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DO-NOT-ATTEMPT-CARDIOPULMONARY-RESUSCITATION DECISIONS IN THE HOSPITAL SETTING

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Do-Not-Attempt-Cardiopulmonary-Resuscitation decisions in the hospital setting
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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“Patienten önskar ej intensivvård eller några plågsamma åtgärder. Vid akut försämring vill han att naturen ska ha sin egen gång”
-exempel ur fritextanalys återspeglande en patients inställning till begränsning av livsuppehållande behandling

ABSTRACT

Background: A Do-Not-Attempt-Cardiopulmonary-Resuscitation (DNACPR) order can be placed when CPR is not in accordance with the patient's will, when CPR is considered not to benefit the patient, or when CPR is very unlikely to be successful because the patient is dying from an irreversible condition. The decision to withhold CPR involves assessment of the predictors for favourable outcome, in compound with the patient's values and goals of care to make a decision that is of benefit to the patient. Throughout this process there are ethical directives and legislations to relate to. Previous studies have shown that it is difficult for medical personnel to accurately predict outcome after cardiac arrest, but there is no supportive prediction model established in clinical practice. There are indications of shortages in adherence to legislation regarding DNACPR orders in our setting, but clinical practice has not been evaluated on a larger scale. Further, there is scarce knowledge about the grounds for DNACPR decisions based on the clinical practice, about the use of DNACPR orders, and the characteristics of those receiving them.

Aims: The overall aim of this thesis was to facilitate and investigate the decision process for DNACPR order placement in the hospital setting and fill knowledge gaps in the epidemiology of DNACPR orders. More specifically, the aim was external validation of the pre-arrest prediction model the Good Outcome Following Attempted Resuscitation (GO-FAR) score (study I), model update of the GO-FAR score with development of a prediction model for the Swedish setting (study II), evaluation of adherence to the Swedish legislation regarding documentation of DNACPR order placement, exploration of the decision process in clinical practice (study III), and assessment of the use of DNACPR orders, characteristics and outcome for the patients (study IV).

Methods: Study I and II included adult in-hospital cardiac arrests (IHCA) in the Swedish Registry for Cardiopulmonary Resuscitation (SRCR) from 2013 to 2104 in the Stockholm region. Outcome in study I was neurologically intact survival defined as Cerebral Performance Category score (CPC) 1 and in study II outcome was favourable neurological survival defined as CPC 1–2. Outcome and patient characteristics were retrieved from SRCR, predictor variables from manual review of electronic patient records and from the National patient registry (NPR). External validation of the GO-FAR score was based on assessment of the discrimination with area under the receiver operating characteristics (AUROC) curve, calibration and risk group categorisation. Model update was based on the results in study I and included change of outcome and addition of the predictor chronic comorbidity. The study population and variables in III and IV was obtained from Karolinska University Hospital's local administrative database and NPR and included adult admissions through the Emergency Department (ED) from 1 January to 31 October 2015. Study III included only patients with DNACPR orders issued during hospitalisation. In study III the DNACPR form in the electronic patient record was used to evaluate adherence to legislation regarding documentation of DNACPR orders and to explore aspects of the decision process in clinical practice through qualitative content analysis.

Results: Study I and II included 717 IHCA. In study I the GO-FAR score showed good discrimination with AUROC of 0.82 (95% CI 0.78–0.86), but risk group categorisation and calibration showed an underestimation of the probability of neurologically intact survival. Study II provided the updated prediction model the Prediction of outcome for In-Hospital Cardiac Arrest (PIHCA) score. The AUROC for the PIHCA score was 0.81 (95% CI 0.807–0.810). With a cut-off of 3% likelihood of favourable neurological survival the PIHCA score could classify patients with favourable neurological outcome correctly (99% sensitivity), but for patients with poor outcome (death or CPC >2) the PIHCA score's correct classification was limited (8% specificity). This was outweighed by a high negative predictive value (97%) for classification into low likelihood of favourable neurological survival (≤ 3%). Study III included 3,583 DNACPR forms. Mainly due to impaired cognition, it was not possible to consult with the patient 40% of cases. For these patients, a relative was consulted in 46%. For competent patients, consultation took place in 28% and the most common patient attitude was that the DNACPR order adhered with their preferences. Severe chronic comorbidity, malignancy or multimorbidity alone or in combination with acute illness was most common as grounds for DNACPR orders. All requirements in the legislation regarding documentation of DNACPR orders were fulfilled in 10%. Study IV included 25,646 adult admissions to Karolinska University Hospital of whom 11% received a DNACPR order during the hospitalisation. Patients with DNACPR orders were older, with higher burden of chronic comorbidities and more severe acute illness, hospital mortality and one-year mortality compared to those without. Characteristics of patients with DNACPR orders were similar regardless of hospital mortality, however, patients who died in-hospital presented more acutely unwell in the ED. Change in CPR status during hospitalisation was 5% and upon subsequent admission 14%. For patients discharged with DNACPR orders, reversal of DNACPR status upon subsequent admission was 32%, with uncertainty as to whether this reversal was active or a consequence of a lack of consideration.

Conclusions: The GO-FAR score should only with caution be taken into clinical practice in our setting without update. The updated PIHCA score has a potential to be used in our setting, but external validation and further exploration of clinical use is warranted before implementation. There are shortcomings in the decision process regarding documentation of DNACPR orders and further research is warranted to establish the most effective interventions to strengthen clinical practice. For most patients DNACPR order placement was in line with their preferences, but for a substantial proportion of patients impaired cognition made shared decision impossible. The perspective of risk for cessation of circulation for patients with severe comorbidity can lay in the present situation, but also with the perspective of the near future. One out of ten adult patients received a DNACPR order after emergency admission to a Swedish University hospital. Upon subsequent admissions, for patients with a DNACPR order on previous hospitalisation, reversal of DNACPR status occurred for one-third. This should merit attention as it was uncertain if this reversal was active or represented a lack of consideration.

LIST OF SCIENTIFIC PAPERS

I. Piscator E, Göransson K, Bruchfeld S, Hammar U, el Gharbi S, Ebell M, Herlitz J, Djärv T
Predicting neurologically intact survival after in-hospital cardiac arrest-external validation of the Good Outcome Following Attempted Resuscitation score. Resuscitation 128 (2018) 63-69

II. Piscator E, Göransson K, Forsberg S, Bottai M, Ebell M, Herlitz J, Djärv T
Prearrest prediction of favourable neurological survival following in-hospital cardiac arrest: The Prediction of outcome for In-Hospital Cardiac Arrest (PIHCA) score. Resuscitation 143 (2019) 92-99

III. Piscator E, Djärv T, Rakovic K, Boström E, Forsberg S, Holzmann J.M, Herlitz J, Göransson K
Low adherence to legislation regarding Do-Not-Attempt-Cardiopulmonary-Resuscitation orders in a Swedish University Hospital. Resuscitation Plus 6 (2021) 100128

IV. Piscator E, Göransson K, Forsberg S, Herlitz J, Djärv T
Do-Not-Attempt-Cardiopulmonary-Resuscitation orders in patients admitted through the emergency department in a Swedish University Hospital - an observational study of outcome, patient characteristics and changes in DNACPR order placement. *Submitted manuscript*

CONTENTS

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AUROC	Area Under the Receiver Operating Characteristics
BiPAP	Bilevel Positive Airway Pressure
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPC score	Cerebral Performance Categories score
CPR	Cardiopulmonary Resuscitation
CR	Creatinine
DNACPR	Do-Not-Attempt-Cardiopulmonary-Resuscitation
DNR	Do-Not-Resuscitate
ED	Emergency Department
ERC	European Resuscitation Council
$ETCO_2$	End-Tidal Carbon dioxide pressure
FiO_2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GO-FAR	Good Outcome Following Attempted Resuscitation
GWTG-R	Get With The Guidelines-Resuscitation
HDU	High Dependency Unit
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IHCA	In-Hospital Cardiac Arrest
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile Range
LLST	Limitation of Life-Sustaining Treatments
MAP	Mean Arterial Pressure
MS	Multiple Sclerosis

NPR	National Patient Registry
OHCA	Out-of-Hospital Cardiac arrests
OR	Odds Ratio
$PaCO_2$	Partial arterial pressure of Carbon dioxide
PaO_2	Partial arterial pressure of Oxygen
PEA	Pulseless Electrical Activity
PIHCA	Prediction of outcome for In-Hospital Cardiac Arrest
PROM	Patient-Reported Outcome Measures
qSOFA	quick Sequential (sepsis-related) Organ Failure Assessment
RETTS©	The Rapid Emergency Triage and Treatment System
ROSC	Return Of Spontaneous Circulation
SaO_2	arterial Oxygen Saturation
SBP	Systolic Blood Pressure
SD	Standard Deviation
STEMI	ST-Elevation Myocardial Infarction
CI	Confidence Intervall
SRCR	The Swedish Registry for Cardiopulmonary Resuscitation
$TcCO_2$	Transcutaneous Carbon dioxide pressure
TEAL plan	Treatment Escalation and Limitation plan
UK	United Kingdom
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1 INTRODUCTION

In-hospital cardiac arrest (IHCA) is a sudden cessation of circulation where cardiopulmonary resuscitation (CPR) is delivered in the hospital setting.[1-3] Overall survival is 30% in our setting.[3] Initiation of CPR is the standard procedure upon cessation of circulation, however a Do-Not-Attempt-Cardiopulmonary-Resuscitation (DNACPR) decision can be made when the patient does not wish to receive CPR, when the potential burdens of CPR outweigh the benefits, or when CPR is very unlikely to be successful because the patient is dying from an irreversible condition.[4-6] In fact, most patients who die in hospitals do not undergo CPR,[7-12] and in Sweden CPR is initiated in only 6–12% of in-hospital deaths.[7-10]

The decision to withhold CPR is a complex process that involves prediction of outcomes, with an overall assessment of predictors for favourable outcomes, in compound with the patient's values and goals of care with the aim of making a decision that is in the best interests of the patient. Throughout this process which essentially lies in the hands of the clinician, there are ethical directives and legislative requirements to relate to.[4-6,13-15]

DNACPR directives differ from other decisions in health care as they concern withholding rather than providing a treatment that can be lifesaving, for an event that you cannot place in time and where an unfavourable outcome from all perspectives is difficult to anticipate. CPR can be a lifesaving procedure, but for some patients, should their clinical course be complicated by a cardiac arrest, the balance between benefit and burden is not in favour of CPR, since CPR has the potential to cause harm, with treatments and outcomes that are not acceptable to the patient.[16,17] In these situations, it is important to safeguard the patient's right to be involved in decision-making and the expression of autonomy.

Medical personnel have difficulties with accurately predicting outcome after cardiac arrest,[18,19] but there is no supportive prediction model established in clinical practice. There are indications of shortages in adherence to ethical guidelines and legislation regarding DNACPR orders in Sweden, but clinical practice has not been evaluated on a larger scale.[8,20-24] Further, in our setting, there is scarce knowledge about the grounds for DNACPR decisions,[8,24] use of DNACPR orders,[25] and demographics of those receiving them.[21]

Throughout the studies in this thesis, the main focus has been to facilitate and investigate the decision process for DNACPR orders in the hospital setting and fill knowledge gaps in the epidemiology of DNACPR orders. This has been done by focusing on providing a pre-arrest prediction model to identify patients with a low likelihood of favourable neurological survival and by exploring clinical practice concerning adherence to legislation for DNACPR orders. Further, focus has been on DNACPR order placement and description of patient and hospital characteristics for patients with DNACPR orders.

2 LITERATURE REVIEW

2.1 CARDIOPULMONARY RESUSCITATION

2.1.1 In-hospital cardiac arrest

The burden of IHCA is substantial and constitutes a major health concern. A recent estimation indicate that approximately 300,000 hospitalised patients are treated for IHCA in the US annually,[26] and the corresponding number for Sweden is at least 2,500.[3] Although survival has improved over the last decade (see figure 1),[27-29] IHCA is associated with significant mortality and morbidity. One fifth to one third survive an episode of IHCA, most commonly with favourable neurological function,[27,28,30-36] but for some there is an impact on their health and wellbeing.[31,37,38]

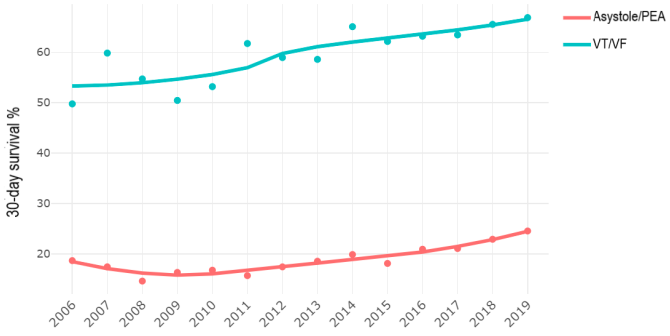

Figure 1. Temporal trends in survival following in-hospital cardiac arrest according to initial rhythm from the Swedish Registry for Cardiopulmonary Resuscitation. Abbreviations: PEA, Pulseless Electrical Activity. VT, Ventricular Tachycardia; VF, Ventricular Fibrillation.

2.1.2 Definition of in-hospital cardiac arrest

An IHCA is defined as loss of circulation within the walls of a hospital prompting chest compressions and/or defibrillation.[1-3]

2.1.3 Incidence of in-hospital cardiac arrest

Published estimates of the incidence of IHCA range from 1.3-2.8 events per 1,000 hospital admissions in Europe[30-34,36] to 6.7-9.7 events per 1,000 admissions in the US.[39-41] The variability between published estimates partly reflect that despite efforts to unify the reporting of IHCA[1,2] there is significant heterogeneity in the definition of IHCA regarding inclusion and exclusion criteria, patient population and clinical practice. Some studies report the incidence for index IHCA only,[32,34,36] whereas others exclude cardiac arrests not managed by the hospital-based resuscitation team, not fully capturing cardiac arrests in areas such as the intensive care unit (ICU) or catheterisation laboratory.[26,30] Cardiac arrest registries are used in some studies, with varying national coverage[27,34,36] or regional coverage,[32] while others are

based on multicentre hospital participation[31] or retrospective health administration data.[33] Furthermore, some publications are extrapolations of registry-based data.[39-41] This introduces complexity in the interpretation of causes for the differences in incidence.

2.1.4 Characteristics and survival after in-hospital cardiac arrests

Patients suffering IHCA have a mean age 66-74 years, are predominantly male (57-65%) and have a previous history of renal insufficiency (34-65%), heart failure (21-36%), diabetes (26–31%), respiratory insufficiency (21-43%) and malignancy (18-19%).[27-36] The IHCA most commonly occur 1-2 days after admission, are witnessed in the vast majority (79-91%) and most commonly occur on general wards (46-62%), often preceded by hours of vital sign deterioration.[27,28,30-32,34,36,42-45] Although difficult to determine, cardiac causes of cardiac arrest events, such as myocardial infarction, heart failure, or arrhythmia are most common (53-59%), followed by respiratory insufficiency (11-26%%).[32,34,36]

The initial rhythm analysed upon cardiac arrest is most commonly non-shockable (asystole and pulseless electrical activity (PEA),70-78%), about 50% survive the initial resuscitation and 15–32% survive to hospital discharge/30-days, with multiorgan failure being the main driver of mortality.[3,27-36,39]

Although the vast majority (85–98%) survive with a favourable neurological outcome (Cerebral Performance Category (CPC)[46] 1-2, see definition table 1), concern has been raised about the remaining effects on health-related quality of life for the survivors.[3,27,30-32,34,35,37,38]

Table 1. Definition of the Cerebral Performance Category (CPC) scale.[46]

CPC	Functional status
CPC 1	Good cerebral performance: conscious, alert, able to work and lead a normal life, may have minor psychologic or neurologic deficits (mild dysphagia, hemiparesis, or minor CNS abnormalities)
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life (dress, travel by public transportation, food preparation). Able to work in sheltered environment. May have hemiplegia, seizures, ataxia, dysarthria, or permanent memory or mental changes
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis
CPC 4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness
CPC 5	Brain death

Survival after IHCA is highly dependent on initial rhythm, where the less prevalent shockable rhythms (ventricular tachycardia (VT) and ventricular fibrillation (VF)) have survival rates of 49-65% as compared to the more prevalent non-shockable rhythms, with survival rates of 11-22%.[28,30-32,34,47] This is illustrated in figure 1. Other factors of importance include whether the cardiac arrest event was witnessed, and the place of arrest, with higher survival rates if the patient was monitored.[28,31,34,47,48]

As for incidence, there is corresponding heterogeneity in the definition, reporting of variables, underlying patient population and clinical practice, making comparisons complex.

