Predictors of survival in cardiac arrest

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“Think off-center.”
– George Carlin

ABSTRACT

Background
Cardiac arrest (CA) refers to the cessation of cardiac function. It is divided based on whether it takes place inside or outside the hospital. Survival is around 30% for in-hospital cardiac arrest (IHCA), and 10% for out-of-hospital cardiac arrest (OHCA). Many factors influence survival, ranging from the patient's age, gender, and comorbidities, to the conditions surrounding the arrest (e.g. initial rhythm and witnessed status or ECG-monitoring), to the delay times to cardiopulmonary resuscitation (CPR) and defibrillation, and finally post-arrest treatment options (e.g. percutaneous coronary angiography).

Aim
To further explore the influence of various factors at resuscitation on outcome and on treatment with a particular focus on age and gender.

Methods: The data was provided by the Swedish Registry of Cardiopulmonary Resuscitation (SRCR). In **study *I*,** the characteristics and outcome of ca 15,000 cases of IHCA were studied from a national perspective. **Study *III*** examines ca 22,000 bystander-witnessed cases of OHCA to determine the influence of age and gender on the delays to treatment, and on the association between delay and survival. **Studies *II and IV*** utilize machine learning (ML) to rank the most important predictors of survival in ca 45,000 cases of OHCA, and ca 5,000 cases of IHCA, respectively.

Results: In **study *I*,** we found men to have a 10% lower chance of survival to 30 days after IHCA than women. Older individuals were

managed less aggressively and had lower 30-day survival, but a comparable cerebral function to younger survivors.

Study *II* shows that in IHCA, a shockable presenting rhythm was by far the strongest predictor of survival, followed by the location and the cause of CA, the presence of hypoxia within one hour before the arrest, and then age. The delays to start of CPR and to defibrillation were short in the majority of patients, which may explain why the delay was not the most important factor for outcome. Gender did not seem important when using ML.

In study *III,* patients aged >70 years had a longer delay from collapse to start of CPR after OHCA (median time 4 vs 2 minutes, $p < 0.0001$). Men had a more pronounced decrease in survival with increasing delay to CPR than women ($p=0.0002$), whereas the decrease in survival with increasing delay to treatment was similar between older and younger patients.

Study *IV* shows that the top five predictors of survival after OHCA are: initial rhythm, age, early CPR, EMS response time, and place of CA. Gender did not seem important when using ML.

Conclusions: A number of factors influence survival after cardiac arrest. Initial rhythm is the most important. Gender does not seem important when using ML. In IHCA, CPR is initiated rapidly. Despite their worse prognosis, older individuals are managed less aggressively than younger patients. Increasing age does not seem to be associated with a worse cerebral function among survivors. In OHCA, patients >70 years of age still face double the delay time to start CPR, a modifiable, and important predictor of survival.

KEYWORDS: cardiac arrest, cardiopulmonary resuscitation, predictors, survival, machine learning

SAMMANFATTNING PÅ SVENSKA

Plötsligt och oväntat hjärtstopp är vanligt. I Sverige inträffar drygt 20 gånger varje dag ett plötsligt och oväntat hjärtstopp där hjärt-lungräddning (HLR) påbörjas. Tidigare forskning har visat att både patientens kön och ålder kan ha betydelse för chansen att överleva. Kvinnor tenderar att drabbas av hjärtstopp i högre åldrar än män. Den bakomliggande orsaken till hjärtstoppet kan skilja mellan könen. I Sverige finns sedan 1990 ett register som kartlägger alla plötsliga oväntade hjärtstopp utanför sjukhus. Detta register omfattar idag drygt 82 000 fall av hjärtstopp där HLR har påbörjats. Sedan 2005 finns även ett register som kartlägger hjärtstopp som inträffar på sjukhus och detta register omfattar ca 20,000 fall av hjärtstopp där HLR har påbörjats.

Målsättningen med denna avhandling har varit att belysa vilka faktorer som är avgörande för att överleva ett hjärtstopp. Vi har studerat hur kön, ålder, samsjuklighet och behandling påverkar patientens prognos vid hjärtstopp. Avhandlingen bygger på fyra delarbeten där två undersöker hjärtstopp på sjukhus och två studerar hjärtstopp som inträffar utanför sjukhus. I ett arbete inom varje grupp använder vi oss av så kallad maskin-inlärning, vilket innebär att den statistiska modellen är uppbyggd utifrån maskin-inlärda data, med minst möjliga risk för att undersökaren blir lurad av egna observationer.

Arbete I är det största och mest heltäckande arbete som beskriver hjärtstopp som inträffar på sjukhus i Sverige. Här beskrivs hur ålder, kön, sjukhistoria, behandling, var hjärtstoppet sker, typ av hjärtrytm, samt bakomliggande orsaker till hjärtstoppet påverkar prognos och överlevnad. Vi fann att män hade 10% sämre chans att överleva jämfört med kvinnor och att patienter >65 år inte fick lika aggressiv behandling som yngre. Däremot kunde vi inte påvisa att hjärnfunktionen bland överlevare påverkades av ålder.

Arbete II handlar om hjärtstopp på sjukhus och här har vi använt oss av maskin-inlärningsteknik. I detta arbete visar vi att en defibrillerbar hjärtrytm är den överlägset viktigaste faktorn för att överleva. Näst viktigast är på vilken typ av avdelning som hjärtstoppet inträffar där möjligheten att snabbt ingripa förutsätter att patienten är tex hjärtövervakad. Den tredje viktigaste faktorn är den bakomliggande orsaken till hjärtstoppet. Den fjärde viktigaste faktorn var huruvida det förelåg en låg syrehalt i blodet under den närmaste timmen före hjärtstoppet. Femte viktigaste faktorn var patientens ålder. Det faktum att tid till påbörjande av behandling inte återfanns bland de fem viktigaste faktorerna för chansen att överleva tror vi kan bero på att behandlingen överlag påbörjades väldigt snabbt och att det inte förelåg någon egentlig tidsgradient.

I arbete III kartläggs huruvida ålder och kön påverkar tid till behandling men också sambandet mellan tid till behandling och överlevnad vid hjärtstopp utanför sjukhus. Tre tidsaspekter har studerats; tid från hjärtstopp till larm, tid till start av HLR samt tid till defibrillering. Vi fann längre fördröjningstid till påbörjad HLR i den äldre patientgruppen. Vi fann också att kvinnor tenderade att få HLR senare än män. En fördröjning av påbörjad HLR minskade chansen att överleva mera påtagligt hos män jämfört med kvinnor. Om behandling vid hjärtstopp fördröjs minskar chansen att överleva på ett likartat sätt bland de äldre jämfört med de yngre.

I arbete VI beskriver vi olika faktorers betydelse för chansen att överleva ett hjärtstopp utanför sjukhus. Överlägset viktigast var typen av hjärtrytm och om denna rytm gick att defibrillera eller ej. Näst viktigast var patientens ålder. Den tredje viktigaste faktorn var hur lång tid det dröjde innan HLR påbörjades. Den fjärde viktigaste faktorn var ambulansens fördröjningstid dvs tiden från det att ambulansen larmades ut tills ambulansen var framme hos patienten. Den femte viktigaste faktorn var platsen där hjärtstoppet inträffade dvs om det inträffade i hemmet eller utanför hemmet. Huruvida

patienten var kvinna eller man påverkade chansen att överleva endast marginellt.

Slutsatsen av arbete I-IV är att det finns ett flertal faktorer som påverkar prognosen vid ett hjärtstopp. På sjukhus påbörjas HLR snabbt efter hjärtstopp medan fördröjningstider till HLR utanför sjukhus är betydligt längre. Initial hjärtrytm är den absolut viktigaste faktorn för överlevnad. Kön förfaller ha mindre betydelse för överlevnad än ålder. Hög ålder är prognostiskt ogynnsamt vid hjärtstopp men verkar inte vara associerad med sämre hjärnfunktion hos de som överlever. Att dödligheten är högre hos de äldre kan bero på att denna grupp har en dubblerad fördröjningstid till påbörjad HLR utanför sjukhus och att de äldre får en mindre aggressiv behandling än yngre. Denna fördröjningstid är påverkbar och här finns en tydlig förbättringspotential inför framtiden.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Al-Dury N, Rawshani A, Israelsson J, Strömsöe A, Aune S, Agerström J, Karlsson T, Ravn-Fischer A, Herlitz J. Characteristics and outcome among 14,933 adult cases of in-hospital cardiac arrest: A nationwide study with the emphasis on gender and age. The American Journal of Emergency Medicine, 2017 Dec;35(12):1839-1844.

II. Al-Dury N, Rawshani A, Hirlekar G, Hollenberg J, Israelsson J, Nordberg P, Herlitz J, Ravn-Fischer A. In-hospital cardiac arrest: A machine learning study with focus on predictors of survival. *Manuscript.*

III. Al-Dury N, Rawshani A, Karlsson T, Herlitz J, Ravn-Fischer A. The influence of age and gender on delay to treatment and its association with survival after out of hospital cardiac arrest. The American Journal of Emergency Medicine, 2021 Apr;42:198-202.

IV. Al-Dury N, Ravn-Fischer A, Hollenberg J, Israelsson J, Nordberg P, Strömsöe A, Axelsson C, Herlitz J, Rawshani A. Identifying the relative importance of predictors of survival in out of hospital cardiac arrest: a machine learning study. Scandinavian Journal of Trauma, Resuscitation, & Emergency Medicine, 2020 Jun 25;28(1):60.

