Resuscitation Outcomes in the Netherlands

Marc Schluep

Results from the
'Resuscitation Outcomes in the Netherlands'
or
ROUTINE- project

Marc Schluep

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Resuscitation Outcomes in the Netherlands

De uitkomsten na reanimaties in Nederlandse ziekenhuizen

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Contents

Het heden is eeuwig
Alles is waar

God of Jehova
Allah Jahweh

De één is de ander
De ander de één

Ontsteekt uw geweten
Kijkt om u heen

Het lot dat we delen
Laat niemand alleen

Jules Deelder, uit 'Ruisch', 2011

(tevens te bewonderen op de hoek van de Aleidisstraat en 2e Middellandstraat in Rotterdam-West)

Introduction

General introduction

Cardiac arrest is the sudden cessation of cardiac activity so that the patient becomes unresponsive, with no normal breathing and no signs of circulation of blood. This inevitably means the end of life. In-Hospital Cardiac Arrest (IHCA) occurs in 1-5 per 1000 hospital admissions[1]. Because our lives are finite cardiac arrest does not always warrant intervention. However, if it does, one could attempt cardiopulmonary resuscitation (CPR) for the return of spontaneous circulation of blood, hereby restoring oxygen delivery to organs and tissues. Hereafter the patient hopefully recovers from the damage done to the organs by the lack of oxygen. The organ that is most susceptible to hypoxic damage is the brain, which at the same time is the most crucial organ for the quality of life of survivors[2].

Cardiopulmonary resuscitation, the act of *reanimating* patients, or rather returning the spirit (Latin *'anima')* to the body, dates back to five thousand years ago. The preferred method then was the introduction of smoke into the rectum as depicted in hieroglyphics and cave drawings of the Mayan and Inca people of South and Central America. There is a mention in the Bible of the prophet Elisa who performs mouth-to-mouth ventilation on an unconscious adolescent boy, who subsequently sneezes and opens his eyes[3]. Throughout the medieval period several other methods have been implemented to bring people back from the dead. These include whipping people back to life (flagellation), returning heat to the body with hot water baths and also early mentions of intubations by the Persian medic Avicenna. Later, bellows from a fireplace were used to blow hot air into a person's lungs, combining two of the previous hypotheses. In the 18th century we revisited blowing smoke up someone's rectum after colonist brought this practice to England from the Americas. Although this idea appears ludicrous, a 2021 study shows the benefit of enteral oxygenation in mammals[4].

Simultaneously, mouth-to-mouth resuscitation and inversion (hanging from the feet) were proposed for resuscitation of drowning victims[5]. To this extent the Dutch society for the recovery of drowned persons (Maatschappij tot redding van drenkelingen) was established in 1767. They proposed a holistic approach, in which the victim was warmed, water was removed from the mouth, the lungs were ventilated with a balloon, they performed bloodletting and the rectum was again fumigated with tobacco[6]. This method was propagated in a large part of Europe and more institutions were founded that were dedicated to resuscitation. Eventually more and more techniques were designed that approach modern-day CPR. For example, in and 1773 a barrel was used to roll people back and forth, resulting in chest compression and release of pressure letting air in and out. In 1812 victims were draped over a horse while it ran, leading to alternate compression and relaxation of the chest cavity. Forty years later, in 1856, rolling the patient from stomach to prone and applying pressure for exhalation made ventilation with volumes up to five hundred milliliters possible[7].

On March 21st, 1892 Dr. Friedrich Maass, resident at the Department of Surgery at the University of Goettingen, Germany, published his paper "Resuscitation technique following cardiac death after inhalation of chloroform" in the Berlin Clinical Weekly. In that publication, Maass described

the first successful performance of external cardiac massage[8]. In the 1960s this technique gained interest of Kouwenhoven, who proved the restoration of normal blood pressures with external cardiac massage, rather than the customary thoracotomy and internal cardiac massage[9]. Peter Safar published a landmark paper integrating chest compressions with endotracheal intubation and ventilation of the lungs[10]. After this discovery CPR began to become common practice in hospitals. In the 1970's CPR became part of the medical curriculum and it was introduced to the public[11].

In the early years of CPR, it rapidly became more popular and it was applied to many patients with cardiac arrest. Also as experience grew, studies were performed to evaluate the efficacy of CPR. A division was made between patients who received CPR outside of the hospital, out-of-hospital cardiac arrest and patients who suffered cardiac arrest while admitted to hospital, in-hospital cardiac arrest (IHCA). We would learn survival to hospital discharge after IHCA from 1960 – 1990 was 15% on average. During this period survival did not improve significantly[12]. A pooled estimate of survival rates showed a decline in survival with advancing age. Survival after IHCA was even nil percent in patients over the age of 89. Critics voiced their concerns about the inappropriateness of resuscitation and life-sustaining treatment of certain patients, which led to jurisprudence and the introduction of the first formal Do Not Resuscitate orders (DNR)[13]. Figures 1 and 2 show the results from the meta-analysis of survival rates over the studied period and stratified for age, respectively.

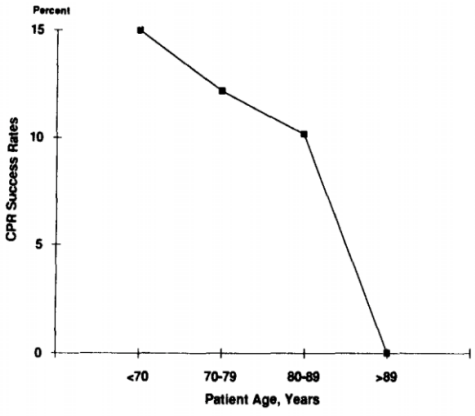

Figure 1. Pooled estimates of cardiopulmonary resuscitation (CPR) success rates among the elderly declined from 15 percent for patients younger than 70 years to 0 percent for those patients older than 89 years.

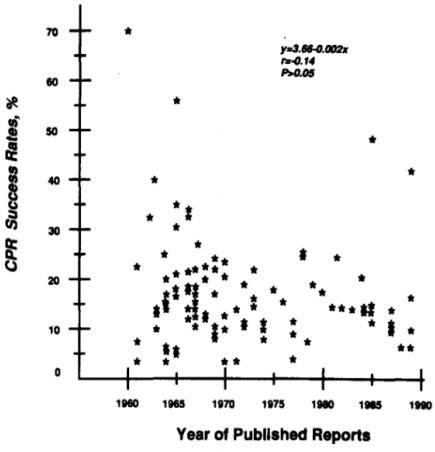

Figure 2. Cardiopulmonary resuscitation (CPR) success rates (survival-to-discharge) by year (1960 –1990) for 98 reports.[5-7,9-103] Perioperative patients were included. There was no significant trend in success rates.

So what could be possible strategies for improving survival rates of In-Hospital Cardiac Arrest? In the process leading up to cardiac arrest and CPR a number of actions follow in sequence. These are homologous to the links in the Chain of Survival of cardiac arrest[14].

First: preventing cardiac arrest. If IHCA cases are prevented, the incidence is lowered. This would not necessarily lead to an increase in survival rates, but the net number of surviving patients could increase. The Early Warning Score (EWS) system was designed for the recognition of deterioration of a patient's vital functions. This would allow for early intervention by Rapid Response Teams (RRT) and it would lead to prevention of unnecessary cardiac arrest[15]. An initiative of Dutch hospitals brought forth the implementation of EWS and RRT in 2008. The primary goal was to lower the incidence of cardiac arrest, however the incidence before and after the intervention was never measured[16,17]. Recording incidence and survival rates will provide a baseline measurement from which future interventions can measure their success.

Second: determining the chances of successful CPR in case of cardiac arrest. To do so we must first know what defines success in this context. When talking to patients, their main concern is often quality of life rather than quantity of life. When discussing the possibilities for escalation and limitation of treatment, they often ask what the chances are of becoming a *'vegetable'*[18–20]. This term symbolizes the need for prognostication that focusses on long-term survival with functional independence. To date, evidence that provides clinicians with tools to give such prognoses is scarce.

Furthermore the main focus has previously been survival, rather than health-related quality of life, cognitive or psychological wellbeing[21,22]. These patient-reported outcome measures (PROMs) are becoming increasingly important in medical research. However, PROMs are not intended to be used in isolation or indeed to replace clear clinical judgement; their judicious integration into practice must recognize the philosophical underpinning of patient-reported assessment and its role within patient-centered care. This warrants the use of a defined set of objectifiable clinical variables and outcome measures, alongside PROMs. These objectifiable variables for cardiac arrest research have been summarized in the Utstein Criteria and the Core Outcome Set for Cardiac Arrest research (COSCA)[21,23]. Which PROMs are best to use for IHCA research is yet undefined.

Third: installing advance care directives. Knowing the risk of cardiac arrest and the possible prognosis we can make shared decisions on attempting or refraining from CPR in case of cardiac arrest. Survival rates of cardiac arrest are dependent on the proportion of patients who have a do not resuscitate (DNR) order installed. Ideally, CPR is not attempted for patients who have limited chance of survival with good quality of life. The decision to install a DNR-order is preferably made using variables that are present before hospital admission (age, comorbidity, functional independence), rather than data that only becomes available when cardiac arrest has already occurred (e.g. cause of arrest, primary cardiac rhythm, duration of CPR)[24,25]. Decisions to attempt or refrain from CPR are considered an integral part of advance care planning, and can coincide with similar decisions about other invasive treatments (i.e. mechanical ventilation, surgery, dialysis). It must be made very clear that refraining from certain therapies still means a patient will be cared for in the best possible way. Patients should receive optimal care within set limits and symptoms of discomfort should be alleviated[24].

Fourth: defining the best treatment strategies for CPR. Similar to patient-related factors, some organizational and systems level factors could lead to improved survival rates. For example training personnel in basic life support, the use of a standardized CPR protocol and the use of a designated team leader are proposed in international consensus and guideline recommendation[26]. Furthermore the use of a cardiopulmonary bypass by means of extracorporeal membrane oxygenation is considered a promising technique in cardiac arrest treatment. To perform extracorporeal CPR (E-CPR) has shown improved survival rates, but at the same time is considered very costly and carries risks of severe complications[27,28]. Whether this technique leads to survival of neurologically intact individuals and if it is cost-effective has not yet been proven.

Fifth: providing post-resuscitation care. Once a patient is successfully resuscitated and brought to the intensive care unit (ICU), treatment must be aimed at minimizing damage to organs and tissues. Most notorious is post-anoxic encephalopathy, for which targeted temperature management is recommended. Furthermore a patient should receive treatment for problems such as myocardial dysfunction, kidney failure or infection[29]. Patients who survive to ICU discharge should be rehabilitated both physically and mentally[30]. However, longitudinal follow-up of health-related quality of life is readily available for patients who suffer out-of-hospital cardiac arrest, but is scarce for their IHCA counterparts[31,32]. Knowing which somatic and cognitive domains warrant attention could prove useful in establishing rehabilitation programs specifically for IHCA patients.

To address these five themes in the 'Chain of Survival' of In-Hospital Cardiac Arrest in the Netherlands the studies presented in this thesis cover the following subjects:

Part I: The historic perspective. These chapters will focus on outcomes of In-Hospital Cardiac Arrest from both international literature **(chapter 1)** and a retrospective study performed in the Onze Lieve Vrouwe Gasthuis (**chapter 2)**. Establishing a framework of incidence and survival rates, as well as temporary trends in survival rates, will help to put the results from future research in perspective. Variables associated with survival will be used to create the dataset for our prospective studies. Moreover, defining knowledge gaps will give rise to new research ideas.

Part II: Current practice. These chapters will focus on describing the present-day practice of In-Hospital Cardiac Arrest prevention and treatment, as well as communication of decisions whether to attempt or refrain from CPR; so called CPR-decisions. First, present day practice of CPR in the Netherlands will be studied by means of a questionnaire **(chapter 3)**. This will gather information on the use of rapid response teams, the constitution of CPR teams and the level of life support schooling of medical personnel. Secondly, a cross-sectional interview study performed in thirteen hospitals will help evaluate how CPR-decisions are made **(chapter 4)**. Moreover, patients will be asked if they remember talking about CPR and their recollection will be compared to the CPR-decisions that is documented in the patient record. Patients' personal experiences will be gathered with regard to timing and localization of said conversation. This ultimately will provide a comprehensive view of how often Do Not Resuscitate orders are installed and what patients perceive. Thirdly we will evaluate a relatively new treatment modality for cardiac arrest: ECPR.

Using a systematic review the neurologic prognosis of patients that are treated with ECPR will be evaluated **(chapter 5)** and a cost-effectiveness analysis will be made using a Markov decision model **(chapter 6)**.

Part III: Outcomes of cardiac arrest patients. These chapters will focus on the prognosis of In-Hospital Cardiac Arrest patients. This project will be called the Resuscitation Outcome in the Netherlands (or ROUTINE) study. From a multicenter prospective cohort study we aim to evaluate four items that are relevant to cardiac arrest prognostication. First: the incidence and characteristics of in-hospital cardiac arrest patients in the Netherlands. Second: survival after in-hospital cardiac arrest up to one year after the incident **(chapter 7)**. Third: the health-related quality of life of survivors **(chapter 8)**. And fourth: factors associated with survival and health-related quality of life, both patient-related as related to healthcare system characteristics **(chapter 9)**. By integration of the aforementioned items we aim to provide an overview of (cardiopulmonary) Resuscitation Outcomes in the Netherlands.

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Part I

Looking at outcomes in the past

I did then what I knew how to do.
Now that I know better, I do better.

Maya Angelou

Chapter 1

Survival after in-hospital cardiac arrest: an update on survival throughout the world and temporal trends of the past 30 years

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Abstract

Introduction

In-hospital cardiac arrest is a major adverse event with an incidence of 1-6/1000 admissions. It has been poorly researched and data on survival is limited. The outcome of interest in IHCA research is predominantly survival to discharge, however recent guidelines warrant for more long-term outcomes. In this systematic review we sought to quantitatively summarize one-year survival after in-hospital cardiac arrest.

Methods

For this systematic review and meta-analysis we performed a systematic search of all published data on one-year survival after IHCA up to March 9th, 2018. Results of the meta-analyses are presented as pooled proportions with corresponding 95% prediction intervals (95%PI). Between-study heterogeneity was assessed using I^2 statistic and the DerSimonian-Laird estimator for τ^2. Subgroup analyses were performed for cardiac and non-cardiac patients.

Results

We included 40 studies in our systematic review and meta-analysis. The pooled one-year survival after in-hospital cardiac arrest was 13.4% (95%PI: 5.6-28.8%, I2=100%). Subgroup analysis of cardiac patients revealed a one-year survival of 39.3% (16.1%-68.6%) in patients with a non-cardiac admission characteristic one-year survival was 10.7% (4.4%-23.6%). These data cover the period 1985 – 2018 and show a modest change in survival over that period (10-year OR: 1.70, 95% CI: 1.04 – 2.76).

Discussion

One-year survival after in-hospital cardiac arrest is poor. Survival is higher in patients admitted to cardiac wards. The time trend between 1985-2018 has shown a modest improvement in one-year survival rates. Research into IHCA population characteristics might elicit the issue of heterogeneity and stagnated survival over the past decades.

Introduction

Cardiac arrest, cardiopulmonary arrest, or circulatory arrest is the loss of mechanical heart function and effective blood circulation. If not treated by cardiopulmonary resuscitation (CPR) it inevitably means the end of life. However, if treated, circulation can be restored. Cardiac arrest is usually divided into two categories: out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). The latter is poorly researched; data on incidence and survival of IHCA are limited. Current literature describes an incidence of 1-6 events per 1000 hospital admissions.[1–4]

The outcome of interest in IHCA research is predominantly survival to discharge. A recent meta-analysis shows a pooled survival rate at discharge of 15.0% (95%CI, 12.0-18.0%) with little change over time[5], while an analysis in the UK over the same period of time shows a significant increase in hospital survival after IHCA (9.0% in 2004 to 12.2% in 2014) [6]. Survival to discharge is an important outcome measure, however little is known about the long-term outcomes of patients discharged from the hospital. Recent guidelines warrant for more research into long-term outcomes and associated factors[7]. As patient-centred outcomes are increasingly important to biomedical and clinical research, long-term survival could be regarded as such and could serve as important information in clinical decision-making. This systematic review aims to quantitatively summarize one-year survival after in-hospital cardiac arrest.

Methods

Search strategy and study selection

This systematic review and meta-analysis was reported following the PRISMA and MOOSE guidelines for reporting of systematic reviews and meta-analyses of observational studies[8,9]. The protocol was registered with PROSPERO (2017:CRD42017072037). We performed a systematic search of published data on one-year survival of IHCA using Embase, Medline Ovid, Cochrane Central, Web of Science, PubMed recent and Google scholar from their inception through March 9th, 2018. The search strategy is shown in supplemental table 1. We set no limitations on type of study or language. Mendeley (2017 Mendeley Ltd.) was used for the selection of relevant articles. Study selection was performed in a 2-staged process. Two reviewers (MS and BG) independently screened titles and abstracts (stage 1), and full-text papers for inclusion (stage 2). Disagreements were resolved with discussion and involvement of a third researcher (SH). Pre-defined inclusion criteria were: 1) In-hospital cardiac arrest, using conventional CPR (CCPR); 2) One year survival reported; 3) Adult patients; 4) Clinical study. Cardiac arrest definitions per article are provided in supplemental table 2. Conventional CPR is defined as chest compressions with or without use of compression devices, as opposed to extracorporeal CPR via cardiopulmonary bypass. Studies were excluded if they did not fit inclusion criteria, if they were only published as abstract or written in a language none of the reviewers was proficient in.

Data extraction and quality assessment

Data extraction from selected studies was performed independently by two investigators (MS and BG) using a standardized form. To describe study design, we extracted the sample size of patients who underwent CCPR, the country of origin, the investigated period, the definition of the study population, whether the study was retrospective or prospective, how the investigators attained their data, which comparisons were made, how they defined one year survival and which patients were excluded from the cohort. Patient populations were checked for overlap to prevent patients from appearing multiple times in our analysis. If this was the case the study with the smallest sample size was excluded. The characteristics of the study population included were: age, gender, prevalence of cardiac patients, percentage of witnessed arrests or monitored patients and prevalence of ventricle fibrillation or ventricle tachycardia as initial rhythm. A common denominator for comorbidity or severity of disease was sought. If age was defined in strata or ranges a weighed mean was calculated without SD. Finally, one-year survival of patients who underwent CCPR in hospital was extracted. Survival was defined as the survival of one single CPR attempt. Authors were contacted for the exact survival rate when the one-year survival was not directly available from the manuscript. We specifically looked at conventional CPR, and excluded extracorporeal CPR. When a study included both, only the conventional CPR group was extracted.

The quality of the studies was evaluated using the method of Hayden et al. for the evaluation of the quality of prognosis studies in systematic reviews[10]. Known prognostic factors such as initial rhythm and witnessed arrest were assessed. Two authors individually assessed all six items and discrepancies were resolved by a third researcher (SH).

Statistical analysis

One-year survival data were pooled across studies using the inverse variance method. A random-effects model was used to estimate the pooled one-year survival probability after IHCA as considerable heterogeneity was expected. A random-effects meta-analysis model assumes the observed estimates can vary across studies because of real differences in each study as well as sampling variability (chance). Results of the meta-analyses are presented as pooled proportions with corresponding 95% confidence intervals (CI). Between-study heterogeneity was assessed using I^2 statistic and the DerSimonian-Laird estimator for t^2. Furthermore in order to address heterogeneity between studies better, a 95% prediction interval was reported[11,12].

A sensitivity analysis was performed to assess the presence or absence of heterogeneity. Subgroup analyses were performed for cardiac and other patients. Cardiac, or a cardiac admission characteristic, was defined as a study in which all patients came from cardio (-thoracic) units, or were predominantly admitted to the hospital for cardiac disease or cardiac surgery. The non-cardiac subgroup consisted of studies that included patients who were not specifically admitted for cardiologic or cardiac surgical reasons (i.e. general nursing wards, but also critical care units). Other subgroup analyses were done for study quality, geographical distribution (i.e. continents) and initial arrest rhythm. Furthermore, a random intercept meta-regression analysis (binomial-normal model) with corresponding bubble plot was carried out to assess the influence of study period on one-year survival. This model is appropriate for probability meta regression, since it avoids the bias that occur when a normal-normal model would be used for logit transformed proportion[13,14]. Studies were allocated in time using the median of the period the study covered. After careful evaluation of all articles a post-hoc analysis of cognitive outcome was done with use of a random effects model to analyse available data on the fraction of one-year survivors with a cerebral performance category score (CPC) of 1 or 2. Secondly a post-hoc analysis was performed for survival to discharge.
All data was extracted into Microsoft Excel and then statistically analysed by importing the data in R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). The packages used for the analysis were 'meta' and 'metafor', of which we used the 'metaprop', 'forrest' and 'rma.glmm functions.

Results

Search results and characteristics of included studies

Our search strategy retrieved 7331 records, of which 4999 remained after duplicates were removed. The parallel exclusion of studies based on title and abstract resulted in 239 full text articles eligible for detailed assessment. Finally, we included 39 studies in our systematic review and meta-analysis[15–54]. Full details of study selection are summarized in figure 1.

Characteristics of the included studies and study populations are given in table 1 and 2. All studies were performed between 1985 and 2015, predominantly in North America and Western Europe. Data was available on age in 35 (89.7%) studies, on gender in 33 (84.6%), on the proportion of cardiac patients in 14 (35.9%) studies and on shockable rhythm in 27 (69.2%) of the included studies. Of the included studies 18 (46.1%) described level of patient monitoring at the time of arrest (e.g. critical care units). Number of inclusions ranged from 25 to 471,962 patients and mean age of the study population ranged from 54 to 86 years.

Quality assessment

The quality assessment of the included studies is given in supplemental table 3. The study population was adequately defined and described in 26 (66.6%) studies. The study attrition, referring to the manner in which patients were recruited for inclusion, was of good quality in 28 (71.8%) studies. Prognostic factors were adequately measured in 21 (53.8%) studies. The means of outcome measurement were not or inadequately described in 16 (41.0%) studies, and were sufficiently described and measured in 12 (30.8%) studies.

Outcome

The meta-analysis of all studies showed a pooled one-year survival of 13.4% (95%PI: 5.6%-28.8%) summarized in figure 2. Statistical heterogeneity was high: I^2=100%, τ^2=0.22, p<0.01. Subgroup analysis of cardiac patients revealed a one-year survival of 39.3% (95%PI: 16.1%-68.6%; I^2=85.0%), while repeating this analysis in studies of the non-cardiac subgroup analysis resulted in a one year survival of 10.7% (95% PI: 4.4%-23.6%; I^2=100%) Survival plots for cardiac and non-cardiac patients are available in supplemental figures 1 and 2. As displayed in figure 3 survival to discharge was available in 35 studies. Pooled survival to discharge was 17.6% (95%PI: 13.1-22.7%, I^2=99%). All survival statistics are summarized in table 3.

Finally, when analysing the temporal trend of one year survival, a significant and modestly positive trend was observed (OR=1.70 per 10-year period, 95%CI: 1.04-2.76), as shown in figure 4. Seven studies reported CPC scores for one-year survivors. A pooled estimate shows 92.0% (95% CI: 85.0%-96%) of patients alive at one year after cardiac arrest have a CPC score of 1 or 2 (figure 5). Pooled estimates stratified by study quality, geographical distribution or initial arrest rhythm

did not produce any significant differences in effect estimates or heterogeneity. We were not able to identify a common denominator of comorbidity or severity of disease to perform analyses on.

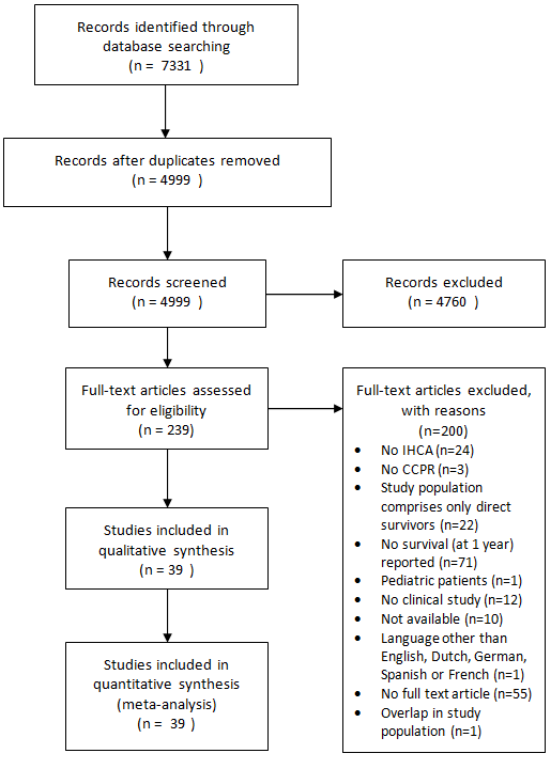

Figure 1. PRISMA Flow Diagram of search strategy and included studies.

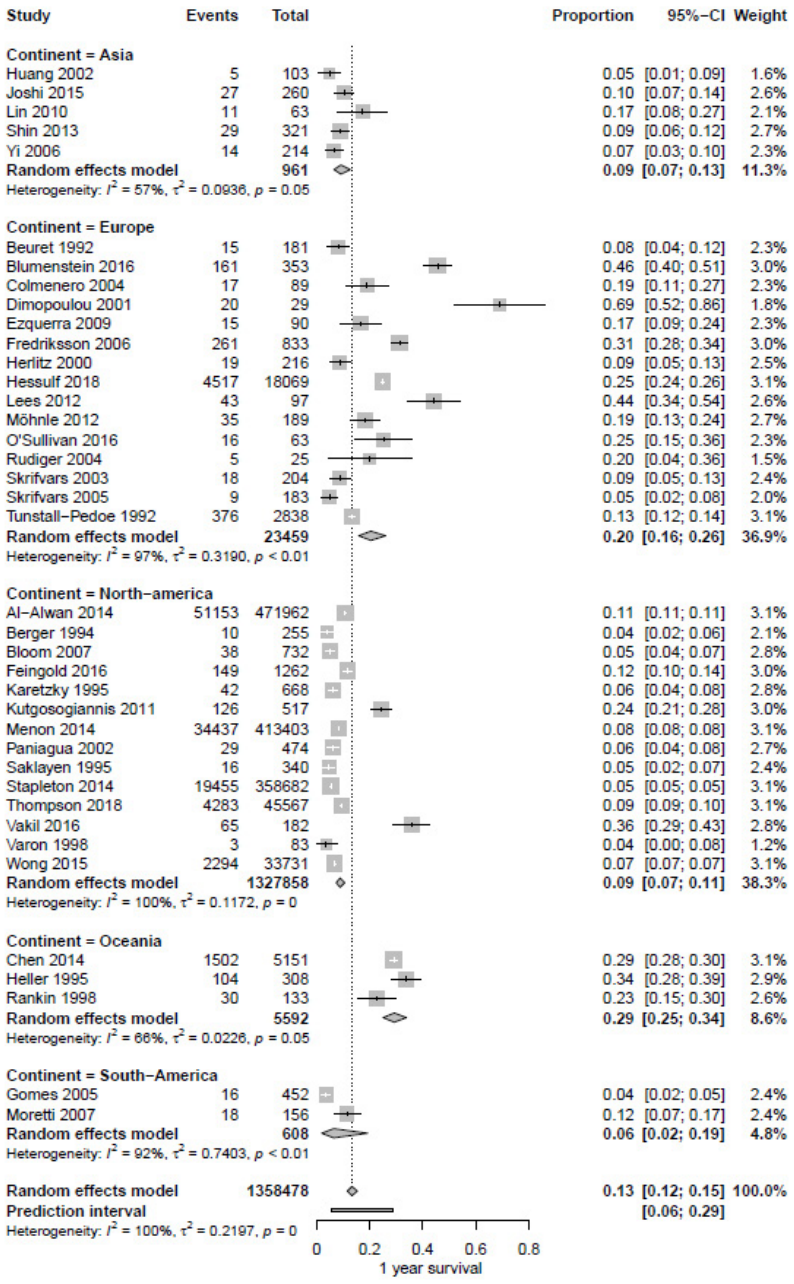

Figure 2. Pooled one-year survival rate after in-hospital cardiac arrest.

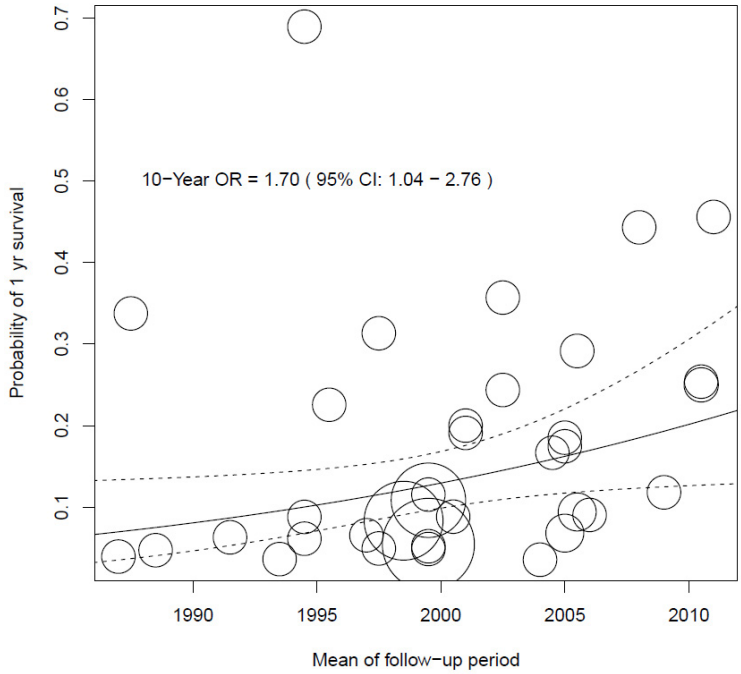

Figure 4. Bubble-plot for meta-regression analysis of the influence of study period on one-year survival (OR = 1.70, 95% CI: 1.04– 2.76 per ten year increase).

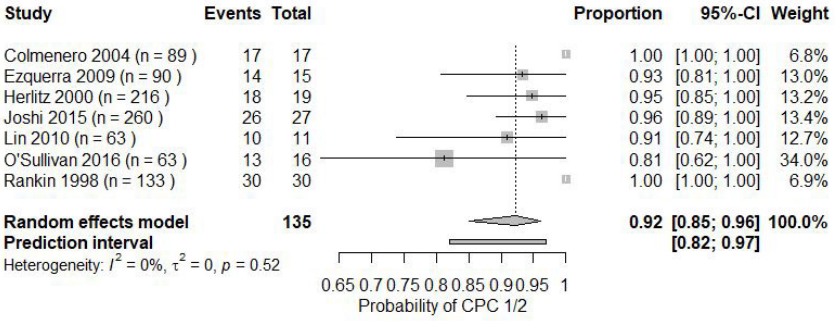

Figure 5. Pooled fraction of survivors at 1 year with a cerebral performance category of 1 or 2.

Discussion

In this systematic review one-year survival after in-hospital cardiac arrest is 13.4% (95%PI: 5.6%-28.8%). When viewed separately one-year survival in cardiac vs. non-cardiac patients is 39.3% and 10.7% respectively. As far as we have found these data represent the first documentation of a systematic overview on one-year survival after IHCA through most recent publications and covers the period 1985 – 2018.

One-year survival of 13.4% after IHCA is poor. When compared to survival to discharge this implies a large portion of patients discharged alive survive the following year[5,6]. The low survival rate is probably attributable to the presence of underlying disease. Comorbid disease has been demonstrated to worsen survival. This is most evident for severe COPD, cirrhotic liver disease, chronic kidney disease and heart failure and is supported by recent evidence that links comorbidity and age to 30-day survival[56]. Although we did not have sufficient data for a subgroup analysis, some of the studies we have included suggest a similar relationship between comorbidity and long-term survival[4056].

We found significant heterogeneity in outcomes across the studies. These differences may be related to the variability in study populations, treatment strategies and/or international differences in life expectancy [57]. With regard to differences in study population, subgroup analyses showed a survival of 39.3% in patients who are admitted to hospital for cardiac disease or cardiac surgery. In these patients survival is higher than for patients admitted for other reasons and part of the heterogeneity can be explained by this subgroup analysis. The higher survival rates are related to the presence of monitored wards, a higher incidence of shockable rhythm (also demonstrated in this review) and presumably a higher incidence of reversible causes (e.g. tamponnade, coronary occlusion)[58]. This supports the hypothesis of earlier recognition and intervention, as well as higher baseline survival in cardiac patients compared to other patients after cardiac arrest. To further explain heterogeneity we have performed several subgroup analyses with the available information, but did not find any sufficient answer.

The heterogeneity of data can to greater extent be attributed to the epidemiological nature of the populations, rather than being selected or randomized groups. We believe that pooling of data was reasonable for outcome measures for different reasons. First (I) this approach is pragmatic and clinically relevant; (II) we took measures to reduce potential clinical heterogeneity by performing subgroup analyses on the basis of clinical criteria (i.e. cardiac vs. non-cardiac patients) (III) by contrast with comparative meta-analyses in which the presence of statistical heterogeneity might limit conclusions about effect size or exposure, pooling of data is an accepted method in single-group meta-analyses done for epidemiological purposes and (IV) pooling the data was necessary to appraise the available data on one-year survival in a comprehensive manner that could help inform the clinical context and related clinical decision making [59]. Although generalizability is limited due to a large diversity in study populations, pooling due of data provides a clinically relevant estimate for one-year survival after IHCA. In reporting survival rates we used the prediction interval, rather

than the confidence interval. This provides an estimate of what survival rates can be expected in future studies. As to be expected with large heterogeneity in outcomes the prediction intervals we found were very broad and make prognostication difficult.

