per capita	18		0		6		0	
Lower-middle income	1 (2400)	3.00% (2.35–3.72)	0	–	–	–	–	–
Upper-middle income	4 (6785)	40.13% (25.88–55.29)	0	–	1 (384)	12.76% (9.60–16.30)	–	–
High-income	13 (30,811)	46.79% (34.12–59.48)	0	–	5 (20,156)	9.54% (5.72–14.21)	–	–
Study continent	18		0		6		0	
Asia	8 (19710)	31.58% (18.70–46.09)	0	–	4 (14,001)	8.40% (5.13–11.52)	0	–
Europe	5 (8441)	52.62% (38.40–66.63)	0	–	0	–	0	–
Middle East	2 (1389)	18.39% (0.00–62.94)	0	–	0	–	0	–
North America	2 (9450)	64.97% (64.00–65.93)	0	–	1 (9022)	18.00% (17.21–18.80)	0	–
Oceania	1 (1076)	58.78% (42.41–74.21)	0	–	1 (1076)	10.87% (9.04–12.81)	0	–
Overall prevalence of AED training (all studies)	6 (13,305)	21.08% (10.16–34.66)	0	–	1 (4192)	3.70% (3.15–4.29)	–	–

CI, 95% confidence interval; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; GNI, gross national income.
Ever trained: defined as having ever received training.
Valid Training: defined as valid training received within 2-years.

Table 2 – Meta-Regression & Comparative Meta-Analyses.

Meta-regression	Moderator	Studies	Effect size	LCI	UCI	*P* value
National prevalence of CPR-E training	Female proportion	18	β: −0.3295	−1.0816	0.4226	0.3905
	Mean age	14	β: 0.0086	−0.0040	0.0211	0.1799
	GNI group	29	β: 0.1933	0.0228	0.3638	0.0262*
	Last year of data collection	27	β: −0.0001	−0.0153	0.0152	0.9915
National prevalence of CPR-V training	Female proportion	7	β: 1.1317	−0.6306	0.1498	0.2272
	Mean age	5	β: 0.0054	−0.0014	0.0123	0.1180
	GNI group	12	β: 0.0288	−0.0973	0.1550	0.6544
	Last year of data collection	11	β: 0.0033	−0.0040	0.0105	0.3765
National prevalence of AED-E training	Female proportion	3	β: −15.3760	−22.6357	8.1163	<0.0001*
	Mean age	3	β: 0.0985	−0.1332	0.3301	0.4047
	GNI group	6	β: −0.5104	−0.3215	0.3968	0.8062
	Last year of data collection	5	β: 0.0342	−0.0033	0.0717	0.0742
Comparative Meta-analyses	**Moderator**	**Studies**	**Effect size**	**LCI**	**UCI**	***P* value**
National prevalence of CPR-E Training	Female	11	OR: 0.91	0.62	1.33	0.62
	Education (above primary)	6	OR: 4.39	3.45	5.57	<0.00001*
	Occupation (employed)	5	OR: 1.89	0.59	6.12	0.29
National prevalence of CPR-V Training	Female	3	OR: 1.00	0.93	1.07	0.98

OR, Odds ratio; LCI, Lower confidence interval; UCI, Upper confidence interval; CPR-E training, Cardiopulmonary resuscitation training (ever); CPR-V training, Cardiopulmonary resuscitation training (valid); GNI, Gross national income; GDP, Gross domestic product; GSP, Gross state product.
* P value < 0.05.

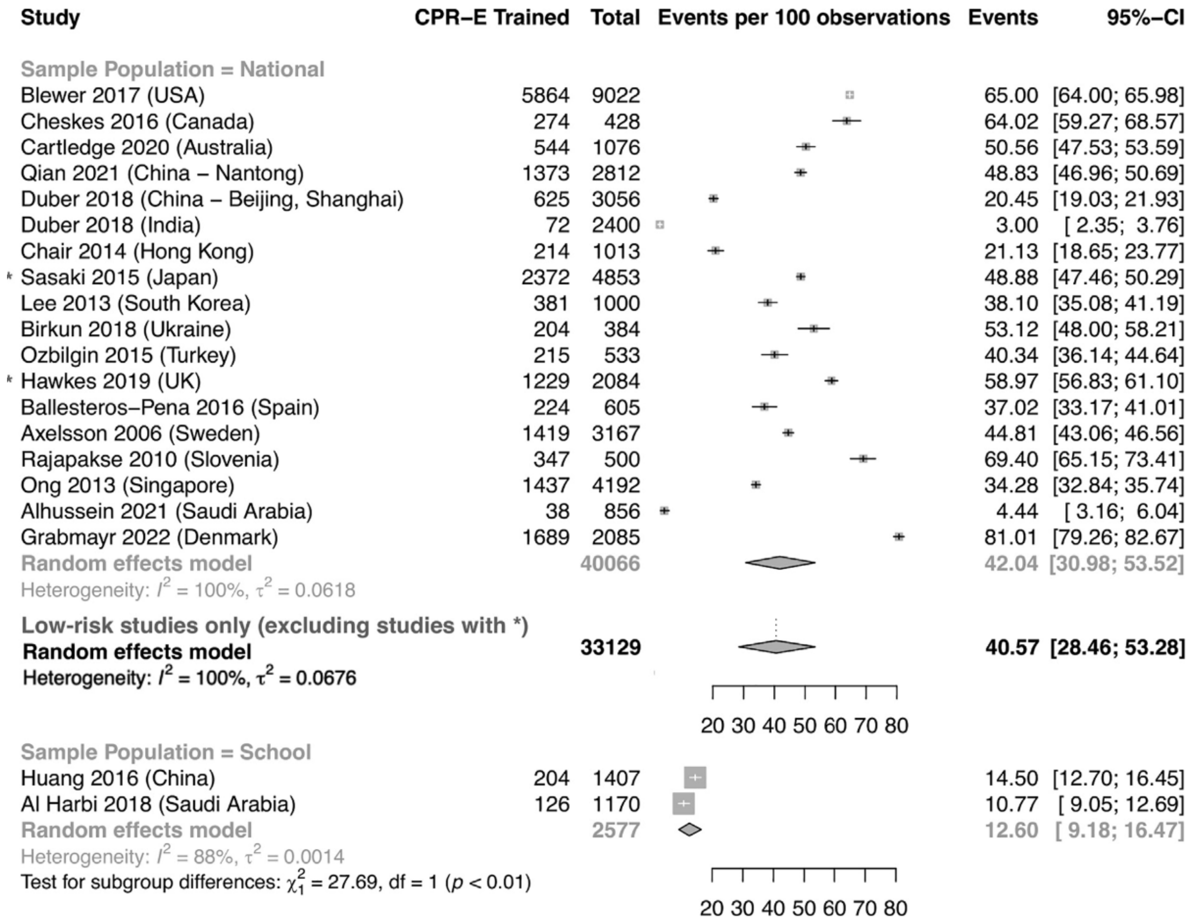


Fig. 2 – Overall CPR-E Prevalence.

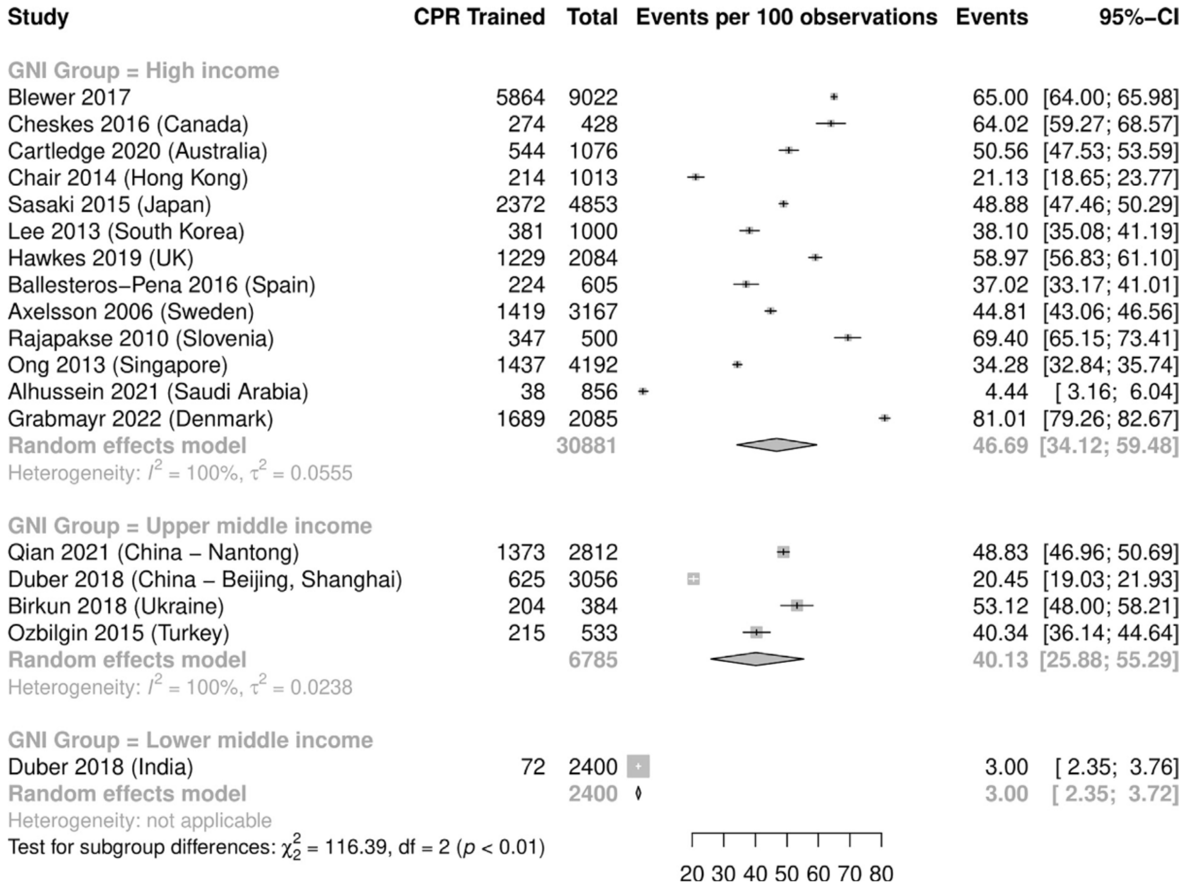


Fig. 3 – National CPR-E Prevalence by GNI Group.

Meta-regression & comparative Meta-analyses

Meta-regression

On univariate meta-regression of all 29 studies, the higher a country's GNI group, (b: 0.1933, 95%CI 0.0228 to 0.3638, p = 0.0262) the higher the national prevalence of CPR-E training (Table 2). This bubble plot can be found in Supplementary Material 3: Bubble Plot for CPRE/GNI Group Regression. However, proportion of females and mean age did not significantly influence the national prevalence of CPR-E training. On univariate meta-regression, proportion of females and GNI per capita did not significantly influence the national prevalence of CPR-V training. The last year of data collection did not influence the prevalence of CPR-E or CPR-V training. Meta-regression for other moderators was not attempted due to an insufficient number of studies.

Comparative Meta-analyses

On comparative meta-analysis, education above the primary school level (OR: 4.39, 95%CI 3.45 to 5.57, p <0.00001) significantly influenced the national prevalence of CPR-E training based on six studies. Female gender and being employed in an occupation did not significantly influence the national prevalence of CPR-E training. On comparative meta-analysis, female gender did not significantly influence the national prevalence of CPR-V training. On visual inspection, funnel plot for the comparative meta-analyses for sex (female and male) revealed no publication bias for comparative meta-analysis. This funnel plot can be found in Supplementary Material 2: Funnel Plot for Comparative Meta-analyses (Female).

Discussion

In this study, we found that the prevalence of ever having been trained in CPR in the general population globally ranged from 3% to 65%, with a pooled prevalence of 42.04%. This prevalence was lower, at 10.02%, when using a stricter definition of CPR training (valid training within 2-years). We found evidence of differences in prevalence between continents, a positive correlation with a country's income, and positive correlations with employment rate and education level. As compared to CPR training, the data surrounding prevalence of AED training is much scarcer. This is, to our knowledge, the most updated systematic review, and the only meta-analysis addressing this research question.

Contemporary guidelines, including the 2020 American Heart Association Guidelines for CPR and Emergency Cardiovascular Care,[64] advocate for the promotion of CPR mass training and awareness campaigns in the community. Having a sizeable proportion of the general population as lay rescuers can increase the chance of an OHCA victim receiving bystander CPR. A Singaporean study has showed that public health interventions such as dispatch-assisted CPR, CPR and AED training, and a first responder mobile application (myResponder) were associated with increased bystander training, increasing CPR frequency and improving survival to hospital discharge after OHCA, compared with the preintervention time period.[65] However, large-scale programs to train and influence large groups of the population are resource-intensive, and an under-standing of the global baseline, regional differences and disparities are essential to guide resource allocation, design and implementation of such programs. Our study found a wide range of prevalence of CPR training across communities, which partially explains the large regional variation in bystander CPR rates observed in previous studies.[66] These findings suggest inequity in access to life-saving training globally, and by corollary, a gap in governmental and non-governmental funding priority in this area. Our study also provides a possible explanation of reduced bystander CPR rates observed in socioeconomically disadvantaged communities in some regions.[67–70]

The Hoy. et al [25] tool for quality assessment of prevalence studies was used to identify studies which had a lower risk of bias. Such studies possessed qualities such as having a sample with a close representation of the national population in relevant variables, a sampling frame with a true or close representation of the target population, or the usage of a census or random selection to select the sample, among other factors. When restricting our analysis to the highest quality studies, our estimate of the global prevalence of CPR-E training was 40.57%, and the estimate of global CPR-V training prevalence was 11.14%. Since several studies reported that a high percentage of bystanders are receptive to CPR training and that CPR training predicts bystander CPR, these low estimates suggest that global efforts to provide CPR training remain inadequate to maximise the performance of bystander CPR. Furthermore, the prevalence of CPR-E training was significantly different between countries of different GNI levels, with CPR prevalence at 46.79%, 40.13%, and 3.00% for high-, upper middle-, and lower middle-income levels respectively, hence suggesting a correlation between higher SES and higher CPR training.[71–73] On the national level, high GNI countries may have the financial capability to place a larger emphasis on CPR training, resulting in better national measures and resource allocation regarding CPR training applied across all states, regardless of individual state income. On the individual level, lower SES may create barriers such as financial barriers, information barriers, and barriers which lower personal motivation which discourage individuals from seeking CPR education.[68,69] As a result, the lower middle-income countries should be prioritised when it comes to BLS training.

In schools, the prevalence of CPR-E training was 12.60%, and the prevalence of CPR-V training was 5.76%. The "Kids Save Lives" Statement 2015, which highlights the importance of teaching CPR to school children worldwide, recommends two hours of CPR training annually from the age of twelve in schools worldwide, especially since children are responsive to instructions and learn easily.[70] However, our study revealed a gap in knowledge on CPR and AED training in schools despite the potential benefit of such training among younger age groups, which should be explored in future research.

