

Survival, prognostication and secondary prevention in cardiac arrest

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UNIVERSITY OF GOTHENBURG

Gothenburg 2024

“Life is a journey, not a destination.” – Ralph Waldo Emerson

“In the blink of an eye, everything can change. So, forgive often and love with all your heart. You may never know when you may not have that chance again.” – Unknown

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ABSTRACT

Background: Sudden Cardiac Arrest (SCA) is a highly lethal medical emergency, caused by an abrupt cessation of cardiac function. Despite extensive research efforts, increased public awareness and systematic healthcare improvements, overall survival is still very low. Individuals suffering an out-of-hospital cardiac arrest (OHCA) exhibit the lowest survival rates, with only 10% surviving to 30 days. Highly stochastic factors, such as the time and place of the cardiac arrest, exert a fundamental impact on survival. The emergence of technical advancement, accompanied by artificial intelligence (AI), holds new opportunities that may enable the prediction, and thus prevention, of SCA, in addition to reducing the delay to evidence-based interventions.

Methods: **Study I** aimed to characterise the impact of the COVID-19 pandemic on the epidemiology of in- and out-of-hospital cardiac arrests in Sweden. **Study II** aimed to characterise long-term trends in in-hospital cardiac arrest (IHCA) and OHCA, highlighting temporal differences in epidemiology, management and survival. **Study III** explored the potential benefit of having an implantable cardioverter defibrillator (ICD) at discharge among patients who survived an OHCA with an initial shockable rhythm. **Study IV** aimed to improve the Swedish Cardiac Arrest Risk Score-1 (SCARS-1), by optimising the machine learning strategy. All studies utilised data from the Swedish Cardiopulmonary Resuscitation Registry (SCRR).

Results: **Study I** demonstrated a notable shift in epidemiology in IHCA and OHCA during the pandemic, with a 2.3- and 3.4-fold increase in mortality rates, respectively. Patients with COVID-19 and cardiac arrest were much more likely to suffer from respiratory insufficiency prior to SCA, typically with a non-shockable rhythm. **Study II** revealed a 2.2-fold increase in survival rates in OHCA during 1990–2020, albeit without any improvements during the final decade. For the same time period, we observed more than a two-fold increase from ambulance dispatch to arrival. On the other hand, survival rates in IHCA increased by 47% during 2011–2020, with unabated improvement in survival. For both OHCA and IHCA a cardiac aetiology causing the cardiac arrest decreased, 55% and 70%, respectively. **Study III** suggested OHCA cases with a cardiac aetiology and initial shockable rhythm discharged with an ICD had superior survival rates compared to patients without. Specifically, the study suggested a 60% reduction in the probability of recurrent SCA or death among those discharged with an ICD. **Study IV** showed we were able to enhance our previous prediction model, SCARS-1, creating a parsimonious model with excellent calibration and discriminatory performance, suitable for evaluation in future clinical trials. The final model displayed a AUC ROC score of 0.96.

Conclusion: Using both classical epidemiological- and cutting-edge machine learning methods, we have elucidated important epidemiological and clinical gaps in knowledge. We provided novel insights into the COVID-19 pandemic, long-term trends in survival

and the potential benefit of broader use of ICDs. We have also demonstrated that survival can be predicted with excellent predictive performance by the time the patient arrives in the emergency department. Importantly, this thesis highlights that future resuscitation practices will face many challenges, ranging from reducing ambulance response times, finding new means of treating the increasing number of cases with non-cardiac causes, and identifying patients who would benefit from secondary preventive measures.

Keywords: OHCA, IHCA, ICD, Machine Learning

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SAMMANFATTNING PÅ SVENSKA

Plötsligt hjärtstopp orsakas av ett plötsligt upphörande av hjärtfunktionen, vilket leder till en så kallad cirkulatorisk kollaps. Den enda möjligheten att överleva är genom omedelbar hjärt- och lungräddning (HLR). I Sverige drabbas cirka 10,000 personer årligen av ett plötsligt hjärtstopp på eller utanför sjukhus. Incidensen i Europa är cirka 55-113 fall per 100,000 person-år. Sedan 1990 har Svenska Hjärt-Lungräddningsregistret (SHLR) insamlat data för hjärtstopp utanför sjukhus, och från 2004 påbörjades även registrering av hjärtstopp som inträffade på sjukhus. Sedan registrets begynnelse har närmare 140,000 människor inkluderats i SHLR, vilket gör registret till en världsunik datakälla för forskning och utveckling. Registrering i SHLR följer i mycket hög grad det standardiserade protokoll som fastslogs i Utstein.

Även om överlevnaden har ökat sedan 1990, är den fortsatt förhållandevis låg. Enligt den senaste årsrapporten är överlevnaden vid 30 dagar endast 12% efter hjärtstopp utanför sjukhus och 35% efter hjärtstopp på sjukhus. Den stora skillnaden i överlevnad förklaras av att tid till effektiv HLR, vilken är mycket kortare vid hjärtstopp på sjukhus. Kedjan som räddar liv är ett koncept som beskriver de komponenter som är essentiella för överlevnad. Kedjan inbegriper (1) tid till upptäckt och larm, (2) tid till HLR, telefonassisterad HLR om nödvändigt, (3) tid till defibrillering, (4) tid till avancerad HLR, (5) eftervård, och slutligen (6) rehabilitering och återhämtning för de som överlever.

Syftet med denna avhandling var att kartlägga epidemiologiska skillnader vid hjärtstopp över tid i Sverige, inklusive effekter av COVID-19-pandemin. Vi undersökte också om överlevnaden vid hjärtstopp kunde förutsägas med hjälp av maskininlärning. Slutligen avsåg vi kartlägga om fler överlevare borde erhålla en inopererad hjärtstartare (s.k. ”ICD”) efter hjärtstopp. Dessa frågeställningar har belysts i SHLR med olika metoder och kohorter. Avhandlingen inbegriper både klassisk epidemiologi, liksom mer avancerad maskininlärning för att belysa orsakssamband i den mån möjligt, givet datas observationella natur. Kartläggning av orsakssamband är en mycket åtråvärd uppgift i all medicinsk forskning och med maskininlärning har nya metoder för detta ändamål uppkommit, vilket denna avhandling utforskat.

Studie I. I samband med COVID-19-pandemin rapporterades i flera länder att antalet som drabbades av hjärtstopp, liksom dödligheten vid hjärtstopp steg kraftigt. I dessa studier kunde man tyvärr inte klargöra vilka som var smittade av COVID-19. Tack vare att SHLR inkluderade information om COVID-19-smitta tidigt under pandemin kunde vi undersöka hur COVID-19 påverkade karaktäristika och utfall vid hjärtstopp i Sverige. Vi fann att patienter med COVID-19 som drabbades av hjärtstopp hade en klart sämre prognos. Faktum var att under studieperioden, från 1 januari till 20 juli, 2020, hade fortfarande ingen med hjärtstopp och samtida COVID-19-infektion skrivits ut levande från sjukhus.

Studie II. SHLR påbörjade registrering av hjärtstoppfall i Sverige år 1990, vilket är tidigare än något annat register i världen. Målet med delstudie II var att kartlägga karaktäristika och överlevnad från 1990 till 2020, vilket inkluderade 106,296 hjärtstopp på och utanför sjukhus. Överlevnaden utanför sjukhus ökade mellan 1990-2020 från 5.7% till 10.1%. Sista decenniet har överlevnaden inte förändrats. Detta samband sågs dock inte för hjärtstopp på sjukhus, där överlevnaden sista decenniet ökat med 46.6%. Andelen hjärtstopp förorsakade av hjärtsjukdom minskade från 74.6% till 60.3% utanför sjukhus. För hjärtstopp på sjukhus minskade motsvarande andel från 58.6% till 30.1%. Det innebär att andelen med hjärtsjukdom som bakomliggande orsak minskat mycket fort. Tidsfördröjningen från hjärtstopp till HLR har minskat dramatiskt, vilket sannolikt förklaras av ökad medvetenhet och kunskap om HLR i befolkningen. Andelen lekmän som idag utför HLR har mer än fördubblats. Dessvärre noterades en kraftig ökning av tidsfördröjningen för ambulansen, vilket sannolikt förklarar att överlevnaden utanför sjukhus inte förbättrats senaste decenniet.

Studie III. Ett omdiskuterat ämne inom hjärtstoppsvården är sekundärprevention efter hjärtstopp med hjälp av inopererade hjärtstartare (s.k. ”ICD”). Enligt nuvarande riktlinjer från Europeiska Kardiologförbundet rekommenderas inte att ICD skall erbjudas om orsaken till hjärtstoppet har kunnat avhjälpas, t ex genom ballongsprängning av kranskärl. Vi studerade den något kontroversiella frågan om huruvida det är lönsamt att behandla alla överlevare efter hjärtstopp där man kunnat defibrillera hjärtat (vilket är

den funktion som en ICD har). Detta gjordes genom att studera 3,005 patienter i SHLR. Vi fann att den största risken för nytt hjärtstopp eller död förelåg tidigt efter det första hjärtstoppet och patienter som hade en ICD vid utskrivning hade 60% lägre risk för nytt hjärtstopp eller död.

Studie IV. Kombinationen av SHLR och modern maskininlärning skapar möjligheter att utveckla tillförlitliga prediktionsmodeller, vilka kan implementeras i klinisk praxis. I den sista delstudien utvecklades en prediktionsmodell för prognostisering av överlevnad vid hjärtstopp utanför sjukhus. Vi använde sammantaget 55,615 patienter med hjärtstopp för att skapa ett stort antal prediktionsmodeller, varav den bästa utvärderades i detalj. Modellerna konstruerades för att maximera den prediktiva förmågan bland patienter med låg chans att överleva, eftersom modellens användning är särskilt känslig i det intervallet. Den slutgiltiga modellen uppvisade mycket hög precision, lämplig för uppgiften att prognosticera överlevnaden vid hjärtstopp utanför sjukhus. Sistnämnda kräver dock validering i en randomiserad studie.

Således har denna avhandling kartlagt epidemiologiska aspekter över tid och under COVID-19-pandemin. I arbetena har förklaringar och förbättringsförslag diskuterats. I studie III demonstrerades att fler patienter kan gagnas av en ICD och därför måste mer forskning genomföras i denna patientgrupp. Slutligen visade vi hur registerdata kan användas för att skapa robusta kliniska beslutsstöd vid vård av hjärtstopp.

LIST OF PAPERS

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ABBREVIATIONS

AED	Automated External Defibrillator
AI	Artificial Intelligence
AMI	Acute Myocardial Infarction
AUC-ROC	Area Under the Receiver Operating Characteristic
CCO	Compression Only Cardiopulmonary Resuscitation
CI	Confidence Interval
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CRT	Cardiac Resynchronization Therapy
CT	Computed Tomography
DNAR	Do Not Attempt Resuscitation
ECG	Electrocardiogram
ED	Emergency Department
EMS	Emergency Medical Services
ERC	European Resuscitation Council
HIBI	Hypoxic-ischaemic brain injury
HR	Hazard Ratio
HT	Hypertension
ICU	Intensive Care Unit
IHCA	In-Hospital Cardiac Arrest

LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NSTEMI	Non-ST Elevation Myocardial Infarction
OHCA	Out-of-Hospital Cardiac Arrest
OR	Odds Ratio
PaO ₂	Partial Pressure of Oxygen
PCI	Percutaneous Coronary Intervention
PEA	Pulseless Electrical Activity
PM	Pacemaker
PR AUC	Precision-Recall Area Under the Curve
pVT	Pulseless Ventricular Tachycardia
SCA	Sudden Cardiac Arrest
SCARS	Swedish Cardiac Arrest Risk Score
SCD	Sudden Cardiac Death
SCRR	Swedish Cardiopulmonary Resuscitation Registry
SPHA	The Swedish Public Health Authority
SSEP	Somatosensory Evoked Potential

STEMI

ST elevation Myocardial
Infarction

TOR

Termination of Resuscitation

TTM

Targeted Temperature
Management

1 INTRODUCTION

1.1 EPIDEMIOLOGY

Sudden cardiac arrest (SCA) is a major health concern worldwide, ranking among the leading causes of death in Europe and the United States. SCA affects approximately 55-113 per 100,000 individuals annually in Europe.¹⁻⁴ It can strike the seemingly healthy individual throughout the lifespan. The vast majority of all victims have no known cardiovascular disease, while only a minority have previously known cardiovascular conditions.⁵ Survival depends on multiple factors, the most important being; time to cardiopulmonary resuscitation (CPR), initial rhythm and age.^{6,7} Victims displaying ventricular fibrillation (VF) as the initial cardiac rhythm can be treated with defibrillation. This is associated with survival rates up to 50-70%.⁸ Roughly 25–50% of out-of hospital cardiac arrests (OHCAs) exhibit ventricular fibrillation, and this proportion has declined over the last decades. It is believed that this decline is to a large extent explained by increased delays from cardiac arrest to recording of the first electrocardiogram (ECG), which in turn is explained by prolonged delays to ambulance arrival.⁸⁻¹⁰ Fortunately, an increasing number of automated external defibrillators (AED) have been deployed in high-risk areas of society, and these can be utilised by laymen. Certainly, the best available treatment for SCA is immediate CPR, with defibrillation of ventricular fibrillation.¹¹

The latest annual report from the SCRR concluded that 2022 was the year with the highest survival rates noted for OHCA since 1990, with 12% of all victims surviving. The corresponding figure for in-hospital cardiac arrest (IHCA) was 36% in 2022. The annual report in recent years have suggested a doubling of survival after OHCA and a significant improvement for IHCA.^{12,13} However, no study has formally addressed, with multivariable adjustment, long-term trends and sought to explain these trends. Several studies have demonstrated that most survivors of cardiac arrest have good neurological function, categorised as cerebral performance category (CPC) 1-2.^{14,15}

1.1.1 NEUROLOGICAL FUNCTION AFTER CARDIAC ARREST

Approximately 80% of patients admitted to an intensive care unit (ICU) post-OHCA are in a comatose state. Of these patients, two-thirds will succumb from post-cardiac arrest sequelae, related to hypoxic-ischaemic brain injury (HIBI).¹⁶⁻¹⁹ The most common cause of death from HIBI occurs as an indirect effect, causing neuronal cell death and oedema, as opposed to direct neuronal damage.¹⁹

Cerebral performance category (CPC), Glasgow outcome scale extended (GOSE) and modified Ranking scale (mRS) are clinical tools for estimating neurological outcome. For neuroprognostication and outcome assessment, CPC score is the most used scoring system. CPC scores ranges from 1 to 5, where 1) represents good neurological performance, 2) moderate neurological disability, 3) severe

neurological impairment, 4) coma or vegetative state, and 5) brain death. CPC score has received criticism, mainly due to the isolated focus on mental status, and less so on bodily functions, which could explain discrepancies in CPC score and quality of life measures.²⁰ The GOSE score ranges from 1 to 8, with 1) denoting brain death, and 8) good cerebral performance. GOSE also entails information regarding social status, activity of daily life, etc. The mRS ranges from 0 to 6, with 0) representing no symptoms, 1) no clinically significant disability, 2) slight disability, 3) moderate disability, 4) moderately severe disability, 5) severe disability, and 6) death. Many factors render the neurological evaluation among survivors difficult and challenging. The instruments are blunt and many patients are assessed during a state of shifting neurological function. Indeed, improvements in neurological function can be observed up to six months after cardiac arrest.²¹ Studies have shown that three months after the cardiac arrest may be a good trade-off between loss to follow-up and enough time to allow for neurological recovery.

There are various methods to assess neurological injury post-cardiac arrest, including clinical assessment, biomarkers, neuroimaging by CT-scan/MRI, electrophysiology by electroencephalogram (EEG) and short-latency somatosensory evoked potentials (SSEP).

1. There are various clinical examinations that can reflect outcome and prognosis after ROSC. Absent pupillary light reflex (PLR) at 72 h is indicative of poor outcome, with high specificity but low sensitivity.²²⁻²⁴ Absent corneal reflex at 72 h

is also indicative of poor prognosis, with marginally lower specificity than PLR and low sensitivity as well.²⁵ Myoclonus is a less reliable clinical tool for assessment of neurological outcome, only applicable with other measures for predicting outcome.²⁶ Lance-Adams syndrome (LAS), is a post-hypoxic syndrome that can occur after a cardiac arrest, characterised by action myoclonus. EEG can further classify myoclonus, thus a reasonable secondary measure for predicting outcome.^{27,28}

2. Blood biomarkers such as neuron specific enolase (NSE) and S-100B are released into the bloodstream following neuronal injury. Unlike clinical assessment, biomarkers are not affected by sedatives. NSE is the most studied biomarker for neuroprognostication, and have proven to show low level of false positive rate (FPR) with moderately good sensitivity.¹⁹
3. Neuroimaging by computerised tomography (CT) and magnetic resonance imaging (MRI) can detect tissue changes within minutes to hours after cardiac arrest. There is no consensus recommending optimal timing for performing a CT scan for neuroprognostication. Specificity and sensitivity for predicting poor neurological outcome using CT scan within 24 hours after ROSC is 97.6% (91.8-99.4%) and 14.4% (9.4-21.4%).²⁹ From 24 hours to seven days, corresponding specificity and sensitivity is 100% (87.9-100%) and 56.5% (47.3-65.3%) respectively. HIBI appears as hyperintense foci on diffusion

weighted imaging (DWI) MRI. Emerging evidence show that MRI can be used to predict neurological function hours after ROSC, even though clinical guidelines recommend DWI MRI two to five days after the event.¹⁹ Currently, neuroimaging for predicting neurological outcome is only recommended in centres with experience, combined with other diagnostic tools.¹⁹

4. Electrophysiology, by EEG and SSEP, can further help to aid the clinician in predicting neurological outcome after cardiac arrest. The EEG is a well-established method, that could predict outcome within 24 hours after event.³⁰ A study including 430 comatose patients with ROSC showing poor neurological outcome at six months of follow-up was achieved with 100% (98-100%) specificity and 29% (22-36%) sensitivity. Absence of SSEP accurately predicts poor neurological function 72 hours after ROSC. Sensitivity, however, rarely exceeds 50%.¹⁹

1.2 THE 3-PHASE MODEL OF CARDIAC ARREST

The 3-phase model of cardiac arrest is a theoretical framework, divided into three distinct pathophysiological phases. This approach is based on the time-sensitive changes that occur after a cardiac arrest. These changes exert a dramatic impact on treatment effects. The time-dependent natural course of cardiac arrest is not taken into account by current treatment guidelines. This may be explained by the fact that it

is frequently difficult (or even impossible) to determine the exact phase of a cardiac arrest at the time of encounter, and taking the phases into account would complicate an otherwise simple treatment algorithm.³¹

The 3-phase model comprises an (1) electrical phase (0-4 minutes), a (2) circulatory phase (4-10 minutes) and a (3) metabolic phase (>10 minutes after collapse).