We compared one-year survival to survival to discharge from a recent meta-analysis (i.e. 15.0% 95% CI: 12.0% -18.0%) and to survival to discharge from this meta-analysis (i.e. 17.6%, 95%CI 13.1% - 22.7%)[5]. It suggests death after IHCA occurs mainly during hospital admission rather than after discharge. Furthermore, when pooled survival for in-hospital cardiac arrest patients is compared to one-year survival after out-of-hospital cardiac arrest survival it is nearly identical: 13.4% for IHCA vs. 12.0% for OHCA [60,61]. These data give rise to new questions regarding the aetiology of IHCA in non-cardiac patients and factors that influence survival. It could be argued that factors concerning pre-existing health status have added value in predicting one-year survival after in-hospital cardiac arrest. A positive finding came from our analysis for cognitive performance showed CPC scores were 1 or 2 in 92.0% (95% CI: 85.0%-96.0%) of one-year survivors. This however pertains to performance and not necessarily to quality of life.

Certain limitations should be taken into account. Most studies have reported one-year survival from the moment of cardiac arrest, with a few reporting survival from the moment of discharge. We have considered this difference to be negligible to the interpretation of our outcome because survival is measured at least one year from the occurrence of cardiac arrest. Secondly we need to consider the heterogeneity of outcomes, as population-level data was not available for many of the included studies and therefore only stratification for cardiac and non-cardiac patients rather than for comorbidity or age was possible. No difference could be analysed between monitored or non-monitored wards or initial arrest rhythms, as sufficient data was not available. Although some subgroup analyses were attempted no clear explanation for this heterogeneity could be pinpointed. Lastly health care developments and changes in public health will have influenced incidence and outcome of IHCA. The meta-regression we have performed shows a trend in one-year survival that shows a slight improvement when viewed on a basis of 10-year intervals. One could state that survival improves over time, however this trend is only modestly positive and we hope this effect will become more evident in the future. Whether patient case mix has significantly altered, treatment strategies are insufficient or it is a combination of factors remains uncertain.

In the future heterogeneity in structure and processes of care should be explored. This variation in practice also adds to the heterogeneity in outcome. We do believe that careful assessment of quality of care should be performed, taking into account statistical uncertainty and case-mix. Being able to explain differences in outcome through quality of care could enable improving overall quality of care by identifying the most effective policy[62]. Secondly subgroup analyses can be performed if predefined subgroups are available. These subgroups need to be defined by known predictors and need to be comparable between studies[63]. We would recommend the implementation of nationwide registries and the use of standardized sets for reporting populations and outcomes, in this case the Utstein criteria and Core Outcome Set for Cardiac Arrest (COSCA)[64–66]. This will help improve comparability and enhance future implementation research[67].

This meta-analysis contains important information pertaining to all patients worldwide. In-hospital cardiac arrest is a global health issue, which concerns all patients and health care workers. Before making decisions about cardiopulmonary resuscitation and treatment restrictions, physicians must communicate accurate expectations of outcome to patients and families. However, one important caveat when reviewing these survival data is that its applicability to individual patients is limited. Although data on long-term outcome can inform patients on medical decisions about CPR, these data represent survival spread over a large population rather than predicting the trajectory for any individual patient. Overall we can conclude that one-year survival is poor in patients admitted to hospital for non-cardiac disease. Specific patient-level prognostication may probably require more knowledge about age, comorbidity and intercurrent disease.

In conclusion, our systematic review showed a one-year survival of 13.4% in IHCA patients. The time trend between 1985-2018 has shown a modest improvement in one-year survival rates. Future research is needed, specifically into the subject of prognostic factors for long-term qualitative outcome. Furthermore description of IHCA populations might elicit the issue of stagnated survival over the past decades. Moreover, more studies are published randomizing extracorporeal CPR vs. conventional CPR, which in the future could be a more common method of resuscitation[68]. We feel multicentre prospective research in a known source population is needed to improve current knowledge on this subject.

First author	Year of publication	N	Country	Investigated period	Study population	Design	Excluded	Outcome
Al-Alwan	2014	471962	USA	1994-2005	IHCA patients without intubation and one or more days after intubation	RC	patients who were intubated or received CPR on the same day	1 year survival post-CA
Berger	1994	255	USA	1985-1989	IHCA, in non-critical hospital areas.	PC	-	1 year post-discharge
Beuret	1992	181	Switzerland	N/A (2 year period)	IHCA patients	RC	respiratory arrests not complicated by a malignant arrhythmia, syncopal episodes and seizures	1 year survival post-CA
Bloom	2007	732	USA	1995-2004	Veterans hospital CA patients	RC	-	1 year survival post-CA
Blumenstein	2016	272	Germany	2009-2013	IHCA patients in a specialized centre for cardiology	RC	-	1 year survival post-CA
Chen	2014	5151	Australia	2002-2009	IHCA patients	RC	-	1-year survival post discharge
Colmenero	2004	89	Spain	2000-2002	IHCA patients	PC	Perioperative cardiac arrests	1 year survival post-CA
Dimopoulou	2001	29	Greece	1993-1996	Post-cardiac surgery IHCA patients	PC	IABP, maximal inotropic support, massive bleeding <2 hrs post-op	1 year survival from discharge
Ezquerra	2009	90	Spain	2003-2006	IHCA patients >18 years	RC	DNAR	1 year survival post-CA
Feingold	2016	1262	USA	2008-2010	IHCA patients	PC	-	1 year survival from discharge
Fredriksson	2006	833	Sweden	1994-2001	IHCA patients	PC	-	1 year survival from discharge
Gomes	2005	452	Brazil	2004	IHCA patients >14 years	PC	-	1 year survival post-CA
Heller	1995	308	Australia	1984-1991	Myocardial infarction in in hospital patients aged 25-69	PC	-	1 year survival post-CA
Herlitz	2000	216	Sweden	1994-1995	IHCA patients	PC	-	1 year survival from discharge

First author	Year of publication	N	Country	Investigated period	Study population	Design	Excluded	Outcome
Hessulf	2018	18069	Sweden	2006-2015	IHCA (inside hospital walls) > 18 years	RC	-	1 year survival post-CA
Huang	2002	103	Taiwan	1999-2000	Patients, receiving CPR	PC	<17 years	1 year survival from discharge
Joshi	2015	260	India	N/A (1 year period)	IHCA patients	PC	-	1 year survival post-CA
Karetzky	1995	668	USA	1990-1992	IHCA patients	RC	Patients only receiving limited CPR (without compressions)	1 year survival post-CA
Kutgsogiannis	2011	517	Canada	2000-2005	Adult IHCA patients in critical care units	PC	Secondary arrests, patients that didn't need life support	1 year survival post-CA
Lees	2012	99	UK	2005-2011	Post-cardiac surgery IHCA patients	PC	-	1 year survival post-CA
Lin	2010	63	Taiwan	2004-2006	IHCA patients, cardiac origin, 18-75 years	PC	CPR <10 min, non-witnessed and no ROSC	1 year survival post-CA
Menon	2014	413403	USA	1992-2005	IHCA patients ≥65 years, one vs multiple CPR events	RC	-	1 year survival
Möhnle	2012	189	Germany	2004-2006	IHCA patients	RC	-	1 year survival post-CA
Moretti	2007	156	Brazil	1998-2001	ICHA patients in a "service or unit"	PC	<20 years, found dead, futile CPR, DNAR order, <15 days ago surgery, drug overdose or trauma	1 year survival from CA
O'Sullivan	2016	63	Ireland	2011	IHCA patients who occupied a bed, >18 years old	RC	DNAR order	1 year survival post-CA
Paniagua	2002	474	USA	1993-1996	IHCA, >80 years old	RC	-	1 year post-discharge
Rankin	1998	133	New-Zealand	1995-1996	IHCA	PC	-	1 year survival post-CA
Rudiger	2004	25	Switzerland	2000-2002	IHCA patients	PC	ICU patients	1 year survival post-CA

First author	Year of publication	N	Country	Investigated period	Study population	Design	Excluded	Outcome
Saklayen	1995	340	USA	1988-1989	Veterans hospital CA patients	RC	-	1 year survival post-CA
Shin	2013	321	Korea	2003-2009	IHCA patients >20 years	RC	>80 years, previous serious neurological damage, current intracranial hemmorhage, terminal malignancy, traumatic origin of CA, septic origin of CA, MOF, DNAR order, CPR <10 min and unwitnessed arrest	1 year survival post-CA
Skrifvars	2003	204	Finland	2000-2001	IHCA	PC	-	1 year survival post-CA
Skrifvars	2005	183	Finland	1993-2002	IHCA on general wards	PC	-	1 year survival post-CA
Stapleton	2014	358682	USA	1994-2005	IHCA patients, suffering from chronic illness	RC	-	1 year survival post-CA
Thompson	2018	45567	USA	2000-2011	IHCA ≥65 years, in an inpatient ward or ICU.	PC	Patients without documented initial rhythm and unable to link to medicare claims data.	1 year survival post-CA
Tunstall-Pedoe	1992	2838	UK	N/A (1 year period)	IHCA, or CPR continued on arrival	PC	false alarms, recurrences within 24 hours	1 year survival post-CA
Vakil	2016	182	USA	1991-2014	Post-cardiac surgery veteran IHCA patients	RC	<18 years	1 year survival post-CA
Varon	1998	83	USA	1993-1994	IHCA cancer patients	RC	Respiratory arrests, patients in shock	1 year survival from discharge
Wong	2015	33731	USA	2000-2010	Medicare beneficiaries 18 years or older, initiating dialysis	RC	-	1 year survival from discharge
Yi	2006	214	South-Korea	1992-2002	IHCA in the neurosurgical ICU	RC	-	1 year survival post-CA

Table 1. General characteristics of included studies (n=39). Study design: PC = prospective cohort, RC= retrospective cohort

First author	Mean age (±SD)	% male	% cardiac patients	% monitored/witnessed	% VF/VT	% CPC 1 or 2 at 1 year
Al-Alwan*	73.3 (±11.9) vs 75.0 (±11.4)	50.4 vs 50.4	N/A	N/A	N/A	N/A
Berger	67.4	N/A	N/A	N/A	25.0	N/A
Beuret	61.5 (17.0-89.0)**	69.0	N/A	34.0	39.0	N/A
Bloom	59.0	N/A	N/A	N/A	N/A	N/A
Blumenstein	75.3 (67.4 – 79.1)***	61.4	100	100	2.9	N/A
Chen	68.2 (±16.9)	61.2	N/A	N/A	N/A	N/A
Colmenero	68.0 (56-74.5)**	57.3	N/A	N/A	34.8	100
Dimopoulou	61.0 (±11.0)	87.5	100	N/A	44.0	N/A
Ezquerra	73.1 (±12.3)	68.9	N/A	N/A	22.2	93.0
Feingold	61.1 (±14.3)	50.8	N/A	N/A	N/A	N/A
Fredriksson	69.4	63.0	66.0	N/A	48.6	N/A
Gomes	54.1	54.9	N/A	76.8	39.0	N/A
Heller	60.4	63.0	N/A	N/A	N/A	N/A
Herlitz	68.0***	62.0	N/A	N/A	N/A	95.0
Hessulf	75***	71.0	29.0	50.0	32.0	N/A
Huang	66.8	71.0	17.0	N/A	14.0	N/A
Joshi	N/A	N/A	31.2	91.0	21.9	96.0
Karetzky	59.2	48.2	N/A	65.7	15.7	N/A
Kutgsogiannis	66.5 (±14.9)	62.3	60.6	100	33.7	N/A
Lees	N/A	N/A	100	100	26.8	N/A
Lin	60.6 (±12.7)	65.1	47.6	N/A	41.3	91.0
Menon	78.3 vs. 77.4	50.5 vs 50.7	N/A	N/A	N/A	N/A
Möhnle	65.2 (±16.1)	69.8	N/A	21.7	32.3	N/A

First author	Mean age (±SD)	% male	% cardiac patients	% monitored/witnessed	% VF/VT	% CPC 1 or 2 at 1 year
Moretti†	64.4 (±17.2) vs 63.6 (±15.8)	58.6 vs 55.2	N/A	90.3 vs 74.6	32.7 vs 22.1	N/A
O'Sullivan	74.3***	63.4	44.4	87.3	30.2	81.0
Paniagua	86.0 (±4.8)	42.0	N/A	N/A	N/A	N/A
Rankin	N/A	N/A	N/A	47.4	32.3	100
Rudiger	72.8	72.0	N/A	N/A	28.0	N/A
Saklayen	66.9	N/A	N/A	57.0	18.0	N/A
Shin	61.6 (±14.2)	62.6	49.5	100	22.7	N/A
Skrifvars	68.0 (±15.8)	59.3	N/A	72.1	28.0	N/A
Skrifvars	73 (64.0 – 78.0)**	60.0	N/A	75.4	33.3	N/A
Stapleton	78.9 (±7.2)	50.3	N/A	N/A	N/A	N/A
Thompson	77.2 (±7.4)	55.5	26.7	25.3	20.3	N/A
Tunstall-Pedoe	N/A	64.2	N/A	N/A	N/A	N/A
Vakil	68.0 (±8.0)	98.0	100	N/A	71.4	N/A
Varon	56.2	49.3	N/A	N/A	N/A	N/A
Wong	>65.0	53.9	16.7	N/A	N/A	N/A
Yi	54.0 (±9.4)	65.5	19.2	100	29.0	N/A

Table 2. Patient characteristics of included studies (n=39). *= Intubated vs non-intubated; **= Mean (range); ***= Median with/without IQR; † =With vs without cardiac life support training groups (the survival is the overall survival).

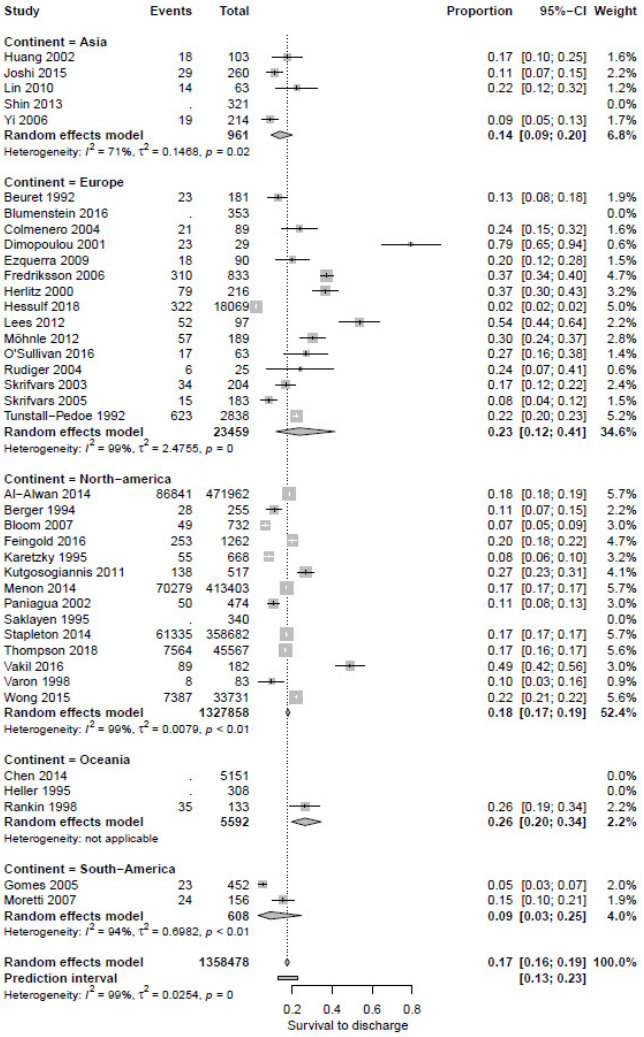

Figure 3. Pooled survival to discharge rate after in-hospital cardiac arrest for studies that reported this outcome measure.

Survival rates (%, 95%PI)	Survival to discharge	I^2, τ^2, p-value	One-year survival	I^2, τ^2, p-value
Overall	17.6 (13.1 – 22.7)	99%, 0.03, <0.01	13.4 (5.6 - 28.8)	100%, 0.22, <0.01
Cardiac	49.7 (3.8 - 96.2)	88%, 0.44, <0.01	39.3 (16.1 - 68.6)	85.0%, 0.16, <0.01
Non-cardiac	15.9 (12.0 – 20.7)	99%, 0.02, <0.01	10.7 (4.4 – 23.6)	100%, 0.21, <0.01

Table 3. Summary of outcomes from the performed meta-analyses. All survival rates are presented with a 95% prediction interval (95%PI). Non-cardiac was defined as studies not included in the cardiac subgroup analysis.

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History does not repeat itself,
but it rhymes.

Margaret Atwood, The Testaments

Chapter 2

One-year survival of patients admitted to the intensive care unit after in-hospital cardiac arrest: a retrospective study

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Abstract

Purpose

Little is known about long-term survival after In-Hospital Cardiac Arrest (IHCA). The purpose of this study is to report the one-year survival of patients after IHCA and to identify predicting factors.

Methods

Single-centre retrospective study of all adult in-hospital CPR attempts conducted between 2003 - 2014 in a tertiary teaching hospital. Demographic and clinical variables of patients were obtained at 24 hours pre-arrest, during CPR and post-CPR. All patients were tracked one year after discharge from hospital.

Results

CPR was performed for IHCA on 417 patients. Return of spontaneous circulation (ROSC) was achieved in 283 (68%) patients, 234 were admitted to ICU. Overall, 95 (23%) patients survived one year after discharge, The survival rate of patients who were admitted to ICU after IHCA was 38% (89/234) at hospital discharge and 26% (61/234) at one year. Univariate analysis showed numerous variables are associated with one-year survival, for example comorbidity index and time to ROSC.

Discussion

One-year survival of patients admitted to the ICU after IHCA was 26%. Severity of disease pre-arrest and at ICU-admission could prove useful in prognostication. No multivariate model could be constructed and large prospective studies are needed to elicit the role of pre-arrest factors on survival.

Introduction

In-hospital cardiac arrest (IHCA) is one of the major adverse events in hospitalized patients, with a reported incidence of 1 to 5 per 1,000 admissions[1-4]. For a patient to regain a sufficient circulation, or return of spontaneous circulation (ROSC), cardiopulmonary resuscitation (CPR) can be attempted according to life support guidelines[5,6]. Patients with ROSC are most often transferred to an intensive care unit (ICU) for additional treatment.

The survival to discharge of patients after IHCA is currently 18-27%[4,7,8], compared with studies performed in the 1980s and 1990s which showed a 15% survival rate[9,10]. A limited number of studies have reported the long-term outcome, in which the one-year survival of patients who were discharged alive varied between 59% and 86%[1,11-23].When considering the trend of survival rates, survival to discharge shows improvement in time, whereas long-term survival remains nearly unchanged[1-23].

Only a few patient factors have been found to be associated with one-year survival, e.g., lower age and the level of patient monitoring[20,22]. An initial arrest rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) is associated with a higher one-year survival[4,21,22]. The prediction of survival is preferably based on pre-arrest variables such as age and type of admission. Co-morbid disease can also be a relevant factor because it has been shown to influence 30-day survival35 Evidence however is still conflicting regarding the role of comorbidity and age and its interactions[22,23,35]. Other factors that could affect one-year survival include post-arrest factors such as ICU treatment, subsequent complications and neurologic status upon discharge. One-year survival has been shown to be lower among the group of patients discharged with neurologic impairment, defined as severe disability or coma[16,22]. This is 10-20% of the patients in younger cohorts[1,4,14,15] and up to 56% in older cohorts[22,23].

These data indicate that the likelihood of survival after IHCA is still low and little is known about its contributing factors. The objectives of this study were to obtain information on the one-year survival of patients admitted to the ICU after IHCA in the last 10 years and to identify possible predictors of one-year survival. Within the IHCA population, we assessed the mortality of the entire cohort and of patients not admitted to the ICU separately. Secondly we made a comparison to survival in the general population. The results from this retrospective study will aid in the design of a prospective cohort study.

Methods

Setting

This retrospective chart study of patients with IHCA was performed between January 6, 2003 and February 6, 2014. This study was conducted at the Onze Lieve Vrouwe Gasthuis (OLVG) hospital in Amsterdam, The Netherlands, a tertiary teaching hospital with 555 beds, including 24 mixed ICU beds. An average of 26,022 patients per year are admitted and hospitalized for a mean duration of 5.0 days. The ICU has 1,646 admissions per year, with an average length of stay (LOS) of 4.1 days per admission. In 2009 a rapid response system was introduced using a set of vital parameters to identify patients at risk for adverse events, including IHCA. Initial response was done by a physician on the ward, who could ask for intervention of the intensivist. All patients with an IHCA were screened for inclusion in this retrospective analysis. Patients were excluded if no CPR had been performed defined by lack of chest compressions. We excluded children (<18 years) and patients in whom OHCA had occurred the same day and in whom IHCA was clearly of the same aetiology. Additional exclusion criteria were IHCA in the operating theatre (OR), emergency department (ER) or ICU. Although part of the Utstein definition of IHCA5, data control in these patient groups are poor, as many reanimations in these departments are short, only consist of defibrillation without performing CPR, CPR is giving shortly for low circulation status (instead of no circulation) and most of the times the ALS team is not called in for support.

Resuscitation calls

In the event of cardiac arrest, the ward nurse calls a central number, which dispatches the resuscitation team. This team is available 24/7 and consists of an intensivist, an emergency physician, a cardiologist, an emergency department nurse and a cardiac care nurse. Patients with ROSC admitted to the coronary care unit (CCU) or thoracic surgery high care unit and in whom a cardiac aetiology was suspected, could remain in these departments after evaluation by the on-call intensivist. The decision to not transport a patient to ICU is mainly influenced by time to ROSC, initial post-arrest Glasgow Coma Scale (GCS) and hemodynamic stability. All other patients were transported to ICU. All the resuscitation calls were documented in Metavision Patient Data Management System (PDMS) v5.45.64 (iMDsoft, Needham, MA, USA), and each record was individually checked for validity.

Outcome

The primary outcome was one-year survival. Secondary outcome measures were initial survival, ICU-survival, survival to discharge and factors that could predict one-year survival. Initial survival was defined as a patient who had ROSC after the IHCA arrest and did not have an unfavourable prognosis that led to death within 24 hours after the initial arrest. The death dates were obtained from the Dutch municipal records system, which registers each death and links it to a national database. The patients were considered to have died post discharge if the date of death was 1 day or more after the date of discharge, allowing for a delay in registration or incorrect registration. The likelihood of one-year survival for post-CPR patients was compared to the likelihood of survival in the general population, for whom survival statistics were provided by the Dutch National Statistics Agency(CBS).

Data collection

The demographic and clinical variables collected included age, sex, the medical specialty for which a patient was admitted, type of ward (i.e. monitored or non-monitored), first documented cardiac rhythm and outcome of CPR. The clinical data on patients admitted to the ICU were gathered at three time points: 24 hours before cardiac arrest, at the time of ICU admission and upon discharge from the ICU. Such data was not fully available for patients not transferred to ICU. To ensure data completeness we only investigated predictive factors for patients after IHCA who were transferred to ICU. The pre-arrest Charlson Comorbidity Index (CCI) to compare comorbidities was retrospectively calculated by the authors (MS, HE) using the medical records of the patients. This score is a measure for the burden of comorbidities and most commonly used in comparative research[29]. Using CCI and stratifications of age an Age-combined Charlson Comorbidity Index (ACCI) was calculated. This score has been used in prior research to combine comorbidity and age in prognostication of outcome[29,35]. Although an updated version is available we used the version of Sundarajan et al. (2004) for comparison to other studies[29,35,36]. The calculation of this score is summarized in table 1.

Statistical analyses

Dichotomous variables were analysed using crosstabs and $\chi 2$ tests with continuity correction or Fisher's exact test. The Mann-Whitney-U test was used to assess difference of continuous data. Age stratification per decade was performed to assess differences in age groups. All of the statistical analyses were performed using the SPSS statistics processor v18 (IBM corp., Chicago, IL, USA).

Ethical considerations

The study protocol was approved by the local medical ethics board which granted a waiver for informed consent on account of its non-interventional design. This study was registered as WO 14.006.

Results

A total of 417 patients underwent a CPR attempt for an IHCA during the study period. Table 2 displays baseline characteristics. The median age was 70 years (IQR, 62-79), and 261 (61%) were male. Of all patients, 183 (44%) had initially been admitted to the department of cardiology and 119 (29%) to another non-surgical specialty; 263 (63%) were in a non-monitored nursing ward at the time of cardiac arrest. The initial arrest rhythm was pulseless electrical activity in 197 (47%) of these 417 patients, followed by asystole in 91 (22%). Shockable rhythms (VF/VT) comprised 86 (21%) patients.

Initial IHCA survivors

As shown in figure 1, a total of 283 (68%) patients survived the initial arrest (i.e., initial IHCA survivors). Characteristics of these initial IHCA survivors versus non-survivors are summarized in Table 2. A shockable rhythm was the only statistically significant univariate predictor of initial survival of CPR (ROSC) (87% survival vs. 65% survival for non-shockable rhythms; $p<0.001$).

One-year IHCA survivors from ICU

Of the 283 initial IHCA survivors 234 (83%) were transferred to the ICU and 49 (17%) were transferred to the CCU or special care units. A total of 89 of these 234 (38%) patients transferred to ICU survived to hospital discharge and 61 (26%) survived to one-year follow-up (Figure 1). Characteristics of patients who survived one year or more after admission to ICU and one-year non-survivors of IHCA after ICU are summarized in Table 3. Shockable rhythms were observed in 40% survivors and 17% of non-survivors ($p=0.002$). The time to ROSC was shorter in the one-year survivor cohort, with a median time of 8 minutes to ROSC (range, 5-10) vs. 10 minutes (range, 5-20) among the non-survivors ($p=0.012$). Survivors had a lower median CCI than the non-survivors: 4 (IQR, 3-6) and 5 (IQR 4-6) ($p=0.04$), respectively. No specific group of co-morbid diseases was more prevalent in either group. In survivors an ACCI of >8 points was less prevalent than in one-year survivors (44% vs. 61%, $p=0.014$). Glasgow Coma Scale was higher upon admission in one-year survivors (12 vs. 3, $p<0.001$). APACHE II, SAPS and SOFA scoring was significantly different between one-year survivors and non-survivors, although relatively high for both groups. APACHE-IV predicted mortality was high for both groups (80% for survivors and 91% for non-survivors, $p<0.001$) and significantly associated with a lower survival rate.

Temporal trends and comparison to the general population

Distribution of survival from 2003 till 2014 is displayed in figure 2. During the study period, survival to discharge remained between limits of 60-70%. There was a rise in the number of deaths directly post-CPR, with a decline in direct post-CPR survival of 77% in 2003 to 59% in 2014. In the same period ICU-survival rose from 71% to 79%. APACHE-IV, SAPS and SOFA scores did not alter during the study period. The likelihood of one-year survival for post-CPR patients was compared to the likelihood of survival in patients the same age from the general population. The risk difference was 22% lower survival for patients 70 years and older and 30% lower for patients under the age of 70 compared to peers who had not undergone CPR.

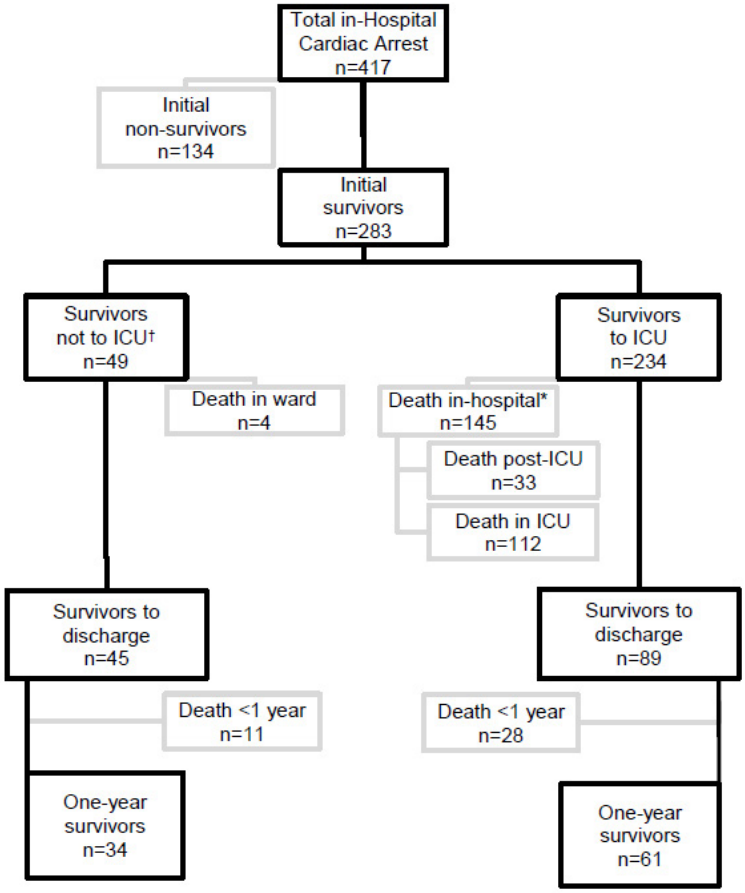

Figure 1. Flowchart of data collection and outcomes for all patients who received CPR for IHCA. †Patients who were not in need of ICU-treatment, and were able to remain in the ward or be transferred to the coronary care unit or high care unit after careful assessment by an intensivist. *The relation between cause of death and recent CPR was assessed for in-hospital deaths of ICU-admitted patients. Cause of death could be directly related (n=44) (e.g., post-anoxic encephalopathy, traumatic bleeding), indirectly related (n=58) (usually also a cause of the initial cardiac arrest such cardiogenic shock, respiratory insufficiency), not related (n=21) (e.g., subsequent infection) or unknown (n=22) (no relation could be either proven or excluded).

Discussion

This study provides insight into the survival of patients admitted to the ICU after IHCA in our hospital over the last 10 years. Initial survival after CPR was 68%. For all IHCA patients survival to discharge and one-year survival were 32% and 23% respectively and for patients admitted to ICU 38% and 26%. Next to initial rhythm at the start of CPR, clinical scores such as the APACHE IV and SOFA were highly associated with survival in ICU patients. Compared to findings in current literature, survival to discharge is high, although one-year survival is consistent with the results of prior studies[4,18,19,21-23].

. It is important for both patients and physicians to be aware of long-term outcomes. Although the one-year survival we found for patients who were discharged alive is high, this number decreases to 22% if viewed from the perspective of all resuscitation attempts. The findings of this study concur with recent data[4,8], as with data from earlier periods[15-18]. Our study further specifies that the majority of patients who suffer IHCA does not survive hospital admission. Although initial ROSC rate is 67.9%, more than half of these patients subsequently die either in ICU or in the hospital wards. This emphasizes the necessity for further research into factors that may yield better clinical outcomes.

Predictors and predicting models for survival to discharge after IHCA have been previously reported[30-34]. Two studies have succeeded in independently associating age with one-year survival[20,22] and one has combined age with comorbidity to predict 30-day survival[35]. The current study confirms the trend of age combined with comorbidity (ACCI) being linked to one-year survival. We identified several patient factors (ACCI, admission type) and CPR characteristics (time to ROSC, (non)shockable rhythm) being associated with one-year outcome. Most of these findings have been previously stated and confirm the tendency of pre-existent morbidity combined with current health status to be linked to outcome. This study found ICU scoring systems as APACHE-IV and SAPS to be associated with long-term survival. These systems were designed to predict hospital mortality using information from the first 24h of ICU admission. A large part of patients died while admitted to hospital (87%) rather than after discharge (13%) and this mainly explains the association between these scoring systems and survival. Factors that make up these scoring systems could prove useful for IHCA patients in ICU, however no valid multivariate model could successfully be designed. The APACHE-IV is however not an ideal tool for risk assessment prior to cardiac arrest, i.e. upon admission to the hospital. More research into predictive factors is needed.

The improving survival rate over time found in literature could be attributed to advances in medicine and ICU treatment[4,7-10]; however, our study shows a shifting trend in the location of death. More patients died directly after CPR and fewer in the ICU. It is believed that the case-mix of patients has an increasing number of co-morbidities in time[7]. This was not evident from our study. Higher mortality rates directly post-CPR implies that more resuscitations with poorer chances of success are being attempted. Furthermore we found that the implementation of a rapid response system did not bring forth lower incidence or higher survival. We could not pinpoint the cause of this contradictory finding, as usually rapid response teams have a positive effect in this

regard. We emphasize that these are single-centre findings, and we were not able to compare this to findings in literature. A factor associated with higher survival rates in other studies is shockable rhythm[4,21,22]. In this study however VF/VT incidence was lower than in the majority of populations and it did not change over time. This is probably explained by the fact that this study focuses on patients admitted to the ICU after IHCA. Patients with an IHCA after VF or VT, especially as this occurs on a monitored ward, will only need to be admitted to the ICU in a limited number of cases. As displayed in figure 1, some patients were not brought to ICU. This group mainly consists of patients from cardiac(-surgical) wards, who had short CPR duration and an initial rhythm of VF/VT. This explains the higher survival rate in this group. Although the univariate analysis confirmed that shockable rhythms are associated with higher survival to discharge, the effect diminished in terms of one-year survival, probably because other factors, such as severity of disease at ICU admission (such as the APACHE IV score) may have more impact on long-term outcome than initial rhythm.

This study benefits from a relatively large sample size when compared to other retrospective studies, a long study period and no loss to follow-up. It is the second-largest study in the last 30 years, which has not been conducted using insurance or hospital claims, but by collecting clinical data. The OLVG is a large teaching hospital that provides comprehensive medical care to patients of all ages. These facts mean that this study distinguishes itself from previous studies[1,11-23]. Although the overall trend was a decrease in mortality, no specific change was observed in relation to implementation of new resuscitation guidelines in 2005 or 2010. Another advantage is the analysis of pre-arrest variables and comorbidity in relation to one-year mortality, which has been rarely researched[22,29].