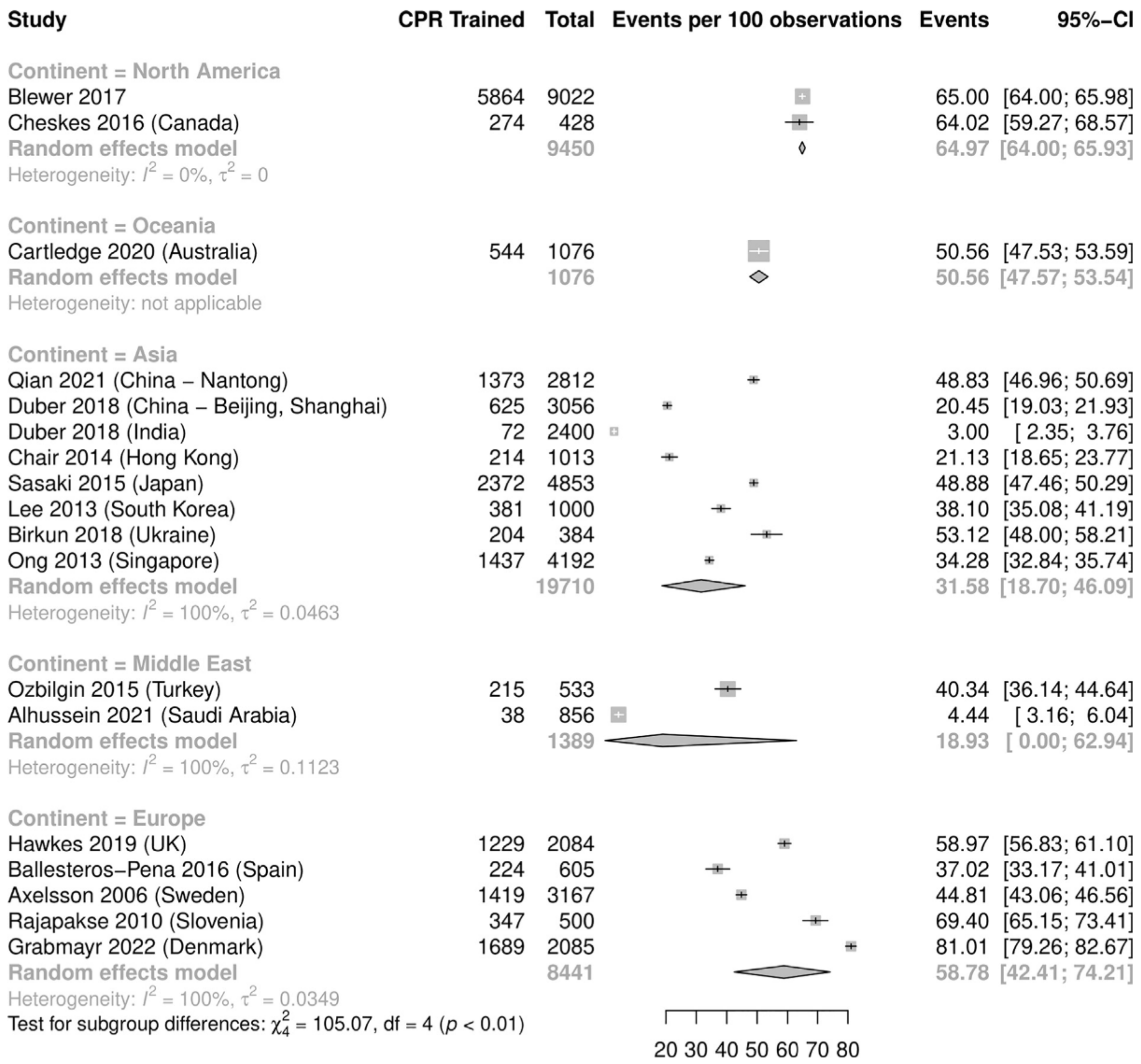


Fig. 4 – National CPR-E Prevalence by Continent.

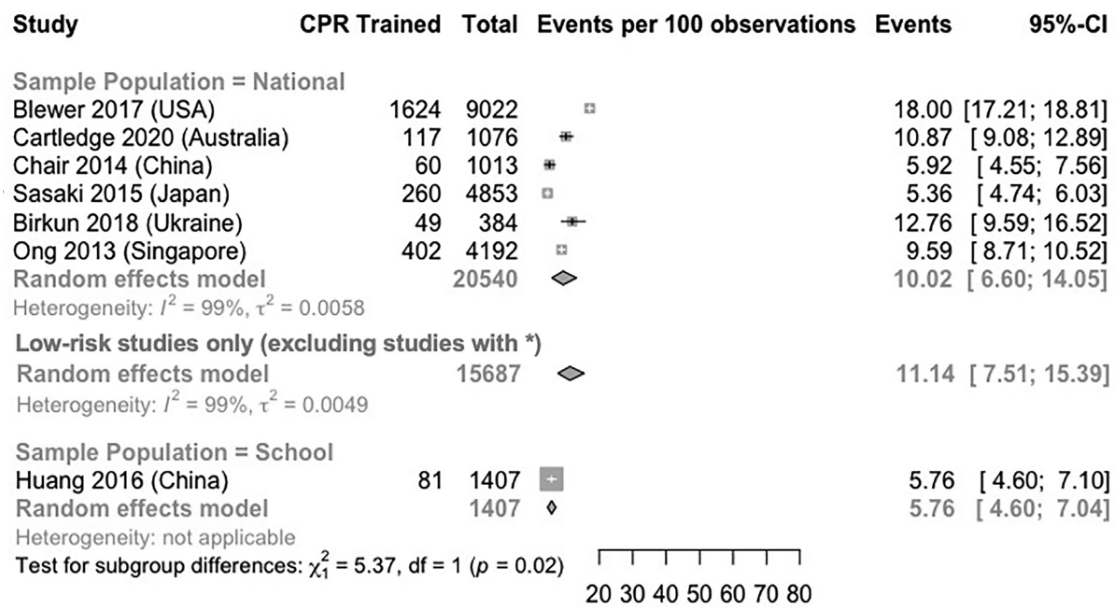


Fig. 5 – Overall CPR-V Prevalence.

Overall, the paucity of studies investigating the prevalence of only AED training although bystander AED intervention improves survival and functionally favourable outcomes.[71] suggests that more research is needed in this area. Internationally, resources should be channeled towards establishing CPR training guidelines, which may eventually involve training locals to become CPR trainers themselves, working with local policymakers, healthcare professionals and experts to come up with CPR guidelines specific to their countries' needs and culture, and the provision of training resources tailored to the country's local languages. At a national level, governmental policies aiming to increase the reach of CPR training could be instituted. These measures could include the creation of a combined self-instruction and instructor-led courses with hands-on training, alternatives for self-directed training,[64] mandatory CPR training for workplaces, those applying for a drivers' license, and as a prerequisite for school graduation,[72] and CPR training which is provided at low or subsidised rates at accessible locations.[68] Finally, individuals may be motivated at a personal level to pick up CPR as a life skill if there is greater education about the value of CPR in improving survival in cardiac arrest,[68] so greater public education is required especially among countries with a low prevalence of CPR training. This is particularly relevant among geographic regions which have a lower prevalence of CPR training, such as the Middle East and Asia.

For future research, we recommend that stakeholders in each geographical region conduct robust studies to estimate the proportions of the general population trained in CPR and AED. Data from these studies would serve as the basis for comparison to assess trends and evaluate public health programs and policies aimed at improving access to life-saving skills training. These studies need to employ probability sampling methods, and have clearly-stated definitions of what it means for someone to be trained. We also recommend that the prevalence of the general population trained in key life-savings skills such as CPR, be monitored as a metric when characterizing health systems, with community bystander interventions being an important component of an emergency care system.

Strengths and Limitations

This study is the first study to date which investigates the prevalence of CPR and AED training in populations worldwide. The limitation of this study is the high heterogeneity observed in the statistical analysis. This may be attributed to many factors, such as the lack of South American and African papers, the different methods in which data was collected and analysed, and the different ways CPR or AED training was defined. Additionally, the selection of only English language papers further limits the number of studies from non-English speaking countries, which are already underrepresented in our analysis. There was also no limitation on the year of publication, and the inclusion of older studies may have affected our current estimates of the global prevalence of CPR and AED training. Finally, there is a risk of misclassifying individual persons' socioeconomic statuses using GNI, which is a regional-level indicator of socioeconomic status[73] However, we note that the finding of a significant, positive correlation was invariant even in our comparative meta-analysis of individual-level socioeconomic indicators (education level, employment status).

Conclusions

This systematic review and meta-analysis found that large regional variation exists in the data availability, and prevalence of CPR and AED training amongst laypersons. Socioeconomic status correlated with prevalence of CPR training and regional disparities were apparent between continents. As such, community bystander training should be promoted, particularly in Asia, Middle East and low-income regions, while data availability should be encouraged from under-represented regions.

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CRediT authorship contribution statement

Trina Priscilla Ng: Writing – original draft. Sean Wai-Onn Eng: Writing – original draft. Joel Xin Rui Ting: Writing – original draft. So Yeon Joyce Kong: Writing – review & editing. Willem Stassen: Supervision. Lin Zhang: Supervision. Dominique P.V. de Kleijn: Supervision, Writing – review & editing. Marcus Eng Hock Ong: Supervision. Audrey L Blewer: Supervision, Formal analysis, Investigation, Writing – review & editing. Jun Wei Yeo: Supervision, Investigation, Resources. Andrew Fu Wah Ho: Supervision, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft.

Conflicts of Interest

So Yeon Joyce Kong is an employee of Laerdal Medical, but has no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.resuscitation.2023.109771.

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Chapter 11

Implementation of a National 5-Year Plan for Prehospital Emergency Care in Singapore and Impact on Out-of-Hospital Cardiac Arrest Outcomes From 2011 to 2016

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Journal of the American Heart Association. 2020 Nov 3;9(21):e015368.

Background: Outcomes of patients from out-of-hospital cardiac arrest (OHCA) vary widely globally because of differences in prehospital systems of emergency care. National efforts had gone into improving OHCA outcomes in Singapore in recent years including community and prehospital initiatives. We aimed to document the impact of implementation of a national 5-year Plan for prehospital emergency care in Singapore on OHCA outcomes from 2011 to 2016.

Methods and Results: Prospective, population-based data of OHCA brought to Emergency Departments were obtained from the Pan-Asian Resuscitation Outcomes Study cohort. The primary outcome was Utstein (bystander witnessed, shockable rhythm) survival-to-discharge or 30-day post-arrest. Mid-year population estimates were used to calculate age-standardized incidence. Multivariable logistic regression was performed to identify prehospital characteristics associated with survival-to-discharge across time. A total of 11 465 cases qualified for analysis. Age-standardized incidence increased from 26.1 per 100 000 in 2011 to 39.2 per 100 000 in 2016. From 2011 to 2016, Utstein survival rates nearly doubled from 11.6% to 23.1% ($P=0.006$). Overall survival rates improved from 3.6% to 6.5% ($P<0.001$). Bystander cardiopulmonary resuscitation rates more than doubled from 21.9% to 56.3% and bystander automated external defibrillation rates also increased from 1.8% to 4.6%. Age ≤65 years, non-residential location, witnessed arrest, shockable rhythm, bystander automated external defibrillation, and year 2016 were independently associated with improved survival.

Conclusions: Implementation of a national prehospital strategy doubled OHCA survival in Singapore from 2011 to 2016, along with corresponding increases in bystander cardiopulmonary resuscitation and bystander automated external defibrillation. This can be an implementation model for other systems trying to improve OHCA outcomes.

CLINICAL PERSPECTIVE

What Is New?

- Outcomes of patients from out-of-hospital cardiac arrest vary widely globally because of differences in prehospital systems of emergency care.
- Data from the Pan-Asian Resuscitation Outcomes Study, a prospective, population-based study of out-of-hospital cardiac arrest presenting to Emergency Departments, showed that between 2011 and 2016, national Utstein (bystander witnessed, shockable rhythm) survival-to-discharge or 30-days post-arrest nearly doubled from 11.6% to 23.1% in Singapore ($P=0.006$).

What Are the Clinical Implications?

- This was associated with the implementation of a 5-year national plan of prehospital emergency care consisting of both policy and implementation measures in community and prehospital areas.
- Increases in both bystander cardiopulmonary resuscitation and bystander automated external defibrillation were independently associated with the rapidly improved survival.
- This can be an implementation model for other systems trying to improve out-of-hospital cardiac arrest outcomes.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a global disease, being a leading cause of death in Singapore, paralleling worldwide trends.[1] Outcomes from OHCA vary widely between communities, relating to differences in patient demographics and emergency care systems.[2,3] Survival rates in the Asia-Pacific region showed great variation, ranging from no reported survivors to 31.2% (Japan),[3] and this was associated with systemic differences in emergency care delivery.[3–5] In Singapore, the Utstein (bystander witnessed, shockable rhythm) survival-to-hospital discharge rate in Singapore was 11.0% between 2010 and 2012.[6] While this was a marked improvement from the 2.5% found between 2001 and 2004,[7] when benchmarked against sites such as Seattle, Washington, there was significant room for improvement.

Effective treatment of OHCA hinges on the "Chain of Survival" concept, which describes the rapid commencement and seamless provision of rescuer actions.[8] More recently, there is increased recognition of the important role of fundamental elements not confined to the traditional sphere of influence of the Emergency Medical Services (EMS) in enabling optimal OHCA care. These were encapsulated under the Modified Frame of Survival framework by the Global Resuscitation Alliance, and included cultural views, political commitment, and legislative environment.[9,10]

Despite advancement in resuscitation science, OHCA outcomes have not consistently improved.[1,11] A 2010 systematic review of 79 studies concluded that from 1980 to 2008, aggregate survival remained unchanged at 6.7% to 8.4%.[12] Since this systematic review, steady improvements in survival over time have been subsequently reported in Denmark,[13] Sweden,[14] the Netherlands,[15] Canada,[16] and the United States.[17] It has been recognized, such as through the work of the Global Resuscitation Alliance, that OHCA care (OHCA being a prototypical time-critical emergency condition) benefits from medical science only if there is educational efficiency and local implementation. This requires strategic policy, multi-agency coordination, and systematic implementation measures.

Extensive national efforts have gone into improving OHCA outcomes in Singapore[6,18] through community and prehospital interventions. A period of exceptionally intense reorganization, policy restructuring, and organized implementation to improve the prehospital emergency care system occurred between 2009 and 2014, codified as the National Pre-hospital Emergency Care System 5-year Plan (henceforth, “5-year Plan” or “Plan”).

This study investigated the epidemiology, treatment, and outcomes trends for OHCA in Singapore over a 6-year period (2011–2016). It was hypothesized that Utstein survival from OHCA has improved over the period, and that the improvement is related to patient, bystander, and system factors. These findings would allow Singapore to “take stock” of the returns from a 5-year Plan consisting of both policy and implementation measures, as well as to benchmark the Singapore emergency care system. In addition, an examination of the effectiveness of these strategies would provide useful lessons for other communities in comparable circumstances.

METHODS

Data and Research Materials Transparency

The data that support the findings of this study may be available from the corresponding author upon reasonable request, subject to approval by the local institution.