List of abbreviations

SRCR	Swedish registry for cardiopulmonary resuscitation
CA	Cardiac arrest
IHCA	In-hospital cardiac arrest
OHCA	Out-of-hospital Cardiac arrest
CPR	Cardiopulmonary resuscitation
ROSC	Return of spontaneous circulation
VT	Ventricular tachycardia
VF	Ventricular fibrillation
PEA	Pulseless electrical activity
PCI	Percutaneous coronary intervention
ECMO	Extracorporeal membranous oxygenation
DNR	Do Not Resuscitate
EMS	Emergency medical services
ICD	Implantable cardioverter defibrillators
CAD	Coronary artery disease
RRT	Rapid response team
TH	Therapeutic hypothermia
TTM	Targeted temperature management
ML	Machine learning
RF	Random forest
AI	Artificial intelligence
CPC	Cerebral performance categories
NEWS	National early warning score
AED	Automatic external defibrillator
MI	Myocardial infarction

1 TABLE OF CONTENTS

1 INTRODUCTION

Cardiac arrest (CA) is a medical challenge that is still associated with a low rate of survival. In short, it refers to the sudden cessation of organized cardiac activity and output, tissue hypoperfusion, and subsequently, death. It is generally divided into two entities based on whether the arrest took place within or outside the hospital perimeters, hence the terminology: In-hospital cardiac arrest (IHCA), and out-of-hospital cardiac arrest (OHCA). In Sweden with about 10 million inhabitants, around seven people suffer from IHCA and fourteen of OHCA per day where resuscitation is attempted. Approximately, one in three victims of IHCA survives, compared to only one in ten when it comes to OHCA [1]. The overwhelming majority of CA cases where resuscitation is attempted are recorded in a national quality registry called The Swedish Registry of Cardiopulmonary Resuscitation. The Registry contains comprehensive data on patient characteristics, treatment times and types, comorbidities, as well as survival data and cerebral performance in survivors.

There is a myriad of factors influencing survival after CA. These range from patient's age, gender, and comorbidities, to the location of CA and treatment delay times, all the way to post-resuscitation care including percutaneous coronary angiography (PCI) or extracorporeal membranous oxygenation (ECMO). Some of these factors are modifiable, whereby improving certain aspects might lead to increased survival. Moreover, a number of those factors may differ in their relative importance between different scenarios of CA, which could, at least in theory, provide for a more tailored treatment approach.

1.1 A SHORT HISTORY OF CPR AND DEFIBRILLATION

Chest compressions as a way of supporting circulation were developed as a technique for treating “chloroform syncope” in the late 1800s at the University Hospital of Göttingen, Germany. It started as simple as applying compressions to the xiphoid at a rate similar to that of respiration. Fast chest compressions were suggested to support circulation after Dr. Friedrich Maas noticed that these compressions produced a carotid pulse in a young boy who had become pulseless with no breathing after chloroform anesthesia [2]. In 1901 the first open chest “cardiac massage” was performed by Dr. Igelsrud in Tromsø in the North of Norway, after a cardiac arrest towards the end of an abdominal operation [3]. In 1958 Kouwenhoven, Knickerbocker, and Jude accidentally found that applying defibrillation pads to the thorax could restore pulse in anesthetized dogs. In 1960 they reported that fourteen out of twenty IHCA patients treated by closed cardiac chest massage survived [4]. In 1946, Dr. James Elam successfully performed mouth-to-nose breathing on a boy with acute bulbar poliomyelitis [5]. By 1957, Dr. Elam and his colleague Dr. Peter Safar concluded that tilting a person’s head backward will produce an open airway. They also demonstrated that external chest compression does not suffice for adequate ventilation, as compared to mouth-to-mouth breathing, and that this technique can be used for resuscitation [6, 7]. In 1955, Dr. Paul Zoll described a mechanical technique for "stimulating" the asystolic heart. In 1956, he published a transcutaneous approach to terminate ventricular fibrillation and ventricular tachycardia [8]. At the Maryland Medical Society meeting in 1960, Kouwenhoven, Jude, and Safar presented their findings on chest compressions and mouth-to-mouth breathing, thereby the concept of cardiopulmonary resuscitation (CPR) as we know it today was born [9]. The first successful defibrillation, however, was performed by a surgeon named Claude Beck, who defibrillated a 14-year old boy, who suffered from ventricular fibrillation towards the end of an operation

and then went on to make a full recovery [10]. The father of modern prehospital emergency care is widely regarded to be Frank Pantridge, who was the first to develop a mobile intensive care unit for the management of myocardial infarction in 1967 [11].

1.2 DEFINITION OF CARDIAC ARREST

The human heart beats 100,000 times per day, pumping around 6000 - 7500 liters of blood to the rest of the body on a daily basis [12]. This muscular powerhouse requires a complex electrical system to keep things running smoothly and without glitches. Certain conditions can cause problems in this electrical system, leading it to malfunction. If this malfunction reaches a level where the heart is sent into a chaotic rhythm that disrupts the effective filling and pumping action of the heart, then that is what is referred to as cardiac arrest. Left untreated, it leads to death. Biologically speaking, three things are usually present during a cardiac arrest: the absence of a detectable pulse, unresponsiveness, and apnea [13]. Clinically, however, international guidelines mandate CPR initiation on any patient that is unresponsive and without normal breathing [14].

The terminology surrounding cardiac arrest can sometimes be confusing. In the literature, one may also see terms like "sudden cardiac arrest" or "sudden cardiac death". The term "sudden cardiac arrest" is usually synonymous with cardiac arrest. Sudden cardiac death usually refers to cardiac arrest that had been left untreated, and ultimately leads to death [15].

1.3 ETIOLOGY

Coronary artery disease has been reported to account for approximately 70% of cardiac arrests [16, 17]. However, due to a low autopsy rate and subjectivity in the reporting, there is some uncertainty surrounding the exact percentage of cardiac arrest of pure cardiac etiology. Non-cardiac causes have been reported to account for 15 – 25% of cases of CA. Examples of non-cardiac causes may include airway obstruction, pulmonary embolism, drowning, trauma, and cerebral hemorrhage [18, 19]. Ten percent of

CA are attributable to anomalies in the coronary arteries, myocarditis, or cardiomyopathies [16, 20]. The remaining 5 – 10% of CA appear to be caused by arrhythmias in the absence of structural heart disease [20-22]. Younger patients are more likely to have an underlying cause of CA that belongs to the latter two groups [17-19]. There are not many studies directly comparing etiologies in IHCA vs. OHCA. In a 2015 study from Belgium involving 1860 CA victims, it was found that the most common cause of arrest in OHCA was cardiac, but non-cardiac in IHCA. However, approximately half of OHCA and a quarter of of IHCA cases were determined to have an unknown etiology [23].

The table below summarizes the reversible causes of CA, which are important to recognize to initiate relevant treatment. Prompt treatment of reversible causes of cardiac arrest infers a substantial survival benefit [24].

The Hs	The Ts
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade
Hypo-/Hyperkalemia	Thrombosis (coronary or pulmonary)
Hypoglycemia	Toxins (or Tablets)
Hypothermia	Trauma
Hydrogen ion (acidosis)	

1.4 PATHOPHYSIOLOGY

A 3-phase time-sensitive model for resuscitation has been proposed by Weisfeldt and Becker in 2002 [25]. The model reflects the evolution of resuscitation physiology, which requires time-sensitive interventions. The model suggests that to treat CA optimally, one must think in a phase-specific manner, whereby there is an electrical phase (extending from the time of CA to approximately four minutes following the arrest); a circulatory phase (starting from approximately 4 – 10 minutes after cardiac arrest); and a final metabolic phase (extending beyond 10 minutes after cardiac arrest). The current literature does not provide an exact delineation between phases, so the time boundaries are approximate.

The electrical phase relies on defibrillation to restore organized cardiac activity. This is backed by decades of research in different scenarios (use by paramedics, police officers, airline personnel, and laypersons) [26-29]. Based on this body of knowledge, it is estimated that for every minute that defibrillation is delayed, the chance of survival is reduced by 10-12% [26, 30, 31].

In the circulatory phase (4 – 10 minutes of VF), the evidence suggests that the most important lifesaving therapy is to first provide oxygen delivery (chest compression/ventilation), followed by defibrillation (i.e, delaying defibrillation by 1-3 minutes). In a swine model of VF, increasing the duration of CPR interruption from 3 to 20 seconds before defibrillation decreased return of spontaneous circulation (ROSC) in a time-dependent manner from 100% to 0% [32]. In humans, it has also been shown that in patients with VF and ambulance response intervals longer than five minutes (i.e. in the circulatory phase of CA), better survival rates to discharge and to one year were achieved when CPR was performed for three minutes before defibrillation [33]. When a "defibrillation first" approach was tested against a “CPR first” approach for 90 seconds, immediate

defibrillation was not significantly superior to providing 90 seconds of CPR within the first three minutes following CA, but the opposite was true after three minutes of CA [34]. It is thought that the physiological mechanism behind this is compressions provide partial circulation of blood to the myocardium, which leads to some restoration of oxygen and washout of accumulated metabolites that has occurred during ischemia. Thus, making the myocardium more receptive to defibrillation.

During the metabolic phase (> 10 minutes of arrest), tissue damage from ischemia and reperfusion can result in circulating metabolic factors that cause additional injury extending focal ischemia. For instance, the translocation of gram-negative bacteria through the gut mucosa can result the suppression of myocardial function after defibrillation due to various endotoxins and cytokines [35]. A "sepsis-like" immunoinflammatory profile has been demonstrated in patients successfully resuscitated after cardiac arrest, with elevated levels of circulating cytokines (mainly interleukin 6, 8, 10, and tumor necrosis factor [TNF]). This is thought to be due to whole-body ischemia/reperfusion [36].

In comatose but hemodynamically stable survivors of OHCA, there is evidence pointing to an improvement in survival with good neurological function when external cooling to 32°–34°C is performed. In other words, a metabolic intervention such as hypothermia, is still protective even when delayed for hours after CA [37, 38]. This suggests some injury in the brain is still ongoing despite the return of circulation.

1.5 INCIDENCE

When discussing the incidence of CA, it is important to note that not all CA are treated. This is either due to preexisting Do Not Resuscitate (DNR) orders, and/or if resuscitation is deemed futile, and hence not initiated based on the EMS crew or hospital staff assessment. The incidence is usually measured in the adult population; since CA is uncommon in the pediatric population [39, 40]. Regarding OHCA, it is estimated that there are around 450,000 cases/year of EMS-treated OHCA in the US [41], and 275,000 cases in Europe [42]. Experiences from Sweden [1], as well as Europe [43], suggest that there are about 50 – 60 OHCA per 100 000 inhabitants and year where resuscitation is attempted. The incidence of IHCA has been reported to vary between 1 and 5 events per 1,000 hospital admissions [44].