Certain limitations should be considered. First, the study involved a single-centre retrospective cohort Selection bias might play a role, because if consultation forms were completed incorrectly, the PDMS search did not include these resuscitations. This effect is however considered to be marginal because the system has a reminder function. Secondly, full data was available only for the patients who were transferred to the ICU, including data on characteristics of CPR (initial rhythm, duration to arrival and ROSC). An important limitation is the lack of a valid multivariate analysis. The number of variables associated with one-year survival largely exceeded the number of variables which would fit in a multivariate model due to the low number of one-year survivors (n = 61). We furthermore excluded CPR in the OR, ER and ICU. As mentioned previously data control in these patient groups is poor, because many CPR attempts consist solely of defibrillation or chest compressions for low-flow output without the call of a resuscitation team. At last, the only endpoint was survival, and functional status neither other cardiovascular endpoints were assessed.

To assess these endpoints, a prospective multicentre cohort study will be conducted. The Resuscitation Outcomes in the Netherlands (ROUTiNE) study will include all cases of IHCA occurring in from January 1st 2017 in fifteen Dutch hospitals. We will include all patients who suffer IHCA in hospital wards, including ER/OR/ICU. Patient data will be collected at the moment of cardiac arrest, at hospital discharge or death in-hospital, and at 3 months and 12 months after cardiac arrest. The latter will include questionnaires concerning quality of life and functional status.

Conclusion

Overall one-year survival of patients admitted to the ICU after IHCA is 26%. Survival is influenced by severity of disease at ICU admission (reflected by APACHE and SAPS score) and other ICU related factors (need of therapeutic hypothermia, length of ICU-stay and SOFA score). This study did not show an improvement in survival over time. A prospective multicentre cohort study will be conducted to further assess quantitative and qualitative outcomes, as well as associated patient and process variables.

	Specification (ICD-10 code)	Points	n=
Charlson Comorbidity Index Disease			
Acute myocardial infarction (<28 days)	I21, I22, I252	1	41
Congestive heart failure	I50	1	43
Peripheral vascular disease (aneurysmatic and occlusive)	I71, I790, I739, R02, Z958, Z959	1	16
Cerebral vascular incident (ischaemic and haemorrhagic)	I60, I61, I62, I63, I65, I66,G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69	1	17
Dementia	F00, F01, F02, F051	1	12
Pulmonary disease (restrictive, obstructive, infectious and inflammatory)	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65	1	27
Connective tissue disease (arthritides, systemic autoimmune disease)	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353	1	1
Peptic ulcer	K25, K26, K27, K28	1	23
Liver disease (sclerosis, fibrosis, cirrhosis; primary, alcoholic, non-alcoholic and toxic)	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745	1	21
Diabetes (with or without peripheral vascular complications)	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145	1	65
Diabetes complications (with ocular, neurological or renal complications)	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144	2	47
Paraplegia	G81 G041, G820, G821, G822	2	6
Renal disease	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25	2	35
Cancer	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96	2	10
Metastatic cancer	C77, C78, C79, C80	3	0
Advanced hepatic disease	K729, K766, K767, K721	3	5
HIV seropositivity	B20, B21, B22, B23, B24	6	2
Age			
≤49 years		0	14
50-59 years		1	25
60-69 years		2	71
70-79 years		3	74
80-89 years		4	49
≥90 years		5	3

Table 1. Calculation of the Age-combined Charlson Comorbidity Index (ACCI) and number of patients specified per diagnosis and per age category. This data was only gathered for patients admitted to ICU (n=236). ICD-10: International Classification of Diseases and Related Health Problems 10th edition.

	Initial survivors n=283	Initial non-survivors* n=134	p
Patient characteristics			
Age – median (IQR)	71(62-79)	71 (62-79)	.676
Male sex – n (%)	171 (60.4)	85 (63.4)	.556
Resuscitation variables – n (%)			
Type of ward†			.110
Non-monitored ward	187 (66.1)	76 (56.7)	
Monitored ward	73 (25.8)	40 (29.9)	
Catheterisation laboratory	23 (8.1)	18 (13.4)	
Type of admission			.336
Cardiology	117 (41.3)	66 (49.3)	
Cardiac surgery	42 (14.8)	15 (11.2)	
Medical non-cardiology	86 (30.4)	33 (24.6)	
Surgical non-cardiac	38 (13.4)	20 (14.9)	
Primary arrest rhythm			.000
Asystole	54 (19.1)	37 (27.6)	
PEA**	139 (49.1)	68 (50.7)	
VF/VT	78 (27.6)	8 (6.0)	
Unknown	12 (4.2)	21 (15.7)	

Table 2. Characteristics of all in-hospital cardiac arrests; survivors vs. non-survivors. *A survivor is defined as a patient who had ROSC after the IHCA arrest and did not have an unfavourable prognosis that led to death within 24 hours after the initial arrest. Among non-survivors, in 134 patients ROSC was not achieved and 2 patients were transferred to the ward with an unfavourable prognosis. †The type of ward was defined as monitored if the patient was continuously monitored for cardiac activity, such as coronary care units, high care units or stroke units. Non-monitored was defined as no cardiac monitoring (all remaining wards) and the catheterisation laboratory was defined as a separate ward. **PEA is defined as pulseless electrical activity and pulseless bradycardia or bradyarrhythmia,

	Mode of reporting	One-year survivors n=61	One-year non-survivors n=173	p
Patient characteristics				
Age	Median (IQR)	69 (59-78)	72 (64-79)	.164
Sex – male	n (%)	41 (67.2)	101 (58.4)	.225
BMI (kg/m^2)	Median (IQR)	27.1 (24.8-32.3)	26.1 (23.2-29.3)	.019
Charlson comorbidity index	Median (IQR)	4 (3-6)	5 (4-6)	.004
Age >80 years	n (%)	10 (16)	42 (24.2)	.218
ACCI	n(%)			.014
0-4 points		10 (16.4)	10 (5.8)	
5-7 points		24 (39.3)	58 (33.5)	
>8 points		27 (44.2)	105 (60.7)	
Admission type	n (%)			.003
Non- cardiology		21 (34.4)	98 (56.6)	
Cardiology incl. cardio-thoracic surgery		40 (65.6)	75 (43.4)	
Emergency admissions	n (%)	38 (62.3)	116 (67.0)	.318
DNR-orders upon admission	n (%)	0 (0)	5 (3.0)	.330
Days in hospital	Median (IQR)	3 (1-7)	4 (1-10)	.076
Arrest-related factors				
Time to CPR (min)	Median (IQR)	0 (0-0)	0 (0-0)	.586
Time to ROSC (min)	Median (IQR)	8 (5-10)	10 (5-18)	.012
Cause of arrest	n (%)			.098
Hypovolaemia		7 (11.5)	35 (20.3)	
Hypoxemia		14 (23.0)	63 (36.4)	
Electrolyte disturbance		3 (4.9)	6 (3.5)	
Hypothermia		8 (13.2)	8 (4.6)	
Cardiac tamponnade		0 (0)	0 (0)	
Thrombo-embolism		26 (39.3)	50 (28.9)	
Toxic		3 (4.9)	4 (2.3)	
Tension pneumothorax		0 (0)	0 (0)	
Unknown		1 (1.6)	3 (1.7)	
Other‡		1 (1.6)	4 (2.3)	
Primary Arrest Rhythm§	n (%)			.002
Shock		23 (39.7)	30 (17.3)	
Non-shock		35 (60.3)	135 (78.0)	
Type of ward	n (%)			.038
Monitored (incl. Cath-lab)		26 (42.6)	48 (27.7)	
Non-monitored		35 (57.4)	125 (72.3)	

	Mode of reporting	One-year survivors n=61	One-year non-survivors n=173	p
ICU-related factors				
Length of stay(days)	Median (IQR)	3.5 (2.0-7.1)	2.9 (0.5-5.1)	.002
Treatment restriction	n (%)	9 (14.8)	43 (24.9)	.213
CRRT	n (%)	17 (27.9)	48 (27.7)	.984
Lowest temperature (°C)	Median (IQR)	34.3 (32.3-35.8)	32.8 (31.9-35.4)	.003
Treatment with TH**	n (%)	37 (39.4)	121 (69.9)	.205
APACHE-II				
Score	Median (IQR)	28 (20-35)	34 (27-39)	.000
Predicted mortality - %	Median (IQR)	69 (42-85)	84 (66-93)	.000
APACHE-IV				
Predicted mortality - %	Median (IQR)	80 (41-90)	91 (73-96)	.000
SAPS-2				
Score	Median (IQR)	59 (44-73)	72 (58-85)	.000
Predicted mortality - %	Median (IQR)	66 (32-87)	86 (64-95)	.000
SOFA-score				
Highest measured	Median (IQR)	10 (7-14)	12 (9-16)	.004
Last measured	Median (IQR)	3 (2-5)	6 (3-11)	.000
Glasgow Coma Scale				
Upon admission	Median (IQR)	12 (3-15)	3 (3-14)	.000
At discharge	Median (IQR)	15 (15-15)	15 (3-15)	.000

Table 3. Baseline characteristics of all patients admitted to the ICU after successful resuscitation for IHCA; one-year survivors vs. one-year non-survivors. †A mean arterial pressure was calculated for blood pressure at 24 hours prior to IHCA. **All patients with a Glasgow Coma Scale score of 8 or lower were treated with therapeutic hypothermia during the study period. ‡Other causes for arrest were primary dysrhythmias or intracerebral pathology. §In 12 patients primary arrest rhythm was unknown. BMI, body mass index; ACCI; Age-Combined Charlson Comorbidity Index; DNR, do-not-resuscitate; bpm, beats per minute; MAP, mean arterial pressure; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; PEA, pulseless electric activity; TH, therapeutic hypothermia; VF, ventricular fibrillation; VT, ventricular tachycardia; CRRT, continuous renal replacement therapy; APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale.

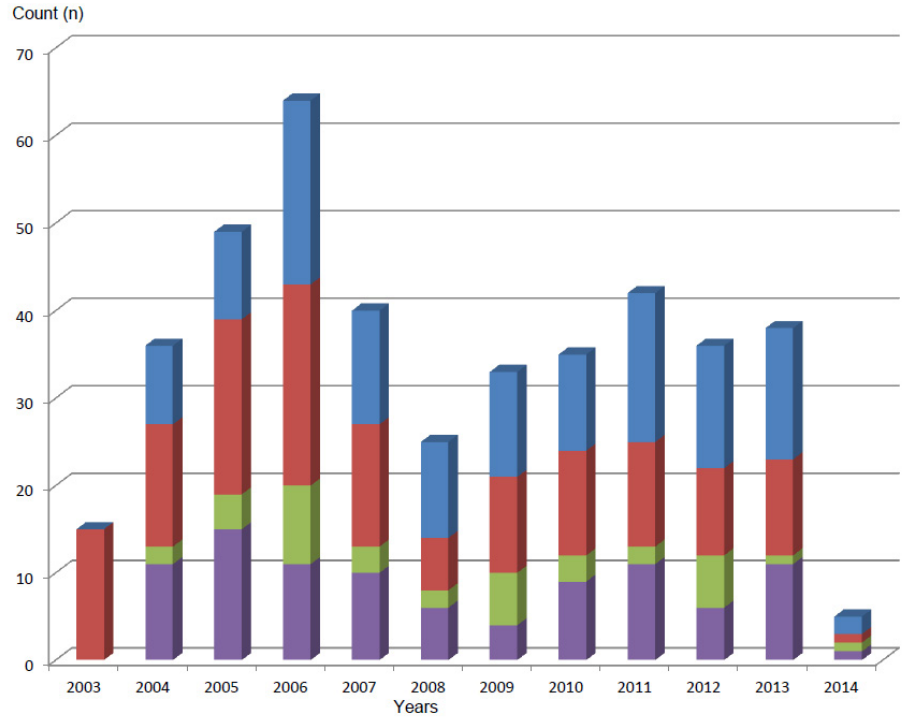

Figure 2. Incidence (n) of IHCA over the study period with survival rates. The years 2003 and 2014 do not have a full year of inclusion.

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Ask, and it will be given to you. Seek, and you will find. Knock, and the door will be opened.

The book of Matthew 7:7-8

Chapter 3

Cardiopulmonary resuscitation practices in the Netherlands: results from a nationwide survey

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Abstract

Introduction

Survival rates after in-hospital cardiac arrest are low and vary across hospitals. The ERC guidelines state that more research is needed to explore factors that could influence survival. Research into the role of cardiopulmonary resuscitation (CPR) practices is scarce. The goal of this survey is to gain information about CPR practices among hospitals in the Netherlands.

Methods

A survey was distributed to all Dutch hospital organizations (n=77). Items investigated were general hospital characteristics, pre-, peri- and post-resuscitation care. Characteristics were stratified by hospital teaching status.

Results

Out of 77 hospital organizations, 71 (92%) responded to the survey, representing 99 locations. Hospitals were divided into three categories: university hospitals (8%), teaching hospitals (64%) and non-teaching hospitals (28%). Of all locations, 96% used the most recent guidelines for Advanced Life Support and 91% reported the availability of a Rapid Response System. Training frequencies varied from twice a year in 41% and once a year in 53% of hospital locations. The role of CPR team leader and airway manager is most often fulfilled by (resident) anaesthetists in university hospitals (63%), by emergency department professionals in teaching hospitals (43%) and by intensive care professionals in non-teaching hospitals (72%). The role of airway manager is most often attributed to (resident) anaesthetists in university hospitals (100%), and to intensive care professionals in teaching (82%) and non-teaching hospitals (79%).

Conclusion

The majority of Dutch hospitals follow the ERC guidelines but there are differences in the presence of an ALS certified physician, intensity of training and participation of medical specialties in the fulfilment of roles within the CPR-team.

Introduction

In-hospital cardiac arrest (IHCA) is a major adverse event for hospitalized patients with a reported incidence of 1.6/1000 admissions in European countries[1]. Cardiopulmonary resuscitation (CPR) is started to restore circulation, but survival rates are low and vary across various countries and hospitals[2–4]. Recent guidelines call for research on long-term and patient-centred outcomes, as well as strategies to help improve survival of IHCA[5,6]. Much research is done on early recognition of patients at risk for IHCA and post-resuscitation care. The role of resuscitation practices itself and inter-hospital differences is far less examined, but is a growing focus in current research[7–9].

Survival after out-of-hospital cardiac arrest is relatively high in the Netherlands and we have learned from large cohort studies that optimisation of pre-hospital resuscitation care leads to higher survival[10]. The current European Resuscitation Council guidelines have several recommendations with regard to life support training of healthcare workers and strategies for prevention of cardiac arrest through Rapid Response Teams (RRT)[6]. Previous studies have demonstrated that quality characteristics such as team training and adherence to Advanced Life Support (ALS) guidelines are related to a higher survival probability for patients[9]. Furthermore hospital characteristics like teaching status, size and urban location are associated with differences in mortality after IHCA[11–15]. Knowledge about CPR practices might be useful for further research to optimise the chain of survival for IHCA.

The Resuscitation Outcome in the Netherlands (ROUTiNE) project is a nationwide initiative aimed at describing outcome of IHCA. Part of this project is a survey on CPR characteristics focussed on use of guidelines, training and organisation in Dutch hospitals. The goal of this survey is to describe the current resuscitation practices in the Netherlands.

Methods

Study population

A total of 77 Dutch hospital organizations with inpatient care facilities were identified in October 2017 by checking the report of the Dutch Hospitals Association (NVZ) on recent hospital mergers and acquisitions. In the Netherlands some hospitals are part of a larger organisation, but consist of different locations with independent facilities.

Measures and data collection

A letter was sent to each board of directors to inform them about this study and to announce our survey. We acquired contact information of the local resuscitation coordinator or CPR committee chairperson via the database of the Dutch Association of Resuscitation Team Coordinators (NVCR) or by calling the hospital directly. A web-based survey was distributed to all Dutch hospital organizations from October 2017 to February 2018. The survey was completed by the resuscitation coordinator, a designated medical specialist or a CPR committee chairperson. Respondents were asked to fill out the survey for each hospital location with inpatient care facilities within their organization. Queries were performed for discrepancies and missing values and completed through reminder mailings.

The survey was developed based on literature[11] and contributions by CPR experts from in and outside the Erasmus University Medical Centre. Several multidisciplinary meetings were held in which we consulted with anaesthetists, cardiologists, intensive care specialists, a nurse resuscitation officer and an epidemiologist. No specific predesigned survey instrument was available, therefore we created our own short-form questionnaire focussed on CPR practices as reported by the designated specialists. Before its acquisition period, a pilot was held by the participants of the ROUTINE study (n=18) to test clarity and comprehensiveness. Only minor adjustments were made to improve legibility.

This nationwide survey samples resuscitation practices with the goal of providing insights of resuscitation protocols at the institute. As no patient related data have been collected a formal IRB approval or waiver was not required to perform this survey. The online survey was built in LimeSurvey and included 63 items on 4 categories: general hospital characteristics, pre-, peri- and post-resuscitation care. We used dichotomous, multiple choice or multiple response questions for each item. Teaching hospitals were defined as providing medical specialty (registrar) training for at least two clinical specialties with an inpatient care facility, acknowledged by the Medical Specialist Registration Committee (RGS). Hospital geographic locations (i.e. metropolitan area, urban area, rural area) were determined by using the database of the Netherlands Environmental Assessment Agency (PBL).

Pre-resuscitation care involved preventive measures such as a Rapid Response Systems (RRS) and mandatory DNR-counselling upon admission. An RRS consists of an afferent component, also

known as the track-and-trigger system, and an efferent component, the Rapid Response Team (RRT). Peri-resuscitation care was regarded as care provided when cardiac arrest had occurred and pertains to team constitutions, training level and frequency and guideline adherence. A multiple response question with more than one answer per participant was provided to indicate all possible CPR team members and their roles, as we assumed that roles are interchangeable and often depend on local agreements, the moment and location of the resuscitation. RRT or CPR team members were presented by medical specialty and by professional level. Professional level is divided in three groups: medical specialists, residents and nurses/paramedics, wherein residents also include house officers. Questions about post-resuscitation care pertained mainly to treatment strategies, intensive care availability and temperature management. Intensive care units are divided into three levels according to the National Dutch Intensive Care Guidelines. A summary of the specifications of intensive care levels can be found in appendix 1.

Statistical analysis

All data were descriptive and presented as absolute numbers and percentages. For each variable with missing answers the number of respondents is mentioned at the sub header and the percentage is given relative to the available answers. Data are presented stratified by hospital teaching status; university hospitals, teaching hospitals and non-teaching hospitals. Analysis was done for hospital locations, unless otherwise stated.

Ethical considerations

This research does not include any patients. Questions were distributed among colleagues from other hospitals in the Netherlands. All respondents consented to participation and publication of the results. No specific legislation applies.

Results

Of the 77 hospital organisations, 71 (92%) hospital organisations responded to the survey. These hospitals represent 99 hospital locations.

General hospital characteristics

Of the 99 hospital locations, 8 (8%) were university hospital locations, 63 (64%) were teaching hospitals and 28 (28%) were non-teaching hospitals. Table 1 shows the hospital characteristics. All university hospital locations had a level 3 Intensive Care Units (ICU), ICU's of teaching hospital locations were mostly level 2 units (59%) and ICUs of non-teaching hospital locations were mostly classified as level 1 (75%). Of all hospital locations, 80 (81%) locations reported having a Coronary Care Unit (CCU). At organizational level, 29 (41%) hospital organizations reported having the ability to perform interventional cardiac catheterization and 16 (23%) reported having the ability to perform thoracic surgery.

Pre-resuscitation care

Table 2 provides an overview of the characteristics of the pre- and peri-resuscitation care across the different hospital types. DNR-counselling upon admission was reported as mandatory in 88 (89%) of all hospital locations. Most locations reported having an RRS (91%), of which one hospital reported an RRS without the use of the efferent component, an RRT. The Modified Early Warning System (MEWS) was the most frequently used track-and-trace system in university hospital locations (71%), while the Early Warning Score (EWS) was reported to be most used in teaching and non-teaching hospitals. It has to be stated that the term EWS can be used in the Netherlands for both using the old (binary) EWS, but also for the MEWS. In 55 (65%) hospital locations the RRT consisted of two persons. More details about pre-resuscitation care can be found in supplemental table 4.

Peri-resuscitation care

The second portion of table 2 summarizes the equipment, structure and organization of peri-resuscitation care across all responding hospital locations and figure 1 shows the distribution of these characteristics by hospital type. Ninety-five (96%) hospital locations reported following the 2015 ERC guidelines. All university hospital locations reported an ALS certified medical doctor available in the team 24/7. In teaching and non-teaching hospital locations this was the case in 37 (60%) and 11 (40%) locations respectively. A total of 22 (22%) hospital locations reported the availability of an ALS certified medical doctor as not strictly regulated in their hospital and 10 (10%) locations reported not having ALS certified medical doctors employed.

Training frequencies of the CPR team members varied across the hospital locations with 41 (41%) training twice a year, 52 (53%) training once a year and 6 (6%) hospitals training less than once a year. Teaching and non-teaching hospital locations reported to offer CPR training with a minimal of twice a year (41% and 46% respectively) more often in comparison with university hospitals (25%). Transthoracic echo use during CPR is reported by 59 (60%) of all hospital locations, performed mainly by a cardiologist or resident cardiology (80%). CPR teams consisted of minimal five team members in three (38%) university hospital locations, 32 (54%) teaching hospital locations and 18 (69%) non-teaching hospital locations.

The absolute frequency distribution of team leader, airway manager and circulation manager roles are shown in figure 2 (by level of profession) and figure 3 (by medical specialty) and specified in supplemental table 5. In teaching hospital locations, residents were reported more often as fulfilling the role of team leader during CPR than medical specialists (80% versus 67%). In university hospital locations (resident) anaesthetists were most often mentioned (in 63% of the cases), when in teaching hospital locations this role assignment was more often attributed to intensive care (36%), emergency care (43%) cardiology (39%) and internal medicine (34%). In non-teaching hospital locations, physicians from the intensive care and emergency department were identified most often (71% and 82% respectively) as being team leader during CPR. This pattern was also seen for the role of airway manager. All respondents of the university hospital locations identified the (resident) anaesthetist as airway manager, while teaching and non-teaching hospital locations identified the intensive care physician mostly (82% and 79% respectively) as responsible for this role.

Discussion

This nationwide survey covering 92% of all Dutch hospital organizations shows that CPR practices differ between hospitals. Although almost all hospital locations reported following the most current European guidelines for ALS, there are differences between hospitals in CPR training frequencies, the availability of ALS certified medical doctors during day and night and constitution of the CPR teams.

The current European Resuscitation Council Guidelines recommend a CPR (re)training more than once a year, because ALS knowledge and skills deteriorate within 6 to 12 months after ALS training[6,16]. Previous studies showed improved survival from IHCA when the responding emergency team included ALS-trained individuals [17–19]. In our study, 94% of all hospital locations report that CPR team members received routine resuscitation training, but only 57% of all hospitals reported round the clock availability of an ALS certified medical doctor. Ten per cent reported not having ALS certified medical doctors employed, although we do not know if other training was provided.

The importance of CPR practices have not yet been fully elucidated, however a recent publication finds that top-performing hospitals with regard to survival rates after IHCA show several common practices[9]. The first is a formally organized team composed of members from diverse disciplines. These members had delineated roles and responsibilities. They speak of strong communication, leadership and a focus on training and education. In our own study these features are clearly depicted. All responding hospitals have a designated CPR team. In general there is no formal organization of CPR teams, however they always consist of medical professionals (residents or specialists) who are trained a field of acute care. As this was not a qualitative study, we cannot make statements about strong communication. We can state that training and education is mostly according to ERC guidelines and 94% of hospitals train their personnel at least once a year.

In previous self-reported survey studies, conducted in 2009 and 2015 in the US, Germany, Austria and Switzerland, only 52-62% of hospitals reported offering routine training for CPR team members[20,21]. Another survey in the UK showed that 49% of junior doctors participating in CPR team not had ALS training, but would like to do so. These differences with our findings may be due to the fact that surveys of Siebig et al and Morgan et al. were anonymous[21,22]. Furthermore, the routine use of resuscitation officers in the Netherlands may contribute to this difference. This is in line with the survey of Edelson, who stated that less than half of the responding hospitals reported the presence of a resuscitation officer, which is correlated with routine CPR training [20]. Our study shows that CPR teams trained more than once a year in 41% of the cases, which is in line with our neighbouring countries[21].

Our results showed that CPR team physicians consisted of cardiologists, anaesthetists, intensivists and physicians from the emergency department. A German survey from 2009 reported that 80% of the physicians in the resuscitation team worked on an intensive care. Furthermore they reported that 55% of the physicians in the CPR team had a specialist qualification[21]. A survey conducted in the UK, reported the team leader is in 73-82% of cases represented by an emergency consultant[23]. In the present study we found comparable results: in the roles of team leader, airway manager and circulation manager the participation of residents and medical specialist was almost equally distributed. When stratified by hospital type, residents were most often participating in CPR teams in university hospitals and least often in non-teaching hospitals. This corresponds with findings of Edelson et al.[20]. An exploratory study showed that junior physicians are competent overall in managing resuscitation attempts but partly failed in the role of team leader[24]. We found a relatively low number of anaesthetists performing airway management. This finding should be elucidated by the fact that intensive care medicine in the Netherlands is performed by anaesthetists or internists with a focus in ICU-medicine, Based on local protocol airway management service is therefore provided by either the department of anaesthesia or the ICU. The total number of team members per CPR team in our survey is comparable with results reported by Porter el al., who stated resuscitation teams consisted in 64-69% of cases of four to six members[23].

In our study, 91% of the responding hospital locations reported to have a Rapid Response System (RRS) in place, which is in line with previous Dutch studies and also with findings of a survey in the US[20,25]. However, in 2008, the implementation of RRS was mandated by the Dutch government. Reasons for not having an RRS implemented yet are unclear.

Strengths and limitations

A limited amount of studies has investigated and described in-hospital CPR care. A key strength of our study is that, to our knowledge, this is the first Dutch survey of in-hospital practices that covers pre-, peri- and post-resuscitation care. We obtained a high response rate. However, it has to be taken in account that we gathered data through a non-anonymous self-report method, which could have negatively influenced the reliability of our data. Thereby, the questions mainly pertain to mandatory characteristics, which could have led to a risk of reporting bias and answers based on organisational policy instead of actual practice. We assessed availability of an ALS-certified physician during day- and night-time rather than the round the clock variance in team constitution. We presumed this to be a proxy of team training level. Lastly, one of the previously identified predictors of better outcome could not be obtained from this survey, i.e. debriefings after CPR attempts[11,26]. The reason is that this is mostly not documented.

This was a descriptive study and we did not investigate survival rates or other patient related outcomes. We conclude there is some variability across hospitals in the Netherlands. Protocol adherence and training frequencies are adequate. We aim to combine these data with our survival figures from the Resuscitation Outcomes in the Netherlands – project to better assess factors that influence survival.

Conclusion

The majority of Dutch hospitals follow the ERC guidelines but there are differences in the presence of an ALS certified physician, intensity of training and participation of medical specialties in the fulfilment of roles within the CPR-team. Knowledge on resuscitation practices and learning from best practice can be useful in improving CPR quality and can be of interest in future research.

Hospital location level n* (%)	University locations (n=8)	Teaching locations (n=63)	Non-teaching locations (n=28)	Total locations (n=99)
Hospital size				
< 300 beds	0	25 (39.7)	21 (75.0)	46 (46.5)
300-600 beds	1 (12.5)	30 (47.6)	7 (25.0)	38 (38.4)
> 600 beds	7 (87.5)	8 (12.7)	0	15 (15.2)
Location				
Metropolitan area	4 (50.0)	24 (38.1)	9 (32.1)	37 (37.4)
Urban area	4 (50.0)	28 (44.4)	3 (10.7)	35 (35.4)
Rural area	0	11 (17.5)	16 (57.1)	27 (27.3)
Availability				
Mobile Cardiac Telemetry	8 (100)	50 (79.4)	24 (85.7)	82 (82.8)
Coronary Care Unit	8 (100)	48 (76.2)	24 (85.7)	80 (80.8)
Medium Care or High Care	8 (100)	29 (46.0)	6 (21.4)	43 (43.3)
Intensive Care Unit	8 (100)	49 (77.8)	24 (85.7)	81 (81.8)
Level 1	0	7/49 (14.3)	18/24 (75.0)	24/81 (29.6)
Level 2	0	29/49 (59.2)	5/24 (20.8)	34/81 (42.0)
Level 3	8/8 (100)	13/49 (26.5)	1/24 (4.2)	22/81 (27.2)
Emergency Room	8 (100)	53 (84.1)	25 (89.3)	86 (86.8)
24/7	8/8 (100)	49/53 (92.5)	24/25 (96.0)	81/86(94.2)
Daytime + evening	0	2/53 (3.8)	1/25 (4.0)	3/86 (3.5)
Daytime	0	2/53 (3.8)	0	2/86 (2.3)
Hospital organisational level	**University organizations (n=8)**	**Teaching organizations (n=39)**	**Non-teaching organizations (n=24)**	**Total organizations (n=71)**
Availability				
Trauma Centre	8 (100)	3 (7.7)	0	11 (15.5)
Abdominal aortic surgery	8 (100)	31 (79.5)	12 (50.0)	51 (71.8)
Neurosurgery	8 (100)	9 (23.1)	0	17 (23.9)
Thoracic surgery	8 (100)	8 (20.5)	0	16 (22.5)
Interventional Cardiac Cath.	8 (100)	20 (51.3)	1 (4.2)	29 (40.8)

Table 1 Hospital characteristics. *In case of missing values or other denominator than all hospitals, the denominator is given.

Hospital location level n* (%)	University locations (n=8)	Teaching locations (n=63)	Non-teaching locations (n=28)	Total locations (n=99)
Pre-arrest variables				
Mandatory DNR-counselling upon admission	8 (100)	57 (90.5)	23 (82.1)	88 (88.9)
Rapid Response System available	7 (87.5)	55/61 (90.2)	25/27 (92.6)	87/96 (90.6)
Type of Rapid Response System				
EWS	2/7 (28.6)	33/55 (60.0)	16/25 (64.0)	51/87 (58.6)
MEWS	5/7 (71.4)	13/55 (23.6)	8/25 (32.0)	26/87 (29.9)
NEWS	0	2/55 (3.6)	1/25 (4.0)	3/87 (3.4)
Own scoring system	0	5/55 (9.1)	0	5/87 (5.7)
Number of team members RRT				
2 persons	6/6 (100)	34/54 (62.9)	15/25 (60.0)	55/85 (64.7)
3 persons	0	15/54 (27.8)	9/25 (36.0)	23/85 (27.1)
4 persons	0	2/54 (3.7)	1/25 (4.0)	3/85 (3.5)
Peri-arrest variables				
ERC/NRR 2015 Guidelines	8 (100)	60 (95.2)	27 (96.4)	95 (96.0)
Availability Medical Doctor with ALS certificate				
24/7	8 (100)	37/62 (59.7)	11 (39.3)	56/98 (57.1)
Daytime + evening	0	4/62 (6.5)	3 (10.7)	7/98 (7.1)
Daytime	0	3/62 (4.8)	0	3/98 (3.1)
No strict regulations	0	12/62 (19.4)	10 (35.7)	22/98 (22.4)
No doctor with ALS certificate	0	6/62 (9.7)	4 (14.3)	10/98 (10.2)
Training frequency				
Twice a year	2 (25.0)	26 (41.3)	13 (46.4)	41 (41.4)
Once a year	4 (50.0)	35 (55.5)	13 (46.4)	52 (52.5)
Less than once a year	2 (25.0)	2 (3.2)	2 (7.1)	6 (6.1)
Transthoracic echo use during CPR	7 (87.5)	35/62 (56.5)	17 (60.7)	59/98 (60.2)
Performed by (resident) cardiologist	7/7 (100)	26/35 (74.3)	14/17 (82.4)	47/59 (79.7)
Mechanical CPR use during CPR	5 (62.5)	23 (36.5)	12 (42.9)	39(39.4)
LUCAS	2/5 (40.0)	15/23 (65.2)	9/12 (75.0)	27/39 (66.7)
AutoPulse	2/5 (40.0)	6/23 (26.1)	3/12 (25.0)	11/39 (28.2)
Team size				
<4 persons	2 (25.0)	10/59 (16.9)	5/26 (19.2)	17/93 (18.3)
4 persons	3 (37.5)	17/59 (28.8)	3/26 (11.5)	23/93 (24.7)
>4 persons	3 (37.5)	32/59 (54.2)	18/26 (69.2)	53/93 (57.0)

Table 2 Pre- and peri-resuscitation care characteristics. *In case of missing values or other denominator than all hospitals, the denominator is given. DNR: Do Not Resuscitate, (M/N)EWS: (Modified/National) Early Warning System, RRT: Rapid Response Team, ERC: European Resuscitation Council, NRR: Dutch resuscitation council, ALS: Advanced Life Support, CPR: Cardiopulmonary Resuscitation, LUCAS: Lund University Cardiopulmonary Assist System.