Setting

Singapore is an urbanized island city-state situated in Southeast Asia with a population of 5.5 million over a land area of 719.1 km^2.[19] A population-based survey in 2010 showed that 31.4% of responders had ever been trained in cardiopulmonary resuscitation (CPR), 10.7% had ever been trained in automated external defibrillation (AED), while 9.6% and 3.7% possessed valid certificates for these skills, respectively.[20]

EMS are provided by the Singapore Civil Defence Force, which operates a fire-based system activated by a centralized “995” dispatch system. This is provided free of charge. Singapore Civil Defence Force handled 131 806 ambulance calls in 2011 and this had increased to 178 154 in 2016.[21] Singapore Civil Defence Force utilized computer-aided dispatch protocols, global positioning satellite vehicle location systems, and road traffic monitoring systems. During the study period, there was a single tier of paramedics (equivalent to North American emergency medical technician-intermediate) who were trained in basic life support, AED, and specific interventions including intravenous adrenaline administration. Sixty-nine percent of OHCA in Singapore occur at home in high-rise apartments[22] with substantial vertical travel time.[23]

Community and Prehospital Interventions and the National Pre-Hospital Emergency Care System 5-Year Plan (2009–2014)

The Plan was ratified as a response to a lack of multiagency coordination, planning, and oversight of prehospital emergency care. It was proposed that a national blueprint focusing on the strategic imperatives of leadership, community responsiveness, ambulance responsiveness, emergency department responsiveness, skills development, and technology be implemented in phases, over the next 5 years. The major interventions during this period were the following: mechanical CPR devices on ambulances (May 2011), Fire Bikers Scheme (April 2012, fire/rescue specialists on motorcycle dispatched ahead of ambulance arrival), dispatcher-assisted CPR (July 2012), Dispatcher-Assisted First Responder community training (April 2014), intraosseous devices on ambulances (April 2014), large-scale deployment of AED in residential areas (April 2015), and crowdsourced community rescuer app (April 2015). Details of these interventions are given in the Appendix.

Study Population—the Pan-Asian Resuscitation Outcomes Study

PAROS (Pan-Asian Resuscitation Outcomes Study) is an ongoing clinical research network for OHCA.[3] It is a prospective, multicenter registry designed to provide baseline information on OHCA epidemiology, describe variations among EMS systems, and compare systemic and structural interventions in the Asia-Pacific area.[3–5] The network was established in 2010 with aims to improve outcomes by informing on cost-effective strategies.[3] For the current study, only data from Singapore were used.

PAROS methodology had been previously detailed.[3] Data definitions follow the Utstein recommendations,[24] and collaboration with the CARES (Cardiac Arrest Registry to Enhance Survival) in the United States enabled a unified taxonomy and data dictionary to allow valid global comparisons.[25] Data were extracted from emergency dispatch records, ambulance case notes, and emergency department and in-hospital records. Quality assurance data checks were built into the data entry system, and data verification checks were implemented to ensure data integrity.[3]

The registry included OHCA from 2011 to 2016 of all causes including traumatic arrests brought in by EMS or presenting to EDs via private or public transport, as confirmed by the absence of pulse, unresponsiveness, and apnea. Both adult and pediatric cases were included. All cases were prospectively collected in compliance with Utstein Style. Patients for whom resuscitation was not attempted and were immediately pronounced dead (because of decapitation, rigor mortis, dependent lividity, and "do not attempt resuscitation" orders) were excluded from the study.

Mid-year population estimates from the Singapore Department of Statistics were used to calculate crude and age-standardized incidence and survival rates. Population estimates pertain to resident population (Singapore citizens and permanent residents). Incidence rates were calculated by dividing the number of OHCA cases by the mid-year population. Age-standardized incidence rates were derived by applying the category-specific incidence rates of each population to the Segi World Standard population.[26] Age-standardized survival rates were calculated by the direct method using the Singapore population as the standard population in the corresponding year.[19]

Outcomes were summarized in a 3-tier cascade manner: (1) Utstein (bystander-witnessed arrest, ventricular fibrillation), (2) cases where resuscitation was attempted, and (3) cases where resuscitation was attempted and who experienced nontraumatic cardiac arrest (not caused by blunt or penetrating trauma, and includes presumed cardiac cause, respiratory cause, drowning, and other causes). The following outcomes were reported: (1) EMS return of spontaneous circulation, (2) emergency department return of spontaneous circulation, (3) survival to admission, (4) survival rate to discharge, (5) post-arrest cerebral performance category score 1 or 2, and (6) post-arrest overall performance category score 1 or 2.

Study Variables, Definitions, and Outcomes

The primary exposure was calendar year as a continuous variable. The primary outcome was Utstein survival-to-hospital discharge or 30-day post-arrest. Utstein survival rates were calculated by dividing the number of those achieving the primary outcome by the total number of cases that are nontraumatic in origin, bystander witnessed, and had shockable initial rhythms (ventricular fibrillation or pulseless ventricular tachycardia).[24] Utstein survival was chosen to be the primary outcome because in these cases there were opportunities to intervene, and therefore reflects the efficiency and efficacy of the emergency care system. Furthermore, it is an agreed-upon convention of measuring OHCA outcomes.[24] This enables comparison with data from other communities.

Secondary outcomes included return of spontaneous circulation, survival to hospital admission, and neurological status on discharge. Neurological status was assessed using Glasgow–Pittsburgh Outcome Scores (cerebral performance category and overall performance category). Neurologic status was evaluated by abstraction from clinical records, telephone, and face-to-face interviews by the attending physician either upon discharge or at 30 days post-arrest.

Response time refers to the interval between time call was received by the dispatch center and time of arrival at scene (location street address) of either the ambulance, or a rapid responder dispatched via the same dispatch center.

Ethics Approval

The Centralised Institutional Review Board (2013/604/C) and Domain Specific Review Board (2013/00929) granted approval for this study with a waiver of patient informed consent.

Statistical Analysis

Data analysis was performed using Stata version 14 (StataCorp LLC, TX). Patient demographics and OHCA characteristics for all cases were summarized as frequency and percentage for categorical data and median and interquartile range for continuous data. Pearson χ^2 test was used for categorical variables and nonparametric *t* test was used for continuous variables. Univariate logistic regression was performed to identify potential predictors of survival retrieved from existing literature. These potential predictors and calendar year were adjusted for in a multivariable logistic regression model. α was set at $P<0.05$.

RESULTS

Study Population

Table 1 shows the summary of patient demographics and characteristics. A total of 11 465 cases were included for analysis between 2011 and 2016. Median age was 67 years (interquartile range, 55–79) and 64.8% were males. Seventy-one percent of the cases occurred in residential locations.

Prehospital and Hospital Characteristics

Considering prehospital and hospital resuscitation characteristics (Table 2), bystander CPR rates increased from 21.9% in 2011 to 56.3% in 2016. Bystander AED rates increased from 1.8% to 4.6%. Prehospital advanced airway and prehospital adrenaline administration increased from 82.6% to 85.3% and 46.2% to 60.1%, respectively. The average EMS response time improved slightly from 8:22 minutes in 2011 to 8:13 minutes in 2016. Age-adjusted incidence rates for all EMS-treated OHCA increased from 25.6 in 2011 to 38.2 per 100 000 population in 2016. Similarly, age adjusted for OHCA cases with initial shockable rhythm also increased from 4.8 in 2011 to 7.0 per 100 000 population in 2016. Post-arrest resuscitation care in the hospital such as initiation of therapeutic hypothermia increased from 1.2% in 2011 to 5.3% in 2016.

Clinical Outcomes

EMS and hospital outcomes are presented in Table 3. Prehospital return of spontaneous circulation improved from 4.6% in 2011 to 12.5% in 2016 ($P<0.001$). Overall survival rates improved over the years from 3.5% in 2011 to 6.5% in 2016 ($P<0.001$). Of those who survived to discharge, 67.7% had good neurological function upon discharge in 2016 compared with 52.1% in 2011 ($P=0.007$). Survival outcomes stratified by sex and initial arrest rhythm did not show statistical significance during the study period (*P*=0.636 and *P*=0.621, respectively). Utstein survival rates nearly doubled from 11.6% in 2011 to 23.1% (*P*=0.006). However, good neurological function upon discharge for this group was not statistically significant (*P*=0.591).

Table 1. Patient Characteristics

	All (n=11 465)	2011 (n=1377)	2012 (n=1440)	2013 (n=1736)	2014 (n=2037)	2015 (n=2372)	2016 (n=2503)
Age, y, median (IQR)	67 (55–79)	65 (53–77)	66 (54–78)	67 (55–79)	68 (55–80)	67 (56–79)	67 (55–79)
Sex (%)							
Male	7431 (64.8)	935 (67.9)	912 (63.3)	1131 (65.2)	1316 (64.6)	1546 (65.2)	1591 (63.6)
Female	4034 (35.2)	442 (32.1)	528 (36.7)	605 (34.9)	721 (35.4)	826 (34.8)	912 (36.4)
Race (%)							
Chinese	7750 (67.6)	893 (64.9)	984 (68.3)	1225 (70.6)	1349 (66.2)	1587 (66.9)	1712 (68.4)
Indian	1259 (11.0)	185 (13.4)	146 (10.1)	161 (9.3)	209 (10.3)	277 (11.7)	281 (11.2)
Malay	1796 (15.7)	201 (14.6)	222 (15.4)	265 (15.3)	362 (17.8)	363 (15.3)	383 (15.3)
Other	660 (5.8)	90 (7.1)	88 (6.1)	85 (4.9)	117 (5.7)	145 (6.1)	127 (5.1)
Location type (%)							
Residential	8196 (71.5)	985 (71.5)	990 (68.8)	1246 (71.8)	1480 (72.7)	1658 (69.9)	1837 (73.4)
Nonresidential	3269 (28.5)	392 (28.5)	450 (31.2)	490 (28.2)	557 (27.3)	714 (30.1)	666 (26.6)
Medical history (%)							
Unknown	803 (7.0)	144 (10.5)	111 (7.7)	139 (8.0)	110 (5.4)	145 (6.1)	154 (6.2)
Heart disease	4163 (36.3)	511 (37.1)	512 (35.6)	624 (35.9)	761 (37.4)	816 (34.4)	939 (37.5)
Diabetes mellitus	3693 (32.2)	382 (27.7)	443 (30.8)	592 (34.1)	679 (33.3)	785 (33.1)	812 (32.4)
Hypertension	6188 (53.9)	653 (47.4)	739 (51.3)	961 (55.4)	1118 (54.9)	1314 (55.4)	1403 (56.0)
Cause of arrest (%)							
Nontrauma	11 073 (96.6)	1330 (96.6)	1403 (97.4)	1681 (96.8)	1979 (97.2)	2275 (95.9)	2405 (96.1)
Presumed cardiac	7848 (68.5)	1064 (77.3)	1003 (69.7)	1166 (67.2)	1386 (68.0)	1552 (65.4)	1677 (67.0)
Respiratory	594 (5.2)	82 (6.0)	129 (9.0)	93 (5.4)	86 (4.2)	104 (4.4)	100 (4.0)
Drowning	82 (0.7)	11 (0.8)	10 (0.7)	10 (0.6)	16 (0.8)	14 (0.6)	21 (0.8)
Electrocution	13 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	2 (0.1)	1 (0.0)	3 (0.1)
Other	2536 (22.1)	171 (12.4)	259 (18.0)	409 (23.6)	489 (24.0)	604 (25.5)	604 (24.1)
Trauma	391 (3.4)	47 (3.4)	37 (2.6)	55 (3.2)	58 (2.8)	97 (4.1)	97 (3.9)
Missing	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

IQR indicates interquartile range.

Factors Associated With Overall Survival

On logistic regression (Table 4), the factors significantly associated with survival-to-discharge or 30-day post-arrest were age ≤65 years old (adjusted odds ratio [aOR] 0.64 for >65 years old, 95% CI, [95% CI, 0.52–0.80]), non-residential location (aOR 0.61 for residential location, 95% CI, 0.49–0.75), EMS witnessed (aOR 7.23; 95% CI, 4.98–10.49), bystander witnessed (aOR 2.14; 95% CI, 1.61–2.85), shockable rhythm (aOR 10.18; 95% CI, 8.17– 12.69), bystander AED (aOR 1.99; 95% CI, 1.40–2.85), and year 2016 (aOR 1.63; 95% CI, 1.13–2.36).

Age-Standardized Incidence and Survival Rates

Figure 1 shows the yearly crude and age-standardized incidence rate. In 2016, the age-standardized incidence rate for OHCA was 39.2 per 100 000 populations. Stratified by age, while incidence rate among people aged <65 years remained relatively low (2.0 per 10 000 population in 2011; 3.0 in 2016), there was a greater increase among people aged >65 years (19.6 cases per 10 000 population in 2011; 29.9 in 2016).

Males overall had a much higher age-standardized incidence rate in 2016 (54.9 per 100 000) compared with females (23.6 per 100 000).

Figure 2 shows the trend of age-standardized survival rates between age groups. Among younger OHCA (age ≤65 years) the survival rate increased from 4.7% to 10.9%. Survival rates among older

OHCA (age >65 years) remained consistently low: 2.3% in 2011 to 3.4% in 2016. Over the same period, age-standardized survival rates significantly increased from 2.9% in 2011 to 12.0% in 2016.

DISCUSSION

This prospective, observational, national registry study of OHCA in Singapore showed a doubling in national Utstein survival from 2011 to 2016. This was associated with increased rates of bystander CPR and bystander AED, and temporally associated with a series of community and prehospital interventions to improve OHCA survival under a national strategic 5-year Plan.