1.2.1 THE ELECTRICAL PHASE

Treatment with immediate defibrillation during the electrical phase has been supported widely in both animal and human studies. The ICD itself is arguably the best evidence of how early defibrillation affects outcome; studies show ICDs are capable of terminating >97% of all impending cardiac arrests by means of immediate defibrillation.³² For every passing minute, survival decreases by approximately 8-10% without defibrillation.^{33,34} Early defibrillation, during the electrical phase is associated with a 50-70% increase in likelihood of survival.^{8,31} The electrical phase is defined by an ongoing electrical chaos in the myocardium. The electrocardiogram typically shows ventricular fibrillation (VF), and less often ventricular tachycardia (VT). The fibrillatory waveforms are initially coarse (indicating a high concentration of cellular energy substrate), but gradually diminish to finer waveforms, less amenable to defibrillations.

1.2.2 THE CIRCULATORY PHASE

Animal studies have shown that the effects of prompt defibrillation during the circulatory phase is not the optimal treatment regimen. Yakaitis et al.³⁵ induced VF in dogs and found that immediate defibrillation was only effective if ≤ 3 minutes had passed. Other treatment regimens such as CPR and epinephrine became critical after a few minutes of cardiac arrest. CPR (notably chest compressions) and epinephrine rendered the myocardium amenable to defibrillations again. These findings have been supported in several animal models,³⁶⁻³⁸ and also in human studies. Cobb et al.³⁹ concluded that immediate defibrillation was more effective than 90 seconds of CPR with subsequent defibrillation if cardiac arrest had persisted up to three minutes. Beyond three minutes, the opposite was true. Wik et al.⁴⁰ observed an increase in survival in patients treated with CPR prior to defibrillation, as opposed to immediate defibrillation. They reported not only an increase in likelihood of survival to hospital discharge, 22% compared to 4%, but also an increase in 1 year survival rate, 20% compared to 4%.

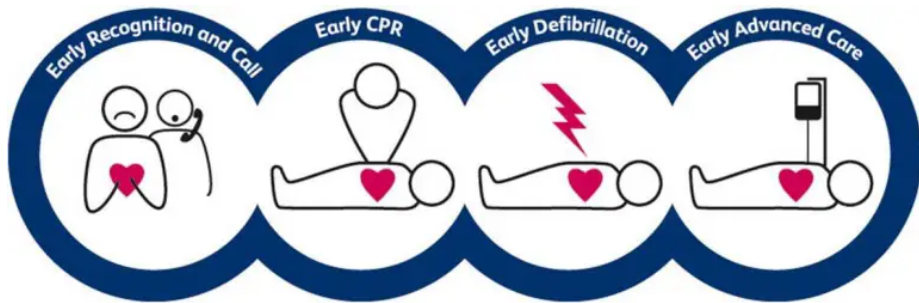
1.2.3 THE METABOLIC PHASE

If a cardiac arrest persists for approximately 10 minutes, global tissue injury becomes evident, and reperfusion may further exacerbate the toxic effects on the myocardium and neurons. The peripheral vasoconstriction that in the early phases are beneficial in increasing blood pressure (BP) and coronary perfusion pressure (CPP) during CPR may further worsen global ischemic injuries during the metabolic phase. Beyersdorf et al.⁴¹ shed light on this issue by conducting a study

where controlled reperfusion was made possible by cardiopulmonary bypass and metabolic therapies in patients with intractable VF. The study concluded that 13 out of 14 were successfully resuscitated, and 11 of the 14 were discharged alive.

1.3 THE CHAIN OF SURVIVAL

Figure 1. The chain of survival



Maximising survival in cardiac arrest, OHCA in particular, requires a highly synchronised and continuous effort from laymen, the emergency dispatch system, ambulances, rescue services, and the hospital system. This includes broad population-based education of laymen to careful planning of the handling of OHCA and IHCA in every phase of the process. The chain of survival refers to a series of interventions which, when implemented promptly, significantly improves the chances of survival. These are (1) early recognition of a SCA followed by emergency call to a dispatch centre; (2) high-quality basic CPR, with telephone-assisted guidance if required; (3) defibrillation; (4) provisioning of advanced CPR; (5) post-resuscitation care; and (6) rehabilitation and recovery.⁴²

Notably, the greatest effect on survival is observed in the initial stages, particularly stages 1–3, stressing the importance of time, refer to Table 1.⁴³ Moreover, these interventions can be executed by laymen, which emphasises the importance of educating and equipping laymen. Therefore, the individual’s geographical location at the time of SCA is a key determinant of survival. The likelihood of successful CPR is higher in densely populated areas.⁴⁴ However, less than 30% of all cases of SCA occur in public locations, with the majority of cases occurring in the victim’s home, where few (if any) bystanders may be present. Sudden cardiac death (SCD) is unwitnessed in half of all cases.^{45–48}

Table 1. Number needed to treat (NNT) for interventions in cardiopulmonary resuscitation.

Intervention	Included in BLS	NNT to save 1 person	Reference
Early detection of cardiac arrest	Yes	11	<i>Berdowski et al.</i> ⁴⁹
Bystander CPR	Yes	15	<i>Hasselqvist et al.</i> ⁵⁰
Early defibrillation	Yes, if AED is available	5	<i>Kitamura et al.</i> ⁵¹
Epinephrine	No	112	<i>Perkins et al.</i> ⁵²

AED = automatic external defibrillator.

1.4 RISK FACTORS OF CARDIAC ARREST

The most important risk factor for SCA is coronary heart disease (CHD), and approximately 50% of all SCAs occur as the first manifestation of CHD. In total, 60-80% of all SCAs are due to CHD.^{53,54} The incidence rates in the general population and low-risk subgroups are low, although their large number implies a large absolute number of cases. High-risk individuals constitute a small proportion of all SCAs, although their individual risk is high. These observations pose great challenges for individual-level prediction of SCA. Heart failure (HF) is another strong risk factor for SCA, irrespective of the underlying cause of HF (although some subtypes, including ischemic cardiomyopathy, are particularly prone to developing SCA). With the emergence of novel treatment regimens in HF, important mechanisms of action such as remodelling, acting as substrates for arrhythmias, appear to be inhibited.⁵⁵ Low left ventricular ejection fraction (LVEF) has been highlighted as a predictor of high risk.⁵⁶ However, LVEF as a marker for SCA does not effectively achieve a clinically acceptable sensitivity or specificity, despite the widespread use of LVEF for this purpose. This notion is emphasised by the high number needed to treat (NNT) for ICD implantation and the fact that SCA occurs in two-thirds of individuals with normal or mildly reduced LVEF.⁵⁷⁻⁵⁹

There are many other cardiac, beyond CHD, as well as non-cardiac conditions, that can cause SCA. Please refer to section 1.9.4 Aetiology, on page 21.

1.5 TREATMENTS

Modern cardiac arrest care, including treatment according to the chain of survival, was first formalised in 1990 by the American Heart Association (AHA).⁶⁰ The concept of the chain of survival was initially aimed at OHCA, but later also adopted and adapted to the setting of IHCA.

1.5.1 OPTIMAL CHEST COMPRESSIONS

High-quality CPR entails (1) correct positioning and hand placement, (2) minimising pre/peri-shock pauses, (3) adequate compression depth and rate, and (4) monitoring of markers, such as end-tidal carbon dioxide (ETCO₂) and parameters, if possible. Guidelines emphasise the following with regards to chest compressions:⁶¹

1. Resuscitation should commence promptly when addressed at the location where the victim is found.
2. Pre- and post-shock pauses should be minimal. Chest compression fraction should be aimed at $\geq 60\%$. To prevent rescuers of experiencing fatigue during compressions, and thus upholding quality of chest compressions, a switch is reasonable, every 2 minutes.
3. Compression depth is recommended in-between 5-6 cm with a compression rate of 100-120 /min. The healthcare provider should allow for the chest wall to recoil, thus, avoiding leaning on the chest during the compression cycle.
4. If possible, to validate the effectiveness and quality of CPR, end-tidal CO₂ and arterial blood pressure can be monitored during CPR.

1.5.2 VENTILATION AND COMPRESSION-TO-VENTILATION RATIO

Ventilation causing a visible rise of the thorax and constituting approximately 500-600 ml is recommended. Without an established advanced airway passage, ventilation should be performed by mouth-to-mouth, or via bag-mask. However, mouth-to-nose is reasonable if the former methods are impractical or impossible to obtain. Excessive ventilation is harmful and not recommended, as it potentially causes overdistension and subsequently reduced venous return, gastric insufflation and aspiration. Insufflation of 1 second is recommended. If ROSC is achieved but the patient still requires ventilation, a ventilation-rate of 10/min may be considered. Compression-to-ventilation ratio is 30:2 before establishing an advanced airway (tracheal tube or supraglottic airway). After establishing an advanced airway, a ventilation ratio of 10 /min is reasonable.⁶¹

1.5.3 DEFIBRILLATION

Early defibrillation in the case of victims displaying VF or pulseless VT (pVT) is pivotal for survival. Biphasic over monophasic defibrillators are preferred. Defibrillation pads are placed on the victim's exposed chest, anterolateral or anteroposterior. AEDs require a pause for rhythm detection, resulting in delaying CPR. After defibrillation, immediate chest compression is advised, rather than post-shock control of rhythm. If the victim displays signs of ROSC – i.e. arterial waveform and sudden increase in ETCO₂ post-defibrillation – a short pause could be made for confirmation.⁶¹

1.5.4 MEDICATIONS DURING CARDIAC ARREST

Epinephrine primarily acts via its affinity to α -receptors and β -receptors, thus increasing venous return due to peripheral vasoconstriction and vasodilation of coronary arteries. However, the stimulation of β -adrenergic receptors by epinephrine may at the same time also act unfavourably, via an increase in oxygen demands from the myocardium, and potentially pro-arrhythmic. The clinical use of epinephrine is based on two RCTs and one meta-analysis, where the latter concluded significant increase in ROSC and survival to hospital discharge in the epinephrine treatment arm.^{52,62,63} To this date, no other vasopressor or dose of epinephrine has proven to be more effective than current clinical recommendations.

Other medications during cardiac arrest include amiodarone and lidocaine, which may be considered in victims with VF or pVT. Amiodarone and lidocaine have demonstrated higher survival rates to hospital admission in OHCA, albeit without any impact on overall survival or survival with low CPC score.^{64,65}

Other measures, e.g. targeted temperature management, advanced airway management, specific arrhythmia management, and use of urgent angiography, etc., are discussed in detail in recent guidelines.⁶¹

1.6 PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

The most effective way of preventing SCA is by reducing CHD in the general population. This can be achieved by broad, population-wide interventions targeting smoking, hypertension, diabetes, obesity, dyslipidemia and a sedentary lifestyle. Mannsverk et al.⁶⁶ have shown that management of modifiable risk factors such as cholesterol, blood pressure and smoking reduced CHD by 66%, predominantly via SCA. Beta-blockers, Angiotensin-converting enzyme inhibitors (ACE-inhibitors), Angiotensin II receptor blockers (ARBs), Mineralocorticoid receptor antagonists (MRAs) have all shown beneficial effects in primary prevention of SCA.⁶⁷ The effect of aspirin in primary prevention for CHD has long been debated.⁶⁸

Since the mid-1990s, several pivotal studies have demonstrated a marked decrease (44%) in SCA in patients with heart failure with reduced ejection fraction (HFrEF). A total of 12 clinical trials, enrolling more than 40,000 patients, have demonstrated this. The results are most likely due to improvements in evidence-based management of HFrEF, with several effective drugs and devices available.⁶⁹ Sodium-glucose cotransporter-2-inhibitors (SGLT-2 inhibitors) have not been studied as extensively regarding the effect on SCA, though a meta-analysis has shown similar positive results.⁷⁰

The benefit of an ICD in high-risk patients, i.e. ischemic HFrEF, was studied in the Multicenter Automatic Defibrillator Implantation Trial II

(MADIT-II), showing 31% reduced mortality risk in comparison to otherwise optimal medical therapy (Hazard Ratio [HR] 0.69 [CI 0.51-0.93; p=0.016]).

1.7 SECONDARY PREVENTION OF SUDDEN CARDIAC ARREST

In terms of secondary prevention, focus has primarily been placed on the implantable cardioverter defibrillator (ICD), beta-blockers and anti-arrhythmic agents. With regards to ICDs, three major randomised controlled trials (RCT) have investigated the potential benefit of an ICD in comparison to medical therapy: the Anti-arrhythmic Versus Implantable Defibrillator Trial (AVID), Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH) trial.⁷¹⁻⁷³ The AVID registry included 1016 patients with successfully resuscitated VF, syncope due to sustained VT or haemodynamically instable VT in patients with HFrEF. The treatment arms were either ICD therapy or anti-arrhythmic drugs (amiodarone in 96% of cases), showing a significant risk reduction for ICD therapy. The treatment group receiving an ICD had a reduced mortality rate 1, 2 and 3 years after implantation of 39%, 27% and 31% respectively. The CIDS registry included 659 patients with the same inclusion criteria as the AVID trial. The study showed reduced all-cause mortality as well as arrhythmic mortality in the ICD arm of 20% and 33% respectively; however, not statistically significant. The CASH registry included 288 patients with successfully resuscitated VT/VF, showing that an ICD was associated with 23% reduced all-cause mortality, as opposed to

amiodarone and beta-blockers; however, the results were also not statistically significant.

A meta-analysis of the three aforementioned RCTs showed a 28% reduction in all-cause mortality (95% CI 0.6-0.87), as well as a 50% reduction in arrhythmic death (95% CI 0.37-0.67). The most pronounced treatment effect was seen in patients with LVEF < 35%.⁷⁴ Based on these studies, current clinical guidelines propose treatment with ICD implantation in subjects without reversible causes, such as a myocardial infarction. The role of malignant arrhythmias post-infarction has been debated within the research community. S holm et al.⁷⁵ concluded that long-term mortality was reduced in individuals with an AMI after receiving ICD before hospital discharge. The study also found that when appropriate shock therapy or death was appointed as endpoint, no difference was seen between the cohorts, indicating the benefit of prompt ICD implantation. The treatment arm that received a device also had higher proportions of comorbidities, including individuals with LVEF < 35%. Despite this fact, five-year mortality was significantly lower for individuals offered an ICD, as opposed to not, with a hazard ratio (HR) after adjusting for prognostic factors of 0.44 (95% CI, 0.23-0.88).⁷⁵

Amiodarone has not shown to improve survival, but is recommended to reduce hospitalisation and ventricular tachycardia.⁷⁶

1.8 EFFECT OF THE COVID-19 PANDEMIC ON CARDIAC ARRESTS

During the early phases of this thesis, the global pandemic caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) temporarily shifted our focus to the impact of SARS-CoV-2 on cardiac arrests in Sweden.

COVID-19 was first recorded in Wuhan (China) in December 2019. The World Health Organisation (WHO) declared a global pandemic in 11 March, 2020. The first cases of COVID-19 in Sweden were reported in early February 2020. The Swedish Public Health Authority (SPHA) declared community spread in Sweden on 16 March. The COVID-19 pandemic has had immeasurable effects on individuals and healthcare systems all over the world.

Studies from Paris, Lombardi and New York reported increasing incidence of OHCA; i.e. a two-fold increase of incidence was noted in the Paris-Sudden Death Expertise Center Registry (Paris-SDEC registry), accompanied with markedly reduced survival. The Lombardia Cardiac Arrest Registry (Lombardia CARE) showed a marked 58% increase in OHCA during the initial period of the pandemic and The New York 911 Emergency Medical Services System (NY 911 EMS) reported up to a 10-fold increase in OHCA cases.⁷⁷⁻⁷⁹

Data from NY 911 EMS showed unfavourable characteristics for both patient attributes as well as the circumstances surrounding the cardiac arrest during the pandemic. OHCA victims during this period suffered from more comorbidities prior the cardiac arrest, i.e. hypertension, diabetes, etc. On the other hand, patient characteristics did not seem to be any different in Paris-SDEC during the pandemic. Both registries, however, showed increases in non-defibrillated rhythms, decreases in ROSC and increased response times by EMS services. In the Paris-SDEC registry, data also showed less use of public AEDs during the pandemic period. All these factors are known to reduce the probability of survival during a cardiac arrest. However, these studies were unable to be applied in an effective manner with respect to reporting their related COVID-19 status.