Figure 1. Resuscitation characteristics by hospital level

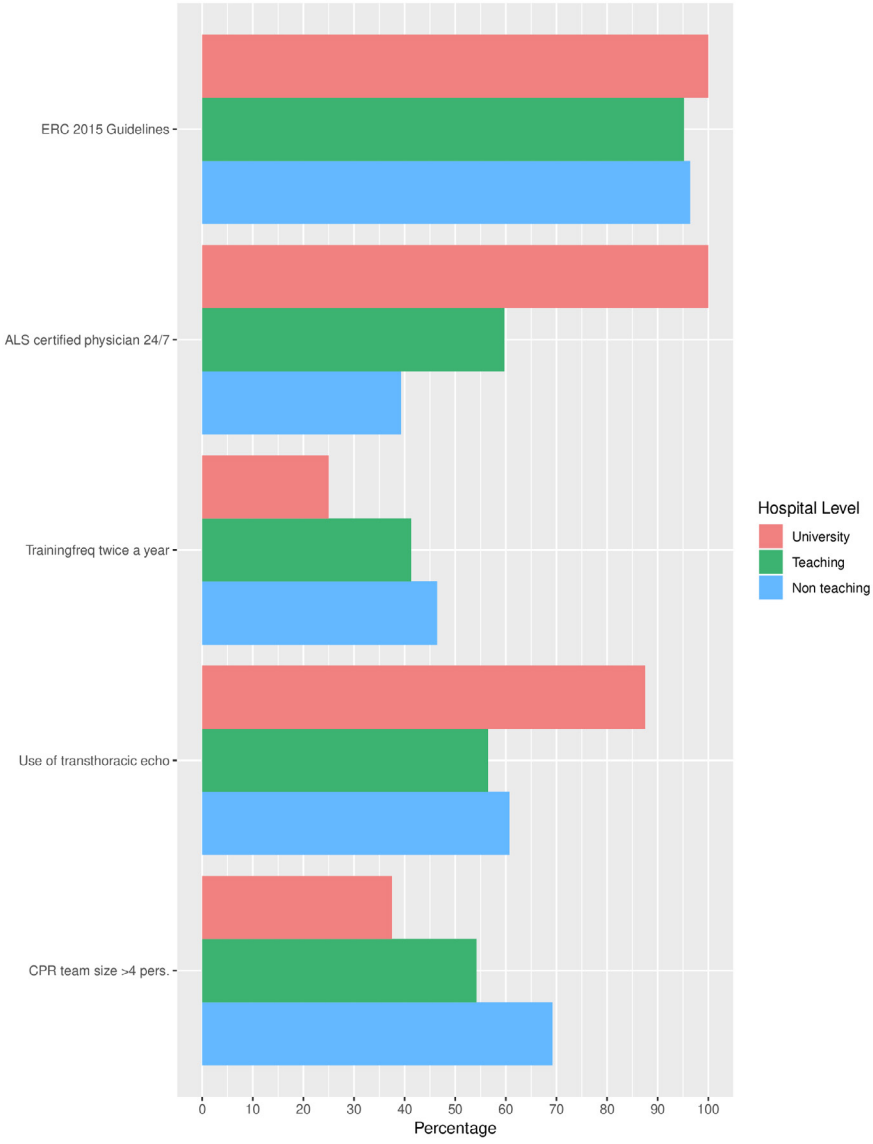


Figure 2. Constitution CPR teams by level of profession

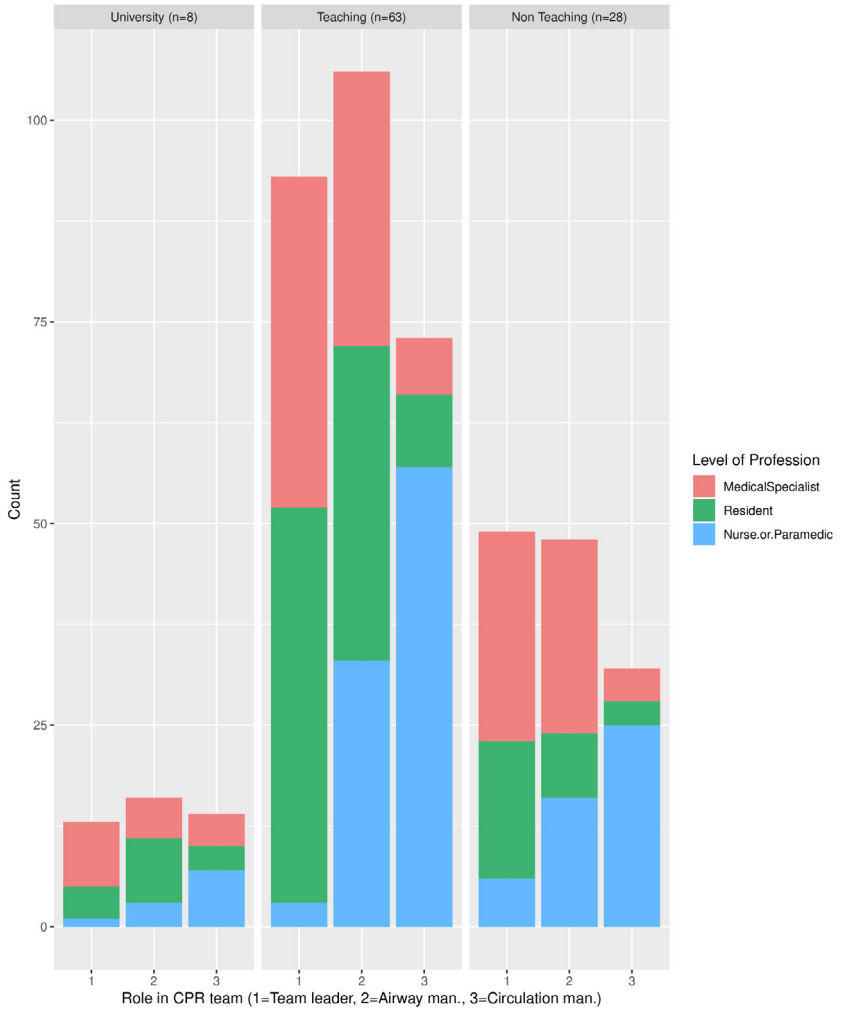
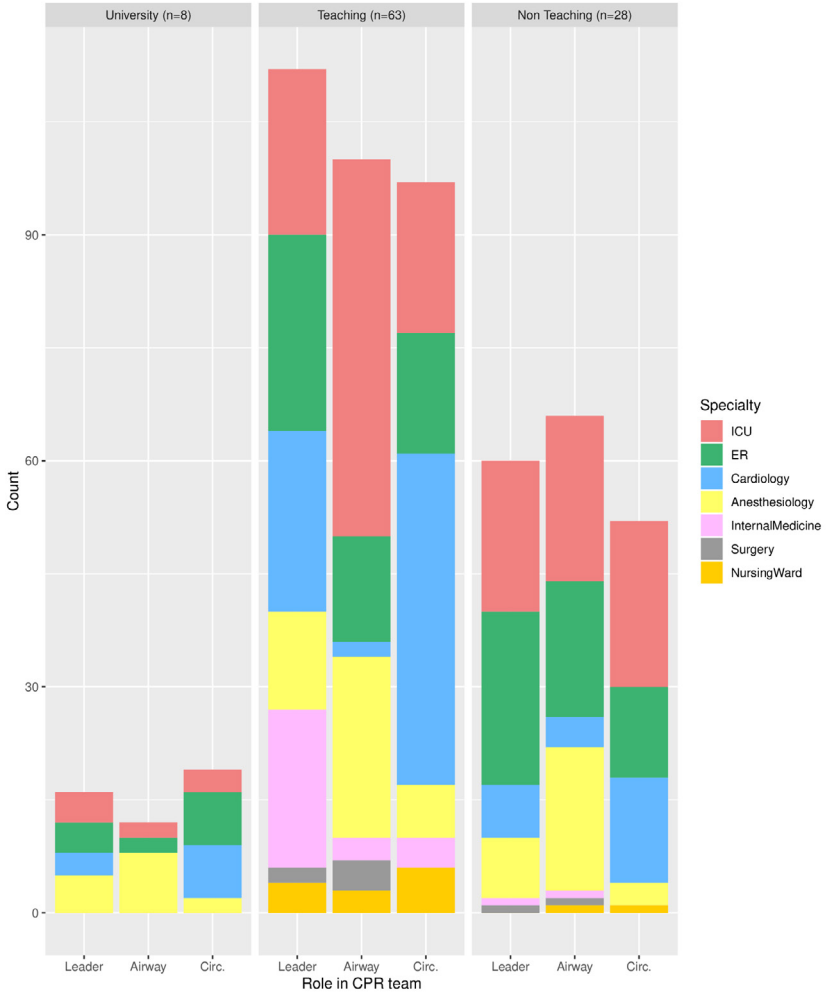


Figure 3. Constitution CPR teams by medical specialty



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Es hört doch jeder nur was er versteht.

Johann Wolfgang von Goethe

Chapter 4

A cross-sectional investigation of communication in Do-Not-Resuscitate orders in Dutch hospitals

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Abstract

Introduction

The decision to attempt or refrain from resuscitation is preferably based on prognostic factors for outcome and subsequently communicated with patients. Both patients and physicians consider good communication important, however little is known about patient involvement in and understanding of cardiopulmonary resuscitation (CPR) directives. The aim is to determine the prevalence of Do Not Resuscitate (DNR)-orders, to describe recollection of CPR-directive conversations and factors associated with patient recollection and understanding.

Methods

This was a two-week nationwide multicentre cross-sectional observational study using a study-specific survey. The study population consisted of patients admitted to non-monitored wards in 13 hospitals. Data were collected from the electronic medical record (EMR) concerning CPR-directive, comorbidity and at-home medication. Patients reported their perception and expectations about CPR-counselling through a questionnaire.

Results

A total of 1136 patients completed the questionnaire. Patients' CPR-directives were documented in the EMR as follows: 63.7% full code, 27.5% DNR and in 8.8% no directive was documented. DNR was most often documented for patients >80 years (66.4%) and in patients using >10 medications (45.3%). Overall, 55.8% of patients recalled having had a conversation about their CPR-directive and 48.1% patients reported the same CPR-directive as the EMR. Most patients had a good experience with the CPR-directive conversation in general (66.1%), as well as its timing (84%) and location (94%) specifically.

Conclusions

The average DNR-prevalence is 27.5%. Correct understanding of their CPR-directive is lowest in patients aged ≥80 years and multimorbid patients. CPR-directive counselling should focus more on patient involvement and their correct understanding.

Introduction

Cardiopulmonary resuscitation (CPR) for in-hospital cardiac arrest has a low one-year survival rate of 13% (95% CI: 11% - 15%)[1]. The decision to attempt or refrain from CPR is preferably based on prognostic factors for outcome and established through shared decision-making[2–5]. Although patients and physicians consider good communication on this subject to be important, this is not always achieved[6]. Evidence concerning optimal timing, location of and specific communication strategies is lacking[7]. Experts stress that decisions should be patient-centred and that CPR-directives should be part of discussions regarding future care planning[8,9].

Communication between patients and physicians seems suboptimal while most patients want to be actively involved in decision-making with regard to CPR[10–12]. Two decades of British newspaper coverage on the subject largely pertains to miscommunication and insufficient information given by physicians, sometimes even leading to legal cases[4]. Patients have limited knowledge about cardiac arrest and they tend to overestimate the probability of survival after CPR[13]. Moreover, DNR-orders are often mistaken for withdrawal of treatment, euthanasia or thought subject to ageism[4,11,14–16].

An international survey on CPR-directive practices reported large heterogeneity in approaches due to differing cultures and economic status[17]. The majority of respondents indicated national guidance on CPR-counselling is warranted, but currently often lacking. Although CPR is not specifically mentioned in Dutch legislation, it is stipulated that patients are informed and provide consent for any proposed treatment[18]. A national guideline on discussing DNR in frail elderly patients is available for general practitioners; no such guideline exists for hospital care[19]. It is proposed that the Dutch ''open culture" facilitates CPR-counselling[17]. Still, the most recent Dutch study (2005) reported that 90% of patient files lacked a CPR-directive[20]. Literature on DNR prevalence and patient perception is scarce. To achieve better patient counselling and to implement the right communication interventions, we must identify which patients need information, when they should receive it and how much is remembered[21]. The objective of this study was to provide an examination of patients' perceptions of CPR-directive counselling. The primary aim was to assess the prevalence of DNR-orders. The secondary aims were to establish how many patients recollected a conversation about a CPR-directive, what CPR-directive the patients then reported and if this was in agreement with the electronic medical record. Furthermore patients were asked about their experiences with the conversation and expectations towards survival rates after IHCA. Lastly an association between the aforementioned outcomes and patients' age, morbidity, familiarity with CPR and type of admission was assessed.

Methods

Study design

A nationwide multicentre cross-sectional observational study was conducted in 13 participating hospitals. We used a group of people to interview patients present at each location at one day. In this case the group of people consisted of our local investigators and student team, and the locations were hospital sites. Participating hospitals were recruited from the 19 hospitals participating in a study assessing long-term outcomes of in-hospital cardiac in the Netherlands[22]. The current study was registered at clinicaltrials.gov (NCT03807206). A structured questionnaire was created through focus group sessions with anaesthetists, intensivists, internists, a nursing scientist, an epidemiologist, a clinical ethicist, and a linguistic consultant. The questionnaire was assessed for legibility, clinimetric value and was pilot-tested to assess readability.

Patient population

The study population consisted of all adult hospitalized patients who were at risk for suffering in-hospital cardiac arrest and who were able to provide informed consent for the study. As mentioned there is no protocol for CPR-directive conversations. In our clinical experience patients who are admitted to the ward or who are scheduled for surgery have a CPR-directive entered in the electronic medical record. No guideline or protocol exists dictating this be discussed with the patient. We excluded patients from the intensive/cardiac/stroke care unit, because most patients are not able to provide consent or answer the questions. We excluded patients from day treatment centres (e.g. day-care surgery, outpatient dialysis), because their hospital stay is very short, and patients with cognitive impairment or a language barrier without interpreter available. Furthermore we excluded patients from the emergency room, because they were likely not have spoken to a physician prior to our survey and participation would be too strenuous. To protect our students patients with contagious disease (influenza, norovirus) were excluded. Cognitive impairment was generally defined as a Cognitive Performance Category (CPC) score ≥4 or CPC 3 and unable to provide consent[23]. Cases were reviewed by local investigators. If patients or nursing staff refused participation, the reason was noted anonymously.

Ethical considerations

Study participants provided consent for participation in the study and were given the possibility to opt-out. The study protocol was considered not to be subject to the Dutch Medical Research in Human Subjects Act (WMO) due to its non-interventional design. This study was registered as MEC 2018-1344 with the Erasmus University Medical Centre Medical Ethics Committee.

Data collection

Data were collected between January 21st 2019 and February 7th 2019. Each hospital location was visited for one day from 09:30am to 6:00pm, leading to 13 planned data collection days. Each hospital had been informed about the planned data collection date beforehand. On the day itself, the principal investigator (MS) and local investigators informed the ward nurses and the head nurse was asked to provide a list of patients who met the exclusion criteria. All eligible patients were asked to participate in the study. After providing consent, the patient completed a structured questionnaire on a tablet computer, aided by a student if necessary. These students had medical, nursing or psychology backgrounds and were instructed to obtain consent and help with the questionnaire. Students were instructed how to clarify questions to avoid misclassification bias.

Outcome measures

Demographic data were collected via the questionnaire, including the nature of the hospital stay and health-related quality of life using the EuroQoL descriptive system with 5 health dimensions and 3 response levels (EQ-5D-3L)[24]. Secondly patients were asked if a CPR-directive had been discussed with them. They were asked how they experienced timing and location of this conversation and what they thought their CPR-directive was. Lastly, they were asked to estimate the one-year survival probability of CPR for in-hospital cardiac arrest (0-100%). A researcher, blinded from the interview, collected the following data from the electronic medical record (EMR): CPR-directive, Charlson Comorbidity Index diseases[25] and number of medications used at home (excluding food supplements and lotions). The CPR-directive from the EMR was divided into three categories: full code (FC), do not attempt cardiopulmonary resuscitation (DNR) and not documented (ND). Patient responses yielded two more categories: code unknown to patient (CU) or not discussed with the patient (NDP). The data were pseudonymized. The translated questionnaire and case report forms are provided in supplement 1.

Open answers with regard to patient experiences were categorized by the investigators (TR, SIJ, MS) into four categories: positive, neutral, negative and self-determined. Finding it useful or appreciating having had a CPR-directive conversation was coded as 'positive'; having thought about a CPR-directive beforehand and expressing this thought was coded as 'self-determined'. With regard to timing and location of the conversation patients responded on a two or three point Likert-scale. We compared the CPR-directives from the EMR with patient recall of having a CPR-directive conversation and whether patients were aware of their CPR-directive (patient understanding). Correct patient understanding was assessed for patients who had a documented CPR directive. Correct understanding consisted of: 1) recollection of having spoken to a health care professional about the CPR-directive, and 2) reporting the same directive as documented in the EMR.

Statistical analysis

Descriptive statistics were used accordingly. Subgroup analyses were done for pre-specified subgroups on the basis of 1) age (per decade), 2) Age-Combined Charlson comorbidity Index (ACCI)[25], 3) number of medications used at home (as a proxy of chronic illness)[26], 4) familiarity with CPR and 5) being a CPR-survivor and 6) admission specialty. For the Charlson comorbidity index (CCI) a cut-off point of 7 points was chosen as it is associated with reduced outcome in several cohorts[25]. Also an ACCI was stratified for low (0-4 points), medium (5-7 points) or high (8+ points) burden of age and disease. A high score was previously associated with lower survival[27,28]. Data were analysed using SPSS statistics v25.0 (IBM, Chicago, IL, USA) and R. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Thirteen hospitals were visited. In total 3409 patients were present in the nursing wards, subsequently 1884 patients were screened for eligibility, 1699 patients were eligible for inclusion and 1136 patients completed the questionnaire. This yields a response rate of 67.0%. The flowchart for inclusion is summarized in figure 1. Included patients had a median age of 70 years (IQR 59-78), half of the population was male and most were born with the Dutch nationality (87.0%). Patient characteristics are shown in table 1.

CPR-directives and patient recollection

The CPR-directives from the Electronic Medical Record (EMR) for the included 1136 patients were distributed as follows: 63.7% full code (FC), 27.5% do not attempt resuscitation (DNR) and 8.8% not documented. The distribution of CPR-directives and patient recollection is depicted in figure 2. Of all questioned patients, 634/1136 (55.8%) recalled a conversation regarding a CPR-directive. Of patients with a full code, 384/724 (53.0%) recalled speaking to a health care professional, of patients with a DNR-order this was 228/312 (73.1%) ($p<0.001$). Of patients with a documented CPR-directive of either FC or DNR 499/1036 (48.1%) reported knowing their status and reported it in accordance with the EMR. For patients with FC this result was 330/724 (45.6%) and for patients with DNR 169/312 (54.2%) ($p=0.01$). For 81/1136 (7.0%) patients the directive they mentioned was not the one registered in the EMR.

Subgroup analyses

Results on subgroups were stratified by 1) DNR-prevalence according to the EMR, 2) CPR-directive conversation patient recall and 3) correct patient understanding. Results are shown in table 2. While none of the patients below 40 years had a DNR-status, the proportion of patients with a DNR-status increased to 66.4% in over 80-year-olds ($p<0.001$). For the Age-Combined Charlson Comorbidity Index (ACCI) a major increase was seen in DNR-prevalence for ≥5 points (49.6%) compared to lower scores (13.4%)($p<0.001$). The DNR-prevalence increased with the number of medications used at home from 7.2% (zero medications) to 45.3% (≥10 medications) ($p<0.001$). DNR-prevalence was higher in cancer patients (37.3%) than in non-cancer patients (24.2%) ($p<0.001$).

CPR-directive conversation recall

In total 634/1136 (55.8%) recalled a CPR-directive conversation. Recall was 28.4% for patients ≤39 years, 50.1% for 40-64 years, 58.9% for 65-79 years and 65.9% in patients ≥80 years old ($p<0.001$). Patients using less versus ≥10 medications had a recall percentage of 53.2% and 68.9% ($p<0.001$) respectively. Inversely a lower correct understanding was seen in patients using more medications from 73.3% (≥10 medications) vs. 83.8% (≤9 medications)($p=0.006$).

Patients' experiences with CPR-directive conversations

With regard to patient experiences patients were asked to provide an open answer. Most patients were positive (34.4%), neutral (16.3%) or self-determined (15.4%) about the CPR-directive conversation (table 1). Of the 25.0% of patients who had a negative reaction about the conversation, the majority was overwhelmed or aghast, whereas the rest found themselves unprepared to answer the question at that time. When specified for location and timing on a Likert-scale, 84% was positive about the timing and 94% was positive or neutral about the location. This is displayed in more detail in figure 3 and supplemental figure 2. Patients reported fewer negative experiences on average if the CPR-directive conversation had taken place in the outpatient clinic or at home (1.7%) compared to the ER or ward (7.4%) ($p=0.016$). No major differences were observed for the predefined subgroups (supplemental figure 3). The one-year survival rate after CPR for in-hospital cardiac arrest was estimated at a median of 55% (IQR 40-75%. When stratified for patient-reported CPR-status estimated survival was lowest in the DNR (median 50.0%, IQR 30.0-62.5%) and CU group (median 50.0%, IQR 30.0-80.0), followed by NDP (median 57.5%, IQR 41.3-80.0%) and FC (median 60.0%, IQR 50.0-80.0%)($p<0.001$). No significant differences in survival estimation were found between patients who were or were not familiar with CPR or between age groups.

Discussion

Of the hospitalized patients included in this study 27.5% had a DNR-order. Of all patients who participated in the study 55.8% recalled speaking to a health care professional about their CPR-directive. The prevalence of DNR-status increased with age and with the number of medications used at home. The prevalence of DNR also increased with a higher Age-Combined Charlson comorbidity Index (ACCI). The most striking discrepancy we found was that 7.0% of patients recalled a different CPR-directive than the one in the EMR.

In our study a CPR-directive was documented in 91.2% of medical records versus 9.8% in a Dutch single centre study from 2005[20]. DNR-prevalence in our study is higher than reported previously. Two studies from the USA reported a 15% DNR-prevalence among trauma patients and 11.7% prevalence in an intensive care setting[29,30]. DNR-orders were more prevalent in patients aged >80 years, with an ACCI >5 points or using >10 medications at home. A higher ACCI has been previously associated with poor outcome[27,28]. In a previous meta-analysis on this subject age was associated with a higher prevalence of DNR, however other important factors that might have affected DNR decisions, such as patients' premorbid status, functional status, and probability of survival were not uniformly included in all studies[31]. The authors did suggest these factors could influence DNR-decisions. The present study confirms the influence of age and severity of illness (by ACCI and use of medications).

Patients estimated one-year survival after IHCA 2.5 times higher than the actual survival rate found in our retrospective study and meta-analysis[1,27]. Patients with a FC have higher expectations of CPR survival in our study, as opposed to patient with other codes. This is in line with findings from a questionnaire in patients (admitted to medical wards) from the USA[32]. No association was observed between the expected survival rate after IHCA and patient's own experience, TV or Internet exposure, nor with age, comorbidity or the number of used medications. This implies there is room for better education on the prognosis of cardiopulmonary resuscitation.

To understand the discrepancies we found between documented CPR-directive and patients recollection, we must consider the possible situations in which patients are admitted to hospital. The first would be elective admission through the outpatient clinic (mostly surgical), in which the CPR-directive is documented in the outpatient clinic and may not be communicated with the patients. Reasons for not doing this may be that there is little time do discuss all aspects of surgery/treatment and the goal of the admission is full curation. Most patients will have a full code documented. Moreover, even if the CPR-directive was discussed, patients could have forgotten by the time they are admitted. The second possible situation is unplanned admission, in which patients may not always receive adequate information because of the emergency setting; meaning they are (considered) too sick to discuss this information with, or because of their severity of disease they cannot recollect later on. Lastly the situation remains that patients have a prior documented CPR-directive and this status is not confirmed or altered when patients are admitted on a next occasion. In this study we could not pinpoint the exact scenarios, as recollection was similar throughout admission types. We therefore think the discrepancies in recollection are surely in part attributable to admission type, however even more so to patients' characteristics.

The cross-sectional research design of collecting data one day per site, using a group of students, is a useful method for assessing point prevalence and gathering information in a short period of time. The response rate the study was 67.0%, which is relatively high[33]. Furthermore the reasons for non-inclusion were clearly described (figure 1). Our study can be considered representative of Dutch society with regard to ethnicity, educational level and religious background[34–36]. With regard to representation of the Dutch health care system our sample contained 1 (out of 8) academic hospital, 8 (out of 37) large regional hospitals and 4 (out of 57) small or rural hospitals. Although this study pertains to the Dutch medical system, we consider our results to be applicable to a broad range of Western countries.

Certain limitations should be taken into account. Firstly we have only assessed data at one day per hospital, and numbers can change throughout the year. Our study design has however enabled us to collect a large amount of data in a short period of time. Secondly inclusion was limited by patients who were not able to participate, i.e. cognitively impaired or severely ill, whereas these patients are of special interest for our research objectives. We encountered this limitation because these patients could not provide informed consent. We consider this effect to be negligible because these cases were specifically reviewed in each hospital and therefore the number of exclusions on these grounds is low. These exclusions might lead to a slight underestimation of the DNR-prevalence, as perhaps the sickest patients were not included. Due to privacy legislation we do not have specific data regarding age or morbidity of the non-included patients. Moreover misclassification bias could exist as we did not use a validated questionnaire. We hope this effect has been minimised by expert-review and pilot-testing of the questionnaire and by having trained students present at the interview. The third possible limitation is bias by refusal of 5/18 hospital organizations to participate in this study. We expect bias to be minimal due to a large sample size and the distribution in hospital types, sizes and patient characteristics. The distribution of codes was different between hospitals. We did not have sufficient data however to explain this finding, as it was not in our primary aims. Lastly, we did not enrol patients from outpatient clinics, intensive care and palliative care units. This might have resulted in an underestimation of the incidence of DNR orders.

The majority of patients stated they recalled a conversation about their CPR-directive. However specific subgroups might warrant more attention for better understanding, as 7.0% of patients mentioned another directive than was registered in the EMR. This situation should be avoided at all cost. Patients were generally not opposed to discussing CPR-directives and were more than willing to answer questions on the subject. The low CPR-directive conversation recall in young patients might be due to this group being generally healthy and therefore by default CPR will be attempted. Growing application of e-health might prove useful, as this group is apt to be informed via multimedia and if necessary a longer conversation may follow[37,38]. For patients who are prone to forget what had been decided, repetition of this conversation or a longer first CPR-directive conversation could aid in recollection and understanding[39].

Resuscitation policy should be tailored to the patients' situation and patients should be aware of their CPR-directive. We should speak to our patients about what is important to them and what

limitations modern medicine has. Initiatives such as the recommended summary plan for emergency care and treatment (ReSPECT) from the UK gives patients and physicians the possibility to talk about advanced directives. This way many misunderstandings can be avoided[4,40]. DNR-orders can become a part of advanced care planning and emergency care treatment plans[9]. We support recommendations for national guidelines and training of CPR-counselling to help physicians guide their patients in shared decision-making[16]. As mentioned there is no protocol for CPR-directive conversations. In most hospitals it is common practice to enter this in the EMR upon admission to the ward. How often this is just an administrative task, rather than a conscious decision is not clear. The current study gives rise to the suggestion that in young and healthy patients it is mostly administrative. We envision three possible scenarios for CPR-counselling. First: CPR is likely to be successful, and CPR will be attempted in case of IHCA if the patient agrees to this. Second: no clear prediction can be made, in which case the decision will be made based on the best available evidence and in agreement with the patient. Third: the potential burdens of CPR outweigh the benefits, the patient should be informed of these burdens and a DNR order is discussed with the patient. In all three scenarios the focus should be lay on the benefits and shared decision-making[40].

We conclude from this study that patients should be more involved in CPR-counselling and physicians should focus on correct patient understanding of the directive that will be documented. In this process physicians should pay attention to patient understanding in specific subgroups, such as elderly and multimorbid patients. We propose that the emphasis in future research lay on finding optimal timing for CPR-counselling and possible incorporation in early advanced directive conversations.

Characteristics*	
Age (median, IQR)	70 (59-78)
Sex, male	567 (49.9)
Admission specialty	
Medical	449 (39.5)
General surgery	217 (19.1)
Cardiology/cardiac surgery	193 (17.0)
Neurology/neurosurgery	101 (8.9)
Other surgical specialties	176 (15.5)
Born nationality	
Dutch	989 (87.0)
of which second generation immigrant	75 (6.5)
Surinam	40 (3.5)
Moroccan	12 (1.1)
Turkish	9 (0.8)
Other	86 (7.6)
Religion	
None	560 (49.3)
Christian	406 (35.7)
Islamic	44 (3.9)
Other	126 (11.0)
Level of education	
Primary school or none	170 (15.0)
Secondary school – prevocational	275 (24.2)
Secondary school – higher level	75 (6.6)
Vocational education	337 (29.7)
Univ. of applied sciences	215 (18.9)
University	64 (5.6)
Charlson Comorbidity index(median, IQR)	1 (0-2)
Number medications used at home	
None	139 (12.2)
1-5	476 (41.9)
6-9	331 (29.1)
>10	190 (16.7)
EQ-5D self-reported health state (mean, SD)**	62.1 (18.8)

Table 1 continues on the next page.

Characteristics*	
Familiar with CPR?	
Yes, witnessed in the street or at home	163 (14.3)
Yes, witnessed in-hospital	64 (5.6)
Seen on TV or internet	332 (29.2)
No	456 (40.1)
Did not respond	121 (10.6)
CPR-survivor	54 (4.8)
Estimated one-year survival in %; (med, IQR)	55 (40-75)
How was your reaction to the CPR-directive conversation?†	
Positive	219 (34.4)
Neutral	103 (16.3)
Negative	159 (25.0)
Self-determined‡	98 (15.4)
No response entered	57 (8.9)

Table 1. Characteristics of the patient population (n=1136). IQR, interquartile range; SD, standard deviation; EQ-5D, EuroQol 5 dimension questionnaire; CPR, cardiopulmonary resuscitation. *All values are displayed as (n, %), unless otherwise specified. **ranges from 0 (worst imaginable health) to 100 (best imaginable health), † Patients were only able to reply if a CPR-directive conversation had taken place(n=636). ‡ Self-determined means patients had already thought about their status prior to the conversation and felt confident and /or prepared for this conversation.

Subgroup *n/group n (%)*	n=	DNR-prevalence in EMR		CPR conversation patient recall		Correct patient understanding*	
All patients	1136	**312**/1136	(27.5)	**634**/1136	(55.8)	**499**/612	(81.5)
Age							
Young adults (18-39)	67	**0**/67	(0)	**19**/67	(28.4)	**16**/18	(88.9)
Older adults (40-64)	349	**51**/349	(14.6)	**175**/349	(50.1)	**141**/170	(82.9)
Seniors (65-79)	494	**111**/494	(22.5)	**291**/494	(58.9)	**232**/282	(82.3)
Elderly (≥80)	226	**150**/226	(66.4)	**149**/226	(65.9)	**110**/142	(77.5)
Charlson Comorbidity Index (CCI)							
0-6 points	1089	**289**/1089	(26.5)	**605**/1089	(55.6)	**479**/583	(82.2)
≥7 points	47	**23**/47	(48.9)	**29**/47	(61.7)	**20**/29	(69.0)
Age-Combined Charlson Index (ACCI)							
0-4 points	695	**93**/695	(13.4)	**342**/695	(49.2)	**275**/325	(84.6)
5-7 points	313	**149**/313	(47.6)	**208**/313	(66.5)	**160**/204	(78.4)
8+ points	128	**70**/128	(54.7)	**84**/128	(65.6)	**64**/83	(77.1)
Number of medications used at home							
0	139	**10**/139	(7.2)	**61**/139	(43.9)	**49**/57	(86.0)
1-5	476	**102**/476	(21.4)	**246**/476	(51.7)	**191**/229	(83.4)
6-9	331	**114**/331	(34.4)	**196**/331	(59.2)	**163**/195	(83.6)
≥10	190	**86**/190	(45.3)	**131**/190	(68.9)	**96**/131	(73.3)
Familiarity with CPR**							
No	456	**293**/456	(29.8)	**254**/456	(55.7)	**202**/246	(82.1)
Yes, seen in real life	227	**41**/227	(18.1)	**125**/227	(55.1)	**96**/118	(81.4)
Yes, seen on TV or internet	332	**95**/332	(28.6)	**189**/332	(56.9)	**145**/185	(78.4)
CPR-survivor							
No	1082	**293**/1082	(27.1)	**603**/1082	(55.7)	**475**/581	(81.8)
Yes	54	**19**/54	(35.2)	**31**/54	(57.4)	**23**/30	(76.7)
Admission specialty							
Internal medicine	449	**171**/449	(38.1)	**269**/449	(39.6)	**208**/262	(79.4)
General surgery	217	**37**/217	(17.1)	**105**/217	(51.2)	**79**/100	(79.0)
Cardiology/cardiac surgery	193	**55**/193	(28.5)	**123**/193	(63.8)	**104**/121	(86.0)
Neurology/neurosurgery	101	**27**/101	(26.7)	**53**/101	(47.5)	**39**/51	(76.5)
Other surgical specialties	176	**27**/176	(15.3)	**84**/176	(47.7)	**67**/76	(88.2)

Table 2. Subgroup analysis of DNR-prevalence, code status/CPR conversation recall and correct patient understanding. Pre-specified subgroups were used. DNR, Do Not Resuscitate; EMR, Electronic Medical Record; Other surgical specialties, e.g. orthopedics, plastic surgery, otorhinolaryngology. *Only applies if patients recalled a CPR-directive conversation . Correct patient understanding means that if the EMR reads ''Full Code", the patients provided the same answer, idem for other directives. Patients with recollection, but no documented directive were excluded (n=22). **Patients who did not answer this specific question were left out of analysis (n=121).