Table 2. Prehospital and Hospital Characteristics

Variables, n (%)	All (n=11 465)	2011 (n=1377)	2012 (n=1440)	2013 (n=1736)	2014 (n=2037)	2015 (n=2372)	2016 (n=2503)
Bystander CPR	5244 (45.7)	302 (21.9)	472 (32.8)	744 (42.9)	1031 (50.6)	1284 (54.1)	1411 (56.3)
Bystander AED applied	378 (3.3)	24 (1.8)	27 (1.9)	43 (2.5)	73 (3.6)	96 (4.1)	115 (4.6)
Bystander defibrillation	157 (1.4)	11 (0.8)	16 (1.1)	22 (1.3)	25 (1.2)	37 (1.6)	46 (1.8)
Arrest witnessed by							
EMS/private ambulance	994 (8.7)	112 (8.1)	121 (8.4)	138 (7.9)	155 (7.61)	216 (9.1)	252 (10.1)
Bystander	5991 (52.3)	775 (56.3)	716 (49.7)	881 (50.8)	1082 (53.1)	1271 (53.6)	1266 (50.6)
Not witnessed	4480 (39.1)	490 (35.6)	603 (41.9)	717 (41.3)	800 (39.3)	885 (37.3)	985 (39.4)
Initial arrest rhythm							
Nonshockable rhythm	9276 (80.9)	1114 (80.9)	1144 (79.4)	1405 (80.9)	1651 (81.1)	1941 (81.8)	2021 (80.7)
Shockable rhythm	1995 (17.4)	251 (18.2)	280 (19.4)	304 (17.5)	347 (17.0)	378 (15.9)	435 (17.4)
Missing	194 (1.7)	12 (0.9)	16 (1.1)	27 (1.6)	39 (1.9)	53 (2.2)	47 (1.9)
Prehospital advanced airway	9764 (85.3)	1132 (82.6)	1201 (83.7)	1515 (87.3)	1751 (85.9)	2031 (85.6)	2134 (85.3)
Prehospital drug administration	6108 (53.3)	634 (46.2)	696 (48.5)	871 (50.2)	1056 (51.8)	1347 (56.8)	1504 (60.1)
Response time in min, median (IQR)	08:22 (06:29–10:44)	07:42 (05:51–10:15)	08:09 (06:15–10:36)	08:05 (06:08–10:50)	09:05 (07:08–11:28)	08:32 (06:47–10:44)	08:13 (06:26–10:23)
Response time							
≤8 min	5105 (45.2)	729 (52.9)	705 (49.0)	849 (48.9)	712 (35.0)	1019 (43.0)	1091 (46.8)
>8 min	6186 (54.8)	648 (47.1)	735 (51.0)	887 (51.1)	1325 (65.0)	1353 (57.0)	1238 (53.2)
Age-adjusted incidence rates (per 100 000 pop.)							
All EMS treated (resuscitation attempted)		25.6 (n=1363)	26.0 (n=1421	29.4 (n=1714)	32.8 (n=2002)	36.9 (n=2321)	38.2 (n=2470)
Initial shockable rhythm		4.8 (n=251)	5.1 (n=280)	5.3 (n=304)	5.8 (n=347)	6.2 (n=378)	7.0 (n=435)
Hospital interventions							
ECMO therapy	31 (0.3)	1 (0.1)	0 (0)	1 (0.1)	11 (0.5)	9 (0.4)	9 (0.4)
Hypothermia therapy	485 (4.2)	17 (1.2)	23 (1.6)	61 (3.5)	117 (5.7)	135 (5.7)	132 (5.3)

AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; EMS, emergency medical services; and IQR, interquartile range.

The pace of improvement in outcomes observed in our cohort is significant, and outpaced the majority of published reports. For example, the Swedish Cardiac Arrest Register showed an increase in 30-day survival from 4.8% to 10.7% (and for shockable rhythms, 12.7%–31.6%), and achieved this over a 10-year period from 1992 to 2011.[14] A similar study of 9 cities in Oregon showed an increase in 30-day survival from 6.7% to 18.2% (and for Utstein survival, from 14.3% to 31.3%), and achieved this over 15 years from 1998 to 2013.[27] Other communities have also reported rapid improvement in Utstein survival such as Toronto, Canada (16%–31% from 2006 to 2013),[16] Chicago, Illinois (16.3%–35.4% from 2013 to 2016),[28] and Detroit, Michigan (12.5%–18.2% from 2014 to 2016).[28] The focus on community training and EMS (particularly dispatcher) interventions appear to have been a common factor.

Increased rates of bystander CPR and public access defibrillation improve survival.[27,29] The role of the community and emergency medical dispatch in coordination of bystander CPR and early defibrillation is increasingly recognized.[27] In a landmark study, the OPALS (Ontario Prehospital Advanced Life Support) study investigators found bystander CPR to be the most important modifiable factor for survival.[30] In our study, bystander CPR rates more than doubled after implementation of dispatcher assistance-CPR. Dispatcher assistance-CPR recruits the dispatch center in the crucial tasks of early identification of OHCA, and giving just-in-time education and persuasion to callers to facilitate bystander CPR. Studies suggest advantages over large-scale community training, which often have not achieved large increases in CPR rates because of high costs to the system, difficulty in identifying OHCA, fear of causing harm, and reluctance to perform mouth-to-mouth ventilation.[29,31,32] In our cohort, response times improved slightly with survival. Indeed, reduction of ambulance response time is challenging for most EMS systems and might not be a cost-effective target. Our results suggest that a focus on proven and cost-effective strategies to strengthen the chain of survival, particularly in the community, ambulances, and dispatch, is essential for developing EMS systems.

Singapore has a fairly recently developed EMS system.[33,34] Having a single national EMS provider in a compact, highly urbanized setting is ostensibly advantageous in terms of policy implementation, monitoring, and enforcement. At the same time, there are unique challenges such as those resulting from high-rise buildings where there is the need to navigate tight corridors and administer CPR in elevators.[35,36] Certainly, every EMS system has unique circumstances and challenges that need to be considered in planning interventions.

The large increase (73%) in OHCA incidence over 5 years observed in this study is likely multifactorial: the population is still growing (5.18 million in 2011 to 5.6 in 2017), there is an aging population, an increased awareness of the population resulting in more EMS calls and resuscitation attempted, and better reporting. The proportion of ethnic groups appears comparable with the total population in Singapore.

Table 3. Clinical Outcomes (All and by Year)

Characteristic, n (%)	All (n=11 465)	2011 (n=1377)	2012 (n=1440)	2013 (n=1736)	2014 (n=2037)	2015 (n=2372)	2016 (n=2503)	*P* Value
Outcomes (overall)								
ROSC at scene	391 (8.1)	63 (4.6)	86 (6.0)	113 (6.5)	148 (7.3)	208 (8.8)	312 (12.5)	<0.001
ROSC at ED	3210 (28.0)	374 (27.2)	400 (27.8)	509 (29.3)	593 (29.1)	684 (28.8)	650 (26.0)	<0.001
Survival to admission	2111 (18.4)	251 (18.2)	249 (17.3)	303 (17.5)	358 (17.6)	453 (19.1)	497 (19.9)	0.175
Survival to discharge	545 (4.8)	48 (3.5)	53 (3.7)	73 (4.2)	83 (4.1)	125 (5.3)	163 (6.5)	<0.001
Good-to-moderate neurological function (of those discharged alive)	343 (63.4)	25 (52.1)	33 (63.5)	36 (49.3)	63 (75.9)	77 (62.1)	109 (67.7)	0.007
Outcomes (Utstein)	n=1315	n=173	n=172	n=210	n=229	n=241	n=290	
Utstein survival	228 (17.3)	20 (11.6)	23 (13.4)	32 (15.2)	35 (15.3)	51 (21.2)	67 (23.1)	0.006
Good-to-moderate neurological function (of those discharged alive)	152 (66.7)	12 (60.0)	14 (60.9)	18 (56.3)	24 (68.6)	35 (68.6)	49 (73.1)	0.591
Survival to discharge—sex	n=545	n=48	n=53	n=73	n=83	n=125	n=163	0.636
Male	422 (77.4)	36 (75.0)	38 (71.7)	53 (72.6)	64 (77.1)	100 (80.0)	131 (80.4)	
Female	123 (22.6)	12 (25.0)	15 (28.3)	20 (27.4)	19 (22.9)	25 (20.0)	32 (19.6)	
Survival to discharge—initial arrest rhythm								0.621
Nonshockable rhythm	174 (31.9)	12 (25.0)	15 (28.3)	25 (34.2)	21 (25.3)	48 (38.4)	53 (32.5)	
Shockable rhythm	357 (65.5)	35 (72.9)	37 (69.8)	47 (64.4)	58 (69.9)	75 (60.0)	105 (64.4)	
Missing	14 (2.6)	1 (2.1)	1 (1.9)	1 (1.4)	4 (4.8)	2 (1.6)	5 (3.1)	

ED indicates emergency department; and ROSC, return of spontaneous circulation.

Table 4. Logistic Regression for Overall Survival to Discharge

Characteristic (N=11 465)	Crude OR (95% CI)	Global *P* Value	*P* Value	Adjusted OR (95% CI)	Global *P* Value	*P* Value
Age						
≤65 y	Ref			Ref		
>65 y	0.39 (0.33– 0.47)		<0.001	0.64 (0.52– 0.80)		<0.001
Sex						
Male	Ref			Ref		
Female	0.52 (0.43– 0.64)		<0.001	1.06 (0.83– 1.35)		0.661
Location type						
Nonresidential	Ref			Ref		
Residential	0.28 (0.24, 0.34)		<0.001	0.61 (0.49– 0.75)		<0.001
Arrest witnessed		<0.001			<0.001	
Not witnessed	Ref			Ref		
EMS/private ambulance	6.05 (4.50– 8.14)		<0.001	7.23 (4.98–10.49)		<0.001
Bystander	3.33 (2.61– 4.23)		<0.001	2.14 (1.61– 2.85)		<0.001
Initial arrest rhythm						
Nonshockable rhythm	Ref			Ref		
Shockable rhythm	13.82 (11.31– 16.89)		<0.001	10.18 (8.17– 12.69)		<0.001
Bystander CPR						
No	Ref			Ref		
Yes	1.53 (1.28– 1.81)		<0.001	1.27 (0.99– 1.62)		0.058
Bystander AED						
No	Ref			Ref		
Yes	4.49 (3.37– 5.97)		<0.001	1.99 (1.40– 2.85)		<0.001
Response time ≤8 min						
No	Ref			Ref		
Yes	1.10 (0.92– 1.31)		0.281	1.05 (0.86–1.28)		0.623
Year		<0.01			0.01	
2011	Ref			Ref		
2012	1.06 (0.71– 1.57)		0.781	1.01 (0.66– 1.55)		0.956
2013	1.22 (0.84– 1.76)		0.303	1.21 (0.81– 1.80)		0.354
2014	1.18 (0.82– 1.69)		0.380	1.03 (0.69– 1.54)		0.888
2015	1.54 (1.10– 2.16)		0.013	1.39 (0.95– 2.01)		0.094
2016	1.93 (1.39– 2.68)		<0.001	1.63 (1.13–2.36)		0.009

Global *P* value=Wald test. Missing variables: initial arrest rhythm—194 (1.69); bystander AED—96 (0.84); response time—174 (1.52). AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OR, odds ratio.

This study has several limitations. First, we did not have data on some possible post-resuscitation care practice changes such as coronary angiography, percutaneous coronary intervention, or intensive care unit bundles that have been suggested to affect survival.[37] These may be potential confounders in the logistic regression for survival. The presence of unmeasured confounders is suggested by how "year of resuscitation" remained independently associated with outcome despite correction for major prognostic factors.

Secondly, there were missing prehospital timings in cases conveyed by private transportation or private ambulances. However, these comprised only ≈2% of cases.

Thirdly, we used survival-to-discharge instead of functional outcomes as the end point. This is because cerebral performance score at discharge and whether the survivors were discharged to care facilities were not consistently available. Also, because of the small population size and low proportion of neurologically intact survivors, there was insufficient power to meaningfully test these outcomes in the Utstein cohort.

Lastly, given the observational design, while there was strong temporal association and plausibility, findings are ecological and do not prove causality between interventional programs and survival benefit. Multiple initiatives that overlapped in timeline made it difficult to make clear inferences on the effect on survival.

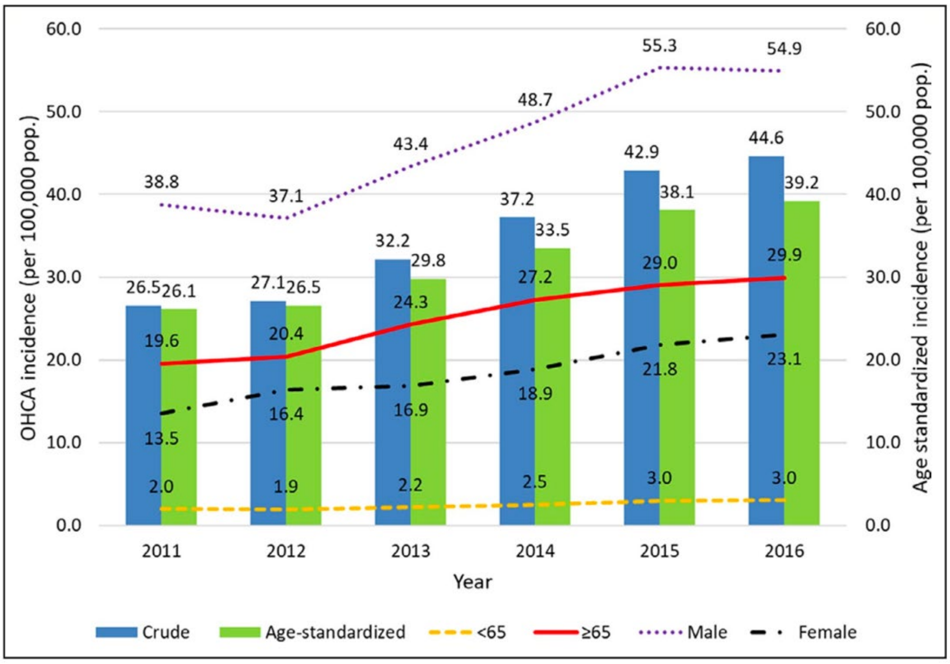

Figure 1. Yearly crude and age-standardized incidence rates.
OHCA indicates out-of-hospital cardiac arrest.

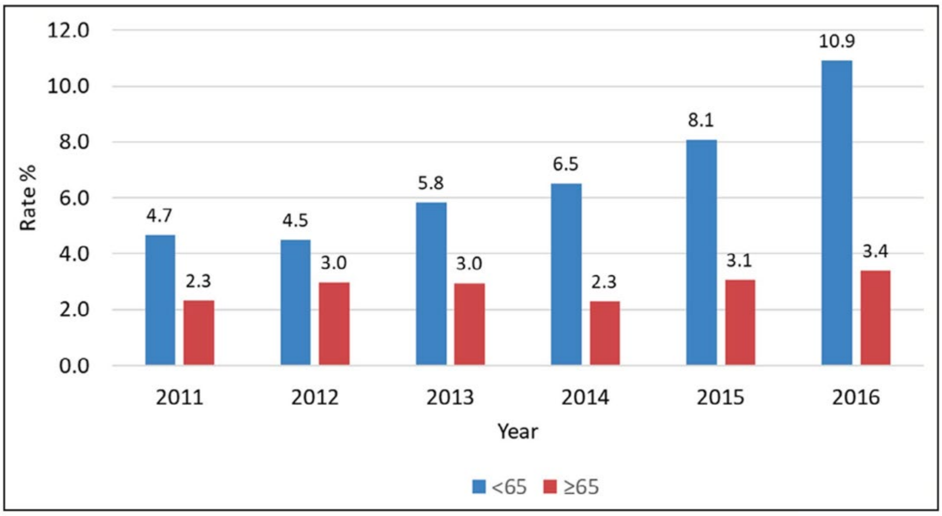

Figure 2. Age-standardized survival rates by age groups.

CONCLUSIONS

Utstein survival for OHCA in Singapore doubled from 2011 to 2016, along with corresponding increases in bystander CPR and bystander AED. These improvements occurred during a period when a series of national community and EMS initiatives were implemented to improve OHCA outcomes under a national 5-year Plan.