1.9 OUT OF HOSPITAL CARDIAC ARREST

1.9.1 DEFINITION

According to the Utstein definition,⁸⁰ a cardiac arrest is defined as an abrupt loss of functional cardiac activity, leading to haemodynamic collapse, with agonal or ceased breathing. Out-of-hospital cardiac arrest (OHCA) is a cardiac arrest occurring outside of the hospital perimeter.^{81,82}

1.9.2 INCIDENCE

The number of reported OHCA to the SCRR is approximately 6,000 cases annually, amounting for 52 cases per 100,000 person-years.^{13,83} In Europe, the mean incidence rate is 56 per 100,000 person-years.⁴⁵

1.9.3 EPIDEMIOLOGY

The predominating aetiology of OHCA is coronary heart disease (CHD), which accounts for approximately 60–80% of cases. However, the latest decades have seen a decrease in CHD-related OHCAs, presumably due to improved primary prevention and early revascularisation in acute coronary syndromes (ACS). The list of non-ischemic cardiac causes includes both inherited and acquired conditions. Among these, cardiomyopathies are the most common, accounting for 10–15% of cases.⁸⁴

1.9.4 AETIOLOGY

Warning signs can precede a SCA. Symptoms include chest and abdominal discomfort, dyspnoea, syncope and cold sweats. The most effective method to prevent a SCA is by primary prevention and recognition of early warning signs. The warning signs are highly non-specific and may often not prompt the individual to seek medical attention. However, seeking medical attention is of utmost importance.^{85,86} Warning signs are absent in roughly 50% of SCAs, with the cardiac arrest therefore being the first manifestation of disease.^{53,87,88}

1.9.4.1 CORONARY HEART DISEASE

Coronary heart disease (CHD) is an umbrella term for acute or chronic ischemic heart disease. This comprises ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina, and chronic coronary syndromes (including stable angina).

There are various mechanisms by which cardiac arrest can occur due to CHD:

1. **Transient ischemia**, refers to the mismatch between myocardial blood supply and demand, such that the latter is greater than the former. Ischemia instigates the ischemic cascade, which induces a proarrhythmic substrate for ventricular arrhythmias and thus SCA.⁸⁹
2. **Acute myocardial infarction (AMI)**, constitutes STEMI and NSTEMI. AMI typically occurs from a ruptured coronary plaque, leading to acute atherothrombosis and severe obstruction of blood flow within the supplied territory. Infarction carries a greater risk of ventricular arrhythmias in comparison to ischemia.
3. **Scar-related arrhythmia**, can occur from previous myocardial injuries. Scar tissue can act proarrhythmic, regardless of aetiology (e.g. myocardial infarction, myocarditis, surgery, etc.).
4. **Ischemic Cardiomyopathy (ICM)**, provides a very potent arrhythmic substrate. The combination of scarring, repeated bouts of ischemia, ventricular dilatation, myocardial fibrosis and neurohormonal stress cause a storm scenario for ventricular arrhythmias. Other forms of cardiomyopathies are also proarrhythmic, albeit generally less so than ischemic cardiomyopathy.⁹⁰

1.9.4.2 NON-ISCHEMIC CARDIAC DISEASES

Congenital coronary anomalies (CCA) constitute abnormalities in the origin, course and size of the anatomy of coronary arteries. These conditions are found in approximately 1% of patients that undergo coronary angiography, and seen in 0.3% of autopsy cases.⁸⁴

Coronary artery embolism, is most often caused by embolus formation from aortic valve endocarditis, where larger vegetations are associated with higher risk.

Coronary arteritis, refers to conditions causing coronary artery vasculitis, causing complications such as aneurysm, coronary stenosis, and sometimes SCD.

Hypertrophic cardiomyopathy (HCM), is an autosomal dominant genetic condition, presented as thickening of the myocardial wall, especially in the left ventricle. It is caused by mutations in proteins coding sarcomeres, which are vital components of the myocardial contractile apparatus. The prevalence in the general population is 1 in 500, making it the leading cause of SCA in younger individuals (< 35 years), often seen among athletes. The risk of SCA is associated with features such as left ventricular hypertrophy (>30 mm), familial burden of SCD, syncope episodes, hypotension induced by exercise and non-sustained VT.⁹¹

Dilated cardiomyopathy (DCM) is characterised by dilatation and general hypokinesia of the ventricles, accompanied by myocardial fibrosis. The five-year mortality rate is close to 50%. The prevalence is approximately 36 per 100,000. It is most commonly idiopathic, but sometimes associated with genetic mutations (e.g. desmin, lamin C and myosin).⁹²

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is frequently caused by mutations in desmosomal genes, predominantly affecting the right ventricle. The disease can be inherited in an autosomal dominant or recessive manner. Autosomal dominant inheritance is more common. Disease penetrance is 28–58% in first-degree relatives. The disease is characterised by myocardial fibro-fatty tissue replacement. The prevalence of the disease ranges between 1:1000 to 1:5000, with male dominance. As the disease progresses, the right ventricle dilates and becomes thinner. Approximately 50% of patients demonstrate biventricular involvement; however, less pronounced in the left ventricle.⁹³ The most common presentation is palpitations or syncope. Nevertheless, the disease is mostly concealed during the first two decades of life. Physical exercise, causing activation of the sympathetic nervous system, increases the risk of syncope, arrhythmias and SCD.

A range of other cardiomyopathies,⁹⁰ arrhythmias⁹⁴ and valvular conditions⁹⁵ may cause SCA, as discussed elsewhere.

1.9.5 CHANNELOPATHIES

Brugada Syndrome – Brugada syndrome is a hereditary autosomal dominant disease, with unknown prevalence. Brugada syndrome is a condition that usually manifests during the years 20–55, often in the form of syncope, pre-syncope, VT/VF or SCA. It is characterised by distinct ECG changes.⁹³

Long QT-syndrome – Long QT-syndrome is a prolongation of the QT-interval, which is either congenital or acquired. Acquired conditions include electrolyte imbalances, hypomagnesaemia, and

medications such as sotalol, amiodarone, antipsychotics, certain antibiotics, antiemetic agents, and anti-histamines. There are various mutations causing long QT-syndrome, and the most common is genotypes in the KCNQ1 gene. Prolongation of the QT interval increases the risk of developing polymorphic ventricular tachycardia, also called *torsade de pointes*, often degenerating to VF.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) –

Catecholaminergic polymorphic ventricular tachycardia is an autosomal inherited condition characterised by instable arrhythmias and SCA during states with increased adrenergic tone. It usually manifests at an early age.

1.9.6 OTHER CAUSES OF CARDIAC ARREST

Drowning

Drowning leads to submersion of water into the airways, potentially leading to respiratory insufficiency and subsequently cardiac arrest. Drowning accounts for approximately 7% of deaths caused by injury, estimated to 236,000 cases annually worldwide, according to the World Health Organization (WHO). Age poses an important risk factor, where children are subjected to the highest rates of deaths; as well as male gender, showing mortality rates twice as high, compared to women. Other risk factors include occupation/work, socioeconomic status, alcohol consumption and medical conditions.⁹⁶

Intoxication

Intoxication accounts for approximately 5.2% of all OHCA in the SCRR, predominantly occurring in younger individuals. Cardiac arrest

due to intoxication is more often unwitnessed, and is less likely to present with a shockable rhythm and bystander-CPR. The European Resuscitation Council (ERC) recommends substance overdose often to be treated with antidotes, i.e. opioids with naloxone, paracetamol with N-acetylcysteine, benzodiazepines with flumazenil, etc. However, poly-substance intoxication accounts for 78% of cardiac arrests related to overdose. Despite unfavourable circumstances, 30-day mortality is lower, as compared to other aetiologies.⁹⁷

Traumatic cardiac arrest (TCA)

The mechanism of traumatic cardiac arrest (TCA) is multifaceted, and depending on the trauma, potentially causing circulatory failure due to hypovolemia, cardiac tamponade, tension pneumothorax, hypoxia, commotio cordis, and contusion cordis. Non-shockable rhythms are overwhelmingly dominant in TCAs, approximately 7% presents as VT/VF upon initial ECG.⁹⁸

A wide range of other conditions may cause sudden cardiac arrest. A comprehensive list can be found elsewhere.⁹⁹

1.9.7 PREDICTORS OF SURVIVAL

Survival in OHCA depends on the time-sensitive sequences that constitute the chain of survival, refer to section 1.3 The chain of survival on page 8.

The Utstein group have proposed the three following strategies for improving survival in OHCA:¹⁰⁰

1. **Research and innovation**, referring to novel research, improving the links in the chain of survival.
2. **Education**, referring to training as many laymen as possible regularly, with up-to-date methods in CPR.
3. **Community adaptation/Local implementation**, referring to translating research advances into specific strategies and changes in infrastructure.

High-quality CPR includes ventilation and chest compressions with minimal pauses in-between cycles to sustain CPP, thus increasing the chances of ROSC. For guidelines, refer to section 1.5.1 on page 12-15. Witnessed cardiac arrest cases, receiving bystander-CPR and early defibrillation have a 3-fold improved rate of survival.⁸⁴ Survival is also substantially improved if defibrillation is performed before ambulance arrival.^{84,101} A novel approach, tested by Schierbeck et al.,¹⁰² using AED-equipped drones have shown promising results. In the study the drones reached the target site before EMS services in the majority of cases. Another important aspect is targeted placement of AEDs, requiring careful planning and awareness of high-risk venues, with the opportunity for relocation upon epidemiological changes.^{103–105}

Patient characteristics and factors

Key factors and circumstances related to cardiac arrest that affect outcome include initial rhythm, age, time to CPR, time to EMS arrival, place of cardiac arrest, bystander CPR, defibrillated rhythm, cause of cardiac arrest, defibrillation before ambulance arrival.⁷

Targeted interventions

Current guidelines recommend immediate coronary angiography in OHCA cases achieving ROSC with new ST segment elevations on ECG. These patients are likely to have a STEMI. An observational study including 746 comatose patients post-cardiac arrest with and without STEMI, showed that those presenting with a STEMI had an overall improved survival rate.¹⁰⁶ For patients without STEMI who underwent immediate coronary angiography, survival rates were similar. A culprit vessel was found in 22.9 % of patients without ST elevation. The European Society of Cardiology has shed light on this issue by giving survivors of OHCA without ST-T changes but with a high clinical probability of myocardial infarction a class IIb indication for urgent coronary angiography.

Regarding targeted temperature management (TTM), conflicting results have emerged. Previous studies supporting the use of TTM have been based on trials with biases and systematic errors. A meta-analysis concluded that the benefit of TTM is not supported by enough clinical evidence. Recently, two large randomised clinical trials have further investigated the issue. Dankiewicz et al.¹⁰⁷ studied 1850 patients in comatose state, post-cardiac arrest, randomised to either 33° C or normothermia. The primary endpoint was all-cause mortality at six months, with no difference between the groups. However, in the group treated with hypothermia, arrhythmia induced complications were more prevalent, (24% in comparison to 18%, $p < 0.001$). Nielsen et al.¹⁰⁸ studied 950 patients, with similar inclusion criteria,

randomised to either 33° C or 36° C. Again, TTM did not confer any survival benefit.

1.10 IN-HOSPITAL CARDIAC ARREST

In- and out-of-hospital cardiac arrest share many epidemiological similarities. However, there are important differences that require consideration. Historically, OHCA has gained a lot more attention, and much of the management of IHCA is based on extrapolation from OHCA data.

1.10.1 DEFINITION

The Utstein definition of an IHCA is (1) absence of a palpable pulse; (2) unresponsiveness due to any cause, and (3) apnea, agonal respiratory breathing, or artificial breathing.

1.10.2 EPIDEMIOLOGY

The incidence of IHCA in Sweden is approximately 2,500 cases annually, constituting 1.7 per 1,000 hospital admissions.^{11,57} In Europe IHCA incidence is approximately 1.5–2.8 per 1,000 hospital admissions.¹¹⁰

The in-hospital setting, with the frequently use of patient monitoring devices, offers excellent opportunities for early detection of cardiac arrest, and thus survival in IHCA.^{33,111,112} In the majority of cases of IHCA, a rescue team is alerted within 1 minute from collapse. The median time to CPR is <1 minute. Approximately 90% of cases presenting with ventricular fibrillation are defibrillated within 3 minutes, which is a fraction of the time required by the EMS to arrive

at the scene in an OHCA. In IHCA, 30-day survival is approximately 36% in Sweden.¹²

1.10.3 AETIOLOGY

The aetiology for IHCA share many similarities with OHCA, however, with some exceptions. The predominating causes of IHCA are cardiac conditions (50–60%). These conditions include acute coronary syndrome, ACS, arrhythmias and heart failure. Following cardiac aetiology, respiratory insufficiency ranks as the second most common cause, accounting for 15–40% of IHCAs.^{113,114} Sepsis, septic shock with subsequent multiorgan failure leading to IHCA constitute for another 13–27%.^{113,115}

1.10.4 PREDICTORS OF SURVIVAL

Depending on the type of hospital ward, the patient's clinical state, and causes for admission to hospital, the level and type of monitoring of vital parameters will too. Monitoring may include continuous measurement of oxygen saturation, telemetry (continuous monitoring of ECG), repeated assessments of vital parameters, i.e. New Early Warning Signs (NEWS score). Clinical deterioration call for further assessment and could signal an impending cardiac arrest.^{116,117}

Assessment of high-risk patients should be done upon hospital admission, including risk stratification by clinical scoring systems, changes in NEWS score, or concerns from ward personnel.

As is the case of OHCA, the fundamental and decisive factor for survival in IHCA is time to CPR and early defibrillation.^{118,119}

Therefore, regular CPR training is mandatory for all hospital

personnel, regardless of education. The quality of chest compressions plays a major part in clinical outcome.¹²⁰ Prompt defibrillation is associated with improved survival, and compared to non-shockable rhythm, a 2–3 time increase in survival.^{111,121} Regarding the use of early drug administration, there is conflicting evidence. Early administration of epinephrine for IHCA cases has been reported to be associated with improved survival in cases presenting with a non-shockable rhythm. However, the benefit for patients presenting with a shockable rhythm is debatable.¹²²

In IHCA, airway management may be less complicated given the proximity to equipment and staff with experience. Likewise, the temporal proximity to extracorporeal circulation (ECMO) in many hospitals may lead to increased use of such circulatory support systems, albeit in highly selected cases.¹¹³

There are numerous patient characteristics that have proven pivotal for outcome. Increased age is associated with worsened outcome, especially in victims >70 years of age. The outcome is similar between the sexes, however, women between 15-44 years of age have proven to have improved survival rates in comparison to males in the same age category.¹²³ Comorbidities also play a key role, e.g. malignancy, sepsis, poor functional status, pneumonia, renal and hepatic dysfunction are all attributed to a worsened clinical outcome. On the other hand, patients with AMI have been observed to have an increased survival rate in IHCA.¹¹³

2 AIM

The objectives of this thesis are to (1) study epidemiological characteristics of cardiac arrest, (2) study predictors of survival after cardiac arrest, (3) and explore whether there is room for increased use of secondary preventive measures.

2.1 STUDY I

Sultanian P, Lundgren P, Strömsöe A, Aune S, Bergström G, Hagberg E, Hollenberg J, Lindqvist J, Djärv T, Castelheim A, Thorén A, Hessulf F, Svensson L, Claesson A, Friberg H, Nordberg P, Omerovic E, Rosengren A, Herlitz J, Rawshani A. Cardiac Arrest in COVID-19: Characteristics and Outcomes of in- and out-of-hospital cardiac arrest. A Report From the Swedish Registry for Cardiopulmonary Resuscitation. *European Heart Journal*, 2021.

Shortly after the initiation of this thesis, the outbreak of the COVID-19 pandemic began, causing unprecedented consequences for societies, healthcare systems, and individuals worldwide. Studies from New York, Paris and Italy showed an increased incidence in out-of-hospital cardiac arrests (OHCAs), along with worsened survival. However, these studies did not reliably identify patients with COVID-19, making it difficult to describe causal links between the virus and the increased incidence. Therefore, we aimed to explore the association between COVID-19 infection and characteristics, as well as survival in in- and out-of-hospital cardiac arrest.

2.2 STUDY II

Jerkeman M¹, Sultanian P¹, Lundgren P, Nielsen N, Helleryd E, Dworeck C, Omerovic E, Nordberg P, Rosengren A, Hollenberg J, Claesson A, Aune S, Strömsöe A, Ravn-Fischer A, Friberg H, Herlitz J, Rawshani A. Trends in survival after cardiac arrest: a Swedish nationwide study over 30 years. *European Heart Journal*, 2022.

