From the Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

PREDICTION AND MONITORING OF IN-HOSPITAL CARDIAC ARREST

Anna Thorén, M.D.

Stockholm MMXXIII

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8017-138-0
Cover illustration: Work in the public domain.

Prediction and monitoring of in-hospital cardiac arrest

Thesis for Doctoral Degree (Ph.D.)

By

Anna Thorén

The thesis will be defended in public in the main auditorium at Danderyd University Hospital, Stockholm, Sweden on

November 17, 2023, at 09:00 a.m.

Principal Supervisor:
Threse Djärv
Professor, M.D.
Karolinska Institutet
Department of Medicine, Solna
Center for Resuscitation Sciences

Co-supervisors:
Johan Engdahl
Associate Professor, M.D.
Karolinska Institutet
Department of Clinical Sciences
Danderyd Hospital
Division of Cardiovascular Medicine

Thomas Kahan
Professor, M.D.
Karolinska Institutet
Department of Clinical Sciences
Danderyd Hospital
Division of Cardiovascular Medicine

Araz Rawshani
Associate Professor, MD.
University of Gothenburg
Department of Molecular and Clinical Medicine
Division of Medicine

Opponent:
Eldar Søreide
Professor, M.D.
Stavanger University
Faculty of Health Sciences

Examination Board:
David Smekal
Associate Professor, MD.
Uppsala University
Department of Surgical Sciences,
Anaesthesiology and Intensive Care

Johanna Albert
Associate Professor, MD.
Karolinska Institutet
Department of Medical Sciences
Danderyd Hospital
Division of Anaesthesia and Intensive Care

Ulf Schött
Professor, MD.
Lund University
Department of Clinical Sciences
Division of Anaesthesia and Intensive Care

To Robert, Julia and Jacob

"Do not judge me by my successes; judge me by how many times I fell down and got back up again"

Nelson Mandela

Resilience

POPULAR SCIENCE SUMMARY OF THE THESIS

Cardiac arrest (CA) occurs when the heart all of a sudden stops beating or beats too fast to be able to pump blood, causing a lack of oxygen in vital organs of the body, such as the brain. In a matter of seconds, a person suffering from CA becomes unconscious and stops breathing normally. Within minutes, the cells of the brain and other organs are damaged, and if left untreated, a CA leads inevitably to death.
The most important initial treatment is to immediately provide an artificial circulation of oxygenated blood by means of Cardiopulmonary Resuscitation (CPR), including chest compressions, mouth-to-mouth ventilation, and defibrillation. This treatment must be continued without interruptions until more advanced emergency treatment is available.

Each year, approximately 2,400 hospitalized Swedish patients suffer from CA where resuscitation is attempted. Despite these events occurring in an environment with access to immediate and advanced emergency treatment, only one patient out of three will survive. Furthermore, these CAs frequently do not come unexpected; patients at risk often show signs of deterioration prior to in-hospital cardiac arrest (IHCA), and many cases are retrospectively considered potentially avoidable.

The National Early Warning Score (NEWS), and the revised version NEWS 2, are standardised scoring models based on vital signs, for example respiratory rate and blood-pressure, designed to facilitate the early identification of general ward patients at risk of IHCA, unplanned admission to the Intensive Care Unit (ICU), or death. The NEWS is used to monitor patients, but also to trigger a team of specially trained physicians and nurses from the ICU in case of deterioration. These teams are called Rapid Response Teams (RRTs), operating in hospitals 24/7 to ensure a timely clinical response for patients at risk.

The prevention of IHCA has been receiving increased attention in CA research over the last decade, and the overall aim of this thesis is to contribute to improved preventive strategies.

In study I, we investigated how 30-day survival after IHCA was affected by electrocardiogram (ECG) monitoring at the time of collapse. We also studied clinical factors of importance influencing the decision of whether patients were ECG monitored adjacent to CA.

We found that ECG monitoring in IHCA was associated with a higher likelihood of survival. The most important factor influencing whether a patient was ECG monitored was which type of hospital ward the patient was admitted to. Furthermore, only every other patient suffering from IHCA was ECG monitored, with substantial variations across hospitals and between regions.

In study II, we studied the abilities of NEWS and NEWS 2 to identify patients at risk of IHCA, unplanned admission to the ICU or death within 24 hours of an RRT-review. NEWS and NEWS 2 performed similarly; however, the predictive performance was not sufficient to serve as a risk stratification tool. Therefore, **in study IV**, we explored if adding information on age to NEWS 2 would improve the predictive power in the same group of patients, reviewed by RRTs. We found that adding age as a covariate improved the ability to identify patients who had an increased risk of death within 30-days, with the greatest benefit identified in the group of patients aged 45-54 years. Furthermore, we investigated the long-term prognosis of patients reviewed by RRTs, finding a high long-term mortality among patients reviewed by RRTs, where one in three patients were dead within 30 days.

In study III, we investigated if there was any difference in 30-day survival between patients suffering from IHCA who were reviewed by an RRT within 24 hours prior to IHCA, as compared to those without such review. We also investigated the circumstances surrounding the RRT-review and the effect of different interventions, with a goal to identify risk factors that could be addressed in future preventive strategies.

We found that the prognosis for RRT-reviewed IHCA patients was worse compared to patients not reviewed by RRTs. A respiratory cause of CA was more common among patients who were not reviewed by RRTs. Our findings indicate that these RRT-reviewed patients were likely severely ill, but also that the aim of RRTs primarily is to prevent IHCA, and to a lesser extent improve outcomes once patients are suffering from CA; although substantial efforts were made to improve the condition of the patients and prevent IHCA, resuscitation was still unsuccessful. Furthermore, we identified patients with abnormal respiratory vital signs as a particular high-risk group. Early identification of these patients in general wards, followed by timely interventions, could have a potential to prevent further deterioration and progress into IHCA.

ABSTRACT

Background: In-hospital cardiac arrest (IHCA) is a global health concern of major importance, associated with a poor prognosis. IHCA is frequently heralded by a deterioration of vital signs, and many cases are considered preventable. Hence, prevention has become a key strategy. The overall aim of this thesis was to study the prevention of IHCA, by means of prediction and monitoring, with a view to improve patient safety.

Methods: Study I and III are observational cohort studies, based on the Swedish Registry of Cardiopulmonary Resuscitation (SRCR). In study III, we also collected additional data from medical records in a small, hypothesis-generating group of patients.

Study II and IV are prospective, observational cohort studies based on patients reviewed by Rapid Response Teams (RRTs) in 26 and 24 Swedish hospitals, respectively. In study IV, additional data on long-term survival was obtained from either medical records or the personal information directory, containing population registration data.

Specific study aims and results: In ***study I***, we investigated how 30-day survival after IHCA was influenced by ECG monitoring at the time of collapse, as well as clinical factors that determined whether patients were ECG monitored adjacent to cardiac arrest (CA).
In all, 24,790 patients were enrolled in the SRCR between 2008 and 2017. After applying the exclusion criteria, 19,225 patients remained, of which 52% were monitored at the time of collapse. In all, 30-day survival was 30%. ECG monitoring at the time of CA was associated with a Hazard Ratio of 0.62 (95% Confidence Interval 0.60-0.64) for 30-day mortality. The strongest predictor of ECG monitoring adjacent to IHCA was location in hospital. There were tangible variations in the frequency of patients who were ECG monitored at the time of collapse between Swedish regions and across hospitals.

In ***study II***, we investigated the predictive power of NEWS 2, as compared to NEWS, in identifying patients at risk of Serious Adverse Events (SAEs) within 24 hours of an RRT-review. In all, 1,065 patients, reviewed by RRTs in general wards during the study period between October 2019 and January 2020, were included. After applying the exclusion criteria, 898 patients were eligible for complete case analyses.

In all, 37% of the patients were admitted to the Intensive care unit (ICU) within 24 hours of RRT-review. In-hospital mortality and IHCA were uncommon (6% and 1% respectively). The Area Under the Receiver Operating Characteristic (AUROC) for both NEWS and NEWS 2 was 0.62 for the composite outcome, and 0.69/0.67 for mortality. Regarding the outcome unanticipated ICU admission, the AUROC was 0.59 and 0.60, respectively, while the AUROC for IHCA was 0.51 (NEWS) and 0.47 (NEWS 2), respectively.

In ***study III***, we investigated 30-day survival and ROSC in patients suffering from IHCA, who were reviewed by an RRT within 24 hours prior to the CA, as compared to those without such review. Furthermore, we studied patient centred factors prior to RRT activation, the timeliness of the RRT-review as well as the reason for the RRT-review. We also investigated the association between RRT interventions and outcome.

During the study period between 2014 and 2021, 19,973 patents were enrolled in the SRCR. After applying the exclusion criteria, 12,915 patients remained. Among these IHCA patients, there was an RRT/ICU contact within 24 hours prior to the CA in 2,058 cases (19%).

The adjusted 30-day survival was lower among patients reviewed by an RRT prior to IHCA (25% vs. 33%, p <0.001). Regarding ROSC, we did not observe any difference between the groups. The propensity score based Odds Ratio for 30-day survival was 0.92 for patients who were reviewed by an RRT (95% CI 0.90 to 0.94, p <0.001), as compared to those who were not RRT- reviewed within 24 hours prior to IHCA. A respiratory cause of CA was more common among IHCA patients who were reviewed by an RRT. In the small, explorative subgroup (n=82), 24% of the RRT activations were delayed, and respiratory distress was the most common RRT trigger. We observed a significantly lower 30-day survival among patients triaged to remain at ward compared to those triaged to a higher level of care (2% vs. 20%, p 0.016).

In ***study IV***, we explored the impact of age on the ability of NEWS 2 to predict IHCA, unanticipated ICU-admission, or death, and the composite of these three SAEs, within 24 hours of review by an RRT. Furthermore, we aimed to investigate 30-, 90- and 180-day mortality, and the discriminative ability of NEWS 2 in the prediction of long-term mortality among RRT-reviewed patients.
In this multi-centre study based on data prospectively collected by RRTs, the NEWS 2 scores of all patients were retrospectively, digitally calculated by the

study team. Age was analysed as a continuous variable, in a spline regression model, and categorized into five different models, subsequently explored as additive variables to NEWS 2. The discriminative ability of NEWS 2 in predicting 30-day mortality improved by adding age as a covariate (from AUROC 0.66, 0.62-0.70 to 0.70, 0.65-0.73, p=0.01). There were differences across age groups, with the best predictive performance identified among patients aged 45-54 years. The 30-, 90-and 180-day mortality was 31%, 33%, and 36%, respectively.

Conclusion: ECG monitoring at the time of IHCA was associated with a 38% reduction of adjusted mortality. Despite this finding, only one in two IHCA patients were ECG monitored. The most important factor influencing ECG monitoring was which type of hospital ward the patient was admitted to. The tangible variations in the frequency of ECG monitoring adjacent to IHCA observed between Swedish regions and across hospitals need to be investigated in future studies. Guidelines for the monitoring of patients at risk of CA could contribute to an improved outcome.

The prognostic accuracy of NEWS 2 in predicting mortality within 24 hours of an RRT-review was acceptable, whereas the discriminative ability in prediction of unanticipated ICU-admission and the composite outcome was rather weak. Regarding the prediction of IHCA, NEWS 2 performed poorly. There was no difference in the prognostic accuracy between NEWS and NEWS 2; however, the discriminative ability was not considered sufficient to serve as a triage tool in RRT-reviewed patients.

In-hospital cardiac arrest among patients who were reviewed by an RRT prior to CA was associated with a poorer prognosis, and a more frequent respiratory aetiology of the CA. In the explorative sub-group of patients, RRT activation was frequently delayed, the most common trigger for RRT-review was respiratory distress, and escalation of the level of care was associated with an improved prognosis. Early identification of patients with abnormal respiratory vital signs, followed by a timely response, may have a potential to improve the prognosis for patients reviewed by an RRT and prevent IHCA.

Adding age as a covariate improved the discriminative ability of NEWS 2 in the prediction of 30-day mortality among RRT-reviewed patients. The ability differed across age categories. Overall, the long-term prognosis of RRT-reviewed patients was poor. Our results indicate that age merits further validation as a covariate to improve the performance of NEWS 2.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original publications and studies, which will be referred to by their roman numerals:

I. Thorén A, Rawshani A, Herlitz J, Engdahl J, Kahan T, Gustafsson L, Djärv T.

   ECG- monitoring of in-hospital cardiac arrest and factors associated with survival

   Resuscitation. 2020 May;150:130-138

II. Thorén A, Joelsson-Alm E, Spångfors M, Rawshani A, Kahan T, Engdahl J, Jonsson M, Djärv T.

   The predictive power of the National Early Warning Score (NEWS) 2, as compared to NEWS, among patients assessed by a Rapid response team: A prospective, multi-centre trial

   Resuscitation Plus. 2021 Dec 24;9:100191.

III. Thorén A, Jonsson M, Rawshani A, Herlitz J, Spångfors M, Joelsson-Alm E, Jakobsson J, Kahan T, Engdahl J, Jadenius A, Boberg von Platen E, Djärv T.

   Rapid response team activation prior to in-hospital cardiac arrest: Areas for improvement based on a national cohort study

   Resuscitation. 2023 Sep 22:109978. Online ahead of print.

IV. Thorén A, Andersson Franko M, Joelsson-Alm E, Rawshani A, Engdahl J, Kahan T, Jonsson M, Djärv T, Spångfors M.

   Exploring the impact of age on the predictive power of the National Early Warning Score (NEWS), and long-term prognosis among patients reviewed by the Rapid response team: A prospective, multi-centre study

   Under review

CONTENTS

LIST OF ABBREVIATIONS

AED	Automated External Defibrillator
ALS	Advanced Life Support
AUROC	Area Under the Receiver Operating Characteristic
BLS	Basic Life Support
CA	Cardiac Arrest
CCI	Charlson Comorbidity Index
CCU	Coronary Care Unit
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
DL	Deep Learning
DNACPR	Do-not-attempt CPR
ECG	Electrocardiogram
ED	Emergency Department
EHR	Electronic Health Record
ERC	European Resuscitation Council
EWS	Early Warning Score
HDU	High Dependency Unit
ICU	Intensive Care Unit
IHCA	In-hospital Cardiac Arrest
IQR	Interquartile Range
LOMT	Limitations of Medical Treatment
MET	Medical Emergency Team
NEWS	National Early Warning Score
OHCA	Out-of-hospital Cardiac Arrest

OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PEA	Pulseless Electrical Activity
ROSC	Return of Spontaneous Circulation
RRS	Rapid Response Systems
RRT	Rapid Response Team
SAE	Serious Adverse Event
SRCR	Swedish Registry for Cardiopulmonary Resuscitation
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

PREAMBLE

Each year, approximately 2,400 Swedish patients suffer from in-hospital cardiac arrest (IHCA), where resuscitation is attempted. In the global context, IHCA constitutes a major health concern and cause of death[1].

Despite a setting that enables monitoring, early identification of patients at risk, with timely interventions to prevent further deterioration, instant detection and treatment of cardiac arrest and often access to advanced peri- and post resuscitation care, only one out of three Swedish IHCA patients survive. Furthermore, IHCA is often heralded by deviating vital signs prior to the event[2, 3], opening a window of opportunity to turn the tide and prevent progression into a catastrophic, often fatal, situation.

Many IHCAs are considered potentially avoidable, highlighting the importance of the preventive strategies[3, 4]. This thesis focuses on the prevention of IHCA by means of prediction and monitoring.

BACKGROUND

1 IN-HOSPITAL CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION

1.1 HISTORICAL GLANCE

The history of Cardiopulmonary Resuscitation (CPR) extends back to the biblical age. One of the earliest references of resuscitation was recorded in the second book of Kings, describing how the prophet Elisha placed his mouth on the mouth of a little lifeless boy, thereby bringing him back to life[5].

Throughout the centuries, the evolution of resuscitation has been diverse. Numerous attempts have been made to accomplish artificial breathing, from fireside bellows used to ventilate drowning victims in the 1500s and "postural techniques" in which body positions were manipulated to achieve ventilation during the 17th and 18th centuries, to the introduction of mouth-to-mouth ventilation in the 18th century[6, 7]. In the late 1960s, Dr James Elam and Dr Peter Safar, of whom the latter has been credited father of the modern CPR, performed what may be some of the most spectacular experiments in medical history, where human volunteers were anaesthetized and paralyzed and the effects of mouth-to-mouth ventilation were observed, resulting in the first scientific studies in the field[8].

Regarding cardiac compressions, they were initially performed in the open thorax[6, 7]. In 1958, Kouwenhoven, Knickerbocker and Jude accidentally discovered the effect of manual compressions over the sternum while studying defibrillation in anaesthetized dogs. The results were expanded into clinical practice, and in 1960, in a landmark article in the Journal of the American Medical Association, they reported 14 patients out of 20 surviving in-hospital cardiac arrest (IHCA) treated by means of closed cardiac chest massage[9]. The authors stated: "Anyone, anywhere can initiate cardiac resuscitative procedures. All that is needed is two hands". Shortly after, Dr Peter Safar, in collaboration with Kouwenhoven and Jude, integrated the combination of closed chest compressions and mouth-to-mouth ventilation, introducing the concept of CPR as we are familiar with today[10].

The final step towards CPR of the modern era was taken when Kouwenhoven, Knickerbocker and Jude introduced the concept of manual chest compressions and defibrillation, publishing their results in another article in the Journal of the American Medical Association in 1960[11]. In 1966, the first consensus standards of CPR were published in the USA, opening the modern era of CPR[6].

1.2 DEFINITION

Cardiac arrest (CA) is most commonly sudden, leading inevitably to death if left untreated. CA is categorized into out-of-hospital cardiac arrest (OHCA) and IHCA based on the location of the CA[12]. The focus of this thesis is on IHCA.

Over the years, there has been a vivid debate as to the definition of CA. Several definitions exist that, to some extent overlap. The most frequently used definition of IHCA internationally is most likely the one established in the Utstein resuscitation registry reporting template: ”the delivery of chest compressions and/or defibrillation to patients admitted to inpatient beds”[13].
In the Swedish context, the definition as stated by the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) is the most commonly used: “an admitted patient who is unresponsive with apnoea or an abnormal breathing pattern (agonal or gasping respiration), where CPR and/or defibrillations have been initiated”[14].

1.3 THE UTSTEIN-STYLE REPORTING OF IN-HOSPITAL CARDIAC ARREST

In 1990, the first consensus conference was held at the Utstein Abbey, located in Norway, which resulted in the publication of guidelines aimed to enhance uniform reporting from OHCA in 1991[15 16]. The first Utstein guidelines for reviews, reporting and research on IHCA was published in 1997 and subsequently updated in 2019[13, 17]. This consensus document, or template, has been recognized as the Utstein-style or simply Utstein[16].

The Utstein guidelines provide clear definitions and indicators of performance regarding CA care, enabling a common approach to implementation, monitoring and measuring. The aim is to improve patient care and outcomes following both OHCA and IHCA. The templates are regularly updated in response to advances in science with subsequent changes in the practice of CA care[16].

Nowadays, there are Utstein publications not only in the field of CA care but also education and simulation, trauma, newborn resuscitation, stroke and also veterinary resuscitation[16]. In the future, the Utstein concept will continue to evolve and improve, providing tools for further improving the care of patients suffering from CA.

1.4 INCIDENCE

In-hospital cardiac arrest constitutes a major health issue worldwide, contributing to substantial mortality. For many reasons, it is difficult to establish the true incidence of IHCA[2]. First, it needs to be taken in consideration that in a majority of patients who die in hospitals, CPR is not initiated; previous Swedish studies have observed that resuscitation was initiated in approximately one patient out of ten who died in hospital[18, 19].

Furthermore, there are substantial variations between countries and institutions around the world[2, 20]. In high-income countries, large registry data give an estimate of the incidence of IHCA, which lies between 1.0-2.8 events per 1000 admissions to European hospitals [1, 2, 21-26], and 9.7 per 1000 admissions in the USA[27]. Recently, the incidence of IHCA in Japan was observed to be 5.1 per 1000 hospital admissions[28]. Trends in IHCA incidence indicate a decline in the UK and Japan, despite an ageing population with potentially more severe co-morbidities, whereas the incidence in the USA has slightly increased over time[20]. The reasons for the respective decline and increase in incidence include global disparities in decisions on Do-Not-Attempt CPR (DNACPR), differences in institutional structure, as well as response systems and disease-panorama[20].

The explanatory model regarding the nearly 10-fold variation in the global incidence of IHCA is multifactorial. First, it can be calculated in several ways, for example in relation to hospital admissions/ hospital beds/ country/ region/ city or state[2]. Today, most registries tend to report the incidence of IHCA in relation to hospital admissions. However, some registries include CAs without resuscitation attempts, some include only CAs where resuscitation attempts were initiated, and others include both groups[29]. Differences in patient case-mix and populations contribute to the variations[29]. Furthermore, there are large variations with respect to the collection and reporting of data[1].

The incidence is also influenced by gender[2]. Previous studies have reported the IHCA men/women incidence ratio to be 1.4-1.6 to 1[30], which most likely can be explained by the previously documented higher prevalence of cardiovascular diseases and a corresponding higher mortality rate among men[31].
In addition to this, country-specific culture and medicolegal aspects surrounding

CRP and differences in DNACPR practices are likely to influence incidence (and outcome)[29]. Previous studies have indicated a more frequent use of DNACPR orders in Europe compared to the USA[23, 32-34], as well as differences in the use of DNACPR orders between different European countries [35, 36].

Finally, the incidence of IHCA is also a measure of the institutional response and system of care in terms of prevention[29]. An inverse relationship between the incidence of CA and survival rates has previously been demonstrated, based on material from the American Heart Association ́s Get With The Guidelines (GWTG-R) Registry; hospitals performing well in preventing IHCA also had the highest survival rates, a correlation that persisted after adjustment for patient case-mix[37]. This might be explained by the fact that hospitals with a low incidence and a high survival rate excel in all links of both the "chain of prevention"[38] and the "chain of survival"[39], besides having well-educated, dedicated cardiac arrest teams and beneficial institutional factors.

1.5 AETIOLOGY

There are many potential causes of IHCA, and patients suffering from CA often have a concurrent acute medical illness[40-42]. In clinical settings, there are several factors that can cause CA; primarily an underlying medical illness, but also complications during treatment (e.g., anaphylaxis, haemorrhage during surgical procedures) and issues associated with hospital organization (e.g., treatment delays)[1].

Historically, the primary distinction of the aetiology of CA has been of cardiac or non-cardiac origin[29]. In the literature, the proportion of cardiac aetiologies of IHCA has been approximately 50-60%, with acute myocardial infarction identified as the single most common cause of IHCA[24, 30, 40, 43-45]. In the Swedish context, a recent nationwide observational study based on the SRCR reported the distribution between cardiac and non-cardiac aetiologies of IHCA to be similar[46]. However, in a recent systematic review and meta-analysis of aetiologies of CA among 27,102 general ward patients, the most prevalent causes were hypoxia, acute coronary syndrome, arrhythmias, hypovolemia, infection and heart failure[41]. In the same cohort, pulmonary embolism, electrolyte disturbances, cardiac tamponade, toxins, pneumothorax and neurological causes were uncommon causes of CA[41].

Identification of the cause or assumed aetiology of IHCA is essential to facilitate identification of a potential reversible cause during resuscitation, and to guide and tailor post-resuscitation care[29]. Recognition of the causes of IHCA has previously been associated with improved outcomes[30]. Furthermore, by addressing the underlying causes of IHCA, the preventive strategies can be improved[29].