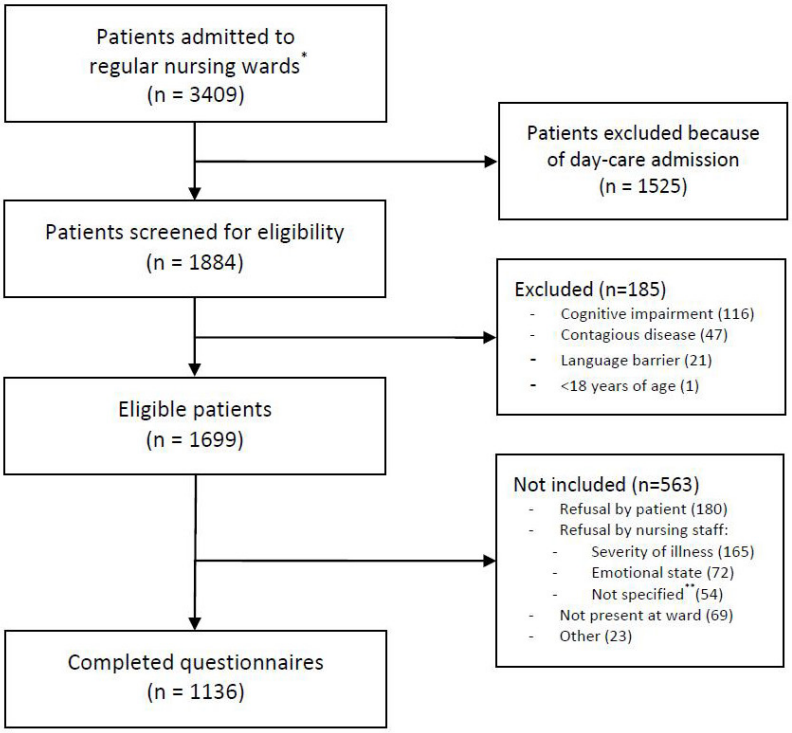

Figure 1. Study flow diagram. *not including: intensive and critical care units, emergency and operating rooms, obstetrics, paediatrics, outpatient haemodialysis; **nurses reserved the right to refuse access to patients if they felt these could not participate.

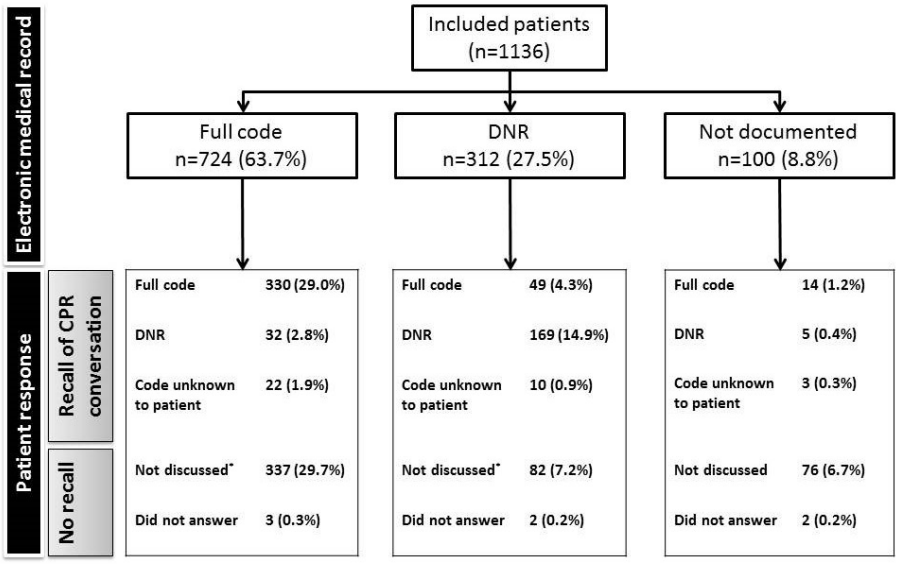

Figure 2. CPR-status prevalence, patients' recall of a conversation and the CPR-status patients recollected. *In two patients, a CPR-directive was not discussed at their own request FC(n=1) and DNR(n=1).

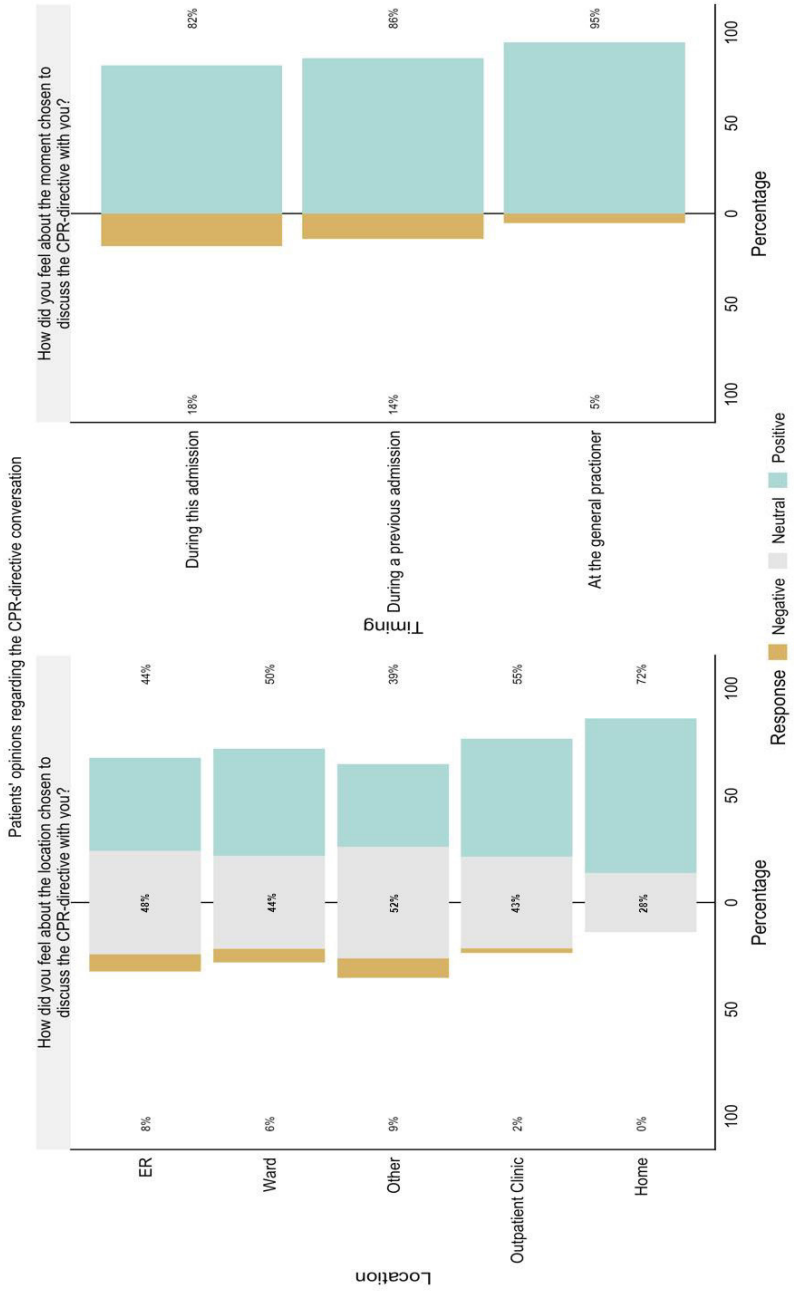

Figure 3. Patients' opinions regarding the CPR-directive conversation with regard to location (n=622) or timing (n=631) of the conversation, specified for the specific location or moment that it was discussed. *Other locations were: day-care clinic, pre-admission clinic or in-hospital not otherwise specified.

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L'art de la médecine consiste à distraire le malade pendant que la nature le guérit.

Voltaire

Chapter 5

Neurological outcome after extracorporeal cardiopulmonary resuscitation for in-hospital cardiac arrest: a systematic review and meta-analysis

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Abstract

Background

In hospital cardiac arrest (IHCA) is a major adverse event with a high mortality rate if not treated appropriately. Extracorporeal cardiopulmonary resuscitation (ECPR), as adjunct to conventional cardiopulmonary resuscitation (CCPR) is a promising technique for IHCA treatment. Evidence pertaining to neurological outcomes after ECPR is still scarce.

Methods

We performed a comprehensive systematic search of all studies up to December 20th 2019. Our primary outcome was neurological outcome after ECPR at any moment after hospital discharge, defined by the Cerebral Performance Category (CPC) score. A score of 1 or 2 was defined as favourable outcome. Our secondary outcome was post-discharge mortality. A fixed-effects meta-analysis was performed.

Results

Our search yielded 1215 results, of which 19 studies were included in this systematic review. The average survival rate was 30% (95% CI: 28-33%, I^2=0%, p=0.24). In the surviving patients, the pooled percentage of favourable neurological outcome was 84% (95% CI: 80-88%, I^2=24%, p=0.90).

Conclusion

ECPR as treatment for in-hospital cardiac arrest is associated with a large proportion of patients with good neurological outcome. The large proportion of favourable outcome could potentially be explained by the selection of patients for treatment using ECPR. Moreover, survival is higher than described in the conventional CPR literature. As indications for ECPR might extend to older or more fragile patient populations in the future, research should focus on increasing survival, while maintaining optimal neurological outcome.

Introduction

In hospital cardiac arrest (IHCA) is a serious adverse event in hospitalized patients that inevitably leads to death if not treated appropriately. It is associated with low survival rates at discharge and at one-year follow-up (13%, 95% prediction interval: 6-29%) [1,2]. The use of extracorporeal membrane oxygenation (ECMO) in addition to chest compressions for cardiopulmonary resuscitation may improve survival after IHCA [3]. Recent guidelines state the use of ECMO for CPR (ECPR) as potentially beneficial for specific patient populations [4], however they also stress the lack of evidence for this novel technique [5]. To our knowledge, there is no large-scale evidence pertaining to neurologic outcomes after ECPR for IHCA [6,7].

Survivors of cardiac arrest also suffer from neurological sequelae, which have been described as the post-cardiac arrest syndrome [8]. An important measure for neurological outcome is the aforementioned CPC. Although the CPC scoring suffers from limited discriminatory capacity, and has a potential ceiling effect and possible overestimation of function, it is to date the most used outcome measure [9]. The neurological outcome of one-year survivors after conventional CPR (CCPR) tends to be high: 92% of patients score a cerebral performance category (CPC) of 1 or 2 (95% prediction interval 82-97%) [2]. Another important neurological score is the Glasgow Outcome Scale (GOS). This outcome scale was developed for scoring outcome after acquired brain injury, but also is used to assess functional outcome after cardiac arrest [10,11].

ECPR facilitates return of circulation, albeit artificial. However, it is much more uncertain whether this recovery of circulation translates into survival, or acceptable neurological outcome. Furthermore, the association between neurologic outcomes and prognostic factors should be elucidated, in particular time to ECMO [12]. This systematic review aims to summarize the evidence on neurologic outcomes after hospital discharge of patients treated with ECPR for in-hospital cardiac arrest.

Methods

Literature search and selection criteria

This systematic review and meta-analysis is reported following the PRISMA and MOOSE guidelines for reporting of systematic reviews and meta-analyses of observational studies [13,14]. For this systematic review we performed a systematic search of all published data on post-discharge neurological outcome after IHCA treated by ECPR up to December 20th 2019. We used the search engines Pubmed, Embase, Medline Ovid, Web of Science and Cochrane Central. Our searches contained the following keywords: in-hospital cardiac arrest, ECMO, neurological outcome, brain injury and neurological outcome. The exact search strategies are included in appendix 1.

Our inclusion criteria were: 1) use of ECPR for in-hospital cardiac arrest; 2) adult patients; 3) reporting of neurological outcome (CPC or GOS); 4) clinical studies; 5) written in English, German, French, or Dutch. We included studies that reported outcome upon or after discharge from hospital. Studies were excluded if they did not fit inclusion criteria or if they were only published as abstract.

After the initial screening, the remaining articles were assessed by reading the full text. Studies often reported characteristics and outcomes of in-hospital and out-of-hospital cardiac arrest simultaneously. The authors of articles in which data for the IHCA cohort was not reported separately were contacted. Data extraction from selected studies was performed independently by two investigators (MD, PG) using a standardized form. Subsequently, the discrepancies were resolved by discussion with the other authors (BG, MS, SH).

Definitions

The primary outcome was defined as favourable neurological outcome post-discharge from hospital using CPC or GOS score. A measurement was considered post-discharge, when the outcome was reported at discharge or later. For a description of the CPC and the GOS score, see table 1 appendix 2. A CPC score of 1 or 2 or a GOS score of 4 or 5 were defined as favourable outcome. The secondary outcome was post-discharge survival. If a study reported survival and neurological outcome at different follow-up moments, we ensured extracting the data for the same follow-up moment per study. Additionally, out of interest in the time to ECMO cannulation on the effect of ECPR we extracted the average time to ECMO per study. Only the effect of the average time to ECMO cannulation on the primary outcome (favourable outcome) was investigated.

Quality assessment

The quality of the included studies was evaluated using the method of Hayden et al. for prognosis studies in systematic reviews [15]. The quality assessment is based on six categories: 1) Study population: whether the study correctly defines and describes the study population; 2) study attrition: whether the study was able to obtain a complete follow up; 3) prognostic factor measurement: whether the

study reports the most important prognostic characteristics; 4) outcome measurement: whether the neurological outcome was measured in a valid and robust way; 5) confounding measurement: whether the authors explored what influenced neurological outcome; and 5) account and analysis: whether the study reports a correct methodology of statistical analysis. Up to two points can be scored in each category. Therefore, the maximum score was 12 points, indicating high quality.

Statistical analysis

For the analysis of the primary outcome, a fixed-effects model was used, because little heterogeneity was observed. Results of the meta-analyses are presented as pooled proportions with corresponding 95% confidence intervals (CI). Between-study heterogeneity was assessed using I^2 statistic and the DerSimonian–Laird estimator for τ^2. Moreover, heterogeneity was analysed by assessing statistical significance based on Cochran's Q statistic.

Furthermore, because of specific interest in the relationship between time to ECMO and outcome in these patients, a meta-regression analysis was performed. A random intercept meta-regression analysis (binomial-normal model) was used with favourable outcome as outcome. This model is appropriate for meta-regression of probabilities, since it avoids the bias that occurs when a normal-normal model would be used for logit-transformed probabilities [16].

Finally, we considered multiple follow-up moments for our primary and secondary outcome. Therefore, a sensitivity analysis was performed for the studies that used the most frequently reported follow-up moment (i.e. at discharge).

All data was extracted into Microsoft Excel and then analysed in R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.). The packages used for the analysis were 'meta' and 'metafor', of which we used the 'metaprop',' forest', and 'rma.glmm functions.

Results

Included articles

Our search yielded 1215 results. Subsequently 1130 articles were excluded by screening of title and abstract (2 because of a language different than Dutch, English, French or German). Full text screening resulted in inclusion of 28 articles, of which 9 did not reported characteristics and outcome of the IHCA cohort separately. For these articles, authors were contacted to provide this data for the IHCA cohort. None replied after multiple attempts, therefore these studies were excluded. Finally, 19 articles were included [17–35] (Fig 1).

The sample size ranged between 10 and 200 patients. The mean age ranged between 18 and 86. All studies were observational studies, of which 10 (53%) were retrospective (table 1). All studies mentioned contra-indications. The most frequently reported contra-indications were CPR duration (58%), advanced age (58%), terminal cancer (84%), previous severe or irreversible brain damage (63%), and uncontrollable bleeding (63%). These have been summarized in table 2.

Fifteen (79%) of the included studies had a score of ≥9 (out of 12) in the Hayden method for quality assessment (table 3). Thirteen studies (68%) did not sufficiently adjusted for confounding bias, while 18 studies (95%) reported important prognostic characteristics. Overall, high quality was observed for study participation (13 studies, 68%, received maximum scores), study attrition (14 studies, 74%, received maximum scores), outcome measurement (14 studies, 74%, received maximum scores), and analysis (17 studies, 89%, received maximum scores).

None of the included articles expressed neurological outcome in GOS. Six studies showed that all survivors were classified as CPC 1-2 (17,18,24,26,30,34). The largest study reported 52 patients with CPC 1-2 (84%) versus 10 patients with CPC 3-4 (16%)(20). There was variation in the timing of assessment of outcome: 15 studies (79%) reported CPC and mortality at discharge, 2 (11%) studies reported CPC and mortality at 6 months, 1 (5%) study reported CPC and mortality at 4-6 weeks after discharge, and 1 (5%) study reported CPC and mortality at discharge from ICU.

Meta-analysis

The average post-discharge survival rate (i.e. discharge until 6 months) was 30% (95% CI: 28-33%). Heterogeneity was low: $I^2 = 0\%$, $p = 0.24$). At the same follow-up moment in these survivors, the pooled proportion of favourable outcome was 84% (95% CI: 80-88%). The heterogeneity was again low: $I^2 = 24\%$, $p = 0.90$. (Fig 2 and Fig 3).

As previously described, there was a variation in timing of assessment of outcome. In the 15 studies (79%) which reported survival to discharge, the pooled survival rate was 30% (95% CI: 0.27–0.34%), with low heterogeneity ($I^2 = 0\%$, $p=0.15$). In these survivors, the pooled proportion of favourable neurological outcome was 83% (95% CI: 78–87%), with again low heterogeneity ($I^2 = 0\%$, $p = 0.93$).

Meta-regression

A total of 16 studies (84%) reported an average time to ECMO (time to cannulation/time to start ECMO), and the reported range was large (31 - 60 minutes). However, the OR per 10 minutes for favourable outcome was 1.29 (95% CI: 0.73 – 2.29): favourable outcome was not explained by the average time to ECMO per study.

Discussion

Our primary goal was to provide a comprehensive overview of current literature pertaining to neurological outcome after ECPR for in-hospital cardiac arrest. In post-discharge survivors, we found a high proportion of patients with a CPC 1-2 (84% [95% CI: 80-88%]), which is lower than described for 1-year survivors CCPR (92% [95% PI: 82 – 97%] [2]). Post-discharge survival was higher than reported for the general IHCA populations (30% [95% CI: 28-33%] versus 17% [95% PI: 13 –23%] [2,36]). We found little heterogeneity in outcome between studies.

Although neurological outcome is good, it remains inconclusive whether neurological outcome of patients receiving ECPR is better than patients receiving CCPR. We did find a lower percentage of "good" neurological outcome (CPC1-2) than in a systematic review in a conventional CPR population [2]. However, in this review CPC score was a secondary outcome. In this review the proportion outcome assessment was also specifically set for one year, rather than after hospital discharge. A systematic review aimed at comparing ECPR and CCPR suggests that the neurological outcome is better in IHCA patients treated with ECPR compared to CCPR [37]. Due to the observational nature of the studies included in these reviews, the selection of patients for ECPR could still lead to better outcomes for this group. For literature pertaining to OHCA the same caveats apply [38,39].

Comparing this study to the literature suggests that survival of IHCA patients undergoing ECPR is higher than IHCA populations who receive conventional CPR (chest compressions) [1,2]. Our estimate of survival is also comparable the reported survival rate of adult ECPR patients by the ELSO registry [40]. This high survival might be explained by the selection of patients with a high chance of good outcome. The American Heart Association guidelines state that ECPR should be considered in patients for whom the suspected aetiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support [41]. In contrast, the European Resuscitation Council simply declares that the technique is a potential rescue therapy in patients where standard advanced life support (ALS) measures are not successful [5]. In practice, however, a much broader range of contra-indications are being used: this study found that the primary reported contra-indications were CPR duration, age, severe comorbidities such as terminal cancer or pre-existing neurological impairments, and uncontrolled bleeding. These contra-indications are known to impact prognosis. Excluding these patients from ECPR effectively results in a higher survival compared to patients receiving conventional CCPR. Especially the age criteria are quite stringent, and therefore likely affect the apparent survival [42], given the average age of the CPR population [43]. Moreover, the finding that we

found substantially less heterogeneity in survival rates between studies than a systematic review of the CCPR literature[1,2] also supports the hypothesis that this is a selected population. Nevertheless, part of the difference might be explained by the effect of ECPR versus CCPR on outcome [44–46].

On the other hand, ECPR is only indicated in patients with refractory cardiac arrest. Therefore, patients eligible for ECPR have, by indication, a worse prognosis than patients with conventional CPR as a portion of these patients ROSC after a short resuscitation period [47]. As a result, ECPR patients might not be the patient population with the most favourable outcome.

Evidence in the literature suggests that a longer time to ECMO time is associated with lower benefit of ECPR [48–51]. Bartos et al. suggest the association between time to ECMO and survival is explained by the metabolic derangements, which develop during prolonged low-flow time, leading to a worse outcome [52]. In our meta-analysis, this association between time to ECMO and survival is not found. However, most of the studies included in our meta-analysis do find a relationship between time to ECMO and survival, when this was investigated [18,19,26,31–35]. Possibly, our results can be explained due to an aggregation effect: our results imply that –because the variation in outcome between studies was small- differences in mean calculated time to ECMO do not explain differences in mean survival between studies. Additionally, our results might be explained by the long time to ECMO in the included studies (>30 minutes). Given that the success rate of CPR is very low when the duration is longer than 30 minutes [53,54], it might be more relevant to assess the effect of time to ECMO in when the time to ECMO is shorter. Since the effect of timing of ECPR on outcome impacts implementation, more high-quality evidence is needed.

Certain limitations should be taken into account. First, the time of CPC assessment was not the same for all studies. Most studies only scored CPC at the moment of discharge. This was not clearly defined in all studies. Some studies mentioned CPC scores at 6 months, others report a CPC score at discharge. We did show in a sensitivity analysis with the studies that reported data for the same follow-up moment that the estimates were very similar to the main analysis. However, a standardized and comprehensive assessment of neurologic and functional outcomes in cardiac arrest research is needed [9]. In spite of these differences, we encountered homogenous results, which suggests that the time of outcome assessment did not significantly influence the results: the neurological outcome and survival seem to remain constant at different follow-up times. Second, the included studies had two main shortcomings: they were relatively small (the largest study included 200 patients), and often reported their data non-standardized and non-structured, which complicated the process of data extraction. Remarkably, we observed little heterogeneity between these small studies, which enabled us to perform a fixed-effects meta-analysis. Finally, we were not able to do an individual patient data meta-analysis. Since heterogeneity between studies was found, the effect of prognostic factors on outcome in these patients could not be explored effectively. An individual patient data meta-analysis would enable this [55], and could be of interest for future research.

By showing that treating a selected group of IHCA patients with ECPR can result in a high proportion of good neurological outcome, this study illustrates what next step the field should take. When centres become more experienced, the indications of ECPR will shift towards a less selected, but probably also more fragile patient population: older patients with more comorbidities might be considered eligible for ECPR in the near future. Nevertheless, we should focus on treating these patients while maintaining such a high proportion of favourable neurological outcome.

Conclusion

ECPR as treatment for in-hospital cardiac arrest is associated with a large proportion of patients with good neurological outcome (CPC 1-2). The large proportion of favourable outcome could potentially be explained by the selection of patients for treatment using ECPR. Nevertheless, both conventional and extracorporeal CPR are associated with low survival rates. The survival after ECPR, however, is higher than described in the conventional CPR literature. As indications for ECPR might extend to older or more fragile patient populations in the future, research should focus on increasing survival, while maintaining optimal neurological outcome.

Table 1: Overview and characteristics of the included studies.

Authors	Year and journal of publication	Study timeframe	Study type	Country	ECPR Age median	Cardiac arrest to ECMO time (range)	Time of CPC assessment
Avalli et al.	Resuscitation. 2012	Jan 2006 - Feb 2011	Retrospective	Italy	67 (61–73)	55 (40–70)	6 months
Bednarcyzk et al	Resuscitation. 2014	Feb 2008 - Sep 2013	Retrospective	Canada	-	48.78	Discharge
Blumenstein et al.	Eur Heart J Acute Cardiovasc Care. 2016	Jan 2009 - Jan 2013	Retrospective	Germany	72 (55-72.9)	33.0 (19.0–47.0)	Discharge (30d)
Chen et al.	Lancet 2008	Jan 2004 - Dec 2006	Prospective	Taiwan	61.5 (18-74)	40 (16-251)	Discharge
Dennis et al.	Int J Cardiol. 2017	2009 - 2016	Retrospective	Australia	-	40 (30–55)	Discharge
Ellouze et al.	Artificial Organs 2018	Jan 2011 - Jan 2015	Retrospective	France	-	60 (45-89)	6 months
Fagnoul et al.	Resuscitation. 2013	Jan 2012 - Jan 2013	Prospective	Belgium	-	55 (42–59.5)	Discharge from ICU
Jung et al.	Clin Res Cardiol. 2016	2002 - 2013	Retrospective	Germany	66 (56-78)	-	Discharge (30d)
Lazerri et al.	Acute Cardiac Care 2013	Jan 2007 - Jan 2012	Prospective	Italy	54.8 ± 9 yrs (24-74)	51.9 ± 24.8	Discharge
Lee et al.	ann thorac surg. 2016	Jan 2004 - Dec 2013	Prospective	S. Korea	-	-	Discharge
Lin et al.	Resuscitation. 2010	2004 - 2006	Prospective	Taiwan	62.3 (21–73)	40 (16–150)	Discharge
Liu et al.	Interac cardiovasc thorac surg. 2011	Jan 2001 - Aug 2010	Prospective	Taiwan	53 (50-69)	-	Discharge
Mazzeffi et al.	J thorac cardiovasc surg. 2016	Jan 2010 - Dec 2015	Prospective	USA	57 ± 15 (34-86)	31 (15-52)	Discharge
Peigh et al.	J thorac cardiovasc surg. 2015	Jun 2010 - Jul 2014	Retrospective	USA	46 ± 12	52 ± 28	4-6w after discharge
Pozzi et al.	Ann thorac surg. 2019	Jan 2007 - Dec 2016	Prospective	France	46.2 ± 13.5 (18-76)	46.9 ± 19.0	Discharge
Shin et al.	Int J Cardiol. 2013	Jan 2003 - Jun 2009	Retrospective	S. Korea	59.9 ± 15.3	38.8	6 months

Authors	Year and journal of publication	Study timeframe	Study type	Country	ECPR Age median	Cardiac arrest to ECMO time (range)	Time of CPC assessment
Spangenberg et al	Catheter Cardiovasc Interv. 2016	Jan 2014 - Oct 2015	Retrospective	Germany	-	73.2	Discharge
Stub et al.	Resuscitation. 2015	Nov 2010 - Jul 2014	Prospective	Australia	-	56 (40–85)	Discharge
Wang et al.	Resuscitation. 2014	Jan 2007 - Aug 2012	Retrospective	Taiwan	55.7 ± 15.1*2	40 (15–162)	Discharge

Table 2, Reported contra-indications for ECPR per study.

Authors	CPR duration in minutes	Non-witnessed arrest	Severe comorbidity precluding ICU treatment	Advanced age (years)	Terminal cancer	Advanced CAD/heart failure	Non pre-selected patient categories*	Previous severe or irreversible brain damage	Liver cirrhosis	Renal failure	Uncontrollable sepsis	Uncontrollable bleeding/ trauma	Irreversible (multi) organ failure	Arrest of septic origin	Coagulation disorder	BMI > 40	Weight <30 kg	Aortic dissection	Extensive peripheral artery disease	Bed-ridden, care-dependant	At the discretion of the CPR team
Avalli et al.	<30			>75	x	X							x					x	x		
Bednarcyzk et al	<15	x			x						x	x	x	x	x	x		x	x		
Blumenstein et al.		x	x		x	X		x				x			x			x			
Chen et al.	<10	x		>75	x		x	x				x									x
Dennis et al.																					x
Ellouze et al.	<30	x		>75	x			x				x									
Fagnoul et al.	<10	x	x	>65	x	X		x	x			x			x		x				
Lazerri et al.	<30			>75	x			x				x	x	x							
Liu et al.	<10				x		x	x				x									x
Jung et al.				>74	x																x
Lee et al.					x																
Lin et al.				x	x	X		x				x									
Mazzeffi et al.	<10						x														x
Peigh et al.				>70	x	X		x			x	x									
Pozzi et al.	<20	x			x	X		x				x									

Authors	CPR duration in minutes	Non-witnessed arrest	Severe comorbidity precluding ICU treatment	Advanced age (years)	Terminal cancer	Advanced CAD/heart failure	Non pre-selected patient categories*	Previous severe or irreversible brain damage	Liver cirrhosis	Renal failure	Uncontrollable sepsis	Uncontrollable bleeding/ trauma	Irreversible (multi) organ failure	Arrest of septic origin	Coagulation disorder	BMI > 40	Weight <30 kg	Aortic dissection	Extensive peripheral artery disease	Bed-ridden, care-dependant	At the discretion of the CPR team
Shin et al.				>80	x			x				x	x	x							
Spangenberg et al.	<20						x														
Stub et al.				>65	x			x	x	x											X
Wang et al.	<10	x	x	>80	x			x				x	x							x	

* Some studies selected pre-specified groups based on cardiac arrest aetiology. Liu: acute myocardial infarction, Mazeffi: post-cardiac surgery, Chen/Spangenberg: cardiac origin, Stub: cardiac origin with ventricular fibrillation, Jung: cardiac origin or pulmonary embolism.

Table 3: Risk of bias assessment, using the method of Hayden et al. for prognosis studies in systematic reviewshhay.

Author	PMID	Participation	Attrition	Prognostic factors	Outcome	Confounding	Analysis	Total
Avalli et al.	22056265	+	±	+	+	-	+	**9**
Bednarcyzk et al	25449345	+	+	+	+	-	±	**9**
Blumenstein et al.	26503919	+	+	+	±	+	+	**11**
Chen Y.S.	18603291	+	±	+	+	+	+	**11**
Dennis et al.	27986281	+	+	+	+	-	+	**10**
Ellouze O	28877346	+	+	+	+	-	+	**10**
Fagnoul et al.	23816899	±	+	+	+	-	+	**9**
Jung et al.	26303097	±	+	+	+	-	+	**9**
Lazzeri et al.	23915221	±	±	+	+	-	+	**8**
Lee, DS et al.	26431921	±	+	+	±	-	+	**8**
Liu, Y et al.	21172947	±	+	+	±	-	+	**8**
Mazzeffi et al.	27422361	±	+	+	+	-	+	**9**
Lin et al.	20413202	+	+	+	+	+	+	**12**
Peigh et al.	26383007	+	+	+	±	±	±	**9**
Pozzi et al.	30365965	+	+	+	+	-	+	**10**
Shin et al.	23664696	+	+	+	+	+	+	**12**
Spangenberg et al	27315227	+	+	±	±	-	+	**8**
Stub et al.	25281189	+	±	+	+	-	+	**9**
Wang et al.	24992872	+	±	+	+	±	+	**10**

Hayden scoring system. + is 2 points, ± is 1 point and - is 0 points

-Study participation comprises whether the study correctly defines and describes the study population

-Study attrition comprises whether the study was able to obtain a complete follow up

-Prognostic factor management comprises whether the study reports the most important prognostic characteristics, as described in the characteristics table (e.g. Utstein-style reporting)

-Outcome measurement comprises whether the neurological outcome was measured in a confidential manner

-Confounding measurement and account comprises whether the authors explored what influenced neurological outcome/survival rate

-Analysis comprises whether the study reports a correct methodology of statistical analysis (2)

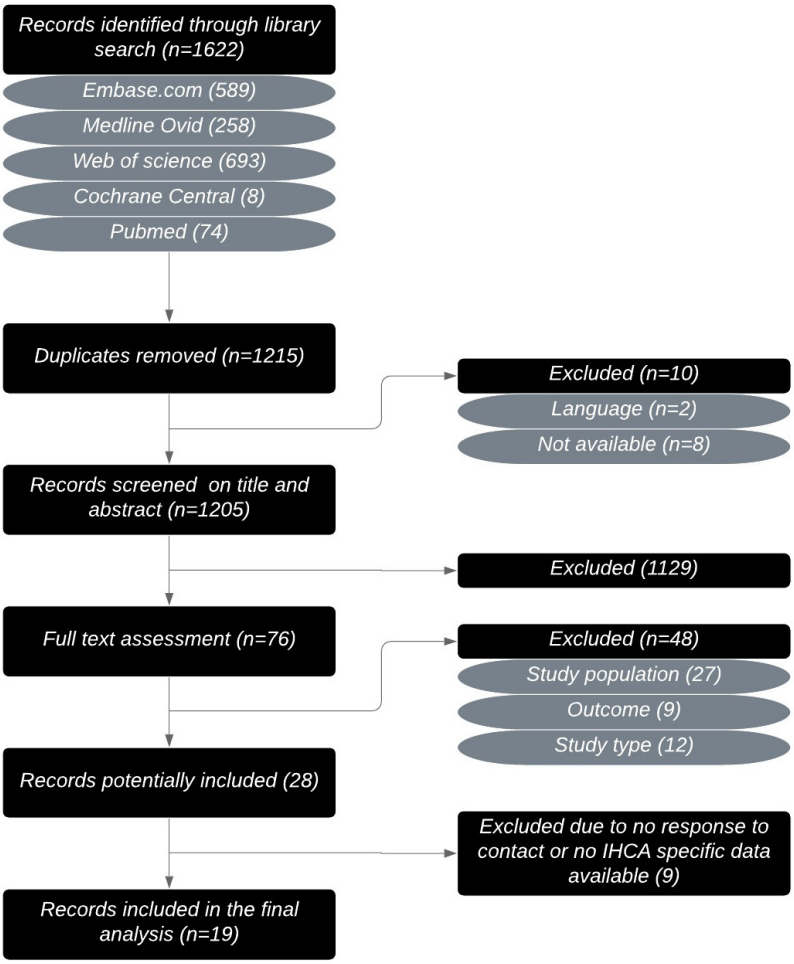

Figure 1. Flowchart showing the process of inclusion of studies. The search strategy was performed on 20th December 2019.

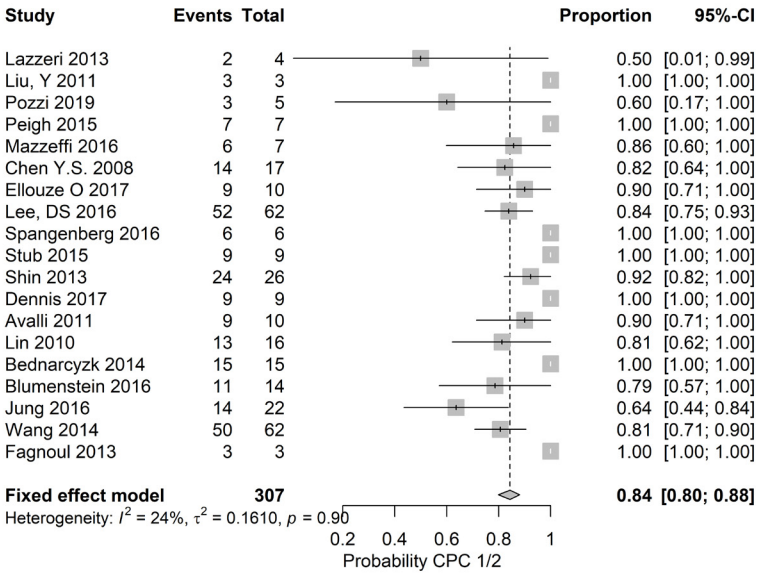

Figure 2. Forest plot showing the results for the primary outcome of this study, neurological outcome.