APPENDIX

Singapore PAROS Investigators

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Details of Interventions

In May 2011, mechanical CPR devices were deployed in SCDF ambulances, initially as a pragmatic cluster-randomized prehospital trial comparing LUCAS 2 (Physio-Control, Redmond, WA) with manual CPR. Subsequently, LUCAS 2 was rolled out to all ambulances as standard procedure for all eligible OHCA cases. In April 2012, the Fire Bikers Scheme was implemented where in times of traffic congestion, fire/rescue specialists on a motorcycle trained in CPR/AED were dispatched ahead of an ambulance. In July 2012, Singapore implemented a comprehensive dispatcher-assisted CPR (DA-CPR) protocol comprising of dispatcher training focused on communication and persuasion, review of audio recordings of all OHCA calls, feedback to dispatchers, and public education. After a planned six-month "run-in" program, all dispatchers were able to provide DA-CPR.

In April 2014, a community-based Dispatcher-Assisted first REsponder (DARE) training initiative, which simulates a rescuer-dispatcher sequence that is initiated by a call to '995' was implemented. This was developed to be an abbreviated (45 minutes) course including a video and instructor-led hands-on manikin session with hands-only CPR, and was administered to groups of schoolchildren or other laypersons. DARE program has since trained over 50,000 providers.

In August 2014, intraosseous (IO) access was introduced to ambulances as part of a cluster-randomized prehospital trial. This was used in OHCA cases for administration of adrenaline when intravenous access (IV) attempts had failed. Unpublished data (under review) showed that IO use when IV failed led to a higher rate of vascular access and faster adrenaline administration.

In April 2015, Save-A-Life (SAL) initiative was developed by SCDF, in collaboration with Singapore Heart Foundation and Ministry of Health Singapore to improve community first response to cardiac arrest cases in residential areas. SAL initiative involves installation of an AED in the lift lobby of every two public housing apartment block in Singapore. Installation of AEDs were done in phases and first phase began in July 2015. By end of 2016, total number of AEDs installed were 360. In the same month, a mobile phone application known as myResponder app was implemented to allow community responders to register and receive alerts from SCDF's dispatch center if a potential cardiac arrest case occurs within 400 meters of their vicinity.

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Chapter 12

Predictors of major adverse cardiac events among patients with chest pain and low HEART score in the emergency department.

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Abstract

Aim: For patients who present to the emergency departments (ED) with undifferentiated chest pain, the risk of major adverse cardiac events (MACE) may be underestimated in low-HEART score patients. We aimed to identify characteristics of patients who were classified as low risk by HEART score but subsequently developed MACE at 6 weeks.

Methods: We studied a multiethnic cohort of patients who presented with chest pain arousing suspicion of acute coronary syndrome to EDs in the Netherlands and Singapore. Patients were risk-stratified using HEART score and followed up for MACE at 6 weeks. Risk factors of developing MACE despite low HEART scores (scores 0-3) were identified using logistic and Cox regression models.

Results: Among 1376 (39.8%) patients with low HEART scores, 63 (4.6%) developed MACE at 6 weeks. More males (53/806, 6.6%) than females (10/570, 2.8%) with low HEART score developed MACE. There was no difference in outcomes between ethnic groups. Among low-HEART score patients with 2 points for history, 21% developed MACE. Among low-HEART score patients with 1 point for troponin, 50% developed MACE, while 100% of those with 2 points for troponin developed MACE. After adjusting for HEART score and potential confounders, male sex was independently associated with increased odds (OR 4.12, 95%CI 2.14-8.78) and hazards (HR 3.93, 95%CI 1.98-7.79) of developing MACE despite low HEART score.

Conclusion: Male sex, highly suspicious history and elevated troponin were disproportionately associated with MACE. These characteristics should prompt clinicians to consider further investigation before discharge.

Introduction

Chest pain is a common presenting complaint to the emergency department (ED), representing around 10% of ED visits [1]. With an extensive differential diagnosis, identification of life-threatening causes such as acute coronary syndrome (ACS) may be challenging and poses significant pressure on resources in the emergency and medical departments. Therefore, scoring systems were developed to assist in the risk stratification of patients with chest pain and suspected ACS in the ED, facilitating safe discharges and effective use of inpatient resources. One of the most utilized scores is the HEART (History, Electrocardiogram [ECG], Age, Risk factors and Troponin) score, which is recommended by the 2021 American Heart Association (AHA) guidelines [2]. The HEART score risk stratifies patients aged >21 years with acute chest pain and no ST elevation on ECG into low, moderate and high-risk groups. Patients with low risk may be safe for ED discharge without additional cardiac evaluation or inpatient admission [3-5].

However, the HEART score is not foolproof, and around 1.0-2.5% of low-risk patients proceed to develop acute myocardial infarction (MI), require revascularization or die within 4 to 6 weeks of the ED evaluation [4-7]. Factors traditionally associated with increased risk of ACS not considered in the HEART score may further identify patients at risk of ACS within the low HEART score subgroup. For example, males are 2-3 times more likely to experience acute MI than females, even after adjusting for comorbidities and age [8]. The risk of cardiovascular diseases may also be higher in South Asian and Black individuals than in Caucasians [9], suggesting possible ethnic or geographical variations. While only a small proportion of ACS is missed in patients with low-risk HEART scores, the clinical consequences may be grave, thus it is important to identify characteristics that predict ACS in low risk groups.

In this study, we aim to characterize the risk factors for major adverse cardiovascular events (MACE) in patients with low HEART score. This may assist clinicians in detecting cases that require further cardiac monitoring and investigation, and reduce the risk of missed cardiac events in the ED.

Methods

Study design

In this multicenter, multiethnic cohort study, we reviewed the data of patients who presented to the ED with symptoms suspicious of ACS. Patients were enrolled across three centers: Meander Medical Centre Amersfoort, the Netherlands (January 2012–June 2014), National University Hospital Singapore (December 2010–April 2013) and Singapore General Hospital (January 2010–September 2011). The study has been evaluated and approved by the ethics committees of all participating centers and all participants have provided written informed consent. The study conforms to the Declaration of Helsinki.

Study population

Patients presenting to the ED with possible cardiac symptoms for a duration of at least five minutes and in whom the physician intended to perform serial cardiac troponin measurements were eligible for inclusion [10]. Possible cardiac symptoms were defined according to the AHA case definitions as acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without an apparent non-cardiac source [11]. We excluded patients who (1) were younger than 21 years, (2) were unable or unwilling to give their informed consent, (3) belonged to an ethnic group other than Caucasian, Chinese, Indian or Malay, (4) had insufficient data to calculate the HEART score, (5) had missing or incomplete follow-up data or (6) had an ST-segment elevation MI as they were directly referred for percutaneous coronary intervention (PCI).

Data acquisition

After patients gave informed consent, clinical data (including clinical presentation, duration of symptoms, medical history, cardiovascular risk factors, ECG evaluation, blood biochemical parameters and the results of additional investigations) were gathered from medical records and recorded in a digital case record form. Ethnicity was self-reported in the Netherlands and was determined at hospital registration in Singapore, based on information from state-issued identification cards. Smoking was defined as current smoking or smoking within the last three months. Diabetes mellitus was defined as any type of diabetes mellitus diagnosed previously by a physician or during the index visit [12]. Dyslipidemia was scored when diagnosed previously by a physician or diagnosed during the index visit, according to the European Society of Cardiology/European Atherosclerosis Society guidelines [13]. Hypertension was scored when reported in the medical history, when diagnosed during the index visit or when the patient was treated for hypertension [14]. Renal impairment was defined as a glomerular filtration rate (GFR) of <60 ml/min (moderate renal impairment GFR 30–60 ml/ min, severe renal impairment GFR <30 ml/min, calculated using the Cockroft–Gault equation).

HEART score protocol

Patient data collected at the time of presentation to the ED were used to calculate the HEART score. The HEART score algorithm is depicted in Supplementary Table 1 [6]. Briefly, across the five subdomains of history, ECG findings, age, cardiovascular risk factors and troponin levels, patients were given zero, one or two points for each subdomain, with increased points reflecting poorer predicted outcomes. Based on the total score, patients were categorized as low risk (0–3 points), intermediate risk (4–6 points) or high risk (7–10 points).

Clinical outcome

The primary outcome was MACE, defined as MI, coronary revascularization or all cause death, within 6 weeks after presentation to the ED (as defined by previous studies) [4]. This included the diagnosis adjudicated during the index visit. The diagnosis of MI was made according to European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation guidelines (2012) [15]. Diagnoses were determined in retrospect by two cardiologists, taking into consideration all patient information available, including investigations and treatment after the index presentation. In the case of dispute, a third cardiologist decided the final diagnosis. Coronary revascularization was defined as PCI or coronary artery bypass grafting (CABG).

Statistical analysis

All statistical analyses were performed using the R software (version 4.1.2). Continuous variables were presented as median (interquartile range [IQR]) and categorical variables as percentages, unless stated otherwise. Comparisons of continuous variables between two groups were performed using the Wilcoxon rank sum test. Comparisons of continuous variables among more than two groups were performed using the Kruskal-Wallis rank sum test. The Pearson's Chi-squared test was used for the comparison of categorical variables with all expected cell counts more than or equal to 5, and the Fisher's exact test was used for comparing categorical variables with any expected cell count less than 5. We considered p-values of less than 0.05 to be significant.

To account for the non-linear relationship between body mass index (BMI) and cardiovascular events [16], BMI was stratified into tertiles. Amongst patients with low HEART score, in the troponin levels and ECG findings subdomains, patients who scored one or two points were grouped together as too few patients scored two points in these subdomains.

Crude adverse event rates of MACE within 6 weeks after inclusion were presented using Kaplan–Meier curves and subgroups were compared with the log-rank test. Univariate and multivariate logistic and Cox regression models were constructed, with MACE at the end of or throughout the 6 weeks as the primary outcome respectively. Variables with a p-value <0.1 in the univariate model and variables agreed upon by domain experts were included in the constructed multivariate models. We present the final model in the results, along with the odds and hazard ratios respectively and their 95% confidence intervals (95%CI).

Results

Patient population

Between 2010 and 2014, 3857 eligible patients were enrolled at the three participating centers. Sufficient data to calculate the HEART score as well as complete 6-week follow-up data were available in 3456 patients: 1791 from Meander Medical Centre Amersfoort, 1513 from Singapore General Hospital and 152 from National University Hospital Singapore. Of these patients, 1376 (39.8%) patients had low HEART scores (0-3 points).

Clinical outcome

Among the 1376 patients who had low HEART score, 63 (4.6%) patients developed MACE over the observed timespan of 6 weeks. Within this low HEART score group, the incidence of MACE between sexes was significantly different (p<0.001), where 53/806 (6.6%) of males who had low HEART score developed MACE, compared to 10/570 (2.8%) of females who had low HEART score (Table 1). While the baseline characteristics of age, gender, patients who smoked, patients who had hypertension, hypercholesterolemia or diabetes mellitus had significantly different distributions amongst the four included ethnic groups (Supplementary Table 2), there was no significant difference in the proportion of patients who had low HEART scores and developed MACE when stratified by ethnic group (p=0.9) (Table 1).

Incidence of MACE per HEART score category among low HEART score patients

Among low HEART score patients with two points for the history subdomain, 21% developed MACE. Among low HEART score patients with one and two points for the troponin level subdomain, 50% and 100% developed MACE respectively (Table 2).

Risk factors associated with developing MACE despite having a low HEART score

In the preliminary univariate logistic regression analyses (Table 3), sex, history of PCI, renal failure, BMI, having ≥1 point for the history or troponin level HEART subdomains, having an increased HEART score had a p-value of ≤0.1. In the final multivariate model, after adjusting for HEART score and other potential confounders, male sex was associated with increased odds of developing MACE within 6 weeks (OR 4.12, 95%CI 2.14-8.78).

In the preliminary univariate Cox regression analyses (Table 4), sex, history of percutaneous coronary intervention, renal failure, body mass index, having ≥1 point for the history or troponin level HEART subdomains, having an increased HEART score had a p-value of ≤0.1. In the final multivariate model, after adjusting for HEART score and other potential confounders, male sex was associated with increased hazards of developing MACE throughout the 6 weeks (HR 3.93, 95%CI 1.98-7.79). On the plotted Kaplan-Meier curves for MACE-free survival (Supplementary Figure 1), the survival functions for males and females significantly diverged (log-rank p-value<0.001). MACE-free survival probabilities at 6 weeks for males and females were 93.4% (95%CI 91.7%-95.2%) and 98.3% (95%CI 97.2%-99.3%) respectively.

As it is unlikely that ED physicians send patients with elevated troponin home, we conducted a sensitivity analysis and removed all patients with 1 point or 2 points in the troponin subdomain. In the final multivariate models, male sex was still associated with increased odds (OR 4.20, 95%CI 2.11-9.34) and increased hazards (HR 4.02, 95%CI 1.96-8.26) of developing MACE throughout the 6 weeks.

Discussion

In this study, the main findings were 1) male sex was a significant predictor for MACE in patients with low HEART score, with males having around four times the risk of females, even after adjustment for potential confounding factors, and 2) within the HEART score, highly suspicious history and raised troponin were most strongly associated with MACE. These findings were consistent among the different ethnicities, and our study provides important evidence for the generalizability of the impact of sex, chest pain history and troponins on the risk of MACE even in low-risk patients.

The HEART score is a rapid and relatively simple risk stratification tool designed to assess patients presenting with chest pain in the ED, and patients with low risk may be safe for discharge from ED, avoiding unnecessary hospital admissions. Several meta-analyses have shown that low HEART score has high sensitivity and negative predictive value for MACE, compared to other risk stratification scores such as Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores [17, 18]. Overall, low HEART score had a sensitivity for short-term MACE of 0.96, and negative predictive value of 0.99 across 25 studies. The use of clinical decision pathways such as HEART Pathway reduces admission or further testing in 21-43% of patients [19, 20], and as such, is recommended by the AHA 2021 guidelines to be used in standard clinical practice [2]. In a 2019 meta-analysis of 25 studies, the overall prevalence of low HEART score was 39.3%, across studies performed in North America, Europe and Asia-Pacific [21]. Our finding of 39.8% of patients with low HEART score is largely comparable to the previous cohorts published in literature.

Despite the overall high sensitivity of the HEART score, among patents with low-risk scores, around 2.1% developed MACE from within 30 days to 6 weeks [21]. In our study on a European and Asian cohort, the prevalence of MACE was 4.6% within 6 weeks, which could be due to the previously reported higher incidence of false negatives on HEART score in European and Asian-Pacific studies compared to North American studies. In North American studies, 0.7% of patients developed MACE in the low risk group, while 2.4-2.6% developed MACE in European and Asian-Pacific studies in the 2019 meta-analysis [21]. While reasons for this discrepancy are unclear, differences in burden of cardiovascular diseases across the continents were also observed in the Global Burden of Diseases 2019 Study [22], with highest disability-adjusted life years (DALYs) in Central Asia, Eastern Europe and Oceania. We explored ethnic differences in patients with low HEART scores, which identified that Malay patients were youngest, but had greatest proportion of smokers, diabetes mellitus and BMI. Caucasian patients were the oldest with most females and lowest prevalence of hypercholesterolemia, diabetes mellitus and history of stroke. Irrespective of this, the risk of MACE in low risk patients was similar among the different ethnicities in our study, and the sensitivity of HEART score remained above 94% across the continents and ethnicities [21, 23], suggesting that the utility of the HEART score remains high despite geographic variation.