However, the cause of CA is often unknown, since patients with uncertain aetiologies are often being classified as cardiac. In a recent study on CA in general wards, the cause was unknown in 14% of the cases[41]. Furthermore, there is often a "mismatch" between clinical diagnoses and autopsy diagnosis[29]. When comparing assumed causes of CA based on for example medical records, clinical examinations and results of autopsies, cardiac causes of CA are often over-diagnosed[40, 44, 47, 48]. Today, only approximately one in ten patients are examined post-mortem at teaching hospitals, which is to be considered the golden standard[49].

1.6 PATIENT AND CARDIAC ARREST CHARACTERISTICS

The mean age of patients suffering from IHCA is 66-74 years, and the male gender is more frequent among IHCA patients (57-65%). Patients suffering from IHCA commonly present comorbidities such as diabetes, renal insufficiency, heart failure, respiratory insufficiency, and malignancy[21-26, 50-54].

The most common location for IHCA to occur is in general wards (47-62%). The CAs are often witnessed (73-81%), and approximately every other patient is ECG-monitored at the time of CA (45-53%)[21-25, 50, 51, 54].

In patients suffering from IHCA, a non-shockable rhythm is the most common initial rhythm (i.e., asystole or pulseless electrical activity (PEA), 70-83%)[21, 22, 41, 43, 50, 54]. Furthermore, bradycardia may be frequent among patients suffering from IHCA, and non-ICU CAs preceded by bradycardia have previously been associated with a worse outcome[55].

1.7 OUTCOMES

As is the case with incidence, outcomes following IHCA vary significantly between countries but also across hospitals within the same country[29, 56-59]. The reasons behind the variations between countries is to a great extent consistent with those causing the variations in incidence[29], reflecting differences in (1) definitions of IHCA, data collection and the coverage and quality of registries (2) patient case-mix and populations, (3) culture and medico-legal aspects surrounding CPR, withdrawal of care and DNACPR orders and (4) the quality of the peri- and post CA care[29]. Therefore, comparisons between different registries or countries should be performed with great caution[29].

However, the reason for the substantial variations previously observed across hospitals in the US, but also in a large, recent Swedish registry study, is less clear [57-59]. There might be differences in the quality of resuscitation care, but also in organizational variables (e.g., the nurse-to-patient ratio, staff working conditions), staff education and training, and hospital culture related to, for example, CPR and leadership[57, 58, 60]. Finally, another plausible factor is differences in prearrest systems including routines for monitoring of vital signs and the use of Rapid Response Systems (RRS), affecting the ability to timely respond to and effectively treat patients suffering from CA[57].

According to the 2021 European Resuscitation Council (ERC) guidelines, the overall 30-day survival/survival to discharge following IHCA in high-income settings vary between 15% and 34%[56]. The SRCR reports a 30-day survival of 36% following IHCA in 2022, out of which approximately 90% were discharged from hospital with a favourable neurological function (Cerebral Performance Category (CPC) 1 or 2)[14].

Survival after IHCA has gradually improved over time[20, 29]. In the USA, survival to hospital discharge increased from 14% to 22% between the years 2000 and 2009[61], after which the trend reached a plateau, with a 30-day survival rate of 26% in 2017[62]. A recent Swedish study, based on the SRCR and covering a period of 30 years, reports a 1.2-fold increase in survival after IHCA with a J-shaped trend, and the greatest improvements in younger patients and men[54]. Over the last decade, there was a 47% increase in probability of survival following IHCA, showing no signs of plateauing[54]. During the last decade, more than half of Swedish IHCA patients aged under 60 years survived until 30-days[54].

There are several plausible explanations as to the gradual improvement in outcome, including a shift in comorbidities, a more knowledgeable hospital staff trained to defibrillate patients before arrival of the cardiac arrest team, a more determined approach in diagnostics and treatment of potentially reversible causes of CA, and advances in post resuscitation care[51]. Furthermore, it has been suggested that changes in attitude regarding CPR among healthcare professionals and an improved quality of CPR may contribute to the improved survival[63]. It is also possible that changes regarding decisions on DNACPR have influenced outcomes over time[51].

1.8 PREDICTORS OF SURVIVAL

Survival after IHCA is determined by several factors, which can be divided into non-modifiable or modifiable[2].
Non-modifiable factors include the gender, age, and comorbidities of the patient. In a recent meta-analysis of the adjusted results from 23 studies – out of which one reported a patient cohort of more than 90.000 patients - male gender, a higher age, malignancy, and renal insufficiency were associated with a lower rate of survival after IHCA[64].

Recently, frailty[65] has been identified as another non-modifiable factor with a strong association to survival after IHCA[66 67]. Among hospitalized patients, frailty is common[67]. In patients categorized as moderately to severely frail, survival rate to hospital discharge after IHCA may be less than 2%[68]. Frail patients have also been shown to have a poorer long-term prognosis and more commonly suffer from depression and a worse general health[69].

The cause of CA is to be considered a non-modifiable factor at most times[2]. Furthermore, the time of day when the CA occurs cannot be influenced. Several studies have previously reported CAs during the night or weekend to be associated with a lower likelihood of survival[23, 70, 71].

Initial rhythm is one of the strongest predictors of survival after IHCA[72, 73], where a shockable rhythm, e.g., pulseless Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF), recorded as initial rhythm is associated with a better prognosis[72, 74, 75]. This is at most times considered a non-modifiable factor.

The modifiable factors are of particular interest, since interventions addressing these may have a potential to improve outcomes following IHCA. The location in hospital where the CA occurs is an important, modifiable factor[23, 74]. Cardiac arrests occurring in a general ward, where there is a lower likelihood that the patients are ECG-monitored or that the CA is witnessed, are associated with a worse prognosis[23, 74]. In a recent study based on the SRCR, Jerkeman et al. location in hospital and age were the most important predictors of 30-day survival[54].

Time is essential to survival after IHCA, where all factors correlated to an early detection of CA, e.g., a witnessed CA or ECG-monitoring at the time of collapse, are associated with improved survival[72, 76, 77].

1.9 TREATMENT OF CARDIAC ARREST AND THE "CHAIN OF SURVIVAL"

The cornerstones in the treatment of IHCA are chest compressions, ventilation, early defibrillation and, when applicable, the treatment of potentially reversible causes of CA. Survival after IHCA is highly dependent on a particular sequence of key interventions, occurring as rapidly as possible[39]. The "chain of survival" concept, first introduced in 1991 in an American Heart Association (AHA) statement, demonstrates the interrelationship between these time-sensitive interventions (Figure 1). Furthermore, the need for all links to be optimized to maximize the chance of survival is emphasized[39, 78, 79], where the chain is no stronger than the weakest of the links[79]. The "chain of survival" consists of the links (1) early recognition of symptoms and call for help, (2) early CPR, (3) early defibrillation and (4) post-resuscitation care.

Figure 1:

Nolan et al. [79]. Reproduced with permission from Elsevier.

The number of patients included in each link of the "chain of survival" rapidly decrease as patients flow through the chain[80]. This is graphically visualized in the revised version of the "chain of survival", where the size of the links is adjusted to the number of patients available for intervention in each step (Figure 2). By focusing on improvements at links containing the greatest number of patients, the benefits in improving outcome will be maximized[80].

Figure 2: Revised chain of survival - not all links are equal

Deakin et al.[80]. Reproduced with permission from Elsevier.

1.9.1 Early recognition and call for help- to prevent cardiac arrest

Early recognition and call for help are fundamental to survival after IHCA. Previous studies have reported delays in time to recognition, call for help, initiation of CPR and time to defibrillation to be strongly associated with a lower chance of survival after IHCA[23, 56, 81, 82]. The SRCR reports that there is a call for help within 1 minute in approximately 80% of the IHCA cases in Swedish hospitals, a figure that has remained unchanged since 2008[14].

Furthermore, a majority of the IHCAs are heralded by a deterioration of vital signs prior to the event, opening a window of opportunity to prevent the progression into CA given the early identification of the patient at risk, and a timely and adequate response. The RRS concept is designed to improve the crucial preventive strategies, offering a framework for detection and response to patient deterioration in general wards, with a view to prevent SAEs, including progress into CA[83].

1.9.2 Early CPR

During the CA, there is a crucial need for an artificial circulation of blood flow to vital organs, mainly the brain and the heart, in order to prevent ischaemic injuries. Hence, immediate initiation of high-quality chest compressions performed with minimal interruptions constitutes the key cornerstone in successful resuscitation[82, 84]. Time from CA to onset of chest compression has previously been described as inversely associated with survival[85].

According to the SRCR, the median time from CA to onset of CPR has been < 1 minute yearly since 2008, and 90% of patients suffering from IHCA receive CPR within 1 minute in Swedish hospitals[14].

1.9.3 Early defibrillation

In case of a shockable rhythm (VF/pulseless VT), defibrillation is required to restore circulation, and early defibrillation is strongly associated with an improved outcome[23, 82, 84, 86]. In addition, the association is graded - for every minute of delay from CA until defibrillation is performed, the chance of survival decreases[86].

In 2022, 86% of Swedish IHCA patients who presented with an initial shockable rhythm were defibrillated within 3 minutes. Of these patients, approximately 80% were defibrillated before or in connection with the arrival of the cardiac arrest team [14]. However, only approximately 20% of the patients presented with an initial shockable rhythm[14].

1.9.4 Advanced Life Support

Basic Life Support (BLS) includes CPR and the use of an Automated External Defibrillator (AED)[56]. With the BLS as a foundation, Advanced Life Support (ALS) also encompasses advanced airway management and ventilation, the establishment of an intravenous/intraosseous access and the administration of medication. Furthermore, as stated by the ERC in the 2021 guidelines, coronary angiography/percutaneous coronary intervention, mechanical chest compressions and extracorporeal CPR (eCPR) should be considered in selected patients if applicable[56]. The details of the ALS concept are beyond the scope of this thesis.

Peri-resuscitation identification of the triggering cause of the CA has been associated with an improved outcome, with the greatest benefit observed among patients presenting with a non-shockable rhythm and non-cardiac cause of IHCA[30] . Reversible causes of CA are categorized into the mnemonic 4H (hypo-/hyperkalemia, hypothermia, hypovolemia, and hypoxia) and 4T (tamponade, tension pneumothorax, thrombosis (coronary/pulmonary), as well as toxins)[40, 87].

Furthermore, the guidelines also recognize the increasing role of Point-Of-Care Ultrasound (POCUS) for diagnosis, emphasizing that this must be performed while maintaining minimal interruptions during chest compressions which requires an experienced operator[56].

The ALS algorithm for treatment of CA can be applied to all CAs. However, if the CA is caused by special circumstances, there may be an indication for additional interventions[56, 87].

1.9.5 Post resuscitation care

The post resuscitation care is initiated immediately after sustained Return of Spontaneous Circulation (ROCS) is achieved and extended throughout the rehabilitation phase. As stated in the 2021 ERC guidelines, immediate treatment includes stabilization of ventilation and circulation by means of the Airway Breathing Circulation (ABC) approach, followed by diagnostics including ECG, an eventual rapid cardiac catheterization and CT-scan (brain and/or lung)[56]. Optimization of recovery in the ICU includes neuroprotective strategies (e.g., target temperature management if the patient remains unresponsive) and multimodal prognostication. Furthermore, functional assessments prior to hospital discharge as well as a structured follow-up post discharge are also included in post resuscitation care[56]. However, the details of such care are out of the scope of this thesis.

2 PREVENTION OF IN-HOSPITAL CARDIAC ARREST

2.1 THE CHAIN OF PREVENTION

Deviating vital signs and clinical deterioration is common within hours or days prior to IHCA, and on retrospective review, many CAs are considered avoidable or preventable[3, 4, 29, 88]. Therefore, ERC guidelines emphasize the importance of improving the preventive strategies, and prevention is included in the first link of the "chain of survival"[39].

In order to strengthen and visualize this first link in the "chain of survival", the concept was further developed by professor Gary B. Smith in 2010, who introduced the "chain of prevention"[38] (Figure 3).

Figure 3:

Smith, G. B[38]. Reproduced with permission from the author.

The aim of the "chain of prevention" is to support hospitals in organizing care processes and preventive strategies, but also to provide a structure for research in the field[38]. Furthermore, it can be seen as a simplified visualization of the process of RRS, designed to facilitate a timely identification and response to in-hospital emergencies, with a goal to prevent progress into IHCA[38].

2.2 ECG MONITORING AND MONITORING OF VITAL SIGNS

Patient monitoring is defined as the intermittent or continuous observation of vital parameters to ensure patient safety and supervise therapeutic interventions[89]. Today, continuous advanced cardiorespiratory monitoring is commonly used in the Coronary Care Unit (CCU), the ICU, the operating room and the post- anaesthesia care unit. Furthermore, some High Dependency Units (HDUs) and cardiology wards have access to continuous ECG monitoring. However, almost 50% of SAEs occur among patients admitted to general wards, where most of the monitoring tends to be intermittent[89].

There are several rationales for continuous ECG monitoring: (1) immediate recognition of CA, enabling early CPR and reducing time to defibrillation, hence improving survival[75], (2) early diagnosis of malignant arrhythmias may prevent CA or mitigate the effects of CA, and (3) early identification of non-cardiac causes of deterioration[90]. For example, it is well established that sinus heart rhythm variability is reduced by illness, and there are signatures of illness that are detectable in the patterns of the respiratory rate and heart rate[90, 91]. Furthermore, sepsis and septic shock cause specific patterns of dysregulation of the autonomous nervous system, which is in turn detectable with continuous ECG monitoring[92]. ECG monitoring at the time of CA is a strong predictor of survival [29, 76, 93]. However, due to resource limitations not all patients can be continuously

ECG monitored. Therefore, a key issue is how to identify the right patients for ECG monitoring.

Monitoring of patients is also performed by means of the measurement of vital signs. However, it usually consists of intermittent observations by a nurse approximately every 4-8 h, thus leaving patients unmonitored most of the time when admitted to a general ward[89, 94].

Electronic systems for the continuous monitoring of vital parameters could help improve patient safety in general wards. Surveillance monitoring is a novel strategy based upon pulse oximetry, aiming to facilitate early recognition and relay information about patient deterioration, preferably in low-risk patients in medical and surgical wards[95, 96]. By means of wearable devices, patients are remotely monitored, and the vital signs recorded (e.g., respiratory rate, oxygen saturation and heart rate) are connected to an Electronic Health Record (EHR), enabling threshold based alarm notifications and automated procedures of escalation[95, 97]. As for the prevention of IHCA, continuous measurement of oxygen saturation could be of particular interest since hypoxia is a common cause of IHCA among a general ward population, who in these days are frequently unmonitored[41]. Hypoxemia, but also hypotension, is frequently missed among general ward patients [97]. In a recent study, significant differences in SpO2 and pulse rate features derived from surveillance monitoring prior to CA were observed between cases of PEA and control groups, which potentially could facilitate early identification of patients at risk and enable timely preventive interventions[98].

To conclude, recent studies on surveillance monitoring have shown promising results in reducing the rate of SAEs; however, challenges remain as to balancing these advances in patient safety against workability and cost efficiency[99, 100].

2.3 RAPID RESPONSE SYSTEMS

2.3.1 Definition and concept

As stated by Subbe et al., an RRS is defined as "a whole system for providing a safety net for patients who suddenly become critically ill and have a mismatch of needs and resources"[101]. In everyday clinical practice, the RRS constitutes a hospital-wide system designed to facilitate the early identification of deteriorating general ward patients and ensure a tailored and timely response[102-104]. In all links of the RRS, time is essential since delayed interventions in previous studies have been associated with a worse prognosis[105]. The aim of the RRS is not only to prevent IHCA, but also to limit in-hospital mortality and unanticipated ICU-admission[106].

First introduced in Australia in the early 1990s[107], the concept and structure of RRS was officially introduced in 2005 at the First International Conference on Medical Emergency Teams (METs)[106]. At the conference, the structure was defined as an interlinked system based on four components: (1) the afferent limb (the process of recognizing the patient at risk, and criteria for triggering an escalation of care), (2) the efferent limb (the response algorithm, clinical including assessment, intervention and, if needed, escalation of the level of care, as well as response teams with expertise in critical care, e.g., RRTs), (3) the administrative limb (with responsibility for the overall resource allocation, and an update of system policies and staff education and training), and (4) the quality improvement limb (reviews programme compliance, data collection, evaluation and feedback) (Figure 4).

Figure 4: Rapid Response System structure

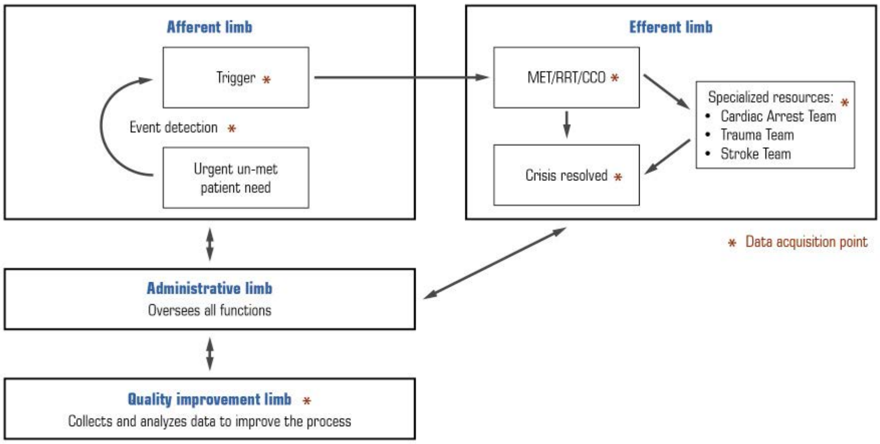


Figure 4: MET, Medical Emergency Team, RRT, Rapid Response Team, CCO, Critical Care Outreach Team.
Difonzo M[108]. Reproduced with permission from the author.

The four components in this complex system must interact with each other and patients, and the benefits of the RRS depends to a great extent on proper implementation and use[108]. The afferent and efferent limbs are dynamic and consist of several sequential steps, involving nurses and physicians and relying on their competence, collaboration and communication (Figure 5)[109].

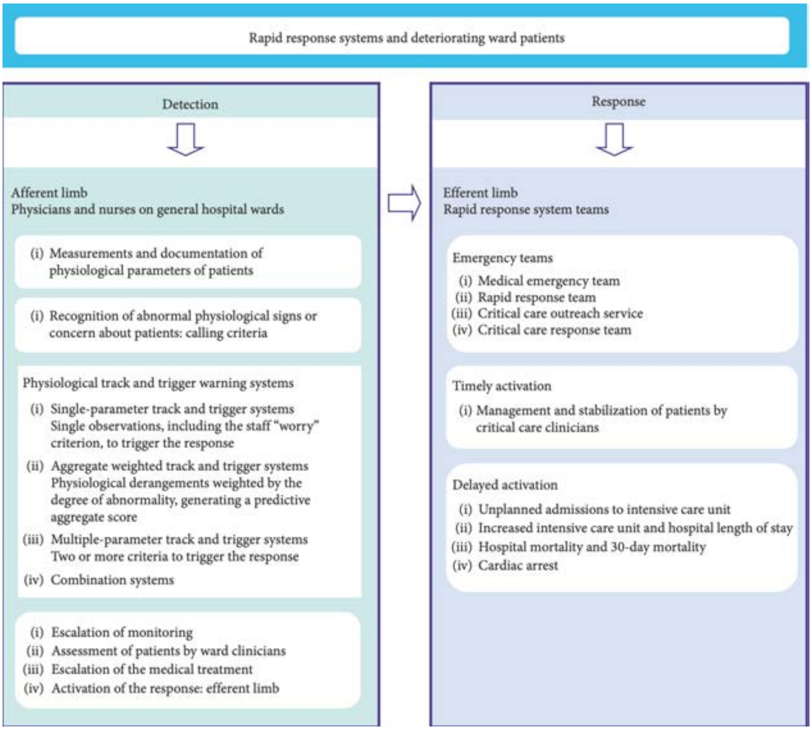
Despite the intuitively appealing concept and widespread use all over the world, the effectiveness of RRTs has not yet been consistently demonstrated[108]. Hence, there is an ongoing debate not only on whether the use of RRS improves patient outcomes, but also how RRS should be evaluated[103, 108].

2.3.2 Rapid Response Systems, current level of evidence

Historically, several observational studies have reported significant reductions in mortality and/or IHCA following implementation of an RRS[110-112]. Conversely, the only multi-centre, parallel, cluster randomized controlled trial, the Medical Early Response Intervention and Therapy (MERIT) study, was unable to demonstrate a significant reduction in a composite outcome consisting of the SAEs unanticipated ICU admission, non-ICU IHCAs, and in-hospital mortality[113]. Subsequent literature reviews and meta analyses have reported conflicting results[114, 115], but there are also meta-analyses reporting moderate strength evidence of a reduced incidence of in-hospital mortality and IHCA following implementation of RRS[102, 116 104]. A recent Cochrane analysis found low-certainty evidence that Early Warning Scores (EWS) and RRS may lead to a small or no difference as for mortality, unanticipated admissions to the ICU or length of hospital stay[117]. However, the review underlined that in many studies investigating RRS, the methodological quality was poor. Moreover, there was a diversity in the selection of outcome measures[117]. This notwithstanding, the authors concluded that the widespread adoption of RRS suggests there are perceived benefits in everyday clinical practice that are currently not captured when measuring objective patient outcomes[117].

In summary, an overall balancing of evidence indicates that RRS implementation is associated with a reduced rate of SAEs and improved patient safety, and most studies report a positive effect. Hence, implementation of RRS is strongly supported by quality improvement organizations and recommended in international guidelines as an important strategy to prevent IHCA and improve patient safety for hospitalized patients[56, 83, 108, 116].

Figure 5: Rapid Response Systems and deteriorating ward patients



Difonzo M [109]. Reproduced with permission from the author.

2.3.3 The afferent limb and Track and Trigger Systems

The afferent limb of the RRS withholds both the systematic process of event detection by patient monitoring, and the response trigger. This process is called Track and Trigger warning systems (TTSs)[118]. Conceptually, TTSs can be categorized into three essential parts: (1) the identification/diagnostic/trigger criteria, (2) monitoring by health care providers and/or technological devices and (3) a mechanism for triggering interventions[104].

Rapid Response Systems are highly dependent on accurate and reliable calling criteria. There is no universal standard as to the calling criteria; hence, variations are observed between countries and across hospitals[109]. The calling criteria are either objective (e.g., physiological parameters, vital signs, and the level of consciousness) or subjective (e.g., staff or family members' concern about the patients' condition). There may also be additional calling criteria such as uncontrolled pain[109, 119]. The physiological calling criteria can be divided into (1) single parameter systems, (2) multiple parameter systems and, (3) aggregated weighted warning systems. There are also combinations of systems[109, 118, 120-122]. The single parameter calling criteria are also referred to as MET calling criteria. Since the introduction of MET calling criteria in 1995, a plethora of other single calling criteria have been published and evaluated[107, 121]. These calling criteria are frequently used in Australia and the USA, but also in Europe, including Sweden[104]. A high or a low respiratory rate or systolic blood pressure are examples of MET-/single-parameter calling criteria. Based on the derangement of vital signs from a range considered as normal, the aggregated warning systems allocate points in a weighted manner, added together to calculate a total score known as the EWS[122].

The afferent limb is considered one of the most crucial components of the RRS[104]. However, given the complexity and many steps included in the chain of event detection and triggering of response, this limb is most likely the most error-prone component of the RRS. Furthermore, the dominant intermittent monitoring of hospitalized patients contributes to this vulnerability [104]. Not only is the afferent limb error-prone, it is also practically difficult to evaluate the performance of the system[109].