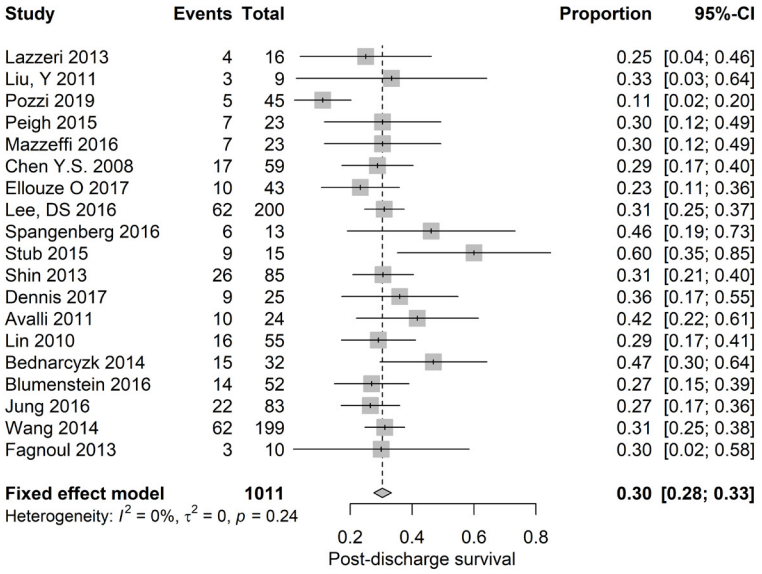

Figure 3. Forest plot showing the results for the secondary outcome of this study, post-discharge survival.

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Is the pious pious because God loves pious?
Socrates asks: who's bias do y'all seek?

Jay-Z, No church in the wild

The point which I should first wish to understand is whether the pious is beloved by the gods because it is holy, or holy because it is beloved of the gods.

Plato, Euthyphro 10a

Chapter 6

Cost-effectiveness of Extracorporeal Cardiopulmonary Resuscitation after in-hospital cardiac arrest: a Markov decision model

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Abstract

Background

This study aimed to estimate the cost-effectiveness of extracorporeal cardiopulmonary resuscitation (ECPR) for in-hospital cardiac arrest treatment.

Methods

A decision tree and Markov model were constructed based on current literature. The model was conditional on age, Charlson Comorbidity Index (CCI) and sex. Three treatment strategies were considered: ECPR for patients with an Age-Combined Charlson Comorbidity Index (ACCI) below different thresholds (2 - 4), ECPR for everyone (EALL), and ECPR for no one (NE). Cost-effectiveness was assessed with costs per quality-of-life adjusted life years (QALY).

Measurements and main results

Treating eligible patients with an ACCI below 2 points costs 8,394 (95% CI: 4,922 – 14,911) euro per extra QALY per IHCA patient; treating eligible patients with an ACCI below 3 costs 8,825 (95% CI: 5,192 – 15,777) euro per extra QALY per IHCA patient; treating eligible patients with an ACCI below 4 costs 9311 (95% CI: 5,478 – 16,690) euro per extra QALY per IHCA patient; treating every eligible patient with ECPR costs 10818 (95% CI: 6,357 – 19,400) euro per extra QALY per IHCA patient. For WTP thresholds of 0 to 9,500 euro, NE has the highest probability of being the most cost-effective strategy. For WTP thresholds between 9,500 and 12,500, treating eligible patients with an ACCI below 4 has the highest probability of being the most cost-effective strategy. For WTP thresholds of 12,500 or higher, EALL was found to have the highest probability of being the most cost-effective strategy.

Conclusions

Given that conventional WTP thresholds in Europe and North-America lie between 50,000 – 100,000 euro or U.S. dollars, ECPR can be considered a cost-effective treatment after in-hospital cardiac arrest from a healthcare perspective. More research is necessary to validate the effectiveness of ECPR, with a focus on the long-term effects of complications of ECPR.

Introduction

Cardiac arrest, cardiopulmonary arrest, or circulatory arrest is the loss of effective blood circulation, which inevitably leads to death if cardiopulmonary resuscitation (CPR) is not started. Cardiac arrest is usually divided based on location into out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). OHCA is described to occur around 19 – 104 times per 100,000 population per year and results in 10% survival at hospital discharge [1]. The incidence of IHCA is 1-6 events per 1000 hospital admissions [2–4] and recent meta-analyses showed a pooled survival to discharge of 15% (ranging from 3% to 40%) and a one-year survival of 13% (ranging from 4% to 69%)[5,6]. Patient-specific factors associated with survival are age [7,8], comorbidities [9–12] and presence of shockable rhythm [13].

A possible advantage for patients suffering IHCA versus OHCA is that hospitals are equipped with advanced life support teams, who could employ extracorporeal cardiopulmonary resuscitation (ECPR) using veno-arterial extracorporeal membrane oxygenation (VA-ECMO). This technique has seen an increase in use over the last decades [14,15]. By taking over cardiac and respiratory function, VA-ECMO ensures oxygenation and circulation [16]. Although evidence from randomized controlled trials is lacking [17], observational studies have repeatedly shown an increase in survival after ECPR compared to conventional CPR [18–20]. Furthermore, the American Heart association recommends the in-hospital use of ECPR in patients with a reversible cause of CA (e.g.: acute coronary syndrome).

When assessing whether or not to implement ECPR, cost-effectiveness should be taken into account. Ethical and economic considerations are of increasing importance in decision making pertaining to intensive care allocation [21]. Financial resources are limited and health care should be focused more on therapies that do not only extend life, but rather offer a reasonable health-related quality of life (HRQoL). This study was designed to provide cost-effectiveness evidence for international comparison and to provide an overview of current knowledge of the economic aspects of ECPR.

Two small observational studies (US and Australia) have shown indications of cost-effectiveness of ECPR for both OHCA and IHCA[22,23]. There are however several caveats. Because of low sample size and estimates pertaining to local situations these studies are not likely to be generalizable to all settings. Furthermore, for the in-hospital and out-of-hospital setting, effectiveness should be assessed separately.

The primary aim of this study was therefore to assess the cost-effectiveness of ECPR treatment after IHCA based on current literature. By using all available evidence, this modelling approach would ensure a high generalizability of our results. For this purpose, a decision tree and Markov model were developed. Both models are frequently used in health-economic evaluations, because they are able to calculate quality of life adjusted life years (QALY) [24,25]. The secondary aim was to assess in which patient group ECPR is most likely to be cost-effective.

Methods

This cost-effectiveness evaluation is reported according to the CHEERS reporting guidelines [26]. We searched PubMed for relevant studies to inform on all parameters used for the models. We used the search terms "in-hospital cardiac arrest" and "extracorporeal cardiopulmonary resuscitation" in combination with the specific parameter of interest. Furthermore, we found literature using the reference list of already found studies.

Decision tree

A three-strategy decision tree was created, which encompasses the in-hospital phase. This type of model uses known absolute and relative risks to calculate the probability of an outcome. The decision tree calculates the probability of dying before discharge. The strategies considered were ECPR for no one (NE), ECPR for every eligible patient (EALL) and ECPR for eligible patients with an age-combined Charlson Comorbidity Index (ACCI) score below a certain threshold (EACCI_lo). The thresholds for the ACCI analysed ranged from two to four: patients with an ACCI above the threshold did not receive ECPR. The ACCI thresholds have been based on best available ECPR guidelines to exclude patients with a terminal illness, comorbidities that form a contraindication for ICU admission or for intravascular cannulation[27]. Furthermore patients >75 years of age are generally not considered eligible. The ACCI score is described in table 1, supplement 1.

The ACCI threshold can be illustrated by the following example: a patient of 50 years old with moderate renal disease (GFR<40mL/min/1.73m^2) will have an ACCI of 3. If the patient would suffer a myocardial infarction the score will rise to 4.

The decision tree consists of multiple nodes with probability estimates found in literature (figure 1 and table 1). The first node represents patients with a Do-Not-Resuscitate (DNR) status. This is an agreement between a patient and a health care professional not to attempt cardiopulmonary resuscitation in case of cardiac arrest. Since a DNR status is more often agreed upon by patients with higher age [28], we assumed higher probabilities for higher aged patients. We assumed that for patients who suffered cardiac arrest with a DNR status, no CPR would be attempted and death is certain. When patients did not have a DNR status, CPR would be attempted. The next node represents the probability of having a contra-indication for ECPR. Having a contra-indication, e.g. refractory cardiac disease or metastatic cancer, was assumed to increase the risk of dying after CPR. If CPR was started and no contra-indication was present, the next node represents the probability of having return of spontaneous circulation (ROSC) within 20 minutes after cardiac arrest [29]. If ROSC would not be achieved within 20 minutes, ECPR could be started and could increase the remaining survival probability [18]. The probability of having a complication of ECPR and the probability of subsequent death are also taken into account [30–32]. These probabilities were calculated from the ELSO database [33]. The extra probability of mortality, given that the patient had a complication was: the mortality rate of patients with a complication minus the overall mortality rate. Finally, the mortality rate after CPR increases with increasing age-combined Charlson comorbidity index (ACCI) [9,10].

The prevalence of DNR status below 75 years was assumed to be around 5% (range 2- 10%), based on experience in our hospital: the Erasmus Medical Center, Rotterdam. The probability of having a contra-indication for ECPR was also based on experience in our hospital, where we implemented ECPR in 2016. We assumed that 20% (range 10-30%) of the patients have the contra-indications described by Makdisi et al. Since the described contra-indications (e.g. refractory cardiac disease or metastatic cancer) are severe conditions, the risk of dying was assumed to double (OR: 2.0, with a minimum of 1.4, and a maximum 2.9).

Markov model

For the calculation of long-term outcomes, a Markov model was used. A Markov model uses states and transition probabilities to calculate long-term outcomes [24]. We propose a model consisting of two states: an alive state (with decreased HRQoL) and a dead state (the absorbing state). Markov models can be used to calculate the time spent in each state. Therefore, QALYs can be calculated, making this type of model useful for cost-effectiveness analysis [25]. Each individual probability of dying at the end of the decision tree described above is used as input in the subsequent Markov model. The model simulated 20 years of follow-up and the model cycles were one year long. The data on age and sex specific mortality rates were provided by Statistics Netherlands (CBS) [34]. We did not assume a lasting effect of IHCA on long-term survival [35]. The amount of life-years were then multiplied by the sex-specific utility score after IHCA to obtain QALYs for men and women [36] (table 1).

As an example, consider a patient with a 100% chance of surviving the in-hospital phase: the Markov model will calculate the amount of life years this patient will spend after discharge. For a patient with 0% chance of surviving the in-hospital phase, the Markov model will estimate 0 life years after discharge. For chances between 0% and 100%, the model calculates the average life years that patients with the same characteristics will spend after discharge.

Cost-effectiveness analysis

The total costs of ECPR were calculated based on how many patients received ECPR following the decision tree outcomes: a patient received ECPR according to the treatment strategy if they did not have a DNR status, no contra-indication, and no ROSC within 20 minutes (Fig. 1 and table 1).

Only direct additional costs of ECPR treatment were taken into account, taking a health care's perspective. The average additional costs of ECPR described in the literature were used in the model. A detailed description of the items included in the total costs has been described by Lansink-Hartgring et al. [37]. A discount rate of 4% was applied, the appropriate rate for cost-effectiveness analyses in the Netherlands [38]. To assess cost-effectiveness of the strategies, incremental cost-effectiveness ratios (ICER) were calculated, where NE serves as the reference category. The ICER informs about how many extra euro per QALY a strategy costs, compared to NE. The incremental costs and QALYs were plotted and the cost-effectiveness acceptability curves were calculated and drawn to obtain the most cost-effective strategy.

Important to take into account is that the calculated costs for ECPR are notably lower than the costs of ECMO. This is due to the model structure, in which costs are calculated for an average patient who suffers IHCA, thereby including also patients who do not receive ECPR.

Probabilistic sensitivity analysis

To take the uncertainty of our model parameters into account, a probabilistic sensitivity analysis (PSA) was performed. A PSA repeats the model a large number of times with different (but probable) parameters. The type of distributions that were used were beta distributions for probabilities, log-normal distributions for the odds ratios and relative risks, and log-log-normal distribution for the log-odds increase in mortality for an ACCI point increase. The characteristics of the distributions were adjusted so that the median and interquartile range were identical to the estimate and 95% confidence interval. The type and characteristics of the distributions of the parameters are described in table 1. From these distributions, 1000 random samples were drawn, resulting in 1000 replicates of the model. Additionally, a representative cohort of 1000 patients was randomly sampled [10,39](table 2). After running the 1000 replicates of the model in this cohort, outcomes were calculated 1000 times. We calculated the QALYs and costs per strategy. The median was taken as the most probable estimate of the model. The 2.5th and 97.5th percentile were calculated, which indicated the borders of the 95% credibility interval.

To estimate whether the conclusions were affected by the parameters that were not found in literature, linear regression was performed. As the dependent variable, the ICER of the EALL strategy per iteration was used. As predictors, the standardized parameter values were used. The coefficients of the model could therefore be interpreted as "with one standard deviation (SD) increase in the parameter, the ICER for the EALL strategy increases with x".

All analyses were performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). For the Markov model, the "dampack" package was used [40]. The code of the model is online available in appendix 2, for transparency and reproducibility [41].

Results

In the decision tree, survival rates between 9% and 13% were observed for the NE strategy, and between 30% and 35% for the EALL strategy (Fig 1., supplement 1). After applying a Markov model, expected life years after CPR per patient for the NE strategy ranged from 0.79 to 2.48 and for the EALL strategy from 2.57 to 6.55 years (Fig 2., supplement 1).

The expected costs per ICHA patient for treating eligible patients below an ACCI of 2 points with ECPR are 3,975 (95% CI: 2,418 – 5,780) euro, and increased to 23,272 (95% CI: 14,159 – 33,838) euro for treating all eligible patients (Table 3). The associated QALYs for treating no patients with ECPR are 1.2 (95% CI: 1.0 - 1.5); for treating eligible patients below an ACCI of 2 points 1.7 (95% CI: 1.4 – 2.0); for treating eligible patients below an ACCI of 3 points 2.1 (95% CI: 1.7 - 2.6); for treating eligible patients below an ACCI of 4 points 2.6 (95% CI: 2.0 - 3.2); and for treating all eligible patients 3.4 (95% CI: 2.4 - 4.2).

Compared to treating NE, the expected incremental costs per extra QALY (ICER) for treating eligible patients with an ACCI below 2 points is 8,394 (95% CI: 4,922 – 14,911) euro per extra QALY; for treating eligible patients with an ACCI below 3, the ICER is 8,825 (95% CI: 5,192 – 15,777) euro per extra QALY compared to NE; for treating eligible patients with an ACCI below 4, the ICER is 9,311 (95% CI: 5,478 – 16,690) euro per extra QALY; for treating all eligible patients, the ICER was 10,818 (95% CI: 6,357 – 19,400) euro per extra QALY. Table 3 displays an overview of the economic evaluation. The considered strategies are comparable in terms of mean ICER, but the incremental costs and incremental QALYs vary significantly between the considered strategies (figure 3 supplement 1).

The cost-effectiveness acceptability curves depicted in Fig. 2 show that for WTP thresholds of 0 to 9,500 euro, NE has the highest probability of being the most cost-effective strategy. For WTP thresholds between 9,500 and 12,500, treating eligible patients with an ACCI below 4 has the highest probability of being the most cost-effective strategy. For WTP thresholds of 12,500 or higher, EALL was found to have the highest probability of being the most cost-effective strategy.

The only parameter that was found to influence the cost-effectiveness significantly was the relative risk of dying of ECPR (effect of one unit increase of the parameter on the ICER was -255 (-481 - -28) euros per incremental QALY), see table 2 supplement 2.

Discussion

In this study we found that the expected costs per IHCA patient of treating each eligible IHCA patient with ECPR are approximately 23,000 euro. A patient was eligible when no contraindications was present, and in whom ROSC cannot be achieved within 20 minutes after cardiac arrest. Per QALY increase, the associated costs were around 15,000. The Willingness-To-Pay thresholds in Europe and North-America are between 50,000-100,000 euro per incremental QALY. Within this range, performing ECPR in every eligible IHCA patient, is likely to be costs-effective.

The use of ECMO has steadily increased from 2007 onwards [14]. Positive results from observational studies and increasing clinical applicability led to the inclusion of ECPR in the Advanced Life Support Guidelines by the European Resuscitation Council [42]. However, ECPR is costly and labour-intensive and careful economic evaluation was still lacking.

Because ECPR was found to be cost-effective, this study substantiates its increased implementation and inclusion as possible treatment in the guidelines. The allocation of intensive care treatments should be critically evaluated, especially when financial resources are limited [21]. The difference in survival probability after ECPR seems to be sufficient to render the therapy cost-effective. Because we performed an analysis taking all uncertainties of parameters into account, we believe that we reliably estimated the average cost per IHCA patient when every eligible patient is treated with ECPR: around 11,000 euro per extra QALY.

Our cost-effectiveness analysis based on literature supports findings of empirical studies. Firstly, our study confirms the results of a recent small retrospective study in the United States that suggested that ECPR after IHCA is cost-effective, considering only in-hospital costs [22]. This study suggested that the costs per extra QALY saved is around 56,000 U.S. dollars. This estimate is larger than our estimate of 11,000 euros, but health care expenditures in the United States tend to be higher than in Europe [43]. Nevertheless, it is reassuring that both studies conclude that ECPR after IHCA is cost-effective, since they both assess primarily in-hospital costs. Secondly, our study confirms the results of Dennis et al. This study showed that for IHCA, 15,000 euros (25,000 AUD) per extra QALY was expected, which is similar to our estimate [23].

The results of our study are also similar to results of the cost-effectiveness of a mobile ECPR team [44]. This team is able to treat patients with ECPR in multiple centres, and its application was found to be potentially cost-effective. The application could benefit centres that do not have the resources for ECPR or lack experience with its application. Centres that often use ECPR rely on perfusionists for aid in initiation and maintenance of treatment, which enhances the costs. Therefore, it could well be that ECPR is mostly cost-effective when there is no need for these extra costs. This hypothesis, however, warrants further investigation.

The range of costs of ECMO found in the literature is large [45]. Mostly because studies inconsistently report their results, there are no factors described that explain this variation. We used a structured Dutch study as input for our cost-effectiveness analysis, since it describes clearly the incremental costs for ECPR [37]. This study found that the majority of the costs are composed of nursing days. Being able to shorten the length of ICU stay would therefore enhance cost-effectiveness of ECPR after IHCA.

We did not find that treating a subgroup of IHCA patients with ECPR based on age-combined Charlson comorbidity index affected cost-effectiveness. Since others described that cost-effectiveness depends on patient characteristics [44], we consider this to be attributed to two factors. First, the effect of comorbidity on survival of CPR is uncertain [9,10]. More research into this relationship is necessary. Second, if there is an effect of comorbidity, this effect is more likely to be significant in a cohort with a high prevalence of comorbidities. The prevalence in our representative cohort, however, was low [10,39].

This study has several limitations. Unfortunately, not all information needed for the model could be found in the literature. The lack of evidence had two consequences. First, it was necessary to base some of the parameters on clinical knowledge; e.g., for the probability of having a contraindication for ECPR. However, a sensitivity analysis showed that these parameters were not likely to influence the overall cost-effectiveness of ECPR. Second, cost-effectiveness might be somewhat overestimated. Evidence from randomized controlled trials was unfortunately absent at this moment [17]. Observational studies could have overestimated the effect of ECPR on survival because of confounding bias [18,19]. An overestimated effect of ECPR would result in an overestimated cost-effectiveness. Additionally, we were not able to model long-term effects of complications of ECPR: the extra health care costs and lower quality of life after major complications of ECPR (stroke, acute kidney injury) could decrease overall cost-effectiveness.

Although we did not take non-direct costs of ECPR into account, we still believe this study provides a valid economic evaluation. Other identifiable costs are costs of rehabilitation, future health care costs and non-medical costs such as loss of participation in working life. However, these costs are more interesting from a societal perspective than a health care perspective. Other costs that are not taken into account are the costs of implementation. These expenses are large and could explain the stagnating increase in the use of ECPR [46,47]. Therefore, we believe that our findings are most applicable to large hospitals in western countries, which often do have access to these resources to overcome the first barrier to an apparent cost-effective therapy.

We believe future studies should have three goals. First, to identify patients who could benefit most from ECPR. Second, randomized controlled trials are necessary, as indicated in the advanced life support guidelines [42]. Fortunately, five ongoing randomized controlled trials will hopefully fill this knowledge gap in the upcoming years [20]. Third, the long-term effects of complications of ECPR should be investigated, since they could decrease the cost-effectiveness of the intervention. The knowledge gained from further research could improve implementation and cost-effectiveness of this costly and labour-intensive intervention.

Conclusion

For in-hospital cardiac arrest patients, extracorporeal cardiopulmonary was demonstrated to be cost-effective from a healthcare perspective given that conventional WTP thresholds lie between 50,000 - 100,000 euro or U.S. dollars. More research is necessary to validate the effectiveness of ECPR, with a focus on the long-term effects of complications of ECPR.

Table 1, assumed estimates and their distributions for the decision tree in the probabilistic sensitivity analysis.

Abbr.	Parameter	Median (IQR)	Distribution	Source
Decision tree				
P_1	Probability of having DNR status if <75 years	0.05 (0.02 - 0.10)	Beta(5,95)	Clinical insight
P_2	Probability of ECPR contraindication	0.19 (0.11 - 0.32)	Beta(10,40)	Clinical insight
P_3	The probability of dying after CPR	0.85 (0.83 - 0.87)	Beta(850,150)	Zhu 2016 [5]
P_4	The probability of having ROSC within 20 min	0.38 (0.35 - 0.41)	Beta(338,556)	Khan 2014 [27]
P_5	Probability of complication	0.38 (0.29 - 0.47)	Beta(38,62)	Sheu 2010, Muller 2016 and Sakamoto 2012 [28–30]
P_6	Probability of dying because of complication	0.1 (0.05 - 0.17)	Beta(10,90)	Extracorporeal Life Support Organization 2019 [14]
RR_1	The relative risk of dying, ECPR vs non ECPR	0.43 (0.3 - 0.62)	Lognormal(-0.85, 0.19)	Chen 2013 [17]
OR_1	OR of dying when contraindication for ECPR	2.00 (1.40 - 2.93)	Lognormal(0.69, 0.2)	Clinical insight
OR_2	OR of having DNR status if 75 - 84 years, compared to <75 years	1.71 (1.23 - 2.32)	Lognormal(0.53, 0.16)	Cook 2017 [26]
OR_3	OR of having DNR status if >85 years, compared to <75 years	2.98 (2.38 - 3.75)	Lognormal(1.09, 0.12)	Cook 2017 [26]
$Beta_1$	The log odds increase in dying per ACCI increase	0.09 (0.03 - 0.14)	Log-Lognormal(0.09, 0.03)	Hirlekar 2018 [9]
Costs and utilities				
	In-hospital incremental cost of ECPR after cardiac arrest	51786.52 (31377.52 - 73978.54)	Normal(51997, 10767)	Oude Lansink-Hartgring 2016 [35]
	Utility score for men	0.8 (0.69 - 0.87)	Triangle(a=0.66, b-0.89, c=0.82)	Israelsson 2017 [34]
	Utility score for women	0.74 (0.62 - 0.81)	Triangle(a=0.58, b=0.82, c=0.81)	Israelsson 2017 [34]

ECPR = Extracorporeal cardiopulmonary resuscitation; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; ACCI = age-combined Charlson Comorbidity Index; DNR = do not resuscitate;

Table 2, patient characteristics of the simulated cohort, based on literature [10, 39].

Characteristic	N = 1000
Age (mean (sd))	65.49 (15.71)
Male (%)	578 (57.80)
CCI (%)	
0	373 (37.30)
1	230 (23.00)
2	183 (18.30)
3	107 (10.70)
4	43 (4.30)
5	40 (4.00)
6	15 (1.50)
7	4 (0.40)
8	5 (0.50)

CCI = charlson comorbidity index

Table 3, the health economic evaluation for each strategy.

Strategy	Costs*	QALY	ICER**
NE	-	1.2 (1.0 - 1.5)	-
ACCI < 2	3,975 (2,418 – 5,780)	1.7 (1.4 - 2.0)	8,394 (4,922 – 14,911)
ACCI < 3	8,066 (4,909 – 11,731)	2.1 (1.7 - 2.6)	8,825 (5,192 – 15,777)
ACCI < 4	12,942 (7,881 – 18,829)	2.6 (2.0 - 3.2)	9,311 (5,478 – 16,690)
EALL	23,272 (14,159 – 33,838)	3.4 (2.4 - 4.2)	10,818 (6,357 – 19,400)

The strategies are nobody ECPR (NE), treating everyone with an age-combined Charlson comorbidity index (ACCI) of 2, 3 or 4 or less, and treating everyone with ECPR (EALL). The ranges indicate 95% credibility intervals (CI).

* In Euro, only direct additional ECPR costs

** The incremental cost-effectiveness ratio (ICER) is calculated with the most conservative method (NE: nobody ECPR) as the reference method. It represents the costs per extra QALY.

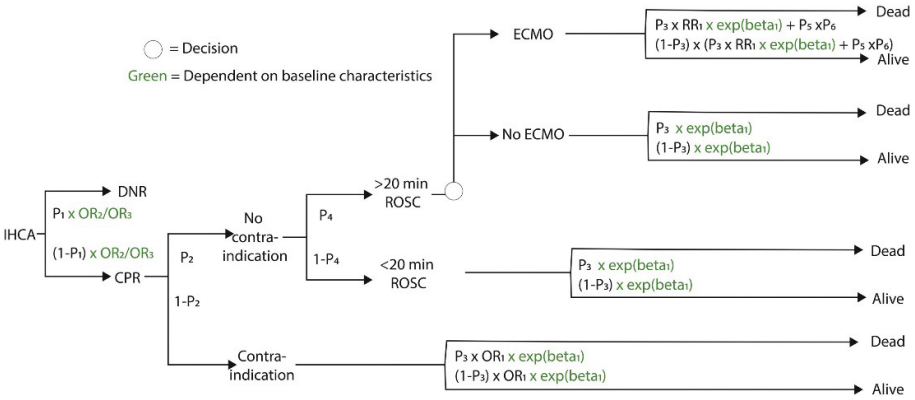

Figure 1. Decision tree of the in-hospital phase of the model. For the assumed probabilities (P), odds ratio's (OR), relative risks (RR), and betas, see Table 1. DNR = do-not-resuscitate; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.

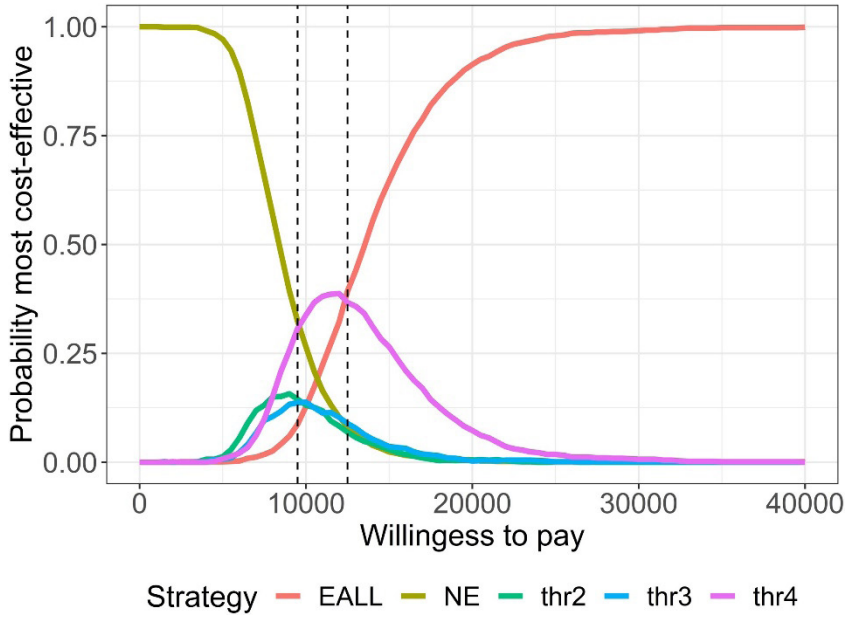

Figure 2. Cost-effectiveness acceptability curves. For given willingness to pay (WTP) thresholds, the probability of being the most cost-effective strategy is plotted. The strategies are nobody ECPR (NE), treating everyone with an Age-Combined Charlson Comorbidity Index (ACCI) of 2, 3 or 4 or less (thr2, thr3, thr4 respectively), and treating everyone with ECPR (EALL). The dotted lines indicate the WTP thresholds of 9500 and 12,500.

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All my work, my life, everything I do is about survival.
Not just bare, awful, plodding survival, but survival with grace
and faith. While one may encounter many defeats, one must
not be defeated.

Maya Angelou

Chapter 7

Long-term survival and health-related quality of life after in-hospital cardiac arrest

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Abstract

Introduction

In-hospital cardiac arrest (IHCA) is an adverse event associated with high mortality. Because of the impact of IHCA more data is needed on incidence, outcomes and associated factors that are present prior to cardiac arrest. The aim was to assess one-year survival, patient-centred outcomes after IHCA and their associated pre-arrest factors.

Methods

A multicentre prospective cohort study in 25 hospitals between January 1st 2017 – May 31st 2018. Patients ≥18 years receiving cardiopulmonary resuscitation (CPR) for IHCA were included. Data were collected using Utstein and COSCA-criteria, supplemented by pre-arrest Modified Rankin Scale (MRS, functional status) and morbidity through the Charlson Comorbidity Index (CCI). Main outcomes were survival, health-related quality of life (HRQoL, EuroQoL) and functional status (MRS) after one-year.

Results

A total of 713 patients were included, 64.5% was male, median age was 63 years (IQR 52-72) and 72.8% had a non-shockable rhythm, 394 (55.3%) achieved ROSC, 231 (32.4%) survived to hospital discharge and 198 (27.8%) survived one year after cardiac arrest. Higher pre-arrest MRS, age and CCI were associated with mortality. At one year, patients rated HRQoL 72/100 points on the EQ-VAS and 69.7% was functionally independent.

Conclusion

One-year survival after IHCA in this study is 27.8%, which is relatively high compared to previous studies. Survival is associated with a patient's pre-arrest functional status and morbidity. HRQoL appears acceptable, however functional rehabilitation warrants attention. These findings provide a comprehensive insight in in-hospital cardiac arrest prognosis.

Introduction

In-hospital cardiac arrest (IHCA) is a serious adverse event that can potentially affect any hospitalized patient. Although it still occurs frequently, evidence is relatively scarce.[1,2]. Because of this, there is much interest in long-term outcomes of IHCA and its predictors[3,4]. Several strategies to improve outcomes have been proposed, aimed at both prevention and treatment[5,6]. Prevention focuses on early recognition of patients who are at risk of cardiac arrest, as well as patient-centred counselling to install do-not-resuscitate (DNR) orders for patients in whom cardiopulmonary resuscitation (CPR) is not expected to be successful[1,7,8]. Preferably, the decision to attempt or refrain from CPR is made based on patient preferences and characteristics that are present prior to cardiac arrest[9]. Outcomes should focus on good long-term quality of life, rather than survival to hospital discharge. Studies from different populations will allow for international comparison and increase learning from good practice[3,9].

Although 1-year long-term survival data is available, there is limited knowledge on long-term functional outcomes and factors that predict these outcomes. As previously reported, survival in European studies is 20.0% (95% prediction interval: 16.0-26.0%,) and we reported a one-year survival rate of 23.0% from a single-centre retrospective study[2,10]. The majority of evidence has been derived from retrospective single-centre studies or studies that do not assess the relationship between pre-arrest variables and long-term outcomes[2]. We therefore initiated a prospective cohort study to describe IHCA epidemiology in the Netherlands. The overall goal of our endeavour is to provide information in order to establish patient-centred CPR-directives. This also means that patients can then make an informed decision about their CPR-directive. The primary objective of the current study is to assess the one-year survival of adult patients after IHCA. The secondary objectives are to determine pre-arrest factors for prognostication of outcome and to describe overall functional outcome and health-related quality of life after IHCA. In this paper we report on variables that are present prior to cardiac arrest (age, functional status, comorbidity) and hospital factors (patient monitoring, admission specialty, post-arrest treatment).

Methods

Design and setting

A multicentre prospective cohort study was performed in 25 hospital localizations. The call for participation were done through the Dutch Society for CPR-coordinators (NVCR). Data were collected through an online registration system (OpenClinica, Walton, MA, USA). CPR practice and hospital characteristics of all Dutch hospitals were assessed through a prior nationwide survey[11]. The study was registered at clinicaltrials.gov (NCT03120507) and the Dutch trial registry (NTR6145).

Patient population and follow-up process

The population included were adults (≥18 years of age), who received cardiopulmonary resuscitation, defined by starting manual chest compressions for a circulatory arrest occurring in-hospital. The inclusion period was January 1st 2017 – May 31st 2018. Patients from all hospital wards, departments, outpatient clinics and common areas were included. This means we also included patients from the intensive care (ICU) and cardiac care units (CCU), as well as the emergency room (ER). Exclusion criteria were: OHCA <24 hours prior to IHCA, purposely induced arrhythmia (e.g. electrophysiological interventions) or cardiac arrest (e.g. cardioplegia in cardiac surgery) or refusal to participate. The CPR-team generally attends all cases of IHCA, except for some peri-operative cases in the OR. Therefore all patients were prospectively included through registrations done by each hospital's CPR-team and crosschecked with ICU-admissions for cardiac arrest. In-hospital follow-up was done by the local investigator in each hospital until hospital discharge. After discharge survival was checked with the Dutch Personal Records Database (BRP) at 3 months and 12 months after cardiac arrest. Surviving patients received questionnaires addressing their functional status and quality of life. Up to two reminders were sent and subsequently patients received a phone call to ask for follow-up data.