1.6 CLASSIFICATION

Cardiac arrest is usually classified based on whether it takes place inside or outside the hospital perimeter. This distinction is ingrained in the cardiac arrest field and is based on the inherent differences not only in the characteristics of immediate treatment providers and delay times to interventions [13, 45], but also to some extent in patient characteristics. Usually, the witness of an OHCA is a layperson, while a healthcare provider is usually the witness of an IHCA. The delay time to defibrillation is generally much longer in OHCA simply because defibrillators are not as readily available outside the hospital, as they are within the hospital. To a certain extent, patient characteristics may also vary between IHCA and OHCA [46, 47], although this does not always seem to be the case. A recent study from Denmark has shown that these two patient groups were very similar in demographics and comorbidities [48].

From an electro-mechanical perspective, the heart can be in one of 4 conditions during an arrest, each of which conditions with a unique electrical signature. However, they all lead to ineffective pumping. These conditions are usually grouped into shockable rhythm (comprising of hemodynamically unstable, or pulseless ventricular tachycardia [pVT] and ventricular fibrillation [VF]), and non-shockable rhythm (referring to pulseless electrical activity [PEA] and asystole). What separates these two groups is the possibility of converting shockable rhythm to a normal, or near-normal effective rhythm (also called return of spontaneous circulation [ROSC]) if early defibrillation and adequate CPR are provided. Non-shockable rhythm, on the other hand, requires the administration of Adrenaline as soon as feasibly possible after the initiation of CPR, to increase the chances of ROSC [49].

Three decades ago, approximately three out of four initial ECGs recorded during CA showed VF or pVT [50]. This pattern has changed dramatically since then, and recent data show the rate of VT/VF on initial ECGs to be around 25% [51, 52]. The mechanism behind this change is unclear. Hypothetically, it could be - at least in part - attributed to the increasingly aggressive management approach in heart failure, including beta-blockers and implantable cardioverter defibrillators (ICD). Beta-blockers are known to be effective in the control of ventricular arrhythmias in various scenarios ranging from stress-induced arrhythmias to acute myocardial infarction and heart failure [53-57]. ICDs have been proven to be extremely effective in terminating VT and VF (although the extent to which that extends survival is dependent on how severe the underlying heart disease and associated comorbidities are) [58-64]. Another contributing factor (in terms of OHCA) might be increasing EMS response time. Indeed, it has been shown that for every added minute of EMS response time, the odds of a shockable initial rhythm decreased by 8% [65].

1.7 IHCA AND RAPID RESPONSE TEAMS

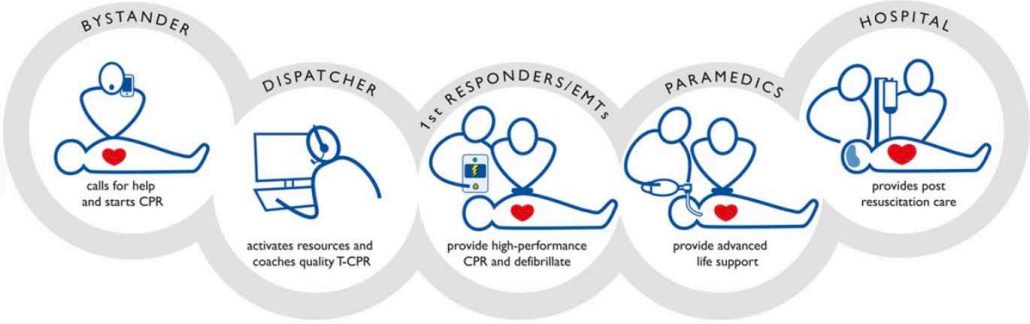
Within hospitals, there usually are specified teams consisting of physicians and nurses that are charged with receiving alerts when a patient deteriorates in their vital functions. These teams have different names around the world (Rapid Response Team, Critical Care Response Team, Mobile Intensive Group, etc.). Despite the different nomenclature, the objective is the same; to rapidly identify life-threatening conditions, start advanced medical therapy, and escalate the level of care if required. In a hospital setting, these teams either arrive at the patient bedside either right before CA takes place (due to other vital signs having deteriorated beforehand), or they get alerted once a CA has taken place, so they arrive at a patient receiving CPR, and take over from there.

1.8 OHCA AND THE CHAIN OF SURVIVAL

This concept encompasses to the chain of events that must take place in quick succession to increase the chances of survival after CA. It suggests that each step is vital, and that the Chain of Survival is only as strong as its weakest link. This metaphor dates back to 1991 [66], and has since then served as the template on which to educate the public and apply improvement efforts. It has evolved throughout the years and has come to include the use of cell phones to optimize communication between the dispatcher and the bystander in real-time (so-called dispatcher-assisted, or telephone CPR [T-CPR]).

The Chain of Survival, as depicted in the original 1991 publication [66].

T-CPR



Source: The Laerdal Foundation (www.Laerdal.com)

1.9 RISK FACTORS FOR CARDIAC ARREST

Among persons without prior clinically recognized heart disease, several clinical characteristics are associated with an increased risk of CA [67-69]. Coronary artery disease (CAD) and cardiac arrest share many risk factors, including obesity, diabetes mellitus, hypertension, dyslipidemia, cigarette smoking, physical inactivity, and premature CAD or myocardial infarction in the family history [70-73]. Below is a summary of some of the less well-known risk factors for cardiac arrest.

FAMILY HISTORY

There is a 1.5 to 1.8-fold increased risk of CA in persons who have a family history of CA [71, 74]. This increase in risk is not explained by traditional risk factors such as obesity and metabolic syndrome. In a 2017 study, Mellor et. al performed comprehensive genetic testing (50 – 100 cardiac genes) on 174 CA survivors without a definite clinical phenotype, and where the initial evaluation revealed no pathology in the coronary arteries, left ventricular function, and resting ECG. It was found that 17% of these individuals had a mutation either in arrhythmia-related or cardiomyopathy-related genes [75]. Moreover, a positive genetic result was independently associated with prior syncope and a family history of sudden death [75].

CIGARETTE SMOKING

Smokers have a significantly greater risk of CA than non-smokers, regardless of whether or not they have CAD. The opposite seems also to be true; i.e. patients who quit smoking experience a significant reduction in CA risk. [76,77]. In a large prospective cohort of women without known coronary heart disease, small-to-moderate amounts of cigarette smoking (1-14 per day) were

associated with a significant 1.8-fold increase in CA risk. Every five years of continued smoking was associated with an extra eight percent increase in CA risk [77]. Current cigarette smoking has also been shown to be a powerful independent predictor of CA risk in patients with CAD [76]. Two mechanisms could explain these findings: Not only do current smoking and cumulative smoking exposure contribute to worsening atherosclerosis [78], but smoking also appears to be a major risk factor for vasospastic angina without significant coronary stenosis [79]. Moreover, Nicotine is known to cause a marked elevation of serum catecholamine concentrations, which is potentially arrhythmogenic [79].

ALCOHOL INTAKE

A previous study of over 21,000 US male physicians who were followed up for 12 years has demonstrated that light-to-moderate alcohol consumption (1 drink/day) led to a significantly reduced risk of CA compared to rare consumption, total abstinence, and heavy/binge drinking [80]. Another study that followed around 85,000 women for 26 years found similar results, with CA risk being the lowest in women who consumed ½ – 1 drink per day. Women in the highest category of alcohol intake (≥2 drinks/day) had the highest risk for CA [81]. The mechanism behind the favorable effect of light-to-moderate alcohol intake seems to be attributable to the fact that any arrhythmogenic effect of alcohol is only minimal, and is outweighed by favorable effects on plaque rupture and thrombosis [82, 83]. In addition, alcohol may depress the stressor-induced elevation of plasma catecholamines [84]. However, this does not mean that alcohol consumption is beneficial. Indeed, the largest global study on alcohol consumption concluded that with increasing levels of alcohol consumption, there is an increase in the risk of all-cause mortality, and of cancers specifically, effectively putting the level of consumption that minimizes health loss at zero [85].

CAFFEINE

Consistently, at least 3- of the 5-top caffeine-consuming countries in the world are Scandinavian. According to www.statista.com, Sweden was the 3rd largest coffee-consuming nation in the world during 2020, preceded by the Netherlands and Finland, and followed by Norway as no. 4. Luckily, there is no solid evidence in the literature between normal caffeine consumption (up to 5 cups per day or ca 700 mg) and cardiac arrest.

EXERCISE

Regular exercise is known to be linked with a lower resting heart rate and increased heart rate variability, both being characteristics tied to a reduced risk of CA [86, 87]. Although strenuous exercise transiently increases CA risk during and up to 30 minutes following exercise, the actual risk during any one episode of vigorous exercise has been reported to be very low (1 per 1.5 million episodes of exercise) [88]. Moreover, the magnitude of this transient increase in risk is decreased further in individuals who exercise regularly [68, 88]. In fact, the Onset Study estimated that the risk of myocardial infarction during or soon after vigorous exercise was 50 times lower for the most active individuals compared to the least active individuals [89]. In addition, the small transient increase in risk during exercise is clearly outweighed by a reduction in the risk of CA at other times [69, 86].

PSYCHOSOCIAL FACTORS

The relationship between psychosocial factors and cardiac arrest is not easy to quantify, mainly due to the difficulty in objectively measuring emotional distress. It has been proposed that emotional stressors can trigger ventricular arrhythmias through the autonomous nervous system, potentially leading to cardiac arrests specifically in individuals with occult coronary artery disease [72, 90-92]. Indeed, up to 50% of coronary artery disease will not be clinically apparent before death, and most cases of sudden cardiac death have been shown to have coronary artery disease at autopsy [93, 94]. Overall, the majority of published research investigating social and psychosocial aspects of arrhythmic risk support a causal association, which remained consistent across different populations and study designs [90].

1.10 WHAT DETERMINES THE CHANCE OF SURVIVAL AFTER CARDIAC ARREST?

With larger and larger amounts of data being collected, it is useful to collect factors surrounding cardiac arrests into a few groups containing factors that are somewhat similar to one another. Generally, five groups are recognized:

1- Patient characteristics (age, gender, and comorbidity).
2- Warning signs (e.g. dyspnea, chest pain).
3- Circumstances surrounding the arrest (e.g. initial rhythm, place, witnessed status, etc.).
4- Systemic factors (e.g. time delays to alert, CPR, and defibrillation).
5- Other factors (CPR quality, cause of CA, time of the day).

These groups may have other names in the literature, such as pre-, peri-, and post-arrest conditions. Overall, they tend to refer to the same factors; the only difference is that they are grouped solely based on their temporal relation to the actual arrest. Since it would be much larger than the scope of this thesis to discuss every single factor in detail, what follows below is a general summary of the factors relevant to this thesis.