There is an ongoing debate as to which calling criteria are the most effective and safe. The ideal triggering system would be the one providing the highest discriminative ability of patient outcome, at the lowest rate of triggers, hence minimizing the risk of missing deteriorating patients as well as excessive workload for the staff[123]. Previous studies have found aggregated weighted warning scores/EWS superior to single-parameter systems in identifying patients at risk of SAEs[123, 124]. The MET-/single-parameter criteria are most likely easier to use in everyday clinical practice. However, important information might not be picked up since subtle changes in one or more vital signs might pass undetected. Furthermore, there is no graded response, which is integrated in EWSs.

2.3.4 Early Warning Scores

The EWS was introduced in the early 1990s as a simple, feasible tool to facilitate early detection of patient deterioration in general wards, in order to improve patient safety[125]. Initially, EWS was limited to vital signs being routinely collected in everyday clinical practice. Today, the use of EWS systems has been widely adopted internationally and become more complex. Currently available as a paper or digital tool with substantial variations in modelling, design and escalation recommendations, EWS systems are increasingly becoming a part of EHRs[125].

Although EWS have broad appeal, robust evidence to support their effectiveness in preventing SAEs is still lacking, as stated by McGaughey et al. in their 2021 Cochrane review[117]. The authors highlighted diversity in outcome definition and selection, moderate-to-poor methodological quality, and an inconsistent implementation of EWS and RRS criteria, team composition, dose, and process of the EWS across different contexts and countries as possible causes of a lack of evidence[117]. However, the authors concluded that the widespread use of EWS suggests benefits in general practice that are currently unsubstantiated in the measured objective patient outcomes. The use of EWS is also recommended by the ERC in their 2021 guidelines as one of several important strategies aiming to prevent IHCA[56].

Globally, there are more than 100 different EWS available. The National Early Warning Score (NEWS) was introduced by the Royal College of Physicians in London in 2012 and has outperformed other EWS in terms of predictive accuracy in identifying patients at risk of SAEs[126, 127].

2.3.5 The National Early Warning Score

The NEWS provides a standardized concept for the assessment of illness severity and risk of deterioration among non-pregnant adults aged 16 years and above. It also provides a "common language" for communication, which in turn enables acuity and consistency[128], and is a commonly used EWS system.
The NEWS scale consists of the vital signs respiration rate, oxygen saturation, body temperature, systolic blood pressure, heart rate and level of consciousness. The vital signs receive a score from 0 to 3 according to the magnitude of deviation from a value considered normal, added into a summed score and correlated to predefined trigger thresholds. Supplementary oxygen renders 2 additional points to the summed score[126].
Based upon the total score, patients are stratified into risk categories. Triggering thresholds generated by the total score are used to activate a predefined clinical response as described in the clinical outreach scale, including assessments regarding escalation of care by RRTs[126]. However, emphasis should be given to the fact that NEWS is designed to serve as a supplement and not a substitute for a clinical assessment-clinical judgement should in all situations remain paramount[128].

In 2017, the revised version NEWS 2 was launched, with minor modifications as to the weights of the vital signs as well as the addition of an optional SpO2 scale for use in patients with hypercapnic respiratory failure. As to the level of consciousness, the variable "new confusion" (including disorientation, delirium or any new onset alteration to mentation) was added to the scale[129] (Figure 6). Further development was also made aiming to improve precision and early identification of sepsis[129]. Today, most Swedish hospitals use EWS, preferably NEWS 2.

NEWS, NEWS 2, and EWS in general, are limited by the intermittent nature of monitoring, the "one-size-fits all" scoring model, and user-dependency[130]. This can be addressed by new continuous monitoring systems and automation, but adding variables including patient age, frailty, comorbidities, and various laboratory datasets have also shown to improve the predictive power[130-134]. Furthermore, as NEWS 2 is dynamic, a more detailed analysis at specified time points and evaluation of changes and trends over time has shown to improve the prognostic accuracy[135].

Figure 6: The National Early Warning Score (NEWS) 2

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Reproduced with permission from the Royal College of Physicians, London[129].

2.3.6 Respiratory rate - the most important yet frequently neglected vital sign

Respiratory rate has been identified as the most powerful predictor of deterioration, disease severity and SAEs (e.g., IHCA, unanticipated ICU admission and mortality)[136-140]. In almost all cases of clinical decline, the normal values of the respiratory rate are frequently breached before signs of abnormalities develop in other vital signs[141].

A respiratory rate exceeding 27 breaths per minute has previously been identified superior to blood pressure or heart rate in predicting risk of CA within 72 hours[136]. Furthermore, among patients reviewed by RRTs in general wards who presented with a respiratory rate of 25-29 breaths per minute, the in-hospital mortality rate was 21%[142]. In a study of RRT trigger criteria, approximately every other patient suffering from a SAE in a general ward had a respiratory rate of 24 breaths/minute[139]. Recently, in a study introducing a new Machine Learning (ML) analytic for the prediction of SAEs among general ward patients, Akel et al. identified respiratory-related vital signs as the strongest predictor of unanticipated ICU admission or the composite outcome of ICU admission and mortality[143].

Besides pulmonary diseases, any condition causing metabolic acidosis or hypercapnia/hypoxia (e.g., intracranial catastrophes, abdominal catastrophes, hypovolemia, or hypotension) can cause an increased respiratory rate. In many potentially life-threatening conditions, such as sepsis, respiratory insufficiency, heart failure, shock, or systemic inflammatory response syndrome, an increased respiratory rate is commonly seen as the first warning sign[141, 144]. Hence, respiratory rate is a key predictor of SAEs and a vital indicator of severe derangements not only in the respiratory system but in several body systems[144].

Despite overwhelming evidence of respiratory rate being an early and strong predictor of preventable patient deterioration, it remains the most frequently missing vital sign in both general wards and Emergency Departments (EDs). Furthermore, the respiratory rate is commonly measured or estimated inaccurately, with a bias towards normal values[140, 141, 145, 146]. There are several reasons that have been cited as plausible explanations for these shortcomings, including lack of knowledge among both clinicians and hospital decision makers, practical difficulties in measurement, shortage of time and absence of hospital compliance measures or audits as follow-up[141].

The introduction of EWS has been shown to improve the rate of patients having their respiratory rate recorded[145], and the introduction of pulse oximetry based surveillance monitoring in general wards, facilitating the recording of respiratory parameters and generating automated alerts, will most likely also contribute to an increased staff alertness[145].

2.3.7 The efferent limb

The efferent limb of the RRS contains all resources mobilized to respond to deteriorating patients in general wards. This includes equipment and the expert team operating with the aim to restore balance in critical situations, where the needs of the patient exceed the resources of the ward, and time is essential[104]. These teams are called MET in Australia, Critical Care Outreach Service (CCOS) in the UK, RRT in the USA and Critical Care Response Team in Canada[108, 117]. Potential members of the teams include physicians, nurses, respiratory therapists, and pharmacists. However, the optimal composition of these teams is unknown and varies between different hospitals based on hospital resources, preferences, and goals[83].

In Sweden, critical care teams have been introduced in a majority of hospitals, referred to as a Mobile Intensive care Group (Mobil Intensivvårdsgrupp, MIG-team). The MIG-teams provide assessments of patients 24 hours a day, regardless of weekday and day of the year. The most frequent composition of the MIG-team is an ICU specialist at the consultant level or an ICU resident and an ICU nurse, who have clinical responsibilities within the ICU parallel to the MIG-team.

In some settings, METs or RRTs operate separately from cardiac arrest teams, where the intention is to bring intensive care expertise to the patient with the aim to prevent CA, whilst other METs or RRTs are also responsible for managing CAs[108]. In the Swedish setting, most hospitals have implemented separate teams operating 24/7.

2.3.8 Rapid Response Teams

The RRTs are designed to respond to deteriorating patients in general wards. The team composition is typically multidisciplinary (e.g., a physician, a nurse and sometimes also a respiratory therapist); however this varies according to guidelines and institutional policies[119]. Operating 24/7 as an "ICU without walls", the RRTs provide urgent clinical evaluations, an initiation of stabilizing and/or lifesaving interventions, triage, and/ or-if needed- escalation of the level of care[106, 115, 147, 148]. Furthermore, RRTs are frequently involved in end-of life care and the initiation of appropriate decisions on Limitations of Medical Treatments (LOMT) if indicated[148]. Previous studies have reported 24%-33% of all RRT assessments to involve end-of life decision making[149, 150]. Moreover, the RRTs are a part of a comprehensive hospital wide system, highlighting the importance for team members to possess not only clinical expertise but also inter-professional collaboration abilities and contributions to training and education[103].

Calling criteria for RRT activation have previously been described (sub-section 1.11.3).

Although the RRT concept is intuitively appealing, the effectiveness of the teams has not been consistently demonstrated[110, 113, 151, 152]. This is most likely explained by disparities in design, implementation, and maintenance of the system across hospitals, given the complexity and multidisciplinary concept of RRTs[152].

2.3.9 Delayed activation of Rapid Response Teams

An important cause of afferent limb failure is delayed RRT activation, defined as a documented RRT activation criterion being present at a pre-specified time (e.g., from 15 minutes up to hours) before the RRT is alerted[153]. Delayed RRT activation is more frequent during on-call hours (i.e., all other than office hours except those during weekends), and associated with increased morbidity, a higher risk of IHCA within 48 hours of an RRT assessment, and an increased mortality[105, 153-158].

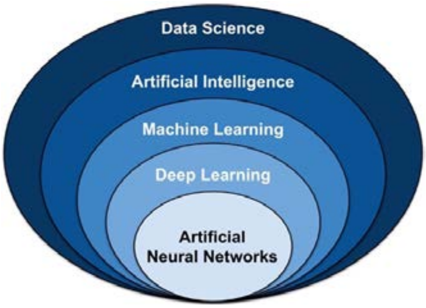
Previous studies report a frequency of delayed RRT-reviews ranging from 21% to 56% of all calls, notably these were unselected cohorts of hospitalized patients [105, 156, 159]. In a Finnish cohort of patients suffering from IHCA, who were assessed by an RRT within 24 hours prior to CA, 26% of the RRT-reviews were delayed[160]. Furthermore, in the MERIT study, documented RRT activation criteria were present for 15 minutes or more in approximately one out of three patients suffering from IHCA[113].

The causes of delayed RRT activation can be divided into three separate areas: (1) failure to monitor, (2) failure to recognize, and (3) failure to escalate[161]. Removing factors causing a delay is predominantly a matter of education[162], but also resources. However, the needs and pre-requisites are likely to be highly variable between different hospitals, requiring adaptations. Several explanations for the inconclusive findings of previous studies investigating the efficacy of RRS have been proposed, among which a delayed RRT activation has been considered the most important[163-165].

3 MACHINE LEARNING MODELS

Over the last decades, artificial intelligence (AI) has become increasingly popular within the field of medicine. Simply explained, AI systems are used in automated management of complex intellectual tasks, imitating human strategies when solving problems. Machine learning (ML) is a subfield of AI, which also includes Deep learning (DL) and Artificial Neural Networks (ANN)[166] (Figure 7).

Figure 7: Umbrella of different techniques within data science



Choi, R. Y. et al. [166] *Reproduced with permission from the authors.*

The ML algorithms are trained to make classifications or predictions, by means of statistical methods, with an ability to handle very large data sets. However, ML is not an entirely automatic problem solver but requires humans to be involved in the process. In the field of medicine ML is, for example, used in diagnostics and the construction of prediction models.

There are four frequently used methods of learning in ML; (1) supervised, (2) unsupervised, (3) semi-supervised and (4) reinforcement learning[166].
In the method supervised ML, labelled outcome data are used in classification regression models. Gradient boosting and random forest are two commonly used supervised ML models. In study I, gradient boosting was used to analyze data. This model builds decision trees integrated with each other in series, where every tree strives to minimize the error of the previous one, aiming to present the most accurate predictor[167].

Random forest also operates by building decision trees. The main difference between these two are how trees are built; random forests build each tree independently as compared to gradient boosting where one tree is built at a time by means of “boosting”. Furthermore, gradient boosting evaluates results along the way whilst random forests evaluate the results at the end by averaging or “majority rules”[168].

Unsupervised ML is used to detect hidden patterns and identify new associations in large, complex datasets but also categorizes individual instances in the dataset[166]. Clustering association and anomaly detection are two examples of frequently used unsupervised learning tasks[166]. In semi-supervised ML, both unlabelled and labelled data are introduced into the model. Finally, reinforcement learning is a specific technique where an algorithm is trained to maximize specific outcomes by optimizing a chain of decisions[166].

One very popular family of ML methods is DL. Unlike other ML algorithms, DL can automatically construct suitable data representations thus enabling it to manage of extremely large datasets. At the heart of DL, ANN is another subset of ML algorithms. The name, structure, and function of ANNs are inspired by the biological neural network of human brains. Briefly, in each ANN there are nodes communicating with each other through connections, weighted based upon their ability to provide a pre-specified outcome[166]. ANN is a powerful AI tool, allowing the classification and clustering of large datasets at a high velocity.

3.1 MACHINE LEARNING MODELS IN THE PREDICTION OF SERIOUS ADVERSE EVENTS

There is a plethora of previous studies that have used EHR linked to ML to model inpatient deterioration, unanticipated admission to the ICU, CA, and mortality[169]. The electronic Cardiac Arrest Risk Triage (eCART) score utilizes 33 parameters including vital signs, laboratory results and demographic data, delivering a real-time risk prediction, which has shown to be superior to NEWS and other EWS in predicting ICU-transfer and mortality within 24 hours in adult general ward patients, with fewer false alarms[170]. Moreover, Akel et al. reported that a revised version of eCART, the eCART-lite, predicts SAEs slightly better than eCART as well as commonly used EWS using only age, heart rate and respiratory rate and their 24-hour trends as predictors[143].

Recently, Romero et al. introduced a gradient boosting ML model ready to use in the afferent limb of an RRS, the Mayo Clinic Early Warning Score (MC-EWS). This model has outperformed the NEWS 2 in identifying patients at risk of SAEs whilst reducing the alert rate[171]. Furthermore, Cho et al. developed the DL-based EWS for the more effective detection of patient deterioration. When validated in a multi-centre study, the DL-based EWS predicted unanticipated ICU admission and IHCA better than both traditional EWS and logistic regression, using only four variables[172].

However, several barriers and practical challenges exist in relation to the development and implementation of AI in health, based on the rapid pace of change, multiplicity of techniques and diversity of tuning parameters [173]. There are question marks as to the accuracy of the ML methods in clinical practice and reproducibility in different hospital contexts, as well as a lack of consensus as to the reporting of bias[173]. This is compounded by the lack of "human" oversight and understanding as to the process of decision making in ML algorithms, referred to as a "Black box problem"[173, 174], which might create a barrier to implementation in clinical practice. There are models to address these specific issues; however, this is out of the scope of this thesis.

4 KNOWLEDGE GAPS

Historically, IHCA has gained less attention in terms of research focus and resource allocation as compared to for example OHCA. Current guidelines for the management of IHCA are to a great extent based on science that has been extrapolated from OHCA, which is to be considered as suboptimal given the significant differences between the conditions [29]. Thus, there are knowledge gaps related to several links of the "Chain of prevention".

Given the well-established benefit in survival after IHCA among patients being monitored prior to CA, it would be desirable to monitor all patients at risk of IHCA. However, due to limited resources not all patients can be monitored, stressing the importance of identifying and prioritizing the right patients to monitoring. There are knowledge gaps related to identification of which patients benefit most from ECG-monitoring.

Regarding the afferent arm of the RRS and specific knowledge gaps related to NEWS and NEWS 2, little is known about their discriminative abilities in different cohorts of patients. Today, there are few previously published studies comparing the discriminative ability of NEWS and NEWS 2 in prediction of unplanned admission to the ICU, IHCA and mortality within 24 hours of review by an RRT.

Most of the literature available on NEWS and NEWS 2 is based on retrospectively collected data, stressing a need for prospective study designs. Furthermore, the NEWS and NEWS 2 are "one size fits all" scoring models, and there are indications that NEWS requires adjustments for specific conditions and categories of patients. Age has previously been suggested as an additional covariate to NEWS/NEWS 2 with a potential to improve the discriminative ability in predicting SAEs [175].

There is also a limited knowledge of the efferent function of RRTs (e.g., initiating timely interventions and triaging patients to a higher level of care), vital sign abnormalities preceding RRT, the reasons for RRT activations and the long-term prognosis of RRT reviewed patients. An accurate risk stratification when triaging patients who are subjects of RRT review is of vital importance with a goal to prevent SAEs, thereby improving patient safety, and enable an adequate resource allocation.

5 AIM OF THE THESIS

The overall aim of this PhD-project was to study the prevention of IHCA, by means of prediction and monitoring, with a view to improve patient safety.

Study specific aims:

I. To investigate how 30-day survival after IHCA is influenced by ECG monitoring at the time of CA and factors in everyday clinical practice that determine whether a patient is ECG monitored adjacent to CA.

II. To investigate the prognostic accuracy of NEWS 2, as compared to NEWS, regarding the prediction of unanticipated ICU-admission, IHCA or mortality, and the composite outcome of these three SAEs, within 24 hours of an RRT-review.

III. To study 30-day survival and ROSC in patients suffering from IHCA, who are reviewed by an RRT within 24 hours prior to CA, as compared to patients with no RRT-review. Furthermore, the aim was to describe (1) patient-centred factors prior to RRT activation, (2) the cause and timeliness of the RRT-review, and (3) the association between RRT interventions and outcome.

IV. To explore the impact of age on the discriminative ability of NEWS 2 in the prediction of unanticipated ICU-admission, IHCA or mortality within 24 hours of an RRT-review. Furthermore, to investigate 30-, 90- and 180-day mortality, as well as the discriminative ability of NEWS 2 in the prediction of long-term mortality, among RRT-reviewed patients.

6 METHODS

6.1 OVERVIEW OF THE STUDY DESIGNS

Table 1 presents an overview of the study designs.

Table 1: Overview of the design of studies I-IV

Overview of design, study I – IV				
	Study I	**Study II**	**Study III**	**Study IV**
Design	Retrospective observational cohort study	Prospective observational cohort study	Retrospective observational cohort study	Prospective observational cohort study
Data sources	SRCR	Data reported by RRTs	SRCR, medical records	Data reported by RRTs, personal information directory
Inclusion criteria	IHCA patients aged 18 years and older	Patients aged 18 years and older reviewed by RRTs	IHCA patients aged 18 years and older, reviewed by RRTs within 24 hours prior to CA	Patients aged 18 years and older reviewed by RRTs
Study period	2008-2017	October 2019-January 2020	2014-2021	October 2019-January 2020
Number (n)	19,225	1,065	12,915	1,065
Statistical methods	- Descriptive statistics - Cox-adjusted survival curves - Propensity score - Logistic regression -Gradient boosting - Multiple imputation	- Descriptive statistics - Logistic regression - Hosmer & Lemeshov test - AUROC - DeLong test - Relative true-positive ratio - Relative false-positive ratio -NNE	- Descriptive statistics - Chi-square - Propensity score - Logistic regression	- Descriptive statistics - Logistic regression - GAM with spline components - Hosmer & Lemeshov - AUROC
Outcome	30-day survival	Unanticipated ICU-admission, IHCA or in-hospital death, and the composite of these three, within 24 hours of RRT review.	30-day survival, ROSC	Unanticipated ICU-admission, IHCA or in-hospital death, and the composite of these three, within 24 hours of RRT review.

Table 1. SRCR, Swedish Registry of Cardiopulmonary Resuscitation, IHCA, In-hospital cardiac arrest, RRT, Rapid Response Team, ICU, Intensive Care Unit, CA, Cardiac Arrest, AUROC, Area Under the Receiver Operating Characteristic, GAM, General Additive Models, NNE, Number Needed to Evaluate, ROSC, Return of Spontaneous Circulation.

6.2 DATA SOURCES

Study I was based on patients enrolled in the SRCR.

In studies II and IV, the study population was prospectively recruited by RRTs in 26 and 24 Swedish hospitals, respectively. In study IV, additional data on long-term survival was obtained from either medical records or the personal information directory, containing population registration data.

In study III, the study population was recruited from the SRCR. In a small subgroup of patients, additional in-depth data was collected from medical records.

Data was collected per Utstein Style for IHCA and RRT-reviews[13, 148]. All registration, data curation and analyses were performed in secure, online systems.

6.2.1 The Swedish Registry for Cardiopulmonary Resuscitation

The SRCR was introduced in 1990, initially encompassing OHCA only. In 2006, the SRCR was extended to include IHCA.
The aim of the registry is to study the incidence, demographics and survival following CA, and the registration is designed to comply with the Utstein guidelines for reporting IHCA and OHCA[13, 176]. The Swedish personal identification numbers and high-quality registries allow for complete information on the outcome[177].

All patients suffering from CA within the walls of the hospital, where resuscitation is attempted, are included in the in-hospital registry[14]. Hospitals qualify to report data on IHCA if they have implemented a cardiac arrest response team, there is an ICU in the hospital and patients can be provided post resuscitation care. The registry has gradually expanded over the years, to date achieving a complete coverage where 74/74 qualifying hospitals report to the registry, which in all contains approximately 35,000 cases of IHCA in 2023[14]. However, it is likely that not all IHCAs are reported to the SRCR. Particularly, IHCAs located in the ICU, CCU, operating room or catheterization lab where patients are more often immediately resuscitated without alerting the cardiac arrest team, are prone to be underreported.

Registration in the SRCR is completed in three steps.

1. The first part of the report is filed by a cardiac arrest team crew member or the nurse in charge of the patient adjacent to collapse. The 61 variables in this section include patient characteristics, a description of the circumstances surrounding the CA and the peri-arrest care.

2. The second part is filed by a local CPR coordinator and contains 48 variables regarding post-resuscitation care and follow-up. Through the 10-digit Swedish personal number and linkage to the Swedish National Population Register, 30-day survival is obtained. In this section, the assumed cause of CA is registered along with information on neurological function at discharge. The neurological function at hospital discharge is assessed according to the 1-5 level CPC scale[178].

3. There is also a follow-up 3-6 months after CA, which is performed by the local CPR coordinator. This part is the same for both IHCA and OHCA and is composed of Patient-Reported Outcome Measures (PROM), which addresses cognitive dysfunction, anxiety disorders and difficulties in coping with activities in everyday life following CA. For this purpose, the EuroQol 5 dimensions 5 levels (EQD-5), and the EuroQol Visual Analogue Scale (EQ VAS), which are assessments regarding health-related quality of life, and Hospital Anxiety Depression Scale (HADS), are being used. A questionnaire is sent home to the patient along with an invitation to a telephone follow-up. However, there is a substantial loss to follow-up in PROM (43%)[179].

All patients who survive IHCA receive information on their participation in the SRCR and the purpose of the registry. Furthermore, they are informed that they have the option to withdraw their data from the registry at any time. However, the frequency of "drop out" from the SRCR has remained very low during the recent decades[180].

6.3 STUDY SETTING, POPULATION AND OUTCOME

6.3.1 Study I

In this study, we included all adult patients (18 years or older) registered in the SRCR between January 1st, 2008, and December 31st, 2017. We did not exclude any patients or any locations of CA. However, if the patient suffered from multiple CAs within the same hospital admission, we included the first event only. The outcome measure in study I was 30-day mortality.

6.3.2 Study II

This study was conducted in 26 Swedish hospitals between October 22nd, 2019, and January 13th, 2020. Only hospitals that had implemented NEWS or NEWS 2 and had an RRT were eligible for participation. All RRT-reviewed patients aged 16 years and older were eligible for inclusion. Exclusion criteria included a decision of no ICU-admission prior to the RRT-review, scheduled follow-up after ICU discharge, and pregnancy and the postpartum period (i.e., 6 weeks following childbirth).