Studies on temporal changes in survival after cardiac arrest have rarely been able to cover longer periods of time, or study whole populations, with conflicting results.^{1,6-8} Survival is a function of multiple critical and highly time-sensitive factors, i.e. time to CPR, ambulance response time, location of cardiac arrest, skills of the first responders, quality of CPR, initial rhythm, etc. During the last 30 years, much has evolved within the field of medicine, and there have been profound changes in public health, demographic composition and societal structure. Urbanisation has been dramatic, and urbanised areas are more densely populated, while an increasing proportion of the population is elderly, with more comorbidities. Automatic external defibrillators (AEDs) have been disseminated in public places, with a total of almost 20,000 being available in Sweden.¹³ This allows for virtually anyone to deliver shocks. In this study we explored long-term trends in characteristics and outcomes in in- and out-of-hospital cardiac arrest.

2.3 STUDY III

Sultanian P, Lundgren P, Rawshani A, Möller S, Hadi-Jafari A, David L, Yassinson S, Myredal A, Rorsman C, Taha A, Ravn-Fischer A, Martinsson A, Herlitz J, Rawshani A. Early ICD implantation following out-of-hospital cardiac arrest – A retrospective cohort study from the Swedish Registry for Cardiopulmonary Resuscitation. *BMJ Open* 2024;14:e077137. Doi: 10.1136/bmjopen-2023-077137.

Optimal use of implantable cardioverter defibrillator (ICD) after myocardial infarction and cardiac arrest is an unresolved issue. There are critical gaps in knowledge, further exacerbated by considering the use of ICDs after cardiac arrest, irrespective of aetiology. A previous study comparing survival in patients after OHCA due to myocardial infarction with and without prompt ICD implantation demonstrated a significantly improved survival rate among the former group.⁷⁵ Current European guidelines recommend implantation of an ICD after myocardial infarction for patients with malignant arrhythmias if the patient previously has left ventricular dysfunction, or if the patient during coronary angiography is incompletely revascularised (class IIb C indication). Current guidelines also recommend ICD implantation for patients suffering cardiac arrest with dilated cardiomyopathy or hypokinetic non-dilated cardiomyopathy, if the victim displays an initial shockable rhythm or has a haemodynamically unstable ventricular tachycardia (class I recommendation). Thus, patients with OHCA presenting with an initial shockable rhythm, completely revascularised, without structural heart disease or LVEF dysfunction are ineligible for ICD implantation. In this study, we explored whether

all individuals with cardiac aetiology and initial shockable rhythm should receive an ICD.

2.4 STUDY IV

Sultanian P, Lundgren P, Louca A, Andersson E, Djärv T, Hessulf F, Henningson A, Martinsson A, Nordberg P, Piasecki A, Gupta V, Mandalenakis Z, Taha A, Redfors B, Herlitz J, Rawshani A. Prediction of survival in out-of-hospital cardiac arrest: The updated SCARS Model. *European Heart Journal – Digital Health*, ztae016. Doi: 10.1093/ehjdh/ztae016

Despite impressive advances in resuscitation care, OHCA still remains a highly fatal condition, with an overall survival rate of one in ten. Our research group has previously developed a prognostication model for survival in OHCA, named SCARS-1 (Swedish Cardiac Arrest Risk Score-1).¹²⁴ However, our previous model suffered from important shortcomings, notably the lack of comprehensive machine learning strategies, use of imputation for missing data, absence of optimising model performance in the lower likelihood (of survival) ranges, etc. In this study, we improved the methods and evaluation of our prediction model, by addressing and handling the shortcomings of SCARS-1.

3 PATIENTS AND METHODS

3.1.1 DATA SOURCES

The Swedish Cardiopulmonary Resuscitation Registry

The cornerstone of data in this thesis is the Swedish Cardiopulmonary Resuscitation Registry (SCRR). The SCRR is a Swedish national quality registry, covering the vast majority of all cardiac arrests, with the first cases recorded in 1990. To date, more than 135,000 patients have been included in the registry. SCRR complies with the Utstein Style of reporting variables and outcomes. Each report includes circumstances, characteristics, critical time intervals, management and outcomes during resuscitation and, among those achieving ROSC, information regarding in-hospital care and outcomes. Patient data are retrieved from pre-hospital and in-hospital medical records, electronically transferred to the registry. Reporting to SCRR occurs in a two-step process; the first is completed by EMS personnel promptly after event (Appendix A), and the second is carried out after discharge or death (Appendix B).

The inclusion criteria in the SCRR are:

- Unconsciousness, with absent breathing/agonal breathing.
- Initiation of CPR before or upon arrival of EMS in OHCA and rescue team in IHCA.

In some cases, unequivocal signs of death are evident upon arrival of healthcare professionals, making them ineligible for registration to the SCRR.

Today, millions of Swedes have been educated in basic CPR.¹²⁵ This enormous task of educating a large proportion of the entire population started in 1983, when the Swedish Cardiology Association's working group assigned 24 medical doctors to become primary instructors in CPR, with the objective to educate healthcare personnel and laymen in basic CPR. A cascade-teaching principle was applied, which resulted in rapid dissemination of basic resuscitation knowledge among millions of Swedish citizens.

The National Board of Health and Welfare

The National Board of Health and Welfare manages several nationwide healthcare databases, with the purpose of monitoring public health and research. The earliest database was established in 1968. Since then, several databases have been founded, such that data now covers information on all in-hospital and outpatient clinic visits, diagnoses, interventions, demographics, prescribed medications, causes of death, etc. These sources can be interlinked and subsequently merged with the SCRR using the unique personal identification number assigned to all Swedish citizens. For this thesis, the patient registry, the cause of death registry and the prescribed drug registry have been used and merged with the SCRR.

The Patient Registry contains information on diagnoses using International Classification of Disease (ICD) codes, healthcare visits and interventions. The registry contains data on both inpatient (since year 1987) and outpatient care (since year 2002).

The Cause of Death Registry contains information on vital status and causes of death. Dates and causes of death are adjudicated by the attending physician in each individual case.

Prescribed Drug Registry was established in 2005 and contains data on all prescribed and dispensed medications throughout Sweden.

Statistics Sweden is a government agency, established in 1749, and contains demographic data, country of birth, educational attainment, profession, income, social security benefits, and other socioeconomic variables. Statistics Sweden manages and oversees the longitudinal integrated database for health insurance and labour market studies (LISA).

3.1.2 METHODS

An overview of the methods used in all studies is listed below, refer to Table 2.

Table 2. An overview of the cohorts, methodology and registries utilised for studies I-IV.

	Paper I	Paper II	Paper III	Paper IV
Design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Population	All cases of OHCA and IHCA, 1 January - 20 July 2020	All cases of OHCA, 1990–2020. All cases of IHCA, 2004–2020.	All cases of OHCA discharged alive, 2010–2020, with information on ICD.	All cases of OHCA, 2010–2020.
Final study population (n)	3,026	106,296	3,005	55,615
Ethical approval (DNR)	DNR: 2020-02017	DNR: 2019-01094	DNR: 2020-02017	DNR: 2020-02017
Merged Registries	Swedish cause of death registry	Swedish cause of death registry	Swedish cause of death registry, the patient registry, the Swedish prescribed	Swedish cause of death registry, the patient registry, the Swedish prescribed

			drug registry, LISA	drug registry, LISA
Primary Outcome	30-day survival for OHCA and IHCA	30-day survival for OHCA and IHCA	30-day survival for OHCA	30-day survival for OHCA
Cox proportional hazard	✓		✓	
Logistic Regression	✓	✓	✓	✓
Extreme Gradient Boosting			✓	✓
LightGBM				✓
Bayesian additive regression trees (BART)			✓	
Random Forest			✓	✓
Gradient Boosting		✓	✓	
Neural Networks			✓	✓
Propensity Score			✓	

3.1.3 STUDY DESIGNS

All papers in this thesis are based on data from the SCRR, merged with other registries, described above. A retrospective cohort design was utilised in all studies.

3.1.4 STATISTICAL METHODS

3.1.4.1 CLASSICAL REGRESSION METHODS AND SURVIVAL ANALYSIS

Cox proportional hazards model (Cox regression)

Cox regression is a powerful, semiparametric survival model that allows for flexible modelling of survival functions. Cox regression models survival time and allows for univariate or multivariate adjustments. Covariates can enter the model as categorical or continuous predictors. The hazard ratio (HR) is the ratio of the comparing groups' hazards.

Kaplan Meier

The Kaplan Meier estimator is used to visualise the cumulative survival rate, by employing a survival function. The survival function graphically illustrates the cumulative survival of the studied cohorts over time. Individuals who are lost to follow-up during the study period become censored, thereby not affecting the results. The Kaplan Meier estimator can only make crude assumptions about data, inapplicable to covariate adjustments, possible for other methods such as cox regression or logistic regression. The log rank test is used for making comparisons of survival between the cohorts studied.

Logistic Regression

Logistic regression is a statistical method for binary classification problems. It allows for modelling continuous and categorical covariates. It does not allow for the modelling of survival time, but may still be suitable for studying binary outcomes (e.g. 30-day survival). Odds is fundamental in logistic regression. Via a link function, the logarithm of odds depends on the predictors as a linear function. Logistic regression does not take survival time into account.

3.1.4.2 MACHINE LEARNING

Machine learning (ML) models have seen an increase in popularity in recent years. These methods offer the means to study and handle highly complex non-linear relationships and large datasets with many candidate predictors, able to create models with impressive performance. Machine learning models do not require explicit pre-specified assumptions about data distributions, correlations, strength of associations or existence of interactions. Machine learning is the most popular and successful subfield within artificial intelligence (AI). There are four major branches of machine learning: supervised learning, unsupervised learning, self-supervised learning, and reinforcement learning.

All analyses in thesis fall under the framework of supervised learning. Supervised learning equals data with annotations pertaining to a dependent feature being studied. In medical research, those annotations are typically patient outcomes or other relevant measurements. The model building process is guided (i.e. supervised) by the annotations

(i.e. outcomes). The goal of supervised learning is making correct predictions on unseen data.

In order to evaluate a machine learning model, data is typically split into several sets. A training set is mandatory to train the model. Model evaluation and adjustments can be performed in a validation set. The final evaluation of the model, however, is completed in a testing set. It is critical that the final model – i.e. the model presumed to be the best performing model – is evaluated in a test set it has never encountered during training. A central problem of ML is the trade-off between optimisation and generalisation. A model that fails to generalise, suffers from overfitting, meaning that the trained model performs well on previously observed data (training data), but fails to achieve similar precision on test data. There are various methods for handling and preventing overfitting. *K-fold cross-validation* is an approach that splits the training data into random partitions (folds) of equal sizes. The model is constructed in all folds except from one, which is used for model evaluation. This process is repeated multiple times, which allows for the model to be built and evaluated in the training data. Many different models can be tested this way, and the overall best performing model can be selected for final evaluation in the test set.

Model building can be very computationally intensive, requiring intensive resources and time. To alleviate this burden, several techniques exist. *Early stopping* halts training when model performance starts to plateau or decrease as validation error increases. Ensemble methods (discussed below) have built-in methods to reduce

overfitting. *Regularisation* reduces overfitting by adding a penalty to overly complex models via a loss function.

Hyperparameter tuning is another pivotal step in optimising machine learning models. Depending on the specific model being used, a number of parameters can be tweaked to improve the model performance. Tuning of these parameters constitute one of the most computationally intensive tasks in ML. The goal is to obtain the best combination of hyperparameters. This is typically evaluated during cross-validation. For neural networks, this tuning implies adjustments of the model's weights. General characteristics of the ML frameworks used in this thesis follows below.

Ensemble methods

Ensemble methods comprise of multiple prediction models that collectively achieve greater predictive performance than their individual components. There are three main types of ensemble methods; *boosting*, *bagging*, and *stacking*. The ensemble methods used in this thesis are boosting and bagging; Gradient Boosting Machine (GBM), Extreme Gradient Boosting (XGBoost), LightGBM, and Random Forrest, respectively.^{126–129}

Boosting

The boosting methodology leverages the collective misclassifications of numerous weak learners, refined through a specified loss function, to construct a powerful predictive model. This process initiates with the assignment of an initial prediction across all samples, which is

generally the mean value for regression tasks or the foundational probability for classification tasks. Subsequently, the model adjusts for the residual errors of each sample's predicted value, referring to this cumulative discrepancy as the *pseudo residual*. With each iteration, there is a recalibration of residuals aimed at minimising the pseudo residuals. The introduction of a learning rate function acts as a safeguard against overfitting. This cyclical procedure persists for a predefined number of iterations, culminating in the construction of a robust ensemble model composed of several weak learners. Collectively, these learners constitute a powerful prediction model.

Bagging

The bagging technique, also known as bootstrap aggregation, combines multiple learners independently, most often by decision trees (random forest) to produce a final prediction. Initially, the original dataset is bootstrapped to create n samples, with a set of covariates randomly selected. The bootstrapped sample is trained by an independent decision tree. The aggregated prediction score is then appointed to a final score by majority voting.

Deep Neural Networks

In deep learning, the deciphering of information from input to output occurs through a structured hierarchy of sequential layers. As the data progresses through increasingly deeper layers, it becomes more refined and informative. Each layer is comprised of input nodes that process incoming data points by applying a specific weight to them, followed

by the addition of a bias term. The aggregate of these computations for each node is then forwarded through an activation function.

Commonly, a sigmoidal function is employed for this purpose, outputting a value that ranges between 0 and 1. The performance of a neural network is a function of its weights. As data propagates through the network during each forward pass, these weights are updated and refined. Initially, set to random values, the weights are iteratively adjusted in response to the network's performance, as dictated by the loss function and the chosen optimiser. The loss function plays a pivotal role by quantifying the deviation between the network's predictions and the actual target values (during supervised learning) for each batch of data. Based on this calculated loss, the optimiser then makes informed adjustments to the weights, aiming to minimise the discrepancy between predicted and actual outcomes. This iterative refinement process enables the neural network to progressively enhance its accuracy and predictive capabilities. Neural networks are capable of deciphering multimodal data of virtually any type, ranging from images to videos and data frames.

3.1.4.3 PROPENSITY SCORES AND CAUSAL INFERENCE USING OBSERVATIONAL DATA

The main obstacle for causal inference using observational data is residual confounding. A randomised control trial (RCT) is the gold standard for assessing the effect of an intervention, since randomisation evenly distributes potential biases across studied treatment groups. However, an RCT is a costly experiment and

sometimes even ethically challenging, as well as potentially impractical to execute. The propensity score is a theoretical and mathematical framework that aims to minimise residual confounding and even mimic an RCT. Rosenbaum et al.¹³⁰ have showed that simple propensity score matching removes 98% of bias caused by confounding covariates.

The propensity score is calculated based on a set of covariates provided by various models, such as logistic regression or machine learning models. The propensity score represents the probability of an individual having an exposure (i.e. receiving a treatment), given their observed characteristics. The propensity scores can be used in different ways to make the final inference. One common approach is to perform propensity score matching, in which each treated individual is matched to an untreated individual, provided that they exhibit comparable propensity scores. Another approach is to use the propensity score as the only covariate in the final model (e.g. in a final logistic regression or Cox regression). Other approaches include using the inverse probability of treatment weighting (IPTW), which begins by calculating the propensity score for each individual. Each individual is then assigned weights based on these scores: for the treated, the weight is the inverse of the propensity score, and for the untreated, it is the inverse of 1 minus the propensity score. These weights help to create a pseudo-population where the distribution of characteristics is balanced between the treatment and control group. The treatment effect is then

estimated in this weighted population. Please refer to Austin et al.¹³¹ for more details.

In an RCT, the average treatment effect (ATE) and the individual treatment effect (ATT) overlap in such manner, that the final effect estimate is a representation of the expected effect (or lack thereof) if the entire population of interest were to be treated, as well as the expected impact on the individual level. Propensity score methods allow for estimating ATE and ATT separately, using methods described by Austin et al.¹³¹

3.1.5 METHODS, PAPER 1-4

3.2 STUDY I

Patients were enrolled from 1 January to 20 July, 2020.

Initially, we did not have information regarding COVID-19 status; however, the Swedish Public Health Authority (SPHA) declared the COVID-19 outbreak as a pandemic as of 16 March. From 1 April onwards, the registry stratified patients into the following groups; ongoing COVID-19 infection, no COVID-19 infection, unknown status/not assessed. The subgroup consisting of patients classified as having an ongoing infection constituted approximately 5% and 11% of OHCA and IHCA respectively. Patients stratified within this group had either confirmed COVID-19, suspected COVID-19 infection, or had recently suffered from the infection.

Outcome measures

Overall mortality was analysed using Cox regression. Adjustments were made for the variables, i.e. age, sex and initial rhythm.

30-day mortality and ROSC

Since the observation time was until 20 July, not all cases were observed for the primary endpoint of 30-day survival. This accounted for 5.3% of OHCA and 1.8% of IHCA cases. The calculations were based on logistic regression, with the same variable adjustments as the Cox regression, see section above. Logistic regression was also used to obtain odds ratio (OR) for return of spontaneous circulation (ROSC) with the same procedure for adjustments.

3.3 STUDY II

Patients were enrolled from 1 January 1990 to 22 August 2020. All cases of OHCA, no matter the age, where CPR had been attempted were included. For IHCA, reporting to the registry has varied over time, where cases of IHCA younger than 17 years were not reported before 2018.

Outcome measures

The main endpoint was 30-day survival. Time delays, interventions, and bystander CPR were measured as secondary outcomes.