PATIENT CHARACTERISTICS

Age is generally recognized to be inversely correlated to survival both after IHCA and OHCA. Survival decreases with increasing age, starting around 35 years of age [95-98]. One gap in knowledge here is whether age negatively affects the cerebral performance category of survivors, and this has been addressed in study I.

Gender and CA is a recurring theme in this thesis, simply because it is not clear-cut in the literature whether it is an independent predictor of survival. There is, however, some evidence that younger women might have a survival advantage over their male counterparts [98-100]. This thesis aims to add to that body of knowledge both in IHCA and OHCA.

It has proven hard to quantify how much prearrest comorbidity affects survival, largely because of the heterogeneity in the manner comorbidity is reported (whether as individual conditions or by using an indicative score, such as the Charlson Comorbidity Index) [101]. In addition, most research in this area has been done on OHCA patients. Directionally, it seems logical that a higher prearrest disease burden would negatively affect survival [102]. In the case of IHCA, there is some evidence that patients admitted for cardiac conditions have higher survival rates than those admitted for non-cardiac causes [103]. We have attempted to shed some light on this using machine learning in studies II and IV.

WARNING SIGNS

Symptoms that would lead the patient, or anyone nearby, to call for help before OHCA has taken place, have been shown to have a favorable effect on survival after a cardiac arrest in several studies [104-106]. Some of these symptoms include chest pain, dyspnea, palpitations, and presyncope/syncope. This is possibly mediated by the fact that warning signs lead to earlier calls for help, and by extension shortening EMS response time (or in the best of scenarios, the event witnessed by EMS). Inside the hospital, deploying rapid response teams (RRTs) makes intuitive sense for increasing survival. Some studies did find RRTs effective in either preventing the incidence of IHCA, or decreasing mortality [107, 108]. However, other studies did not [109, 110]. Warning signs as a group are included in our machine learning model in study II.

CIRCUMSTANCES

A shockable initial rhythm has been consistently shown to be a strong predictor of survival both in IHCA [45, 111, 112], and OHCA [113, 114]. Outside the hospital, patients who have a witnessed CA have been shown to have better survival rates [114, 115]. This makes intuitive sense since the prompt treatment of cardiac arrest would not be possible if the arrest is not seen or heard. Inside the hospital, a good analogy is being monitored. Indeed, monitored patients have been shown to have a better prognosis after IHCA, both in Sweden [116], and in the US [117]. Having a witnessed OHCA goes in many cases hand-in-hand with being at a public location. Arrests that occur at home have been shown to have a lower incidence of initial shockable rhythm and worse prognosis [118-120]. All four studies in this thesis discuss different aspects of circumstances surrounding CA.

SYSTEMIC FACTORS

These usually refer to the various delay times which are, in many cases, quite modifiable. A shorter time delay to alert, to the initiation of CPR, and to defibrillation, as well as shorter EMS dispatch times, have all been implicated in achieving better survival [121-125]. Indeed, a recent study has shown that as ambulance response times increase, survival to 30 days after a witnessed OHCA decreases. This correlation was independent of initial rhythm and bystander CPR [126]. We explore these time delays further throughout the studies presented in this thesis.

OTHER FACTORS

These may include the quality of and general attitudes towards CPR. In addition, socioeconomic, geographical, and temporal factors might also play a role in survival after CA. None of these factors will be discussed in detail in this thesis. In short, attitudes towards CPR are not only hard to measure subjectively, but vary tremendously throughout different parts of the world, and between laypersons and healthcare providers [127-131]. A tendency towards better survival during daytime was noted in some studies [111, 132, 133]. As for geographical location, there is some evidence that lower population density is associated with longer EMS response times, leading to lower survival rates [124, 134]. Socioeconomic factors have been shown to be strongly associated with survival both after IHCA [135], as well as OHCA [136].

1.11 MANAGEMENT OF POST-CARDIAC ARREST PATIENTS

A multidisciplinary approach is required in the management of the post-cardiac arrest patient, since several problems can converge and have to be addressed simultaneously. One must determine and treat the cause of CA while trying to manage cardiovascular function to minimize brain injury, and then address any issues arising from global ischemia and reperfusion injury. Cardiovascular collapse is a major immediate threat to survival during the first hours after CA. Interventions to optimize blood pressure and maintain end-organ perfusion (IV fluids, vasopressors, and inotropes) can help minimize the risk of secondary injury from hypotension. Other important goals during the first few hours of care include optimizing oxygenation and ventilation and correcting any electrolyte abnormalities. To prevent recurrent arrest, determining the etiology of cardiac arrest and the initiation of relevant treatments are vital for optimizing outcomes. Current guidelines support the use of therapeutic hypothermia (TH) or targeted temperature management (TTM) to minimize brain injury. In practical terms, this refers to maintaining a constant target temperature between 32°-36°C for patients with initial shockable rhythms for at least 24 hours. TTM is suggested in OHCA patients with initially non-shockable rhythms and for IHCA of any initial rhythm [137, 138].

2 AIMS

The overall aim of this thesis is to shed more light on certain gaps in knowledge in both IHCA and OHCA in Sweden, focusing on survival predictors, and with extra attention paid to age and gender. Study-specific aims are as follows:

- To utilize a nationwide registry covering the majority of hospital beds in a single country to describe different aspects of IHCA with focus on age, gender, and 30-day survival. The high coverage facilitates the generalizability of the results and limits the effects of any inter-hospital variation.

- To provide an overarching sense of how important various factors are for 30-day survival in IHCA, at the point of emergency team arrival, and before any further treatment has been given. Here, a Machine Learning algorithm would be used on an up-to-date dataset from the past three years.

- To study the influence of age and gender on the delay to treatment, and on the association between delay to treatment and 30-day survival after OHCA.

- To use Machine Learning to investigate the relative importance of 16 well-recognized factors in OHCA at the time point of ambulance arrival, and before any further interventions or medications were given. The outcome measure is 30-day survival.

3 METHODS

3.1 DATA COLLECTION

This research is based on data from the Swedish Registry for Cardiopulmonary Resuscitation (SRCR) [1], which was started in 1990. Initially, the data collection included OHCA only. Recording of IHCA cases started in 2005. Registration is carried out using an online system that allows ambulance organizations and hospitals to record and follow up individual cases and obtain statistics for their unit.

In the SRCR, all cases of cardiac arrest in which CPR had been initiated, are recorded. Currently, the very vast majority of OHCA cases are included in the registry, with a near 100% national coverage. When it comes to IHCA, the number of participating hospitals has been growing steadily and reached 100% coverage in 2019.

The registry aims to document the details of care in cardiac arrest. By analyzing registry data, hospitals and emergency medical services are provided with information on the procedure as well as the outcome of their resuscitation efforts, individually and compared to others. This makes it easier to identify room for improvements in the chain of survival [1]. The standardized Utstein-style definitions are applied to all variables and outcomes in the registry [139].

Reporting to the IHCA part of the SRCR occurs in two steps, the first of which takes place at the actual event. Here, patient characteristics, circumstances of the cardiac arrest, and any interventions (including delay times to treatment), are recorded by a nurse or physician attending the event. The second step takes place more than one month later and includes follow-up data,

comorbidities, probable etiology, and 30-day survival. A CPC score is also obtained in the majority of survivors.

Reporting to the OHCA part of the SRCR is done by the Emergency Medical Service (EMS) crew. The crew completes a form for each case. This form contains information on age, location of the cardiac arrest, probable etiology, and a standardized description of the CPR procedure (various intervention times, bystander CPR, defibrillation, and medical treatment). The first recorded rhythm is entered as either shockable on non-shockable (if an automated external defibrillator is used). Otherwise, it is entered as VF, VT, PEA, or asystole. In witnessed cases, the EMS crew interviews bystanders about delays from arrest to call. The etiology of the cardiac arrest is assessed based on the evaluation of the EMS crew and available bystander information. In cases where bystander-CPR has been performed, the profession of the bystander (layperson or off-duty healthcare practitioner) is recorded. The immediate outcome is reported by the EMS as dead on arrival, dead in the emergency room, or admitted alive to the hospital. A follow-up on survival to 30 days is carried out at a later time point, where other details of the post-resuscitation care including TTM and revascularization are described as well.

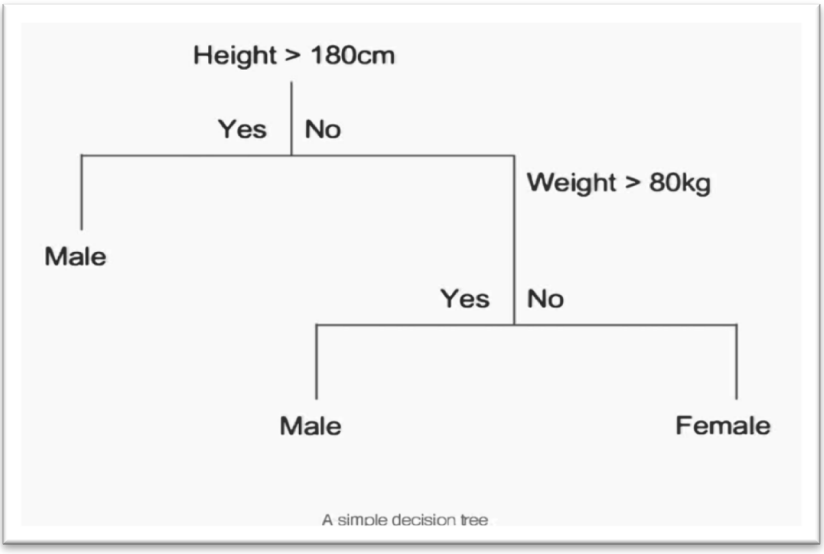
3.2 OVERVIEW OF PAPERS & STATISTICAL METHODS