All RRT-reviews were performed according to clinical practice. The RRTs collected data on patient demographics, all vital signs required for calculation of NEWS and NEWS 2, and decisions made by the RRT regarding eventual new LOMT and level of care following RRT-review. Miscalculation is a well-established source of error in the use of NEWS or NEWS 2; hence, for each patient the scores were retrospectively, digitally calculated by the study team. After 24 hours or more, a follow-up was performed, in which data on unanticipated ICU admission, IHCA or death within 24 hours of RRT-review was retrieved from medical records.

The outcomes were unanticipated ICU-admission, IHCA, and in-hospital death within 24 hours of an RRT-review. Furthermore, a composite outcome of these three SAEs were analyzed in line with the Tripod guidelines[181].

6.3.3 Study III

Study III was based on the SRCR. On January 1st, 2014, the variable RRT/ICU contact within 24 hours prior to IHCA was introduced, allowing us to include all adult patients (18 years or more) who received CPR between January 1st, 2014, and December 31st, 2021. Patients admitted to Swedish hospitals do not return to the ED and receive an RRT-review; thus, such CAs were excluded. All other locations of CA were included. Only the first CA was included in patients suffering from multiple events in the same hospital admission. Furthermore, we performed an additional hypothesis-generating, explorative in-depth data collection from medical records in a subgroup of RRT-reviewed general ward patients in five hospitals, with various locations and demographics.

The exposure was RRT-review within 24 hours prior to IHCA. The primary outcome measure was 30-day survival, and the secondary outcome was ROSC.

6.3.4 Study IV

In study IV, we used the same study setting and population as described in study II. In addition, a follow-up on long time survival was performed approximately 21 months after the inclusion period, where data was collected from either medical records or the personal information directory, containing population registration data.
Age was explored as an additive variable to NEWS 2 by categorizing it according to two well-established ICU scoring models developed as severity-of-disease classification systems and risk prediction tools; the Acute Physiology, Age and Chronic Health Evaluation system (APACHE) 2, designed to predict mortality in the ICU[182], and the Simplified Acute Physiology Score (SAPS) 3, originally designed to predict in-hospital mortality, but in clinical practice in Sweden it is used for prediction of 30-day mortality[183]. Furthermore, we explored the age categories as previously stated by Smith et al.[184].
The APACHE 2 age categories were 18-44, 45-54, 55-64, 65-74 and ≥75 years. We used the original SAPS 3 age categories 18-39, 40-59, 60-69, 70-74, 75-79 and ≥80 years, modified into a collapsed version SAPS 3a categorized as 18-59, 60-69, 70-74, 75-79 and ≥80 years and further into a SAPS 3b categorized in three levels, 18-65, 66-74 and ≥75 years. The age categories as previously defined by Smith et al were 18-39, 40-64, 65-79 and ≥80 years[184].
Regarding the distribution of the NEWS 2 score within the different age categories, the scores were weighted in proportion to the frequency of the specific score.

The primary outcomes were unanticipated ICU-admission, IHCA, in-hospital death, and the composite of these three SAEs, within 24 hours of an RRT-review. Secondary outcomes include 30-, 90- and 180-day mortality.

6.4 STATISTICAL METHODS AND DATA ANALYSES

In all four studies, descriptive data was presented as mean values, median and proportions, with appropriate dispersion measures.

6.4.1 Study I

In study I, we calculated Cox-adjusted survival curves to study 30-day survival after IHCA, adjusted for age, gender, and the presenting rhythm (non-shockable vs. shockable). Furthermore, we used propensity scores to investigate the association between ECG-monitoring and 30-day survival. The following variables were introduced in the propensity score: calendar year, geographical region, academic hospital (Y/N), time of day, patient age, patient gender, presenting rhythm (non-shockable vs. shockable), ongoing myocardial infarction and ongoing stroke. We also introduced the variables a previous history of heart failure, diabetes, acute myocardial infarction, cancer, respiratory insufficiency, and stroke. Logistic regression was used to obtain the propensity score. We modelled continuous variables by means of restricted cubic splines with 5 knots.

In the next step, we investigated 30-day survival by means of propensity score adjusted logistic regression models. We also adjusted for potential confounders, namely minutes to alarm, minutes to CPR, minutes to defibrillation and the number of defibrillations, witnessed status, minutes to arrival of the alarm group, CPR before the arrival of the alarm group, the use of adrenaline and the use of antiarrhythmic medication. Furthermore, with the aim to allow non-linear associations, we expanded the propensity score into a restricted cubic spline with 5 knots.

We also used Gradient boosting [167] to estimate the relative importance of all predictors in the propensity score. The importance of each predictor was visualized by means of the relative influence. A grid search was used when performing the hyperparameter tuning. We found the best model to have 1000 trees, a shrinkage 0.01 and a depth of interaction of 5.

All of the analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria)[185].

6.4.2 Study II

We used logistic regression to predict unanticipated ICU-admission, IHCA, mortality, and the composite outcome of these three within 24 hours of RRT-review. The results were presented as Odds Ratios (OR) with 95% Confidence Intervals (CI), adjusted for gender and age. The Hosmer & Lemeshov test was conducted to determine the goodness-of-fit of the model. The accuracy of NEWS and NEWS 2 in predicting the outcomes was evaluated using the Area Under the Receiver Operating Characteristic (AUROC)[186]. De Longs test was used to quantify the differences in AUROC between NEWS and NEWS 2.

The effect of the commonly used thresholds for triggering specific actions (e.g., aggregated NEWS or NEWS 2 scores ≥5 and ≥7, respectively) was evaluated using sensitivity, specificity, and positive predictive values. When comparing the relative accuracy of NEWS and NEWS 2, the relative true-positive ratio (indicative of superiority in sensitivity of a test) and relative false-positive ratio (indicative of superiority in specificity in a test) were calculated[187, 188]. Furthermore, the number needed to evaluate (NNE) was calculated.

The statistical analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria)[185], and IBM SPSS Inc. version 26.0 (Chicago, IL, USA).

6.4.3 Study III

Patients reviewed by RRTs within 24 hours prior to CA vs. patients who were not reviewed by the RRT were compared using Chi-square and Mann-Whitney U-tests. We calculated the adjusted association between RRT-review within 24 hours prior to IHCA and 30-day survival, described as ORs. Unadjusted association was examined using univariate logistic regression, with RRT-review as the only predictor in the model. The adjusted estimate was obtained using propensity score, which was used as a covariate in the model. The predictors of the propensity score included age, gender, comorbidities, heart failure, respiratory insufficiency, diabetes, ejection fraction, renal function, previous myocardial infarction, previous stroke, ongoing myocardial infarction, and ongoing stroke.
All tests were two-sided, $p < 0.05$ was considered significant, and 95% CIs were used. No imputations were performed. R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria)[185] and STATA version 17.0 (Stata Corp LLP, College Station, Texas, USA) were used for the analyses.

6.4.4 Study IV

Logistic regression was used for the prediction of outcomes. We also used General Additive Models (GAM) with spline components for age and NEWS 2 when investigating non-linear associations. Furthermore, the AUROC was used to evaluate the discriminative ability of NEWS 2 and age in identifying patients at risk of unanticipated ICU admission, IHCA, mortality or the composite of these three outcomes. Differences in AUROC between the models were compared by the DeLong test.

All tests were two-sided with a significance level of $p<0.05$. All statistical analysis were performed with R (R Foundation for Statistical Computing, Vienna, Austria) version 4.2.1 [185], and IBM SPSS Inc., version 29 (Chicago, IL, USA).

6.5 ETHICAL CONSIDERATIONS

All studies encompassed in this thesis have been approved by either a Regional Board of Ethics or the Swedish Ethical Review Authority. Study I was approved by the Regional Board of Ethics in Stockholm (#2013/1959-31). Studies II, IV, and III obtained ethical approval from the Swedish Ethical Review Authority (#2019-04269 for studies II and IV, #2021-06989-01 for study III).

Study I and III are retrospective, cohort studies based on data from the SRCR. Patients suffering from IHCA are unconscious, hence incapable of deciding on participation in a national registry. Hence, in the SRCR there is a standard opt-out approach adjacent to follow-up, which means that the patient is included in the national registry unless they actively express a decision to be excluded. However, questions can be raised whether all patients are able to assimilate this information, which is to be considered an important ethical issue. In order to reduce the risk of patients misunderstanding the information, they receive written information followed by a telephone call.
There was no intervention included in these studies, and all study subjects received standard care. However, these studies included handling of sensitive personal data which is to be considered an integrity risk for the study subjects. Hence, all data was pseudonymized and saved on a secure server aiming to minimize this risk.

In study III, we collected additional data from medical records to obtain detailed information on the circumstances surrounding the RRT-review. Thus, this procedure introduces an additional element involving data directly obtained from medical records, constituting another potential integrity risk for study subjects.
Potentially, patients being subject to in-depth data collection from medical records could feel offended and their trust in the caregivers might be compromised. In this study, informed consent for the additional data collection was waived since this had already been obtained in connection with inclusion in the SRCR. In order to safely collect and incubate data, whilst protecting patient integrity, an electronic Case Report Form (CRF) was created.

Patients subject to RRT-review are in one of the poorest conditions of all hospitalized patients[158, 189]. Study II and IV consisted of prospectively collected data on RRT-reviewed patients. The study subjects included in this project frequently suffer from critical conditions, hence considered a vulnerable group. It might be very hard for these study subjects to decide whether they should approve study participation. However, it is of vital importance that this group of high-risk patients are included in the study, since the results will increase the knowledge in the field of early identification and clinical management of high-risk patients. Therefore, inclusion in these studies was considered exempt from informed consent. As in Study I and III, these studies included the handling of sensitive personal data, which is considered a risk for the study subjects. To minimize this risk, and in line with study I and III, all data was pseudonymized, and saved on a secure server.

All studies were published without the possibility of linking the results to individual study subjects.

7 RESULTS

7.1 STUDY I - "ECG – MONITORING OF IN-HOSPITAL CARDIAC ARREST AND FACTORS ASSOCIATED WITH SURVIVAL"

7.1.1 Main results

In total, 24,790 patients were enrolled in the SRCR between January 1st, 2008, and December 31st, 2017. After applying the exclusion criteria, 19,225 patients remained. Approximately every other patient was monitored at the time of collapse (52%). Monitored patients were slightly younger (71 years vs. 74 years), more commonly men (63%), had an overall lower burden of comorbidities and more frequently an initial shockable rhythm (38% vs. 13%).

For the total cohort, the overall 30-day survival was 30%. ECG monitoring at the time of collapse was associated with a Hazard ratio (HR) of 0.62, 95% CI 0.60-0.64, for overall 30-day mortality (Figure 8).

Figure 8: Adjusted Hazard Ratio for overall 30-day mortality,

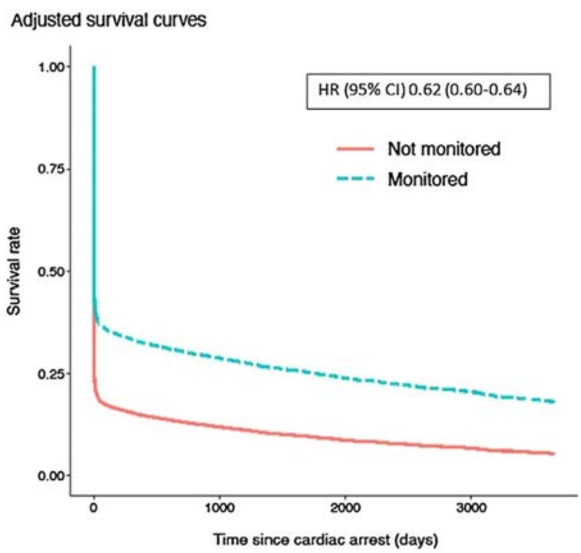


Figure 8: Adjusted Hazard Ratio for overall 30-day mortality, ECG monitored vs. non-ECG monitored patients (n=19,925).
Thorén et al.[190]. Reproduced with permission from Elsevier.

The strongest predictor of ECG monitoring in IHCA patients overall, as well as when analyzing the groups of initial rhythm separately, was location in hospital followed by geographical region. When excluding the variable location in hospital, the strongest predictor was ongoing myocardial infarction followed by geographical region (Figure 9 A-D).

Figure 9: The relative influence of 15 variables on ECG monitoring in IHCA

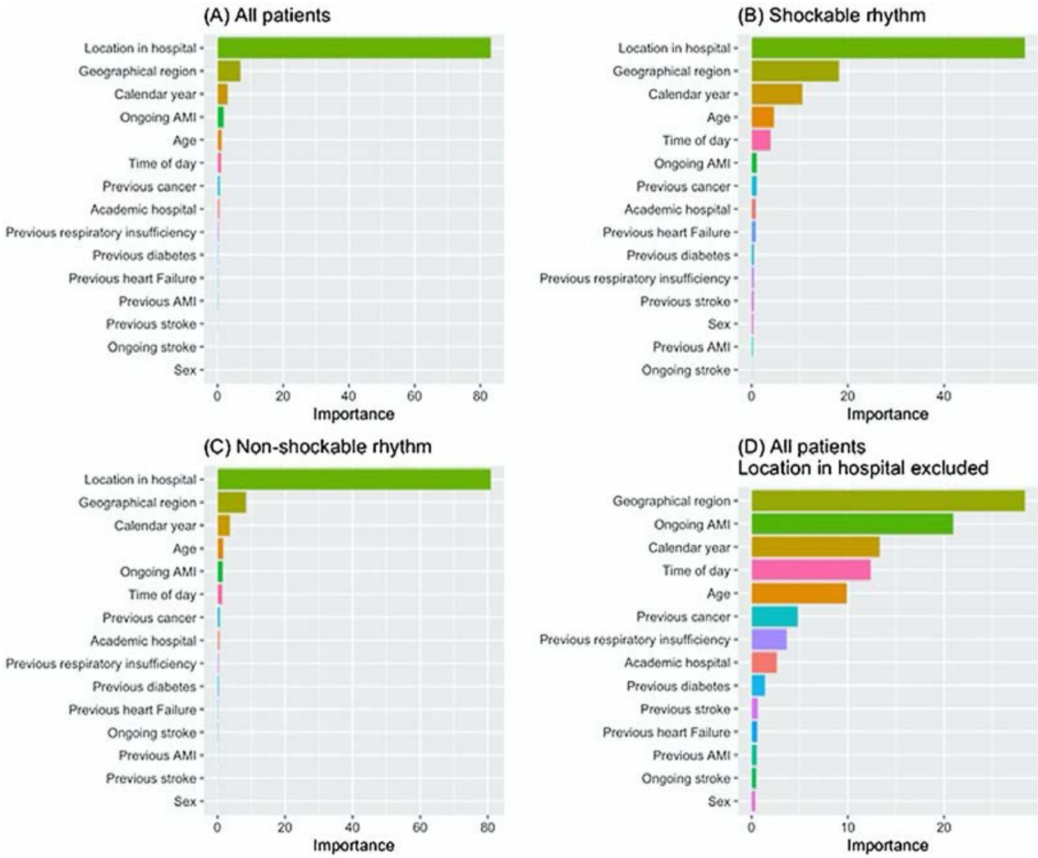


Figure 9: AMI, Acute Myocardial Infarction.
Thorén et al.[190]. Reproduced with permission from Elsevier.

During the study period, the number of patients who were ECG monitored adjacent to IHCA increased from 51% to 55%. Within hospitals, the proportion of patients being ECG monitored adjacent to IHCA in general wards was 22%, in the ED 58%, in the HDU 73%, in the CCU 92%, in the ICU 97% and in the catheterization lab 98%. Notably, we observed a tangible variation in the frequency of ECG monitoring between regions and across hospitals, ranging from 38% to 59% and 10% to 86%, respectively.

7.2 STUDY II – "THE PREDICTIVE POWER OF THE NATIONAL EARLY WARNING SCORE (NEWS) 2, AS COMPARED TO NEWS, AMONG PATIENTS ASSESSED BY A RAPID RESPONSE TEAM: A PROSPECTIVE MULTI-CENTRE TRIAL"

7.2.1 Main results

During the study period between October 2019 and January 2020, 1,065 RRT-reviewed patients were included. After applying the exclusion criteria and excluding patients with vital signs missing, 898 patients with complete cases of data was eligible for analyses (Figure 10).

Figure 10: Study cohort

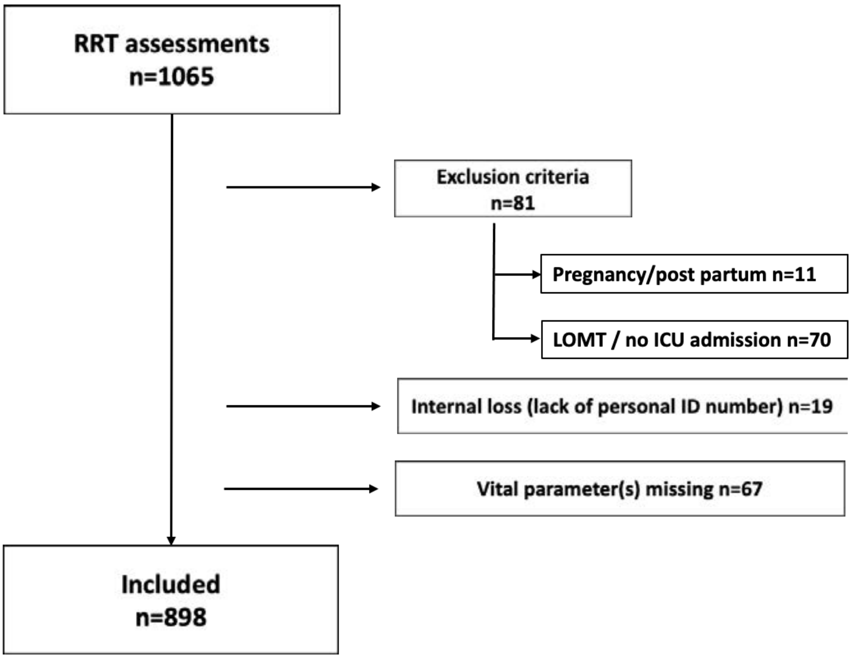


Figure 10: RRT, Rapid Response Team, LOMT, Limitations of Medical Treatment, ICU, Intensive Care Unit.
Thorén et al.[191]. Reproduced with permission from Elsevier.

The median age was 72 years, and 57% of the patients were male. There was a decision on LOMT prior to RRT-review in 13% of the cases, and the most common cause of hospital admission was infectious diseases, followed by surgical and orthopedic diseases.

In 60% of the RRT-reviews, the trigger was an elevated NEWS/NEWS 2 score. In 25% of the cases staff concern was the cause of RRT-review. Most RRT- reviews were performed during on-call hours in medical and surgical wards. A NEWS/ NEWS 2 score of 7 or more was present in approximately 70% of the patients. Regarding level of care after RRT-review, 27% of the patients were immediately admitted to the ICU, and an additional 10% were transferred to the HDU or CCU. In 8% of the cases, there was a new decision on LOMT. Within 24 hours of RRT-review, a total of 37% of the patients were admitted to the ICU. In-hospital mortality and IHCA was uncommon within 24 hours of RRT- review (6% and 1%, respectively). Regarding the composite outcome, 44% patients were affected by it.

Regarding predictive performance, the AUROC for both NEWS and NEWS 2 was 0.62 for the composite outcome, and 0.69/0.67 for mortality (Figure 11). As for the outcome unanticipated ICU admission, the AUROC was 0.59 and 0.60, respectively. The AUROC for prediction of IHCA within 24 hours of RRT review was 0.51 (NEWS) and 0.47 (NEWS 2), respectively.

Figure 11: AUROC curves for prediction of the composite outcome and mortality within 24 hours of RRT review

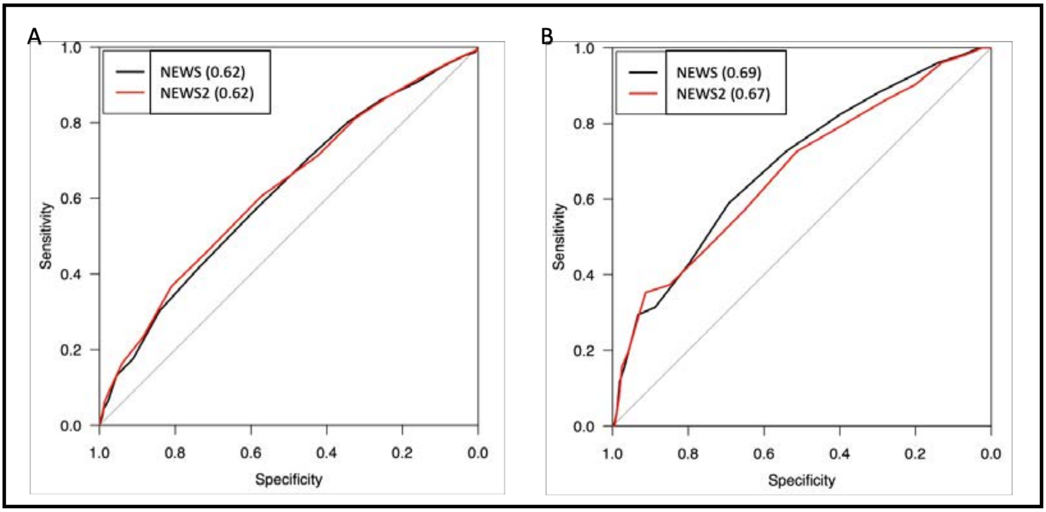


Figure 11 A: AUROC curves for prediction of the composite outcome (unanticipated ICU admission, mortality or IHCA all within 24 hours after RRT assessment) for NEWS and NEWS 2 (AUROC 0.62/0.62) (n = 898).
B. AUROC curves for prediction of mortality within 24 hours after RRT assessment for NEWS

(0.69) and NEWS 2(0.67) respectively (n = 898). AUROC, Area Under the Receiver Operating Characteristic, NEWS, National Early Warning Score, RRT, Rapid response team, ICU, Intensive care unit, IHCA, in-hospital cardiac arrest.
Thorén et al.[191]. Reproduced with permission from Elsevier.

7.3 STUDY III – "RAPID RESPONSE TEAM ACTIVATION PRIOR TO IN-HOSPITAL CARDIAC ARREST: AREAS FOR IMPROVEMENT BASED ON A NATIONAL COHORT STUDY"

7.3.1 Main results

During the study period, 19,973 patents were enrolled in the SRCR. In all, 12,915 patients remained after applying exclusion criteria of which there was an RRT/ICU contact within 24 hours prior to IHCA in 2,058 cases (19%, Figure 12).

Patients reviewed by an RRT had a lower median age and were more commonly men. Regarding comorbidities, we observed small differences between the groups, except for ongoing myocardial infarction, which was less frequent (18 % vs. 25% p<0.001) and respiratory insufficiency, which was more frequent (33% vs. 23%, p<0.001) among RRT-reviewed patients. The rates of missing variables were 5% or lower, except for the cause of IHCA (26%), an RRT/ICU contact within 24 hours prior to IHCA and the initial rhythm (22% respectively).

Among patients reviewed by RRTs, the CAs were more commonly non-shockable (asystole or pulseless electric activity) and located in the ICU. The CAs following RRT-review were more common during on-call hours. Regarding aetiology, a respiratory cause of IHCA was more common among patients who were reviewed by an RRT, compared to those with no RRT-review within 24 hours prior to CA (22% vs. 15%, p<0.001). In all, 82 patients out of 369 were RRT-reviewed in general wards within 24 hours prior to CA, hence eligible for an in-depth review of medical records (Figure 12). In this small explorative subgroup, median age was 74 years and 66% of the patients were men. There were few decisions on LOMT prior to RRT-review (1%). The most common cause of RRT-review was respiratory distress. Activation of RRT was frequently delayed (24%), with a delay of 4 hours or more in 3 out of 4 cases. A preceding RRT-review and a surgical procedure were quite common within 24 hours of RRT-review (27% and 15%, respectively).