Statistical analysis

Logistic regression, adjusted for covariates, age and sex, was used to calculate OR for 30-day survival. ORs for both OHCA and IHCA were calculated, with pooling of the first four calendar years since start of inclusion as reference.

3.4 STUDY III

Patients were enrolled from 1 January 2010 to 11 June 2020. Initially, a total of 54,956 OHCA cases were assessed, of which 54,568 were first-time events of cardiac arrest. Recurring cardiac arrests were excluded. Subsequently, all cases with available information on implantable cardioverter-defibrillator (ICD) status, and victims discharged alive, only with cardiac aetiology or initial shockable rhythm were included. The final study population comprised 3,005 individuals.

Outcome measures

The primary outcomes included all-cause mortality and cardiac arrest, in- or out-of hospital.

Variable selection and feature selection

In order to estimate propensity scores for covariates, we initially included all available variables from the SCRR and merged registries. These variables included patient phenotype, initial rhythm, socioeconomic status, comorbidities, medications, prehospital and in-hospital management. After data pre-processing and pruning, the final dataset contained 438 candidate variables of ICD implantation. Feature selection was conducted by machine learning models, random forest (RF) and gradient boosting machine (GBM), identifying the 50 most important variables for ICD implantation. Propensity scores and corresponding weights were generated by various machine learning models as well as deep learning models, including neural networks.

The weights were then used in a Cox proportional hazards-based model to calculate the primary endpoint.

3.5 STUDY IV

Patients were enrolled from 2010 to 2020, accounting for a total of 55,615 cases of OHCA.

Outcome measures

The primary outcome was 30-day survival after OHCA.

Statistical analysis

We compared logistic regression to various machine learning models, as well as one deep learning model. We found that the best performing models were the Extreme Gradient Boosting Machine (XGB) and the Light Gradient Boosting Machine (LightGBM). After hyperparameter tuning, data was split into two subsets for training and validation. A total of 384 covariates were included in the models, where the top 40 predictors by feature importance was extracted for further modelling. Two different approaches for XGB and LightGBM were used; the weighted F1 score and the Precision-Recall Area Under the Curve (PR AUC). The best model for each strategy was then retrained on the full dataset and tested on unseen data. To assess performance of the full model, the Receiver Operating Characteristic Area Under the Curve (ROC AUC) and calibration curves were chosen. Evaluation of the feature importance of the full model was also measured, enabling the

contribution of each predictor. The top 10 predictors were selected for inclusion for the final model. Isolating the top 10 predictors, ROC AUC was calculated after isotonic and sigmoid calibration.

4 RESULTS

4.1 STUDY I

Characteristics and survival of OHCA cases

Regarding OHCA, 930 cases were reported before the pandemic, and 1,016 cases during the pandemic, of which 422 had data on COVID-19 status. Comparing COVID-19 positive cases to COVID-19 negative cases, 87.5% of COVID-19 positive cases suffered cardiac arrest at home, compared to 76.9% of COVID-19 negative cases. Shockable rhythm (VT/VF) were equally common during the two periods, however, COVID-19 positive cases displayed a shockable rhythm in 7.5% of cases compared to 22.8% among cases without COVID-19. Additionally, bystanders provided compression-only CPR more frequently during the pandemic period (74.8% vs. 66.2%), leading to a reduction in cases receiving both chest compressions and ventilation (23.2% vs. 33.3%), refer to Table 3 and Table 3 continued.

Table 3. Baseline table for out-of-hospital cardiac arrest, before and during the COVID-19 pandemic

	Period			During pandemic ^a			SMD
	Pre-pandemic	Pandemic	SMD	No infection	Ongoing infection	Unknown/NA	
n	930	1016		334	88	455	
Age, mean (SD)	70.8 (16.6)	69.6 (17.8)	0.071	70.6 (16.4)	66.5 (18.4)	70.0 (17.6)	0.130
Female sex, n (%)	326 (35.1)	319 (32.6)	0.055	93 (28.4)	29 (33.3)	146 (33.6)	0.073
Location of cardiac arrest, n (%)			0.021				0.249
Home	710 (76.3)	784 (77.2)		257 (76.9)	77 (87.5)	337 (74.1)	
Public place	129 (13.9)	138 (13.6)		35 (10.5)	5 (5.7)	82 (18.0)	
Other place	91 (9.8)	94 (9.3)		42 (12.6)	6 (6.8)	36 (7.9)	
Time to EMS arrival, min, median (IQR)	12.00 (7.00–19.00)	12.00 (7.00–20.00)	0.030	12.00 (7.00–21.00)	11.00 (6.00–19.00)	12.00 (7.00–19.00)	0.065
Time to CPR, min, median (IQR)	2.00 (0.00–8.00)	2.00 (0.00–9.00)	0.004	2.00 (0.00–9.00)	4.00 (0.00–10.00)	2.00 (0.00–9.00)	0.103
Time to defibrillation, min, median (IQR)	13.00 (8.00–20.00)	14.00 (9.00–24.00)	0.087	14.00 (8.00–23.00)	15.00 (10.50–25.00)	15.00 (10.00–24.00)	0.105
Aetiology, n (%)			0.337				0.433
Medical condition	785 (90.8)	640 (80.2)		230 (81.3)	50 (73.5)	271 (81.1)	
Trauma	19 (2.2)	26 (3.3)		7 (2.5)	1 (1.5)	15 (4.5)	
Intoxication	26 (3.0)	34 (4.3)		10 (3.5)	0 (0.0)	18 (5.4)	
Drowning	1 (0.1)	12 (1.5)		3 (1.1)	0 (0.0)	4 (1.2)	
Electrical accident	0 (0.0)	2 (0.3)		1 (0.4)	0 (0.0)	1 (0.3)	
Asphyxia	34 (3.9)	84 (10.5)		32 (11.3)	17 (25.0)	25 (7.5)	
Witnessed arrest, n (%)	534 (57.5)	571 (57.6)	0.002	203 (61.5)	53 (63.1)	243 (55.1)	0.095
Bystander witnessed, n (%)	453 (85.8)	454 (94.0)	0.275	158 (95.8)	37 (94.9)	201 (83.1)	0.189
Bystander defibrillated, n (%)	13 (22.0)	12 (32.4)	0.235	4 (28.6)	0 (0.0)	8 (42.1)	0.622
Initial rhythm, n (%)			0.017				0.232
Ventricular fibrillation/pulseless ventricular tachycardia	168 (20.6)	170 (20.2)		63 (22.8)	6 (7.5)	80 (21.6)	
Pulseless electrical activity	139 (17.0)	148 (17.6)		49 (17.8)	19 (23.8)	62 (16.8)	
Asystole	510 (62.4)	522 (62.1)		164 (59.4)	55 (68.8)	228 (61.6)	
Bystander CPR, n (%)			0.256				0.282
No	2 (0.4)	10 (1.7)		3 (1.6)	3 (5.9)	3 (1.1)	
Chest compressions	354 (66.2)	439 (74.8)		142 (74.3)	40 (78.4)	200 (75.8)	
Ventilation	1 (0.2)	2 (0.3)		1 (0.5)	0 (0.0)	1 (0.4)	
Compressions/ventilation	178 (33.3)	136 (23.2)		45 (23.6)	8 (15.7)	60 (22.7)	
Defibrillated, n (%)	260 (28.2)	275 (30.2)	0.044	102 (33.6)	16 (21.3)	124 (30.2)	0.146
Adrenaline given, n (%)	683 (73.5)	770 (80.0)	0.153	257 (80.3)	71 (85.5)	344 (80.0)	0.152

Continued

Table 3. Characteristics of patients in out-of-hospital cardiac arrest, inclusion period from 1 January to 20 July. COVID-19 status was stratified from 1 April and onwards.

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OR with respect to 30-day mortality for COVID-19 positive patients during the pandemic was 3.40 (95% CI 1.31-11.64), as compared to patients without the infection. OR for men was 5.75 (95% CI 1.65-36.44), and 1.15 (95% CI, 0.26-8.12) for women. Additionally, our findings revealed that the rate of patients being discharged alive declined from 38.9% during the pre-pandemic period to 33.0% during the pandemic period. During the period of this study, no patient suffering an OHCA with concomitant COVID-19 infection was discharged alive, and only a small percentage of 4.5% apparently survived at 30 days, refer to Table 3, continued.

Table 3. Baseline table, continued

	Period			During pandemic ^a			SMD
	Pre-pandemic	Pandemic	SMD	No infection	Ongoing infection	Unknown/NA	
Amiodarone given, n (%)	94 (10.2)	110 (13.1)	0.089	42 (15.1)	3 (4.2)	53 (13.9)	0.207
Active temperature control, n (%)	31 (34.4)	11 (26.2)	0.180	3 (14.3)	2 (33.3)	1 (25.0)	0.272
Coronary angiography, n (%)	44 (38.9)	13 (25.0)	0.302	9 (36.0)	1 (16.7)	0 (0.0)	0.641
Follow-up							
ROSC, n (%)	310 (33.4)	297 (30.3)	0.067	106 (32.3)	22 (25.9)	126 (29.1)	0.094
Treatment completed before hospital arrival, n (%)			1.097				0.612
No	469 (50.4)	508 (50.2)		180 (54.1)	42 (48.3)	217 (47.8)	
Yes	51 (5.5)	398 (39.3)		120 (36.0)	37 (42.5)	186 (41.0)	
Unknown	410 (44.1)	106 (10.5)		33 (9.9)	8 (9.2)	51 (11.2)	
Discharged alive, n (%)	65 (38.9)	17 (33.3)	0.117	9 (36.0)	0 (0.0)	1 (16.7)	0.641
Death within 30 days, n (%)	833 (89.6)	905 (89.1)	0.016	291 (87.1)	84 (95.5)	408 (89.7)	0.151
Death, overall, n (%)	838 (90.1)	908 (89.4)	0.024	293 (87.7)	84 (95.5)	408 (89.7)	0.144

Table 3, continued. Characteristics of patients in out-of-hospital cardiac arrest, inclusion period from 1 January to 20 July. COVID-19 status was stratified from 1 April and onwards.

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Characteristics and survival of IHCA cases

The pre-pandemic period constituted 532 individuals, and the pandemic period 548, of which 357 had data regarding COVID-19 status. Cardiac arrest cases during the pandemic period were approximately two years younger than the pre-pandemic group, 70.1 and 67.8 years respectively. The number of patients suffering a cardiac arrest in the ED increased from 10.2% to 16.2%. Respiratory insufficiency increased more than three-fold for patients with an ongoing infection. Subsequently, the proportion of myocardial infarction (MI) decreased from 33.9% to 23.9% between the two periods. The proportion of patients with comorbidities, such as previous MI, heart failure and stroke decreased in IHCA cases during the pandemic period; on the other hand, diabetes was more common among COVID-19 subjects (40.7% vs 26.9%). Another interesting finding was that witnessed arrests were less common among COVID-19 cases (76.4% vs 83.7%), as well as the monitoring of patients with ECG. Patients presenting with a shockable rhythm was lower for patients infected with COVID-19 as opposed to patients with no infection, 18.5% and 26.4% respectively, refer to Table 4 and Table 4, continued.

Table 4. Baseline table for in-hospital cardiac arrest, before and during the COVID-19 pandemic

	Period			During pandemic ^a			SMD
	Pre-pandemic	Pandemic	SMD	No infection	Ongoing infection	Unknown/NA	
n	930	1016		334	88	455	
Age, mean (SD)	70.8 (16.6)	69.6 (17.8)	0.071	70.6 (16.4)	66.5 (18.4)	70.0 (17.6)	0.130
Female:sex, n (%)	326 (35.1)	319 (32.6)	0.055	93 (28.4)	29 (33.3)	146 (33.6)	0.073
Location of cardiac arrest, n (%)			0.021				0.249
Home	710 (76.3)	784 (77.2)		257 (76.9)	77 (87.5)	337 (74.1)	
Public place	129 (13.9)	138 (13.6)		35 (10.5)	5 (5.7)	82 (18.0)	
Other place	91 (9.8)	94 (9.3)		42 (12.6)	6 (6.8)	36 (7.9)	
Time to EMS arrival, min, median (IQR)	12.00 (7.00–19.00)	12.00 (7.00–20.00)	0.030	12.00 (7.00–21.00)	11.00 (6.00–19.00)	12.00 (7.00–19.00)	0.065
Time to CPR, min, median (IQR)	2.00 (0.00–8.00)	2.00 (0.00–9.00)	0.004	2.00 (0.00–9.00)	4.00 (0.00–10.00)	2.00 (0.00–9.00)	0.103
Time to defibrillation, min, median (IQR)	13.00 (8.00–20.00)	14.00 (9.00–24.00)	0.067	14.00 (9.00–23.00)	15.00 (10.50–25.00)	15.00 (10.00–24.00)	0.105
Aetiology, n (%)			0.337				0.433
Medical condition	785 (80.8)	640 (80.2)		230 (81.3)	50 (73.5)	271 (81.1)	
Trauma	19 (2.2)	26 (3.3)		7 (2.5)	1 (1.5)	15 (4.5)	
Intoxication	26 (3.0)	34 (4.3)		10 (3.5)	0 (0.0)	18 (5.4)	
Drowning	1 (0.1)	12 (1.5)		3 (1.1)	0 (0.0)	4 (1.2)	
Electrical accident	0 (0.0)	2 (0.3)		1 (0.4)	0 (0.0)	0 (0.0)	
Asphyxia	34 (3.9)	84 (10.5)		32 (11.3)	17 (25.0)	25 (7.5)	
Witnessed arrest, n (%)	534 (57.5)	571 (57.6)	0.002	203 (61.5)	53 (63.1)	243 (55.1)	0.095
Bystander witnessed, n (%)	453 (85.8)	454 (84.0)	0.275	158 (95.8)	37 (94.9)	201 (83.1)	0.189
Bystander defibrillated, n (%)	13 (22.0)	12 (32.4)	0.235	4 (28.6)	0 (0.0)	8 (42.1)	0.622
Initial rhythm, n (%)			0.017				0.232
Ventricular fibrillation/pulseless ventricular tachycardia	168 (20.6)	170 (20.2)		63 (22.8)	6 (7.5)	80 (21.6)	
Pulseless electrical activity	139 (17.0)	148 (17.6)		49 (17.8)	19 (23.8)	62 (16.8)	
Asystole	510 (62.4)	522 (62.1)		164 (59.4)	55 (68.8)	228 (61.6)	
Bystander CPR, n (%)			0.256				0.282
No	2 (0.4)	10 (1.7)		3 (1.6)	3 (5.9)	3 (1.1)	
Chest compressions	354 (66.2)	439 (74.8)		142 (74.3)	40 (78.4)	200 (75.8)	
Ventilation	1 (0.2)	2 (0.3)		1 (0.5)	0 (0.0)	1 (0.4)	
Compressions+ventilation	178 (33.3)	136 (23.2)		45 (23.6)	8 (15.7)	60 (22.7)	
Defibrillated, n (%)	260 (28.2)	275 (30.2)	0.044	102 (33.6)	16 (21.3)	124 (30.2)	0.146
Adrenaline given, n (%)	683 (73.5)	770 (80.0)	0.153	257 (80.3)	71 (85.5)	344 (80.0)	0.152

Continued

Table 4. Characteristics of patients in in-hospital cardiac arrest, inclusion period from 1 January to 20 July. COVID-19 status was stratified from 1 April and onwards.