Study	I	II	III	IV
Design	Retrospective	Retrospective	Retrospective	Retrospective
Population	Patients > 18 years with an IHCA where CPR was initiated	Patients > 18 years with an IHCA where CPR was initiated	Patients > 18 years with a bystander-witnessed OHCA where CPR was initiated	Patients > 18 years with an OHCA where CPR was initiated
Study Period	2007 – 2014	2018 – 2020	2011 – 2015	2008 – 2016
Age groups	18 – 50 years, 50 –65 years, >65 years	None	18 – 70 years, >70 years	None
Included (n)	14,933 patients	5,322 patients	21,799 patients	45,067 patients
Outcome	30-day survival	30-day survival	30-day survival	30-day survival
Univariate analysis	Mann-Whitney U test	---	Mann-Whitney U test	---
Multivariate analysis	Logistic regression	Relative variable importance using Random Forest (1000 trees)	Logistic regression	Relative variable importance using Random Forest (1000 trees)
Handling missing data	50 imputations using the MCMC* method	MICE**	Only cases with available delay times	MICE

*Markov Chain Monte Carlo method
** Multivariate Imputation by Chained Equations

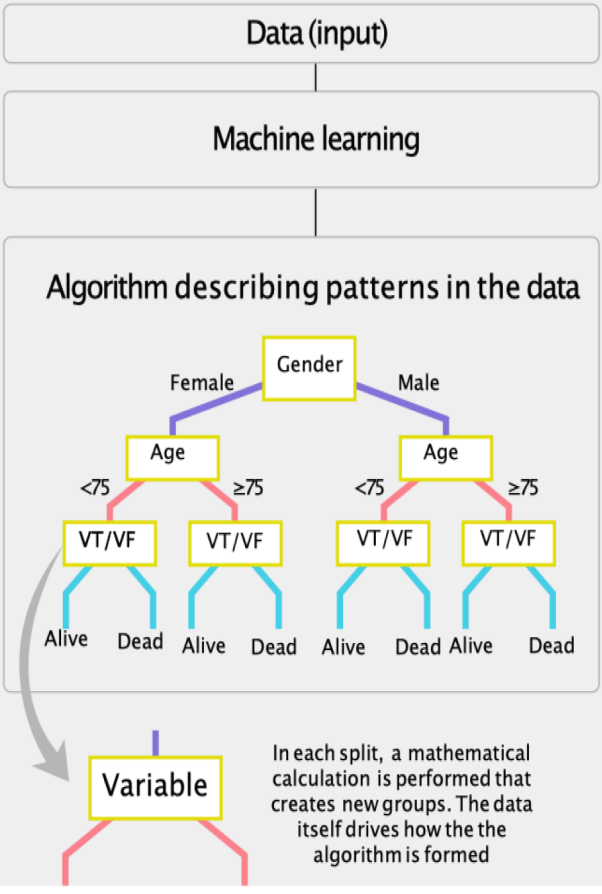
3.3 RANDOM FOREST

Random Forest is a tree-based ensemble model that was originally proposed by Breiman [140]. It has proven to be one of the most efficient prediction models, allowing for highly scalable modeling of structured data, including data with non-linear associations and complex higher-order interactions. Random Forest is similar to, although typically somewhat less efficient than, gradient boosting [141]. Random Forest allows for both classification and regression. It utilizes decorrelated decision trees. A decision tree is conceptually a decision algorithm that uses repeated splits to partition data into smaller portions. At the center of each split is a variable (e.g. age, sex, initial rhythm) which is used to subdivide the observations into subgroups according to distributions of that variable. A split is efficient if it maximizes the difference in the outcome (the dependent variable being studied, e.g. survival) across the resulting groups. Hence, a split is effective if it maximizes the heterogeneity – *with regards to the outcome* – in the resulting groups. Below is an example of a decision tree to determine if a person is male or female. It is evident from this example that a split is rarely perfect.



The *forest* in Random Forest refers to the fact that a large number of trees are required to produce an accurate prediction model, or more correctly, an *ensemble* of prediction models, with each tree being a single prediction model. Indeed, each individual tree constitutes a poor prediction model, but thousands of weak models (i.e. the ensemble) generally yield impressive predictive performance. *Random* refers to the fact that tree building follows a stochastic principle; each tree is built using a random sample of patients, and a random sample of their variables. These stochastic mechanisms improve generalizability and reduce overfitting. Another advantage of this algorithm is that it is easy to measure the relative importance of each variable (also referred to as *feature)* with regard to predicting the outcome being studied. This is typically done using *permutation importance*, which implies measuring the model performance before and after removing a predictor, whereby the removal of important predictors results in larger drops in accuracy [142].

	Machine learning (e.g. deep learning)
Input	Information (data)
Input volume	Can consider all available data
Learning method	General learning procedure
Algorithm creation	Data-driven
Algorithm example	



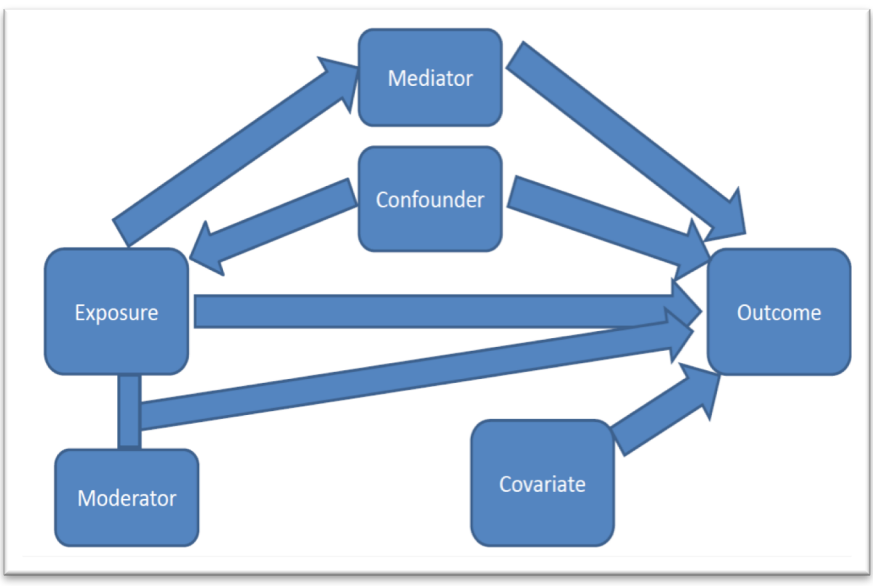
One of the limitations of Random Forest is that a large number of trees can make the algorithm too slow for real-time predictions. A more accurate prediction requires more trees, which results in a slower model, although this issue is not relevant to this thesis. It is also noteworthy that Random Forest is primarily a tool for predictive modeling and not for description, meaning that while predictions are easy to perform, inferences can be more difficult to make. This stands in stark contrast with conventional regression models that produce coefficients (e.g. odds ratios, hazard ratios, *etc.*) that are easy to grasp and interpret. Conventional regression models, however, have several drawbacks. They do not capture any non-linearity and require the analyst to define interactions, which is a complicated and time-consuming task. Moreover, as the number of predictors grows, the model becomes increasingly complicated which may hamper the model's ability to produce parameters. Machine learning methods, particularly Random Forest, do not exhibit these drawbacks.

3.4 CAUSAL INFERENCE

Causal inference is the process of determining the independent, i.e. actual, effect of a particular phenomenon that is a component of a larger system. It is important to discuss this in the context of machine learning because at the heart of clinical research lies the ambition to explain causal associations between various exposures and outcomes. While an increasing number of methods exist to perform causal inference using observational data, true causality is very difficult to infer from non-randomized experiments. Certainly, there are specific conditions in which observational design allows for causal inference (notably in the context of Mendelian randomization and instrumental variable analysis). However, even in these settings, causality may be rendered impossible if specific assumptions are violated [143]. Machine learning does not alter this

reality. While machine learning methods are generally better than conventional regression models, they do not remedy the problems with the observational design. As a general rule, if the validity of the inferences is a function of the predictive performance of the model, machine learning will generally outperform traditional regression frameworks. For example, when using propensity score for causal inference, machine learning can produce better balance (and thus increase the validity of the inferences) than regression methods. However, the mere use of machine learning methods does not automatically improve causal inference or the validity of the results. The same sound reasoning must be done when using machine learning, as when using regression methods.

A frequent issue when using machine learning to compute relative importance is the finding that some variables which are generally regarded as important may appear to be non-important. This is frequently an issue when saturating the model with a large number of predictors, which inevitably leads to effect mediation and collinearity.



For example, the introduction of both time to CPR and time to ambulance arrival in the same model may render one of these predictors completely unimportant in gradient boosting, despite the fact that the model may outperform any regression model. Thus, machine learning does not per se enable causal inference, but it may improve some of the inferences that are dependent on the predictive performance of the model. This may come at the cost of finding unexpected variable importance, which can be remedied with reasoning and subject matter knowledge.

The rationale for using machine learning for variable importance is the fact that these models entail a natural measure of importance, not dependent on the analyst's biases and modeling preferences. The variable importance produced by tree-based ensemble methods is completely data-driven and, in that sense, unbiased [144, 145].

4 OVERVIEW OF MAIN RESULTS

What follows is only a summary of the results of each study. The detailed results, along with tables and figures, can be found in each respective paper.

4.1 STUDY I: CHARACTERISTICS AND OUTCOME IN IHCA

IHCA AND GENDER:

The mean age of the patients in our cohort was 72.7 years. Almost 40% were women, who were significantly older than men. A history of myocardial infarction (MI) was significantly more common in men, as well as the odds of having MI as the underlying cause of the arrest. Men had 50% higher odds of being found in VT/VF, and 40% higher odds of receiving anti-arrhythmic drugs compared with women (unchanged when adjusting for MI as the underlying cause). Regarding the delay to alert, CPR, and defibrillation, no significant gender differences were found. Approximately one-third of the patients survived to 30 days, and around 90% of survivors had a favorable neurological outcome at discharge. Being male was associated with a 10% lower 30-day survival when adjusting for confounders.

IHCA AND AGE:

Patients were grouped into 3 age groups (18–50, 50–65, and >65 years). The proportion of ongoing MI at the time of the arrest was nearly doubled in patients >50 years of age. Despite higher rates of comorbidity, the rates of ECG monitoring were significantly lower in the older age groups. Younger age was significantly associated with having VT/VF as the presenting rhythm. A longer delay to defibrillation was significantly associated with increasing age. A lower frequency of intubation, vasopressors, and anti-arrhythmic drugs was seen with increasing age. Survival to 30 days had a significant inverse association with and increasing age. We did not

see a significant association between CPC score among survivors and age group.