Figure 12: Study cohort

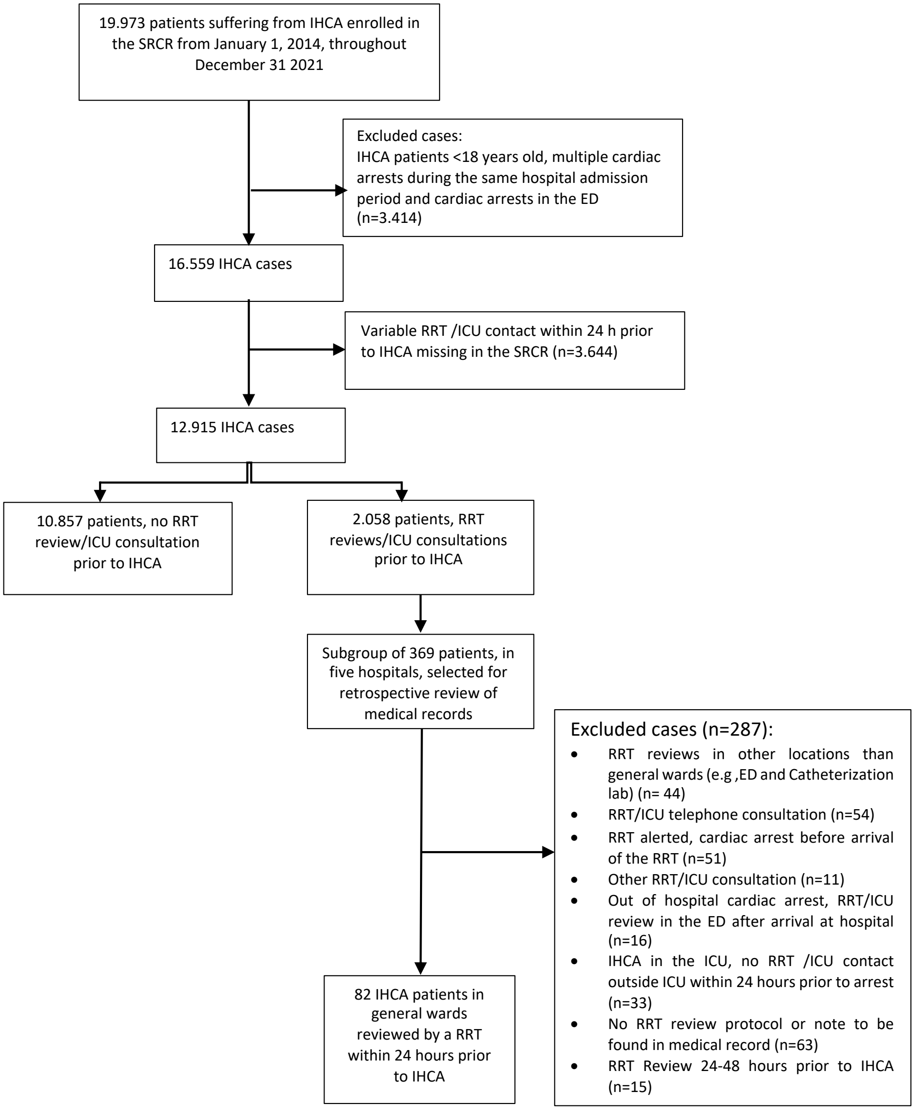


Figure 12: IHCA, In-hospital cardiac arrest, SRCR, Swedish Registry for Cardiopulmonary Resuscitation, ED, Emergency Department, RRT, Rapid Response Team, ICU, Intensive Care Unit. Thorén et al.[192]. Reproduced with permission from Elsevier.

After RRT-review, 60% of the patients remained at ward. These patients were slightly older, and more commonly female. The median Charlson comorbidity index (CCI) score was 2 in both groups, however diagnoses of Chronical obstructive lung disease (COPD), cancer and renal disease were common among patients triaged to remain in the general ward. One patient (1%) received a new decision on LOMT, and two patients (2%) died whilst being reviewed by the RRT. Regarding the NEWS scores, patients triaged to remain at ward had a median score of 8 compared to 9 among those transferred to the ICU.

Overall, 30-day survival was 32%. Among patients reviewed by RRTs within 24 hours of CA, the adjusted 30-day survival was lower (25% vs. 33%, p <0.001). Regarding ROSC, we did not observe any difference between the two groups. The propensity score based OR for 30-day survival was 0.92 for patients reviewed by an RRT prior to CA (95% CI 0.90 to 0.94, p <0.001), compared to those who were not reviewed by an RRT.
In the small subgroup of patients reviewed by an RRT in general wards (n=82), 30-day survival was significantly lower among patients triaged to remain at ward compared to those triaged to a higher level of care (2% vs 20%, p 0.016). Furthermore, the prognoses were poorer for patients with respiratory distress as a cause for RRT-review and for those reviewed by RRTs during on-call hours (p 0.049 and 0.029, respectively).

7.4 STUDY IV – "EXPLORING THE IMPACT OF AGE ON THE PREDICTIVE POWER OF THE NATIONAL EARLY WARNING SCORE (NEWS) 2, AND LONG-TERM PROGNOSIS AMONG PATIENTS REVIEWED BY A RAPID RESPONSE TEAM: A PROSPECTIVE, MULTI-CENTRE TRIAL"

7.4.1 Main results

A total of 1,065 RRT-reviews were performed in the 24 participating hospitals. After applying the exclusion criteria, 981 patients remained (Figure 13). Furthermore, 151 patients (14%) were excluded because of missing data, including lack of personal ID number, which made follow-up impossible, one or several vital parameters missing (most frequently body temperature), and loss to follow-up when collecting data on long-term survival. In all, 830 patients were included in the analyses (Figure 13). In the study cohort, 43% of the patients were female, and the patients had a median age of 72 years. The most frequent location in hospital for RRT-review was medical wards (45%), followed by surgical wards (26%) and orthopaedic wards (10%).

Figure 13: Study cohort

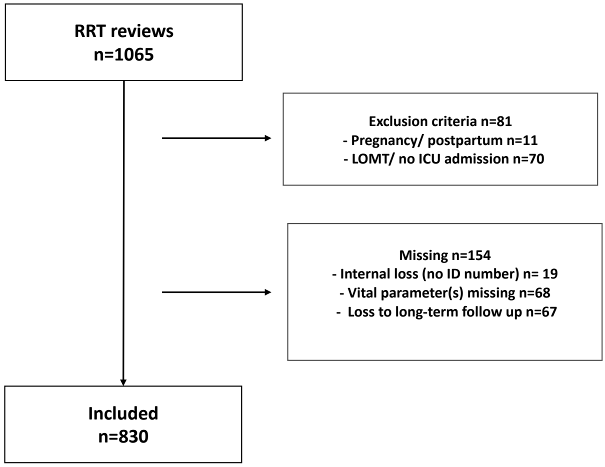


Figure 13: RRT, Rapid Response Team, LOMT, Limitations of Medical Treatment, ICU, Intensive Care Unit.

An elevated NEWS 2 score was the most frequent RRT trigger (59%), followed by staff concern (26%). There was a decision on LOMT prior to RRT-review in 15% of the cases. The median NEWS 2 score at the time of RRT-review was 9 (interquartile ranges 6-11). A total NEWS 2 score of 7 or more was calculated in 74% of the patients.

The RRT-review resulted in an immediate transfer to the ICU in 218 cases (26%). Within 24 hours of RRT-review, a total of 300 patients (36%) were admitted to the ICU. There was an escalation of the level of care in another 11% of the patients, by transfer to a HDU or CCU. The 24-hour mortality was 6%, and 1% of the patients suffered from CA. In all, 331 patients (40%) were affected by the composite outcome. 30-day mortality was 31%, 90-day mortality 33% and 180-day mortality 36%.

The AUROC of NEWS 2, without adding age, in predicting 24-hour and 30-day mortality among RRT-reviewed patients was 0.69 (0.62-0.76) and 0.66 (0.62-0.70) respectively. Adding age as a covariate in the prediction of 24-hour mortality did not increase the AUROC. Regarding the prediction of 30-day mortality among RRT-reviewed patients, adding age as a covariate improved the discriminative ability of NEWS 2 in all models, with the best performances observed using age as a continuous variable and the spline model, where the AUROC increased from 0.66 (0.62-0.70) to 0.70 (0.65-0.74, p 0.01). There appeared to be a difference in the discriminative ability of NEWS 2 according to age groups, with the apparent best predictions of mortality made by adding age among patients aged 45-54 years (Figure 14). Compared to the prediction of 30-day mortality, the discriminative ability of NEWS 2 was poorer in predicting 90-day and 180-day mortality among RRT reviewed-patients.

Figure 14: The discriminative ability of NEWS 2 alone and with age as a covariate

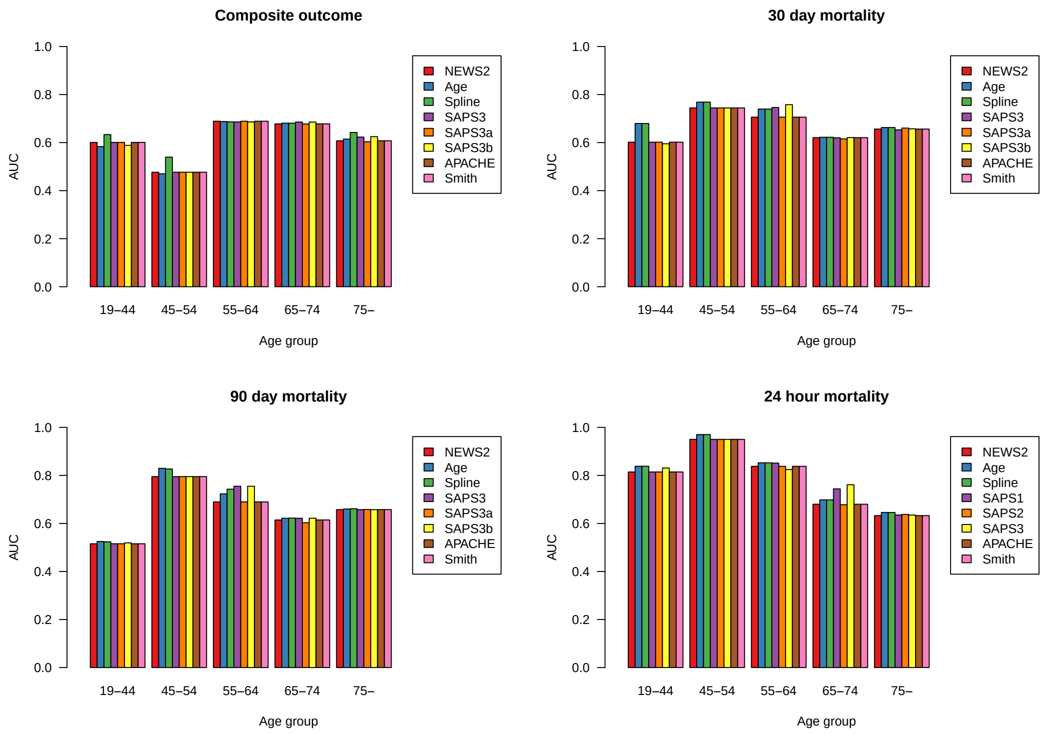


Figure 14: The discriminative ability of NEWS 2 alone and with age as a continuous variable, in a spline regression model and categorized into different age models, to identify patients at risk of the composite outcome (unanticipated ICU admission, IHCA or mortality) within 24 h of RRT-review and in prediction of 24-hour, 30-, and 90-day mortality.

NEWS 2, National Early Warning Score 2, ICU, Intensive Care Unit, IHCA, In-hospital cardiac arrest, RRT, Rapid Response Team, SAPS, Simplified Acute Physiology Score, APACHE, Acute Physiology, Age and Chronic Health Evaluation system.
The model "Smith" refers to the age categorizations by Smith et al. See Methods.

Regarding IHCA within 24 hours of RRT review, the discriminative ability of NEWS 2 was improved by adding age as a covariate according to the APACHE, SAPS 3b and Smith models. The best performance was achieved using the SAPS 3b model, which increased the AUROC from 0.54 (0.32-0.76) to 0.67 (0.49-0.84, p=0.003), as compared to NEWS 2.

As for unanticipated ICU admission within 24 hours of RRT-review, AUROC for NEWS 2 was 0.61 (0.57-0.65). The AUROC increased to 0.66 (0.62-0.69, p=0.001), by using the spline model to predict unanticipated ICU admission as compared to NEWS 2.

Adding age as a covariate to NEWS 2, in the prediction of the composite outcome, improved the AUROC according to the continuous, spline, and APACHE models, where the best performance was achieved using the spline model (from AUROC 0.63 (0.59-0.67) to 0.66 (0.63-0.70).

8 DISCUSSION

8.1 MAIN FINDINGS

The main findings in this thesis include an association between ECG monitoring at the time of CA and a significantly reduced 30-day mortality, and approximately every other patient suffering from IHCA being monitored at the collapse. The most important predictor of ECG monitoring was which type of hospital ward the patient was admitted to. Furthermore, we observed tangible variations in the frequency of ECG monitoring between different regions and across hospitals.

Another main finding was that NEWS and NEWS 2 performed equally in predicting SAEs in a cohort of patients within 24 hours of RRT-review. The predictive power of NEWS 2 was acceptable for the prediction of mortality within 24 hours of RRT-review, whereas the performance in predicting IHCA was poor. However, the predictive power of NEWS and NEWS 2 was not sufficient to serve as a triage tool for patients reviewed by RRTs.

Furthermore, IHCA among patients who were reviewed by an RRT prior to IHCA was associated with a poorer prognosis. A respiratory cause of CA was more frequent among RRT-reviewed patients. In the small, hypothesis-generating sub-group of patients reviewed by RRTs in general wards, delayed RRT activation was frequent, and the most common trigger for RRT-review was respiratory distress. Early identification of patients with abnormal respiratory vital signs, followed by a timely response, may have a potential to improve the prognosis for RRT-reviewed patients and prevent CA.

We also found that adding age as a covariate in NEWS 2 increased the discriminative ability to predict 30-day mortality in the same cohort of patients to a level considered acceptable. There were differences across age categories, with the most beneficial effect identified among patients aged 45-54 years.
The long-term prognosis of RRT-reviewed patients was poor, and the discriminative ability of NEWS 2 alone in prediction of 30-day mortality prognosis was weak.

8.2 ECG MONITORING AND IN-HOSPITAL CARDIAC ARREST

8.2.1 What is the rationale behind the lower adjusted 30-day mortality among patients who were ECG monitored prior to in-hospital cardiac arrest?

In study I, we identified ECG monitoring adjacent to collapse as an important predictor of 30-day survival after IHCA, associated with a 38% reduction in adjusted 30-day mortality.

First, monitoring reduces the time to alarm, initiation of treatment and defibrillation, given a shockable rhythm. Early detection of CA, and factors associated with a short time to initiation of treatment, are associated with survival following IHCA regardless of whether the first recorded rhythm is shockable or non-shockable[2, 23, 29].

Second, one of the factors most strongly associated with survival is the initial rhythm; patients who presented with an initial VF have a 2 to 3 times higher likelihood of survival to hospital discharge compared with patients who presented with an initial non-shockable rhythm[50, 73]. Monitoring could hypothetically increase the proportion of patients with an initial shockable rhythm, since the likelihood of having a patient presenting with an initial VF is higher the earlier ECG is recorded[193]. This is most likely explained by findings in previous animal studies, illuminating that CAs with an initial VF given time often degenerates into PEA which in turn can degenerate into asystole due to energy depletion of myocytes and metabolic alterations[193, 194].

All this taken together might explain our finding of a reduced risk of death after IHCA in patients being ECG monitored at the time of collapse.

8.2.2 Could ECG monitoring be somewhat a confounder for the likelihood of better outcome?

In study I, we observed only every other IHCA patient to be monitored at the time of collapse despite of the significantly increased chances of survival for ECG monitored patients.

Patients with a primary cardiac diagnosis are more likely to be ECG monitored, and a cardiac aetiology, e.g., myocardial infarction/ischaemia, of CA is associated with a better prognosis following IHCA [2]. However, in the absence of national guidelines for in-hospital monitoring for patients at risk of CA, the competence and experience of the admitting physician is of crucial importance in prioritizing whether patients should be monitored. Limitations in the number of monitored ward beds have a great impact on this decision making with respect to everyday clinical practice. Decisions made by the admitting physician is somewhat a selection process when forced to prioritize, which might benefit patients with a likelihood of a better outcome.

Thus, it is possible that ECG monitoring might be somewhat of a cofounder for the likelihood of better outcome. Surrogate measures in study I possibly supporting this theory are the facts that ECG monitored patients were younger and had a lower frequency of previous stroke, diabetes, heart failure, cancer, and respiratory insufficiency. Furthermore, ECG monitoring is probably more likely to detect shockable rhythm, i.e., rhythms associated with better outcomes[50, 73].

In summary, the association between ECG monitoring and an improved survival has been reported in many other previous studies[2, 29, 77, 93, 195, 196]. The analysis based on propensity scores in study I also reduces the risk of confounding factors interfering with outcome. Thus, it is likely that there is an association between ECG monitoring and increased 30-day survival, even though the retrospective, register based study design does not permit any conclusions on causality to be drawn.

This notwithstanding, the only way the effectiveness of ECG monitoring can be optimally evaluated is with a prospective RCT. However, this would be a very difficult task considering both ethical, logistical, and economical aspects, since ECG monitoring is such a well-established and strong predictor for 30-day survival following IHCA, and the cost for such RCTs would be substantial.

8.2.3 The Swedish Registry for Cardiopulmonary Resuscitation-can we trust data?

In study I and III, data was retrieved from the SRCR.
The quality of registries depends on the accuracy and coverage of data reported. There is always a risk of recall bias or errors associated with the filing of data, which in turn make data prone to selection and information bias. Incomplete (missing) data is another challenge when conducting register-based research. Study I and III are based on data from the SRCR. The nationwide registry has previously been described under sub-section 3.3.

The level of ascertainment is considered high, based on results from a validation of reported data on a total of 1,338 patients in 34 hospitals (out of 71 reporting to the SRCR) during the period 2014-2018. Medical records and hospital data were compared with data reported to the SRCR, illuminating that information about the variables "location in hospital" and "witnessed status" was consistent with source data in 99% and 96% of the cases, respectively. Regarding the variable "initial rhythm", data in the SRCR was consistent with source data in 94% of the cases [197]. Furthermore, the validation identified reporting bias of CAs managed by the cardiac arrest team. Every other hospital reported that they included all these CAs; however, there was underreporting in 5%-30% of the hospitals.

Missing variables in individual patients may introduce bias. Research involving emergency situations and time registrations are always more prone to be imprecise or missing, due to the aggravating circumstances. This is also the case of the SRCR variables involving time registrations. Nevertheless, some of these variables have repeatedly been associated with survival in different settings, which is why the exclusion of time-related variables would be most unfortunate. The SRCR variables affected by the highest rates of missing data during the study period of study III, between 2014 and 2021, were the cause of IHCA (26%), an RRT/ICU contact within 24 hours prior to IHCA and the initial rhythm (22% respectively).

For many years, the SRCR was gradually expanding. Hence, the external validity of the SRCR might also have been lower during the early time periods due to fewer hospitals reporting to the hospital. Furthermore, some hospitals started reporting to the SRCR early on, which possibly reflects a greater dedication to and interest in CA care. The hospitals who started reporting to the SRCR early on have contributed with more data over time, which in turn might have skewed and affected, for example, 30-day survival.

Despite some areas of uncertainty, SRCR is to be considered representative of the Swedish IHCA population where resuscitation was attempted, with its nationwide coverage, Utstein style of reporting data, high level of ascertainment, continuous reporting and definitions remaining constant over time. The registry has come to serve as an international role model for other CA registries. Many scientific publications and theses have been based on the SRCR, and several of the publications are cited in international guidelines for CPR.
Furthermore, it constitutes an invaluable source of data available for quality improvement and research on IHCA, enabling monitoring of the real time benefit of all interventions. The SRCR is beneficial for not only Swedish patients but in an

international context, in the strive to both prevent IHCA and improve survival after IHCA.

8.2.4 What is the rationale behind the variability in the frequency of ECG monitoring adjacent to in-hospital cardiac arrest between regions and across hospitals?

In study I, 73 hospitals with varying demographics and geographical locations, contributed with data. Interestingly, we illuminated tangible variations in the frequency of ECG monitoring at the time of CA at different centres- between 38% and 59% across Swedish counties; with regard to Swedish hospitals, ECG monitoring rates ranged from 10% to 86%.

First, it must be taken into consideration that results from hospitals with a very small number of beds and a low number of CAs on a yearly basis must be interpreted with caution, since results from such hospitals are more prone to be influenced by random variation.

One important explanation could be variations in the patient case mix between different hospitals[77, 196]. Regional differences in recommendations and clinical practice associated with these decisions might also contribute to the disparities. Furthermore, demographic factors might be of importance (e.g., the number of beds, academic status, urban/rural location, primary/secondary/tertiary hospital). The local practice and culture regarding decisions on DNACPR-orders are also most likely of importance.

This notwithstanding, differences between hospitals and regions regarding resources, staffing and work conditions could most likely be captured in a nationwide study like this, expressed as a significant variability in the rate of ECG-monitoring adjacent to IHCA.

It would indeed have been interesting to correlate the findings of study I to the incidence and outcome of CA in the participating hospitals. However, this was out of the scope of study I. We can only speculate whether a higher frequency of ECG monitoring would have correlated with a lower incidence of IHCA in the participating hospitals, by means of an early detection of signs concerning preventable deterioration. Future studies are needed to further investigate the nationwide differences in the rate of patients being ECG monitored at the time of collapse. National guidelines for ECG monitoring of patients at risk of IHCA could be a valuable contribution aiming to equalize the geographical variations, holding a potential to further improve survival after IHCA.

8.3 RAPID RESPONSE SYSTEMS

8.3.1 Why is it so difficult to evaluate Rapid Response System efficacy?

The short and simple answer to this question may be that the RRS is not a "clean" intervention amenable to traditional analysis forms due to the complexity of both the intervention itself and the system in which it is implemented[108, 198]. A complex, inter-linked intervention system such as the RRS can involve both interactions between patients and caregivers and depend on its weakest link; thus, reliability and effectiveness in all parts of the chain with a timely progression is vital[103]. Different components of the system can also interact and potentially affect outcome[108]. Furthermore, the outcome measures of choice also influence evaluation.

8.3.2 Which outcomes are meaningful when evaluating the effect of Rapid Response Systems and how should we measure them?

There are a number of outcome measures that can be used to evaluate the performance of an RRS. In the literature, the most commonly used outcome measures are IHCA, unanticipated ICU admission and mortality[108]. However, all of these are associated with different challenges making evaluation of RRS efficacy complicated.

In the literature, there are substantial variations as to both definitions and reporting of IHCA. In many study designs, CAs in the ICUs are excluded, which might introduce a bias. In a meta-analysis, Chan et al. reported a reduced number of general ward CAs; however, there was no decrease in the hospital mortality, which might reflect this specific concern[115]. Furthermore, the incidence of IHCA is under strong influence of the frequency of DNACPR orders issued by the RRT[199].