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Table 4. Baseline table, continued

Variable	Period			During pandemic ^a			
	Pre-pandemic	Pandemic	SMD	No infection	Ongoing infection	Unknown/NA	SMD
Suicide attempt	1 (0.3)	1 (0.6)		1 (1.1)	0 (0.0)	0 (0.0)	
Cancer	5 (1.5)	3 (1.7)		1 (1.1)	0 (0.0)	1 (10.0)	
Technical system failure	0 (0.0)	1 (0.6)		1 (1.1)	0 (0.0)	0 (0.0)	
Dehydration	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
COPD, asthma	5 (1.5)	2 (1.1)		1 (1.1)	0 (0.0)	0 (0.0)	
Primary arrhythmia	59 (18.0)	16 (8.9)		13 (13.8)	1 (4.0)	0 (0.0)	
Cardiomyopathy	3 (0.9)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Arrhythmia post-cardiac surgery	1 (0.3)	2 (1.1)		1 (1.1)	0 (0.0)	0 (0.0)	
Aspiration	3 (0.9)	4 (2.2)		0 (0.0)	0 (0.0)	0 (0.0)	
Respiratory insufficiency	38 (11.6)	37 (20.6)		15 (16.0)	9 (36.0)	3 (30.0)	
MI, ischaemia	111 (33.9)	43 (23.9)		24 (25.5)	1 (4.0)	5 (50.0)	
Other thrombo-embolism	10 (3.1)	7 (3.9)		3 (3.2)	1 (4.0)	0 (0.0)	
Aortic dissection/rupture	6 (1.8)	11 (6.1)		6 (6.4)	2 (8.0)	0 (0.0)	
Cardiac tamponade	4 (1.2)	2 (1.1)		2 (2.1)	0 (0.0)	0 (0.0)	
Other	45 (13.8)	25 (13.9)		13 (13.8)	4 (16.0)	1 (10.0)	
Stroke	1 (0.3)	3 (1.7)		3 (3.2)	0 (0.0)	0 (0.0)	
Witnessed arrest, n (%)	440 (82.9)	445 (82.6)	0.008	236 (83.7)	55 (76.4)	76 (89.4)	0.179
ECG monitored, n (%)	310 (58.9)	307 (57.4)	0.031	177 (62.8)	36 (50.7)	44 (53.0)	0.142
CPR before arrival of alarm group, n (%)	415 (90.2)	416 (91.8)	0.057	218 (91.6)	55 (93.2)	64 (90.1)	0.064
Defibrillated before arrival of alarm group, n (%)	90 (20.6)	72 (16.4)	0.109	43 (18.6)	5 (8.5)	16 (23.5)	0.218
Shockable rhythm, n (%)	138 (28.0)	116 (23.8)	0.096	68 (26.4)	12 (18.5)	20 (25.3)	0.117
Defibrillated, n (%)	181 (35.1)	152 (29.7)	0.115	86 (31.5)	15 (22.4)	26 (33.3)	0.148
Intubated, n (%)	271 (52.8)	239 (47.6)	0.104	113 (42.0)	35 (52.2)	42 (55.3)	0.135
Ventilated, n (%)	318 (81.7)	250 (62.3)	0.443	140 (66.7)	20 (37.0)	35 (56.5)	0.528
Adrenaline given, n (%)	327 (63.2)	336 (65.6)	0.050	176 (64.2)	49 (73.1)	49 (63.6)	0.109
Antiarrhythmics given, n (%)	74 (15.0)	59 (12.1)	0.085	34 (12.9)	6 (9.2)	10 (14.1)	0.094
Mechanical compressions, n (%)	67 (13.1)	62 (12.4)	0.022	33 (12.2)	6 (8.8)	10 (13.7)	0.082
Temperature control, n (%)	17 (7.2)	5 (5.0)	0.093	3 (5.6)	0 (0.0)	0 (0.0)	0.257
Coronary angiography, n (%)	62 (26.1)	27 (27.3)	0.028	16 (30.2)	1 (11.1)	2 (22.2)	0.257
Follow-up							
ROSC, n (%)	251 (47.2)	257 (46.9)	0.006	150 (52.6)	22 (30.6)	40 (44.9)	0.236
30-day mortality, n (%)	318 (59.8)	334 (60.9)	0.024	166 (58.2)	54 (75.0)	46 (51.7)	0.253
Overall mortality, n (%)	340 (63.9)	340 (62.0)	0.039	169 (59.3)	54 (75.0)	46 (51.7)	0.263

Table 4, continued. Characteristics of patients in in-hospital cardiac arrest, inclusion period from 1 January to 20 July. COVID-19 status was stratified from 1 April and onwards.

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30-day mortality for IHCA in patients with COVID-19 infection showed an increase in OR of 2.27 (95% CI 1.27-4.24) overall, 1.63 (95% CI 0.84-3.28) for men and 7.63 (95% CI 1.97-50.93). The same trend was observed for IHCA cases with COVID-19 compared to the pre-pandemic group, exhibiting an OR 2.34 (95% CI 1.33-4.29) overall.

4.2 STUDY II

For the period between 1990-2000, survival rates of OHCA for both men and women were approximately 5%. From 2000 to 2011, survival rates increased steadily, but have remained unchanged in the last decade (2011 to 2020), accompanied with a significant difference between the sexes. In the final four years, survival for men and women was approximately 12% and 8% respectively. OR for 30-day survival during the years 2017–2020, compared to 1990–1993, was 2.17 (95% CI 1.93-2.43) overall; 2.36 (95% CI 2.07-2.71) for men and 1.67 (95% CI 1.34-2.10) for women: refer to Figure 2.

Figure 2. Trends in 30-day mortality in out-of-hospital cardiac arrest

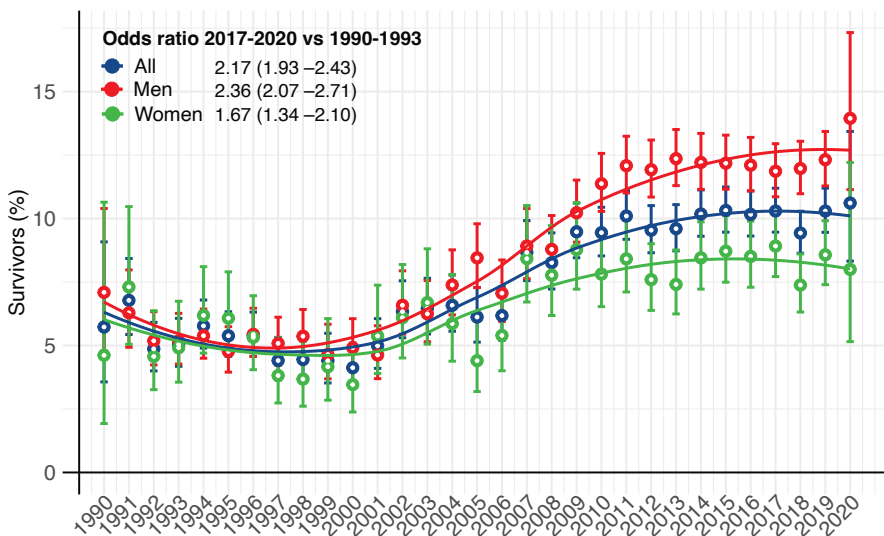


Figure 2. 30-day mortality in out-of-hospital cardiac arrest. The y-axis depicts survival in percentage (%), the x-axis, and the year.

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The rate of return of spontaneous circulation (ROSC) increased from 31.2% in 2009-2012 to 36.9% in 2017-2020. Survival rates for patients aged 0–39 years increased from 9.1% in 1990 to 17.5% in 2020 (OR for survival was 4.05 from 2017-2020 vs 1990-1993). The highest survival rate was found in patients aged 40–49 years, with survival increasing from 9.8% in 1990 to 18.9% in 2020 (OR for survival was 2.77, 2017-2020 vs 1990-1993). Survival also increased among patients aged 50–59 and 80–89 years, but not significantly for patients 90 years or older. Survival for patients presenting with a shockable rhythm increased from 14.4% in 1990 to 35.8% in 2020 overall, 15.4% in 1990 to 38.2% in 2020 for men, and 13.4% in 1990 to 33.5% in 2020 for women. OR for 30-day survival was 3.26 from 2017-2020 vs 1990-1993 (95% CI 2.81-3.79) overall, 3.46 (95% CI 2.92-4.11) for men, and 2.65 (95% CI 1.95-3.63) for women. These improvements were similar for patients with non-shockable rhythms. Among patients discharged alive after OHCA, the percentage with CPC score 1 decreased from 81.2% in 2008 to 68.3% in 2015 and then increased to 79.5% in 2020. Survival for patients with cardiac aetiology increased from 6.9% in 1990 to 14.7% in 2020 (OR was 2.39 from 2017-2020 vs 1990-1993). The proportion of cardiac arrests due to presumed cardiac aetiology decreased from 80.5% to 58.7%. This trend was similar in both genders.

Bystander cardiopulmonary resuscitation

The rate of bystander cardiopulmonary resuscitation (CPR) increased from 30.9% to 82.2% between 1990-2020. This corresponds to an overall OR of 4.80 (95% CI, 4.49–5.13). OR for witnessed arrests was 2.96 (95% CI 2.73–3.21) and 10.79 (95% CI 9.54–12.22) for non-witnessed arrests. Additionally, the gap between witnessed and non-witnessed cases has decreased over time.

Critical time delays

From 2005-2020, the median time from collapse to emergency call and dispatch to ambulance arrival remained largely unchanged. However, the median time from collapse to CPR decreased dramatically from approximately 12 minutes in 1990 to just 2 minutes in the final decade. Moreover, the median time from collapse to defibrillation has not changed significantly. However, the median time from ambulance dispatch to arrival have increased from 6 (95% CI 4.0-10.0) to 11 (95% CI 7.0-19.0) minutes, comparing 1990 to 2020, refer to Figure 3.

Figure 3. Trends in critical time delays

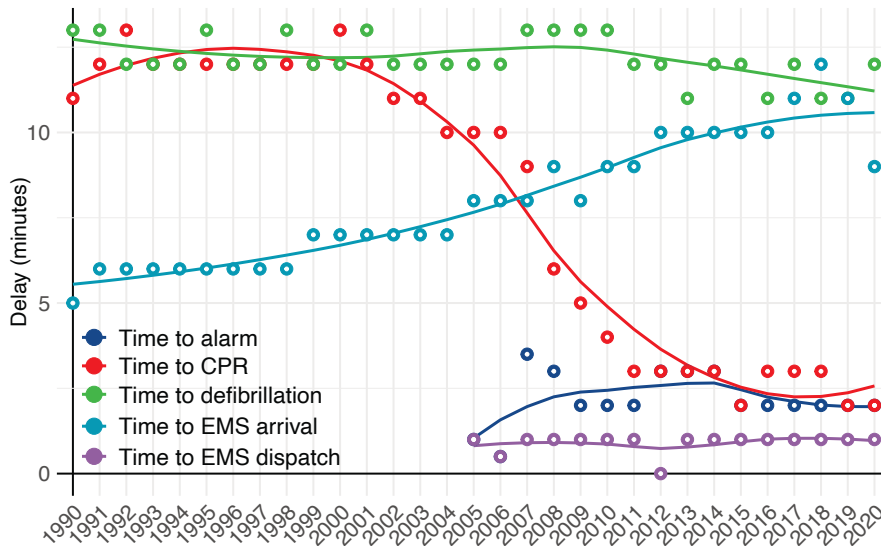


Figure 3. Trends in critical time delays; blue dotted line = time to alarm, red dotted line = time to CPR, green dotted line = time to defibrillation, turquoise dotted line = time to EMS arrival, purple dotted line = time to EMS dispatch. The Y-axis shows delays in minutes; the x-axis year.

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Trends in characteristics and outcomes in, in-hospital cardiac arrests

It was difficult to determine trends from 2004 to 2008 due to wide CIs. However, from 2008 to 2020, survival rates increased from 25.5% to 35.6%. OR for survival between 2017-2020 vs 2004-2007 was 1.18 (95% CI 1.06-1.31) overall, 1.22 (95% CI 1.07-1.39) for men and 1.12 (95% CI 0.95-1.33) for women. In the last decade (2011-2020), the chance of survival increased by an average of 3.9% annually (95% CI

2.8-5.0%), resulting in a an increase of 46.6%. About half of the patients under 60 years of age survived during this period. In terms of initial cardiac rhythm, OR for 30-day survival between 2017–2020 and 2004–2007 was 1.41 (95% CI 1.18-1.70) given a shockable rhythm, with survival rates increasing from 55.8% in 2008 to 61.6% in 2020. Survival among patients with a non-shockable rhythm were also seen to increase, from 14.2% in 2008 to 24.6% in 2020 (OR 1.41, 95% CI 1.20-1.66).

4.3 STUDY III

A total of 3,005 OHCA cases with cardiac aetiology were enrolled in the study, with 959 patients receiving an implantable cardioverter-defibrillator (ICD), whereas 2046 did not. In the cohort studied, patients that received an ICD were generally younger, predominantly males, and had a higher burden of comorbidities, such as ischaemic heart disease, dyslipidaemia, atrial fibrillation, heart failure, myocardial infarction and diabetes. Bystander-CPR was performed in 78.6% of patients discharged with an ICD, compared to 54.4% in those without. Additionally, patients defibrillated in OHCA received an ICD more frequently, 91.1% and 85.8% respectively. Upon ambulance arrival, an initial shockable rhythm was observed in 96.2% in the ICD group, compared to 92.6% in the group without. Percutaneous coronary intervention (PCI) was more frequently performed in patients who did not receive an ICD, 74%, compared to 38.9% with an ICD.

Survival

During the period studied, a total of 320 deaths were reported, constituting 138 recurrent OHCA and 70 IHCA after hospital discharge. The most striking survival trend was noted for cases not receiving a device, where the majority of deaths occurred within 90 days, refer to Kaplan Meier plot, Figure 4. The most pronounced decline in survival for the endpoints, however, was seen within 30 days of discharge from hospital.

Figure 4. Kaplan-Meier plots for ICD vs no ICD

Kaplan-Meier plots with landmarks at 90 days

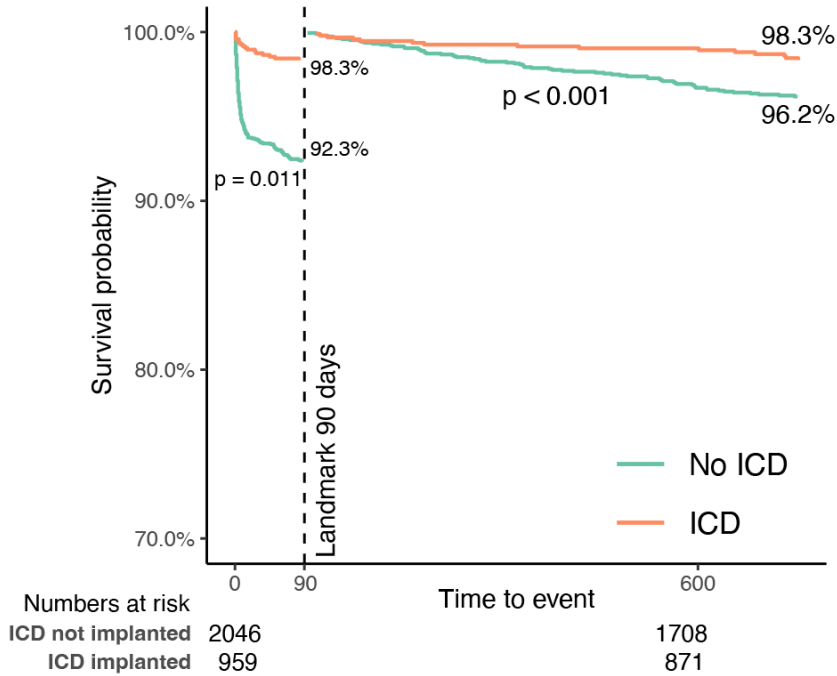


Figure 4. Kaplan-Meier plots for patients with and without an ICD at discharge, red and green line, respectively. The y-axis shows survival probability in percentage (%) and the x-axis time point.

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Propensity score-related outcome

After calculating propensity scores and subsequently estimating average treatment effect (ATE) and average treatment effect on those treated (ATT), the top predictors were identified for analysis with Cox regression, refer to Figure 5. All point estimates for ATE and ATT favoured ICD implantation, with the overwhelming majority of subgroup analysis being statistically significant. However, exceptions were observed for ATE scores in women, type 1 diabetes, obesity; PCI or CABG performed. With regard to ATT, exceptions were noted in patients with type 1 diabetes, obesity, acute heart failure; PCI or CABG performed.

Figure 5. Treatment effects in OHCA, with and without an implantable cardioverter defibrillator.

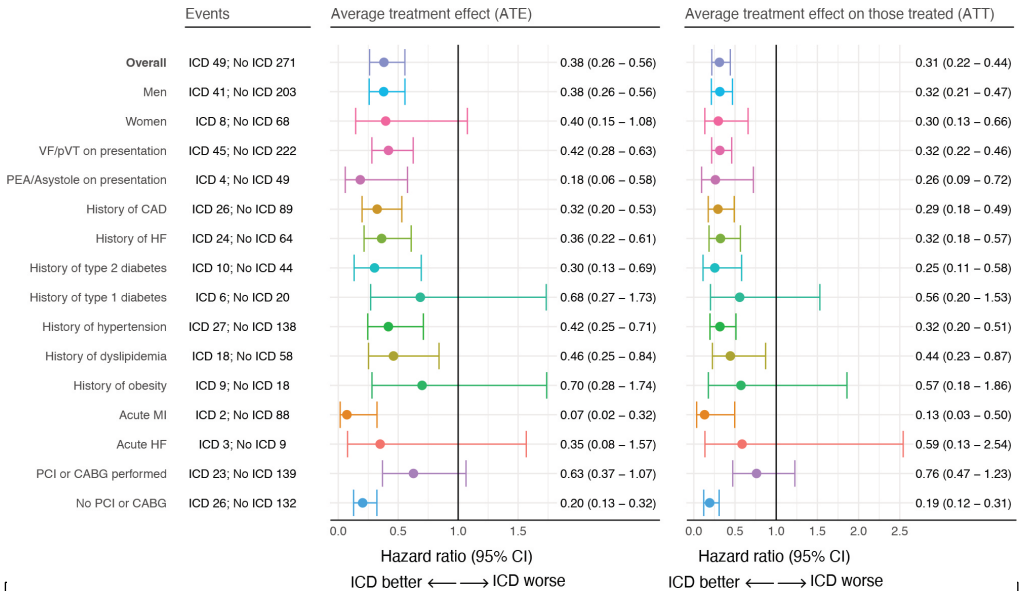


Figure 5. Average treatment effect (ATE) and average treatment effect on those treated (ATT), left and right column, respectively.

For most variables, both ATE and ATT showed that an ICD was beneficial for the composite of death or recurrent cardiac arrest.