Another key factor influencing the incidence of and survival after IHCA is the use of DNACPR orders. The prevalence of DNACPR orders effects the population at risk of IHCA. The frequency of cardiac arrest events and the proportion of favourable neurological survival depends on the selection of patients for CPR. Studies have shown differences in the use of DNACPR directives in European countries,[22,49] and there is data indicating lower use of DNACPR orders in the US as compared to Europe.[7-10,34,50-56]

2.1.5 Patient-related predictors for survival following in-hospital cardiac arrest

Patient-related factors associated with poor survival after IHCA include increasing age, altered mental status and functional disability before the arrest.[28,29,31,32,34,35,47,57-61] Acute and chronic comorbidities such as hypotension, sepsis, pneumonia, respiratory insufficiency, renal insufficiency, hepatic insufficiency and malignancy, as well as combined chronic comorbidities according to the Charlson Comorbidity Index (CCI) are additional predictors associated with poor survival.[31,34,47,58-66] There are several versions of the CCI,[67] the one used in this thesis is displayed in Appendix 1.[68,69]

Frailty is an important risk factor for adverse outcomes in critical illness.[70,71] Frailty is a state of vulnerability to poor compensation after a stressor event characterised by a cumulative decline in physiologic systems during a lifetime, until even minor stressor events trigger disproportionate changes in health status, with failure to complete recovery.[72] It is due to the accumulation of age- and disease-related deficits,[72] and can be assessed with different scoring systems.[73] The Clinical Frailty Scale (CSF) is a tool that can be used in the hospital setting and assesses frailty in older adults from 1 (least frail, very fit) to 9 (most frail, terminally ill) and is inversely associated with survival after IHCA.[63,74,75]

Although increasing age is an independent predictor of survival after IHCA, for patients older than 80 years suffering IHCA, favourable neurological survival (CPC 1–2) of 11–18% has been shown.[29,57] Consequently, CPR could be of benefit for some patients of higher age, and age should not constitute sole grounds to withhold CPR in case of a cardiac arrest event, but be a part in the overall assessment in the decision process.[29,57,76]

2.2 ETHICS OF RESUSCITATION

CPR was introduced to clinical practice in the 1960s to maintain intact circulation and oxygenation of the brain until further measures could be taken for them to be restored.[77] It has become the standard procedure upon unexpected loss of circulation but was never intended to hinder patients from dying in the course of irreversible conditions.[4,5] CPR is a potentially beneficial treatment, but also has the potential to cause harm, with intrusion upon the integrity of the patient, causing physical insult and pain, with treatments and outcomes that would not be acceptable to the patient.[16,17,78] Survivors of resuscitation often experience physical

complications such as rib and sternal fractures and often undergo aggressive treatment in the ICU, for some with neurological, mental and functional sequelae affecting the quality of life.[16,31,37,38,78] The value of this lies in the hands of the patient to decide. The balance between benefit and burden is a composition of assessment by the clinician, and by the patient.

DNACPR orders were introduced in the 1970-80s to protect patients from treatments that had little chance of success and a potential to cause harm,[16,79] and for patients who die in hospital, 74-89% of patients have a DNACPR order in place.[7,8,55,56] The use of DNACPR orders has been shown to increase over time in the US,[80] but no such comparison has been made in the Swedish setting. Though, in reviewing a study from 1990 performed in Sweden,[81] practice would seem to have changed a great deal, as this quote from the abstract implies:

"In a nation-wide survey, procedures related to do-not-resuscitate (DNR) orders in Swedish medical wards were investigated by means of a questionnaire given to internists-in-charge. The response rate was 89% (286 out of 323). of whom all but 2% (seven individuals) stated that DNR orders were used in their wards. The most common procedure was an oral direction to the nurse, who documented the order in the nurses' day-to-day work sheet. The DNR orders were signed by 28% of the physicians. A wide range of symbols and code words were used, and there was considerable disagreement regarding the meaning of a DNR order. Such orders were often associated with withdrawal and withholding of life-sustaining treatments other than cardiopulmonary resuscitation. Most physicians stated that they never discuss DNR order with the patients, and that only in a minority of DNR decisions do they involve family members. There was considerable conflict with regard to DNR ordering procedures not only between internists in different hospitals, but also within individual hospitals."

Today, there are legislative and ethical directives that in more detail guide clinical management concerning the limitation of life-sustaining treatments (LLST) including DNACPR decisions.[4-6,13,14] Other LLST include invasive ventilation, intensive care and vasoactive drugs among others.

2.2.1 Do-Not-Attempt-Cardiopulmonary-Resuscitation (DNACPR) orders

Ethics of resuscitation are based on the principles of autonomy, beneficence, non-maleficence, and justice. A DNACPR order may be issued when in the event of a cardiac arrest, CPR is not aligned with the patient's values and goals of care, the potential burdens of CPR outweigh the benefits and CPR is considered not to benefit the patient, or when CPR is very unlikely to be successful because the patient is dying from an irreversible condition.[4,5] It is a decision documented by the clinician based on known patient preferences and/or the treating team's estimates of a poor patient prognosis if the clinical course is complicated by an episode of cardiac arrest. Consideration should be taken to involve the patient, medical team and the patient's relatives.[4,5,15]

Consensus definitions of the ethical principles according to the European Resuscitation Council (ERC) guidelines 2021 are presented in table 2.[5]

Table 2. Consensus definitions of the principles of ethics according to the European Resuscitation Council Guidelines 2021[5]

Principle	Definition
Autonomy	Respect for the right of self-determination in the context of informed, healthcare decision-making by patients and/or their families
Beneficence	Selection of beneficial interventions for the patient after assessment of the risk-to-benefit ratio
Non-maleficence	Avoiding harm or inflicting the least possible harm in the course of achieving a beneficial outcome
Justice	Means fair and equal distribution of benefits, risks, and costs; pertains to the equality of rights to healthcare, and the legal obligation of healthcare providers to adhere to appropriate care and allocation of burdens and benefits

2.2.2 Futility

Futility is part of the assessment of beneficence and non-maleficence. Futility has a quantitative and a qualitative aspect. Quantitative futility is the cut-off where the likelihood of favourable outcome is unacceptable and has been proposed to be defined as a likelihood of a favourable outcome of less than 1% or less than 3%.[82-84] Qualitative futility is the outcome that is perceived as unacceptable to the patient, and cannot be judged by anybody else but the patient.[82] In that sense there is no valid definition of futility taking into account both aspects.[82,85,86] The concept of futility has been questioned, as defining an unfavourable outcome is challenging and the value of an outcome is individual. There has been a shift from futility to a broader consideration of what lies in the best interest of the patient, taking into consideration burden versus benefit.[5,86]

2.3 THE USE OF AND CHARACTERISTICS OF PATIENTS WITH DNACPR ORDERS

2.3.1 The use of DNACPR orders

Frequency of use and characteristics of subgroups of patients with DNACPR orders have been published, but differ substantially depending on clinical condition and setting.[87-101] For example, the frequency of DNACPR orders among patients with cancer was 44%,[91] among patients with sepsis 28%,[89] heart failure 10-12%[95,96] and among patients admitted to a medical acute assessment unit 15%.[92] The use of DNACPR orders increases with higher age and increasing burden of comorbidities.[80,89,96,99,101,102]

For a mixed patient population prevalence studies are more scarce, but have been reported in the range of 13-28%[80,102,103] For Sweden, the point-prevalence of DNACPR orders outside of the ICU from one of the two sites at Karolinska University Hospital 2004 was 4%,[25] but have hitherto not been further explored. In a study of all in-hospital deaths in Kalmar County Hospital 2016, 89% had a DNACPR order in place.[8]

2.3.2 Characteristics of patients with DNACPR orders

Patient characteristics for patients with DNACPR orders vary with the subgroup that was studied. For a mixed patient population with DNACPR orders patients has been reported to be female in 35-68%, with mean age 81-83 years, and with a median combined burden of chronic comorbidity according to CCI of 6.[21,55,80,104] Although more than half (51-70%) are discharged from hospital, one-year mortality for patients with DNACPR orders is high (70-83%).[21,55,104] The decision for DNACPR was placed in median one to three days after hospital admission,[55] and for patients with DNACPR orders and in-hospital mortality, time from DNACPR order placement to death was 4 days.[8]

There are no contemporary studies further elaborating patient and in-hospital characteristics of a mixed population of patients with DNACPR orders in Sweden.

2.4 THE DECISION PROCESS FOR DNACPR ORDERS

The decision process for DNACPR orders includes assessment of the individual patient's predictors of favourable outcome in terms of underlying chronic comorbidities, general health status and acute medical conditions. This is balanced against the patient's values and goals of care to respect patient autonomy and assess benefit.[4,5]

2.4.1 Prediction models for favourable outcome following in-hospital cardiac arrest

Previous studies have shown that it is difficult for medical personnel to accurately predict outcome after cardiac arrest.[18,19] A pre-arrest prediction model could be a mean to support the clinician's decision-making through an objective assessment of predictors associated with outcome following IHCA.

Two previously developed prediction models for survival after IHCA, the Pre-Arrest Morbidity index[53] and the Prognosis After Resuscitation score[105] did not perform satisfactorily in validation[106-109] and have not been taken into clinical practice. In 2013, the prediction model Good Outcome Following Attempted Resuscitation (GO-FAR) score,[60] and predictions through classification and decision trees were developed.[110] They were mentioned as potential tools in assessing futility in the European Resuscitation Council (ERC) guidelines 2015.[111]

The rationale when planning for study I in 2015 was that the GO-FAR score had not been externally validated and in comparison, it was assessed as more appealing for clinical application than the models based on classification and decision trees.

The GO-FAR score was later externally validated in cohorts from Sweden[112]and Korea[113] with encouraging results. The GO-FAR score has undergone further external validation in the US setting[114] and was updated in 2020 to produce the GO-FAR score 2.[61]

There is no pre-arrest prediction model established in clinical practice today, and the role of such a prediction model in clinical practice has not been evaluated.

2.4.2 Grounds for DNACPR orders

Exploration of grounds for DNACPR orders based on the clinicians' assessment show that age, quality of life, general clinical condition, frailty, futility, and comorbidities such as malignancy, heart failure and chronic obstructive pulmonary disease are aspects taken into consideration.[93,104,115-117]

Interview studies in the Swedish setting have shown that from the perspective of the clinicians, chance of survival and quality of life after resuscitation, medical prognosis, and the patient's right to a peaceful death all constituted grounds for DNACPR orders.[24] The analysis of the explanatory text for DNACPR orders in patients who died in hospital included high age, metastasised cancer, comorbidity and dementia.[8] There are no contemporary studies further exploring grounds for DNACPR orders in clinical practice in the Swedish setting.

2.4.3 Respect for autonomy

Patient involvement in DNACPR decisions differ within a broad range from six to 70%.[8,20-24,55,93,102,118-120] Barriers to include patients and relatives in shared decision-making includes the fear of causing harm or of conflicts developing, lack of knowledge and experience, lack of time, and patients not capable of having the discussion[20,21,23,116,117,121-123] In fact, for as many patients as 21-66% shared decision making is not an option due to a lack of decision-making capacity [8,21,22,93,104,118] For competent patients 27-93% have been reported to be involved in the discussion.[21,22,104] Studies evaluating clinical practice in Sweden have been smaller, questionnaire- or focus group-based [8,20-24] and few with an evaluation of the actual clinical practice.[8,21]

2.5 LEGISLATION AND CLINICAL PRACTICE

There is a wide range of legislation and clinical practices in different parts of the world.[49,124,125] Although varying, in many European countries physicians are the ultimate decision-makers for DNACPR orders, even though the information is shared with patients or relatives,[4,49,102,126,127] whereas in the US this is shifted towards patients being the ultimate decision-makers.[125]

Swedish legislations states that healthcare should be carried out in consultation with the patient as far as possible,[6,13] and that it should take into consideration the respect for autonomy and integrity.[14] The decision regarding LLST including DNACPR orders should be documented in the electronic patient record.[15] Unless secrecy applies, relatives should be involved in healthcare planning.[6] The patient's and relatives' values and preferences regarding resuscitation should be documented in the electronic patient record.[15] If consultation with the patient is not possible, the reason should be documented and relatives consulted as far as possible.[6,15] Further, grounds for the DNACPR decision should be documented in the patient record, consultation with at least one other licenced caregiver should be made and documented.[15]

Previous studies have shown that there are shortcomings in the knowledge about and adherence to the legislation concerning DNACPR decisions in Sweden.[8,20-24] These studies however were smaller,[21] and included only an analysis of DNACPR orders for patients who died,[8] or were questionnaire-based.[20,22-24] Thus, adherence to legislation in actual clinical practice has not been examined extensively.

2.6 PREDICTION MODEL DEVELOPMENT AND VALIDATION

Prediction models are mathematical equations that estimate the probability of an event based on the combination of information from several predictors observed in an individual to assist in decision making. The following sections will provide a background to the statistical methods involved in prediction model development and validation to make it easier to follow the statistical analyses in studies I and II.

2.6.1 Prediction model development

Prediction models are commonly developed by combining predictors that are associated with the outcome in multivariable regression analysis. Logistic regression is used for binary outcomes. In the regression analysis each individual predictor is given a weight (beta coefficient) in the risk estimation. The selection of candidate predictors to be included in the model can be made a priori based on knowledge about the most important predictors associated with the outcome, or through multivariable statistical procedures where only those candidate predictors that contribute statistically are kept in the model. The selection procedure can include a combination of both.[128,129]

2.6.2 Internal and external validation

In prediction model development, internal validation refers to the performance of the model in the development setting, the reproducibility. However, the development data set only refers to the underlying population from where it was sampled and does not imply transferability to other settings. Therefore, external validation with confirmation of model performance outside of the original setting is important.[130,131]

In both internal and external validation, the model's predictive performance is evaluated through discrimination, calibration, and classification abilities.

Discrimination is the probability that the model will distinguish those with the outcome from those without. It is quantified by estimating the area under the receiver operating characteristics (AUROC) curve. An AUROC of 0.5 indicates a 50-50% chance for the model to distinguish correctly, indicating poor discrimination.

Calibration is the agreement between observed outcomes and predictions, that is, how close predictions are to the actual outcome. Calibration can be assessed graphically in a calibration plot. The calibration plot has an intercept and a calibration slope, and an ideal model has an intercept of 0 and a calibration slope of 1, see figure 2.

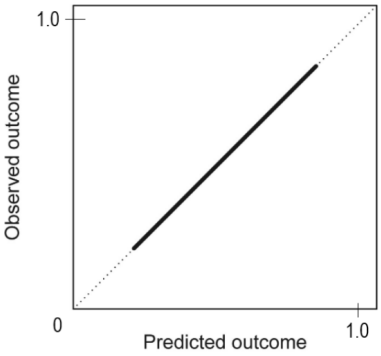

Figure 2. The calibration plot of an ideal model with an intercept of 0 and a calibration slope of 1. Calibration plot of an ideal model with an intercept 0 and calibration slope 1. Reprinted with permission from Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).[132]

The intercept of a prediction model in a calibration plot indicates if the predictions are systematically too high or too low, whereas the slope indicates the accuracy of the weights given to the predictors in the model and can be a measure of overfitting, see below.[130,131]

Classification abilities can guide the evaluation of the prediction model's clinical usefulness. For this, decision thresholds must be defined based on clinical implications. Using the threshold to classify patients, sensitivity, specificity, positive and negative predictive values can be calculated to measure usefulness in clinical practice, see table 3.[131]

Table 3. Classification abilities.

	Has the outcome	Does not have the outcome
Test is positive	a	b
Test is negative	c	d
Sensitivity:a/(a+c)		
Specificity:d/(b+d)		
Positive predictive value:a/(a+b)		
Negative predictive value:d/(c+d)		

In addition, internal validation includes the assessment of optimism or overfitting. In developing a new prediction model, most commonly the only data set available is the development set. Thus, quantifying the predictive abilities in this development set will give optimistic results in relation to how it would perform on other participants in the same underlying population, or indeed in other different settings. This optimism, or overfitting is related to the number of predictors, the number of outcome events in the development data set and the predictor selection process. The model's potential for overfitting can be quantified through different statistical methods, one of which is bootstrap sampling. Bootstrap sampling implies repeatedly creating different sampling data sets through sampling with replacement from the whole data set. By analysing the sampling sets in the same way as for the

development set, an estimate of the overfitting can be established and applied to the developed model. This adjusts the model so that better predictive abilities can be obtained in future validation.[128,129,131]

2.6.3 Prediction model update

In external validation, if the model proves to perform unsatisfactorily, rather than redeveloping the model, it can be updated using the results from the external validation, thus retaining information already obtained. The model can be recalibrated based on the intercept and slope in the calibration plot, or more extensive methods can be used with the addition of predictors and the re-estimation of the beta coefficients. Table 4 gives an overview of different approaches to prediction model updates.[129] In the same way as for new models, the predictive abilities of updated models need to be validated before implementation.[129-131]

Table 4. Overview of different approaches for updating an existing prediction model.[129]

Method	Updating method	Reason for updating
0	No adjustment (the original prediction model)	
1	Adjustment of the intercept (baseline risk/hazard)	Difference in the outcome frequency (prevalence or incidence) between development and validation sample
2	Method 1 + adjustment of all predictor regression coefficients by one overall adjustment factor (calibration slope)	The regression coefficients or combination thereof of the original model are overfitted or underfitted
3	Method 2 + extra adjustment of regression coefficients for predictors with different strength in the validation sample compared with the development sample	As in method 2, and the strength (regression coefficient) of one or more predictors may be different in the validation sample
4	Method 2 + selection of additional predictors (e.g. newly discovered markers)	As in method 2, and one or more potential predictors were not included in the original model, or a new predictor may need to be added
5	Re-estimation of all regression coefficients, using the data of the validation sample only. If the development data set is also available, both data sets may be combined.	The strength of all predictors may be different in the validation sample, or the validation sample is much larger than the development sample
6	Method 5 + selection of additional predictors (e.g. newly discovered markers)	As in method 5, and one or more potential predictors were not included in the original model, or a new predictor may need to be added

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2.7 PREDICTION MODEL FOR EXTERNAL VALIDATION STUDY I

2.7.1 The Good Outcome Following Attempted Resuscitation (GO-FAR) score

The multivariable regression-based prediction model GO-FAR score was chosen for external validation in study I. The score was developed using a cohort of 51,240 index IHCAs in adults from 366 hospitals participating in the Get With The Guidelines-Resuscitation (GWTG-R) registry 2007–2009. It is a summed score of 13 pre-arrest predictor variables with points ranging from –15 to 11. The rate of survival to discharge with CPC 1 was 10% in the development cohort. AUROC for the GO-FAR score was 0.800.[60]

2.7.2 GO-FAR score outcome

Outcome in the GO-FAR score is neurologically intact survival, defined as CPC 1 at discharge.[60]

2.7.3 Predictors in the GO-FAR score

Candidate predictor inclusion in the GO-FAR score was based on a previous meta-analysis[58] in combination with clinical reasoning based on variables in the GWTG-R registry. Final predictor selection was made through multivariable analysis to create a model with 13 pre-arrest predictors. Multivariable logistic regression was used to establish the beta coefficients, which were multiplied by 10 and rounded to assign the points in the GO-FAR score.[60] Definitions of the predictors are presented in table 5.