The rate of transfer to the ICU is a common outcome measure[119]. However, the fact that a potential intervention by the RRT is also an outcome measure contributes to the complexity concerning analyses of RRS efficacy. Furthermore, changes in the rates of ICU-transfer are hard to interpret; an increased number of transfers could indicate an effective RRT triage and appropriate escalation of care, and a reduced number might be a result of RRTs intervening effectively in general wards[119]. Therefore, it has been suggested that this outcome measure should be linked to, for example, ICU mortality, in order to contextualize the findings[119]. As for mortality, it has been suggested that unexpected mortality (i.e., death following resuscitation attempts) could be more appropriate compared to overall mortality[83].

Besides choice of outcome measures, several possible causes of failure to demonstrate RRS efficacy exist – design related, multifactorial or simply due to a malfunctioning system[148]. Regarding study design, an immature RRS system, insufficient baseline and inclusion periods, contamination of the hospital selected as control and lack of study power have been suggested as plausible explanations to failure[148].

Given the complexity of the RRS system, implemented in a likewise complex hospital environment, alternative performance measures have been suggested as preferrable. These performance measures include the frequency of delayed RRT activations, the overall number of RRT activations, and RRT trigger mechanisms[109, 200].

8.3.3 A prospective, observational study design for the evaluation of Rapid Response Team reviews and interventions- is there risk of introducing an observation bias (the Hawthorne effect)?

The study design of study II and IV might introduce a bias known as the Hawthorne effect, meriting further discussion. The Hawthorne effect is a widely used term in the context of research, occurring when people are unconsciously or consciously aware that they are under observation, resulting in a behaviour change[201]. Various descriptions of Hawthorne effect exist in the literature, for example, "the beneficial effect of taking part in research" (Russell & Grimshaw 1992); "an initial improvement in performance following a newly introduced change" (Liebersohn 1977); and "the confounding that occurs if experimenters fail to realize how the consequences of subjects' performance affect what subjects do" (Parsons 1974)[202].
Over the years, the Hawthorne effect has been subject of a vivid debate. In a systematic review, the authors concluded that the Hawthorne effect was not a single effect, but rather several ones. In most studies they found evidence of existence; however, uncertainties remained as to the mechanisms and magnitudes of the effects, or under which circumstances they operate[201].

In study II and IV, data was collected by RRTs operating according to clinical routines. However, it cannot be excluded that RRT interventions were affected by participation in the study, which in turn might have had an impact on outcomes. As to the magnitude and consequence of an eventual Hawthorne effect on outcomes, we can only speculate. It might be beneficial for patients reviewed by RRTs, given that most RRT-reviews result in a treatment and/or other intervention[203]. This notwithstanding, it should be taken into account when interpreting the study results.

8.3.4 How come the discriminative ability of NEWS and NEWS 2 was lower in a cohort of RRT-reviewed patients compared to patients in general wards?

The discriminative ability of NEWS, regarding the identification of patients at risk of SAEs, has been good to excellent in previous studies[127]. In study II, NEWS and NEWS 2 performed worse in identifying patients at risk of SAE. There are several plausible explanations for this finding.

First, and most importantly, NEWS was originally developed and evaluated in a cohort of selected general ward patients[127]. In the study cohort of RRT- reviewed patients, considered as high-risk, few scored low in NEWS/NEWS 2. This has most likely inflicted the discriminative ability of NEWS and NEWS 2.

Previous studies have identified miscalculation as a main cause of error when using NEWS and NEWS 2[204, 205]. In this study we retrospectively and uniformly calculated the NEWS/NEWS 2 score for each patient by means of a statistical program. Hence, this would have minimized the risk of miscalculation as a contributing cause of a worse predictive performance.

Furthermore, previously published studies have suggested that the majority of RRT-reviews result in treatments or interventions[203], aimed to prevent further deterioration and improve patient outcome, which in turn might affect outcomes. Hence, the association between the NEWS/NEWS 2 score and outcomes becomes weaker.

Finally, many previous studies investigating the effects of RRS are observational, retrospective cohort studies. This might affect the effectiveness when implemented in a context other than the observed cohort, since RRS is an intervention of great complexity implemented in a hospital environment, which is to be considered complex as well.

8.3.5 Is there a need for a risk stratification tool as decision support for Rapid Response Team triaging of high-risk patients in general wards?

In study II, we investigated the predictive power of NEWS and NEWS 2 to identify RRT-reviewed patients at risk of SAEs. We did not observe any difference between NEWS and the revised version NEWS 2 regarding the discriminative ability. However, the performance was not sufficient for use as a risk stratification tool and decision support adjacent to RRT-review.

Patients triaged to remain in a general ward after RRT-review, particularly those with deranged vital parameters, have previously been identified as a high-risk group, associated with an increased mortality [189]. Thus, an adequate and effective triage of patients who are subject to RRT-review is of crucial importance, both in terms of the safety of patients admitted to hospitals and resource allocation.

Decisions on the escalation of care are influenced by multiple factors, including RRT staff competence and experience, the number of available beds in higher levels of care and local traditions and recommendations when assessing the need for escalation of care[189]. Given a resource limitation and an ever-present shortage of beds in a higher level of care, RRTs need to prioritize and patients who present with the most severe and urgent illness must be given the highest priority.

Previous research has illuminated combinations of EWS and additional variables, including patient age, comorbidity, and laboratory datasets, to improve the discriminative ability in identifying general ward patients at risk of SAEs[132, 206]. In study IV, we observed that adding age improved the discriminative ability of NEWS 2 to predict mortality at 30-days among RRT-reviewed patients into a level considered as acceptable. There were differences within age categories, with the most beneficial effect identified among patients aged 45-54 years. Furthermore, the implementation of EHRs and introduction of ML algorithms in medicine has yielded several new risk stratification models[207]. However, these models require easily accessible data and significant computer processing power[128].
To conclude, given the complexity in RRT-reviews, a risk scoring model could be a useful decision support and valuable subject of future studies.

8.3.6 How come abnormalities in respiratory parameters appear to be more alarming compared to other vital parameters among patients reviewed by a Rapid Response Team prior to Cardiac Arrest?

In study III, a respiratory cause of CA was more frequent among patients reviewed by an RRT within 24 hours prior to IHCA compared to non-RRT reviewed patients. Furthermore, respiratory distress was the most common trigger for RRT-review in the small, explorative sub-group, and a COPD diagnosis was overrepresented among patients remaining at ward after an RRT-review.

Patients triaged to remain at ward by RRTs had a significantly poorer prognosis with a 24-hour mortality of 20% compared to 2% for patients transferred to a higher level of care. In addition, a previous study has identified a respiratory cause of RRT activation as more common among patients with a delayed RRT-review; notably, this cohort included all hospitalized patients, not only patients who subsequently suffered from CA[153].

As previously described, respiratory rate is a well-established, powerful predictor of SAEs [136, 141, 144]. The respiratory rate serves as a "common pathway" vital sign indicator of severe illness in several body systems[144]. Unfortunately, respiratory rate is also the most neglected vital sign[144]. Notably, Tirkkonen et al. found the documentation of respiratory rate to be alarmingly low among patients with a delayed RRT activation, especially in ward areas without automated monitors[154].

Furthermore, in NEWS 2, oxygen supplementation is binary (yes/no). Hence, a patient in respiratory distress who deteriorates, with a rapidly increasing oxygen requirement, might very well remain on the same NEWS 2 score, even if the supplied oxygen has increased from 1 l/minute to 5, or even 10, l/minute.
As for hypoxia, a reduced oxygen saturation is commonly found among hospitalized patients[208]. The introduction of pulse oximetry has facilitated bedside diagnostics. However, there are several limitations associated with the clinical use of it; the specificity has been found inadequate and the knowledge of its purpose as well as correct use of it insufficient. Previous studies have also illuminated problems with the clinical interpretation of the measured values among different groups of the staff[209-211]. Therefore, it has been recommended that measurement of these two respiratory parameters should be used complementarily[144].

In summary, the combination of respiratory rate as a key vital sign predicting severe illness in several body organs and the high rate of missing in the respiratory rate parameter, in combination with the potential shortcomings of NEWS 2 and bedside diagnostics, most likely contribute to the poor prognosis of patients with deranged respiratory parameters, and the failure to prevent subsequent progress to CA.

8.3.7 Delayed Rapid Response Team activations - why doesn´t anybody call for help?

In study III, we identified a delayed RRT activation in 24% of the cases in the small explorative subgroup (n=82, patients reviewed by RRTs in general wards). Another 51 patients (out of 369 patients subject to in-depth data collection from medical records, with an RRT/ICU contact within 24 hours prior to CA) suffered from CA after RRT activation but before the arrival of the team. Some of these cases might have occurred in the context of an excessively delayed RRT activation[212]. However, among these events there are most likely cases of very rapidly deteriorating patients and an inappropriate activation of the RRT instead of the cardiac arrest team. This notwithstanding, we can only speculate whether a timely activation of the RRT and a subsequent, timely intervention might have prevented some of these IHCA cases.

The process for RRT activation involves several inter-linked actions; vital signs must be controlled by a member of the staff in the ward and properly documented. The staff member performing the measurements must understand that there is an issue and then respond by alerting the RRT. Hence, there are multiple factors in the link potentially causing delayed RRT activation.

First, monitoring can fail. Existing evidence suggests that monitoring of deteriorating patients is not adequate to enable a timely detection of an emergency, especially at night[105]. The intermittent character of patient monitoring in general wards by means of EWS constitute another contributing factor[213]. Poorly adapted and functioning observation and documentation systems constitute other potential obstacles to RRT activation, along with the absence of clear and mandatory escalation protocols[108]. ”Alarm fatigue”, which can occur if many alarms are “false” alarms, is another well-established cause of failure to escalate[214].

A decision to call for help is based upon a complex judgement, balancing a desire for clinical autonomy with the understanding of consequences for patients, colleagues, and self [215]. Sociocultural issues such as hierarchical structures and a perceived negative attitude of members of the RRT have previously been recognized as important factors contributing to delayed RRT activations[165, 214, 216]. Furthermore, the response can be delayed by inadequate or ineffective communication[217].

Staff competence is a key part of an effective RRS[101]. Interestingly, clinical experience has been identified as both a potential barrier and facilitator to the escalation of care[218]. In a mixed-method study, Shearer et al. demonstrated that the most common cause of failure to escalate was that the bedside staff assessed that the clinical situation was under control in the general ward setting [215]. The second most common cause was related to limitations of hospital resources; the RRT had reviewed the patient but there were no ICU beds available[215]. Furthermore, a "patient unit mismatch" (e.g., a medical patient being admitted to a surgical ward) is also associated with an increased risk of delayed RRT activation[219]. As for the impact of patient-to-nurse ratio on delayed RRT activations, there is a trend for more delays with larger assignments, with 75% of the delayed RRT activations occurring when the patient-to-nurse ratio was 5:1 or 6:1[219].

In study II, we found that the difference in NEWS/NEWS 2 scores between patients triaged by RRTs to remain at ward vs. patients transferred to a higher level of care was small (8 vs. 9 points). Hence, patients frequently remain at ward with high NEWS/NEWS 2 scores, well above the threshold for RRT activation. It is possible that ward staff might hesitate to activate RRT once more, since they had already assessed the patient and decided that the patient should remain at ward, which might contribute to delays in RRT activations and a poorer prognosis.

To conclude, there is a plethora of well recognized factors associated with a delayed RRT activation. Many of these factors are to be considered as highly modifiable, opening a window of opportunity as to the reduction of factors inflicting the efficacy of RRS.

9 CONCLUSIONS

Study I:

ECG monitoring at the time of IHCA was associated with a 38% reduction of adjusted mortality. The most important factor influencing ECG monitoring was which type of hospital ward the patient was admitted to, and approximately one in two IHCA patients were ECG monitored. The tangible variations in the frequency of ECG monitoring adjacent to IHCA observed between Swedish regions and across hospitals need to be investigated in future studies. Guidelines for the monitoring of patients at risk of CA could contribute to an improved outcome.

Study II:

The prognostic accuracy of NEWS 2 in predicting mortality within 24 hours of RRT-review was acceptable, whereas the discriminative ability in prediction of unplanned admission to the ICU, and the composite outcome was rather weak. As for prediction of IHCA, NEWS 2 performed poorly. There was no difference in the prognostic accuracy between NEWS and NEWS 2, however the predictive power was not considered sufficient to serve as a triage tool in patients reviewed by RRTs.

Study III:

In-hospital cardiac arrest among patients who were reviewed by an RRT prior to CA was associated with a poorer prognosis, and a more frequent respiratory aetiology of IHCA. In the explorative sub-group of patients, RRT activation was frequently delayed, the most common trigger for RRT-review was respiratory distress, and escalation of the level of care was associated with an improved prognosis. Early identification of patients with abnormal respiratory vital signs, followed by a timely response, may have a potential to improve the prognosis for patients reviewed by an RRT and prevent IHCA.

Study IV:

Adding age as a covariate improved the discriminative ability of NEWS 2 in the prediction of 30-day mortality among RRT-reviewed patients, and the ability differed across age categories. The long-term prognosis of RRT-reviewed patients was poor. Our results indicate that age merits further validation as a covariate to improve the performance of NEWS 2.

10 FUTURE PERSPECTIVES

Despite significant improvements during the last decades, much is still to be done in this field. Future research needs to focus on the prevention of IHCA, but we must also ensure that all IHCA patients are entitled to an equal and state-of-the art resuscitation care-at any time of the day, independent of weekday or which hospital the patient is admitted to. Furthermore, we must continue to strive to make sure that only patients who benefit from ALS are resuscitated. Outcome after IHCA can and should only be assessed in relation to the individual patient. Important core issues of future research includes the following.

10.1 Monitoring and early identification of patients at risk

A wider implementation of surveillance monitoring is most likely one way of effectively addressing and mitigating the complex problem of failure to rescue. Patients reviewed by RRTs and triaged to remain on ward could be admitted to virtual high-risk wards, where real-time surveillance monitoring, alternatively virtual ward rounds, could be performed by RRTs or other staff with critical care competence. This could be a complement to proactive follow-up clinical reviews of high-risk patients remaining in general wards after RRT-review.
Expanding this system of wireless wearable systems to virtual "at-home" wards could allow a safe, early hospital discharge. Furthermore, selected patients could safely be receiving care directly in "at-home" wards without even being admitted to a hospital.

Electronic monitoring systems predicting deterioration, based on ML algorithms, are increasingly being constructed on a research basis. Today, few have been implemented into everyday clinical practice, where the limitations include the need for immense data-power in combination with important negative side-effects, for example an increased rate of false alarms with a negative impact on staff work environment, subsequently and potentially causing "alarm fatigue". Future research needs to focus on cost-effective, user-friendly, and safe technical solutions in combination with meaningful patient outcome measures.

However, these modern monitoring systems could never replace physical evaluations and measurements of patient vital signs by ward staff. Clinical judgement will remain paramount, and some signs of deterioration never present themselves as deranged vital signs. These systems can only serve as a first-line surveillance monitoring, securing a 24/7 baseline monitoring of all hospitalized patients, triggering clinical evaluation by ward staff in case of deterioration.

10.2 Investigation of the causes of significant differences between hospitals regarding rates of ECG monitoring, and incidence of and survival after in-hospital cardiac arrest

Future studies are needed to further investigate modifiable factors with a potential impact on incidence and survival after IHCA. This research should focus on not only medical aspects, hospital-, and organizational factors, but also the association between the nurse-to patient ratio, the working conditions of hospital staff and the incidence and outcomes after IHCA.

10.3 Rapid Response Systems. Are we using the right outcome measures?

The benefits of an RRS are to a great extent dependent on its proper use, including a timely activation and accurate performance of all interdependent parts of the system. Evaluating the RRS by means of traditional outcome measures may not be the best alternative, given the complexity of the RRS. Instead, the whole process needs to be investigated and evaluated. Traditional experimental studies such as randomised trials are neither appropriate nor ethically legislated, given the complexity of environment it is implemented in and the widespread use, with existing evidence of an improved patient safety. Instead, it has been suggested that future studies should focus on barriers and facilitators that can affect integration within hospitals as well as factors influencing “failure to rescue”.

In the end, what really matters for our patients is not the very prediction of the SAEs, but rather the prevention of them. Prevention will always be more complex to evaluate, nevertheless of vital importance. This notwithstanding, we must strive to adapt future study design and investigations in this direction.

11 SAMMANFATTNING PÅ SVENSKA

Ett hjärtstopp uppstår när hjärtat plötsligt slutar att slå eller slår för snabbt för att kunna pumpa blod, vilket orsakar syrebrist i kroppens viktiga organ, såsom hjärnan. På några sekunder blir en person som lider av hjärtstopp medvetslös och slutar andas normalt. Inom några minuter är cellerna i hjärnan och andra kroppsorgan skadade, och om ett hjärtstopp lämnas obehandlat leder det oundvikligen till döden. Den viktigaste initiala behandlingen är att omedelbart ge en konstgjord cirkulation av syresatt blod med hjälp av hjärt-lungräddning (HLR) inklusive bröstkompressioner, mun-till-mun-ventilation, och defibrillering i de fall detta är indicerat, vilket skall fortgå tills mer avancerad akutbehandling är tillgänglig.

Varje år drabbas cirka 2,400 svenska patienter på sjukhus av hjärtstopp där återupplivningsförsök påbörjas. Trots att dessa händelser inträffar i en miljö med möjlighet till övervakning och tidig upptäckt, samt tillgång till omedelbar och avancerad akutbehandling, överlever endast en patient av tre.

National Early Warning Score (NEWS), och den vidareutvecklade versionen NEWS 2, är standardiserade poängmodeller baserade på så kallade vitalparametrar (till exempel andningsfrekvens, hjärtfrekvens och blodtryck), som är utformad för att underlätta tidig upptäckt av patienter i riskzonen på allmänna avdelningar. NEWS används för att övervaka patienter, men också för att vid försämring kunna tillkalla ett team av specialutbildade läkare och sjuksköterskor från Intensivvårdsavdelningen. Dessa team kallas Rapid Response Teams, eller i Sverige Mobil Intensivvårdsgrupp (MIG), och finns tillgängliga på de flesta sjukhus dygnet runt, veckans alla dagar, året runt, för att säkerställa en snabb klinisk bedömning och adekvat åtgärd för patienter som försämras och därmed löper risk för allvarliga komplikationer såsom oplanerad inläggning på intensivvårdsavdelning, hjärtstopp eller död.

Förebyggande av hjärtstopp på sjukhus har fått mer uppmärksamhet inom hjärtstoppsforskningen under de senaste decennierna. Det övergripande syftet med denna avhandling var att studera prevention av hjärtstopp på sjukhus.

Inom ramen för **studie I** undersökte vi hur överlevnaden efter hjärtstopp på sjukhus påverkades av elektrokardiogram (EKG) övervakning vid tidpunkten för hjärtstoppet, och faktorer av betydelse i den dagliga kliniska verksamheten som påverkade huruvida patienter var EKG-övervakade i anslutning till hjärtstoppet.

Vi fann att EKG-övervakning i samband med hjärtstopp på sjukhus var förknippat med en betydligt högre sannolikhet för överlevnad. Endast varannan patient EKG-övervakades när de drabbades av sitt hjärtstopp, med betydande variationer mellan sjukhus och mellan regioner. Den viktigaste faktorn som påverkade om en patient EKG-övervakades eller inte var vilken sjukhusavdelning som patienten var inlagd på.

I **studie II** studerade vi förmågan hos poängmodellerna NEWS och NEWS 2 att identifiera patienter som löper risk att drabbas av för hjärtstopp, oplanerad inläggning på intensivvårdsavdelningen eller dödsfall inom 24 timmar efter bedömning av MIG-team. Vi fann ingen skillnad mellan NEWS och NEWS 2 i förmågan att identifiera patienter som löper hög risk att drabbas av allvarliga komplikationer. Sammantaget var dock förmågan hos NEWS/NEWS 2 att identifiera patienter som löpte risk för allvarliga komplikationer inte tillräcklig för att fungera som ett strukturerat verktyg för riskbedömning av MIG-patienter. Därför undersökte vi i **studie IV** om tillägg av ålder till poängmodellen NEWS 2 skulle förbättra den prediktiva förmågan hos samma patientgrupp, bedömd av MIG-team. Vi fann att tillägg av ålder till NEWS 2 förbättrade förmågan att identifiera patienter som löper ökad risk att avlida inom 30-dagar. Vi undersökte också långtidsprognosen för dessa patienter, och fann att två av tre patienter var vid liv efter 30-dagar.

I **studie III** studerade vi om det fanns någon skillnad i 30-dagarsöverlevnad mellan patienter som bedömts av MIG-team inom 24 timmar före sitt hjärtstopp, jämfört med de patienter som inte bedömts av MIG-team. Vidare undersökte vi omständigheterna kring MIG-bedömningen och effekten av olika behandlingar och åtgärder, med målsättningen att identifiera faktorer som skulle kunna användas i framtida förebyggande strategier.Vi fann att prognosen för patienter som bedömts av MIG-team inom 24 timmar före hjärtstoppet var sämre jämfört med de patienter som inte bedömts av ett MIG-team. Dessa patienter var sannolikt mycket sjuka, men våra fynd belyser också att syftet med MIG-team framför allt är att förebygga hjärtstopp, och i mindre utsträckning påverkar prognosen för de patienter som trots omfattande insatser av MIG-teamet ändå drabbas av hjärtstopp. Vidare identifierade vi patienter med andningsproblem som en högriskgrupp. Tidig identifiering av dessa patienter på vårdavdelningar, följt av snabba bedömningar och åtgärder, kan ha en potential att förhindra ytterligare försämring och i värsta fall utveckling till ett hjärtstopp.

12 ACKNOWLEDGEMENTS

I wish to express my deep and sincere gratitude to all and everyone who supported and helped me and made this work possible.

My main supervisor **Therese Djärv**. I cannot thank you enough for accepting me as your PhD student and for sharing your immense knowledge and experience in the field of resuscitation science. Your extreme working capacity is truly impressive, and your energy, positivity, enthusiasm, and devotion are inspirational and contagious. Thank you for gently pushing me out of my comfort zone, yet always being there by my side, encouraging and ready to provide guidance and support if needed. Despite your extremely busy schedule, you were always accessible. Thank you, Therese.

Johan Engdahl, my co-supervisor. I am most grateful for you sharing your vast knowledge on resuscitation science and your wisdom. For your never-ending support, calmness, and encouragement, somewhat knowing exactly when I needed an extra pat on the shoulder. Always there for immediate and constructive feed-back on early drafts and stimulating discussions. Your enthusiasm and dedication to science is truly inspirational. Thank you for always keeping your office door open, making me feel welcome at any time.

Thomas Kahan, my co-supervisor. Thank you for sharing your brilliant knowledge on cardiology and medical research, and for your unwavering support and encouragement over many years. My deepest appreciation for your enthusiasm, structure, thoroughness, and your dedicated work with the manuscripts, which you have refined and moved forward by means of constructive comments and linguistic elegance. Thank you for always believing in my capabilities, helping me perform at my very best.

Thank you **Araz Rawshani,** my co-supervisor. You are an outstanding researcher with a remarkable capacity, a sharp intellect, and an excellent knowledge in science and advanced statistics, including Artificial Intelligence. You always manage to see the big picture, yet not oversee important details. Thank you for sharing your knowledge, for relentless support, for encouragement and patience when teaching me statistics. For hours of interesting and inspiring discussions on research and life, and for constantly reminding me of the importance of keeping the balance between work and life.