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4.4 STUDY IV

A total of 55,615 patients suffering OHCA were included for predicting 30-day survival. The mean age for all participants was 69 years, and 66% were males. Cardiac arrest took place at home in 71.6% and in public places in 16.2% of the cases. The time to ambulance arrival was on average 13 minutes (IQ-range Q1-Q3, 8,0-20,0) and 9 minutes for patients that survived 9 minutes (IQ-range Q1-Q3, 6,0-15,0). The time from cardiac arrest to defibrillation was in general 15 minutes (IQ-range Q1-Q3, 8,0-24,0), and for those that survived eight minutes (IQ-range Q1-Q3, 2,0-13,0). More than a two-fold increase in defibrillation was seen in cases that survived as opposed to those that did not, 66.4% and 29.1% respectively. ROSC upon hospital arrival was seen in 94.8% in survivors, compared to 33.5%.

After exploring and testing various machine learning as well as one deep learning model, we concluded that LightGBM and XGB excelled in prognostication of survival in OHCA by reference to all other models. Consequently, we proceeded with further model development for these two machine learning models.

After feature selection, the top 40 predictors were extracted. LightGBM proved to put emphasis on more variables, in contrast to XGB, refer to Figure 6.

Figure 6. Feature importance, LightGBM vs XGBoost



Figure 6. Feature importance for LightGBM and XGBoost. The left panel shows LightGBM and the right XGBoost. For the XGBoost model, more emphasis was placed on the top 5 predictors, as opposed to the LightGBM model.

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The AUC ROC scores were excellent for both models, optimised via weighted F1 score (as well as PR AUC), refer to Figure 7 and Figure 8. The XGB model was slightly overestimating survival, especially noticeable in the lowest ranges of survival probability. Another suitable trait, given the task at hand, was the fact that the model reached great performance with only a few predictors, refer to Figure 7.

Figure 7. XGboost optimised for weighted F1

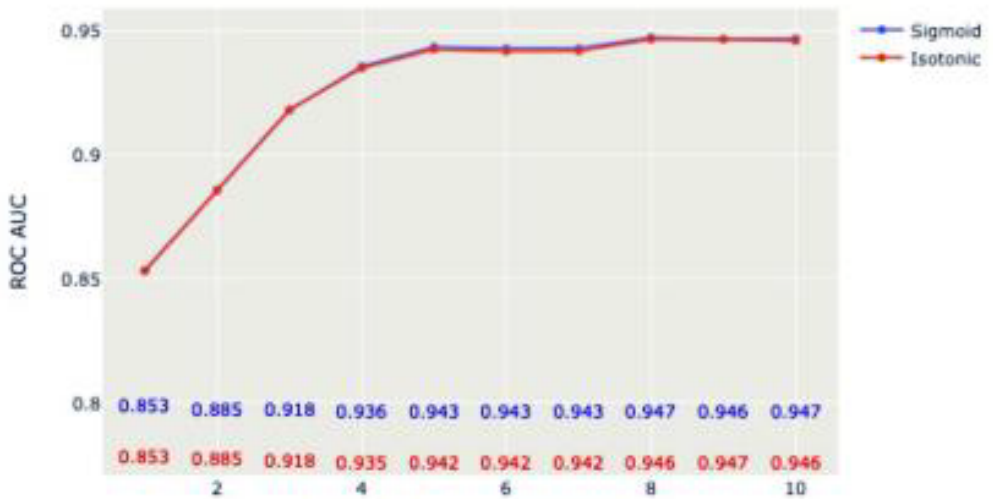


Figure 7. XGBoost, optimised via weighted F1. The y-axis shows the Receiver Operating Curve Area Under the Curve (ROC AUC). The x-axis shows the number of features used, from 1-10.

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Figure 8. LightGBM optimised for weighted F1

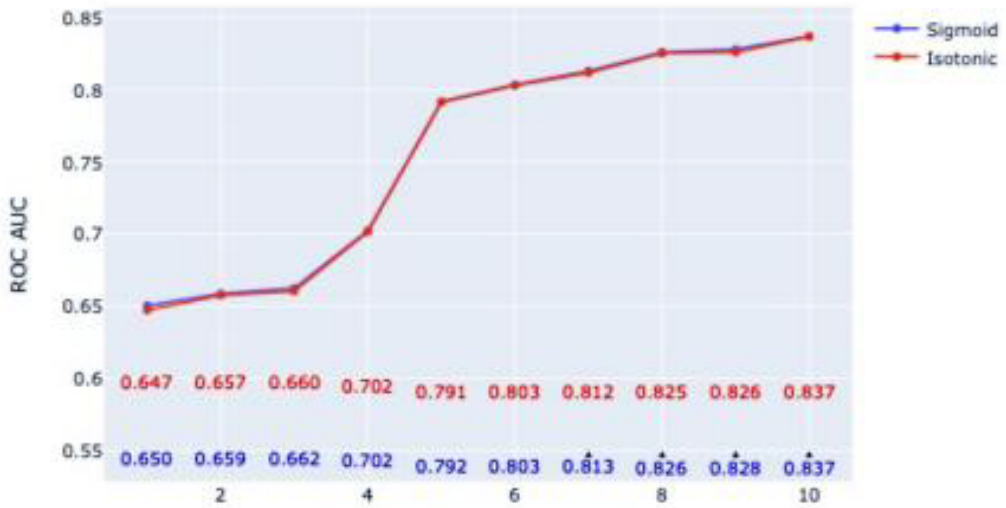


Figure 8. LightGBM optimised via weighted F1 score. The y-axis shows the Receiver Operating Curve Area Under the Curve (ROC AUC). The x-axis shows number of features used from 1–10.

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5 DISCUSSION

5.1 STUDY I

The pandemic changed most aspects of life and living for several years, including the characteristics and outcomes of patients with cardiac arrest. Indeed, the first study showed that no patient infected with COVID-19 survived (during the observation period) an out-of-hospital cardiac arrest, which is a testament to the deadly liaison between COVID-19 and cardiac arrest. Since the start of the pandemic, however, many aspects of the infection have changed. COVID-19 vaccines led to less severe infections, and clinicians developed strategies and routines to handle severe COVID-19 infections, which has likely reduced the rate of severe complications, including cardiac arrests.

Our first study demonstrated several interesting findings. We noted a 2.7-fold increase in hypoxia-induced cardiac arrests and a parallel decrease in shockable rhythms for COVID-19 positive cases. Asphyxia was observed in 25% of cases with COVID-19, as opposed to 11.3% without infection. Although an increase in hypoxia-related cardiac arrests would be expected, given the nature of the infection, we did not expect the dramatic increase confirmed in our study. These cases are, as opposed to cardiac arrests due to myocardial ischemia/infarction, heart failure, etc., generally not shockable, rendering conventional resuscitation much less effective. Indeed, during the pandemic, the Swedish Resuscitation Council recommended laymen, as well as

healthcare professionals, to refrain from mouth-to-mouth inspirations in COVID-19 suspected cases (i.e. perform chest compression only [CCO] CPR), which may be especially harmful, due to the increase in respiratory insufficiency causing the cardiac arrest. We observed a notable decline in the administration of CPR utilising chest compressions and ventilation among OHCA patients from the pre-pandemic to the pandemic period, with rates falling from 33.3% to 23.2%. When isolating cases during the pandemic, patients actively infected with COVID-19 were less likely to receive chest compressions and ventilation CPR, with only 15.7% undergoing this procedure, as opposed to 23.6% of patients not infected with the virus. This clearly suggests a shift in the emergency response protocols and the application of CPR techniques during the pandemic, with notable shifts for COVID-19 positive patients.

The finding that 5.7% of patients who tested positive for COVID-19 experienced cardiac arrest in public spaces, suggests that a few individuals with (presumably) severe infections were engaging in activities in public places, which was not allowed in several other countries. This decision was made by Swedish Public Health Authority (SPHA), which recommended against a lockdown during the pandemic. For OHCA cases with COVID-19, this may have been beneficial since it is well known that cardiac arrests occurring in public places have significantly higher likelihood of survival.

A meta-analysis comprising 67,815 patients in 20 studies from Australia, France, Italy, Korea, Singapore Spain, the Netherlands, United Kingdom and the United States showed similar trends in characteristics and outcomes during the COVID-19 pandemic as Study I, further corroborating the associations observed in Sweden. The meta-analysis reported ORs during the pandemic period, compared to the pre-pandemic period, of 1.95 (95% CI 1.51-2.51) for mortality, 0.65 (95% CI 0.55-0.77) for ROSC, 0.52 (95% CI 0.40-0.69) for survival to discharge, 0.73 (95% CI 0.6-0.88) for shockable rhythm, and 1.17 (95% CI 1.02-1.33) for respiratory insufficiency.¹³² We conclude that there was a shift in epidemiology of OHCA in Sweden, and similar findings were reported elsewhere.

The observed trends in in-hospital cardiac arrest (IHCA) aetiology underscores the exacerbated impact of COVID-19, with respiratory aetiologies more than doubling in cases with active COVID-19 infection. The marked increase in 30-day mortality for cardiac arrest patients with a concurrent COVID-19 infection, standing at 75% compared to 58.2% for non-infected cases, emphasises the severity of the infection, translating to an OR of 2.24, for 30-day mortality. This is supported by a meta-analysis reporting diminished rates of ROSC and lower survival rates to hospital discharge among COVID-19 cases.¹³³ These contrasts may be at least partly explained by the fact that COVID-19 cases were less frequently monitored with ECG, indicating potential gaps in care. This discrepancy is concerning, given the unpredictable nature of the severe respiratory distress and systemic

inflammation caused by COVID-19 as well as the lethal combination of cardiac arrest and COVID-19. These patients would require a more rigorous monitoring protocol, which was not the case. This study therefore raises critical questions about the allocation of monitoring resources during the pandemic and suggests that the increased mortality associated with COVID-19 could be influenced by such differences in clinical surveillance.

Another aspect of the COVID-19 pandemic was the lack of readiness. Since authorities issued stay-at-home orders to the public, several reports showed delays in time to evidence-based care for patients with AMI and HF.^{134–136} A shift in prioritising intensive care for COVID-19 cases also affected individuals with chronic conditions.^{77,137} Overcrowded EDs and delayed ambulance lead times may have also had a detrimental effects on patient outcome for other acute conditions.^{137–139}

In this study, we did not have the basis for diagnosis of COVID-19, which presumably may have resulted in some patients being misclassified.¹⁴⁰ We therefore performed a sensitivity analysis, showing that our results were robust. The gold standard for testing COVID-19 is by RT-PCR. The test is able to detect the virus during the incubation phase, but the peak sensitivity is four to five days after clinical manifestation. On the other hand, the antigen test has a sensitivity of 65.3% and a specificity of 99.9%, with the benefit of providing results within 15 minutes.¹⁴¹ Nevertheless, during the period

of this study, the antigen test was presumably unavailable, and RT-PCR was introduced in February 2021, thus COVID-19 status had to be based on clinical status/history/radiology or RT-PCR, depending on the time being. Also, testing was limited during the beginning of the pandemic, being preserved to high-risk individuals and healthcare workers.

During the time of the study, SCRR did not include OHCA data from Stockholm, due to the fact that Stockholm county transfers data only once annually. Stockholm is the largest county in Sweden, with the highest population density and population, and was also hit the hardest during the pandemic.

5.2 STUDY II

During the period of 30 years, including over 100,000 patients suffering from OHCA, we found that survival increased 2.2-fold, with the most pronounced improvements in men and younger individuals. For IHCA cases, including over 30,000 cases, followed for 17 years, survival increased 1.2-fold. The same trends were seen among men and younger individuals. The trend in survival probability have varied between OHCA and IHCA. While the last decade did not show any improvements for OHCA, survival increased in IHCA cases with 47%. A striking decline in the prevalence of CHD as the underlying aetiology was noted for both IHCA and OHCA. This was especially the case for victims of OHCA, where rates of myocardial ischaemia/infarction almost halved during 1990 to 2020. These

findings are in line with trends showing steady and rapid reductions in the rate of acute myocardial infarction in other reports as well. In the US, a relative decline in CHD-related deaths of 26% has been observed between 1965 to 1980, corresponding to a difference in incidence rate ranging from 466/100,000 to 345/100,000. A further decline of 64% was observed between 1980 to 2008, where the incidence in 2008 was 123/100,000.¹⁴² The SWEDEHEART registry has reported similar reductions in the rate of CHD and CHD related deaths since the inception of the registry.¹⁴³ The decrease in CHD-related events is multifactorial, related to both improved primary and secondary care. Management of risk factors such as smoking, treatment of hypertension, dyslipidaemia, improved glycaemic control, evidence-based dietary advice, establishment of coronary care units, improvements in resuscitation practices, procedures and infrastructure for handling urgent percutaneous coronary interventions and coronary artery bypass surgery (CABG), have all contributed.¹⁴⁴ The most important interventions have likely been primary preventive strategies. For example, smoking in the US decreased from 42% in 1965 to 18% in 2012.¹⁴⁵ Cholesterol levels have declined steadily, particularly since the introduction of statins in 1987.¹⁴⁶ While all these changes have been beneficial in terms of reducing the rate of fatal coronary events, they have also reduced the relative proportion of cardiac arrests caused by acute coronary events. Generally, these cases (i.e. OHCA and IHCA caused by acute or chronic coronary events) show a greater probability of successful resuscitation, owing to the high rate of shockable rhythm. The diminishing rate of underlying coronary

aetiology has therefore likely counteracted the overall improvement in survival in OHCA and IHCA, which underscores the substantial improvement that has been made (i.e. remarkable improvements have been made even though the dominating aetiology, which had the highest likelihood of survival, has diminished in prevalence).

The greatest improvement in survival in OHCA was seen from 1999-2011. During this period, several improvements and changes in CPR were introduced, such as dispatch-assisted CPR, extensive training programs for both laymen and healthcare professionals, increased rates of bystander CPR, reduced delays from cardiac arrest to CPR, and increased distribution of automated external defibrillators (AEDs) in society.

In the last decade, however, no further improvements in survival were observed for OHCA. The most notable trends in critical time delays were seen for EMS arrival and time to CPR. Indeed, it can be argued that the single poorest development observed in the SCRR is the increasing ambulance response time, which is quite likely to exert a negative impact on survival. This, along with the reduced incidence of fatal and non-fatal acute coronary events, is the most likely explanation for the reduction in rates of shockable rhythm, which was 40% in 1990–1993, and 21% in 2017–2020. Other studies have also reported increased ambulance response times.^{147,148}

The steady increase in ambulance response time is multifactorial, including reductions in resources to the EMS and increased use of EMS for non-acute medical conditions; approximately 16–51% of

emergency calls are due to non-acute conditions.^{147,149} Fast-track pre-hospital management of patients with STEMI, stroke and hip fractures could also be linked with delays seen in EMS response times. Additionally, the growing population, coupled with a relative shortage of ambulances, intensifies the demand on emergency services. Urban expansion and changes in traffic patterns further complicate ambulance navigation, prolonging response times in increasingly urbanised environments.

Another interesting finding was the notable difference in survival observed between the sexes, with males showing greater crude improvements than women. However, when stratifying on initial rhythm, the differences were not as pronounced. A study recently conducted by Smits et al.,¹⁵⁰ using data from the Amsterdam Resuscitation Studies (ARREST), concluded similar disparities among the sexes, also concluding that the only explanatory difference was a shockable rhythm. Study inclusion was from 2005 to 2017, showing an increase in 30-day survival for men, from 2005 of 20% to 27.2% in 2017. On the contrary, 30-day survival decreased among women, from 15.0% in 2005, to 11.6% in 2017. A sub-analysis, including shockable rhythm as a predictor to the model of 30-day survival, showed diminished differences after accounting for rhythm. Thus, presentation with a shockable rhythm has decreased more markedly in women than in men, over time. This does not, however, explain why there are gender differences in the initial rhythm, and it can be argued that the SCRR lacks important data on this matter. Gender differences in

shockable rhythm are likely to be explained partly by higher rates of coronary events among men. Differences are less likely to be due to differences in bystander CPR and ambulance response times, since these variables tend to differ less.

Regarding IHCA, we found continuous improvements in survival in the last decade, without signs of reaching a plateau. These results were seen despite the fact that patients presenting with shockable rhythms have decreased over time. For IHCA cases, a substantial decrease was seen for patients with ischaemia/myocardial infarction as aetiology. The management, early detection and early revascularisation are presumably important factors for the increase in likelihood of survival as well as a reduced likelihood of suffering from cardiac arrest. From 2000 and onwards, a gradual change from creatine kinase-MB (CK-MB) to high-sensitive cardiac troponin, have helped physicians in detecting myocardial infarctions. The diagnostic measures and the introduction of highly sensitive troponins have certainly exerted a major impact, now making it possible to detect infarctions several orders of magnitude smaller than previously possible.

The significant increase in the number of laymen performing CPR is an astonishing improvement in pre-hospital care in Sweden. Study II demonstrates that the majority of all cases of OHCA now receive life-sustaining care by laymen who are either trained in basic CPR or instructed by the emergency dispatcher. It could be argued that the dramatic increase in bystander CPR is perhaps the single greatest

improvement in pre-hospital care during the past few decades, particularly in the light of the ever-increasing ambulance response times. Hence, what is currently a failure of the healthcare system is being counteracted by public intervention by laymen. These trends should, if anything, alert healthcare providers to reconsider increasing funding to the EMS, as it is hardly acceptable that improvements in care should depend on the willingness of laymen to intervene during occurrence of one of the most critical medical conditions.

It should be noted that the SCRR does not study survival in cardiac arrest, but in cardiac arrest with attempted resuscitation, which is a subgroup of the former. This leads to an overestimation of survival in the overall group of patients suffering from sudden cardiac arrest. However, within the subgroup for whom resuscitation is attempted, there should be little if any selection bias in the SCRR, which has maintained its original inclusion and exclusion criteria.