One of the factors identified to be most strongly associated with MACE in low HEART score patients was male sex, hence greater caution should be excised in discharging male patients with suspected ACS in ED. Our results are comparable to two large studies in the UK (population-based) [24] and the Netherlands (ED-based) [25] that reported males were more than three times more likely to develop MACE than females. In two multicenter validation studies of the HEART score in the Netherlands and Asia-Pacific population, male sex was an independent predictor of MACE in the overall cohort [4, 7], but this was not analyzed in the specific population of low-risk patients in these studies. Sex should be considered when discharging males with low HEART score from the ED as they are 3.93 times more likely to develop MACE than females. Previous studies found that although the gap in risk of MI between males and females decreases with age, the risk remains higher in men up to 94 years old [8], and men develop MI nine years earlier than women [26]. In our study, the age of patients with low HEART score was lower than the overall cohort, with median ages of 52 and 60 respectively, and thus this population may have a large sex difference in MI risk at baseline. Notably, our study also included 62% males, which was higher than 23 out of 25 studies included in the meta-analysis by Laureano-Philips et al. [21], which may have increased the rate of false negatives on the HEART score reported in our study compared to prior to studies.

Several reasons for the sex difference in the incidence of ACS have been proposed. This could be due to the increased prevalence of cardiovascular risk factors at an earlier age in men. In a study of the Health Survey for England on 49,415 adults, women had fewer cardiovascular risk factors than men, with 36% of women having no cardiovascular risk factors compared to 29% of men in 2017 [27]. However, in our Cox-regression and logistic regression analysis adjusted for smoking, diabetes mellitus, history of PCI and BMI, men remained at significantly higher risk of MACE despite a low HEART score. It has also been suggested that female hormones exert cardioprotective effects through increasing high density lipoproteins, decreasing low density lipoproteins, and releasing vasodilators such as nitric oxide and prostaglandins, which inhibit platelet aggregation and reduce blood pressure [28]. The role of sex hormones on cardiovascular risk reduction remains controversial with trials on hormone replacement therapy showing conflicting results [29]. Further research is therefore required to understand the cause of sex difference in risk of ACS, particularly in the context of those with low HEART score as identified in our study.

Few studies have investigated the relative importance of individual components of the HEART score in predicting MACE. In the original study by Six et al. in 2008, only ECG, history and troponin were significantly associated with acute MI, PCI, CABG and death, but not age or risk factors [6], and this was confirmed in the validation study in 2010 [7]. However, in the larger 2013 cohort study on 2906 patients, all five components were significantly associated with MACE within 30 days, although the relative contributions of each element were not analyzed [4]. In our analysis by specific HEART components, troponin was most strongly associated with MACE development in low-risk patients, and score of 1-2 had HR of 27.6 compared to score of 0. The HEART pathway combines the HEART score with serial troponins, where low risk patients were defined as those with score <4 and serial negative troponins 1-3 hours apart [30]. This clinical pathway has high negative predictive value of >99% [31] and when implemented in the HEART Pathway Randomized Trial, it reduced objective cardiac testing at 30 days by 12.1%, length of stay by 12 hours and increased early discharges by 21.3% [30]. Studies using exclusively high-sensitivity cardiac troponins (hs-cTn) reported a greater proportion of low HEART score, with 62.5% in the TRAPID-AMI trial study (High-Sensitivity Troponin-T Assay for Rapid Rule-Out of Acute Myocardial Infarction) [32], 56.9% in the RAPID-TnT trial [33] and 46% in the study by Willems et al. in the Netherlands [34]. In a multicenter US cohort study of 1462 patients, addition of the HEART score to the initial hs-cTn or 0/1-hour algorithm which considers the absolute change in hs-cTn in 1 hour, improved the negative predictive value for 30-day MACE to 99% and 98.4% from 98.3% and 97.2% respectively [35]. Therefore, in patients low HEART score, serial troponin testing may remain important to reduce the risk of missed ACS, and further observation or investigations in those with raised repeat troponin should be considered.

The improvement in negative predictive value of a combination of HEART score and serial troponins compared to the 0/1-hour algorithm alone may be contributed to the consideration of the level of suspicion based on cardiac history of chest pain in the HEART score, which was also independently associated with MACE. Those with a highly suspicious history score of two had HR of 6.85 for the risk of MACE within 6 weeks compared to those with a score of zero. The history component however could be subjective and a source of inter-clinician variability [36]. While attempts have been made to standardize the scoring of history using various history-taking models, a widely accepted mode of history taking has not been developed and validated [37]. Overall, studies have shown the inter-operator reliability of the HEART score remained high among senior doctors, junior doctors, senior nurses and junior nurses [36]. Therefore, despite a low HEART score, a greater suspicion for risk of ACS should be considered in patients with highly suspicious cardiac history and raised troponins, particularly in men, and this finding may be generalizable to both European and multiethnic Asian cohorts.

Strengths and limitations

One of the main strengths of this study is its multiethnic and multicenter nature, which allowed the investigation into the ethnic differences in risk factors that predicted MACE in low-risk patients. Given the similar proportion of patients with low HEART score in this study compared to published studies [21], impact of selection bias is likely to be low. There were several limitations to our investigation. Around 10% of patients were not included in analysis due to the lack of follow up data at 6 weeks, which was comparable to previous cohort studies using the HEART score [4, 20]. Due to the limitation of follow up data available, we were unable to determine the prediction of these factors with longer term outcomes beyond 6 weeks, although 19 out of 25 studies in a previous meta-analysis reported MACE outcomes within 6 weeks [21], and the relatively short-term outcome in our study may increase comparability with previous published literature. Due to the resource availability, our study used conventional troponin, as per the original HEART score [6], which may be less sensitive than the newer hs-cTn. Follow up studies using hs-cTn may further reduce the risk of false negatives and improve the performance in the HEART score, particularly in the context of the HEART pathway. Lastly, we have identified a strong association of male sex with risk of MACE even with a low HEART score, but the mechanism behind this is not well established and beyond the scope of this study. Further research is needed to identify the cause of the sex difference and potential risk reduction methods to improve the outcomes of these patients.

Conclusions

A small proportion of patients with chest pain and suspected ACS in the ED with low HEART score may remain at risk of ACS and develop MACE within 6 weeks. In our multicenter, multiethnic study of patients in the Netherlands and Singapore, factors most strongly associated with MACE were male sex, raised troponin and highly suspicious cardiac history. Therefore, the use of the HEART score should be combined with clinical judgement, particularly in those with these risk factors, to reduce the risk of missing ACS which may have severe morbidity and mortality consequences.

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Tables

Table 1: Baseline demographics for overall population, low HEART population, low HEART and no MACE at 6 weeks, low HEART and MACE at 6 weeks

Characteristic	Overall, N = 3,456	Low HEART, N = 1,376	Low HEART, no MACE at 6 weeks, N = 1,313	Low HEART, MACE at 6 weeks, N = 63	p-value comparing no MACE vs MACE
Age	60 (51, 69)	52 (44, 60)	52 (44, 60)	53 (45, 60)	0.9
Sex					<0.001
F	1,327 (38%)	570 (41%)	560 (43%)	10 (16%)	
M	2,129 (62%)	806 (59%)	753 (57%)	53 (84%)	
Smoking	986 (29%)	388 (28%)	370 (28%)	18 (29%)	>0.9
Unknown	4				
Hypertension	1,761 (51%)	370 (27%)	349 (27%)	21 (33%)	0.2
Hypercholesterolemia	1,472 (43%)	334 (24%)	317 (24%)	17 (27%)	0.6
Diabetes	733 (21%)	118 (8.6%)	113 (8.6%)	5 (7.9%)	0.9
History of MI	563 (16%)	52 (3.8%)	48 (3.7%)	4 (6.3%)	0.3
Unknown	2				
History of PCI	651 (19%)	72 (5.2%)	65 (5.0%)	7 (11%)	0.042
Unknown	1				
History of CABG	246 (7.1%)	14 (1.0%)	13 (1.0%)	1 (1.6%)	0.5
Unknown	1				
History of stroke	102 (3.0%)	9 (0.7%)	9 (0.7%)	0 (0%)	>0.9
Unknown	1				
History of peripheral arterial disease	80 (2.3%)	2 (0.1%)	2 (0.2%)	0 (0%)	>0.9
Unknown	1				
Renal failure	609 (19%)	75 (6.2%)	74 (6.4%)	1 (1.6%)	0.2
Unknown	228	162	161	1	
BMI	26.2 (23.7, 29.2)	26.0 (23.4, 28.6)	26.0 (23.4, 28.7)	25.6 (23.5, 27.0)	0.2
Unknown	247	163	162	1	
Ethnicity					0.9
Caucasian	1,791 (52%)	642 (47%)	612 (47%)	30 (48%)	
Chinese	1,059 (31%)	461 (34%)	438 (33%)	23 (37%)	
Indian	344 (10.0%)	156 (11%)	150 (11%)	6 (9.5%)	
Malay	262 (7.6%)	117 (8.5%)	113 (8.6%)	4 (6.3%)	

Table 2: HEART score components for low HEART population

Characteristic	Low HEART, N=1376	Low HEART, MACE at 6 weeks, N = 63
HistoryHEART		
0	501 (36%)	17 (3.4%)
1	851 (62%)	41 (4.8%)
2	24 (1.7%)	5 (21%)
ECGHEART		
0	1,228 (89%)	55 (4.5%)
1	145 (11%)	8 (5.5%)
2	3 (0.2%)	0 (0%)
AgeHEART		
0	419 (30%)	20 (4.8%)
1	804 (58%)	38 (4.7%)
2	153 (11%)	5 (3.3%)
RiskHEART		
0	433 (31%)	17 (3.9%)
1	754 (55%)	32 (4.2%)
2	189 (14%)	14 (7.4%)
TropHEART		
0	1,368 (99%)	58 (4.2%)
1	6 (0.4%)	3 (50%)
2	2 (0.1%)	2 (100%)
HEARTscore		
0	23 (1.7%)	0 (0%)
1	166 (12%)	2 (1.2%)
2	425 (31%)	11 (2.6%)
3	762 (55%)	50 (6.6%)

Table 3: Logistic regression for low HEART population, MACE at 6 weeks as outcome

Characteristic	N	OR	95% CI	p-value	OR	95% CI	p-value
Age	1376	1.00	0.98, 1.02	>0.9			
Sex	1376			<0.001			<0.001
F		—	—		—	—	
M		3.94	2.08, 8.29		4.12	2.14, 8.78	
Smoking	1376			>0.9			0.3
No		—	—		—	—	
Yes		1.02	0.57, 1.75		0.75	0.41, 1.32	
Hypertension	1376			0.2			
No		—	—				
Yes		1.38	0.79, 2.34				
Hypercholesterolemia	1376			0.6			
No		—	—				
Yes		1.16	0.64, 2.02				
Diabetes	1376			0.9			0.6
No		—	—		—	—	
Yes		0.92	0.31, 2.12		0.8	0.27, 1.94	
HxMI	1376			0.3			
No		—	—				
Yes		1.79	0.53, 4.57				
HxPCI	1376			0.058			0.4
No		—	—		—	—	
Yes		2.4	0.97, 5.15		1.53	0.60, 3.45	
HxCABG	1376			0.7			
No		—	—				
Yes		1.61	0.09, 8.30				
RenalFailureTotal	1214			0.072			
No		—	—				
Yes		0.24	0.01, 1.11				
BMI Tertiles	1213			0.037			0.007
Medium		—	—		—	—	
High		0.43	0.21, 0.84		0.38	0.18, 0.75	
Low		0.84	0.47, 1.49		0.99	0.54, 1.78	
Ethnicity	1376			0.9			
Caucasian		—	—				
Chinese		1.07	0.61, 1.86				
Indian		0.82	0.30, 1.87				
Malay		0.72	0.21, 1.87				
HistoryHEART	1376			0.007			
0		—	—				
1		1.44	0.82, 2.63				
2		7.49	2.28, 21.3				
ECGHEART	1376			0.6			
0		—	—				
1-2		1.22	0.53, 2.47				
AgeHEART	1376			0.7			
0		—	—				
1		0.99	0.57, 1.75				
2		0.67	0.22, 1.70				
RiskHEART	1376			0.2			
0		—	—				
1		1.08	0.60, 2.02				
2		1.96	0.93, 4.06				
TropHEART	1376			<0.001			
0		—	—				
1-2		37.6	9.02, 187				
HEARTscore	1376	2.58	1.62, 4.47	<0.001	2.66	1.62, 4.77	<0.001

Table 4: Cox regression for low HEART population, MACE as outcome, censored at 42 days

Characteristic	N	HR	95% CI	p-value	HR	95% CI	p-value
Age	1376	1.00	0.98, 1.02	>0.9			
Sex	1376			<0.001			<0.001
F		—	—		—	—	
M		3.83	1.95, 7.53		3.93	1.98, 7.79	
Smoking	1376			>0.9			0.3
No		—	—		—	—	
Yes		1.03	0.59, 1.77		0.76	0.44, 1.33	
Hypertension	1376			0.3			
No		—	—				
Yes		1.36	0.80, 2.29				
Hypercholesterolemia	1376			0.6			
No		—	—				
Yes		1.15	0.66, 2.01				
Diabetes	1376			0.8			0.6
No		—	—		—	—	
Yes		0.91	0.37, 2.27		0.79	0.31, 2.02	
HxMI	1376			0.3			
No		—	—				
Yes		1.73	0.63, 4.77				
HxPCI	1376			0.067			0.4
No		—	—		—	—	
Yes		2.26	1.03, 4.96		1.44	0.64, 3.21	
HxCABG	1376			0.7			
No		—	—				
Yes		1.6	0.22, 11.5				
RenalFailureTotal	1214			0.073			
No		—	—				
Yes		0.24	0.03, 1.76				
BMI Tertiles	1213			0.038			0.008
Medium		—	—		—	—	
High		0.44	0.22, 0.86		0.39	0.20, 0.78	
Low		0.85	0.49, 1.48		1	0.57, 1.74	
Ethnicity	1376			0.9			
Caucasian		—	—				
Chinese		1.07	0.62, 1.84				
Indian		0.82	0.34, 1.97				
Malay		0.74	0.26, 2.09				
HistoryHEART	1376			0.007			
0		—	—				
1		1.43	0.81, 2.52				
2		6.85	2.53, 18.6				
ECGHEART	1376			0.6			
0		—	—				
1-2		1.21	0.58, 2.55				
AgeHEART	1376			0.7			
0		—	—				
1		0.99	0.57, 1.70				
2		0.68	0.25, 1.80				
RiskHEART	1376			0.2			
0		—	—				
1		1.08	0.60, 1.95				
2		1.9	0.94, 3.86				
TropHEART	1376	12.3	6.47, 23.4	<0.001			
TropHEART	1376			<0.001			
0		—	—				
1-2		27.6	11.0, 69.0				
HEARTscore	1376	2.53	1.54, 4.16	<0.001	2.58	1.53, 4.34	<0.001

Chapter 13

Summary and Discussion

Andrew Fu Wah Ho

Out-of-hospital cardiac arrest (OHCA) continues to impose a tremendous disease burden on our society despite advances in treatment and prevention over the past few decades. Its unpredictable and time-sensitive nature poses profound challenges to how we treat and study it. Current issues and priorities in the field of resuscitation research culminated from decades of evolution in how we conceptualize this disease. These are summarized in **Chapter 1**. In this thesis, we describe a journey with multiple steps, collectively aimed at improving OHCA outcomes. Using a number of techniques, we interrogate interrelated topics of current interest surrounding risk factors, prognostication and treatment of OHCA. It comprises one introductory chapter, one textbook chapter, and ten original investigations. In this final summary and discussion, we aim to summarize the methodological approaches, key findings, strengths and limitations, and implications of these investigations.