Table 5. Definition of the predictors in the GO-FAR score.[60]

GO-FAR variable	Definition[a]	Score
Neurologically intact or with minimal deficits at admission	CPC 1	-15
Major trauma	Evidence of multisystem injury or single-system injury associated with shock or altered mental status during the current hospitalisation	10
Acute stroke	Documented diagnosis of an intracranial or intraventricular hemorrhage or thrombosis during the current admission	8
Metastatic or hematologic cancer	Any solid tissue malignancy with evidence of metastasis or any blood-borne malignancy	7
Septicemia	Documented bloodstream infection in which antibiotic therapy has not yet been started or is still ongoing	7
Medical non-cardiac diagnosis		7
Hepatic insufficiency	Evidence of hepatic insufficiency within 24 h of the event, defined by total bilirubin > 34 µmol/l and (aspartate aminotransferase > 2 times the upper limit of normal or cirrhosis)	6
Admission from skilled nursing facility		6
Hypotension or hypoperfusion	Any evidence of hypotension within 4 h of the event, defined as any of the following: SBP < 90 or MAP < 60 mmHg, vasopressor or inotropic requirement after volume expansion (except for dopamine ≤ 3 µg/kg/min) or intra-aortic balloon pump	5
Renal insufficiency/dialysis	Requiring ongoing dialysis or extracorporeal filtration therapies, or serum-creatinine > 2mg/dL within 24 of the event	4
Respiratory insufficiency	Evidence of acute or chronic respiratory insufficiency within 4 h if the event, defined as any of the following: PaO_2/FiO_2 ratio < 300, PaO_2 < 60 mmHg, or SaO_2 < 90% (without preexisting cyanotic heart disease), $PaCO_2$, $ETCO_2$ or $TcCO_2$ > 50 mmHg, spontaneous respiratory rate > 40/min or < 5/min, requirement for noninvasive ventilation (e.g. bag-valve mask, mask CPAP or BiPAP, nasal CPAP or BiPAP), or negative pressure ventilation, or requirement for ventilation via invasive airway	4
Pneumonia	Documented diagnosis of active pneumonia, in which antibiotic therapy has not yet been started or is still ongoing	1
Age, y		
70-74		2
75-79		5
80-84		6
≥85		11

Abbreviations: GO-FAR score, Good Outcome Following Attempted Resuscitation score; CPC, Cerebral Performance Category; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; PaO_2, arterial Partial pressure of Oxygen; FiO_2, Fraction of Inspired Oxygen; SaO_2, arterial Oxygen Saturation; $PaCO_2$, arterial Partial pressure of Carbon Dioxide; $ETCO_2$, End-Tidal Carbon Dioxide pressure; $TcCO_2$, Transcutaneous Carbon dioxide pressure; CPAP, Continuous Positive airway Pressure; BiPAP, Bilevel Positive airway Pressure .
[a]According to the Get With The Guidelines-Resuscitation registry[133]

2.7.4 GO-FAR score risk group categorisation

Based on definition of medical futility,[83,84] the likelihood of neurologically intact survival was categorised into risk groups in the GO-FAR score: very low (< 1%) ≥ 24 points, low (1–3%) 14 to 23 points, average (> 3–15%) -5 to 13 points and above average (> 15%) –15 to –6 points.[60]

2.7.5 Strengths and limitations of the GO-FAR score

Strengths include the large cohort enabling a rigorous process for model development and use of pre-arrest predictors known at hospital admission. Limitations include that selection of candidate predictors was limited to the variables included in the GWTG-R registry, and the underlying problem of unknown factors such as DNACPR order use in the selection process for IHCA constituting the cohort.[60] An additional limitation of the GO-FAR score is the definition of neurologically intact survival as CPC 1 only, as the Utstein definition of good outcome, if CPC is used as an outcome measure, is considered to be CPC 1 and 2.[1]

3 RESEARCH AIMS

The overall aim of this thesis was to facilitate and investigate the decision process for DNACPR order placement in the hospital setting and fill knowledge gaps in the epidemiology of DNACPR orders.

More specifically the aims were:

STUDY I

External validation of the pre-arrest prediction model the GO-FAR score.

STUDY II

Model update of the GO-FAR score with development of a pre-arrest prediction model to identify patients with a low likelihood of favourable neurological outcome in the Swedish setting.

STUDY III

Evaluation of adherence to the Swedish legislation regarding documentation of DNACPR order placement in clinical practice, exploration of the grounds for the decision, the attitudes of patients and relatives towards the decision and reasons why consultation with the patient was not possible.

STUDY IV

Assessment of the incidence of DNACPR orders, characteristics, outcome, and changes in DNACPR orders for patients admitted through the emergency department (ED).

4 MATERIALS AND METHODS

4.1 OVERVIEW OF THE STUDIES

An overview of the studies in this doctoral thesis is shown in table 6.

Table 6. Study overview.

Study	I	II	III	IV
Design	Retrospective cohort study			
	Prediction model external validation of the GO-FAR score	Prediction model update based on the GO-FAR score		
Study population	Index IHCA in adults reported through SRCR	Index IHCA in adults reported through SRCR	Adults admitted through the ED with DNACPR order	Adults admitted through the ED
Outcome	CPC 1	CPC 1–2	Adherence to legislation	DNACPR order Hospital mortality CPR status changes
Data sources	SRCR Patient records	SRCR Patient records NPR	Karolinska University Hospital's central data warehouse Document 33 NPR	Karolinska University Hospital's central data warehouse NPR
Study setting	Stockholm region	Stockholm region	Karolinska University Hospital	Karolinska University Hospital
Study period	2013–2014	2013–2014	1 Jan–31 Oct 2015	1 Jan–31 Oct 2015
Included (n)	717	717	3583	25,646
Statistical methods	Chi-squared Fisher's exact test Wald test Mann-Whitney test Multiple imputation AUROC Calibration Classification accuracy Multiple imputation Logistic recalibration	Chi-squared Wald test Linear regression with bootstrap Mann-Whitney test Logistic regression Quantification of overfitting AUROC Calibration Classification accuracy	Chi-squared Univariable logistic regression Univariable linear regression with bootstrap Quantile regression with bootstrap Inductive qualitative content analysis	Chi-squared Wald test Mann-Whitney test

Abbreviations: GO-FAR, Good Outcome Following Attempted Resuscitation; IHCA, In-Hospital Cardiac Arrest; SRCR, Swedish Registry for Cardiopulmonary Resuscitation; CPC, Cerebral Performance Category score; ED, Emergency department; DNACPR, Do-Not-Attempt-Cardiopulmonary-Resuscitation; NPR, National Patient Registry; AUROC, Area Under the Receiver Operating Characteristics

4.2 DATA SOURCES

In study I-II, the study population was recruited, and outcome obtained through the Swedish Registry for Cardiopulmonary Resuscitation (SRCR).

In study I-II, predictors were obtained through manual review of electronic patient records.

In study II, the predictor chronic comorbidity was obtained through linkage with the National Patient Registry (NPR).

In studies III and IV, the study population was recruited and data on patient demographics, hospital characteristics and outcome obtained through the Karolinska University Hospital central data warehouse. Data on chronic comorbidity was obtained through linkage with the NPR.

In study III free text for qualitative content analysis was obtained through access to the DNACPR form Document 33 (Appendix 2) in the electronic patient record.

4.2.1 The National Patient Registry

All individuals that are residents in Sweden are given a ten-digit personal identity number by the Swedish Tax Agency. This serves as a unique identifier in all national registries enabling linkage between them.[134] One of the national registries is the NPR, since 1987 it has complete nationwide coverage of all inpatient diagnoses in Sweden. Since 2001 the registry also includes hospital-based outpatient physician visits, but primary care is not included. Information on diagnoses and surgical procedures are coded according to the International Classification of Diseases and Related Health Problems (ICD). ICD-10 is the version used since 2011. Underreporting for inpatient data is low and 85-95% of all diagnoses are correct.[135]

4.2.2 The Swedish Registry for Cardiopulmonary Resuscitation

One of the approximately 100 quality registries in Sweden is the SRCR that was established for out of-hospital cardiac arrests (OHCA) in 1990, and for IHCA in 2005. The in-hospital registry includes all cases where CPR is initiated within the walls of the hospital[3] and reports variables according to the Utstein template by hospital staff. The original template focused on OHCA, [136] and in 1997 a separate document for IHCA was published.[137] Since 2002 the International Liaison Committee on Resuscitation (ILCOR) has continued to update and revise reporting templates and definitions.[1,2,138,139] As of 2019, data from 73 out of 74 emergency hospitals with their own resuscitation team have been reported to SRCR, with data on 28,865 IHCA.

Reporting is conducted in three stages. In the first stage variables related to the circumstances of the cardiac arrest are reported with patient-related variables, treatment and time variables and survival at the end of the resuscitation. In the second stage, pre-arrest variables based on information in the electronic patient records are reported with previous medical conditions and comorbidities, medical conditions immediately preceding the cardiac arrest and the precipitating cause. Post-arrest treatment is reported together with survival to discharge from hospital and neurological outcome at discharge. The neurological outcome is assessed according to the CPC score. Through linkage with the Swedish Population Registry, information on 30-day survival is obtained. Since 2013, a third stage report Patient-Reported Outcome Measures (PROM) to evaluate patient impact from the cardiac arrest. This is done after three to six months through the use of a telephone-assisted questionnaire that includes measurements of health status and quality of life. In 2018, 53 out of 74 hospitals reported on PROM.

All survivors of the IHCA are informed by letter of their participation in the registry. They are also informed that the registry is used for quality monitoring and research purposes, and that they can exit at any time. Drop out from the SRCR is low (personal communication Prof. Herlitz) however, loss to follow up in PROM measurements is considerable (43%).[37]

Validation in 2014 and 2018 including 68 hospitals showed that reported variables were correctly reported in 92–99% with low missingness, except for initial rhythm with 23% missing. There was some reporting bias of cardiac arrests managed by the hospital-based resuscitation team. 50% of the hospitals answered that all these cardiac arrests were reported, and the underreporting was estimated to be 5-30%. There is also underreporting of cardiac arrests not managed by the resuscitation team (such as cardiac arrest events in the catheterisation laboratories), the extent of which is not known.[140]

4.2.3 The Karolinska University Hospital' central data warehouse

Karolinska University Hospital holds a central data warehouse, which has drawn data from the electronic health system daily since 2009. It contains data on patient demographics and in-hospital characteristics and can be obtained through the Information Technology department.

4.2.4 DNACPR decisions in the electronic patient record

Based on the legislation for the documentation of decisions regarding to LLST, it is mandatory to fill out a form in the electronic patient record for every DNACPR decision at Karolinska University Hospital. The form was implemented in 2009 and revised in 2013 to comply with legislation published by the National Board of Health and Welfare 2011.[15] The revised form was called Document 33 and is presented (Swedish only) in Appendix 2. After this, several other revisions have been implemented, such as Document 605 in November 2015, and Document 639 in May 2016, which is the one still in use. All versions of the form are designed with tick boxes and sections for free text writing. Besides DNACPR, the form specifies other LLST, such as invasive ventilation, intensive care, vasoactive drugs or dialysis. It can also specify that there are no limitations, and since the standard procedure is to initiate CPR this in clinical practice is the same thing as having no form.[6] To be able to describe changes in DNACPR status, this is called "initiate CPR status" in the reporting of study IV. According to Swedish ethical guidelines, a conversation concerning DNACPR should take place with all patients with increased risk of a cardiac arrest event, or where a DNACPR order could be in line with the values and goals of the patient.[4] It is not mandatory to consider the question of DNACPR and there is no special routine for DNACPR decisions on admission to Karolinska University Hospital. Patients may have multiple DNACPR forms, as a change of ward requires a reassessment of the DNACPR status, and patient conditions may change during hospitalisation. Information on DNACPR orders is available through Karolinska University Hospital's central data warehouse.

4.3 STUDY POPULATION

4.3.1 Study I

The prediction model validation cohort in study I included all index adult IHCAs registered in the SRCR in the Stockholm region during 2013–2014 with a complete personal identity number. Exclusion criteria: 1) IHCAs at Norrtälje Hospital (due to lack of access to the electronic patient record), 2) a person with IHCA who is not a patient at the hospital (e.g. visiting relative), 3) CPR initiated despite DNACPR order and 4) OHCA preceding the IHCA.

The sample size was based on the inclusion of the most recent IHCA data, with the estimation that there would be a sufficient number of events relative to the feasibility of predictor variables extraction requiring a detailed manual review of the electronic patient records.

4.3.2 Study II

The cohort for prediction model update in study II was the same cohort as in study I. This was based on a pragmatic approach using an already available data set, and that the cohort met the rule of thumb suggesting at least 10 outcome events per included predictor in the model.[129]

4.3.3 Study III

The cohort in study III included adult patients with a complete personal identity number admitted through the ED at Karolinska University Hospital from 1 January to 31 October 2015 with at least one DNACPR order issued during hospitalisation. The study sample was a sub-cohort of an already existing cohort of ED visits with pre-collected data. The time-period was chosen as later revised versions of the form could not address the study questions.

The simple size was based on rough estimates of the prevalence of DNACPR orders at the hospital and was assessed as adequate to evaluate adherence to legislation and be representative for the qualitative analysis.

4.3.4 Study IV

The cohort in study IV included adult patients with a complete personal identity number admitted through the ED at Karolinska University Hospital from 1 January to 31 October 2015. Obstetric care was excluded. As for study III, the study sample in study IV was a sub-cohort of an already existing cohort of ED visits with pre-collected data. The time-period based on DNACPR orders in study III established the timeframe for study IV and the corresponding sample size of adult ED admissions was assessed as sufficient to answer the study questions.

4.4 STATISTICAL METHODS AND DATA ANALYSES

4.4.1 Statistical methods for all studies

Normally distributed continuous variables were described by mean and standard deviation and were compared by univariable linear regression with bootstrap sampling, see section 2.6.2. Bootstrap sampling is a sampling method that can be used to estimate standard errors. This produces the corresponding results as the independent t test. Non-normally distributed (skewed) data were described by median, interquartile range and were compared by the Mann-Whitney or with corresponding results by univariable quantile regression with bootstrap. Categorical variables were presented as numbers and percentages, binary variables were compared using the chi-squared test, unless the number in any cell was ≤5 in which case Fisher's exact test was used, and nominal/ordinal variables compared using the Wald test or with corresponding results by univariable logistic regression. Significance tests were two-sided with a significance level of 0.05.

4.4.2 Study I

External validation was performed using the multivariable logistic regression model from the original GO-FAR study.[60]

4.4.2.1 Outcome in the GO-FAR score

The outcome in the GO-FAR score defined as CPC 1 at discharge[60] was obtained through SCRR. Due to missing data on outcome from the SRCR in 25 patients, discharge status was assigned after manual review of the electronic patient records by the research team (EP and TD), blinded to information about the predictors.

4.4.2.2 Predictors in the GO-FAR score

Predictor variables in the GO-FAR score (table 5) were obtained through manual review of electronic patient records, blinded to the outcome. The original definitions of the GO-FAR predictors remained unchanged with the following exceptions:

a) Neurologically intact at admission defined ac CPC 1 was replaced by the Glasgow Coma Scale (GCS) 15 on admission to hospital in order not to introduce information bias. GCS 15 means that the patient's eyes open spontaneously (E4), he/she is oriented, converses normally (V5) and obeys commands (M6). CPC score on admission is a variable that is reported to SRCR, but only for patients alive at discharge from hospital. The CPC score is a variable that is not used in clinical practice in Sweden, and is not noted in the electronic patient records, whereas GCS is a variable used and recorded in all electronic patient records as part of the initial assessment by physicians and/or nurses.

b). For renal insufficiency the time span was expanded from 24 h to 48 h prior to the cardiac arrest event to avoid missing data.

c) Since aspartate aminotransferase and bilirubin are not included in routine laboratory assessment in the Stockholm region, but analysed only on clinical suspicion of hepatic insufficiency, the predictor was treated as follows: if no laboratory testing for hepatic insufficiency was performed and there was no reason to suspect hepatic insufficiency according to notes in the electronic patient record, the condition was regarded absent.

d) The definition of sepsis according to the international definitions 2001[141] was added to the GO-FAR definition of sepsis in order to make the predictor clinically feasible. In this definition sepsis is a clinical syndrome defined by the presence of infection and systemic inflammatory response. The presence of sepsis was based on the treating physician's assessment of sepsis as documented in the electronic patient records.

4.4.2.3 External validation

GO-FAR model performance was assessed by quantifying discrimination with AUROC and calibration through the calibration plot. The classification accuracy was assessed through risk group categorisation according to the original study into very low (< 1%), low (1-3%), average (> 3-15%) and above average (> 15%).[60] Analyses included complete case data and multiple imputation analyses.

4.4.2.4 Simple prediction model update measures

To account for the difference in outcome frequency and overfitting, logistic recalibration was performed fixing the intercept to 0 and the calibration slope to 1.

4.4.2.5 Missing data

Missing data was assumed to be missing at random and handled through multiple imputation with the generation of 20 imputed data sets.[142-144] The imputed data sets were generated through multivariable logistic regression for binary variables or multinomial regression for nominal variables including clinical variables and outcome.

4.4.2.6 Other main variables

Information on patient and cardiac arrest characteristics was obtained from SRCR.

4.4.3 Study II

Update of the GO-FAR score based on the results in study I to create a new model for favourable neurological survival was performed in study II.

The updated model was created with multivariable logistic regression and a priori defined predictors.

4.4.3.1 Outcome in the prediction model update

Outcome in the updated prediction model was favourable neurological survival, defined as CPC 1-2 at discharge. The change was justified based on the definition of a favourable

outcome as CPC 1 and 2 in the Utstein template.[1,2] The outcome was retrieved through SRCR.

4.4.3.2 Predictors in the prediction model update

The updated model included nine predictors set a priori based on the results in study I.