Ethical considerations

Study participants were asked to provide informed consent, unless they did not survive initial CPR. For patients who survived CPR and died subsequently in-hospital without regaining consciousness, a letter was sent to the next of kin to inform of inclusion. Patients who regained consciousness received information about study participation. At this point informed consent was obtained to participate in follow-up. Patients were informed of the non-interventional design and were given the possibility to opt-out at any time. Patients were only able to refuse or opt-out of follow-up. This study was considered subject to the Dutch Medical Research Involving Human Subjects act (WMO) and was approved by the Erasmus University Medical Centre Medical Ethics Committee (ABR55661.078.16).

Data collection

Data was collected from the Electronic Medical Records of patients, according to the Utstein-template and the Core Outcome Set for Cardiac Arrest (COSCA) recommendations[12,13]. Pre-arrest data were gathered retrospectively.

Outcome measures

The primary outcome measure was one-year survival. Secondary outcome measures were return of spontaneous circulation (ROSC), survival to hospital discharge, 3-month survival, quality of life, functional status and psychological distress at 3 and 12 months after cardiac arrest. Functional status was determined through a Modified Rankin Scale (MRS) score. MRS was assessed by the local investigators after cardiac arrest had occurred, either through a proxy, general practitioner or extensive chart review. Post-discharge MRS was reported via questionnaires. At follow-up CCI was assessed via self-reporting, as were new health issues. Patients were asked if they had prior employment and what their current employment status was. Quality of life and psychological distress was determined through validated questionnaires, including the EQ-5D-5L (EuroQoL). This questionnaire has been used before in cardiac arrest research and allows for good comparison. The EQ-5D measures the HRQoL on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) in which patients can report problems in 5 severity levels. EQ-5D-5L Utility Index scores (EQ-Index) were calculated from the five dimensions of the EQ-5D-5L, with a standard set of population based weights validated for the Netherlands[14,15]. Calculated index scores range from 1 (best health state) to -0.446 for the worst health state possible. Additionally, part of the EQ-5D-5L is a visual analogue scale (EQ-VAS) where patients score their current health state from 0 (indicating worst health state imaginable) to 100 (indicating best health state imaginable). [16] The EQ VAS provides a quantitative measure of the patient's perception of their overall state of health. We compared the EQ-5D-5L dimensions to the Dutch referent population and to the population of hospitalized patients we studied in our previous study to assess advance care directives[17]. Other outcome measures that were used are the Short Form 12 SF-12 with its physical and mental component scale (PCS and MCS), and the hospital anxiety and depression scale (HADS). Strain on the relationship between the patient and his/her partner or next of kin was assessed using the caregiver strain index (CSI). In the design of this study we described using Telephonic Interview of Cognitive Status (TICS), but this was not feasible.

Statistical analysis

Data were reported using mean (standard deviation) or median (interquartile range) where appropriate. Comparison between groups was done using designated statistic tests. Kaplan-Meier survival analysis was used. Survival differences were assessed for predefined subgroups: 1) shockable and non-shockable arrest rhythm 2) an Age-combined Charlson Comorbidity Index (ACCI) stratified for low (0-4 points), medium (5-7 points) or high (8+ points) burden of age and disease; 3) pre-admission functional status by Modified Rankin Scale scores. We assessed ACCI because a high ACCI was previously associated with lower survival in IHCA patients[10,18]. The method of

ACCI calculation is summarized in supplemental table 1. Incidences of IHCA were calculated in two ways: 1) by division of the number of IHCA by the total number of hospital admissions during the study period, 2) by division of the number of IHCA by the sum of days of inclusion of all hospitals. For survival differences Log-Rank tests were calculated and hazard ratios (HR) were calculated through Cox regression. Variables that were univariately associated with survival ($p<0.05$) were included in multivariate survival analysis. Data were analysed using SPSS statistics v25.0 (IBM, Chicago, IL, USA) and R. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Fourteen hospital organizations participated, comprising 25 hospital locations (25.3% of Dutch hospitals). Compared to all Dutch hospitals, participating hospitals were mostly classified as teaching hospitals, trauma centres and thoracic/aortic surgery centres when compared to the overall characteristics of Dutch hospitals. A total of 713 patients were included between January 1st 2017 and May 31st 2018, of whom 64.5% was male, median age was 63 years (IQR 52-72) and 72.8% had a non-shockable rhythm (table 1). Of these patients 394 (55.3%) achieved ROSC, 231 (32.4%) survived to hospital discharge and 198 (27.8%, 95%CI 23.9% – 30.5%) survived one year after cardiac arrest. If death occurred within one year after IHCA, 93.6% occurred while patients were in hospital versus 6.4% after hospital discharge. The inclusion period contained 5867 hospital days and a total of 529,679 admissions were done. This yields an IHCA incidence of 0.12 per hospital day and 1.3 per 1000 admissions. A flowchart of survival is displayed in figure 1 and patient characteristics are displayed in table 1.

Survival plots for the total population and for predefined subgroups are depicted in figure 2. Lower survival was found in patients with a non-shockable cardiac arrest rhythm, an ACCI ≥5 points and/or higher pre-admission MRS, indicative of functional disability. One-year survival for patients with no disability prior to admission was 38.2%, for non-significant disability 26.8% and for moderate or severe disability 18.0% (figure 2c). After adjustment for peri-arrest factors several pre-admission variables were associated with a higher mortality: age (HR 1.01 per year increase, 95%CI 1.00 – 1.02, p=0.007) and a higher Charlson Comorbidity Index (HR 1.07 per point increase, 95%CI 1.03 – 1.10, p<0.001). The adjusted HR's are displayed in table 2.

One-year survival varied between patients who were resuscitated in different hospital areas. One-year survival was highest for IHCA in the operation room (50.0%), followed by the emergency room (31.4%) the intensive/cardiac care units (31.9%), the catheterization laboratory (28.6%) and the non-monitored wards (23.0%) (p=0.005). Survival also varied when patients were stratified for the specialty to which they were admitted. The highest probability of survival was found in cardiac surgical admissions (56.3%) and the lowest in medical non-cardiology admissions (17.4%).

Of survivors to discharge 77.5% scored CPC1-2 (none-mild disability), 16.5% CPC3 (severe disability) and 0.9% CPC4 (comatose), and 17.3% was considered to be in need of daily assistance. Need of daily assistance was more numerically prevalent in patients who died in the following year (32.1% vs. 15.7%, p=0.085).

After discharge, 212 (29.7%) patients survived 3 months and 198 (27.8%) patients survived one year, of whom 136 (64.2%) and 110 (55.6%) answered the follow-up questionnaires respectively. Median time for first follow-up time was 94 days (IQR 82-132) and for final follow-up it was at least ≥12 months. The majority of surviving patients reported having no or a slight disability in functional status (MRS 0-1): 62.7% at 3 months, and 69.7% at 1 year as displayed in supplemental figure 1. At one-year follow-up 65.5% of surviving patients retained the same MRS score, and

30.0% had no more than 1-point decrease in MRS, compared to their status before cardiac arrest. Of the patients with a decrease in MRS (n=49) at 12 months only 23.4% reported having been admitted to a nursing or rehab facility. The change in MRS scores before admission and at follow-up is summarized in supplemental figure 1. Of patients who answered the questionnaire at 1-year follow-up reported several problems: readmission to hospital (15.5%), chest pain (8.2%), heart failure (11.8%), heart rhythm disturbances (10.0%) and syncope (4.5%). The proportion of comorbidities in terms of CCI was the similar pre-arrest and at 3- and 12-month follow-up. Of patients who were employed at time of the cardiac arrest, 17.1% had quit working. Caregiver strain was present in 17.1% of patients' partners or family members. These data are displayed in supplementary table 3.

HRQoL was assessed using the EQ-5D VAS score and EQ-5D index score at 3 and 12 months post-IHCA. Median EQ-VAS was 70 (IQR 60-80) at 3 months and 75 (IQR 65-85) at 12 months. Patients reported a median EQ-5D index score of 0.77 (IQR 0.65 – 0.87) at 3 months and 0.81 (IQR 0.70 – 0.91) at 12 months. The reported items (scores≥1 point severity) stratified by the EQ-5D-5L domains are displayed in figure 3. The most frequent reported problems at 12 months were: usual activities (56.9%), followed by mobility (55.0%), pain (53.2%), anxiety/depression (43.2%) and self-care (17.4%). Only a small proportion of patients (≤2.4%) reported severe problems (score ≥4 points severity) for each domain. The percentage of patients reporting severe problems is separately mentioned in figure 3. Results from SF-12 and HADS questionnaires are summarized in supplemental table 3.

Discussion

One-year survival after in-hospital cardiac arrest in this prospective multicentre study is 27.8%. Of all patients who die within one year after cardiac arrest the majority of deaths occurred in hospital (93.6%). In our study the incidence of IHCA is 1.3 per 1000 admissions. We found several pre-arrest variables to influence one-year survival, most notably pre-arrest functional status (MRS) and the combination of age and comorbidity (ACCI).

Survival in this study is relatively high compared to other studies in populations comprising all hospital wards (including critical care wards)[2,3,10]. One-year survival rates from a systematic review range from 9-29% globally, and 16-26% in European studies[2]. The survival rate of 27.8% from this study borders the upper margins of both ranges. Our study population was not notably younger or healthier and did not comprise a larger proportion of shockable rhythms than in prior studies. Furthermore all patients suffering IHCA were included and loss to follow-up was low.

We have two hypotheses to explain this survival rate. The first is that advanced directives are becoming increasingly important. The prevalence of Do Not Resuscitate orders among hospitalized patients is relatively high in the Netherlands: 27.5% [17]. As a consequence, CPR with a low chance of success may be attempted less frequently. As mentioned, our population was not younger or healthier in means of comorbidity (ACCI), compared to other cohorts. Perhaps this means the relation between functional performance (MRS) and poor outcome is more important. We have no data to substantiate this hypothesis. Secondly Dutch hospitals have a 96% adherence to ERC guidelines, 91% availability of rapid response systems and all hospitals have dedicated CPR-teams with frequent team training[11,19]. The exact role of these factors needs to be elucidated further in future research. Our hypothesis is supported by the fact that incidence of IHCA in our sample is in the lower margin of what is described in literature, i.e. 1-6 cases per 1000 admissions.[2] Compared to studies from the US and Denmark, the incidence of IHCA is relatively low in our study[3,20]. A likely explanation of this effect is the widespread availability of rapid response systems[11]. Rapid response systems may lower the incidence of IHCA, although its influence on mortality has yet to be proven[21]. As expected, pre-arrest morbidity and functional status in this study is associated with survival after cardiac arrest [1,10,22]. One-year survival for patients with no previous disability in daily life (MRS 0) is 38.2% and for patients with a low burden of age and disease (ACCI 0-4 points) one-year survival is 33.7%. Inversely, survival was low for patients who suffered disability or had a high burden of disease before hospital admission.

At discharge, 77% of patients had a CPC score of 1-2 and were therefore expected to be able to live independently or with minor assistance. Self-reported functional status at 3 months and 12 months was less than reported by physicians at hospital discharge. In general the health status of IHCA survivors is lower than that of a Dutch norm populations, as reflected by the EQ-5D domains and the EQ-5D index score[15]. IHCA survivors reported a median EQ-5D index score of 0.77. When compared to the Dutch population mean of 0.89, there is a gap that indicates that HRQoL is lower for cardiac arrest survivors. EQ-5D index score compares well to other studies done in IHCA and OHCA patients, where HRQoL was measured after discharge [4,23–25]. EQ-5D-5L visual analogue score was on average 70 at 3 months and 75 at 12 months, where the Dutch population norm is 82 and 62 in Dutch hospitalized patients as described in our previous cross-sectional study [15,17]. Perceived HrQoL (EQ-VAS) in cardiac arrest survivors was lower compared to the Dutch population, but higher than in patients during hospitalization. IHCA survivors perceive less HrQoL than the general population with at least minor problems in all domains of the EQ-5D, but mainly with regard to mobility and daily activities[15,26]. The same results are reflected in the SF-12 and HADS outcome measures. Notably, the majority of patients with a decrease in MRS did not attend a rehabilitation program. This would imply that cardiac arrest survivors might benefit from rehabilitation programs to improve neurological status and exercise capacity[27]. It is known that better neurologic status leads to more work participation[28]. This poses interesting goals for future post-resuscitation care.

Several limitations of our study should be taken into account. Firstly, this is an observational study and may be subject to selection bias. Because the study was voluntary and there are no financial or disciplinary consequences for hospitals, we hope this effect is negligible. Our sample has a relatively high number of teaching hospitals. On the one hand this means the complexity of care increases, e.g. more high-risk surgery, and on the other hand the availability of advanced life support certified doctors increases[11]. This difference could however be small as training level and training frequency does not differ, nor does ICU-level or rapid response team availability; other proxies for the chain of survival. Because our sample of participating hospitals was based on voluntary participation, we might have introduced a sampling bias. Although our sample contains more teaching hospitals, no significant differences were found, regarding hospital size, level of care, guideline adherence, and team training[11], Secondly, MRS was assessed by the local investigators after cardiac arrest had occurred, either through a proxy, general practitioner or extensive chart review. This could have introduced bias. That pre-arrest MRS estimates still produce a survival effect on long-term indicates that a physician estimate of functional status may be a valuable predictor of long-term mortality. Lastly, the response rates were 64.2% at 3 months and 55.6% at 12 months. These numbers are similar to a recent study from Sweden, with a response rate of 55.0% at 3-6 month follow-up[26]. All patients who were eligible for follow-up received telephonic reminders to fill out the questionnaires. The most heard reason not to respond was that they found it too strenuous or difficult. Furthermore, pre-admission mRS was lower in the non-responder group, than among responders. Differences between these two groups have been summarized in supplemental table 2. We therefore think the found HRQoL is possibly overestimated.

Regarding our overall goal, this study yields important results. It appears that in our sample, we can identify groups of patients for whom CPR would be less likely to succeed. Moreover these groups could have been identified upon hospital admission, by means of MRS or ACCI. Our study warrants validation in other cohorts, but its data may serve as a basis for discussing CPR-directives with patients[7]. Furthermore, our study yields the positive message that survival after IHCA in our health care system is relatively high, especially in patient categories with a low burden of disease (ACCI ≤7) or good pre-arrest functional status (MRS<2). In these categories survival is at least double when compared to the global average[2]. As we have previously assessed, knowledge of CPR-directives is often lacking in patients[17]. With our current findings we can improve communication in two ways. First it allows us to reassure young and healthy patients that are overwhelmed by hearing about CPR-directives, that it seldom occurs and that their prognosis is good. Second, it allows us to speak to our older, multimorbid and/or functionally incapacitated patients about their prognosis and it might lower the threshold for clinicians to speak about this subject.

Our study design has several other merits. Patients were included from different hospitals in different regions, providing a variety of health services. We provide a comprehensive view of in-hospital cardiac arrest patients with data on pre-admission status following up to 12 months after cardiac arrest. To combine survival, health-related quality of life (HRQoL) and functional status in a prospective cohort aids in improving the external validity of IHCA prognostication and such studies are scarce[4,23].

We conclude that in this study one-year survival after in-hospital cardiac arrest is 27.8% in this population and survival is associated with pre-admission functional status and morbidity. Outcomes such as cognitive function, daily functionality and work participation warrant more attention in future research. We think future guidelines should incorporate advanced directive planning, of which prognostication and CPR-directive counselling is a vital part[7,29]. Similar studies should be repeated in various populations in order to develop tailor-made prognostication tools.

		Death <1 year*		One-year survivors*		Total		p=
Patient characteristics upon admission		**n=507**		**n=198**		**n=713**		
Age	*Median (IQR)*	69	*(62-77)*	67	*(56-73)*	63	*(52-72)*	*.036*
Male sex	n (%)	327	*(64.5)*	125	*(63.1)*	460	*(64.5)*	*.734*
BMI (kg/m^2)	*Median (IQR)*	25.7	*(23.4-29.4)*	26.6	*(23.9-30.1)*	25.7	*(23.0-30.0)*	*.039*
Charlson comorbidity index	*Median (IQR)*	2	*(0-3)*	1	*(0-2)*	1	*(0-3)*	*<.001*
Functional status at home (Modified Rankin Scale)**/ †	*n(%)*							*<.001*
0-1 – none/slight disability		325	*(67.0)*	157	*(82.2)*	488	*(68.4)*	
2-3 – moderate disability		143	*(29.5)*	30	*(15.7)*	174	*(24.4)*	
4-5 – severe disability		17	*(3.5)*	4	*(2.1)*	22	*(3.1)*	
Cerebral performance cat.1-2**	n(%)	438	*(86.4)*	188	*(95.0)*	634	*(88.9)*	*.010*
Presence of malignant disease	*n(%)*							*<.001*
None		402	*(79.3)*	172	*(86.9)*	582	*(81.6)*	
Solid tumour		43	*(8.5)*	23	*(11.6)*	66	*(9.3)*	
Solid tumour with metastases		35	*(6.9)*	1	*(0.5)*	36	*(5.0)*	
Hematologic		27	*(5.3)*	2	*(1.0)*	29	*(4.1)*	
Type of ward	*n (%)*							*.005*
Non-monitored ward		288	*(56.8)*	87	*(43.9)*	378	*(53.0)*	
Intensive/cardiac care unit		128	*(25.2)*	61	*(30.8)*	191	*(26.8)*	
Operation Room		15	*(3.0)*	16	*(8.1)*	32	*(4.5)*	
Emergency Room		48	*(9.5)*	22	*(11.1)*	70	*(9.8)*	
Catheterization laboratory		28	*(5.5)*	12	*(6.1)*	42	*(5.9)*	
Type of admission	*n(%)*							*<.001*
Cardiology		178	*(35.1)*	89	*(44.9)*	272	*(38.1)*	
Cardiac surgery		14	*(2.8)*	18	*(9.1)*	32	*(4.5)*	
Medical non-cardiology		211	*(41.6)*	45	*(22.7)*	258	*(36.2)*	
Surgical non-cardiac		104	*(20.5)*	46	*(23.2)*	151	*(21.2)*	
No. of cardiac arrest events	*n(%)*							*.652*
One event		477	*(94.1)*	*183*	*(92.4)*	667	*(93.5)*	
Two events								
Current admission		12	*(2.4)*	*7*	*(3.5)*	19	*(2.7)*	
In prior medical history		18	*(3.6)*	*8*	*(4.0)*	27	*(3.8)*	
Arrest-related factors								
Time of day	*n(%)*							
07:00 – 14:59		191	*(37.7)*	*91*	*(46.0)*	284	*(39.8)*	
15:00 – 22:59		172	*(33.9)*	*55*	*(27.8)*	230	*(32.3)*	
23:00 – 06:59		144	*(28.4)*	*52*	*(26.3)*	199	*(27.9)*	

		Death <1 year*		One-year survivors*		Total		p=
Day of the week								
weekday		370	*(73.0)*	158	*(79.8)*	536	*(75.2)*	
weekend		137	*(27.0)*	40	*(20.2)*	177	*(24.8)*	
Witnessed arrest	*n(%)*	372	*(73.4)*	182	*(91.9)*	561	*(78.7)*	*.000*
Time to (min.)	*Median (IQR)*							
basic life support		0	*(0-0)*	0	*(0-0)*	0	*(0-0)*	*.127*
advanced life support		2	*(1-4)*	1	*(0-2)*	1	*(0-3)*	*.414*
Cause of arrest - cardiac	*n (%)*	237	*(46.9)*	120	*(60.3)*	*357*	*(50.7)*	*.001*
Primary Arrest Rhythm	*n (%)*							*.000*
Asystole		171	*(33.7)*	32	*(16.2)*	205	*(28.8)*	
PEA		237	*(46.7)*	65	*(32.8)*	304	*(42.6)*	
VF		71	*(14.0)*	65	*(32.8)*	140	*(19.6)*	
VT		27	*(5.3)*	27	*(13.6)*	54	*(7.6)*	
No rhythm analysis		1	*(0.2)*	9	*(4.5)*	10	*(1.4)*	
After ROSC		**n=194**		**n=200**		**n=394**		
Time to ROSC (min)	*Median (IQR)*	10	*(5-20)*	5	*(3-10)*	9	*(5-15)*	*.393*
Glasgow Coma Scale (after ROSC)*	*Median (IQR)*	3	*(3-14)*	9	*(3-15)*	3	*(3-14)*	*<.001*
Serum lactate (mmol/L)	*Median (IQR)*	6.6	*(2.8-10.8)*	3.3	*(1.8-6.5)*	5.9	*(2.8-10.0)*	*<.001*
Coronary intervention†	*n(%)*	25	*(11.8)*	50	*(24.4)*	79	*(11.1)*	*<.001*
ICU admissions	*n(%)*	168	*(88.9)*	124	*(62.9)*	299	*(75.9)*	*<.001*
At discharge		**n=28**		**n=203**		**n=231**		
Cognitive performance Cat.**	*n(%)*							*.116*
1-2 none/slight disability		17	*(60.7)*	156	*(78.8)*	179	*(77.5)*	
3 – severe disability		9	*(32.1)*	29	*(14.6)*	38	*(16.5)*	
4 – coma		0	*(0)*	2	*(1.0)*	2	*(0.9)*	
Unknown[ǀ]		2	*(7.1)*	11	*(5.6)*	12	*(5.2)*	
In need of daily assistance[§]	*n(%)*	9	*(32.1)*	31	*(15.7)*	40	*(17.3)*	*.085*
Discharge destination	*n(%)*							*.084*
home or family		19	*(69.2)*	128	*(65.0)*	150	*(64.9)*	
rehab centre		3	*(11.5)*	26	*(13.2)*	31	*(13.4)*	
nursing home		1	*(3.8)*	14	*(7.1)*	16	*(6.9)*	
other hospital (for long-stay ward)		3	*(11.5)*	29	*(14.7)*	34	*(14.7)*	

Table 1. Characteristics of all in-hospital cardiac arrests; one-year survivors vs. non-survivors. *patients who were lost to follow-up were excluded from analysis (n=8) (figure 1). **data was missing for the following categories (n): MRS at admission (29), CPC at admission(25), CPC at discharge (13). †For 35 patients, there was no MRS score reported; non-survivors(22), survivors (7). [ǀ]CPC was unknown for patients who were discharged to other hospitals earlier than scheduled, therefore CPC at discharge was not known. [§]Patients requiring assistance for daily activities such as bathing, getting dressed or cooking.

Patient characteristics	Pre-arrest variables			Pre and peri-arrest variables		
	Hazard ratio at death	95% CI	p=	Hazard ratio at death	95% CI	p=
Age, per year increase	1.01	1.00 – 1.02	.003	1.01	1.00 – 1.02	.007
Body Mass Index (kg/m²) (BMI) per point increase	0.98	0.98 – 1.01	.722	1.00	0.98 – 1.01	.583
Charlson comorbidity index (CCI) per point increase	1.07	1.03 – 1.10	<.001	1.07	1.03 – 1.10	<.001
Modified Rankin Scale (MRS) per point increase	1.05	0.96 – 1.14	.290	1.02	0.94 – 1.12	.616
Cognitive Performance Category score (CPC) per point increase	1.11	0.97 – 1.27	.124	1.06	0.92 – 1.21	.436
Non-shockable rhythm				1.89	1.46 – 2.36	<.001
Non-cardiac cause of arrest				0.94	0.75 – 1.17	.571
Non-cardiac admission specialty				1.11	0.87 – 1.40	.354
Non-monitored ward				1.00	0.81 – 1.23	.968
Non-witnessed arrest				1.50	1.19 – 1.89	.001

Table 2. Cox regression of factors associated with death <1 year after cardiac arrest, meaning not achieving ROSC, death in-hospital or death after discharge in the year after surgery. Two analyses were performed for pre-arrest variables, both with and without adjustment for peri-arrest variables.

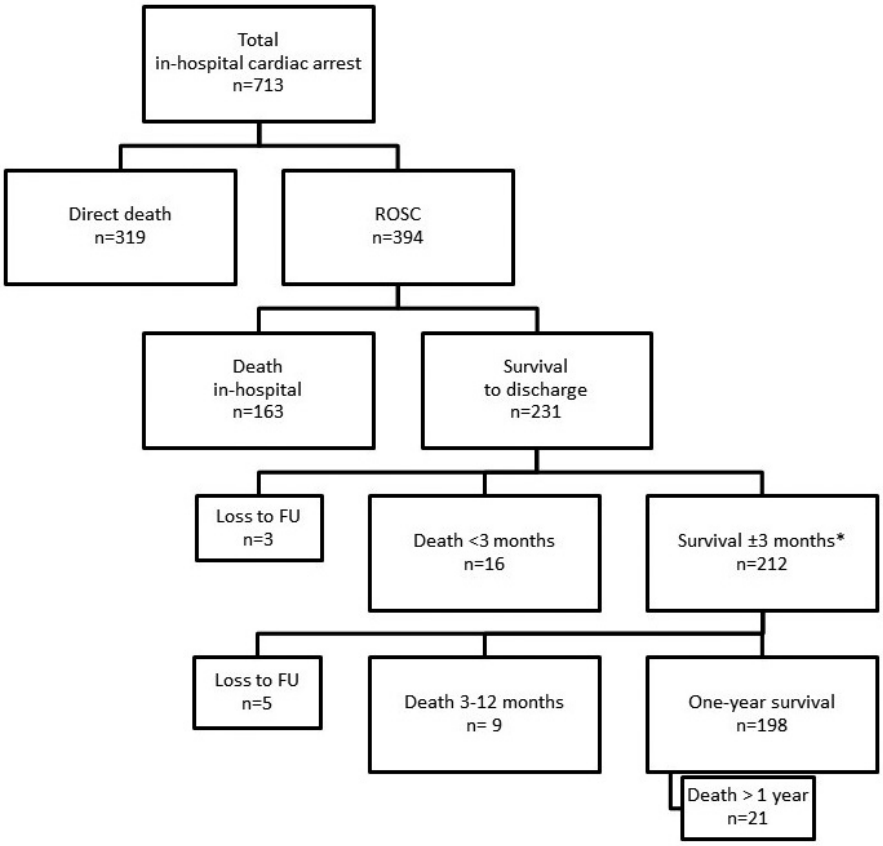


Figure 1. Survival flowchart for all-in-hospital cardiac arrest cases. *survival at this time point was assessed through patients' responses to the questionnaire and was therefore variable with a median follow-up of 94 days (IQR 82-132).

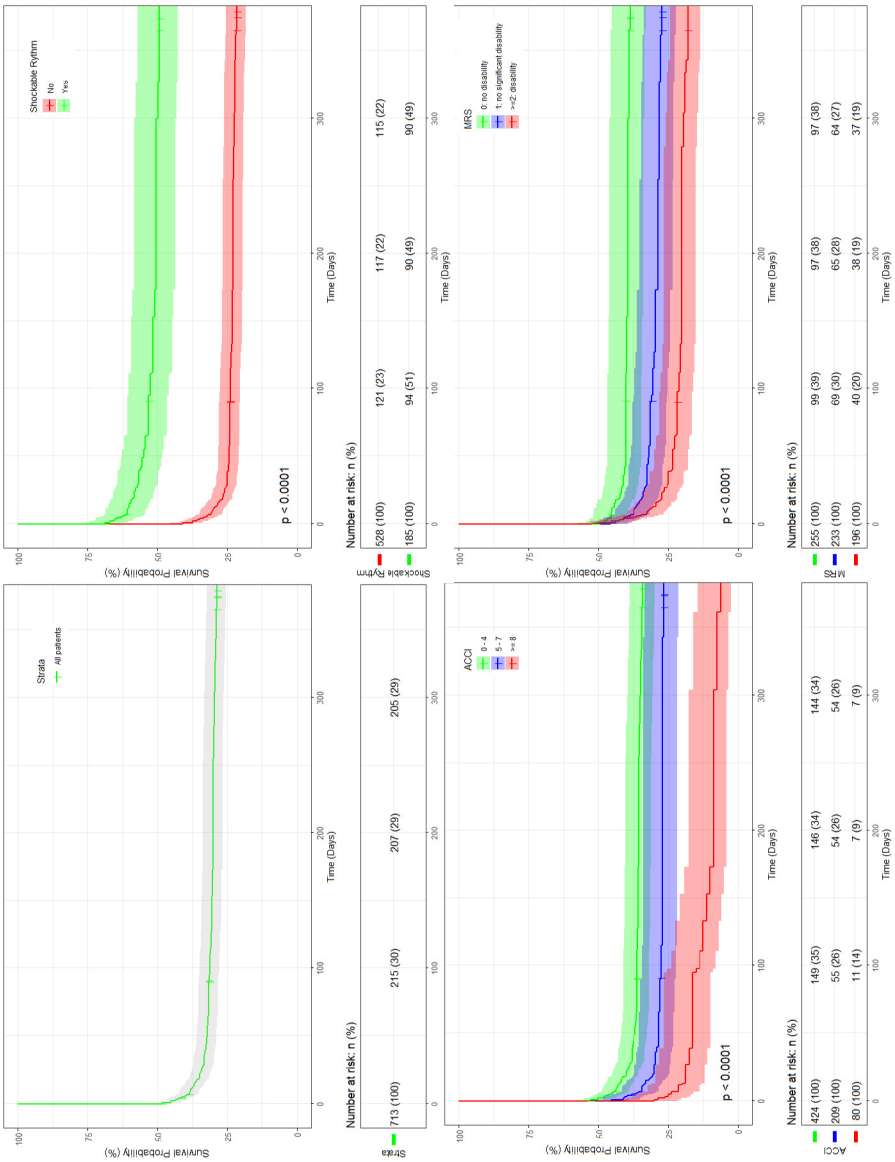


Figure 2. Long-term survival. Survival function is stratified for shockable rhythm, pre-admission functional status (Modified Rankin Scale) and for Age-Combined comorbidity index (ACCI). Log-rank tests were performed: shockable rhythm p<0.001, MRS p<0.001, ACCI p<0.001.

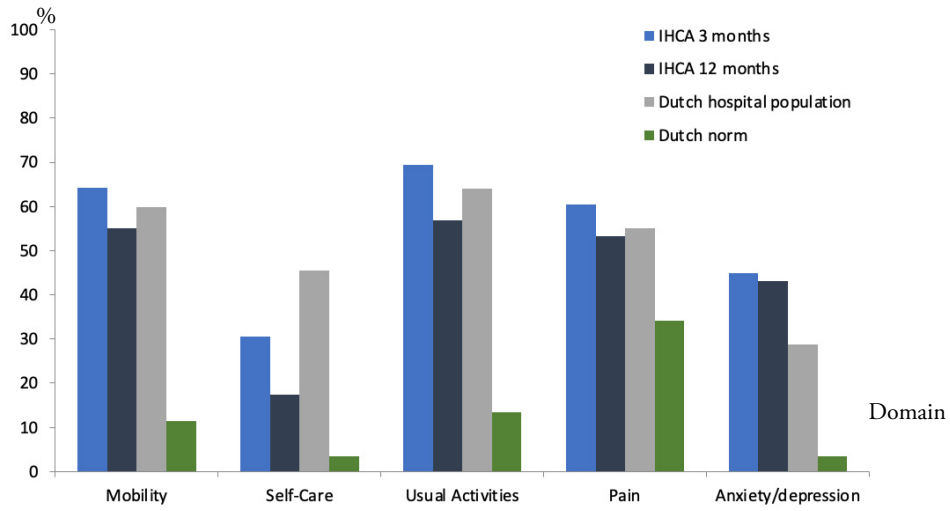
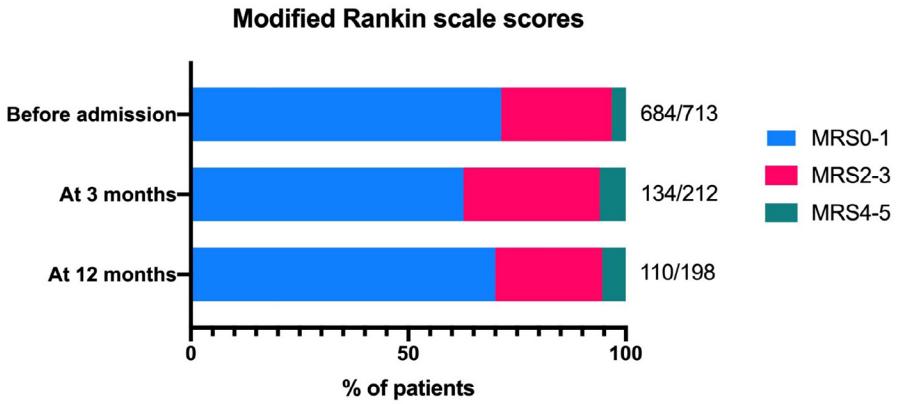


Figure 3. EQ-5D-5L percentage of patients who report any problem in one of the five domains at 3 months and 12 months after cardiac arrest. Reporting of problems was compared to a cross-sectional sample from Dutch hospitalized patients and the Dutch norm population.



Supplemental figure 2. Modified Rankin scale distribution for cardiac arrest patients before admission, at 3-month follow-up and at 12-month follow-up. MRS counts are displayed if reported in regard to the total number of patients alive at that point in time (n/n). MRS 0-1: none or slight disability, 2-3: moderate disability, 4-5 severe disability.

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Better never means better for everyone.

Margaret Atwood, The Handmaid's Tale

Chapter 8

In-depth assessment of Health-Related Quality of Life after In-Hospital Cardiac Arrest.