4.2 STUDY II: PREDICTORS OF SURVIVAL IN IHCA USING MACHINE LEARNING

A shockable presenting rhythm was by far the strongest predictor of survival, followed by the location, cause of CA, the presence of hypoxia within one hour before the arrest. Age came next, followed by witnessed status and ECG-monitoring. Most comorbidities were of minor importance. Surprisingly, the delay from CA to alert, CPR, and defibrillation were some of the least important of all variables (paper II, figure 1).

When grouping variables together according to their clinical or logistical nature (paper II, figure 2), a shockable presenting rhythm remains on top in order of importance, followed by conditions preceding the arrest. The time and place of arrest come third. Age falls in the order of importance after interventions during CA, cause, and ward features. The patient's comorbidities, ejection fraction, and GFR, as well as gender and critical time delays, do not appear important (paper II, figure 2).

4.3 STUDY III: THE INFLUENCE OF AGE AND GENDER ON DELAY TO TREATMENT IN OHCA

AGE, GENDER, AND TREATMENT TIMES:

In patients over 70 years of age, we saw a significantly longer time to start CPR. The median time to CPR was 4 min vs 2 min between the older and younger age groups, $p < 0.0001$. We also noted a significantly longer delay to start CPR in female patients ($p = 0.0002$ (Paper III, table 1).

THE INFLUENCE OF AGE AND GENDER ON THE ASSOCIATION BETWEEN DELAY TIMES AND SURVIVAL:

For each 5-minute increase in the delay to call the EMS, we noticed a 41% drop in the odds for survival. We did not see a statistically significant interaction between age nor gender and the delay to call the EMS regarding 30-day survival. There was a steeper decline in survival in men than in women with increasing delay to CPR. The odds for survival declined by 48% for men (37% for women) for each 5-minute delay. We found no significant interaction between age nor gender and the delay to defibrillation regarding survival.

4.4 STUDY IV: PREDICTORS OF SURVIVAL IN OHCA USING MACHINE LEARNING

The top five predictors of survival in OHCA were: initial rhythm, age, early CPR (time to CPR and CPR before the arrival of EMS), time from EMS dispatch until EMS arrival (EMS response time), and place of CA. The five factors that were of the least importance were: sex, time of the day when CA occurred, time from emergency call to EMS dispatch, the region and calendar year when OHCA took place (Paper IV, figure 1A).

Among patients who were found in a shockable rhythm (figure B), the five most important predictors were: time to defibrillation, age, defibrillation (yes/no), place of cardiac arrest, and time from CA to CPR. The five least important predictors were the same as for the overall population (Paper IV, figure 1B).

For patients with a non-shockable initial rhythm, the most important predictors were age, defibrillation before EMS arrival, time to EMS arrival, place, and cause of CA. We did not note any particularly strong predictor, but a gradual decrease in the relative importance (Paper IV, figure 1C).

5 DISCUSSION

The overall aim of this thesis was to evaluate which factors are the most important for survival after cardiac arrest, with some emphasis on age and gender. In the analyses, we have included patients who suffered from a cardiac arrest where resuscitation was attempted inside as well as outside the hospital. In the evaluation of outcome, we have focused on 30-day survival and estimated cerebral function among survivors.

5.1 AGE AND SURVIVAL

Age is a strong predictor of survival in both IHCA and OHCA. In study II, we found that survival after IHCA decreases by 3% for every year of increasing age. In OHCA, survival chances decreased from 8% at 50 years of age, to 4% when patients are around 80 years of age. This is in line with a large body of literature [95, 98, 146-148]. Explanations to this finding range from the increased disease burden with increasing age, to the fact that the majority of CA in the elderly occurs in residential places, which usually comes with fewer witnesses and longer EMS response times. The elderly also tend to have lower rates of shockable rhythm, which could in turn, be explained by faster energy depletion in the aged heart, secondary to a decline in mitochondrial metabolism in aging muscle cells [149], leading to a more rapid conversion from VF/VT to asystole. That said, we found no evidence that the cerebral outcome of survivors is negatively affected by increasing age among patients suffering from IHCA. This finding supports earlier research that there does not seem to be a specific age threshold beyond which the chance of a meaningful recovery is excluded (at least from a cerebral performance standpoint) [148, 150]. However, one has to keep in mind that the elderly who suffer from IHCA and where resuscitation was attempted is a selected group of patients.

5.2 AGE AND THE DELAY TIMES TO TREATMENT

In IHCA, we note a non-significant trend towards a longer delay to call the rescue team among the elderly. In OHCA, we also found a longer delay to call the EMS in patients older than 70 years, albeit with a doubtful clinical relevance (A median delay of 2 minutes regardless of age, and the absolute standardized difference was 0.11).

There are not many studies examining the delay to alert from an age perspective. One recent study has shown no association between age and the delay to start CPR in IHCA, but a long delay to initial rhythm registration [148]. Our findings can be considered as positive news, since a shorter time to call the EMS has been shown to be an independent predictor of survival [121].

We did not see age-related differences in the delay to start CPR in IHCA. In contrast, we found a significantly longer time to start CPR in OHCA patients older than 70 years compared to those younger than 70 years (median 4 minutes vs 2 minutes). This agrees with previous research [151-153]. The mechanisms behind this finding can be multifaceted. In a recent study from Japan, where over 200,000 OHCA patients > 65 years of age were studied, it was found that approximately 70% of OHCA cases in this age group occurred at home, with significantly lower rates of bystander-witnessed arrests (34% at home vs 45% in public places), bystander CPR (45% vs 50% in public places), and defibrillation (0.1% vs 4% in public places) [154]. The study also reported significantly higher rates of asystole at home (75% at home vs 54% in public places). Therefore, it would be logical to think that in the CA-at-home-scenario, fewer people may be on the scene, and these witnesses may not act as quickly due to their older age and their increased comorbidity, thus leading to a slower activation of the chain of survival.

Increasing age was significantly associated with a longer time to defibrillation in IHCA ($p = 0.04$). We did not find significant differences in delay times to defibrillation in OHCA. The lack of a significantly longer delay to defibrillation with increasing age in OHCA can probably be due most defibrillation being performed by healthcare professionals who are trained to perform rapid defibrillation regardless of age.

5.3 AGE AND THE ASSOCIATION BETWEEN DELAY TIMES AND SURVIVAL

We had hypothesized that in OHCA, the association between delay to start of CPR and to defibrillation and 30-day survival would be stronger with increasing age. In other words, we expected that with increasing delay times, one would see a steeper decline in survival in the elderly compared to younger patients. However, we found no evidence of such interaction, meaning that the decline in survival with increasing delay to CPR and to defibrillation was similar in the two age groups. In a perfect world, this could mean that the elderly population in our cohort is medically optimized (at least from a cardiovascular perspective) to a good enough extent to cancel out the interaction between age and the association between treatment times and survival. A more likely scenario, however, is selection bias. In other words, the mere fact that the decision to resuscitate was made is indicative of the relatively good overall health of these elderly OHCA victims.

5.4 AGE AND THE AGGRESSIVENESS OF TREATMENT

Elderly patients suffering from IHCA tend to receive less aggressive treatment in the form of intubation, vasopressors, and anti-arrhythmic drugs. This is in line with previous reports [148, 155]. Multiple factors might be at play here. Firstly, despite the increase in the elderly population worldwide, the elderly population is consistently underrepresented in clinical trials [156-158]. This leaves clinicians in an awkward position when caring for elderly patients simply due to a lack of evidence for the use of various treatment alternatives. Secondly, there might be insufficient diagnostic work-up of elderly patients, leading to more uncertainty in the effectiveness of a given treatment. Another factor might lie at the opposite end of the spectrum, i.e. confirmed high burden of comorbidities (e.g. malignancy), which manifests in the belief that more aggressive treatment approaches might be futile.

5.5 GENDER AND SURVIVAL

We found male sex to be associated with a 10% lower 30-day survival compared with women after IHCA. This finding is in line with several previous studies [98, 159-161]. Female sex hormones have been hypothesized to might play a protective role in the setting of ischemia-reperfusion injury [162, 163]. Overall in the literature, any advantage that female gender might have in survival after a cardiac arrest has mainly been shown in younger women only [98, 100, 146]. In hindsight, an extension of study I could have been to do a subgroup analysis and see, for example, if women < 50 years of age would have a higher survival rate when other confounders were adjusted for. Several animal studies have reported that estrogen may affect and decrease the activation of the inflammation cascade and apoptotic signaling pathway [164-167]. In humans, however, an interesting study from 2014 has examined sex hormone levels in 149

cases of CA and 149 matched controls and found that low testosterone levels and high estradiol levels are particularly associated with the risk of CA [168]. In contrast, an analysis of CA in a large cohort of postmenopausal women showed no clear relationship between hormone replacement therapy and the incidence of CA [169]. Thus, the role of sex hormones seems to remain an open question, but when incorporating a large number of other factors and using machine learning, sex does not come out to be a particularly strong predictor of survival in the overall picture, neither in IHCA nor OHCA.

5.6 GENDER AND DELAY TIMES TO TREATMENT

In IHCA, we found no significant gender differences in the delay to call for the rescue team, to start CPR, or to defibrillation. In OHCA women had a longer delay to CPR ($p = 0.0002$). A caveat was that the standardized difference was only 0.06, rendering the practical implications of this finding questionable. Ultimately, this finding might not be that far from the truth after all, since women have been reported to receive bystander CPR less often than men [170-173]. Thus, we cannot exclude that there are minor differences between the sexes in delay times to CPR, at least in the setting of OHCA. This may be related to previous findings of sex differences in the early treatment of acute coronary syndrome, where women had a treatment delay [174].

5.7 GENDER AND THE ASSOCIATION BETWEEN DELAY TIMES AND SURVIVAL

In OHCA, the interaction between gender and the delay to CPR regarding survival was significant. The interpretation of this finding is that a longer delay to start CPR on men carries a more pronounced negative effect on survival compared to women. This could be explained by the higher rates of cardiovascular disease in men who suffer from OHCA [100, 161]. A different etiology of CA between men and women could also be a contributing factor to this discrepancy [175, 176]. Another contributing factor may be that survival was much higher among men than among women if the delay to CPR was very short.