The selection process for predictors in the model update included the review of prevalence and feasibility of predictors in study I. Accordance to more recent knowledge on pre-arrest predictors for IHCA, the predictor chronic comorbidity was added.[62,64-66] It was retrieved from linkage with the NPR from 2005 until the date of the cardiac arrest event, and added as a continuous variable assessed as the validated and updated CCI (Appendix 1).[68,69] As a result of adding CCI metastatic or hematologic cancer and hepatic insufficiency were excluded and, renal insufficiency redefined to capture acute kidney injury. Based on the low prevalence and clinical feasibility, acute stroke, major trauma and admission from skilled nursing facility were excluded. To keep up with temporal changes sepsis was redefined,[145] the timeframes for hypotension and respiratory insufficiency were redefined to avoid missing data. Table 7 contains detailed information on the definition of the updated predictors and basis for redefinition or exclusion. Data for redefinition of predictors was obtained through manual review of electronic patient records, blinded to the outcome in the same way as in study I.

Table 7. Definition, reason for addition and exclusion of predictor variables in study II.

Predictor variable	Definition/reason for exclusion. Variable type
Definition unchanged	Admission with medical non-cardiac condition[a]. Binary variable
Medical non-cardiac admission	Evidence of multisystem injury or single-system injury associated with shock or altered mental status during the current hospitalisation
Pneumonia	Documented diagnosis of active pneumonia, in which antibiotic therapy has not yet been started or is still ongoing. Binary variable
Definition revised	
Neurologically intact at admission	GCS 15 according to the definition in study I. Binary variable
Hypotension	Evidence of hypotension extended from within 4 to within 12 hours of the event, defined as any of the following: SBP < 90 or MAP < 60 mmHg; vasopressor or inotropic requirement after volume expansion (except for dopamine ≤ 3µg/kg/min); or intra-aortic balloon pump. Binary variable
Respiratory insufficiency	Evidence of acute or chronic respiratory insufficiency extended from within 4 to within 12 hours of the event, defined as any of the following: PaO_2/FiO_2 ratio < 300, PaO_2 < 60 mmHg, or SaO_2 < 90% (without preexisting cyanotic heart disease); $PaCO_2$, $ETCO_2$, or $TcCO_2$ > 50 mmHg; spontaneous respiratory rate > 40/min or < 5/min; requirement for noninvasive ventilation; or requirement for ventilation via invasive airway. Binary variable
Acute kidney injury	Evidence of AKI is defined as an absolute increase in serum CR by ≥ 26.5 µmol/l within 48 hours or an increase in serum CR to ≥ 1.5-fold baseline within the previous 7 days. Baseline serum CR is defined as the median of CR values two years preceding the cardiac arrest (maximum 50 observations). Cases without history of chronic kidney failure and unknown baseline kidney function were assumed to have a baseline estimated glomerular filtration rate of 75 ml/min/1.73m2 according to CKD-EPI.[146] Binary variable

Table 7. Definition, reason for addition and exclusion of predictor variables in study II (continued).

Predictor variable	Definition/reason for exclusion. Variable type
Sepsis	Evidence of sepsis as a life-threatening organ dysfunction due to a dysregulated host response to infection defined as at least 2 out of 3 of the clinical criteria qSOFA[145]: respiratory rate ≥ 22/min, altered mentation (GCS < 15), or SBP ≤ 100 mmHg during the admission preceding the cardiac arrest. Binary variable
Age, y	Changed from categorical to continuous variable
Predictor addition	
Chronic comorbidity	According to CCI.[68,69] Continuous variable
Predictor exclusion	
Metastatic or hematologic cancer	Chronic condition already included in CCI
Acute stroke	Low prevalence in the cohort in study I (2.9%). Also contributing to the exclusion was that in clinical practice pre-arrest assessment of outcome in case of a cardiac arrest for this group of patients is multi-factorial and influenced by the clinical effect of the stroke in conjunction with patient factors that are not captured by a more general prediction model
Major trauma	Low prevalence in the cohort in study I (2.2%). Also contributing to the exclusion was that in clinical practice pre-arrest assessment of outcome in case of a cardiac arrest for trauma-patients is multi-factorial and influenced by the severity of the trauma in conjunction with other patient related factors that are not captured by a more general prediction model
Hepatic insufficiency	Chronic liver disease is included in CCI both as mild and moderate/severe liver disease. According to our knowledge the most important and prevalent acute liver disease states that influence mortality is based on an underlying chronic liver disease (acute liver failure without underlying liver disease is rare[147]), with for example decompensation of chronic liver disease, hepato-renal syndrome, acute-on-chronic liver failure. The definition of hepatic insufficiency in the GO-FAR score (evidence of hepatic insufficiency within 24 hours of the event, defined by total bilirubin > 34 µmol /l and (aspartate aminotransferase > 2 times the upper limit of normal or cirrhosis) is non-specific for these conditions and include other hepatocellular damage, for example gallstone, pancreatitis, bile-duct/hepatic malignancies. The prevalence of all underlying causes for hepatic insufficiency according to the GO-FAR definition was only 4% in the cohort in study I. In our opinion CCI will capture the underlying increased risk of poor outcomes with chronic liver disease and liver-associated malignancies. The predictor hepatic insufficiency was therefore excluded
Admission from skilled nursing facility	The prevalence of the predictor in the cohort in study I was only 6.1% as compared to 26% in the original GO-FAR cohort, see table 9. In Sweden home help services are well developed while living in skilled nursing facilities is less widespread. In 2012 9% of the population 65 years and older and 24% of 80 years and older in ordinary housing were granted home help services, 5% of the population 65 years and older and 14% of 80 years and older lived permanently in special forms of housing.[148] The extent of the help services granted could complement admission from skilled nursing facility, however there is no access to this information through the electronic patient record or any other registry. Thus, admission from nursing facility is not a clinically feasible predictor in our setting and was therefore excluded

[a]According to the Get With The Guidelines-Resuscitation registry.[133] Abbreviations: GCS, Glasgow coma scale; SBP, Systolic Blood Pressure; MAP, Mean Arterial Pressure; PaO_2, arterial Partial pressure of Oxygen; FiO_2, Fraction of Inspired Oxygen; SaO_2, arterial Oxygen Saturation; $PaCO_2$, arterial Partial pressure of Carbon dioxide; $ETCO_2$, End-Tidal Carbon dioxide pressure; $TcCO_2$, Transcutaneous Carbon dioxide pressure; AKI, Acute Kidney Injury; CR, Creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; qSOFA, quick Sequential (sepsis-related) Organ Failure Assessment; CCI , Charlson Comorbidity Index

Non-linearity between continuous predictors and outcome was assessed using natural cubic splines.

Interactions were explored based on clinical reasoning and the original study[60] for age x CCI, sepsis x hypotension, sepsis x respiratory insufficiency, hypotension x respiratory insufficiency.

4.4.3.3 Risk group categorisation in the mode update

Risk group categorisation in the updated model was based on the GO-FAR score with one change based on the intended clinical use of the model. In clinical practice the main aim is to identify patients with a low likelihood of favourable outcome where a DNACPR order may be indicated, rather than assign the patient's exact likelihood of favourable outcome. Therefore, the likelihood of favourable neurological survival was categorised into the following risk groups: very low (< 1%), low (1-3%), and above low (> 3%). The risk groups average (> 3-15%) and above average (> 15%), in the original study were combined into the risk group above low (> 3%) because risk assessment in clinical practice is based on the notion of futility,[83,84] and risk group categorisation above 3% would not aid in clinical guidance as how to relate to futility.

4.4.3.4 Internal validation

The risk of overfitting was quantified with 1000-bootstrap sampling and applied to the risk model. The recalibrated model's performance was validated in 1000-bootstrap sampling by quantifying discrimination with AUROC and calibration in the calibration plot. Classification was assessed by quantifying classification abilities.

4.4.3.5 Missing data

Model update was performed on complete case data only because missingness was estimated to be low after adjustments in the definitions.

4.4.3.6 Other main variables

Information on background demographics and cardiac arrest characteristics was obtained in the same way as in study I from SRCR.

4.4.4 Study III

Study III contained an analysis of adherence to legislation by quantitative analysis of checked boxes in Document 33, and the analysis of reasons why consultation with the patient was not possible, patient's and relatives' attitudes towards the DNACPR order, and the prognosis of medical condition as grounds for DNACPR orders with qualitative content analysis.

4.4.4.1 Quantitative analysis

Quantitative analysis of adherence to the legislation was based on the completed DNACPR forms (Document 33) and presented as numbers and percentages. Adherence to legislation was evaluated according to:

a) Consultation with the patient or relatives if consultation with the patient was not possible and documentation of their attitudes.

b) Consultation with other licenced caregivers.

c) Documentation of the grounds for the DNACPR order.

4.4.4.2 Qualitative content analysis

Inductive qualitative content analysis[149] with guidance from a medical perspective was performed to explore:

a) Reasons why consultation with the patient was not possible.

b) Patient's attitude towards the DNACPR order.

c) Relatives' attitudes towards the DNACPR order.

c) Prognosis of the medical condition as grounds for DNACPR orders.

Each part was analysed separately based on free text writing in the completed forms. A random selection of 20% for each part was made for content analysis. The free text in the forms in the electronic patient record was copied to an Excel spreadsheet. From this, meaning units were extracted and further condensed. The condensed meaning units were abstracted and labelled with codes. These codes were sorted into subcategories that were fused into broader categories based on similarities and shared content. The categories were sorted into themes if appropriate. Examples of condensed meaning units, codes, subcategories, and categories in exploring prognosis of the medical situation as grounds for DNACPR orders are presented in table 8.

The doctoral student (EP) and two of the authors (KR, EB) performed a preliminary analysis. The analyses performed by KR and EB were supervised by EP. For the sake of credibility, 10% of the meaning units was coded independently by another senior author (TD) and any discrepancies were discussed until consensus was reached. The preliminary analysis was then discussed and revised with the principal investigator (EP, TD, KG) until consensus was reached. Interpretation of the results was discussed with the whole research team.

Table 8. Examples of the content analysis of free text for prognosis of the medical condition as grounds for DNACPR orders.

Condensed meaning unit	Code	Subcategory	Category
Severe COPD. [Form no. 2524]	Chronic comorbidity severe state[a]	Chronic comorbidity severe state	Chronic comorbidity severe state +–acute condition
Progressive pulmonary fibrosis, pulmonary embolism with pulmonary hypertension, unclear infection without treatment response. [Form no. 1811]	Chronic comorbidity severe state Acute condition	Chronic comorbidity severe state with acute condition	Chronic comorbidity severe state +–acute condition
Diabetes Mellitus, dialysis, status post myocardial infarction, non-operable abdominal aortic aneurysm. [Form no. 3778]	Multimorbidity[b]	Multimorbidity	Multimorbidity +–acute condition
95-years, multimorbidity, severe aortic stenosis. [Form no. 2743]	Age Multimorbidity Chronic comorbidity severe state	Age Multimorbidity Chronic comorbidity severe state	Frailty+–acute condition Multimorbidity +–acute condition Chronic comorbidity severe state +–acute condition

Abbreviations: DNACPR, Do-Not-Attempt-Cardiopulmonary-Resuscitation; COPD Chronic Obstructive Pulmonary Disease, authors' comment. [a]A comorbidity that was termed severe/grave/serious/ pronounced/progressive in the condensed meaning unit. [b]Defined as the coexistence of two or more chronic conditions or the word 'multimorbidity' used in the condensed meaning unit.[150] Due to the definition of multimorbidity the category Multimorbidity+–acute condition was not exclusive, and could comprise the category Chronic comorbidity severe state+–acute condition and/or Malignancy+–acute condition

4.4.4.3 Other main variables and analyses

Information on patient and hospital characteristics was obtained from the hospital's central data warehouse and linkage with NPR from 1997 until date of admission. Comorbidities were reported as single comorbidities and according to CCI, see Appendix 1.[68,69] The physician responsible for the DNACPR order was extracted from the completed Document 33 obtained from the central data warehouse. Qualitative content analysis was performed about which relatives, and which other licenced caregiver had been consulted.

4.4.5 Study IV

4.4.5.1 DNACPR orders

Frequency of DNACPR order placement was based on the first DNACPR order issued during the hospital stay. Univariable analyses were performed for associations between patient and hospital characteristics and DNACPR order placement.

4.4.5.2 Hospital mortality

For patients with DNACPR orders, univariable analyses were performed for associations between patient and hospital characteristics and hospital mortality. For patients with DNACPR orders, time variables were based on the first DNACPR order that was placed after arrival to the ED.

4.4.5.3 Assessment of changes in Cardiopulmonary Resuscitation status

Changes in CPR status during hospitalisation were analysed based on admissions with at least one form regarding CPR status. Changes in CPR status upon subsequent admissions were analysed based on cases with known CPR status in the previous hospitalisation during the study period. The CPR status upon subsequent admission (first DNACPR order, initiate CPR, or no form) was compared to the last CPR status on previous hospitalisation.

4.4.5.4 Other main variables

Information on patient and hospital characteristics was obtained from the hospital's central data warehouse and linkage with NPR from 1997 until date of admission. Comorbidities were reported as single comorbidities and according to CCI, see Appendix 1.[68,69] The Rapid Emergency Triage and Treatment System (RETTS©)[151]was used because it was the only variable available representing the severity of acute illness in the pre-collected data set. The RETTS© is a Swedish triage scale, with widespread routine use in Swedish ED.[152] It is used by nurses in ED and weighs together vital signs, major complaints and comorbidities in a structured algorithm that results in a five-level triage scale, where level 1 represents patients in need of immediate medical attendance, levels 1 and 2 are classified as unstable, and levels 3–5 are classified as stable.

4.5 ETHICAL CONSIDERATIONS

All studies were approved by the Ethical Review Board in Stockholm, and later by the Swedish Ethical Review Authority and aspects of the Declaration of Helsinki were taken into consideration.[153] For all research the foreseeable benefits of conducting a study must outweigh the risks and burdens to the participants. Protection of the rights of the individual are contrasted against the potential benefit for future individuals who could benefit from the research.

All studies in this thesis were retrospective and observational without any interventions to the participating study subjects, and in that sense, the studies posed no risk of physical harm to the participants and did not require informed consent. However, sensitive information regarding personal health was handled in all studies and the risk of intrusion upon personal integrity for study participants must be taken into consideration.

For all studies in this thesis, data were described at group level and no individual could be identified.

For studies I-II the cohort of IHCA was retrieved through SRCR. Patients suffering IHCA are unable to give their approval to participate in SRCR beforehand, and research in the field of IHCA must include survivors as well as the deceased. To minimise the negative impact on participants in the SRCR, all IHCA survivors are informed of their participation in the registry, the purpose of the registry for quality monitoring and research, and that they can exit at any time. For the deceased in this retrospective observational cohort, although not informed of participation in the research, the risk of harm was considered low and the

potential benefit for future hospitalised patients involved in the decision process for DNACPR orders outweighs the burdens for the participants.

Study I-III involved the processing of data on personal health which could compromise personal integrity. Studies I-II, involved a manual review of electronic patient records as there was no other way to obtain the GO-FAR predictor variables. Survivors after IHCA have already given consent to participate in the SRCR, thereby accepting their role as participants in research. The risk of further violation of individual rights by review of electronic patient records was considered low. Study III involved the extraction of free text for content analysis, but no further review of the electronic patient record. Studies II-IV involved linkage with NPR, with the processing of personal identity numbers. To protect the integrity of the study participants precautions were taken. Members of the study team that handled review of electronic patient records and personal identity numbers were all accustomed to handling confidential information and to the laws of confidentiality. The deciphering key uniting study identification numbers to personal identification numbers was kept separate, all data was saved on secure servers. In all studies mortality for participating individuals who suffered IHCA or received DNACPR orders was high. Consequently, most participants were not alive by the time the data analysis was conducted and for those still alive, health status can be presumed to be weakened. The study questions in this thesis can be approached only by including patients who received DNACPR orders. The probability for the participating subjects to personally benefit from the results of the studies in this thesis was low, however, the overall risk of violation of individual rights in the studies was considered low, with a potential benefit for future patients being a part of the decision process for DNACPR orders. It was considered that the potential benefits of the research outweighed the potential risks.

In study IV, considering the observational nature of the study the risk of offending individuals' rights was considered low and the potential benefit for future patients outweighed the risks. Information sharing with study participants was not considered feasible due to the large number of patients included in the study.

In conclusion, the foreseeable benefits of conducting the studies in this thesis were considered to outweigh the risks and burdens to the participants.

In developing a prediction model for pre-arrest assessment of prognosis, it is important to bear in mind that the predictor variables will never fully reflect the overall health status of the patient. For example, ICD-10 codes do not reflect the severity of disease and age does not take into account the different biological effects of ageing in different individuals. The value of the prespecified outcome of the prediction model can only be decided by the individual patient. A prediction model can never replace full comprehension of all contributing factors that have to be taken into consideration in the assessment of risk versus burden in the decisions process for DNACPR orders.

As mentioned previously, the concept of trying to set a cut-off for futility can be questioned and needs further exploration. Prediction models will never be able to perfectly predict

outcome for the individual patient, but in evaluating the predictive performance of a pre-arrest prediction model for favourable outcome following IHCA, it is important that the model does not underestimate the outcome for patients with low probability of favourable neurological survival, where a DNACPR order may be an option. CPR can be a potentially lifesaving procedure, and the only thing we can know for sure it that upon cessation of circulation, without further intervention, the patient will die.

5 RESULTS AND METHODOLOGICAL DISCUSSIONS

5.1 STUDY I

The aim of study I was external validation of the pre-arrest prediction tool GO-FAR score.

5.1.1 Study population

A total of 717 adult patients with index IHCA in five out of six hospitals in the Stockholm region were included. Mean age was 72 years, 30-day survival was 28% and neurologically intact survival at discharge (CPC 1) was 22%. Baseline demographics for the original cohort, complete case and missing data are presented in table 9.

5.1.2 Predictors

Data were complete in 523 cases (73%). Predictors for the original cohort, complete case and missing data are presented in table 9.

Table 9. Demographics and GO-FAR predictors for original cohort, complete case and missing data in study I.