Johan Herlitz, my mentor, role model, and a true Nestor of resuscitation science. I am infinitely grateful for you opening the doors to your amazing world of research, generously sharing your immense knowledge and wisdom on resuscitation science and life. Thank you for providing immediate, high-quality feed-back whenever needed. We do not only share the passion for resuscitation science, but also for tennis. To me, you are the Roger Federer of resuscitation science- with excellence, devotion, accuracy, and humbleness impersonated.

Thank you, **Jacob Hollenberg** for being an inspiring and great head of the Centre for Resuscitation Sciences, for welcoming me with open arms and for all support. I am so grateful and proud to be part of such an awesome research group. Thank you, **all researchers, and fellow doctoral students of the group**, for sharing your knowledge in interesting and inspirational research meetings, for support and encouragement along the way and for creating a good atmosphere.

Leif Svensson and **Mårten Rosenqvist**, true Nestors of resuscitation science and founders of the Centre for Resuscitation Sciences. **Leif**, thank you for stimulating and excellent cooperation during my time as head of the CPR-organization at Danderyd University Hospital. You have always believed in and supported me, and you also introduced me to my main supervisor. For that I will be forever grateful. **Mårten**, thank you for encouragement and support, and for helping me finding out the provenance of the beautiful photo on the cover of my thesis.

Thank you, **Eva Joelsson-Alm** and **Martin Spångfors.** I have been fortunate to have you as co-authors of studies II-IV, sharing your immense knowledge, experience, and wisdom with me. Over time, you have become sort of "bonus" co-supervisors, always available for questions or a chat, and for that I will always be grateful. I deeply appreciate our cooperation, your support and encouragement along the way, especially when preparing for the dissertation. I look forward to future research cooperation.

Martin Jonsson, thank you for creating eCRFs and for invaluable statistical and analytical support, as well as your contributions as co-author of studies II, III and IV. Extra thanks for spending a sunny Saturday afternoon at Södersjukhuset with me, analyzing data on study III when we were short of time.

Thank you, **Eva Piscator, Gabriel Riva** and **Akil Awad** for your invaluable support, good advice, and encouragement along the way, and in particular when finishing my doctoral studies and preparing for the defence.

I want to thank my co-authors **Linnéa Gustafsson**, **Jan Jakobsson**, **Erik Boberg von Platen** and **Arvid Jadenius**, for your most valuable contributions to studies I and III. Extra thanks to **Erik and Arvid** for excellent assistance with data collection in study III, and to **Erik** for helping me out when my MacBook broke down and my technical support was bicycling in Italy.

Solveig Aune, thank you for good cooperation during my time as head of the CPR organization at Danderyd University Hospital, and for your most valuable support and encouragement during the preparations for my half-time seminar and defence.

Mikael Franko-Andersson and **Jonny Lindqvist**, thank you for most valuable statistical support. Extra thanks to **Mikael** for your analytical support and co-authorship in study IV.

Thank you **Karolinska Institutet, Department of Medicine, Solna**; **Marie Wahren-Herlenius, Michael Fored, Eva Noréns** and **Sahra Bunner** for providing a good research atmosphere, for administrative support and encouragement.

Fredrik Bäcklund and **Eva Willis,** thank you for the excellent organisation and implementation of the Karolinska Institutet Research School in Epidemiology. Thank you, **Matteo Bottai** for the world-class teaching of biostatistics at the Research School, and for sharing your wisdom. You are a rockstar of biostatistics. I´ll take the following quote with me: "Thinking and trying, thinking and trying, that´s what you have to do. The only thing that can limit you is your imagination".

Thank you, **Karin Malmqvist,** head of the Department of Cardiology and Clinical physiology, for being a strong, visionary, dynamic leader, and female role model. For providing space for research and education, and for always paying kind attention to all staff, creating a good atmosphere. Thank you for believing in my capabilities, for encouragement and support over many years, and for taking great interest in my research and the well-being of me and my family.

Thank you, **Lars-Göran Nordin** for being an enthusiastic, inspirational, and wise boss, and for your relentless visionary work in developing and moving our department forward, whilst caring for the well-being of all staff.
Thank you for supporting research, allocating time for finishing my thesis, and for sharing your outstanding knowledge on echocardiography. For encouragement, professional and personal support, and for giving me the trust to act as director of studies for our residents and head of education for our medical students.

Thank you, all amazing **present and former friends and colleagues at the Departments of Cardiology and Clinical physiology at Danderyd University Hospital** for collegiality, friendship, support and for taking interest in my research. In particular, I would like to thank:

Ann Samnegård. You recruited me to the Department of Cardiology many years ago. Throughout the years, you have generously shared your expertise in cardiology, supported and guided me, always caring for both me and my family. For that I will be forever grateful. You are my role model. Furthermore, you are the only female friend of mine who has sailed across the Atlantic- impressive! My dear friend **Jonas Persson**, for sharing many happy memories over the years, for encouragement and support along the way and for excellent coaching when I was preparing for the defence. **Christina Ekenbäck**, dear Dr E. Thank you for sharing many happy and sometimes crazy memories, laughs but also hard work and hard times, for discussions on cardiology and research as well as everyday life. I am so grateful for your support, encouragement, and for our friendship. **Josephine Muhrbeck,** for being a good friend, sharing many fond memories over the years, for teaching me echocardiography, for all support and a brilliant review of my compilation chapter. **Viveka Fryman,** for never-ending enthusiasm, encouragement, and support along the way. **Samantha Rutherford-Lörstad,** thank you for most valuable support when preparing for my dissertation, for encouraging and supporting me.

Thank you, **Hans Persson, Faris Al-Khalili** and **Carl-Olof Ekman** for excellent clinical supervising, guidance, and support during my residencies in Cardiology and Clinical physiology.

Nassrin Wandy Karlsson. I cannot thank you enough for your invaluable support and help in solving numerous administrative and practical problems along the way, always with a friendly smile on your face. Your enthusiasm, energy and creativeness are truly inspiring and contagious. Extra thanks for making it possible to use the beautiful photo on the cover of my thesis. I also want to thank you and **Catharina Falk** for flawless preparations of everything concerning my dissertation procedure. **Catharina**, I am most grateful for your endless support and your amazing capability to solve all kinds of administrative and practical issues. For keeping structure and an impressive overview, yet never missing a detail, whilst caring for us all, always with a positive attitude.

Thank you, **Liselotte Persson** at the Cardiovascular Research Laboratory within the Clinical Research Centre at Danderyd University Hospital for your support and encouragement. I would also like to thank **Eva Andersson,** although no longer with us, for all support and your most valuable contribution to study II.

Thank you **Jasna Giesecke, Anki Lundberg** and **Pernilla Karlsson,** for your invaluable work in the CPR-organization at Danderyd University Hospital, for the good cooperation over the years, and for your support and encouragement during my doctoral studies. **Åsa Lindström-Hammar** and **Lena Martin,** thank you for the good cooperation, for your support, enthusiasm, and encouragement over the years.

I want to express my deepest gratitude to **all colleagues at the Departments of Anaesthesiology and Intensive care in numerous Swedish hospitals** for your invaluable contributions to studies II and study IV. Extra thanks to **Jimmy Bjelkengren** at Norra Älvsborgs Länssjukhus**,** for your most valuable contribution to study III, besides study II and IV.

Thank you, **all dear and amazing friends.** I am deeply grateful and very happy to have all of you in my life. For wonderful times spent together over the years, for sharing many laughs but also tears, for your love, encouragement, and support. Thank you for always being there-in good times and bad. But most of all, for being who you are; you are all shining stars.

Sarah, our fury little darling friend. Thank you for unconditional love, the joy and happiness you have brought into our family. For keeping me company and my feet warm during late night working sessions, and recreational walks in the forest.

My wonderful family-in-law: **Pia Rautiala-Thorén**, the **Rhenman family,** the **Thorén families,** and the **Colliander family**. My dear godmother and aunt, **Margaretha Gustavsson**, and my dear cousin **Martin** and the **Fröjd family.** Thank you all for love and support, and for always caring for our family. For sharing many happy memories over the years, for taking interest in my research and encouraging me.

My dearest sister **Sofia** and your lovely family; **Andreas, Simon, and Livia**. Thank you for endless love and support, for sharing wonderful memories, laughter and sometimes tears throughout the years, and for being my best friend, someone I can always trust. Thank you for sharing your wisdom and for always being there, not only for me but for our whole family. I love you.

My beloved parents **Märtha** and **Bertil.** Thank you for a lifetime of endless love and support, and for bringing me up to who I am. For teaching me the value of hard and dedicated work, that giving up is never an option, for always believing in me, making me feel that (almost) nothing is impossible, and for encouragement. Thank you for your endless care for me and my family. You are kindness, generosity and thoughtfulness impersonated. I love you.

Robert, my best friend, kindred spirit and the love of my love. Thank you for endless love and support, for encouraging me to take on new challenges in life and for being such a thoughtful and generous person, not only to me but all people surrounding you. I am most grateful for your patience, invaluable 24/7 technical support and for helping me out when my MacBook and I did not get along. But most of all, thank you for sharing your life with me, and for being a wonderful husband and father of Julia and Jacob. I love you more than words can say.

Julia and **Jacob**, our wonderful children and greatest gift of life. Thank you for your love, patience, enthusiasm, and encouragement but above all for being who you are. I am so proud of you. You are the meaning and sunshine of my life, my inspiration, and you bring immense happiness and joy into your fathers and my life every single day. I love you infinitely.

13 REFERENCES

1. Soar J. In-hospital cardiac arrest. Curr Opin Crit Care. 2023;29(3):181-5.

2. Gräsner JT, Herlitz J, Tjelmeland IBM, et al. European Resuscitation Council Guidelines 2021: Epidemiology of cardiac arrest in Europe. Resuscitation. 2021;161:61-79.

3. Kause J, Smith G, Prytherch D, et al. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and the United Kingdom--the ACADEMIA study. Resuscitation. 2004;62(3):275-82.

4. Hodgetts TJ, Kenward G, Vlackonikolis, et al. Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. Resuscitation. 2002;54(2):115-23.

5. The Bible.Second Kings(4):32-5.

6. Aitchison R, Aitchison P, Wang E, Kharasch M. A review of cardiopulmonary resuscitation and its history. Dis Mon. 2013;59(5):165-7.

7. Herlitz J, Claesson, A. Hjärt-Lungräddningens Historia. 2016.

8. Safar P. Ventilatory efficacy of mouth-to-mouth artificial respiration; airway obstruction during manual and mouth-to-mouth artificial respiration. J Am Med Assoc. 1958;167(3):335-41.

9. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac massage. Jama. 1960;173:1064-7.

10. Safar P, Brown TC, Holtey WJ, et al. Ventilation and circulation with closed-chest cardiac massage in man. Jama. 1961;176:574-6.

11. Jude JR. Cardiac resuscitation. Am Heart J. 1961;62:286-7.

12. Wittwer MR, Zeitz C, Beltrame JF, et al. Providing a simple and consistent solution for the definition of in- versus out-of-hospital cardiac arrest. Resuscitation. 2020;156:51-2.

13. Nolan JP, Berg RA, Andersen LW, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A Consensus Report From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia). Resuscitation. 2019;144:166-77.

14. Rawshani A, Herlitz J. Yearly Report 2023, the Swedish Registry for Cardiopulmonary Resuscitation. Swedish National Quality Registry for Cardiopulmonary Resuscitation; 2023.

15. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation. 1991;84(2):960-75.

16. Otto Q, Nolan JP, Chamberlain DA, et al. Utstein Style for emergency care - the first 30 years. Resuscitation. 2021;163:16-25.

17. Cummins RO, Chamberlain D, Hazinski MF, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital 'Utstein style'. A statement for healthcare professionals from the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Australian Resuscitation Council, and the Resuscitation Councils of Southern Africa. Resuscitation. 1997;34(2):151-83.

18. Aune S, Herlitz J, Bång A. Characteristics of patients who die in hospital with no attempt at resuscitation. Resuscitation. 2005;65(3):291-9.

19. Bertilsson E, Semark B, Schildmeijer K, et al. Usage of do-not-attempt-to-resuscitate orders in a Swedish community hospital - patient involvement, documentation and compliance. BMC Med Ethics. 2020;21(1):67.

20. Penketh J, Nolan JP. In-hospital cardiac arrest: the state of the art. Crit Care. 2022;26(1):376.

21. Nolan JP, Soar J, Smith GB, et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. Resuscitation. 2014;85(8):987-92.

22. Andersen LW, Holmberg MJ, Lofgren B, et al. Adult in-hospital cardiac arrest in Denmark. Resuscitation. 2019;140:31-6.

23. Hessulf F, Karlsson T, Lundgren P, et al. Factors of importance to 30-day survival after in-hospital cardiac arrest in Sweden - A population-based register study of more than 18,000 cases. International journal of cardiology. 2018;255:237-42.

24. Radeschi G, Mina A, Berta G, et al. Incidence and outcome of in-hospital cardiac arrest in Italy: a multicentre observational study in the Piedmont Region. Resuscitation. 2017;119:48-55.

25. Schluep M, Hoeks SE, Blans M, et al. Long-term survival and health-related quality of life after in-hospital cardiac arrest. Resuscitation. 2021;167:297-306.

26. Adamski J, Nowakowski P, Goryński P, et al. Incidence of in-hospital cardiac arrest in Poland. Anaesthesiol Intensive Ther. 2016;48(5):288-93.

27. Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. Circ Cardiovasc Qual Outcomes. 2019;12(7):e005580.

28. Ohbe H, Tagami T, Uda K, Matsui H, et al. Incidence and outcomes of in-hospital cardiac arrest in Japan 2011-2017: a nationwide inpatient database study. J Intensive Care. 2022;10(1):10.

29. Andersen LW, Holmberg MJ, Berg KM, et al. In-Hospital Cardiac Arrest: A Review. Jama. 2019;321(12):1200-10.

30. Bergum D, Haugen BO, Nordseth T, et al. Recognizing the causes of in-hospital cardiac arrest--A survival benefit. Resuscitation. 2015;97:91-6.

31. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124(19):2145-54.

32. Sandroni C, Ferro G, Santangelo S, et al. In-hospital cardiac arrest: survival depends mainly on the effectiveness of the emergency response. Resuscitation. 2004;62(3):291-7.

33. Skrifvars MB, Hilden HM, Finne P, et al. Prevalence of 'do not attempt resuscitation' orders and living wills among patients suffering cardiac arrest in four secondary hospitals. Resuscitation. 2003;58(1):65-71.

34. Fritz ZB, Heywood RM, Moffat SC, et al. Characteristics and outcome of patients with DNACPR orders in an acute hospital; an observational study. Resuscitation. 2014;85(1):104-8.

35. van Delden JJ, Löfmark R, Deliens L, et al. Do-not-resuscitate decisions in six European countries. Critical care medicine. 2006;34(6):1686-90.

36. Mentzelopoulos SD, Bossaert L, Raffay V, et al. A survey of key opinion leaders on ethical resuscitation practices in 31 European Countries. Resuscitation. 2016;100:11-7.

37. Chen LM, Nallamothu BK, Spertus JA, et al. Association between a hospital's rate of cardiac arrest incidence and cardiac arrest survival. JAMA internal medicine. 2013;173(13):1186-95.

38. Smith GB. In-hospital cardiac arrest: is it time for an in-hospital 'chain of prevention'? Resuscitation. 2010;81(9):1209-11.

39. Cummins RO, Ornato JP, Thies WH, et al. Improving survival from sudden cardiac arrest: the "chain of survival" concept. A statement for health professionals from the Advanced Cardiac Life Support Subcommittee and the Emergency Cardiac Care Committee, American Heart Association. Circulation. 1991;83(5):1832-47.

40. Tirkkonen J, Hellevuo H, Olkkola KT, et al. Aetiology of in-hospital cardiac arrest on general wards. Resuscitation. 2016;107:19-24.

41. Allencherril J, Lee PYK, Khan K, et al. Etiologies of In-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2022;175:88-95.

42. Soar J, Nolan JP, Bottiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015;95:100-47.

43. Perman SM, Stanton E, Soar J, et al. Location of In-Hospital Cardiac Arrest in the United States-Variability in Event Rate and Outcomes. Journal of the American Heart Association. 2016;5(10).

44. Wallmuller C, Meron G, Kurkciyan I, et al. Causes of in-hospital cardiac arrest and influence on outcome. Resuscitation. 2012;83(10):1206-11.

45. Saarinen S, Nurmi J, Toivio T, et al. Does appropriate treatment of the primary underlying cause of PEA during resuscitation improve patients' survival? Resuscitation. 2012;83(7):819-22.

46. Albert M, Herlitz J, Rawshani A, et al. Aetiology and outcome in hospitalized cardiac arrest patients. Eur Heart J Open. 2023;3(4):oead066.

47. Skogvoll E, Isern E, Sangolt GK, et al. In-hospital cardiopulmonary resuscitation. 5 years' incidence and survival according to the Utstein template. Acta anaesthesiologica Scandinavica. 1999;43(2):177-84.

48. Kürkciyan I, Meron G, Behringer W, et al. Accuracy and impact of presumed cause in patients with cardiac arrest. Circulation. 1998;98(8):766-71.

49. Turnbull A, Osborn M, Nicholas N. Hospital autopsy: Endangered or extinct? J Clin Pathol. 2015;68(8):601-4.

50. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67-e492.

51. Adielsson A, Djärv T, Rawshani A, et al. Changes over time in 30-day survival and the incidence of shockable rhythms after in-hospital cardiac arrest - A population-based registry study of nearly 24,000 cases. Resuscitation. 2020;157:135-40.

52. Wiberg S, Holmberg MJ, Donnino MW, et al. Age-dependent trends in survival after adult in-hospital cardiac arrest. Resuscitation. 2020;151:189-96.

53. Al-Dury N, Rawshani A, Israelsson J, et al. 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;35(12):1839-44.

54. Jerkeman M, Sultanian P, Lundgren P, et al. Trends in survival after cardiac arrest: a Swedish nationwide study over 30 years. Eur Heart J. 2022.

55. Bhalala US, Bonafide CP, Coletti CM, et al. Antecedent bradycardia and in-hospital cardiopulmonary arrest mortality in telemetry-monitored patients outside the ICU. Resuscitation. 2012;83(9):1106-10.

56. Perkins GD, Graesner JT, Semeraro F, et al. European Resuscitation Council Guidelines 2021: Executive summary. Resuscitation. 2021;161:1-60.

57. Merchant RM, Berg RA, Yang L, Becker LB, et al. Hospital variation in survival after in-hospital cardiac arrest. Journal of the American Heart Association. 2014;3(1):e000400.

58. Hessulf F, Herlitz J, Lundgren P, et al. Temporal variation in survival following in-hospital cardiac arrest in Sweden. International journal of cardiology. 2023.

59. Rasmussen TP, Riley DJ, Sarazin MV, et al. Variation Across Hospitals in In-Hospital Cardiac Arrest Incidence Among Medicare Beneficiaries. JAMA Netw Open. 2022;5(2):e2148485.

60. McHugh MD, Rochman MF, Sloane DM, et al. Better Nurse Staffing and Nurse Work Environments Associated With Increased Survival of In-Hospital Cardiac Arrest Patients. Medical care. 2016;54(1):74-80.

61. Girotra S, Nallamothu BK, Spertus JA, et al. Trends in survival after in-hospital cardiac arrest. The New England journal of medicine. 2012;367(20):1912-20.

62. Holmberg MJ, Granfeldt A, Girotra S, et al. Trends in survival and introduction of the 2010 and 2015 guidelines for adult in-hospital cardiac arrest. Resuscitation. 2020;157:112-20.

63. Källestedt ML, Berglund A, Herlitz J, et al. The impact of CPR and AED training on healthcare professionals' self-perceived attitudes to performing resuscitation. Scandinavian journal of trauma, resuscitation and emergency medicine. 2012;20:26.

64. Fernando SM, Tran A, Cheng W, et al. Pre-arrest and intra-arrest prognostic factors associated with survival after in-hospital cardiac arrest: systematic review and meta-analysis. BMJ (Clinical research ed). 2019;367:l6373.

65. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. Lancet. 2013;381(9868):752-62.

66. Mowbray FI, Manlongat D, Correia RH, et al. Prognostic association of frailty with post-arrest outcomes following cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2021;167:242-50.

67. Smith RJ, Reid DA, Santamaria JD. Frailty is associated with reduced prospect of discharge home after in-hospital cardiac arrest. Intern Med J. 2019;49(8):978-85.

68. Wharton C, King E, MacDuff A. Frailty is associated with adverse outcome from in-hospital cardiopulmonary resuscitation. Resuscitation. 2019;143:208-11.

69. Jonsson H, Piscator E, Israelsson J, et al. Is frailty associated with long-term survival, neurological function and patient-reported outcomes after in-hospital cardiac arrest? - A Swedish cohort study. Resuscitation. 2022;179:233-42.

70. Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. Jama. 2008;299(7):785-92.

71. Ofoma UR, Basnet S, Berger A, et al. Trends in Survival After In-Hospital Cardiac Arrest During Nights and Weekends. Journal of the American College of Cardiology. 2018;71(4):402-11.

72. Chan PS, Spertus JA, Krumholz HM, et al. A validated prediction tool for initial survivors of in-hospital cardiac arrest. Arch Intern Med. 2012;172(12):947-53.

73. Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. Jama. 2006;295(1):50-7.

74. Adielsson A, Karlsson T, Aune S, et al. A 20-year perspective of in hospital cardiac arrest: Experiences from a university hospital with focus on wards with and without monitoring facilities. International journal of cardiology. 2016;216:194-9.

75. Herlitz J, Aune S, Bång A, Fredriksson M, et al. Very high survival among patients defibrillated at an early stage after in-hospital ventricular fibrillation on wards with and without monitoring facilities. Resuscitation. 2005;66(2):159-66.

76. Larkin GL, Copes WS, Nathanson BH, et al. Pre-resuscitation factors associated with mortality in 49,130 cases of in-hospital cardiac arrest: a report from the National Registry for Cardiopulmonary Resuscitation. Resuscitation. 2010;81(3):302-11.

77. Brady WJ, Gurka KK, Mehring B, et al. In-hospital cardiac arrest: impact of monitoring and witnessed event on patient survival and neurologic status at hospital discharge. Resuscitation. 2011;82(7):845-52.

78. Nolan J. European Resuscitation Council guidelines for resuscitation 2005. Section 1. Introduction. Resuscitation. 2005;67 Suppl 1:S3-6.

79. Nolan J, Soar J, Eikeland H. The chain of survival. Resuscitation. 2006;71(3):270-1.

80. Deakin CD. The chain of survival: Not all links are equal. Resuscitation. 2018;126:80-2.

81. Hessulf F, Herlitz J, Rawshani A, et al. Adherence to guidelines is associated with improved survival following in-hospital cardiac arrest. Resuscitation. 2020;155:13-21.

82. Olasveengen TM, Semeraro F, Ristagno G, et al. European Resuscitation Council Guidelines 2021: Basic Life Support. Resuscitation. 2021;161:98-114.

83. Lyons PG, Edelson DP, Churpek MM. Rapid response systems. Resuscitation. 2018;128:191-7.

84. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation. 2021;161:115-51.

85. Fredriksson M, Aune S, Bång A, et al. Cardiac arrest outside and inside hospital in a community: mechanisms behind the differences in outcome and outcome in relation to time of arrest. Am Heart J. 2010;159(5):749-56.

86. Chan PS, Krumholz HM, Nichol G, et al. Delayed time to defibrillation after in-hospital cardiac arrest. The New England journal of medicine. 2008;358(1):9-17.

87. Lott C, Truhlář A, Alfonzo A, et al. European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances. Resuscitation. 2021;161:152-219.

88. Andersen LW, Kim WY, Chase M, et al. The prevalence and significance of abnormal vital signs prior to in-hospital cardiac arrest. Resuscitation. 2016;98:112-7.