5.8 INITIAL RHYTHM

Our results confirm what has been shown in earlier research regarding the importance of having a shockable initial rhythm for survival, regardless of where the cardiac arrest takes place [45, 111, 114, 115]. An earlier meta-analysis of 12 studies involving over one million patients has shown that in patients with non-shockable rhythm, spontaneous conversion to a shockable rhythm is associated with a greater chance of return of spontaneous circulation, as well as greater odds of survival and favorable neurologic status at 30 days [177]. The most obvious explanation of why shockable rhythm is so important is due to the possibility of reestablishing organized electrical activity and myocardial contraction through rapid defibrillation. It is important to underline “rapid defibrillation”. Indeed, in the case of ventricular fibrillation (VF), prolonged time to defibrillation allows for the electrical activity in the myocardium to gradually subside, making the cardiomyocytes less responsive to defibrillation. In addition, permanent damage to the central nervous

system and other organs begins to occur, if VF is allowed to continue for more than four minutes [178-180].

5.9 DELAY TO TREATMENT

DELAY TO ALERT

The relationship between the delay to alert and survival in cardiac arrest is sparsely addressed in the literature. This is especially true for IHCA. The vast majority of studies have focused on the time to CPR and time to defibrillation. In IHCA, the concept of "alert" has often been tied to monitoring. An example of this, is the 2013 consensus statement from the American Heart Association, emphasizing early recognition and rescue of the deteriorating patient at risk of cardiac arrest [181]. In study II, the time to alert after IHCA did not appear to be important in the overall picture. A possible explanation is that approximately 90% of our cohort was alerted within two minutes. Another possible explanation is that the importance of "time to alert" as a variable was mediated by two other factors i.e. either being witnessed or being ECG-monitored.

In OHCA, it has been shown that a reduced delay from the estimated time of collapse until the call for an ambulance increases the chance of survival [121]. We see similar results in study III. However, in the Random Forest model of study 4, the delay time to alert appears to be of moderate importance for the chance of survival after OHCA.

DELAY TO CPR AND TO DEFIBRILLATION

Shorter delays to CPR and to defibrillation have been proven to increase survival [26, 30, 182-184]. Both of these delay times appeared to be of little importance in the Random Forest model of IHCA in study II. There is a couple of possible explanations for this finding. Firstly, eighty percent of the patients in our cohort received CPR within one minute from collapse, and around 70% were defibrillated within two minutes. This rapid response is likely to have limited the expected deterioration of shockable rhythm into a non-shockable rhythm [30]. Thus, having the sustained shockable rhythm (the most important predictor of survival overall) may mediate the effect of rapid CPR. Indeed, survival rates have been reported to be > 70% for victims who received their first defibrillation within the first three minutes after collapse [185]. It is also plausible that in recent years, IHCA has been getting more readily recognized, leading to the initiation of rapid, good quality CPR and rendering it difficult to demonstrate a clear association between these time delays and the final outcome. Furthermore, a prolonged delay from collapse to CPR rarely happens nowadays in the modern treatment of IHCA, which may explain why previous studies which were performed two decades ago demonstrated a stronger association between delay from collapse to CPR and survival after IHCA [186].

Out of the different interventions during IHCA, being defibrillated before the arrival of the RRT appears to be important. In the literature, prompt defibrillation (<2 minutes) has not only been linked to higher survival rates to hospital discharge [187], but also to long-term survival to 5 years [188]. What our study adds is that this remains true, even when taking several other factors into account. Thus, prompt defibrillation should be further emphasized, even before the RRT has reached the patients' bedside.

5.10 LOCATION OF CARDIAC ARREST

In both IHCA and OHCA, the actual location of the arrest appears important. In fact, it seems more important than the geographical location where OHCA took place. In IHCA, the location can be synonymous with the type of ward. The odds ratio for survival nearly doubled in monitored wards vs. a regular ward (paper II, table 3). This is consistent with previous reports [189-192] and most likely not only explained by the degree of monitoring but also the number of health care providers in the ward as well as their educational level.

Our results on the importance of the location for OHCA confirm what has been shown in earlier studies. Worldwide, approximately 65 – 80% of OHCA occur at home, and these cases have lower rates of shockable rhythms compared to OHCA occurring in public places, with delays in recognition, initial response including bystander CPR, as well as lower survival [193-196].

One may summarize the experiences from IHCA and OHCA by saying that the preparedness and facilities are important regardless of whether cardiac arrest occurs inside or outside the hospital walls. Therefore, future research should focus on how to improve the facilities in high-risk areas. In terms of IHCA, an increase in monitoring facilities also in general wards may be an alternative. In OHCA placement of AEDs closer to patients' homes is one reasonable approach.

Regarding the geographical location, earlier studies have demonstrated regional differences in survival after OHCA, which points to regional disparities in CA care from the prehospital to the post-resuscitation stage [52, 194, 197, 198]. Experiences from Sweden, however, did not suggest any difference in survival in relation to population density within a specific region. Although the

EMS response time was longer in areas with a lower population density, this was counteracted by a higher rate of bystander CPR in these regions [134].

We found the geographical location to be of little importance in the overall picture, both in IHCA and OHCA. This finding can have multiple explanations. Firstly, the population in Sweden might be more homogenous in baseline health status compared to other places, thus reducing the disparities in outcome. Thus, differences in survival that stem from baseline population health, socioeconomic factors, and the underlying risk of cardiac arrest would be diminished. Another explanation might be related to the selection bias and differences in EMS systems around the world. Indeed, a recent study from Denmark has shown that survival differences between five different Danish regions were found more comparable in cases where EMS response time was shorter than 11 minutes [199].

5.11 Cause of cardiac arrest

The etiologies of cardiac arrest have traditionally been described as cardiac or non-cardiac in the literature. In many instances, patients with no obvious cause of collapse are generally classified as cardiac. In addition, discrepancies between clinical and postmortem findings often render the causes of cardiac arrest uncertain. Overall, half of all IHCA cases have been reported to be attributable to cardiac causes, such as myocardial infarction, arrhythmia, or heart failure [190, 200, 201]. Cardiac causes were the most prevalent causes in both studies II and IV. In IHCA, we show that the cause of CA appears to be a very good predictor of survival. Indeed, we note that having a primary arrhythmia as the cause of IHCA carried more than a five-fold increase in the odds for survival. The cause of CA appears to be of more moderate importance in OHCA. This may have to do with greater uncertainty about the underlying etiology after OHCA where the EMS staff often make a qualified guess about the underlying etiology. The difficulty in estimating the etiology of OHCA as cardiac and non-cardiac has resulted in an altered terminology according to the most recent Utstein criteria, where cardiac etiology has been replaced by medical etiology [13]. Overall, the importance of the cause of CA makes intuitive sense, especially with regard to potentially reversible causes.

5.12 MONITORING, BYSTANDER-CPR, AND WITNESSED STATUS

By this point, it is obvious that any effort to decrease delay to treatment is crucial for cardiac arrest survival. Monitoring inside the hospital, and having a witnessed arrest (both inside and outside the hospital) are likely to contribute to shortened response times and thereby increase the possibility for more rapid treatment. In study II, the odds ratio for survival nearly doubled in monitored wards vs. regular wards (paper II, table 3). Interestingly, a recent survey from Sweden reported that even socioeconomic differences affect the degree of monitoring, suggesting that patients with low socioeconomic status could be subject to discrimination when suffering IHCA [135]. While monitoring every single patient in the hospital does not seem feasible, one could at least argue for an increase in the monitoring capacity since there is overwhelming evidence pointing towards the importance of ECG-monitoring for IHCA survival [147, 190, 202-204]. A simplification of monitoring in general wards including monitoring of the oxygen saturation instead of EKG may be an alternative. Even outside the hospital, monitoring of patients with for example heart failure has become a reality [205, 206]. Research in this field will most likely increase rapidly during the next few years.

The terms “witnessed status” and “bystander-CPR” seem to be used somewhat interchangeably in the literature [207]. Therein lies the assumption that all (or most) witnessed arrests are arrests where bystander-CPR is initiated. However, this assumption might not necessarily be correct. A small German study from 2018 that involved telephone interviews with bystanders of OHCA has demonstrated that if the patient was already found unconscious, bystander-CPR was performed in approximately 75% of cases. In contrast, if the collapse itself was witnessed, only 50% of bystanders performed CPR. In other words, if the change of consciousness was

witnessed, then that led to significantly lower rates of bystander-CPR. In addition, if the bystander detected breathing of any kind, CPR was performed significantly less frequently (83% in apnea vs 54% in agonal breathing) [208]. One might wonder if this was due to the lack of awareness that a visible change in consciousness might indicate a cardiac arrest. What we do know, is that bystander-CPR does not only increase survival [209-211], but it has even been demonstrated that it allows for a whole minute of extra delay in EMS response time without a drop in survival with good neurological outcome [212].

5.13 Cardiac arrest and the time of day

Survival rates from serious medical conditions, including cardiac arrest, are lower during nights and weekends [132, 213-215]. The reason for the lower survival rates during nighttime is likely multifaceted, possibly encompassing clinical/biological differences in patient characteristics as well as differences in hospital staffing and operational factors. In the same vessel, a disproportionately high incidence of unwitnessed arrests has been reported during night hours [189]. We notice that the time of the day does not seem to be a particularly strong predictor of survival overall neither after IHCA nor OHCA when using machine learning for the assessment. However, in the subgroup of patients with non-shockable rhythm in OHCA, time of the day appeared to be more important. This may to some extent be explained by a higher probability of having a witnessed arrest and receiving bystander CPR during the daytime. It has previously been reported that the day of the week and the time of the day appear to be of importance for the chance of survival after IHCA [215]. Indeed, recent reports show that nighttime patients had significantly decreased resuscitation efforts by bystanders compared to those with evening and daytime OHCA [216, 217].