	Original cohort Total number n=51,240	Complete case Total number n=523	Missing data Total number n=194
Survival CPC 1, No. (%)	5,329 (10)	141 (27)	19 (10)
Demographics			
Age, mean (SD) y	65 (16)	71 (14)	74 (14)
Male sex, No. (%)	29,854 (58)	324 (62)	120 (62)
Black race	11,196 (22)		
Cardiac arrest characteristics			
Initial rhythm, No. (%)			
VF and pulseless VT	9,660 (19)	105 (24)	22 (15)
PEA	22,964 (44)	139 (32)	35 (25)
Asystole	16,820 (32)	187 (43)	86 (60)
Missing	2,719 (5)	92 (18)	51 (26)
Hospital location, No. (%)			
Coronary care unit	5,442 (10)	75 (14)	9 (5)
Catheterisation lab	1,099 (2)	46 (9)	2 (1)
Intensive care unit	19,609 (38)	65 (12)	3 (2)
Operating theatre	1,015 (2)	18 (3)	1 (1)
Emergency department	5,520 (11)	43 (8)	8 (4)
General ward	16,700 (32)	241 (46)	163 (84)
Outpatient clinic, radiology, laboratory	1,254 (2)	24 (5)	6 (3)
Other	1,524 (3)	11 (2)	2 (1)
GO-FAR variable, No. (%)			
Neurologically intact or minimal deficits at admission	21,018 (41)[a]	421 (81)[b]	151 (78)[b]
Major trauma	1,791 (4)	13 (3)	3 (2)
Acute stroke	1,601 (4)	16 (3)	5 (3)
Metastatic or hematologic cancer	5,305 (13)	46 (9)	20 (10)
Septicemia	7,082 (17)	91 (17)	35 (18)
Medical non-cardiac diagnosis	23,222 (45)	212 (41)	107 (55)
Hepatic insufficiency	3,101 (7)	21 (4)	8 (4)
Admission from skilled nursing facility	13,043 (26)	30 (6)	14 (7)
Pneumonia	5,708 (14)	69 (13)	31 (16)
Hypotension/hypoperfusion	11,241 (27)	135 (26)	9 (5)
Missing			154
Renal insufficiency/dialysis	14,311 (28)	125 (24)	31 (16)
Missing			34
Respiratory insufficiency	17,247 (41)	262 (50)	35 (18)
Missing			149

Abbreviations: GO-FAR, Good Outcome Following Attempted Resuscitation; CPC, Cerebral Performance Category; SD, Standard Deviation; VF, Ventricular Fibrillation; VT, Ventricular Tachycardia; PEA, Pulseless Electrical Activity. [a]CPC 1. [b]Glasgow Coma Scale 15

5.1.3 Model performance

In the complete case analysis AUROC was 0.82 (95% CI 0.78-0.86) indicating satisfactory discrimination. Assessment of the calibration plot showed non-matching observed and predicted probabilities (figure 3). This miscalibration was systematic, underestimating the probability of neurologically intact survival although predictions in the low range (close to 1 in the calibration plot) were more precise. The interpretation is that the GO-FAR score systematically underestimates the probability of favourable outcome.

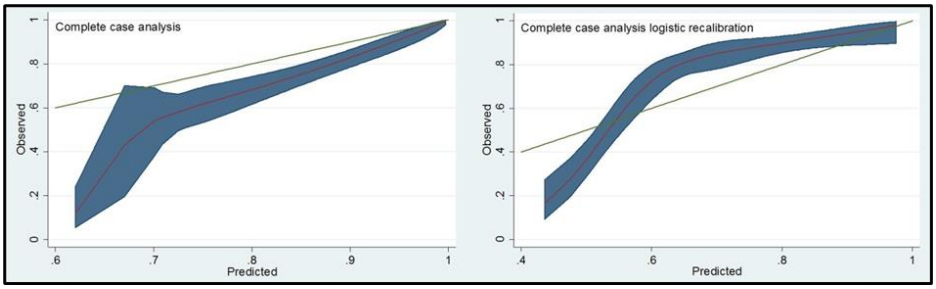

Figure 3. Calibration plots for the GO-FAR score for the validation cohort in study I, complete case with and without logistic recalibration. Abbreviations: GO-FAR score, Good Outcome Following Attempted Resuscitation score.

Classification into risk groups showed that neurologically intact survival was higher in all risk groups as compared to the original publication, indicating an underestimation of neurologically intact survival (table 10).

Table 10. Risk group classification for the GO-FAR score in the validation cohort in study I.

	Risk group[a]			
	Very low (< 1%)	Low (1–3%)	Average (> 3 to 15%)	Above average (> 15%)
	Survival CPC 1 No. (%) [95% CI] Patients in risk group %	Survival CPC 1 No. (%) [95% CI] Patients in risk group %	Survival CPC 1 No. (%) [95% CI] Patients in risk group %	Survival CPC 1 No. (%) [95% CI] Patients in risk group %
Original cohort	37/4,799 (1)	194/9,725 (2)	2531/27,464 (9)	2,568/9,523 (28)
	-	-	-	-
	9	19	54	18
Complete case	1/38 (3)	3/61 (5)	40/258 (16)	97/166 (58)
analysis	[0-14]	[1-14]	[11-21]	[51-66]
	7	12	49	32
Imputation	(3)	(5)	(16)	(58)
analysis	[0-16]	[2-14]	[12-20]	[51-66]
	-	-	-	-

Abbreviations: GO-FAR score, Good Outcome Following Attempted Resuscitation score. CPC, Cerebral Performance Category; CI, Confidence Intervall; [a]GO-FAR points (pts) for risk groups according to likelihood of survival with CPC 1: very low ≥24 pts; low 14 to 23 pts, average -5 to 13 pts, above average -15 to -6 pts

5.1.4 Missing data

In total data for predictors was missing in 27% of cases, and occurred in the variables: hypotension (22%), respiratory insufficiency (21%) and renal insufficiency (5%) and was predominantly due to the timeframes in the definitions. Missing data was imputed in regression analyses with CPC 1 at discharge, GCS 15 at admission, metastatic or hematologic cancer, septicemia, medical non-cardiac diagnosis, admission from skilled nursing facility, pneumonia, age, male sex, hospital ward general ward, coronary care unit, catheterisation laboratory and operating theatre as independent variables. AUROC in imputation analysis

was 0.80 (95% CI 0.76-0.84). Assessment of calibration and classification showed similar results as for complete case analysis, see table 10 and presented in the supplements of the full article efigure 3-4.

5.1.5 Simple prediction model update

Logistic recalibration fixing the intercept to 0 and the calibration slope to 1 with logistic recalibration still resulted in miscalibration, see figure 3.

5.1.6 Methodological discussion

The main finding of this study was that the GO-FAR score had satisfactory discriminatory abilities, but for calibration and classification abilities neurologically intact survival was systematically underestimated. This was not accounted for with simple updating methods.

The main strength of this study was that the validation cohort sample included IHCA from five out of six hospitals in the Stockholm region. The excluded Norrtälje hospital contributed with only 3% of all IHCA in the region in SRCR. Although regions in Sweden may differ in case-mix, the validation cohort matched published data from SRCR in the Swedish population 2014[154] and can be considered generalisable to other regions in Sweden. Other strengths were predefined objective definitions of the GO-FAR variables and complete data on the outcome.

The main limitation of this study was the sample size. There is limited guidance on sample size requirements for validation studies but there is a suggestion of 100 outcome events and 100 non-events.[129] Sample size in study I was based on the inclusion of the most recent IHCA data, with enough outcomes in relation to feasibility of predictor variable extraction. The simple size proved to be limited for risk group classification into very low and low probability of neurologically intact survival and in interpretation this should be taken into consideration. Other limitations were the need for adjustments in predictor definitions and missing data on predictor variables. Although handled through multiple imputation, missing bias can arise because data are often not missing completely at random. Further, although manual review for predictor variables was blinded to the outcome, in the review process it was sometimes inevitable not to obtain information about death immediately following CPR.

5.2 STUDY II

The aim of study II was a model update of the GO-FAR score with the development of a pre-arrest prediction model for favourable neurological survival in the Swedish setting.

5.2.1 Study population

The cohort for the prediction model update was the same cohort as in study I. It consisted of 717 adult patients with index IHCA in five out of six hospitals in the Stockholm region. Mean age was 72 years, 30-day survival was 28% and favourable neurological survival at discharge (CPC 1-2) was 25%. Data was complete in 628 cases (88%). Favourable

neurological survival at discharge was 28% (n=174) for complete cases. Baseline demographics and predictors for complete case and missing data is presented in the full article table 2.

5.2.2 Predictors

The distribution of age proved to be non-linear and was modelled with natural cubic splines. We found one significant interaction between hypotension and respiratory insufficiency. After considering multiple comparisons we assumed that the significance was a type 1 error, and that inclusion would not add to the predictive ability of the model.

Hence, multivariable logistic regression containing the nine prespecified predictors was performed on complete case data to create a full model, presented in table 11.

5.2.3 Internal validation

The full model had an AUROC of 0.808 (95% CI 0.769-0.848).

Quantification of overfitting was limited, see etable 5 the full article. Recalibration based on the overfitting created a new model that was called the Prediction of outcome for In-Hospital Cardiac Arrest (PIHCA) score, presented in table 11. To simplify validation, an online calculator is available at http://www.imm.ki.se/biostatistics/calculators/pihca/.

Table 11. Predictors included in the multivariable model update.

Predictors	OR Full model (95% CI)	β Coefficient Full model (95% CI)	Recalibrated score points PIHCA score
Neurologically intact at admission	1.61 (0.88-2.95)	0.48 (-0.13 to 1.08)	0.42
Sepsis	0.56 (0.22-1.45)	-0.57 (-1.52 to 0.37)	-0.50
Pneumonia	0.52 (0.23-1.16)	-0.65 (-1.45 to 0.15)	-0.57
Hypotension	0.45 (0.25-0.81)	-0.80 (-1.38 to -0.21)	-0.69
Respiratory insufficiency	0.44 (0.28-0.68)	-0.83 (-1.27 to -0.39)	-0.72
Medical non-cardiac admission	0.41 (0.25-0.66)	-0.90 (-1.39 to -0.41)	-0.78
Acute Kidney Injury	0.37 (0.23-0.62)	-0.98 (-1.49 to -0.48)	-0.85
CCI	0.88 (0.80-0.97)	-0.12 (-0.22 to -0.03)	-0.11
Age spline 1[a]	1.01 (0.95-1.07)	0.01 (-0.05 to 0.07)	0.01
Age spline 2[a]	0.94 (0.89-1.00)	-0.06 (-0.12 to 0.00)	-0.05
Constant		0.97 (-1.68 to 3.62)	0.74
AUROC (95% CI)		0.808 (0.769 to 0.848)	0.808 (0.807 to 0.810)

Abbreviations: OR, Odds Ratio; CI, Confidence Intervall; PIHCA score, the Prediction of outcome for In-Hospital Cardiac Arrest score; CCI, Charlson Comorbidity Index; AUROC, Area Under the Receiver Operating Characteristics curve. [a]Natural Cubic splines were used with one internal knot placed at 55 years and two knots placed outside the observed age range

AUROC for the PIHCA score was 0.808 (95% CI 0.807–0.810). The calibration as shown in figure 4 was satisfactory.

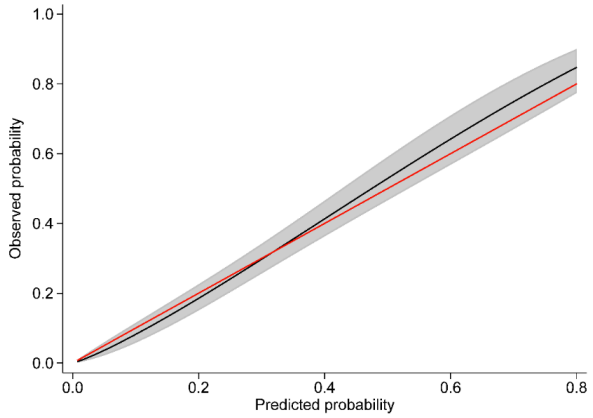

Figure 4. Calibration plot for the PIHCA score. The dotted line indicates the ideal calibration plot, with perfect match between predictions and observed outcomes. Abbreviations: PIHCA score, the Prediction of outcome for In-Hospital Cardiac Arrest score.

Risk group categorisation into very low likelihood of favourable neurological survival could not be performed with the cohort size of this study, instead the likelihood of favourable neurological survival was categorised into ≤ 3% and > 3%. Classification abilities are shown in table 12.

Table 12. Model performance of the PIHCA score with risk-group categorisation into very low/low (≤ 3%) and above low (> 3%) probability of favourable neurological survival.

	True		
Classified into risk groups	Favourable neurological survival[a]	Poor outcome[b]	Total
Above low (> 3%) "positive"	173	416	589
Very low/low (≤ 3%) "negative"	1	38	39
Total	174	454	628
Sensitivity 173/174=99.43%			
Specificity 38/454=8.37%			
Positive predictive value 173/589=29.37%			
Negative predictive value 38/39=97.44%			
False positive rate for true poor outcome 416/454=91.63%			
False negative rate for true favourable neurological survival 1/174=0.57%			
False positive rate for classified positive 416/589=70.63%			
False negative rate for classified negative 1/39=2.56%			

Abbreviations: PIHCA score, the Prediction of outcome for In-Hospital Cardiac Arrest score. [a]Survival with Cerebral Performance Category (CPC) score 1-2. [b]Deceased or survival with CPC > 2

Sensitivity, that is the probability of true favourable neurological survival to be classified into >3% likelihood of favourable neurological survival, was 99.4%. Specificity, that is the probability of true poor outcome to be classified into ≤3% likelihood of favourable neurological survival, was 8.4%. The positive predictive value of classification into >3% likelihood of favourable neurological survival was 29.4%, whereas the negative predictive

value of classification into ≤3% likelihood of favourable neurological survival was 97.4%. False classification into ≤3% likelihood of favourable neurological survival was 0.6%.

5.2.4 Missing data

In total data for predictors was missing in 12% of cases and occurred in the variables: hypotension (7%), respiratory insufficiency (7%), and acute kidney injury (5%). This proportion of missingness was considered acceptable and the initial intention not to impute missing variables was pursued.

5.2.5 Methodological discussion

The result of this study was a pre-arrest prediction model for favourable neurological survival after IHCA for the Swedish setting, the PIHCA score. The aim of the prediction model was to identify patients with a low likelihood of favourable neurological outcome. The PIHCA score showed good discrimination and satisfactory calibration. The sensitivity was high, but specificity low for classification into risk groups with a cut-off of a 3% likelihood of favourable neurological survival.

The main strength of this study was that candidate predictors were set a priori, limiting the risk of overfitting and underfitting (omitting important predictors). Further, the outcome was changed to CPC 1-2, taking into consideration outcomes that include independency in life and adherence to recommendations in the Utstein template.[1,2]

The main limitation of this study was the sample size. There is a rule of thumb for sample size in prediction model development suggesting at least 10 outcome events per predictor variable.[129] The cohort for study II was based on pre-collected data on predictor variables in study I, and the size was adequate for this recommendation. However there proved to be an insufficient number of outcomes for assessment of risk group categorisation into ≤ 1% likelihood of favourable neurological survival. The cut-off of 3% for risk group categorisation, based on medical futility, resulted in a specificity of only 8.4%, indicating that the PIHCA score has limited ability to classify patients into ≤3% likelihood of favourable neurological survival. Other limitations include ICD-10 codes not reflecting on the severity of chronic disease. The proportion of missingness was considered not to introduce large biases. Further, some predictors were not significantly associated with the outcome, see table 11. As overfitting was limited, these predictors were kept in the model.

5.3 STUDY III

5.3.1 Study population

During the study period the ED at Karolinska University Hospital admitted 2,795 patients with at least one DNACPR to the hospital. Since patients could receive multiple forms, a total of 3,861 DNACPR orders were issued during the study period. After the exclusion of 278 forms where DNACPR status was incomplete, 3,583 DNACPR orders was included in the cohort. Baseline characteristics for these patients are presented in table 13.

In 73% a consultant was responsible for the DNACPR orders, in 23% a licenced physician and for the rest there was no documentation regarding the responsible physician.

5.3.2 Consultation with the patient

In 40% of cases (n=1,432), consultation with the patient was not possible. Among these, the reason was stated in 82%, a relative was consulted in 46%, and the attitude of the patient or relatives was documented in 30%. For cases where consultation was possible (n= 2,151), the patient was consulted in 28% and their attitude documented in 15%.

5.3.3 Reasons why consultation with the patient was not possible

Content analysis of 237 forms to determine reason why consultation with the patient was not possible is described in detail in figure 1 in the full article. The analysis yielded two themes: the dominating theme "Patient deemed unable to comprehend information due to medical reason", and "Communication", with two categories each. The main reason why consultation with the patient was not possible was that the patient was cognitively impaired due to an acute or chronic medical condition impairing cognition: *"Lowered consciousness"* [Form no. 657] and *"Too tired"* [Form no. 2,212].

Language barriers, inappropriate setting for the discussion, or the patient wishes were other reasons: *"Not appropriate to do this at the emergency department in a stressful situation"* [Form no. 1,161] and "Language barrier" [Form no. 2,807].

5.3.4 Patient's attitude

The patient's attitude towards the DNACPR order was stated in free text in 387 forms and content analysis of 78 forms is described in detail in figure 2 in the full article. The result of the analysis was two themes: the dominating "Patient's preference" and "Patient's attitude unknown", comprising three and two categories respectively.

The dominating categories in the theme "Patient's preference" was the patient's own wish to refrain from resuscitation: *"Does not want cardiac resuscitation in case of a cardiac arrest."* [Form no. 989] and *"The patient does absolutely not want care in a ventilator or other 'heroic efforts' at a cardiac arrest or deterioration…"* [Form no. 1,719].

Some patients expressed a wish for a natural death: *"The patient does not wish for intensive care or any painful interventions. On acute deterioration, he wants nature to have its own way."* [Form no. 3,970] or *"The patient brings up the question herself and says that she does not want the treatment as she has lived for a long time and there is a time for dying..."* [Form no. 30].