89. Khanna AK, Hoppe P, Saugel B. Automated continuous noninvasive ward monitoring: future directions and challenges. Crit Care. 2019;23(1):194.

90. Monfredi OJ, Moore CC, Sullivan BA, et al. Continuous ECG monitoring should be the heart of bedside AI-based predictive analytics monitoring for early detection of clinical deterioration. Journal of electrocardiology. 2023;76:35-8.

91. Buchman TG, Stein PK, Goldstein B. Heart rate variability in critical illness and critical care. Curr Opin Crit Care. 2002;8(4):311-5.

92. Carrara M, Ferrario M, Bollen Pinto B, et al. The autonomic nervous system in septic shock and its role as a future therapeutic target: a narrative review. Ann Intensive Care. 2021;11(1):80.

93. Cleverley K, Mousavi N, Stronger L, et al. The impact of telemetry on survival of in-hospital cardiac arrests in non-critical care patients. Resuscitation. 2013;84(7):878-82.

94. Leuvan CH, Mitchell I. Missed opportunities? An observational study of vital sign measurements. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2008;10(2):111-15.

95. McGrath SP, Perreard IM, Garland MD, et al. Improving Patient Safety and Clinician Workflow in the General Care Setting With Enhanced Surveillance Monitoring. IEEE J Biomed Health Inform. 2019;23(2):857-66.

96. Eddahchouri Y, Peelen RV, Koeneman M, et al. The Effect of Continuous Versus Periodic Vital Sign Monitoring on Disease Severity of Patients with an Unplanned ICU Transfer. J Med Syst. 2023;47(1):43.

97. Sessler DI, Saugel B. Beyond 'failure to rescue': the time has come for continuous ward monitoring. Br J Anaesth. 2019;122(3):304-6.

98. McGrath SP, Perreard IM, MacKenzie T, et al. Patterns in continuous pulse oximetry data prior to pulseless electrical activity arrest in the general care setting. Journal of clinical monitoring and computing. 2021;35(3):537-45.

99. Leenen JPL, Leerentveld C, van Dijk JD, et al. Current Evidence for Continuous Vital Signs Monitoring by Wearable Wireless Devices in Hospitalized Adults: Systematic Review. Journal of medical Internet research. 2020;22(6):e18636.

100. Peelen RV, Eddahchouri Y, Koeneman M, et al. Comparing Continuous with Periodic Vital Sign Scoring for Clinical Deterioration Using a Patient Data Model. J Med Syst. 2023;47(1):60.

101. Subbe CP, Bannard-Smith J, Bunch J, et al. Quality metrics for the evaluation of Rapid Response Systems: Proceedings from the third international consensus conference on Rapid Response Systems. Resuscitation. 2019;141:1-12.

102. Winters BD, Weaver SJ, Pfoh ER, et al. Rapid-response systems as a patient safety strategy: a systematic review. Ann Intern Med. 2013;158(5 Pt 2):417-25.

103. Olsen SL, Søreide E, Hillman K, et al. Succeeding with rapid response systems - a never-ending process: A systematic review of how health-care professionals perceive facilitators and barriers within the limbs of the RRS. Resuscitation. 2019;144:75-90.

104. DeVita MA HK, Bellomo R, editors. Textbook of rapid response systems: concept and implementation. 2017.

105. Barwise A, Thongprayoon C, Gajic O, et al. Delayed Rapid Response Team Activation Is Associated With Increased Hospital Mortality, Morbidity, and Length of Stay in a Tertiary Care Institution. Critical care medicine. 2016;44(1):54-63.

106. Devita MA, Bellomo R, Hillman K, et al. Findings of the first consensus conference on medical emergency teams. Critical care medicine. 2006;34(9):2463-78.

107. Lee A, Bishop G, Hillman KM, et al. The Medical Emergency Team. Anaesth Intensive Care. 1995;23(2):183-6.

108. Difonzo M. Rapid Response Systems: how to interpret levels of evidence. Clinical Management Issues. 2017;11(2):71-88.

109. Difonzo M. Performance of the Afferent Limb of Rapid Response Systems in Managing Deteriorating Patients: A Systematic Review. Crit Care Res Pract. 2019;2019:6902420.

110. Bellomo R, Goldsmith D, Uchino S, et al. A prospective before-and-after trial of a medical emergency team. Med J Aust. 2003;179(6):283-7.

111. Buist M, Harrison J, Abaloz E, et al. Six year audit of cardiac arrests and medical emergency team calls in an Australian outer metropolitan teaching hospital. BMJ (Clinical research ed). 2007;335(7631):1210-2.

112. Konrad D, Jaderling G, Bell M, et al. Reducing in-hospital cardiac arrests and hospital mortality by introducing a medical emergency team. Intensive care medicine. 2010;36(1):100-6.

113. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. Lancet. 2005;365(9477):2091-7.

114. Winters BD, Pham JC, Hunt EA, et al. Rapid response systems: a systematic review. Critical care medicine. 2007;35(5):1238-43.

115. Chan PS, Jain R, Nallmothu BK, et al. Rapid Response Teams: A Systematic Review and Meta-analysis. Arch Intern Med. 2010;170(1):18-26.

116. Maharaj R, Raffaele I, Wendon J. Rapid response systems: a systematic review and meta-analysis. Crit Care. 2015;19(1):254.

117. McGaughey J, Fergusson DA, Van Bogaert P, et al. Early warning systems and rapid response systems for the prevention of patient deterioration on acute adult hospital wards. Cochrane Database Syst Rev. 2021;11(11):Cd005529.

118. Gao H, McDonnell A, Harrison DA, et al. Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. Intensive care medicine. 2007;33(4):667-79.

119. Hall KK, Lim A, Gale B. The Use of Rapid Response Teams to Reduce Failure to Rescue Events: A Systematic Review. J Patient Saf. 2020;16(3S Suppl 1):3-7.

120. Jansen JO, Cuthbertson BH. Detecting critical illness outside the ICU: the role of track and trigger systems. Curr Opin Crit Care. 2010;16(3):184-90.

121. Smith GB, Prytherch DR, Schmidt PE, et al. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation. 2008;79(1):11-21.

122. Smith GB, Prytherch DR, Schmidt PE, et al. Review and performance evaluation of aggregate weighted 'track and trigger' systems. Resuscitation. 2008;77(2):170-9.

123. Smith GB, Prytherch DR, Jarvis S, et al. A Comparison of the Ability of the Physiologic Components of Medical Emergency Team Criteria and the U.K. National Early Warning Score to Discriminate Patients at Risk of a Range of Adverse Clinical Outcomes. Critical care medicine. 2016;44(12):2171-81.

124. McNeill G, Bryden D. Do either early warning systems or emergency response teams improve hospital patient survival? A systematic review. Resuscitation. 2013;84(12):1652-67.

125. Gerry S, Bonnici T, Birks J, et al. Early warning scores for detecting deterioration in adult hospital patients: systematic review and critical appraisal of methodology. BMJ (Clinical research ed). 2020;369:m1501.

126. (London) RCoP. National early warning score (NEWS). 2012 2019-06-10.

127. Smith GB, Prytherch DR, Meredith P, et al. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest,

unanticipated intensive care unit admission, and death. Resuscitation. 2013;84(4):465-70.

128. Welch J, Dean J, Hartin J. Using NEWS2: an essential component of reliable clinical assessment. Clinical medicine (London, England). 2022;22(6):509-13.

129. Physicians TRCo. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. . 2017:pp. 1-77.

130. Downey CL, Tahir W, Randell R, et al. Strengths and limitations of early warning scores: A systematic review and narrative synthesis. International journal of nursing studies. 2017;76:106-19.

131. Jo S, Yoon J, Lee JB, et al. Predictive value of the National Early Warning Score-Lactate for mortality and the need for critical care among general emergency department patients. J Crit Care. 2016;36:60-8.

132. Rasmussen LJH, Ladelund S, Haupt TH, et al. Combining National Early Warning Score With Soluble Urokinase Plasminogen Activator Receptor (suPAR) Improves Risk Prediction in Acute Medical Patients: A Registry-Based Cohort Study. Critical care medicine. 2018;46(12):1961-8.

133. Nissen SK, Candel BGJ, Nickel CH, et al. The Impact of Age on Predictive Performance of National Early Warning Score at Arrival to Emergency Departments: Development and External Validation. Annals of emergency medicine. 2021.

134. Shamout F, Zhu T, Clifton L, et al. Early warning score adjusted for age to predict the composite outcome of mortality, cardiac arrest or unplanned intensive care unit admission using observational vital-sign data: a multicentre development and validation. BMJ open. 2019;9(11):e033301.

135. Zonneveld L, van Wijk RJ, Olgers TJ, et al. Prognostic value of serial score measurements of the national early warning score, the quick sequential organ failure assessment and the systemic inflammatory response syndrome to predict clinical outcome in early sepsis. European journal of emergency medicine. 2022;29(5):348-56.

136. Fieselmann JF, Hendryx MS, Helms CM, et al. Respiratory rate predicts cardiopulmonary arrest for internal medicine inpatients. J Gen Intern Med. 1993;8(7):354-60.

137. Prytherch DR, Smith GB, Schmidt P, et al. Calculating early warning scores--a classroom comparison of pen and paper and hand-held computer methods. Resuscitation. 2006;70(2):173-8.

138. Smith GB, Prytherch DR, Schmidt P, et al. Hospital-wide physiological surveillance-a new approach to the early identification and management of the sick patient. Resuscitation. 2006;71(1):19-28.

139. Cretikos M, Chen J, Hillman K, Bellomo R, et al. The objective medical emergency team activation criteria: a case-control study. Resuscitation. 2007;73(1):62-72.

140. Alam N, Vegting IL, Houben E, et al. Exploring the performance of the National Early Warning Score (NEWS) in a European emergency department. Resuscitation. 2015;90:111-5.

141. Loughlin PC, Sebat F, Kellett JG. Respiratory Rate: The Forgotten Vital Sign-Make It Count! Jt Comm J Qual Patient Saf. 2018;44(8):494-9.

142. Goldhill DR, McNarry AF, Mandersloot G. A physiologically-based early warning score for ward patients: the association between score and outcome. Anaesthesia. 2005;60(6):547-53.

143. Akel MA, Carey KA, Winslow CJ, et al. Less is more: Detecting clinical deterioration in the hospital with machine learning using only age, heart rate, and respiratory rate. Resuscitation. 2021;168:6-10.

144. Cretikos MA, Bellomo R, Hillman K, et al. Respiratory rate: the neglected vital sign. Med J Aust. 2008;188(11):657-9.

145. McBride J, Knight D, Piper J, et al. Long-term effect of introducing an early warning score on respiratory rate charting on general wards. Resuscitation. 2005;65(1):41-4.

146. Adielsson A, Danielsson C, Forkman P, et al. Outcome prediction for patients assessed by the medical emergency team: a retrospective cohort study. BMC Emerg Med. 2022;22(1):200.

147. Jones DA, DeVita MA, Bellomo R. Rapid-response teams. The New England journal of medicine. 2011;365(2):139-46.

148. Peberdy MA, Cretikos M, Abella BS, et al. Recommended guidelines for monitoring, reporting, and conducting research on medical emergency team, outreach, and rapid response systems: an Utstein-style scientific statement: a scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiopulmonary, Perioperative, and Critical Care; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation. 2007;116(21):2481-500.

149. Sulistio M, Franco M, Vo A, et al. Hospital rapid response team and patients with life-limiting illness: a multicentre retrospective cohort study. Palliat Med. 2015;29(4):302-9.

150. Silva R, Saraiva M, Cardoso T, et al. Medical Emergency Team: How do we play when we stay? Characterization of MET actions at the scene. Scandinavian journal of trauma, resuscitation and emergency medicine. 2016;24:33.

151. Buist MD, Moore GE, Bernard SA, et al. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. BMJ (Clinical research ed). 2002;324(7334):387-90.

152. Dukes K, Bunch JL, Chan PS, et al. Assessment of Rapid Response Teams at Top-Performing Hospitals for In-Hospital Cardiac Arrest. JAMA internal medicine. 2019;179(10):1398-405.

153. Tirkkonen J, Skrifvars MB, Tamminen T, et al. Afferent limb failure revisited - A retrospective, international, multicentre, cohort study of delayed rapid response team calls. Resuscitation. 2020;156:6-14.

154. Tirkkonen J, Ylä-Mattila J, Olkkola KT, et al. Factors associated with delayed activation of medical emergency team and excess mortality: an Utstein-style analysis. Resuscitation. 2013;84(2):173-8.

155. Boniatti MM, Azzolini N, da Fonseca DL, Ribeiro BS, et al. Prognostic value of the calling criteria in patients receiving a medical emergency team review. Resuscitation. 2010;81(6):667-70.

156. Reardon PM, Fernando SM, Murphy K, et al. Factors associated with delayed rapid response team activation. J Crit Care. 2018;46:73-8.

157. Calzavacca P, Licari E, Tee A, et al. The impact of Rapid Response System on delayed emergency team activation patient characteristics and outcomes--a follow-up study. Resuscitation. 2010;81(1):31-5.

158. Calzavacca P, Licari E, Tee A, et al. A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. Intensive care medicine. 2008;34(11):2112-6.

159. Boniatti MM, Azzolini N, Viana MV, et al. Delayed medical emergency team calls and associated outcomes. Critical care medicine. 2014;42(1):26-30.

160. Tirkkonen J, Huhtala H, Hoppu S. In-hospital cardiac arrest after a rapid response team review: A matched case-control study. Resuscitation. 2018;126:98-103.

161. Subramaniam A, Botha J, Tiruvoipati R. The limitations in implementing and operating a rapid response system. Intern Med J. 2016;46(10):1139-45.

162. Cretikos MA, Chen J, Hillman KM, et al. The effectiveness of implementation of the medical emergency team (MET) system and factors associated with use during the MERIT study. Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 2007;9(2):205-12.

163. Chan ML, Spertus JA, Tang F, et al. Missed opportunities in use of medical emergency teams prior to in-hospital cardiac arrest. Am Heart J. 2016;177:87-95.

164. Sandroni C, Caricato A. Are rapid response systems effective in reducing hospital mortality? Critical care medicine. 2013;41(2):679-80.

165. Sandroni C, Cavallaro F. Failure of the afferent limb: a persistent problem in rapid response systems. Resuscitation. 2011;82(7):797-8.

166. Choi RY, Coyner AS, Kalpathy-Cramer J, et al. Introduction to Machine Learning, Neural Networks, and Deep Learning. Transl Vis Sci Technol. 2020;9(2):14.

167. Friedman JH. Stochastic gradient boosting. Computational Statistics & Data Analysis. 2002;38(4):367.

168. Rigatti SJ. Random Forest. J Insur Med. 2017;47(1):31-9.

169. Grant K, McParland A, Mehta S, et al. Artificial Intelligence in Emergency Medicine: Surmountable Barriers With Revolutionary Potential. Annals of emergency medicine. 2020;75(6):721-6.

170. Green M, Lander H, Snyder A, et al. Comparison of the Between the Flags calling criteria to the MEWS, NEWS and the electronic Cardiac Arrest Risk Triage (eCART) score for the identification of deteriorating ward patients. Resuscitation. 2018;123:86-91.

171. Romero-Brufau S, Whitford D, Johnson MG, et al. Using machine learning to improve the accuracy of patient deterioration predictions: Mayo Clinic Early Warning Score (MC-EWS). J Am Med Inform Assoc. 2021;28(6):1207-15.

172. Cho KJ, Kwon O, Kwon JM, et al. Detecting Patient Deterioration Using Artificial Intelligence in a Rapid Response System. Critical care medicine. 2020;48(4):e285-e9.

173. Challen R, Denny J, Pitt M, et al. Artificial intelligence, bias and clinical safety. BMJ quality & safety. 2019;28(3):231-7.

174. Goldstein BA, Navar AM, Carter RE. Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. Eur Heart J. 2017;38(23):1805-14.

175. Vardy ER, Lasserson D, Barker RO, et al. NEWS2 and the older person. Clinical medicine (London, England). 2022;22(6):522-4.

176. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation; and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015;132(13):1286-300.

177. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

178. Phelps R, Dumas F, Maynard C, et al. Cerebral Performance Category and long-term prognosis following out-of-hospital cardiac arrest. Critical care medicine. 2013;41(5):1252-7.

179. Djärv T, Bremer A, Herlitz J, et al. Health-related quality of life after surviving an out-of-hospital compared to an in-hospital cardiac arrest: A Swedish population-based registry study. Resuscitation. 2020;151:77-84.

180. Herlitz J. Post Retirement Professor, MD, former head of the SRCR. Personal communication. 2023.

181. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD Statement. The British journal of surgery. 2015;102(3):148-58.

182. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619-36.

183. Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive care medicine. 2005;31(10):1336-44.

184. Smith GB, Prytherch DR, Schmidt PE, et al. Should age be included as a component of track and trigger systems used to identify sick adult patients? Resuscitation. 2008;78(2):109-15.

185. Computing TRFfS, Mathematics colfSa. The R Project for Statistical Computing 2019 [Available from: https://www.r-project.org/.

186. Hanley J. MB. A method of comparing areas under reciever operating characteristic curves derived from the same cases. Radiology. 1983;148:839-43.

187. Fernando SM, Fox-Robichaud AE, Rochwerg B, et al. Prognostic accuracy of the Hamilton Early Warning Score (HEWS) and the National Early Warning Score 2 (NEWS2) among hospitalized patients assessed by a rapid response team. Crit Care. 2019;23(1):60.

188. Filleron T. Comparing sensitivity and specificity of medical imaging tests when verification bias is present: The concept of relative diagnostic accuracy. Eur J Radiol. 2018;98:32-5.

189. Tirkkonen J, Kontula T, Hoppu S. Rapid response team patients triaged to remain on ward despite deranged vital signs: missed opportunities? Acta anaesthesiologica Scandinavica. 2017;61(10):1278-85.

190. Thorén A, Rawshani A, Herlitz J, et al. ECG-monitoring of in-hospital cardiac arrest and factors associated with survival. Resuscitation. 2020;150:130-8.

191. Thorén A, Joelsson-Alm E, Spångfors M, et al. The predictive power of the National Early Warning Score (NEWS) 2, as compared to NEWS, among patients

assessed by a Rapid response team: A prospective multi-centre trial. Resusc Plus. 2022;9:100191.

192. Thorén A, Jonsson M, Spångfors M, et al. Rapid response team activation prior to in-hospital cardiac arrest: Areas for improvements based on a national cohort study. Resuscitation. 2023:109978.

193. Geddes LA, Roeder RA, Rundell AE, et al. The natural biochemical changes during ventricular fibrillation with cardiopulmonary resuscitation and the onset of postdefibrillation pulseless electrical activity. The American journal of emergency medicine. 2006;24(5):577-81.

194. Geddes LA, Roeder RA, Kemeny A, et al. The duration of ventricular fibrillation required to produce pulseless electrical activity. The American journal of emergency medicine. 2005;23(2):138-41.

195. Schluep M, Gravesteijn BY, Stolker RJ, et al. One-year survival after in-hospital cardiac arrest: A systematic review and meta-analysis. Resuscitation. 2018;132:90-100.

196. Herlitz J, Bang A, Alsen B, et al. Characteristics and outcome among patients suffering from in hospital cardiac arrest in relation to the interval between collapse and start of CPR. Resuscitation. 2002;53(1):21-7.

197. Stigbahr C AS. Validation of the Swedish Registry of Cardiopulmonary Resuscitation, in-hospital cardiac arrests. 2019.

198. Buist M, Mahoney A. In search of the "Holy Grail": will we ever prove the efficacy of Rapid Response Systems (RRS)? Resuscitation. 2014;85(9):1129-30.

199. Petersen JA, Mackel R, Antonsen K, et al. Serious adverse events in a hospital using early warning score - what went wrong? Resuscitation. 2014;85(12):1699-703.

200. Sundararajan K, Flabouris A, Thompson C. Diurnal variation in the performance of rapid response systems: the role of critical care services-a review article. J Intensive Care. 2016;4:15.

201. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. Journal of clinical epidemiology. 2014;67(3):267-77.

202. Holden JD. Hawthorne effects and research into professional practice. J Eval Clin Pract. 2001;7(1):65-70.

203. Flabouris A, Chen J, Hillman K, et al. Timing and interventions of emergency teams during the MERIT study. Resuscitation. 2010;81(1):25-30.

204. Spangfors M, Arvidsson L, Karlsson V, et al. The National Early Warning Score: Translation, testing and prediction in a Swedish setting. Intensive Crit Care Nurs. 2016;37:62-7.

205. Friman O, Bell M, Djarv T, et al. National Early Warning Score vs Rapid Response Team criteria-Prevalence, misclassification, and outcome. Acta anaesthesiologica Scandinavica. 2019;63(2):215-21.

206. Redfern OC, Pimentel MAF, Prytherch D, et al. Predicting in-hospital mortality and unanticipated admissions to the intensive care unit using routinely collected blood tests and vital signs: Development and validation of a multivariable model. Resuscitation. 2018;133:75-81.

207. Churpek MM, Yuen TC, Winslow C, et al. Multicenter Comparison of Machine Learning Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards. Critical care medicine. 2016;44(2):368-74.

208. Harrison GA, Jacques TC, Kilborn G, et al. The prevalence of recordings of the signs of critical conditions and emergency responses in hospital wards--the SOCCER study. Resuscitation. 2005;65(2):149-57.

209. Goldhill DR, McNarry AF. Physiological abnormalities in early warning scores are related to mortality in adult inpatients. Br J Anaesth. 2004;92(6):882-4.

210. Hodgetts TJ, Kenward G, Vlachonikolis IG, et al. The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. Resuscitation. 2002;54(2):125-31.

211. Attin M, Cardin S, Dee V, et al. An educational project to improve knowledge related to pulse oximetry. Am J Crit Care. 2002;11(6):529-34.

212. Jones D, Bellomo R, Bates S, et al. Patient monitoring and the timing of cardiac arrests and medical emergency team calls in a teaching hospital. Intensive care medicine. 2006;32(9):1352-6.

213. Wood KA, Ranji SR, Ide B, et al. Rapid response systems in adult academic medical centers. Jt Comm J Qual Patient Saf. 2009;35(9):475-82, 37.

214. Bedoya AD, Clement ME, Phelan M, et al. Minimal Impact of Implemented Early Warning Score and Best Practice Alert for Patient Deterioration. Critical care medicine. 2019;47(1):49-55.

215. Shearer B, Marshall S, Buist MD, et al. What stops hospital clinical staff from following protocols? An analysis of the incidence and factors behind the failure of bedside clinical staff to activate the rapid response system in a multi-campus Australian metropolitan healthcare service. BMJ quality & safety. 2012;21(7):569-75.

216. Petersen JA, Rasmussen LS, Rydahl-Hansen S. Barriers and facilitating factors related to use of early warning score among acute care nurses: a qualitative study. BMC Emerg Med. 2017;17(1):36.

217. Reardon PM, Seely AJE, Fernando SM, et al. Can Early Warning Systems Enhance Detection of High Risk Patients by Rapid Response Teams? J Intensive Care Med. 2021:885066620978140.

218. O'Neill SM, Clyne B, Bell M, et al. Why do healthcare professionals fail to escalate as per the early warning system (EWS) protocol? A qualitative evidence synthesis of the barriers and facilitators of escalation. BMC Emerg Med. 2021;21(1):15.

219. Schmid-Mazzoccoli A, Hoffman LA, Wolf GA, et al. The use of medical emergency teams in medical and surgical patients: impact of patient, nurse and organisational characteristics. Qual Saf Health Care. 2008;17(5):377-81.