Recognizing the difficulties in executing Randomized Controlled Trials (RCTs) in OHCA research, **Chapter 2** is a textbook chapter on interventional studies other than RCTs.[17] It reviews how to design studies to address important research questions. It starts with outlining the challenges of RCTs specific to pre-hospital research. It is then followed by describing quasi-experiments and natural experiments, comparing and contrasting between them, providing examples of situations when these are suitable, and outlining their advantages and limitations. This chapter also outlined modifications of the RCT design to overcome feasibility issues in the pre-hospital setting. The methods covered in this chapter allow us to test interventions in OHCA, which are often not drug or device-related, but rather, systems and policy interventions which are sometimes better tested using non-RCT designs. When used effectively, they allow us to gain robust causal inference from new interventions. The methodological considerations described in this chapter percolate throughout the rest of the thesis.

Chapters 3 and 4 are two published studies relating to long-term survival after OHCA. They fill gaps in our knowledge of how OHCA survivors do in the long run, given that most disease surveillance tools and registries currently lack the ability to capture long-term follow up. In **Chapter 3**, we performed a systematic review and meta-analysis, which found a troublingly low number of previous studies that followed up patients beyond 12 months.[18] Pooling these 35 studies comprising 7186 patients, we found that amongst OHCA patients that survived to hospital discharge, 78% remained alive at 1-year, 70% remained alive at 3-years, and 63% remained alive at 5-year. We found that long-term survival was better amongst men, cases with an initial shockable rhythm, and cases that occurred in public locations. We also found that long-term survival was better in North America, Europe and Oceania compared to Asia. While this study provided a much-needed initial scope of the literature to determine what we know about long-term survival, its main limitation was that it was based on a small number of previous studies, and the pooled estimates were likely overly-optimistic as they were pooled from the few selected communities that were able to obtain long-term data.

Chapter 4 was a cohort study to investigate long-term outcomes in Singapore. Using an open cohort dataset that we assembled by linking the Pan-Asian Resuscitation Outcomes Study (PAROS) data with the Singapore's Registry of Births and Deaths, we had a unique opportunity to follow up 802 OHCA patients who survived to hospital discharge for up to ten years. We computed the proportion alive at various time-points, produced survival functions, and identified correlates of these. We also computed Standardized Mortality Ratios and through that, found that compared to controls who has not had OHCA, OHCA survivors are at elevated risk of death only in the first two years after the OHCA. While this study provides much-needed data on survival duration, that is only one domain of survivorship. More studies are needed to provide data on other domains, such as physical disability, cognition, social integration and caregiver burden, using a multi-domain survivorship framework. In this regard, our knowledge of patients who survived OHCA lag behind those who survived stroke and traumatic brain injury.

Chapter 5 deals with another dimension of long-term outcome—that is, recurrence. In this systematic review and meta-analysis, we pooled data from 7186 patients across 35 studies. We found the pooled incidence of having a first recurrence to be 15%. Among patients who had a first recurrence, 35% had a second recurrence. We found that among patients who suffered recurrences, most (two-thirds) of them occurred within the first year. We tested several factors in a meta-regression and found that initial shockable rhythm was correlated with increased odds of recurrence. Collectively, these findings reveal opportunities for tertiary prevention in these patients. Particularly, the role of strategies for tertiary prevention, such as implantable cardioverter defibrillators and cardiopulmonary resuscitation (CPR) training of household members, need clarification in future studies. Our study also suggested that preventive strategies should be started early in view of most recurrences occurring in the first year. The major limitation of this study is the preponderance of North American data, which limits the generalizability of the findings to other regions.

In **Chapters 6 and 7**, we examined whether air quality was a risk factor for OHCA. Air pollutant is an emerging risk factor owing to urbanization and has gained substantial public health concern. Both studies are set in the context of Singapore, which experiences transboundary haze from forest-clearing agricultural activities in Southeast Asia. With a network of air quality monitoring stations placed around the island, as well as comprehensive OHCA surveillance, Singapore forms an ideal population laboratory to provide high-quality insights into the relationship between air quality and OHCA. In **Chapter 6**, we used a case crossover design and found a 37% increased risk of OHCA when air quality was in the "unhealthy" range of Pollutant Standards Index (PSI), and 10% increased risk when it was in the "moderate range", compared to when it is in the "healthy range". We found the risk to be elevated for at least five days after exposure. This finding was unfortunately lacking in generalizability because the PSI was not universally used as an air quality metric.

Since the previous study examined PSI as the primary exposure, it could not inform which component of air pollution was responsible for driving the OHCA risk. This motivated **Chapter 7**, where we obtained concentration data of individual pollutants and investigated their association with OHCA risk. Using a time-series approach, we found that particulate matter with diameter of 2.5 μm ($PM_{2.5}$) or smaller, was a major driver of the association between air quality and OHCA risk. Every 10 μg/m³ increase in $PM_{2.5}$ was associated with increased risk of OHCA (RR 1·022 [95% 1·002–1·043]) over the next 2 days. The main limitation of both studies is their observational ecological design which means that the findings are susceptible to the ecological fallacy, where we may made wrong inferences about individuals based on observations about groups. Future studies are needed to evaluate strategies to mitigate the risk of acute illness arising from air pollution, such as health advisories and mask distribution programs.

Chapters 8, 9 and 10 are three studies focusing on bystander cardiopulmonary resuscitation (CPR). **Chapter 8** used a cohort study design to investigate the association between socioeconomic status and the chance of receiving bystander CPR. To classify socioeconomic status, we used an innovative approach of assigning the Singapore Housing Index to each residential building address in Singapore. This index incorporated average property price and acts as a surrogate for socioeconomic status. We found that the average socioeconomic status of the residential building was associated with the chance of a OHCA patient. These findings echo a spate of recent reports from around the world that similarly found disparities in OHCA treatment on account of socioeconomic position, and prompt interventional programs to reduce inequities.

In **Chapter 9**, we used a cohort study approach to assess whether CPR-targeted public health interventions in Singapore have increased bystander CPR rates on a city-wide basis. We found that over the period of 2011-2016, bystander CPR was increased in association with a bundle of three interventions: community CPR training, a mobile phone application (myResponder) and a telephone-CPR program. Due to temporal overlap of the three components of the bundle, this study was unable to examine the isolated effect of each of them. These findings form one of few reports around the world to show that public health interventions can successfully improve bystander CPR rates. This provides encouragement to other communities to explore similar initiatives.

In **Chapter 10**, we used a systematic review and meta-analysis approach to estimate the global prevalence of laypersons trained to provide CPR. From 29 studies across 18 countries, we found that on average among the populations studied, 42% were ever trained in CPR, while 10% had currently-valid training in CPR. We also found that the country's income (measured by Gross National Income per capita), and the individual's education level are both associated with the chance of being trained in CPR. The main limitation of this study is the heterogeneity between studies in methods, definitions, and training programs. This provides an initial scope of the landscape of CPR training in the world.

Next, **Chapter 11** was a descriptive study that examined trends of outcomes and processes for OHCA in Singapore over a 5-year period (2011-2016). We found that in association with the National Pre-hospital Emergency Care System 5-year Plan, which was a period of exceptionally intense reorganization, policy restructuring, and organized implementation to improve the prehospital emergency care system, several changes were seen. First, Utstein survival (which refers to survival to hospital discharge of those OHCA patients whose arrest events were witnessed by a bystander and that involved an initial shockable rhythm) had nearly doubled from 12% to 23%. This was associated with improvements in processes as well, with bystander CPR rate improving from 22% to 56% and bystander use of automated external defibrillators improving from 2% to 5%. Despite temporal associations, this study was unable to prove causation with individual intervention or policy. It is a challenge to tease out the individual effects of multiple initiatives that overlap in time.

In the final study, which is presented in **Chapter 12**, we addressed the challenge of identifying which patients who sought medical attention for chest pain went on to develop major adverse cardiac events (MACE) including OHCA. In a cohort of patients presenting to emergency departments (EDs) across Singapore and Netherlands, we examined patients who were classified as low-risk according to the HEART score. We found that in this low-risk group, 4.6% developed MACE at six weeks. This is much higher compared to the 1.7% found by the original prospective validation for HEART score. Examining the characteristics of these "missed" patients, we found that men, "highly-suspicious" electrocardiogram and elevated troponin levels were disproportionately associated with MACE. The presence of these characteristics should prompt clinicians to exercise caution against discharge and enter shared decision-making with the patient. These findings also prompt future studies to improve HEART score by possibly adding gender as a component, and re-weighing the points system to emphasize the importance of electrocardiogram and troponin levels.

Having now an improved vantage point with the benefit of findings from this thesis as well as other advances in the field, several important priorities for the field have emerged to be pressing problems that remain inadequately addressed at this point:

1. We need to continually target bystander CPR using innovative strategies as it is the largest known determinant of survival, and learn from the pockets of success around the world that manage to achieve this.
2. We need to improve our disease surveillance tools to be able to capture long-term outcomes.
3. We need to bridge disparities in OHCA care that are present on account of gender, ethnicity and socioeconomic position.
4. We need to foster collaboration and share best practices across borders, such that we can strengthen emergency care systems to ultimately save more lives in underserved communities, where most of the world's population reside.
5. We need to address climate change both by reducing its pace, and, to understand ways for populations to mitigate its deleterious health impact.
6. We need to apply principles of personalized medicine to OHCA such that we can understand the underlying genetic, epigenetic, and physiological factors that contribute to cardiac arrest susceptibility and survivability.
7. We need to address ethical concerns surrounding the use of advanced technologies in OHCA like artificial intelligence, predictive modeling, and personalized medicine as they gain in prevalence. These concerns include privacy, data security and equitable access.

In conclusion, this thesis highlights a series of academic pursuits aimed collectively at improving outcomes in patients with OHCA. By advancing our understanding of the risk factors, prognostication, and treatment of OHCA, we better formulate improved strategies that successfully impact the survival rate, long-term multidimensional survivorship, access to care and equity for our patients.

Chapter 14

Summary and Discussion in Dutch

Andrew Fu Wah Ho, Dominique PV de Kleijn

Out-of-hospital cardiac arrest (OHCA) ofwel "hartstilstand buiten het ziekenhuis "blijft ondanks de vooruitgang van de afgelopen decennia in preventie en behandeling een enorme last op onze samenleving leggen. De onvoorspelbare en tijdgevoelige aard van OHCA vormen een grote uitdaging op de manier hoe we OHCA behandelen en bestuderen. De huidige problemen en prioriteiten op het gebied van reanimatieonderzoek vloeien voort uit tientallen jaren van behandeling en onderzoek en heeft geleid tot hoe we de ziekte nu conceptualiseren. Deze ontwikkeling is samengevat in **hoofdstuk 1.**

In dit proefschrift beschrijven we een reis met meerdere stappen, gezamenlijk gericht op het verbeteren van OHCA-. Met behulp van een aantal technieken onderzoeken we onderling gerelateerde actuele onderwerpen rond risicofactoren, prognose en behandeling van OHCA. Het bestaat uit één introductie hoofdstuk, gevolgd door tien originele onderzoeken. In deze samenvatting en discussie willen we de methodologische benaderingen, belangrijkste bevindingen, sterke en zwakke punten en implicaties van deze hoofdstukken samenvatten.

Hoofdstuk 2 erkent de moeilijkheden bij het uitvoeren van Randomized Controlled Trials (RCT's) in OHCA-onderzoek en concentreert zich op andere interventiestudies dan RCT's.17 Het bespreekt het ontwerpen van deze studies om belangrijke onderzoeksvragen aan te pakken en begint met het schetsen van de uitdagingen van RCT's die specifiek zijn voor pre-ziekenhuisonderzoek. Vervolgens worden quasi-experimenten en natuurlijke experimenten beschreven, alsook het vergelijken en contrasteren tussen hen en het geven van voorbeelden van situaties wanneer deze geschikt zijn, met hun voordelen en beperkingen. Ook worden aanpassingen van het ontwerpen van RCT-studies besproken om haalbaarheidsproblemen in de pre-ziekenhuisomgeving op te lossen. De methodes die in dit hoofdstuk worden behandeld, stellen ons in staat om interventies in OHCA te testen, die vaak niet drugs- of apparaatgerelateerd zijn, maar eerder systeem en beleidsinterventies zijn die soms beter kunnen worden getest met behulp van niet-RCT-ontwerpen. Als ze effectief worden gebruikt, stellen ze ons in staat om robuuste causale conclusies te trekken uit deze nieuwe interventies. De methodologische overwegingen die in dit hoofdstuk worden beschreven, sijpelen door in de rest van dit proefschrift.

Hoofdstuk 3 en 4 gaat over lange termijn overleving na OHCA. Ze vullen hiaten in onze kennis over hoe OHCA-overlevenden het op de lange termijn doen, aangezien de meeste tools en registers voor ziektebewaking momenteel niet in staat zijn om follow-up op lange termijn vast te leggen. In **hoofdstuk 3**, voerden we een systematische review en meta-analyse uit, waaruit dat het aantal studies dat patiënten langer dan 12 maanden volgden verontrustend laag bleek.[18] Door deze 35 studies met 7186 patiënten samen te voegen, ontdekten we dat onder OHCA-patiënten die overleefden tot ontslag uit het ziekenhuis nog 78% in leven was na 1 jaar, 70% na 3 jaar en 63% na 5 jaar. We ontdekten dat de overleving op de lange termijn beter was bij mannen, bij gevallen met een initieel schokbaar ritme en bij gevallen die zich voordeden op openbare locaties. We ontdekten ook dat de overleving op de lange termijn beter was in Noord-Amerika, Europa en Oceanië in vergelijking met Azië. Hoewel deze studie een belangrijke eerste overview van de literatuur verschafte om te bepalen wat we weten over overleving na OCHA was p de lange termijn, is het gebaseerd op een klein aantal eerdere onderzoeken wat een beperking is. De samengevoegde schattingen waren waarschijnlijk te optimistisch aangezien ze werden verzameld uit de weinige geselecteerde gemeenschappen die langetermijngegevens konden verkrijgen.