A more accepting attitude towards the DNACPR order was also found: *"The patient does not have own wish to refrain from life-sustaining treatment, but understands and accepts the decision that is based on medical grounds."* [Form no. 3,526]. The patient disagreed with the medical assessment in only one form.

5.3.5 Consultation with relatives

Of the 3,583 forms, consultation with relatives took place in 26% of cases, and relatives' attitude was documented in 15% of the cases.

Content analysis of 108 documents resulted in five categories and showed that the most commonly the relatives agreed with the medical assessment behind the DNACPR order: *"Discussed with the son by telephone, the son agrees with the limitation of life-sustaining treatment."* [Form no. 1,050].

The most common relatives to consult with were children and spouses.

Content analysis for relatives' attitudes towards DNACPR orders and what relatives were consulted is presented in the supplements of the full article etable 2 and etable 3.

5.3.6 Consultation with other licenced caregivers

Of the 3,583 forms, a licenced caregivers were consulted in 36% of cases. In 43% of the forms there was no documentation that the patient, or relatives, or another licenced caregiver were consulted. Content analysis of 253 documents showed most consultations were with a physician followed by a nurse and is presented in the supplements of the full article etable 4.

5.3.7 Grounds for DNACPR orders

In 87% of the decisions, prognosis of the medical condition was part of the ground for issuing the DNACPR order. The patient's own wish to refrain from resuscitation was part of the grounds in 7%, and was the sole ground for the DNAR order in 1%. In 89% of cases the grounds for the DNACPR order was documented.

5.3.7.1 Prognosis of the medical condition as grounds for the decision

Content analysis of free text for prognosis of the medical condition as grounds for the decision of 466 forms resulted in seven categories as presented in figure 5.

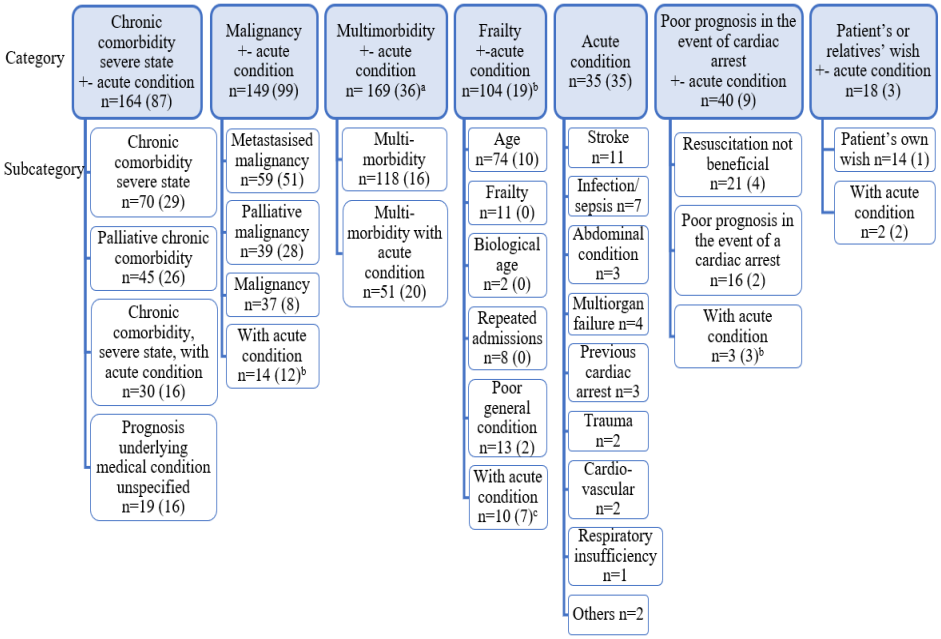

Figure 5. Prognosis of the medical condition as grounds for the DNACPR order. Brackets denote numbers that were exclusive. [a]Multimorbidity was defined as the coexistence of two, or more chronic conditions or the word 'multimorbidity' used in the text. Due to the definition of multimorbidity the category Multimorbidity+–acute condition was not exclusive and could comprise the category Chronic comorbidity severe state+–acute condition and/or Malignancy+–acute condition. [b]Subcategories in Frailty+–acute condition were not exclusive. [c]In combination with any of the above. In one-third of the forms, grounds for issuing the DNACPR order were a combination of two or more categories.

The most common grounds for the DNACPR orders were "Chronic comorbidity in a severe state", "Malignancy" or "Multimorbidity" with or without the presence of an acute condition. "Chronic comorbidity in a severe state" and "Malignancy with or without the presence of an acute condition" dominated as exclusive categories. This could be expressed as: *"Advanced MS (Multiple Sclerosis, authors' comment)."* [Form no. 3,915]; *"Severe Alzheimer's dementia, peripheral myopathy. Fracture of the left distal femur."* [Form no. 1,039] and *"Gastric cancer, acute renal failure, STEMI (ST-Elevation Myocardial Infarction, authors' comment)"* [Form no. 869].

"Multimorbidity" and "Frailty with or without the presence of an acute condition" were common in combination with another category: *"Woman with multimorbidity admitted with severe electrolyte disturbance. Poor general condition lately. Optimised medical treatment, despite this no improvement in five days. Currently the patient's prognosis is pessimistic and CPR is considered ruthless."* [Form no. 3,083] and *"Multimorbidity in combination with high*

age, therefore the patient is assessed not to gain from resuscitation in case of a cardiac arrest." [Form no. 833].

Age was the most predominant subcategory to frailty, although not frequently the sole ground for the decision.

Acute condition not combined with another category occurred quite frequently as the sole ground for the DNACPR decision: *"Patient anuric for >24 hours with sepsis. Very poor prognosis"* [Form no. 3,937].

5.3.8 Adherence to the legislation as a whole

All requirements in the legislation regarding documentation of: a) consultation with patient or relatives if consultation with the patient was not possible and documentation of their attitudes, b) consultation with other licenced caregivers and c) the grounds for the DNACPR order were fulfilled in 375 forms (10%). see figure 6.

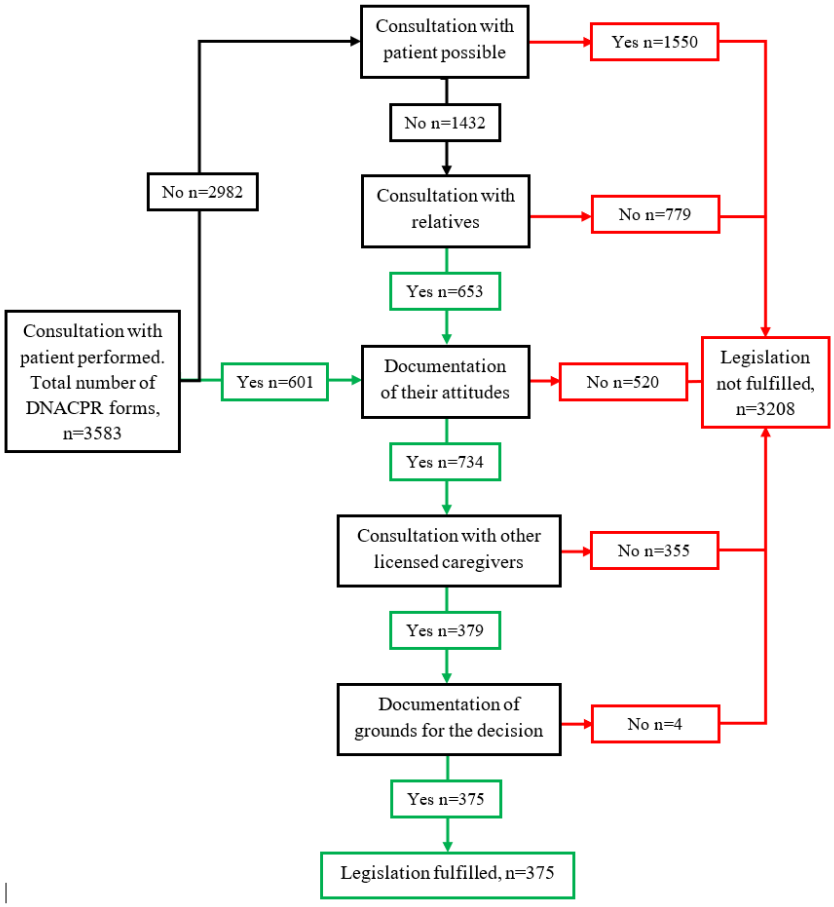

Figure 6. Adherence to the legislation regarding DNACPR orders.

In stratified analysis this was not explained by lower fulfillment of the legislation in subsequent forms as compared to the first form during the admission (107/811; 13.2% and 249/2,626; 9.5% respectively, p-value < 0.01. 146 missing due to inconclusive status in the first form).

5.3.9 Methodological discussion

The result of this study was that there were shortcomings in adherence to legislative requirements for documentation of DNACPR orders in Karolinska University Hospital. The decision for a DNACPR order was mostly based on chronic, severe comorbidity or multimorbidity both with and without acute illness. Further, shared decision-making that included the patient was often not possible based on impaired cognition, and DNACPR was often the dominating attitude of the patient.

The main strength of this study was that it assessed the actual documentation performed in connection to the DNACPR orders, and the attitudes of patients and relatives when the decision was made. Further, the size of the cohort and free texts analysed were large. By confirming the initial analysis with independent validation of the coding scheme and thorough discussions with the principal investigator aspects of trustworthiness with high credibility and accurate dependability were strived for.

The main limitation of this study was that although Document 33 is the form assigned for documentation of the decision process for DNACPR orders, it could have taken place in the electronic patient record outside of the form making adherence to legislation falsely low. Further, as the proportion of free text available for assessment of patients' and relatives' attitudes was low, there could be a selection bias in which free texts were documented. Generalisability is limited outside of Sweden since the use of DNACPR orders is influenced by cultural, religious and legal factors, as well as national, regional, and institutional policies.[49,80,95,155] Although the prognosis of a medical condition as grounds for DNACPR decisions can be assumed to be based on common values and preferences in Sweden, generalisation to other Swedish hospitals should be made with caution as inter-hospital variation in the use of DNACPR orders has been shown.[80,95,155] Although this has not been studied specifically for the Swedish setting, generalisation to other Swedish University hospitals could seem appropriate. Further, this cohort did not include elective admissions (approximately one-third of admissions) and consequently did not reflect upon the whole hospitalised population. However, the impact of elective admissions was considered limited, as they are less likely to receive DNACPR orders. It has previously been shown that 83% of all DNACPR directives were placed for patients admitted through the ED, thus capturing the majority of DNACPR orders.[80]

5.4 STUDY IV

5.4.1 Study population and incidence of DNACPR orders

During the study period, 25,646 patients were admitted through the ED at KUH, of which 11% (n=2,797) received a DNACPR order during the hospital stay.

A total of 4,000 forms were issued, of which 3,861 were DNACPR orders and 139 were forms with a directive to initiate CPR in case of cardiac arrest. In 19% of the DNACPR orders, the directive was only DNACPR, whereas the rest were associated with other forms of LLST. The most common associated LLST were invasive ventilation and intensive care, and 79% of the DNACPR orders were combined with either of these.

5.4.2 Patient and hospital characteristics associated with DNACPR orders

Patient and hospital characteristics associated with DNACPR orders are shown in table 13.

Patients with DNACPR orders were significantly older with an overall higher burden of chronic comorbidities as compared to those without. Further, a larger proportion of patients had unstable triage-scoring according to RETTS© and were admitted to wards with higher levels of care than patients without DNACPR orders. Hospital mortality for patients with DNACPR orders was 37%, 30-day mortality was 37% and one-year mortality was 77% compared to 1%, 1.8% and 12.9% respectively for patients without ($p < 0.01$ for all).

Table 13. Patient and hospital characteristics of patients according to DNACPR order placement for ED admissions in study IV.

	All ED admissions Total n=25,646	ED admissions with DNACPR orders n=2,797[a]	ED admissions without DNACPR orders n=22,849	p-value
Unique patients, No.	19,998	2,345	18,363	
Demographics				
Male sex, No. (%)	12,810 (50)	1,318 (47.1)	11,492 (50.3)	<0.01
Age,				
median [IQR]	66 [48;78]	79 [69;87]	64 [45;76]	<0.01
range	18,105	19,105	18,103	
Comorbidity, No. (%)				
Chronic Kidney Disease[b]	1,942 (7.6)	380 (13.6)	1,562 (6.8)	<0.01
Hypertension[c]	9,369 (36.5)	1,532 (54.8)	7,837 (34.3)	<0.01
COPD[d]	2,320 (9.1)	469 (16.8)	1,851 (8.1)	<0.01
Congestive heart failure[b]	3,591 (14)	833 (29.8)	2,758 (12.1)	<0.01
Diabetes[e]	4,084 (15.9)	588 (21)	3,498 (15.3)	<0.01
Dementia[b]	1,155 (4.5)	404 (14.4)	751 (3.3)	<0.01
Malignancy[f]	5,518 (21.5)	1,217 (43.5)	4,301 (18.8)	<0.01
Charlson Comorbidity Index				
median [IQR]	0 [0;2]	3 [2;6]	0 [0;2]	<0.01
range	0,18	0,14	0,18	
Triage priority on arrival to ED according to RETTS©				
1	4,346 (17)	902 (32.3)	3,444 (15.1)	Ref
2	7,137 (27.9)	785(28.1)	6,352 (27.8)	<0.01
Unstable 1-2	11,483 (44.9)	1,687 (60.4)	9,796 (43)	<0.01[g]
3	10,466 (40.9)	952 (34.0)	9,514 (41.6)	<0.01
4	3,087 (12.1)	148 (5.3)	2,939 (12.9)	<0.01
5	529 (2.1)	4 (0.1)	525 (2.3)	<0.01
Stable 3-5	14,082 (55.1)	1,104 (39.6)	12,978 (57)	
Missing	81 (0.3)	6 (0.2)	75 (0.3)	
Hospital admission characteristics				
Admission ward from ED				
General ward	15,055 (58.7)	1,383 (49.4)	13,672 (59.8)	Ref
High Dependency Unit	9,780 (38.1)	1,222 (43.7)	8,558 (37.5)	<0.01
Intensive Care Unit	811 (3.2)	192 (6.9)	619 (2.7)	<0.01
Hospital length of stay[h],				
median [IQR]	3 [1;8]	10 [4;20]	3 [1;7]	<0.01
range	0, 522	0,186	0, 522	
Mortality[i]				
Hospital mortality, No. (%)	1,252 (4.9)	1,032 (36.9)	220 (1)	<0.01
30-day mortality, No. (%)	1,454 (5.7)	1,046 (37.4)	408 (1.8)	<0.01
1-year mortality, No. (%)	5,090 (19.9)	2,150 (76.9)	3,940 (12.9)	<0.01

Abbreviations: DNACPR, Do-Not-Attempt-Cardiopulmonary-Resuscitation; ED, Emergency Department; IQR, Interquartile Rage; COPD, Chronic Obstructive Pulmonary Disease; RETTS©, Rapid Emergency Triage and Treatment System. [a]First DNACPR order during admission analysed. [b]According to the definition in Charlson Comorbidity Index.[68,69] [c]According to International Statistical Classification of Diseases (ICD-10) code I10.9. [d]According to ICD-10 code J44. [e]According to ICD-10 code E10-E14. [f]According to ICD-10 code C. [g]For comparison with categorisation into unstable and stable RETTS© triage level. [h]Defined as date of hospital discharge minus date of hospital admission. [i]From date of hospital admission

5.4.3 Patients with DNACPR orders and associations with hospital mortality

Table 14 displays associations between hospital mortality and patient and in-hospital characteristics for patients with DNACPR orders in study IV.

Table 14. Associations between hospital mortality and patient and in-hospital characteristics for patients with DNACPR orders in study IV.

	ED admissions with DNACPR orders[a] Total n=2,797		
	Hospital mortality n=1,032 (36.9%)	Discharged alive n=1,765 (63.1%)	p-value
Demographics			
Male sex, No. (%)	513 (49.7)	805 (45.6)	0.04
Age,			
median [IQR]	78 [69;86]	79 [70;88]	0.3
range	19,100	19,105	
Comorbidity, No. (%)			
Chronic Kidney Disease[b]	137 (13.3)	243 (13.8)	0.71
Hypertension[c]	553 (53.6)	979 (55.5)	0.34
COPD[d]	164 (15.9)	305 (17.3)	0.34
Congestive heart failure[b]	283 (27.4)	550 (31.2)	0.04
Diabetes[e]	224 (21.7)	364 (20.6)	0.5
Dementia[b]	116 (11.2)	288 (16.3)	<0.01
Malignancy[f]	475 (46.0)	742 (42)	0.04
Charlson Comorbidity Index			
median [IQR]	3 [2;6]	3 [2;6]	>0.99
range	0,14	0,14	
Triage priority on arrival ED according to RETTS©			<0.01[g]
1	402 (39.1)	500 (28.4)	
2	264 (25.7)	521 (29.6)	
Unstable 1-2	666 (64.7)	1,021 (58)	<0.01[h]
3	322 (31.3)	630 (35.8)	
4	40 (3.9)	108 (6.1)	
5	1 (0.10)	3 (0.2)	
Stable 3-5	363 (35.3)	741 (42)	
Missing	3 (0.3)	3 (0.2)	
Hospital admission characteristics			
Admission ward from ED			
General ward	486 (47.1)	897 (50.8)	Ref
High Dependency Unit	444 (43.0)	778 (44.1)	0.53
Intensive Care Unit	102 (9.9)	90 (5.1)	<0.01
Hospital length of stay until death/discharge, days[i]			
median [IQR]	10 [3;22]	10 [5;20]	>0.99
range	0,125	0,186	
Characteristics of DNACPR directive placement			
Time from arrival ED to first DNACPR directive, days			
median [IQR]	1 [0;4]	1 [0,3]	>0.99
range	0,66	0,94	
Time from first DNACPR directive to death/discharge, days			
median	6 [2;16]	8 [4;16]	<0.01
range	0,116	0,150	

Abbreviations: ED, Emergency Department; DNACPR. IQR, Interquartile Range; COPD, Chronic Obstructive Pulmonary Disease; RETTS©, Rapid Emergency Triage and Treatment System. [a]First order during admission analysed. [b]According to the definition in Charlson Comorbidity Index.[68,69] [c]According to International Statistical Classification of Diseases (ICD-10) code I10.9. [d]According to ICD-10 code J44. [e]According to ICD-10 code E10-E14. [f]According to ICD-10 code C. [g]global p-value RETTS triage level 1-5. [h]For comparison with categorisation into unstable and stable RETTS triage level. [i]Defined as date of hospital discharge minus date of hospital admission

Out of 2,797 ED admissions with DNACPR orders, 63% were discharged from hospital. When comparing these patients to those who died in hospital mortality, we found the two groups to be similar in terms of age, sex, and chronic comorbidities except for patients who had congestive heart failure and dementia which were more prevalent in those discharged, and malignancy which was less prevalent in those discharged. The proportion of unstable RETTS© triage scorings on arrival to ED was higher for patients who died in hospital than for those discharged. Time from the day of ED arrival to the first DNACPR order placement did not differ in the two groups. For patients who died in hospital, the median time until death was 10 days and the median time from the first DNACPR order until death was 6 days. Hospital length of stay for patients with DNACPR orders that were discharged a median of 10 days.