5.3 STUDY III

In this study, we explored the outcome on survival, should everyone with cardiac aetiology or initial VF be equipped with an ICD prior to hospital discharge after OHCA. Based on previous reports, the benefit of an ICD has been conflicting in many situations, with some exceptions. The use of ICDs has been investigated in three major RCTs, as well as one meta-analysis of the former, these data demonstrated reduced mortality and reduced arrhythmic death,

especially for patients with LVEF <35% and, in particular, those with ischemic aetiology.⁷⁴ Current European guidelines suggest that ICDs may be considered (class IIb indication) in patients with a myocardial infarction resulting in malignant arrhythmia, accompanied with LV (left ventricular) dysfunction or incomplete revascularisation.

Regardless of aetiology, however, ICD implantation is recommended (class I indication), regardless of aetiology, after a cardiac arrest with an initial shockable rhythm/or hemodynamically unstable monomorphic VT for patients with non-dilated cardiomyopathy or hypokinetic non-dilated cardiomyopathy.

Since myocardial infarction is, with regards to its pro-arrhythmic effect, considered a reversible condition according to guidelines, ICD implantation is not advised, unless revascularization could not be performed. S holm et al.⁷⁵ approached this by conducting a study between 2007 and 2011, following 1457 patients and exclusively studying patients with myocardial infarction after OHCA. They found a statistically significant improved long-term survival rate five years after OHCA for those receiving an ICD before hospital discharge. Univariable HR was 0.44 (95% CI 0.23-0.88) and multivariable HR 0.42 (95% CI 0.20-0.86). This challenges the notion that an AMI is a transient and reversible condition, which is also in line with the fact that infarctions cause a myocardial scar, which is considered a potent substrate for ventricular arrhythmias. In clinical practice, LVEF (left ventricular ejection fraction) should be assessed post-AMI and after three to four months of optimal medical therapy (including heart

failure medications as required), for consideration of ICD implantation.

According to our results, the most susceptible period occurred early after discharge from hospital. This period poses a threat to patients' lives, as they are unprotected from ventricular arrhythmias and may incur the greatest risk of experiencing such events during their evaluation period.

Previous reports concludes favourable cost effective outcomes for ICD therapy in selected patients as compared to both optimal medical therapy (OMT) and electrophysiology-guided therapy.^{151,152} The incremental cost effectiveness ratio (ICER) for ICD therapy depends on several variables, including risk factors, especially (1) LVEF dysfunction, (2) Advanced age and (3) High New York Heart Association class,¹⁵³ device and battery longevity, the time frame of follow-up, surgery and surgery-related complications, etc. Regarding risk factors, the effect of clinical outcome and ICER was shown in the CIDS registry to vary from 65,195 USD for patients with ≥ 2 risk factors and 916,659 USD for patients with < 2 risk factors, per life-year gained. LVEF dysfunction is especially complicit for improved ICER, observed in the MADIT, AVID and CIDS trials. The short-term cost of an ICD may be associated with an underestimate in efficacy, mostly due to expensive upfront cost. The SCD-HeFT trial showed an ICER from 209,530 per life-year gained at five years, to less than 50,000 > 14 years.¹⁵⁴ As technological advances continues, so does device and battery longevity, and thus cost effectiveness and ICER. In

our study, we observed a 60% reduced probability of death and recurrent cardiac arrest in patients with an ICD at hospital discharge, proving its clinical efficacy in our study population.

Our results, however, come with a few limitations that could hamper drawing conclusions about causal inference. This study also poses many challenges to the reader, as it attempts to do causal inference on a very sensitive research question using registry data. We believe that although registry data may be an excellent source of real-world evidence, it may also be highly biased due to misclassification, selection bias, non-random missingness, etc. While we did our best to mitigate the effect of various biases by means of complicated machine learning models, we realise that the lack of knowledge about timing of ICD implantation may bias our results significantly. We thus draw attention to the uncertainty as to whether patients received ICDs during the hospitalisation for cardiac arrest or prior to the cardiac arrest. We do know, however, that all cases included in the registry have received proper CPR from bystanders or laymen, meaning that ICDs delivering appropriate shocks for non-hemodynamically significant arrhythmias have not been included in the study. Furthermore, the lack of knowledge about final diagnoses, underlying cardiac aetiologies, LVEF, etc, may also have resulted in bias. An RCT (NCT04576130) aiming to delineate ICD-implantation in patients with CHD, including AMI in OHCA, with LVEF > 35% is underway.¹⁵⁵ The results will add great value to previous findings, including study III.

Nevertheless, in order to mimic an RCT we calculated propensity scores to obtain ATE and ATT, which suggested an overwhelming benefit for ICD implantation prior to discharge from hospital, across most analyses.

For ATE, the estimate was not significant for women, though quite aligned with the point estimate for men, indicating that the non-significance may be due to (in addition to less pronounced effect of the exposure studied), low power when studying women (who constituted 23.7% of the overall cohort). Indeed, dozens of subgroup analyses were performed and all displayed quite similar point estimates and CIs, with only a few being non-significant. Overall, this study suggests that survivors of cardiac arrest due to cardiac aetiology or with an initial shockable rhythm may benefit from a broader use of ICDs at discharge from hospital.

5.4 STUDY IV

The last study in this thesis aimed at improving our previous model for prognostication (SCARS-1),¹²⁴ by tweaking and changing some key aspects in model development. We successfully created a parsimonious, yet clinically safe prognostication tool for survival in OHCA cases. This model exhibits discriminatory performance and calibration high enough to be used in routine care within the population it was developed, which is the entire Swedish population. However, the model has not undergone external validation, making it unsuitable for external use and, furthermore, these models are currently

classified as technical products and therefore require, prior to clinical use, classification in accordance with the European device regulations.

Since XGB and LightGBM showed superiority over the other models during the development phase, we proceeded with a more comprehensive model development for these two exclusively. Both XGB and LightGBM demonstrated excellent calibration and discrimination, however, the XGB proved to be slightly better in some important aspects of model development, requiring only a few predictors to reach excellent performance. It slightly overestimated survival in the lower ranges (0-10%) of survival probability (> 8 predictors), making it the most clinically safe model between the two. We believe that it is essential that this approach of creating prediction models, defined as a broad evaluation of many different prediction frameworks and models with extensive model tuning, should become the norm in medicine. There are indications that this is becoming the case in cardiovascular medicine, though most currently used prediction models are derived from much less sophisticated methods.¹⁵⁶

The survival rate of OHCA is only one in ten, whereas ROSC is achieved in approximately three out of ten.¹⁵⁷ The discrepancy is due to differences in tissue properties of neurons and myocardial cells, where the latter can endure longer periods of anoxic stress.¹⁵⁸ From a clinical point of view, this means that the majority of patients suffering an OHCA will succumb due to hypoxic-induced brain injury (HIBI).¹⁵⁹ Prediction models, like SCARS-2, could thus be key in filling the void

that current guidelines fail to address. This has major implications, not only from a patient point of view, but also for family members and healthcare. Modern and sound care should not only be able to effectively diagnose and treat patients, but also being able to manage and handle unnecessary treatments to prevent patient suffering. Also, witnessing a cardiac arrest could lead to severe psychological trauma for family members, with high rates of depression and PTSD observed in several studies.¹⁶⁰ An objective measure of a predicted survival score along with clinical examination could help physicians in aiding difficult decisions, also helping when motivating the choice of future treatment regimens for family members. The decision for termination of resuscitation (TOR) could not only decrease suffering of patient and family member in select cases, but also help allocate resources more efficiently.

A clinically meaningful prediction model must be parsimonious and accept missing data (which our previous model was not trained to do), especially in a situation like cardiac arrest. Determining how many variables are required is a delicate task that requires both subjective and objective considerations. Fortunately, our winning model demonstrated a plateau in discriminatory performance, which allowed us to easily identify the number of predictors required to make a reliable prediction. The final XGBoost model displayed an AUC ROC of 0.958, optimised for a weighted F1 score, including eight predictors. With this work, we successfully addressed and handled the flaws and limitations of the previous model by extensive hyperparameter tuning,

testing various cost functions, allowing for missing data and optimising the ability of the model in the lowest ranges of probability.

Hyperparameter tuning optimises the model parameters so that it can generalise to unseen data. Computationally speaking, tuning is very costly, and can be performed with many different resampling techniques. We used repeated cross-validation, although we realise that other techniques could have ultimately resulted in a better final model. Nevertheless, we decided not to tune the resampling method, as it was deemed too computationally intensive. The decision to evaluate separate objective functions was motivated by our goal to achieve the best possible model after considering as many tuning parameters as possible.¹⁶¹

In developing a model for prognostication of survival in OHCA, it is critical to handle false negatives (FN), since misclassification will have detrimental effects on patient outcome. The precision recall area under the curve (PR AUC) accounts for FNs, while the AUC ROC does not. Using PR AUC as objective function, however, did not outperform weighted F1. It is important to note that ROC AUC can provide an overly optimistic performance in cardiac arrest scenarios due to the class imbalance.

In SCARS-1, we handled missing data by imputation. However, imputation may come with a cost, since it creates artificial values to handle missing predictors. While this may lead to impressive internal

validity, it hampers the external validity and generalisability of the model. Indeed, any cardiac arrest model must be able to handle missing data, and therefore it must be trained on proper rates of it. This is a matter of creating prediction models adhering to real-world scenarios.

Numerous other studies have been developed to prognosticate survival and outcome after OHCA. Seki et al.¹⁶² published in 2012, a machine learning model for one-year survival after OHCA, with an ROC AUC of 0.94 (95% CI 0.93-0.95) using 35 variables, and 0.96 (95% CI 0.95-0.97) for 53 variables. Data was derived from SOS-KANTO 2012 study, including 16,452 victims. The random forest model was developed for OHCA cases with presumed cardiac aetiology only. Kwon et al.¹⁶³ developed a deep learning model to prognosticate neurologic outcome and survival to hospital-discharge. Data was obtained by the Korea OHCA registry (KOHCAR), including 36,190 victims. ROC AUC for neurologic outcome was 0.95 (95% CI 0.952-0.954), outperforming other methods used in the study; logistic regression, random forest, support vector machine. Maupin et al.¹⁶⁴ developed a prognostication tool for neurological outcome after OHCA, identifying prognostic factors via multivariate analysis, validated prospectively and in external datasets. ROC AUC was 0.93 (95% CI 0.91-0.95).

The final model, deployed in this study, is available as an API at www.gocares.se.

5.5 ETHICAL CONSIDERATIONS

Swedish national quality registries have gained much attention in the cardiovascular research community over the past decade. Several seminal papers have been published using these registries. However, the use of these registries, which collect sensitive individual-level patient data from routine care, raises significant ethical considerations. These registries enrol patients who are unaware, at the time of data collection, about the specific future research studies in which their data may be used. Although the oversight of data use is managed by the Ethical Review Authority, this system primarily checks for the ethical soundness of a study rather than aligning with each patient's personal preferences and consent. The quality registries approach to the conduct of observational studies assumes a blanket consent that may not reflect the decisions individual patients would make if they were aware of the specific research purposes. This issue may stretch to randomised registry trials that deploy a cluster randomisation strategy, since these may also be exempted from individual consent. It is crucial that the registries balance the potential benefits of registry-based research with patient consent and autonomy.

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Clinical risk scores designed to prognosticate survival in out-of-hospital cardiac arrest (OHCA) present several potential problems, particularly concerning their implementation and impact on patient outcomes. Despite a high predictive performance, and an intention to reduce unnecessary interventions, these models can inadvertently lead to fatal outcomes. It is fundamental that such models are validated and applied with extreme caution. The proper way of evaluating the safety of these models is by means of randomised trials, which can be heavily influenced by the design. For example, a non-inferiority design with a wide margin stands a substantial chance of proving our model to be safe. The width of the non-inferiority margin is a matter of not only mathematics, but also ethics. Thus, while these clinical risk scores hold promise for optimising resources, their deployment in clinical settings

must be approached with a structured validation process that carefully measures their impact on both survival rates and resource allocation, and ethical aspects should take centre stage when designing such studies.

The reliance on observational data for efficacy studies, especially in situations where randomised trials are impractical (or too costly), presents several challenges. Observational data is appealing in many ways; real-world evidence study has become a buzzword in recent years. Trust in observational studies is a mathematical, clinical and ethical question. Firstly, we believe that it is justified to use real-world data to study associations between interventions and outcomes. Even so, relying on observational data may lead to patient harm within the context of secondary prevention with ICDs. It is important to validate significant findings by means of randomised trials, in order to confirm or refute findings from observational studies. Indeed, the long-term individual and societal costs of erroneous patient care is likely to be greater than the cost of conducting costly and impractical clinical trials. It is also critical that researchers communicate the potential flaws of their studies to readers, in order to avoid misunderstanding and, ultimately, possible patient harm.

6 CONCLUSION

In conclusion, with this thesis we explored important aspects in cardiac arrest care, highlighting epidemiological shifts over the last three decades and during the SARS-CoV-2 pandemic (COVID-19), unravelling implications of prompt ICD therapy in cardiac arrest cases with cardiac aetiology and improved upon our previous prediction model, SCARS-1. We conclude that survival has increased both in- and out-of-hospital (IHCA and OHCA, respectively) since the inception of SCRR in 1990, with more than a two-fold increase in OHCA. The number of patients that receive bystander cardiopulmonary resuscitation has increased dramatically, from 30.9% in 1990 to 82.2% in 2020. However, during this time, ambulance delays have increased from a median of 6 to 11 minutes. The last decade has shown no improvements in survival for OHCA; however this has not been the case for IHCAs, in which a 46.6% increase was seen in the last decade. In March 2020, the Swedish Public Health Authority (SPHA) declared community spread of COVID-19 in Sweden, affecting healthcare, society and patients in an unprecedented manner, and causing a shift in epidemiology in both in- and out-of-hospital cardiac arrest. Cardiac arrest with concomitant COVID-19 infection were observed to be highly lethal and, during the study period, no patients with an out-of-hospital cardiac arrest and COVID-19 infection were discharged alive from hospital. Additionally, we have shed light on current clinical guidelines, challenging the notion of reversible cardiac causes of OHCA due to cardiac aetiology. Patients discharged with an implantable cardioverter defibrillator (ICD) had a

60% reduction in death and recurrent cardiac arrest. With our last study, we successfully improved upon previous modelling framework, SCARS-1, via extensive hyperparameter tuning and handling of missing data, creating a parsimonious model with excellent calibration ready for external validation and, presumably, also internal (i.e. in Sweden) clinical trial testing.

7 FUTURE PERSPECTIVES

The field of cardiac arrest have improved remarkably over the past few decades. As evident from our study on long-term trends, further improvements in survival, particularly in OHCA, require new approaches. Undoubtedly, the most promising technology is currently artificial intelligence (AI). Physicians and researchers must implement AI, where possible, in their daily routine in order to accelerate advances and improve patient outcomes. This is a highly complex task, requiring collaboration, data sharing and joint efforts from academia, industry, policy and law makers. Indeed, recent years advances in AI have proven it to be an extremely resource intensive technology and in order for it to be utilised to improve patient outcomes, a highly synchronised effort is warranted. Thus, AI is included as a core component of future cardiac arrest care and research.

A paradox in preventing SCD is the difference between relative risk and absolute risk numbers, within this context meaning, patients within the highest risk group are those with structural heart disease, however, making up only a fraction of all SCDs in the population as a whole. The majority of patients with SCD appear in the general population. Today, there are no known markers or standardised measurements for adequate and effective risk stratification. Although this has proven a very hard task, efforts must continue to find new means of predicting sudden cardiac arrest. Again, emerging technologies like AI, wearables, etc., may be key in this regard.

Much emphasis for preventing SCA has been placed on the implantable cardioverter defibrillator (ICD). However, current clinical guidelines do not identify all subgroups at high-risk of arrhythmias. Many individuals eligible for an ICD will never receive shock therapy, and conversely, many high-risk individuals do not meet the selection criteria within the scope of current guidelines, due to LVEF > 35%.⁵⁸ The results in Study III showed a major benefit in OHCA victims discharged with an ICD, challenging the notion regarding transient and reversible causes of SCA of cardiac aetiology. Currently, an RCT is ongoing (NCT04576130) which aims at outlining the potential benefit of an ICD in patients with coronary heart disease, including AMI, with LVEF > 35%.¹⁵⁵ ICDs as well as other types of device therapies, including pacemakers (PMs) and cardiac resynchronising therapy (CRT), are sources of continuous intracardiac ECG that could be used for developing AI algorithms in prediction models of SCA.

To further increase survival in victims of cardiac arrest, it is essential to continually improve every step of the chain of survival. This includes increasing population-based education of laymen, careful planning of infrastructure, and allocating resources more carefully. One of the key findings presented in this thesis, is the alarming increase in ambulance response times, which is absolutely fundamental for survival in OHCA. In order to counteract this, resources are needed and existing resources must be spent more wisely. Policy makers and healthcare providers must invest more resources in the EMS, while also finding new ways of reducing the use of ambulances for non-acute

conditions. In parallel, novel approaches may improve outcomes, as demonstrated by AED-equipped drones and smartphone-based dispatch of laymen.^{102,165} Such innovative approaches must continue.

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