Hoofdstuk 4 was een cohortstudie om lange termijn resultaten in Singapore te onderzoeken. Met behulp van een open cohort dataset samengesteld door de Pan-Asian Resuscitation Outcomes Study (PAROS)-gegevens te koppelen aan de Singapore's Registry of Births and Deaths, hadden we een unieke kans om 802 OHCA-patiënten te volgen die overleefden tot maximaal 10 jaar na ontslag uit het ziekenhuis. We berekenden de relatieve overleving op verschillende tijdstippen, produceerden overlevings statistieken en identificeerden onderlinge verbanden. We berekenden ook gestandaardiseerde mortaliteitsratio's en ontdekten daardoor dat in vergelijking met controles die geen OHCA hebben gehad, OHCA-overlevenden alleen in de eerste twee jaar na de OHCA een verhoogd risico op overlijden hebben. Hoewel deze studie de broodnodige gegevens over de lange termijn overleving verschaft, is dit slechts één domein van overleving. Meer studies zijn nodig om gegevens te verschaffen over andere domeinen, zoals lichamelijke handicap, cognitie, sociale integratie en belasting van zorgverleners, met behulp van een overlevingskader met meerdere domeinen. In dit opzicht blijft onze kennis van patiënten die OHCA hebben overleefd achter bij degenen die een beroerte en traumatisch hersenletsel hebben overleefd.

In **hoofdstuk 5** bestuderen we een belangrijke complicatie na OHCD op de lange termijn, namelijk herhaling. In deze systematische review en meta-analyse hebben we gegevens van 7186 patiënten uit

35 onderzoeken samengevoegd. We vonden de gepoolde incidentie van het hebben van een eerste recidief op 15%. Van de patiënten die een eerste recidief hadden, kreeg 35% een tweede recidief. We ontdekten dat van de patiënten die deze recidieven kregen, dat de meeste (tweederde) van hen binnen het eerste jaar optraden. We hebben verschillende factoren getest in een meta-regressie en ontdekten dat het initiële schokbare ritme gecorreleerd was met een verhoogde kans op herhaling. Gezamenlijk laten deze bevindingen de mogelijkheden zien voor tertiaire preventie bij deze patiënten. Met name de rol van strategieën voor tertiaire preventie, zoals implanteerbare cardioverter-defibrillatoren en cardiopulmonale reanimatie (CPR) -training van gezinsleden, moet in toekomstige studies worden verduidelijkt. Onze studie suggereerde ook dat preventieve strategieën vroeg moeten worden gestart, aangezien de meeste recidieven zich in het eerste jaar voordoen. De belangrijkste beperking van deze studie is het overwicht van Noord-Amerikaanse gegevens, wat de generaliseerbaarheid van de bevindingen naar andere regio's beperkt.

In het onderzoek beschreven in **hoofdstuk 6 & 7** hebben we onderzocht of luchtkwaliteit een risicofactor was voor OHCA. Luchtverontreinigende stoffen zijn een opkomende risicofactor als gevolg van verstedelijking en hebben geleid tot aanzienlijke bezorgdheid over de volksgezondheid. Beide onderzoeken spelen zich af in de context van Singapore, dat te maken heeft met grensoverschrijdende luchtverontreiniging door boskap-landbouwactiviteiten in Zuidoost-Azië. Met een netwerk van meetstations voor de luchtkwaliteit die over het gehele eiland zijn geplaatst, evenals uitgebreide OHCA-bewaking, vormt Singapore een ideale plaats om hoogwaardige inzichten te bieden in de relatie tussen luchtkwaliteit en OHCA. In **hoofdstuk 6** gebruikten we een case-crossover-ontwerp en vonden we een 37% verhoogd risico op OHCA wanneer de luchtkwaliteit in het "ongezonde" bereik van de Pollutant Standards Index (PSI) lag, en een 10% verhoogd risico wanneer het in het "matige" bereik lag. bereik", in vergelijking met wanneer de PSI zich in het "gezonde bereik" bevindt. We vonden dat het risico gedurende ten minste vijf dagen na blootstelling verhoogd was. Deze bevinding was helaas niet generaliseerbaar omdat de PSI niet universeel werd gebruikt als maatstaf voor luchtkwaliteit.

Aangezien in **hoofdstuk 6,** PSI als primaire blootstelling werd onderzocht, kon het niet aangeven welk bestanddeel van luchtverontreiniging verantwoordelijk was voor het OHCA-risico. Dit motiveerde de tweede studie in **hoofdstuk 7**, waar we concentratiegegevens van individuele polluenten verkregen en hun associatie met OHCA-risico onderzochten. Met behulp van een tijdreeksbenadering ontdekten we dat fijnstof met een diameter van 2,5 μm (PM2,5) of kleiner een belangrijke oorzaak was van het verband tussen luchtkwaliteit en OHCA-risico. Elke toename van PM2,5 met 10 $\mu g/m^3$ ging gepaard met een verhoogd risico op OHCA (RR 1·022 [95% 1·002–1·043]) gedurende de volgende 2 dagen. De belangrijkste beperking van beide onderzoeken is hun observationele ecologische opzet, wat betekent dat de bevindingen vatbaar zijn voor de ecologische misvatting, waarbij we verkeerde conclusies kunnen trekken over individuen op basis van observaties over groepen. Toekomstige studies zijn nodig om strategieën te evalueren om het risico op acute ziekte als gevolg van luchtverontreiniging te verminderen, zoals gezondheidsadviezen en maskerdistributieprogramma's.

Hoofdstuk 8, 9 en 10 zijn gericht op reanimatie door omstanders. **Hoofdstuk 8** gebruikte een cohort studieontwerp om de associatie tussen sociaal-economische status en de kans op reanimatie door omstanders te onderzoeken. Om de sociaal-economische status te classificeren, hebben we een innovatieve benadering gebruikt om de Singapore Housing Index toe te wijzen aan elk woongebouwadres in Singapore. Deze index bevat de gemiddelde vastgoedprijs en fungeert als surrogaat voor de sociaaleconomische status. We vonden dat de gemiddelde sociaaleconomische status van het woongebouw samenhing met de kans op een OHCA. Deze bevindingen reflecteren een wereldwijde golf van recente rapporten die op vergelijkbare wijze ongelijkheden in OHCA-behandeling aantroffen vanwege de sociaaleconomische positie, en aanleiding gaven tot interventieprogramma's om ongelijkheid te verminderen.

In **hoofdstuk 9** gebruikten we een cohortstudie benadering om te beoordelen of op reanimatie gerichte volksgezondheidsinterventies in Singapore de reanimatiecijfers van omstanders in de hele stad hebben verhoogd. We ontdekten dat in de periode 2011-2016 de reanimatie van omstanders werd verhoogd door een combinatie van drie interventies: reanimatietraining voor de gemeenschap, een applicatie voor mobiele telefoons (myResponder) en een reanimatieprogramma via de telefoon. Vanwege overlap van de drie componenten van de bundel, kon deze studie het geïsoleerde effect van elk van hen niet onderzoeken. Deze bevindingen vormen een van de weinige rapporten die aantonen dat interventies op het gebied van de volksgezondheid met succes de reanimatiepercentages van omstanders kunnen verbeteren. Dit stimuleert andere gemeenschappen om soortgelijke initiatieven te onderzoeken.

In **hoofdstuk 10** gebruikten we een systematisch review en meta-analyse om de wereldwijde prevalentie te schatten van leken die zijn opgeleid om reanimatie toe te passen. Uit 29 onderzoeken in 18 landen hebben we vastgesteld dat gemiddeld 42% van de bestudeerde populaties ooit een reanimatietraining heeft gevolgd, terwijl 10% momenteel een geldige reanimatietraining heeft gevolgd. We ontdekten ook dat het inkomen van het land (gemeten aan de hand van het bruto nationaal inkomen per hoofd van de bevolking) en het opleidingsniveau van het individu beide verband houden met de kans om getraind te worden in reanimatie. De belangrijkste beperking van deze studie is de heterogeniteit tussen studies in methoden, definities en trainingsprogramma's. Het geeft echter een eerste beeld van het landschap van reanimatietrainingen in de wereld.

Hoofdstuk 11 is een studie waarin trends van overleving en preventie/behandel methoden voor OHCA in Singapore over een periode van 5 jaar (2011-2016) werden onderzocht. We ontdekten dat verschillende veranderingen, in verband met het National Pre-hospital Emergency Care System 5-jarenplan (een periode van uitzonderlijk intense reorganisatie, beleidsherstructurering en georganiseerde implementatie om het pre-hospital emergency care-systeem te verbeteren) tot resultaten leiden. Ten eerste was de Utstein-overleving (wat verwijst naar de overleving tot ontslag uit het ziekenhuis van die OHCA-patiënten bij wie een omstander getuige was van de OHCA en waarbij een aanvankelijk schokbaar ritme betrokken was) bijna verdubbeld van 12% naar 23%. Deze veranderingen verbetererde ook de methoden, waarbij het reanimatiepercentage van omstanders verbeterde van 22% naar 56% en het gebruik van automatische externe defibrillatoren door omstanders verbeterde van 2% naar 5%. Ondanks deze associaties kon deze studie geen oorzakelijk verband aantonen met individuele interventie of beleid. Het is een uitdaging om de individuele effecten van meerdere initiatieven die elkaar in de tijd overlappen, te ontrafelen.

In de laatste studie, in **hoofdstuk 12** gingen we in op de uitdaging om te identificeren welke patiënten die medische hulp zochten voor pijn op de borst, een Major Adverse Cardiovascular Event (MACE) kregen, waaronder OHCA. In een cohort van patiënten die zich presenteerden op spoedeisende hulpafdelingen (ED's) in Singapore en Nederland, onderzochten we patiënten die volgens de HEART-score als laag-risico werden geclassificeerd. We ontdekten dat in deze laag risico groep 4,6% MACE ontwikkelde na zes weken. Dit is veel hoger in vergelijking met de 1,7% gevonden door de oorspronkelijke prospectieve validatie voor de HEART-score. Bij het onderzoeken van de kenmerken van deze "gemiste" patiënten, ontdekten we dat mannen, "zeer verdacht" elektrocardiogram en verhoogde troponinespiegels onevenredig geassocieerd waren met MACE. De aanwezigheid van deze kenmerken zou clinici ertoe moeten aanzetten om voorzichtig te zijn met ontslag en samen met deze patiënt een beslissing te nemen. Deze bevindingen zijn ook aanleiding voor toekomstige studies om de HEART-score te verbeteren door mogelijk geslacht als component toe te voegen en het puntensysteem opnieuw te wegen om het belang van elektrocardiogram- en troponine niveaus te benadrukken.

Toekomst perspectieven
Mede door de bevindingen uit dit proefschrift en andere ontwikkelingen in het veld, hebben we nu een beter overzicht, dat duidelijk maakt dat verschillende belangrijke prioriteiten en urgente problemen voor het veld op dit moment nog steeds onvoldoende worden aangepakt:

1. We moeten ons vooral richten op de reanimatie van omstanders met behulp van innovatieve strategieën, aangezien dit de grootste bekende overlevingsdeterminant is. Hierbij moeten we leren van de succesvolle strategieen in de wereld om reanimatie door omstanders te verbeteren.
2. We moeten onze middelen voor vroege detectie en voorspelling van plotselinge hartstilstand verbeteren om zo goede resultaten op de lange termijn te verkrijgen.
3. We moeten de verschillen in de gezondheidszorg voor behandeling van plotselinge hartstilstand op

basis van geslacht, etniciteit en sociaal-economische positie overbruggen.
4. We moeten samenwerking bevorderen en bevindingen delen tussen landen, zodat we de spoedeisende hulp voor plotselinge hartstilstand kunnen versterken om uiteindelijk meer levens te redden met name in achtergestelde gemeenschappen, waar het grootste deel van de wereldbevolking in woont.
5. We moeten de klimaatverandering aanpakken door het tempo ervan te verlagen, en methoden vinden die de schadelijke gevolgen voor de gezondheid door klimaatverandering kan verzachten.
6. We moeten de principes van gepersonaliseerde geneeskunde toepassen op plotselinge hartstilstand buiten het ziekenhuis, zodat we de onderliggende genetische, epigenetische en fysiologische factoren kunnen begrijpen die bijdragen aan het risico van het krijgen van een hartstilstand en de overlevingskansen.
7. We moeten de ethische problematiek rond het gebruik van geavanceerde technologieën in plotselinge hartstilstand, zoals kunstmatige intelligentie, voorspellende modellen en gepersonaliseerde geneeskunde, onderkennen en daar naar handelen zeker omdat deze steeds vaker voorkomen. Deze problematiek omvat onder meer privacy, gegevensbeveiliging en eerlijke verdeling van de toegang tot deze technologieën.

Concluderend belicht dit proefschrift een reeks academische studies gericht op het verbeteren van de uitkomsten bij patiënten met OHCA. Door beter begrip van de risicofactoren, prognose en behandeling van OHCA, kunnen we strategieën formuleren die met succes de overlevingskans, inclusief overleving op lange termijn en toegang tot zorg voor onze patiënten beïnvloeden. Met de bevindingen van dit proefschrift en ontwikkelingen in het veld, hopen we een beter gezichtspunt te hebben wat verschillende belangrijke prioriteiten kan verduidelijken. We moeten blijvende aandacht geven aan het bevorderen van reanimeren door omstanders met behulp van innovatieve strategieën, aangezien dit de grootste bekende bepalende factor voor overleving is, en we moeten leren van de successen elders die erin slagen dit te bereiken. We moeten onze tools voor ziektesurveillance verbeteren om langetermijnresultaten te kunnen vastleggen. Ook zouden verschillen in de OHCA-zorg die aanwezig zijn op grond van geslacht, etniciteit en sociaaleconomische positie verminderd moeten worden. Ten slotte is wereldwijde samenwerking cruciaal om noodhulpsystemen te verbeteren, zodat achtergestelde gemeenschappen welke een groot deel van de wereldbevolking zijn, toegang hebben tot de zorg die nodig is om OHCA te overleven. Door samenwerking te bevorderen en best practices over de grenzen heen te delen, kunnen we noodhulpsystemen versterken en uiteindelijk meer levens redden.

Appendix

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Curriculum Vitae

Andrew Fu Wah Ho was born on 30th March 1989 in British Hong Kong. At the age of five, he moved with his family to Singapore where he has lived since. He received his basic and postgraduate medical degrees from the National University of Singapore (NUS) and received specialist training in Emergency Medicine at SingHealth Residency. This was a five-year residency program which he completed as Chief Resident. He spent an additional year on clinical research training as a clinician scientist resident.

He received public health training at the NUS, resulting in Master of Public Health (specialization in Epidemiology & Quantitative Methods). He received fellowship clinical training in Pre-hospital Emergency Medical Care. He subsequently embarked on doctoral education in epidemiology at the Utrecht University, with a thesis centered around improving outcomes in sudden cardiac arrest.

Presently, he is Consultant Emergency Physician at the Singapore General Hospital, which is Singapore's oldest and largest tertiary hospital. He delivers direct clinical care at an emergency department that receives more than 120,000 attendances a year. He is also Assistant Professor at Duke-NUS Medical School jointly appointed by the Emergency Medicine Academic Clinical Program and the Pre-hospital and Emergency Research Center.

Andrew's research philosophy is grounded in an interdisciplinary approach that integrates methodologies from clinical epidemiology, population health sciences, and implementation science. By combining these diverse disciplines, he strives to drive continuous improvement in patient outcomes for sudden cardiac arrest and other emergency conditions, as well as contribute to advancements in population health.

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