5.4.4 Changes in CPR status during hospitalisation

During the study period, 2,798 admissions received at least one form regarding CPR status (one admission had one decision to initiate CPR that was unchanged). In relation to the first form regarding CPR status, 5% (n=126) of admissions changed CPR status during hospitalisation. In 48% of these cases (n=61), the change was from a form with initiate CPR to DNACPR and in 21% (n=27) from DNACPR to initiate CPR. Changes back and forth occurred in 13% (n=16) of cases with changed CPR status (n=16), and the exact pattern was uncertain in 18% (n=22). This was because they were issued on the same date, and we did not have access to the exact time for documentation. Detailed information on changes in CPR status during hospitalisation is presented in the manuscript, table 3.

5.4.5 Changes in CPR status upon subsequent hospital admission

Out of the 25,646 admissions through the ED, we excluded 16,285 cases that were admitted only once, and 3,709 cases that were cases with unknown previous admissions outside of the study period. For the remaining 5,652 admissions, discharge CPR status in the previous hospitalisation was known. Detailed information on changes in CPR upon subsequent hospital admission is presented in the manuscript, table 4.

In 86% of cases (n=4864), CPR status was unchanged upon subsequent hospitalisation. Out of 577 cases discharged with DNACPR orders, a reversal of DNACPR status upon subsequent admission occurred in 32% (n=186) of the cases. In 98% (n=182) of these cases this was an effect of no form being issued during subsequent admission, and thus there was uncertainty whether this reversal was active or a consequence of a lack of consideration. For 67% (n=388) of those discharged with DNACPR orders, DNACPR status was unchanged upon subsequent admission, with an iteration of the DNACPR order. In nine cases it could not be determined whether CPR status was changed, due to lack of access to the exact time of documentation.

Out of 983 cases where a DNACPR order was issued upon subsequent admission, CPR status was changed from initiate CPR (n = 2) or no form in the previous hospitalisation (n = 591) to

DNACPR orders in 60% of the cases. For 91% of these cases, there was no previous documentation regarding CPR status in previous hospitalisations during the study period.

A sensitivity analysis of the 577 cases discharged with DNACPR status showed that upon subsequent admission they were admitted from the ED to a general ward in 48% of cases, HDU in 48%, and ICU in 5%.

5.4.6 Methodological discussion

The result of this study was that 11% of patients admitted though the ED received a DNACR order during the hospital stay. Patients with DNACPR orders were older, with more acute illness and chronic comorbidities than those without such directives. They were admitted to higher levels of care and had longer hospital lengths of stay compared to those without. Although most patients with DNACPR orders survived to discharge, one-year mortality was significant. Age and comorbidities for patients with DNACPR orders were similar regardless of hospital mortality. Patients with hospital mortality showed signs of more severe acute illness on arrival to the ED. The overall change of CPR status during hospitalisation and upon subsequent admission was low, but for patients discharged with DNACPR orders, reversal of DNACPR status was substantial upon subsequent admission (32%) with uncertainty whether this reversal was active or a consequence of a lack of consideration.

The main strength of this study was the large sample size and the mixed patient population of the cohort.

The main limitation of this study was the observational nature of the study that enabled the identification of associations but without the possibility to establish causality. However, it can constitute grounds for hypothesis generation to be tested in future studies. Further, for the same reasons as for study III, generalisability outside of Karolinska University Hospital is limited, see section 5.3.9. For changes in CPR decisions upon readmission, we do not know if patients were admitted to another institution or electively to Karolinska University Hospital with decisions regarding CPR status made in between admission through the ED. Administrative data and ICD-10 coding have biases, and do not consider the severity of illness. In this study there, was a misclassification bias with a risk of over estimation of CCI because data from the NPR did not fulfil the detailed classification of diseases that CCI requires. Details can be found in the supplements of the manuscript (eTable 1).

6 DISCUSSION

6.1 MAIN FINDINGS

The main finding in this thesis was that the GO-FAR score as a pre-arrest prediction tool for neurologically intact survival should be taken into clinical practice in settings such as Sweden only with caution without further model update. Carrying through such a model update the PIHCA score has the potential to be used as part of the decision-making process for DNACPR orders, to identify patients with a low likelihood of favourable neurological survival. There are shortcomings in the fulfilment of the legislative requirements for documentation of DNACPR orders, as well as in the admission procedures regarding identification of previous DNACPR orders on hospitalisation. Grounds for the DNACPR order placement in terms of the prognosis of the medical condition are diverse, based on severe chronic comorbidity, a combination of several comorbidities or other aspects of general health status with or without acute illness. The main reason why patients could not be consulted was cognitive impairment and patient preference was the dominating patient attitude towards DNACPR orders. One out of ten patients admitted through the ED at a Swedish University Hospital received a DNACPR order during their hospital stay. DNACPR order placement was not equivalent to hospital death, the assessment of benefit had a perspective beyond the current hospitalisation.

6.2 IS THERE A PLACE FOR PRE-ARREST PREDICTION MODELS IN THE DECISION PROCESS FOR DNACPR ORDERS?

It has been shown that prognostic information influences patient wishes regarding CPR,[156,157] and that it is difficult for medical personnel to accurately predict outcome after cardiac arrest.[18,19] A DNACPR decision should be made through shared decision-making, preceded by information sharing between clinician and patient or relatives.[5] In that information sharing, a prediction model could aid in the assessment of the likelihood of an unfavourable outcome which would therefore be of use. However, this would presume that all factors that influence decision-making were included in the prediction model. Findings from studies III and IV indicate that DNACPR orders are often based on a chronic disease in a severe state as well as other underlying factors such as frailty, representing vulnerability in underlying general health status. This is not captured in the PIHCA score and may be difficult to capture in any prediction model. Further, the clinical application of a pre-arrest prediction model for assessing outcome following cardiac arrest involves a definition of futility, however, the definition of futility is complex.[85,86] As a DNACPR order is based on the assessment of what lies in the best interest of the patient, what ever the likelihood of favourable survival is calculated by a prediction model, it must be related to the overall assessment of the patient and their values and goals of care. A prediction model for outcome after IHCA could serve as an aid in the assessment of benefit but cannot replace full comprehension of all contributing factors that have to be taken into consideration.

One of the drawbacks of prediction models for assessing outcome after IHCA is the difficulty in defining an outcome that can be seen as unfavourable to the patient. Attention has been made to focus more on patient-related outcomes that take into consideration the experiences of the survivors after IHCA.[158]

6.2.1 Why did the GO-FAR score not perform well in the validation setting?

In study I, the GO-FAR score showed satisfactory discriminatory abilities, but for calibration and classification abilities neurologically intact survival was systematically underestimated. This was not accounted for with simple updating methods.

There are several possible explanations for this result.

The outcome, neurologically intact survival at discharge was much lower in the original cohort (10% versus 22%). This could be a temporal effect as the original cohort was sampled in 2007-2009 and there is a trend for increased survival over time.[27-29] There is evidence to support a broader use of DNACPR orders in Sweden[7-10,34,50,52-54,56] which may result in a population with higher neurologically intact survival. Further, the use of DNACPR orders has been reported to increase over time.[80] Other factors that may affect the likelihood of neurologically intact survival in the two populations are possible but not known, such as differences in the severity of chronic comorbidities or differences in intra- and post resuscitation treatments. The predictor selection process based on statistical analyses in the development of the GO-FAR score may have led to overfitting.[129]

In addition, there are some substantial differences in the demographics of the original and validation cohort that could influence predictor-outcome associations. In the original cohort, patients were younger (mean age 65 versus 72 years), the prevalence of some chronic comorbidities (metastatic and hematologic cancer and hepatic insufficiency) and cardiac arrests in the ICU was higher. In the original cohort, the prevalence of shockable initial rhythm was lower (although this should be interpreted with caution due to 20% missing data in this variable in the validation cohort). This indicates differences in the underlying patient populations, treatment and monitoring practices including the use of DNACPR orders. The compound effect of these differences is difficult to fully comprehend.

Other differences could be related to the feasibility of the predictors. The definition of neurologically intact on admission was changed to reduce the risk of information bias and there was a marked difference in this variable between the two cohorts (40% versus 80%). Although evidence support a lower proportion of CPC 1-2 before the cardiac arrest events in the US (81-83%)[159,160] as compared to Sweden (95%)[3] the interpretation of the marked difference is that GCS 15 is not a feasible proxy for CPC 1. In addition, there was a marked difference in admission from a skilled nursing facility (26% in the original cohort versus 6% in the validation cohort), most likely due to different social structure systems for the elderly in the underlying populations. Sweden has well-developed home help services[148] which enables the elderly to live in their own home up to old age. Therefore, this predictor variable would seem not to have the same significance in the Swedish setting.

Simple update to account for overfitting and differences in the prevalence of outcome with an adjustment of the intercept and calibration slope did not fully account for the misprediction in calibration. The interpretation is that the underlying differences in the characteristics of the patients and conditions preceding the cardiac arrest, together with the differences in prevalence and feasibility of predictors, result in skewed weights when the GO-FAR score was validated in the Swedish setting.

Previous external validation of the GO-FAR score using a cohort of 287 IHCA from one hospital in Sweden between 2007 and 2009 showed good discrimination (AUROC 0.85) and classification abilities.[112] However calibration was not reported, and more extensive information on demographics was not available, making full comparison difficult. There was a less marked difference in neurologically intact survival at discharge between the original and validation cohort in the study by Ohlson et al.[112] (10% versus 16%), as compared to the difference between the original and validation cohort in study I (10% versus 22%). This could partly explain the satisfactory classification into risk groups in the study by Ohlsson et al. that was reduced as neurologically intact survival increased further over time.

6.2.2 Was there a need for an updated model?

The significance of the underestimation of neurologically intact survival by the GO-FAR score seen in study I was that it could potentially deprive a patient of lifesaving treatment with CPR. An option to the more extensive update performed in study II could have been to adjust the cut-off scores in the GO-FAR-score. Given the changes in predictor definitions required and the questionable clinical feasibility of some predictors, in combination with the intent to add the predictor chronic comorbidity, the choice was made to perform a model update and create a model for the Swedish setting. The notion that the GO-FAR score was underfitted with regards to the burden of chronic comorbidity was based on publications highlighting an independent association between CCI and outcome after IHCA.[62,64,65] In 2020 an updated GO-FAR score 2 was published, with a revision of predictor variables and outcome to include CPC 2 which is reasonable since many patients surviving with moderate disability likely finds it favourable.

6.2.3 How can the PIHCA score be used?

One concern that prevails in the development of all pre-arrest prediction models for outcome following IHCA is that the sample is based on patients selected for CPR, that is without a prespecified decision not to attempt CPR in the event of the cessation of circulation. This introduces a selection bias that affects predictor-outcome associations in the model, which has implications for clinical applicability when used in a non-selected population in the decision process for DNACPR orders. Ideally the prediction model would be based on performing CPR on a non-selected population, however it would not be ethical to perform CPR on all patients with cessation of circulation in hospital. One way to approach this limitation could be not to use the prediction model for patients where the burdens of CPR obviously outweigh the benefits.

The clinical difficulty is to identify patients with a low probability of favourable outcome after CPR, especially so in situations where it is not obvious. A prediction model could aid in this assessment. However, for patients with poor outcome (death or CPC >2) the PIHCA score had limited ability to classify patients correctly. This could be outweighed by the high negative predictive value (97%) and low false classification (0.6%) into this risk group. The clinical implication is that if the PIHCA score assigns a patient to the risk group indicating futility, there is a low probability of favourable neurological survival and a DNACPR order can be considered without disadvantage to the patient.

Part of the process of model development is the implementation into clinical practice. The work in this thesis does not include an elaboration as to how to implement the PIHCA score in daily practice. This will have to be investigated further in future research.

As with all prediction models, the transferability of the PIHCA score will depend on the similarity of the case-mix, restricted to settings similar to the Swedish development setting.

6.2.4 Can the PIHCA score be further improved?

Frailty has been shown to be a risk factor for adverse outcomes in critical illness,[70,71] and has emerged as an independent predictor of survival after IHCA.[63,74,75] Findings in study III confirm previous findings that frailty and the associated general health condition[115,117] is part of the grounds determining DNACPR orders in clinical practice. It could also have the potential of replacing the predictor neurologically intact at admission which was not significantly associated with favourable neurological survival in the regression model of the PIHCA score. This predictor was assessed with the Glasgow Coma Scale (GCS) in studies I and II and replaced the assessment of CPC in the original GO-FAR score. CPC is an assessment of functional status based on neurological function, and frailty could be a way of assessing functional status from another point of view. Therefore, it could be justified to include frailty in a future prediction model for outcome after IHCA.

6.3 WHAT PROPORTION OF PATIENTS RECEIVE A DNACPR ORDER?

Study IV showed that 11% of patients hospitalised through the ED at Karolinska University Hospital received a DNACPR order. As previously mentioned in the methodological discussion of study III in section 5.3.9, this should not be generalised outside of Sweden, or to all Swedish hospitals but could be reasoned to apply to other University hospitals, although this has not been further examined.

The frequency of use in study IV is in line with two previous studies of mixed patient populations admitted through an ED in the US, with 13% and 15% prevalence of DNACPR orders.[80,103] However, direct comparison is difficult because there was a substantial difference in admission procedures, with CPR directives being an obligation upon admission in these studies. Although not directly comparable, our findings are in contrast with a previous point-prevalence study from 2004 from one of the two sites at Karolinska University Hospital, which excluded patients in the ICU and showed a 4% prevalence of DNACPR orders.[25] A

contributing factor to this discrepancy might be an increased use of DNACPR orders over time.[80] As the cohort in study IV was from 2015, the contemporary frequency of use may be higher than 11%.[80]

6.4 WHAT ARE THE CHARACTERISTICS OF PATIENTS WITH DNACPR ORDER PLACEMENT?

Based on the same reasoning as the frequency of placement, patient-, hospital characteristics and grounds for DNACPR orders should not be generalised outside of Sweden or to any Swedish hospital, but it would seem reasonable to generalise to other Swedish University hospitals.

For a mixed patient population admitted through an ED, two previous reports from the US showed that age, CCI, hospital length of stay, and hospital mortality was in line with results in study IV.[80,103] In line with previous studies for a mixed patient population and subgroups of patients with DNACPR orders, study IV showed that patients with DNACPR orders were older with more chronic comorbidities than those without such directives.[80,87,89,96]

For patients admitted through the ED with DNACPR orders the proportion of males in study IV was similar to that of two studies from the UK (46% and 48%)[55,104] but higher than a study from the US (38%).[80] Male patients have been associated with a lower prevalence of DNACPR orders in mixed populations and different subgroups of patients with DNACPR orders,[80,89,96] but has not been explored in our setting. Age was in accordance with the two studies from the UK.[55,104]

Regarding the burden of chronic comorbidities for patients with DNACPR orders, study IV showed lower CCI compared to a previous study of a mixed patient population in the UK in 2009 (median 3 versus 6).[55] Hospital and one-year mortality was higher (51% and 83% versus 37% and 77% in study IV). As in our study, for patients with DNACPR orders discharged alive, underlying comorbidities and time to DNACPR directive placement from admission did not differ noticeably from those who died in hospital. Patients who died presented more acutely unwell on admission. Qualitative analysis in study III showed that grounds for DNACPR orders were based on severe chronic comorbidity or multimorbidity both with and without acute condition. All together, these findings consolidate the notion of DNACPR decisions being heterogenous and a result of complex decision processes involving the assessment of severity of underlying chronic comorbidities, general health status, severity and progress of acute illness in combination with patient preferences and goals of care in the present situation as well as with the perspective of the near future.[8,24,98,99,116,117] Together with the finding in study III that many patients have impaired cognition at the time of DNACPR order placement, it supports the objective to make use of the situations for shared decision-making when the opportunity arises, and incorporate DNACPR decisions into individualised overall emergency treatment plans originating in the present situation but with the perspective of the near future.[161,162]

In a more recent study of a mixed patient population in the UK 2017-2020, hospital mortality was more in line with our study, with 32% hospital mortality for all patients with a Treatment Escalation and Limitation (TEAL) form, out of which 89% had DNACPR decisions.[104]

Further research is warranted to better understand temporal changes in DNACPR order placement and to elaborate on differences in DNACPR order use in different hospitals in our setting.

On arrival to the ED, more than 50% of patients with DNACPR orders were classified as being unstable, showing signs of more severe acute illness. Approximately 50% were admitted from the ED to higher levels of care, indicating that they were at least initially given the opportunity to obtain more intensive emergency care. Sensitivity analysis of admission ward for patients with DNACPR order from a previous hospitalisation showed the same results. However, the observational nature of this study did not allow for analysis of the sequence of events in relation to DNACPR order placement, and there are other factors that could influence what ward the patient was first admitted to from the ED, such as availability of beds in the hospital at the time of admission.