5.14 COMORBIDITY AND CARDIAC ARREST

The evidence of the relationship between comorbidities and outcome after IHCA is sparse in the literature. Cardiac comorbidity (having an ongoing MI and heart failure) is virtually responsible for the entire weight of the comorbidity group in IHCA (study II, figure 2). Diabetes, being a notorious risk factor of atherosclerosis, seems to play a minor role, and so does having an MI in the patients' previous medical history. Hjalmarsson et. al have recently shown that age-adjusted Charlson comorbidity index (ACCI) scores remained almost constant from 2007 - 2015, while survival more than doubled over time in patients with low or moderate ACCI scores [218]. This suggests that comorbidity might not be such an important predictor of survival. Our results support those findings and may serve as a reminder in clinical settings, where one might be inclined to make quick decisions about either starting or prematurely ending resuscitation efforts due to the degree of comorbidity. However, one has to keep in mind that the patients with the most severe comorbidity were not included in the analyses. As a result, resuscitation is usually attempted only on 10-15% of the total number of patients suffering from IHCA [219, 220]. Comorbidities were unfortunately not available to be included in our Random Forest model for OHCA in paper IV. However, there is evidence that with a heavier burden of comorbidity, there is a drop in the chance of survival to 30 days after OHCA [221]. It is reasonable to assume that comorbidity plays a stronger role in the chance of survival after OHCA than after IHCA simply because the selection of cases for a resuscitation attempt is not that strong after OHCA as compared with IHCA.

5.15 WARNING SIGNS AND SYMPTOMS

Warning signs preceding the arrest are important for predicting survival in IHCA. Indeed, a high National Early Warning Score (NEWS) in general has been associated with a high risk of death in IHCA [222]. Individual warning signs preceding IHCA have not been stratified in order of their importance in earlier research. Hypoxia seems to carry most of the weight in this group (study II, figure 2). This underlines the importance of recognizing hypoxia as a warning sign prior to IHCA.

Our findings are in some agreement with previous research indicating that the deterioration of respiratory parameters is more alarming than the deterioration of circulatory parameters [223-225]. Our data may indicate that monitoring of oxygen saturation should be more frequently used.

We did not study the importance of warning symptoms prior to OHCA. Previous research has highlighted that the proportion of OHCA that was witnessed by EMS (indicating that patients dialed 112 due to warning symptoms) has increased over time in Sweden [226]. It has also been shown that the increase in crew witnessed cases has been one of the factors that may explain the increase in 30-day survival after OHCA that has been shown in Sweden [227].

6 STRENGTHS AND LIMITATIONS

6.1 REGISTER STUDIES

The most obvious strength in the SRCR is the size of the data it contains, as well as the increasing details with which cardiac arrest events are being recorded. Another aspect is the near-complete national coverage it exhibits, which helps to reflect an overarching image of different aspects of cardiac arrest in Sweden. As with all register studies, there can be missing data. We have attempted to deal with that issue using different methods throughout the studies in this thesis.

In terms of IHCA, one of the problems is that there are patients where resuscitation is attempted although the rescue team is not called upon. These cases mostly take place in the intensive care unit, in the angiography laboratory, or in the operation theatre. This makes it difficult for the register staff to control whether all these cases have been reported to the register. The IHCA part of the register has been validated. A good correlation between register data and source data has been documented for most of the variables. However, the first recorded rhythm and etiology are missing in a relatively high proportion of the patients. Efforts will be raised during the coming years to assess the external validity of the register.

CPC scores have been criticized for having poorly defined, subjective criteria, and questionable associations with measures of disability and quality of life, in addition to lacking psychometric validation [228, 229]. It also has the drawback of having substantial inter-rater reliability, due to the lack of formal standardized training in calculating CPC scores [230]. Several alternatives have been proposed, including the Cerebral Performance Categories-Extended (CPC-E), Modified Rankin Scale (mRS), and discharge disposition.

The problem is, different instruments produce widely different estimates of what is considered as a “good outcome”. There does not seem to be a consensus in the literature on which instrument is best, and thus CPC remains the “historical” gold standard.

In terms of OHCA, smaller studies have indicated that the internal validity is relatively high. However, studies on external validity indicated that about 25% of the patients were not prospectively reported to the register [231]. Since then, the missing cases have started to be retrospectively reported to the register by local coordinators each year.

For both parts of the register, we lack the information on all patients who suffer from cardiac arrest regardless of whether CPR was attempted or not. Such information would be valuable to obtain an overview of all patients who theoretically would have been available for resuscitation. Who are these patients where CPR is not attempted? In OHCA, one can assume that the majority are patients who were dead on arrival had unwitnessed OHCA/no bystander CPR, or very long EMS response times, or both. In IHCA, one may assume that the majority had DNR orders. It is also worth mentioning that there are also patients with DNR orders in the prehospital setting. One unanswered question is whether DNR routines are different from hospital to hospital in Sweden? And are there patients who suffer from OHCA and where the witnesses choose not to call for EMS due to cultural reasons? We simply do not know.

6.2 MACHINE LEARNING AND RANDOM FOREST

Machine learning is undoubtedly one of the most important tools in medical research. Modern machine learning is capable of deciphering complex multi-dimensional data on a scale and complexity beyond the capabilities of conventional regression models. We used machine learning to quantify the relative importance of several predictors of survival in cardiac arrest. We recognize that conventional regression models are, however, capable of handling the number of predictors that were introduced into our models. We justify the use of machine learning by the fact that we aimed to provide completely data-driven results, with no subjective variable selection.

However, we encountered some unexpected results. An example from study IV is the time from alert to EMS dispatch i.e. the handling time at the dispatch center. Theoretically, this should play a role in the chance of survival after OHCA, and that has been shown in earlier work from Finland [125]. In our study, this variable seems almost completely irrelevant, yet it is probably more likely that its effect has already been mediated by variables that appear more important in the model, namely time from CA to CPR and time from EMS dispatch to EMS arrival at the patient's side. This is a good example of one main drawback of machine learning and Random Forest, which not only requires huge amounts of good quality data but mainly focuses on prediction, rather than explanation [232].

It is worth considering that certain variables were not available to be included in the ML models. Examples include socioeconomic factors, ethnicity, and comorbidities (in the case of OHCA).

7 FUTURE PERSPECTIVES

Realistically, it is nearly impossible to draw a line in the sand regarding exactly when to start, or not start, treatment in cardiac arrest. This could, however, be doable using a large database with plenty of variables and a robust machine learning algorithm to predict survival. In theory, this could be as simple as entering the pre-determined 5 or 10 most important patient variables into an algorithm. The algorithm would then calculate the likelihood of survival with favorable neurologic function, which could guide clinical decision-making. Such an algorithm would be the closest one can get to an actual crystal ball, and it might not be so far off into the future. Recently, researchers from the Mayo Clinic were able to create an AI algorithm that picked up the electrical signature of atrial fibrillation during sinus rhythm with 95% accuracy, which is practically impossible for clinicians [233].

In IHCA, recognizing the presence of hypoxia within one hour before the arrest appears to be an important predictor for a reduced chance of survival. A known shortcoming of the currently implemented early warning systems such as NEWS is their poor sensitivity [234]. In addition, there is heterogeneity in the methodologies and performance metrics used in validating early warning systems, making it difficult to interpret and compare the performance of these systems [235]. Here too, the implementation of machine learning algorithms can be of great help. Indeed, a recent multicenter study has demonstrated that a deep learning algorithm was able to achieve high sensitivity and a low false-alarm in detecting patients with IHCA [236]. In addition, a recent meta-analysis has also shown that ML-based early warning systems incorporating easily accessible vital sign measurements do not only exhibit improved prediction performance compared to traditional risk-stratification tools, but also decreased false alerts and increased early detection of warning signs for timely intervention [237].

ECG monitoring systems have been an integral part of healthcare systems or the past few decades, and have constantly evolved over time due to new technologies [238-240]. An example of this is wearable wristbands or activity trackers. Similar to a pulse oximeter, these trackers use a light-emitting diode (LED) to illuminate the capillary bed and thus monitor for pulsatile changes in light absorption [241]. Some of the commercially available wristbands have been shown to have good performance overall, with a +/- 20 bpm difference from an ECG [242]. In fact, there is an ongoing clinical trial for predicting heart failure decompensation utilizing an FDA-approved patch with an ECG monitor and radiofrequency sensor and transmitter to measure pulmonary fluid content [243]. These technologies, combined with a robust cardiac-arrest-predicting algorithm can likely do wonders for early detection and warning, thus shortening response times in OHCA. An example of such an algorithm is one developed by Kwon et al. [244], which did not only predict CA using a conventional 12-lead ECG, but also with a wearable device using a single-lead ECG. Indeed, cardiovascular monitoring is on the verge of dramatic technological advances through developments in biosignal acquisition, automated diagnosis, and secure data transmission [245].

An important development in the cardiac arrest field is the increased involvement of laypersons in response to OHCA through mobile phone technology. In many cases, first responders alerted through either text messages or mobile apps were able to reach the patient, start CPR, and attach an Automated External Defibrillator (AED) before ambulance arrival, A recent meta-analysis of such efforts showed that they are effective in improving the rates of CPR performed before ambulance arrival and, and probably also increase survival to 30 days [246].
One of the promising advances is the utilization of drone-delivered defibrillators. One study from Sweden has shown that fully autonomous drones were able to deliver an AED using less time than

the EMS in all simulated cases, thereby shortening the delay to defibrillation by up to 16 minutes [247]. Chu et al. have taken it a step further and combined this with machine learning. They developed specific rules for the dispatch of a network of drones carrying defibrillators, and deployed them based on a predicted ambulance response time (i.e. dispatching a drone only in cases where it is predicted to arrive no more than 60 s after the ambulance). They demonstrated that machine learning-based dispatch rules can achieve decreased response times by approximately two minutes, while substantially reducing the drone flight times by 30% compared to universal drone dispatch [248].

In conclusion, it seems like with the increasingly large amount of data being collected in the cardiac arrest field, and the ever-increasing computational power and technology adoption, the most obvious area where we can improve cardiac arrest survival both in and out of the hospital would be to design and test machine learning algorithms to aid in monitoring, early warning/detection, dispatch of emergency services, and selection of patients where resuscitation efforts are deemed most fruitful. An example of this, albeit not using machine learning, is the Prediction of outcome for In-Hospital Cardiac Arrest (PIHCA) score that has recently been developed by Piscator et al, which appears promising as an objective tool in the prearrest outcome prediction after IHCA [249].

8 ETHICAL CONSIDERATIONS

The ethical review board at the University of Gothenburg has approved all studies in this thesis. The privacy and anonymity of the individuals are secured since all the data are analyzed at a group level. Moreover, survivors are informed about their inclusion in the SRCR and are given the opportunity to opt out. So far, no patients that we are aware of have requested to withdraw their data. In addition, our studies did not involve any interventions that could have a negative influence on the outcome. Instead, any eventual individual disadvantages were assumed to be outweighed by the potential future benefits from a broader understanding of the subject matter.

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