6.5 ARE THERE SHORTCOMINGS IN IDENTIFYING PREVIOUS DNACPR ORDERS UPON REHOSPITALISATIONS?

Study IV showed that for patients discharged with DNACPR orders in the previous hospitalisation, reversal of DNACPR status occurred in one-third of cases. For the majority, it was not certain whether the decision was an active process or simply represented a lack of consideration, because no document was issued on readmission. Although not completely transferable to our setting, a study from the US[100] similarly showed high DNACPR reversal upon readmission (45%) that was hypothesised to be driven by patient preferences but was instead strongly associated with institutional factors. This could be true for our setting as well, with a lack of clear routines for DNACPR decisions upon hospital admission contributing to the increased risk of previous decisions being overlooked. For these patients, there was a risk that reversal of DNACPR status was inconsistent with these patients' preferences regarding CPR or could lead to medical treatment that was previously assessed as non-beneficial for the patient. It is not known in what way previous DNACPR orders influence decision-making. Exploration of what lies behind the reversal of DNACPR decisions upon subsequent admission should merit further attention as there may be a need for strengthening of the admission procedures in identifying DNACPR orders on previous admissions.

For two-thirds of patients discharged with DNACPR orders, the decision was unchanged upon subsequent admission. Although we did not have knowledge about of the grounds for the DNACPR orders, as study III and other previous studies have shown that patient involvement in discussions regarding DNACPR decisions can be low.[8,20-24] Hence it would be wise upon iteration of a DNACPR order to scrutinise the previous decision process and

take responsibility for fulfilment of the ethical and jurisdictional principles of the DNACPR order placement.[4,5,15]

6.6 WHY DO WE FALTER IN ADHERENCE TO LEGISLATIVE REQUIREMENTS?

Although conducted in a single University hospital, study III broadens and confirms previous publications that there are shortcomings in the documentation of the decision process for DNACPR in Sweden.[8,20-24] The work in this thesis does not elaborate on the underlying causes for this.

However, it draws attention to the known fact that due to impaired, cognition shared decision making involving the patient is not possible in many situations,[8,20,21,23,116,118,163-165] and consolidates that there are shortcomings in the routine to seek consultation with relatives in this situation in the Swedish setting.[8,20,21] This should be seen in light of the limitation that documentation could have taken place outside of the form for DNACPR orders.

6.6.1 Are there practical barriers?

In study III, practical reasons why consultation with the patient was not possible were mentioned but were not so prevalent. Previous findings from our setting show that there are practical situations that hinder consultation with patients or relatives to take place, such as language barrier, inappropriate setting, or lack of time.[21] Although not truly legitimate reasons to omit patients or relatives from being involved in the decision-making process, it mirrors the working conditions that clinicians face on a daily basis. In a smaller study from Helsingborg 2018, 93% of patients receiving a first-time DNACPR order survived the first 24 hours of admission.[21] In study IV, 63% of patients with DNACPR orders were discharged from hospital, and the median time from ED arrival until placement of DNACPR order was 1 day; time from admission until death or discharge was 10 days. It is important to address the question of DNACPR promptly, however, it would seem for patients without imminent risk of clinical deterioration into a cardiac arrest situation, to better ensure shared decision-making, the decision regarding DNACPR can be planned for to take place during the hospitalisation. For those with clinical conditions that requires prompt assessment of benefit versus burden of CPR, the situation will determine what can best be done in terms of shared decision making.

6.6.2 Does the conversation cause harm?

Although it is important to physicians to consult with patients regarding DNACPR decisions[24,116,119,126,163] there are barriers for the conversation to take place,[116,117,163] one of which is the fear of causing conflicts, distress, or harm and take away patients' hope.[23,49,116,117,121-123] Studies have shown that patients in general have a positive attitude towards having the conversation,[102,164-168] but individualisation of the discussion is required as it there can be a question of timing in relation to the course of the disease, and starting of treatment.[122,126,164,165] Exploring the attitudes of patients and relatives according to physician

notes in study III showed that the DNACPR order most often was in line with the patient's preferences. For most patents it was that their own wish was to refrain from CPR, and it could be part of the process of natural death. In interpreting these results however, it is important to keep in mind that there was a potential for selection bias in which free texts were documented in the DNACPR forms, and that it was seen from the physician's perspective. As patients' emotional reactions is an essential part in the communication regarding DNACPR directives,[116,122,123] it seems important to address this and help provide the necessary skills for communication in the decision process for DNACPR orders.

6.6.3 Are there knowledge gaps?

Swedish physicians seem to have knowledge about the ethical and legislative directives concerning DNACPR directives,[20,23] but there is a need for further educational efforts.[20] Part of the explanation for the low adherence to the legislation could be that physicians are not aware that documentation of DNACPR orders is regulated in such detail.[20] Future educational efforts should focus on this subject. The design of the documentation of DNACPR orders in the patient record could be improved to better ensure adherence to legislation.

6.6.4 Does decision-making occur in medical teams?

Study III confirms that DNACPR decisions are usually made by a senior physician.[16,23,116,117,163] As these decisions can be complex, with uncertainties about the prognosis as well as the patient's wishes and values, this seems appropriate.[116,117,163] Previous Swedish studies have implicated that DNACPR decisions are made without the physician consulting with the rest of the treating team to a certain extent.[23,24] The finding that 43% of DNACPR decisions were made without documentation about consultation with patients, relatives, or other licenced caregivers is in line with this, and calls for further research.

6.7 WHAT DOES THE FALTERING ADHERENCE TO LEGISLATION IMPLY FOR THE PATIENTS?

It is difficult to establish whether DNACPR orders are justified as they are based on the values of the patient in conjunction with the assessment of beneficial outcome by the clinician, and there is no gold standard.

Do we know what patients are likely to die? In a study from Kalmar County Hospital, 89% of those who died in hospital in 2016 had a DNACPR order in place, median time from DNACPR order placement until death was 4 days.[8] In study IV, median time from DNACPR order placement until death was 6 days. Although not allowing for analysis of the sequence of events or underlying grounds for the decisions, it would seem that patients with a high risk that the clinical course could involve cardiac arrest that was assessed as non-beneficial were identified in advance. However, for these patients and relatives, not including them in the discussion regarding DNACPR directives could impair the possibility for preparation and expression of will regarding palliative care approaches near the end of life.

Study III showed that grounds for DNACPR orders are often based on severe chronic comorbidity without acute condition, and a DNACPR directive is not synonymous with in-hospital death.[21,55,92,104] Study IV, with support from a previous study[55] shows that patients with DNACPR orders discharged from hospital had a similar burden of comorbidities as those who died. 63% of patients who were discharged from hospital died within one year. Again, we did not evaluate the grounds for the DNACPR directives but put in relation to the high one-year mortality for patients discharged from hospital, it seems adequate that a DNACPR order was issued in the assessment of burden versus benefit. For these patients with a supposedly severe underlying health condition, it is important to safeguard the right to be involved in the decision-making and the expression of autonomy.

It is important to bear in mind for all DNACPR directives, that it only relates to the event of a cardiac arrest and does not relate to other aspects of care. In study IV, a DNACPR order was associated with other forms of limitations of life-sustaining treatments in 80% of cases which is in line with the notion that often, cessation of circulation is not an isolated event (such as arrhythmia associated with reperfusion in myocardial infarction), but the last event in a clinical course of deterioration based on previous health conditions and/or ongoing acute illness. As there is contradictory evidence that a DNACPR directive is associated with inappropriate withholding of other treatments,[87,91,97,101,115] it is important to ensure that other aspects of care and overall goals of treatment are taken into consideration. This can be formulised into overall treatment plans in different ways[80,161,162] and could be a way as to clarify overall goals of care and ensure that the expression of autonomy is guarded.

Clinicians are obliged to follow requirements for documentation regarding DNACPR orders according to Swedish legislation, and this should be pursued. Future educational efforts,[20] improved design of DNACPR orders in the electronic patient records to increase correct documentation, and introducing adherence to the legislation as an indicator of hospital quality could contribute to improved practice.

6.8 THOUGHTS ABOUT THE DECISION PROCESS FOR DNACPR ORDERS

Based on the results in this thesis, aspects to take into consideration in the decision process for DNACPR orders include:

Upon admission, identify patients at risk of IHCA where CPR could be considered not to benefit the patient, or where it is not aligned with the patient's values and goals of care. Make an assessment of prognosis and balance against the patient's values and goals of care. A pre-arrest prediction model such as the PIHCA score could be of aid in the objective assessment and identify patients with a very low of likelihood of favourable outcome.

Identify any previous DNACPR orders, if they exist assess whether grounds for the DNACPR order are still valid and scrutinise the previous decision process to safeguard expression of autonomy for the patient in the coming decisions.

Do as best you can to respect patient autonomy and balance the need for prompt decision-making with the possibility of shared decision-making. If the patient is cognitively impaired and secrecy does not apply, information should be shared with relatives. If necessary, provide information as to what conversations have taken place, so that such conversations can be held in a more planned approach during hospitalisation.

In setting overall goals for emergency treatments through shared decision-making, when appropriate, incorporate the discussion regarding DNACPR decisions, as later on the opportunity to include the patient can be lost.

Engage the treating team or other licenced caregivers in the decision-making process for DNACPR orders, and make sure the documentation necessary to fulfil legislation is in place, ideally the documentation design can be of guidance.

7 CONCLUSIONS

This thesis has focused on the decision process for DNACPR order placement in the hospital setting and the epidemiology of DNACPR orders. The thesis provides a prediction model for identification of patients with a low likelihood of favourable neurological outcome should a cardiac arrest event occur, it explored clinical practice with regards to adherence to legislative requirements for DNACPR orders and the demographics of patients with DNACPR orders.

Conclusions that can be drawn from this thesis include that the prediction tool GO-FAR score only with caution should be taken into clinical practice in our setting without update. An updated version, the PIHCA score has the potential to be used in our setting, but external validation and further exploration of clinical use is warranted before implementation. There are shortcomings in the decision process regarding documentation of DNACPR orders and further research is warranted to establish the most effective interventions to strengthen adherence to legislative requirements. For most patients DNACPR order placement was in line with their preferences, but due to impaired cognition shared decision was not an option for a substantial proportion of patients. Grounds for DNACPR orders were based on severe chronic comorbidity or multimorbidity, for some in conjunction with acute illness. Many patients with DNACPR order placement died during their hospital stay, but the majority were discharged from hospital. The perspective of the risk for cessation of circulation for patients with severe comorbidity can lay in the present situation, but also with the perspective of the near future. Upon admission through the ED, one out of ten adult patients received a DNACPR order during hospital stay in a Swedish University hospital. Upon subsequent admissions, for patients with a DNACPR order on previous hospitalisation, reversal of DNACPR status occurred for one-third. This should merit attention as it was not certain whether this reversal was active or a consequence of lack of consideration, there is a potential need for strengthening of admission procedures for identification of previous DNACPR orders.

8 FUTURE PERSPECTIVES

Some questions have been raised during the work on this thesis that merits further investigation:

As for all newly developed prediction models, external validation must assess the predictive abilities of the PIHCA score outside of the development setting.

The clinical application of a prediction model for outcome following IHCA will have to be further investigated in future studies.

The compound measures that could be effective in strengthening clinical practice regarding documentation of DNACPR orders in our setting is an area of further investigation.

What lies behind the high proportion of reversal of DNACPR orders upon subsequent admissions? The need for strengthening of admission procedures regarding DNACPR orders merits further investigation.

Further exploration of the use of DNACPR orders throughout Swedish hospitals could give a broader picture of DNACPR order practice in our setting.

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11 APPENDIX

11.1 APPENDIX 1. COMBINED CHRONIC COMORBIDITY ACCORDING TO CHARLSON COMORBIDITY INDEX

Table 15. The Charlson Comorbidity Index.[68,69]

Disease	ICD-10	Points
Chronic pulmonary disease	I27.8-9, J40-J47, J60-J67, J68.4, J70.1, J70.3	1
Rheumatic disease	M05, M06, M31.5, M32-M34, M35.1, M35.3, M36.0	1
DM with chronic complications	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	1
Renal disease	I12.0, I13.1, I31.2, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50.	2
Dementia	F00-F03, F05.1, G30, G31.1	2
Mild liverdisease	B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73, K74, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	2
Hemiplegia, paraplegi, tetraplegi	G04.1, G11.4, G80.0-G80.2, G81, G82, G83.0-G83.4, G83.9	2
Any malignancy, including lymphoma, leukemia, melanoma[a]	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7	4
AIDS/HIV	B20-B24	4
Metastatic solid tumor	C77-C80	6

[a]Except other malignant neoplasm of the skin. Abbreviations: ICD-10, international statistical classification of diseases-10; DM, diabetes mellitus; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

11.2 APPENDIX 2. DNACPR FORM DOCUMENT 33

Ställningstagande till livsuppehållande behandling

Gällande:

Dokumentet är ett hjälpmedel i form av checklista vid ställningstagande till livsuppehållande behandling vid livshotande tillstånd enligt SOSFS 2011:7. Detta dokument är bara en del i dokumentationen och planeringen av patientens vård.

LÄS innan beslut tas:

- Verksamhetschefen ska för patient med livshotande tillstånd utse en fast vårdkontakt (leg. läkare) så snart det är möjligt. (2 kap, 3 §)
- Den fasta vårdkontakten ska ansvara för planeringen av patientens vård. (2 kap, 4-8 §)
- Det är den fasta vårdkontakten som ombesörjer att patientens önskemål respekteras, om att en livsuppehållande behandling inte sätts in eller inte längre fortsätter (4 kap.).
- Det är ett krav att beslut angående livsuppehållande behandling sker i samråd med annan legitimerad yrkesutövare, utöver patient och närstående (3 kap, 1-3§).
- Ställningstagandet ska omprövas vid ändring i patientens tillstånd.
- Ställningstagandet ska omprövas om patienten ändrar inställning (vill ha, alternativt vill avstå från, erbjuden livsuppehållande behandling).
- Ställningstagandet gäller endast för det aktuella vårdtillfället (på vårdavdelningen och när patienten går på undersökningar/annat).
- Ställningstagandet ska omprövas i samband med att patienten skrivs ut eller flyttas till annan vårdform.
- Om en patient är medvetslös - eller vid medvetande men ändå inte kan uttrycka en egen vilja - är det den fasta vårdkontaktens ansvar att försöka ta reda på om patienten tidigare har uttalat sig för eller emot viss livsuppehållande behandling (Socialstyrelsens handbok Din skyldighet att göra patienten delaktig s.15 + s.17).

Ansvarig läkare för ställningstagandet: **Datum:**

som är:

☐ Fast vårdkontakt för patienten
☐ Annan specialistkompetent läkare som deltar i patientens vård
☐ Annan leg läkare

Ställningstagandet innebär:

☐ Ingen begränsning av (livsuppehållande) behandling
☐ Avstå från att påbörja livsuppehållande behandling, nämligen:
☐ Avbryta pågående livsuppehållande behandling, nämligen:

☐ MIG (mobila intensivvårdsgruppen)
☐ IVA(intensivvård)
☐ HIA (hjärtintensivvård)
☐ Återupplivning efter hjärtstopp
☐ Pacemaker ☐ ICD (intern defibrillator)
☐ Invasiv ventilatorbehandling
☐ Noninvasiv ventilatorbehandling
☐ Dialys
☐ Operation
☐ Strålbehandling
☐ Blodtransfusion

☐ Andningsoxygen
☐ Vasoaktiva läkemedel
☐ Antibiotika
☐ Cytostatika
☐ Nutrition
☐ Vätska
☐
☐

Grund för ställningstagande till livsuppehållande behandling

☐ **Sjukdomens prognos**

☐ **Patientens önskan att avstå från eller avbryta viss livsuppehållande behandling**

En läkare får inte ge en behandling eller fortsätta en behandling som patienten inte vill ha. Om patienten inte vill att en viss livsuppehållande behandling ska fortsätta, ska den fasta vårdkontakten ta ställning till patientens önskemål (Socialstyrelsens handbok Din skyldighet att göra patienten delaktig s 15).

Den fasta vårdkontakten ska dock först försäkra sig om att:

- ☐ Patienten har fått en individuellt anpassad information
- ☐ Patienten har förstått informationen och kan inse och överblicka konsekvenserna av att behandlingen inte inleds/fortsätter
- ☐ Patienten har haft tillräckligt med tid för sina överväganden
- ☐ Patienten står fast vid sin inställning
- ☐ Patienten har fått tillgång till den habilitering och rehabilitering och de hjälpmedel som han eller hon behöver och har fått stöd att begära de insatser från socialtjänsten som han eller hon är berättigad till
- ☐ Patienten har blivit erbjuden en palliativ vård med så god livskvalitet och symtomlindring som möjligt

Samråd

☐ **Samråd med patienten**

☐ **Ej möjligt** Ange orsak:

☐ **Ja** När:

Patientens inställning till den livsuppehållande behandlingen:

☐ **Samråd med vårdnadshavare** när patienten är under 18 år. Barnets egen inställning inhämtas med hänsyn till mognadsgrad och ålder.

När: Med vem/vilka:

Vårdnadshavares inställning till den livsuppehållande behandlingen:

☐ **Samråd med närstående** (om samråd inte kan ske med patienten)

När: Med vem/vilka:

Närståendes inställning till den livsuppehållande behandlingen:

☐ **Samråd med andra legitimerade yrkesutövare samt i förekommande fall med patientansvarig läkare i öppenvård/annan vårdform**

När: Med vem/vilka:

Etisk analys och motivering av ställningstagandet i relation till sjukvårdens etiska plattform

När:	Med vem/vilka:

Referenser

Hälso- och sjukvårdslag SFS 1982:763

Patientsäkerhetslag SFS 2010:659

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Socialstyrelsen. Om att ge eller inte ge livsuppehållande behandling. Handbok för vårdgivare, verksamhetschefer och personal. 2011.

Socialstyrelsen. Nationellt kunskapsstöd för palliativ vård. 2012.

SOU 2000:6. Döden angår oss alla – värdig vård vid livets slut.