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Abstract

Introduction

Evidence on physical and psychological well-being of in-hospital cardiac arrest (IHCA) survivors is scarce. The aim of this study is to describe long-term health-related quality of life (HRQoL), functional independence and psychological distress 3 and 12 months post-IHCA.

Methods

A multicenter prospective cohort study in 25 hospitals between January 2017 – May 2018. Adult IHCA survivors were included. HRQoL (EQ-5D-5L, SF-12), psychological distress (HADS, CSI) and functional independence (mRS) were assessed at 3 and 12 months post-IHCA.

Results

At 3-month follow-up 136 of 212 survivors responded to the questionnaire and at 12 months 110 of 198 responded. The median (IQR) EQ-utility Index score was 0.77 (0.65 – 0.87) at 3 months and 0.81 (0.70 – 0.91) at 12 months. At 3 months, patients reported a median SF-12 (IQR) physical component scale (PCS) of 38.9 (32.8-46.5) and mental component scale (MCS) of 43.5 (34.0-39.7) and at 12 months a PCS of 43.1 (34.6-52.3) and MCS 46.9 (38.5-54.5).

Discussion

Using various tools most IHCA survivors report an acceptable HRQoL and a substantial part experiences lower HRQoL compared to population norms. Our data suggest that younger (male) patients and those with poor functional status prior to admission are at highest risk of impaired HRQoL.

Introduction

In-hospital cardiac arrest (IHCA) is a major adverse event in hospitalized patients. Its outcome has improved over the past decades, although survival rates remain low[1–3]. Outcome assessment after cardiac arrest traditionally focuses on survival rates and clinician-based description of functional outcome. Historically, good outcome was defined as a Cognitive Performance Category of 1 or 2, indicating none to mild neurologic disability[4]. The 2018 International Liaison Committee On Resuscitation (ILCOR) statement on reporting in cardiac arrest research advocates the use of patient-reported outcome measures. In this regard, the Core Outcome Set for Cardiac Arrest research (COSCA) contains a well-constructed set of recommendations of which outcome measures to use[5]. The principal recommendation is to use health-related quality of life (HRQoL) and functional status at 90 days and 1 year via validated instruments. In addition to the use of a Cognitive Performance Category (CPC) scale to measure neurologic performance. To date, determinants of HRQoL in ICU patients and cardiac arrest survivors have not been studied extensively[6–10].

To survive a cardiac arrest is a close encounter with death and many patients report some form of existential suffering, alongside physical symptoms resulting from cardiopulmonary resuscitation and hospital treatment[11,12]. Identifying patients in need of (more specific and intensive) rehabilitation can help increase HRQoL among cardiac arrest survivors, but evidence is scarce[11,13–17]. Moreover, the role of age, sex and functional status on quality of life are not well described. We started the Resuscitation Outcomes in the Netherlands (ROUTINE) project to establish the characteristics of IHCA and its outcomes [2,3,18–20]. In a prior publication we presented a one-year survival rate of 27.8% and we described the influence of comorbidity and functional status on survival. The current manuscript adds a more in-depth analysis of HRQoL and its association with pre-arrest factors.[3]. As mentioned earlier, reported outcomes in cardiac arrest research need to focus more on what matters to patients [5,10]. The primary aim of this study is to describe HRQoL, anxiety, depression, and caregiver strain 3 and 12 months after IHCA. The secondary aim is to determine factors associated with HRQoL.

Methods

Design and setting

A nationwide multicenter prospective cohort study was performed.[3]. Our previous article contains more information on the follow-up in terms of survival and HRQoL in general. A call for participation was done through the Dutch Society for CPR-coordinators (NVCR). This resulted in 14 participating hospital organizations, comprising 25 hospital locations (25.3% of all Dutch hospitals). Data were collected through an online registration system (OpenClinica, Walton, MA, USA).

Patient population

Patients eligible for inclusion were adults (≥18 years of age), who received in-hospital cardiopulmonary resuscitation, defined as the start of manual chest compressions for a circulatory arrest. The inclusion period was January 1st 2017 – May 31st 2018. Patients from all hospital wards, departments and outpatient clinics were included. Patients from the intensive care (ICU) and cardiac care units (CCU), as well as the emergency room (ER) were also included. Exclusion criteria were: OHCA <24 hours prior to IHCA, purposely induced arrhythmia (e.g. electrophysiological interventions) or cardiac arrest (e.g. cardioplegia in cardiac surgery), or refusal to participate. Last follow-up was completed August 1st 2019.

Follow-up process

All patients were prospectively included through registration by each hospital's CPR-team and crosschecked with ICU-admissions for cardiac arrest. In-hospital follow-up was done by the local investigator in each hospital until hospital discharge. At discharge, the Cognitive Performance Category (CPC) score was assessed and the discharge destination was registered. After 3- and 12-months post-discharge the survival status was checked using the Dutch Personal Records Database (Basis Registratie Personen; BRP). Survivors received questionnaires addressing their functional status and HRQoL. Up to two reminder questionnaires were sent and, in case of no response, patients were contacted by telephone.

Outcome measures

The primary outcome measure was health-related quality of life (HRQoL) measured by the EQ-5D-5L Visual Analogue Scale (EQ-VAS, explained below). Secondary outcome measures comprised an in-depth examination of HRQoL (EQ-5D-5L, Short Form-12) and measures of psychological distress (Hospital Anxiety and Depression Scale/HADS, Caregiver Strain Index/CSI) at 3 and 12 months after cardiac arrest, and survival rates.

Functional status and comorbidity

Functional status was determined through a self-reported Modified Rankin Scale (mRS)[21]. The mRS is a 5-point disability scale describing severity of functional disability: 0 means no disability and 5 means the patient is bedridden. Furthermore, reported functional status was confirmed by the SF-12 Physical Component Scale(PCS) and EQ-5D-5L mobility and usual activities domains. The Charlson Comorbidity Index was established at hospital admission and cross-checked with self-reported comorbidities at 3 and 12 months[22].

Health-related Quality of Life
EuroQol: EQ-5D-5L

The EQ-5D-5L questionnaire measures HRQoL on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in which patients can report problems in 5 severity levels. EQ-5D-5L Utility Index scores (EQ-Index) were calculated from the five dimensions of the EQ-5D-5L, with a standard set of population based weights validated for the Netherlands[23]. Calculated index scores range from 1 (best health state) to -0.59 for a health state deemed worse than death. The visual analogue scale (EQ-VAS), a part of the EQ-5D-5L questionnaire, allows patients to score their perceived health state from 0 (indicating worst health state imaginable) to 100 (indicating best health state imaginable). [24] The EQ VAS provides a quantitative measure of the patient's perception of their overall state of health. In a previous study we assessed patients' experiences with CPR-directive counseling and as a general demographic we gathered EQ-5D data on these 1136 hospitalized patients from all types of hospital wards in fifteen hospitals, which we now used for comparison with our study population[20]. The hospitals in this cross-sectional cohort have an 85,7% overlap (12/14 hospitals) with the current study. Normative data for the Dutch population were obtained through the EuroQoL project[23].

Short-form 12

The Short Form-12 is validated standardized questionnaire that uses a mental component scale (MCS) and physical component scale (PCS) [25]. SF-12 scores are standardized and result in composed scores for physical and mental health ranging from 0 (worst) to 100 (best health imaginable). Normative data for the Dutch population were obtained through Tilburg University[26].

Psychological well-being

Symptoms of depression and anxiety are assessed using the Hospital Anxiety and Depression scale, or HADS. The HADS is a 14-item scale that generates ordinal data and is commonly used to determine the levels of anxiety and depression that a person is experiencing. Seven of the items relate to anxiety and seven relate to depression. The

HADS yields a depression and anxiety sum score, ranging from 0 to 21 with higher scores indicating more severe symptoms. A cumulative score above 8 of either the depression or anxiety subscale is classified as clinically significant symptoms of depression or anxiety. HADS scoring permits dividing into categories of severity according to its original manual: less than 7 no symptoms; 8–10 mild; 11–14 moderate; 15–21 major[27]. The Caregiver Strain Index (CSI) can be used to quickly identify families with potential caregiving concerns. It is a 13-question tool that measures strain related to care provision. There is at least one item for each of the following major domains: Employment, Financial, Physical, Social and Time. Positive responses to 7 or more items on the index indicate a greater level of strain. This instrument can be used to assess individuals of any age who have assumed the role of caretaker. Because HADS and CSI have not been evaluated for cardiac arrest patients, we calculated Cronbach's alpha to test their internal validity[28].

Ethical considerations

Patients who survived to hospital discharge received study information at the hospital of admission. Prior to discharge patients were informed of the non-interventional design and informed consent was obtained for the use of their medical data, and for being approached within follow-up. This study was considered subject to the Dutch Medical Research Involving Human Subjects act (WMO) and was approved by the Erasmus University Medical Centre Medical Ethics Committee (ABR55661.078.16). The study was registered with clinicaltrials.gov (NCT03120507) and the Dutch trial registry (NTR6145).

Statistical analysis

Data were summarized with descriptive statistics in terms of mean (standard deviation) or median (interquartile range) when appropriate. Normal distribution was visually assessed through histograms and Q-Q plots. Comparisons between responders and non-responders (e.g., age, comorbidity, or admission specialty) were made by the c^2-test or Fisher exact (categorical) Mann-Whitney-U/Wilcoxon test (non-normal distribution). For comparison of SF-12 scores to normative standardized mean differences (SMD; *Cohen's d*) were calculated. For this goal the mean PCS and MCS scores were used as this was advised in the SF-12 manual. To investigate the influence of age and gender on EQ-5D-5L index score, Tobit regression was performed and right censored at 1. This censoring was performed because of skewed data on the one hand and a maximum performance limit of 1 on the other. Regression coefficients are presented along with their 95% confidence interval (CI). To determine the associations of CPC, functional status, and comorbidity with HRQoL, we performed subgroup analyses on the EQ-5D5L index scores and SF-12 PCS/MCS scores. The predefined subgroup analyses were made for age, the Charlson Comorbidity Index (CCI) (0-1; 2-3; 4 and higher) and the Modified Rankin Scale (0-1;2-3;4-5) at admission and at follow-up and the Cognitive Performance Category (1-2 and 3-4) at hospital discharge, Association between EQ-5D-5L index

scores/SF-12 scores and subgroups were tested using a Kruskal-Wallis test. For effect size e^2 was calculated[29]. Epsilon-squared (e^2) is the equivalent of R^2, but rather for the Kruskal-Wallis test. An e^2 of >0.16 is considered a relatively strong effect size, >0.36 is considered strong. For normally distributed data ANOVA was used. For all tests, a probability value for significance of less than 0.05 (two-sided) was used. Data were analyzed using SPSS statistics v25.0 (IBM, Chicago, IL, USA) and R (The R Foundation for Statistical Computing, Vienna), using the 'censReg' package.

Results

A total of 713 patients suffered an in-hospital cardiac arrest during the inclusion period. Two hundred-thirty-one (32.4%) patients were discharged alive after cardiac arrest of whom 212 (29.7%) survived to 3 months and 198 (27.8%) to 12 months. The survival flowchart is depicted in supplemental figure 1. At follow-up 136/212 (64.1%) at 3 months and 110/198 (55.5%) of patients at 12 months responded to the questionnaires (i.e. responders). Table 1 summarizes data on responders. Demographics, cardiac arrest characteristics and hospital treatment were comparable between responders and non-responders (supplemental table 1). Functional disability prior to cardiac arrest (at home) was higher in non-responders vs. responders when evaluated at the 3-month time point (mRS≥2 at home: 22.3% vs. 16.1%; p=0.032), and also at the 12-month time point (19.3% vs. 15.4%; p=0.243), albeit not significantly. The proportion of patients with a CPC score of 1-2 at discharge was similar between responders and non-responders, at 3 months (81.6% vs. 75.0%, p=.158) and 12 months (81.8% vs. 75.0%, p=.332). The majority of responders reported none to slight functional disability (mRS 0-1) at 3 months (62.7%) and at 12 months (69.7%). For a longitudinal evaluation of mRS a Sankey plot is provided in supplemental figure 2. This figure shows the transition of patients to other states of functional capacity over time.

HRQoL: EQ-5D-5L

Median EQ-VAS was 70 (IQR 60-80) at 3 months and 75 (IQR 65-85) at 12 months (p=.022). The reported EQ-5D-5L domains are displayed in figure 1. The most frequent reported problems at 12 months were: *usual activities* (56.9%), followed by *mobility* (55.0%), *pain* (53.2%), *anxiety/depression* (43.2%) and *self-care* (17.4%). Only a small proportion of patients (≤2.4%) reported severe problems (score ≥4) for each domain. Patients with higher pre-admission mRS and CCI, reported more and more severe problems in the EQ-5D-5L domains at 12-month follow-up (figure 1C-D).Patients reported a median EQ-5D index score of 0.77 (IQR 0.65 – 0.87) at 3 months and 0.81 (IQR 0.70 – 0.91) at 12 months (p=.007).

We compared mean EQ-index scores stratified for predefined subgroups, as displayed in table 2. EQ-index scores at follow-up were lower in patients with a lower mRS (e^2 =0.133 p=.001) and a higher CCI score (e^2 =0.199 p=.001) at admission. Patients who were discharged with none to mild neurologic disability (CPC 1-2) had the same median EQ-index as patients discharged with moderate-severe neurologic disability (CPC 3-4) (e^2 =0.003 p=.598) (table 2). In addition, median EQ-5D-5L index score did not differ when patients were subdivided based on age (e^2=0.02) or sex (e^2=0.06) (figure 2). Similar results were obtained when these variables were analyzed using a Tobit regression model (age -0.003, 95%CI -0.007; 0.001, p=.173; male sex: -0.01, 95%CI -0.1; 0.01, p=.826).

HRQoL: Short Form-12

At 3 months, patients reported a median (IQR) PCS of 38.9 (32.8-46.5) and MCS of 43.5 (34.0-39.7) and at 12 months a PCS of 43.1 (34.6-52.3) and MCS 46.9 (38.5-54.5). Median MCS (p=.002) and PCS (p=.001) scores increased between 3 and 12 months (table 1 and figure 3). Overall, at 12 months patients reported a lower MCS (SMD -1.422, 95% CI -1.691 to -1.152) and PCS (-1.102, 95% CI -1.536 to -0.507) compared to a Dutch norm population. Figure 3 displays the SMD for patients, subdivided for sex at both the 3- and 12-month follow-up. Men reported significantly lower scores than women on MCS at both 3 months (SMD -1.950, 95%CI -2.222 to -1.686) and 12 months (SMD -1.422, 95%CI 1.691 to -1.152). Stratified for the predefined groups, there was a significant decrease in reported quality of life on both the physical and mental component scale for patients with a lower Modified Rankin Scale (table 2).

Hospital Anxiety and Depression Scale

Reliability of HADS questionnaire at 3 months and 12 months after IHCA was assessed by Cronbach's alpha and was questionable for the anxiety subscore (respectively 0.60 and 0.71) and good for the depression score (respectively 0.86; 0.90)[30]. Table 1 summarizes the results on the HADS questionnaire at 3 months and 12 months. Moderate-major problems on the anxiety scale (i.e. ≥ 11 points) were reported by 12.0% (15/125) at 3 months and 14.8% (16/108) at 12 months. Moderate-major problems on the depression scale (i.e. ≥ 11 points) were reported by 5.6% (7/125) at 3 months and 11.3% (12/106) at 12 months. No significant association was observed between pre-arrest, hospital-related factors or CPC-score at discharge and the occurrence of anxiety or depression at 12 months. Moderate-major symptoms of depression at 12 months were more prevalent in male patients (table 2).

Caregiver Strain Index

The Caregiver strain index evaluates the burden among patient's caregivers. Cronbach's alpha for the caregiver strain index was good (0.89; 0.88). At 3 months caregiver strain was reported by 23.9% of responders' caregivers and by 20.5% at 12 months, respectively (table 3). Caregiver strain was more prevalent in patients with moderate-major depression symptoms versus none-mild symptoms (44.4% vs. 15.6%, p=0.035) as described in table 3. A separate analysis showed caregiver strain was also more prevalent in patients with higher mRS scores ≥2 points versus 0-1 points as well (45.8% vs. 11.3%, p<0.001),

Discussion

In this large multicenter cohort study various tools were used to measure HRQoL and psychological wellbeing of In-Hospital Cardiac Arrest survivors. Most survivors report an acceptable HRQoL. Still a number of patients reported moderate or severe problems, mostly in usual activities, mobility and depression symptoms. Our findings suggest that HRQoL is lower in patients that are functionally incapacitated and that psychological distress is more prevalent among male survivors. Also, pre-arrest functional disability seems to predispose for impaired HRQoL at follow-up. Our study highlights the existence of problems in all daily aspects of life for cardiac arrest survivors, as well as its relationship with psychological well-being.

In general the HRQoL of IHCA survivors is lower than that of a Dutch norm populations, as reflected by the functional and psychological domains of the EQ-5D, the EQ-5D index score, and both SF-12 domains[23]. Male survivors more frequently reported psychological distress based on the SF-12-MCS and HADS. When we compared the EQ-index score to the Dutch population mean, a gap remains indicative of a lower HrQoL for cardiac arrest survivors. EQ-5D index scores are similar to those found in earlier studies on HRQoL at discharge in IHCA and OHCA patients [13,14,31,32] and in Dutch ICU-survivors[33]. Median EQ-5D-5L visual analogue scale score was 70 at 3 months and 75 at 12 months, as compared to 82 in the Dutch population norm and 62 in the cohort of hospitalized patients as described in our previous cross-sectional study [20,23]. A similar proportion of IHCA survivors reported problems concerning mobility, usual activities and pain as was reported by hospitalized patients, but IHCA survivors more frequently suffered from anxiety and depression[20]. Although IHCA survivors are discharged home in most cases and quality of life was measured while they were no longer in hospital, the reported problems in the ED-5D-5L domains were similar to patients during hospitalization. The proportion of patients with severe problems was however lower than in hospitalized patients, as described earlier[3]. Overall HRQoL, as determined by SF-12 and EQ-5D-5L was lower in IHCA survivors compared to a Dutch cohort of OHCA survivors[34]. The high incidence of caregiver strain and psychological distress was similar when we compare our cohort to these OHCA survivors[34]. Similar SF-12 scores at 3 month and 12 month follow-up were observed in a Norwegian study [35].

Despite limitations inherent to such comparisons, our data delivers important signals. First, the prevalence of HRQoL problems is relatively high and perceived quality of life is lower compared to a reference population (figure 2). Nonetheless, the fraction of severe problems is relatively low (figure 1). Second, pre-arrest functional independence and comorbidity appears to resonate in more problems in the quality-of-life domains and lower HRQoL scores at follow-up (figure 1 and table 2). Third, anxiety and depression are frequent in IHCA survivors (table 3). We can only speculate on possible explanations for the findings on lower HRQoL. First, pre-existing illness and cerebral hypoxia may synergistically create a decline of quality of life in both physical and mental domains. After IHCA, in our cohort, most patients died after cessation of treatment for multi-organ failure (49.7%), or hypoxic brain damage (29.7%) and only a minority died without cessation of treatment (i.e. re-occurrence of cardiac arrest without subsequent medical intervention)(20.5%).

It is possible that these number reflect on the survivors, i.e. the presence of both (less severe) multi-organ failure and hypoxic damage. For OHCA cessation of treatment is largely based on the presence of irreversible severe brain damage, whereas multi-organ failure is less common[1]. Secondly, there may be a lack of recognition of the problem of IHCA survivors. IHCA survivors return to the hospital ward after an ICU session to be treated for their underlying disease rather than receiving physical and neurocognitive rehabilitation aimed at cardiac arrest survivors. Lastly, in our own cohort, only 23.4% attended a rehabilitation program. We believe this may also contributed to diminished HRQoL. These findings show the impact of cardiac arrest and subsequent critical illness on patients' lives and indicate the presence of suffering[20]. The relation to functional incapacitation is relevant, as it might prove useful for rehabilitation purposes.

To date, this is the second largest prospective study to describe HRQoL and psychological distress among IHCA survivors[14]. In the heterogeneity of reported outcome measures, our study is one of the first to adhere to the Core Outcome Set for Cardiac Arrest recommendations by the ILCOR. No specific instrument is available for assessing HRQoL in cardiac arrest survivors. As each of the used measurements has its merits and demerits, the simultaneous use of qualitative instruments and functional and survival outcome measures is currently the most practical mode of reporting[36]. Several interactions or the lack thereof, are notable. First, the CPC scores at discharge were not associated with HRQoL at 3 or 12 months, nor with psychological well-being. CPC has often been used to describe ''good outcome" [13,36,37]. As CPC does not clearly correlate with HRQoL in our study, this finding expresses once more that quality of life warrants a more in-depth examination. Secondly, patients with more severe depression or anxiety more often reported functional disability. This is in accordance with prior reports from OHCA populations and supports the need for more structured rehabilitation programs aiming at both physical as psychological wellbeing[16,38,39].

In a prior publication we reported findings from this cohort that focused mainly on survival and observed that survival was associated with pre-admission functional status (mRS) and the level of comorbidity (ACCI)[3]. The current manuscript adds challenges to the topics of cardiac arrest prognostication and subsequent patient counselling. We have now described survival, health-related quality of life and the possible problems IHCA survivors may encounter. We however do not yet have a clear picture of the weight patients attribute to these outcomes and future CPR-directives counselling should take this into account. How and on what specific topics patients need to be informed about during a CPR-directive conversation is not yet fully elucidated but probably requires an individualised approach[10,40]. As patient centred care and advance care planning have become increasingly important, based on our findings, a patient's condition and functional status at admission should be taken into account when speaking about CPR-directives.

Three important caveats need consideration when interpreting our results. Because not all survivors responded, the possibility of response bias is realistic. Notwithstanding, several lines of data suggest non-response bias in our study to be limited. First, baseline demographics, cardiac arrest characteristics and hospital treatment characteristics were similar between responders and non-responders. Second, functional status prior to cardiac arrest was similar in both groups. Third,

the proportion of patients with a CPC score of 1-2 was similar between responders and non-responders, at all study time points evaluated. Although the actual impact is not quantifiable, non-participation in itself might be a proxy for psychological distress. Especially non-participation in elderly and frail patients tend to skew the results of HRQoL research. This may lead to the results being more positive than the actual perceived HRQoL of the entire group[41]. If this effect applies to our data, HRQoL for IHCA survivors may actually be lower than we have now described. Future research, with more in-depth follow-up should elucidated this phenomenon. The second caveat pertains to validation. As noted earlier all methods used to quantify HRQoL and psychological distress have not been formally validated for cardiac arrest survivors. They are, however, in itself well-validated, widely used and recommended in current guidelines for post-resuscitation care[5,17]. Also, cardiac arrest survivors are in most cases also ICU survivors. And [35]. HRQoL appears lower in patients with functional disability at home, although it is hard to make a definite conclusion due to the number of responders that was too low. Although we cannot formally determine whether pre-arrest factors, the cardiac arrest itself, or subsequent ICU treatment is the main driver of diminished HRQoL, the message remains unaltered; HRQoL is diminished and requires our attention in the post-resuscitation period. The third caveat pertains to selection. We feel is it plausible that patients, who report longstanding incapacitation and diminished quality of life at hospital admission, will have been given a Do Not Resuscitate order. In our studies on survival characteristics and on CPR-directives, we report a relatively high survival rate and we explained that one of the causes might be selection of patients for whom CPR is deemed likely to be successful[3,20]. If these patients had been resuscitated, survival might have been lower, as well as HRQoL of the surviving group. This needs to be taken into account when comparing our results to other studies. However, it also stresses even more the importance of CPR prognostication and adequate communication of CPR-directives[10].

This study underlines the added value of more patient-reported outcome measures in cardiac research, confirms the burden of physical and psychological impairments among IHCA survivors and highlights certain groups of survivors at particular risk. We suspect patients suffering from IHCA, unlike OHCA survivors are not recognized as cardiac arrest survivors. IHCA survivors frequently return to the hospital ward after an ICU admission to be treated for their underlying disease. Physical and neurocognitive rehabilitation had less priority in these cardiac arrest survivors. Screening and risk stratification for physical and psychological issues should be implemented in post-cardiac arrest care. Our data suggest that younger (male) patients and those with a pre-existing poor functional status are at highest risk. In these patients, early recognition of problems and subsequent early rehabilitation could prove especially useful with regard to improving quality of life and return to daily life.

Patient characteristics	All IHCA		3-month FU		12-month FU	
During hospital admission	n=713		n=136		n=110	
Age, median (IQR)	63	*(52-72)*	68	*(58-73)*	*69*	*(59-73)*
Male gender	460	*(64.5)*	91	*(66.9)*	*77*	*(70.0)*
BMI (kg/m²), median (IQR)	25.7	*(23.0-30.0)*	26.7	*(23.9-30.3)*	*26.5*	*(24.1-26.5)*
CCI, median (IQR)	1	*(0-3)*	1	*(0-2)*	*1*	*(0-2)*
Cerebral performance category 1-2	634	*(88.9)*	131	*(96.3)*	*107*	*(97.3)*
Modified Rankin Scale (at home)						
0-1 – none/slight disability	488	*(68.4)*	112	*(82.4)*	*90*	*(81.1)*
2-3 – moderate disability	174	*(24.4)*	21	*(15.4)*	*16*	*(14.5)*
4-5 – severe disability	22	*(3.1)*	1	*(0.7)*	*1*	*(0.9)*
Unknown	29	*(4.1)*	2	*(1.5)*	*3*	*(2.7)*
After ROSC						
Time to ROSC (min), median (IQR)	9	*(5-15)*	5	*(2-10)*	*5*	*(2-10)*
ICU admission	299	*(75.9)*	89	*(65.9)*	*72*	*(65.5)*
ICU LOS (days), median (IQR)	5	*(2-15)*	12	*(6-21)*	*11*	*(5-22)*
After hospital discharge						
Cerebral performance category 1-2	179	*(77.5)*	111	*(81.6)*	*90*	*(81.8)*
Discharge destination						
home or family	150	*(64.9)*	92	*(67.6)*	*75*	*(68.2)*
medical facility	81	*(35.1)*	44	*(32.4)*	*35*	*(31.8)*
Modified Rankin Scale at FU			*missing n=3*		*missing n=1*	
0-1 – none/slight disability			84	*(62.7)*	76	*(69.7)*
2-3 – moderate disability			42	*(31.3)*	27	*(24.8)*
4-5 – severe disability			8	*(6.0)*	6	*(5.5)*
Charlson Comorbidity Index (CCI) at FU			*missing n=1*		*missing n=1*	
0-1 – none/mild comorbidity			*94*	*(69.6)*	*70*	*(64.2)*
2-3 – moderate comorbidity			*35*	*(25.9)*	*32*	*(29.4)*
≥4 – severe comorbidity			*6*	*(4.5)*	*7*	*(6.4)*
HADS – Anxiety			*missing n=11*		*missing n=2*	
Normal (0-7)			*84*	*(67.2)*	73	*(67.6)*
Minor (8-10)			*26*	*(20.8)*	19	*(17.6)*
Moderate (11-14)			*14*	*(11.2)*	16	*(14.8)*
Major (15-21)			*1*	*(0.8)*	0	*(0)*
HADS – Depression			*missing n=11*		*missing n=4*	
Normal (0-7)			*103*	*(82.4)*	89	*(84.0)*
Minor (8-10)			*15*	*(12.0)*	5	*(4.7)*
Moderate (11-14)			*5*	*(4.0)*	12	*(11.3)*
Major (15-21)			*2*	*(1.6)*	0	*(0)*
Short-Form 12 (SF-12)			*missing n=19*		*missing n=7*	
PCS, median (IQR)			*38.9*	*(32.8-46.5)*	43.1	*(34.6-52.3)*
MCS, median (IQR)			*43.5*	*(34.0-39.7)*	46.9	*(38.5-54.5)*
EQ – visual analogue scale, median (IQR)			*70*	*(60-80)*	75	*(65-85)*
EQ – utility index score, median (IQR)			*0.77*	*(0.65-0.87)*	0.81	*(0.70-0.91)*
CSI – Caregiver strain indicated, n (%)			*28*	*(23.9)*	18	*(20.5)*

Table 1. Characteristics of the study population. BMI: body mass index; CCI: Charlson Comorbidity Index; LOS: length of stay; HADS: Hospital Anxiety and Depression Scale; SF-12: short form 12 question quality of life questionnaire MCS: mental component scale of SF-12; PCS: physical component scale of SF-12; CSI: caregiver strain index; IQR interquartile range; EQ: EuroQoL or EQ-5D-5L; FU: follow-up.

Patient characteristics		HADS anxiety normal or minor n=92		HADS anxiety moderate-major n=16		Follow-up at 12 months p=
Prior to admission						
Age median (IQR)		59	(60-78)	70	(60-78)	.470
Sex male	n(%)	63	(82.9)	13	(17.1)	.302
Female		29	(90.6)	3	(9.4)	
Charlson comorbidity index	med (IQR)	1	(0-2)	2	(0-3)	.269
Cerebral performance category 1-2	n(%)	89	(96.7)	16	(100)	.765
Modified Rankin Scale (at home)	n(%)					.103
0-1 – none/slight disability		78	(87.6)	11	(68.8)	
2-3 – moderate disability		10	(11.2)	5	(31.3)	
4-5 – severe disability		1	(1.1)	0	(0)	
After ROSC						
ICU admission	n(%)	59	(64.1)	12	(75.0)	.398
Length of stay after cardiac arrest	med (IQR)	11	(4-22)	14	(9-22)	.279
After discharge						
Cerebral performance category 1-2	n(%)	75	(81.5)	13	(81.3)	.990
Discharge destination	n(%)					.206
home or family		60	(65.2)	13	(81.3)	
medical facility		32	(34.8)	3	(18.7)	
At 12 month follow-up						
Modified Rankin Scale (at 12 months)	n(%)					<0.001
0-1 – none/slight disability		72	(78.3)	4	(25.0)	
2-3 – moderate disability		18	(19.6)	8	(50.0)	
4-5 – severe disability		2	(2.2)	4	(25.0)	
Caregiver strain indicated	n(%)					.062
Yes		12	(16.2)	5	(38.5)	
No		62	(83.8)	8	(61.5)	

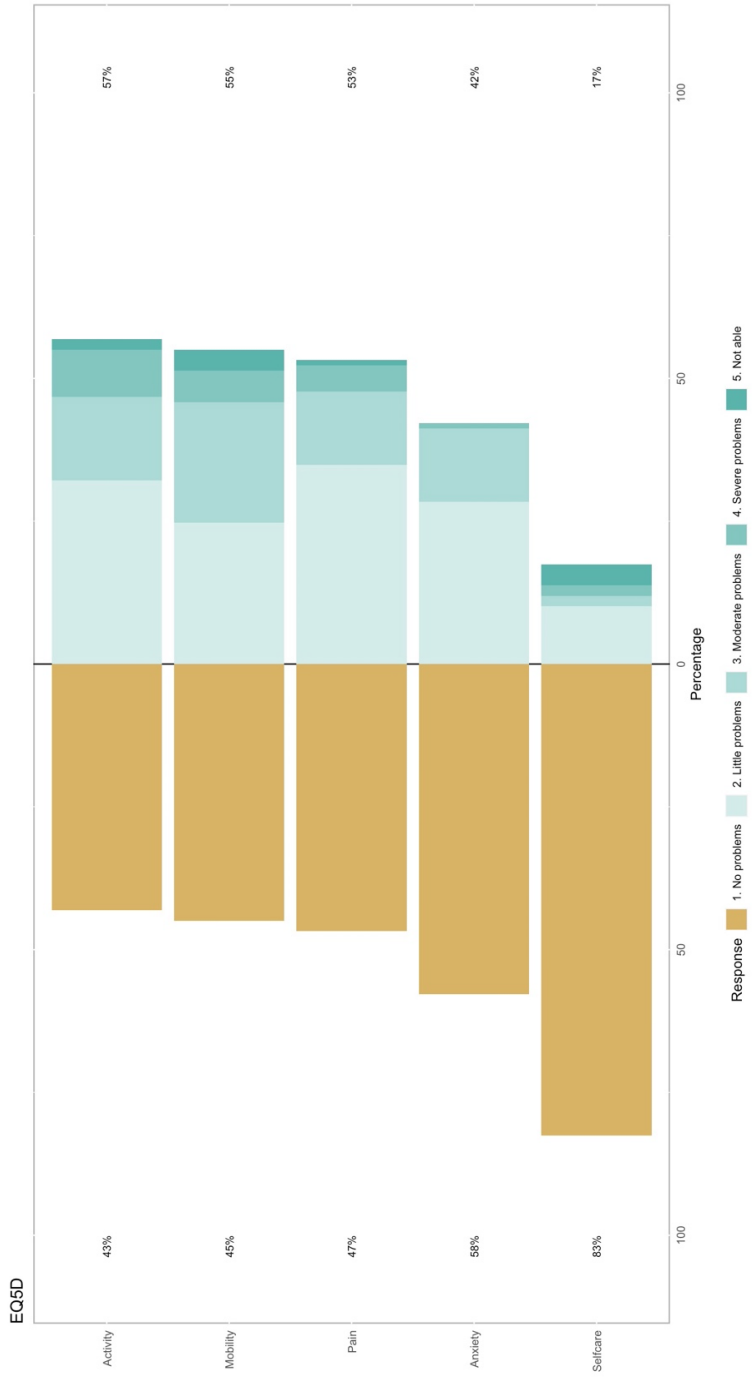
Table 2. Anxiety and depression divided into none-mild and moderate-severe symptoms on the Hospital Anxiety and Depression Scale (HADS). HADS was divided into validated subgroups according to the scoring system: less than 7 no symptoms; 8–10 mild; 11–14 moderate; 15–21 major. p-values have been calculated for the differences between severity groups.

after cardiac arrest				
	HADS depression			p=
	normal or minor n=94		moderate-major n=12	
59	(58-73)	70	(59-78)	.394
62	(84.9)	11	(15.1)	.070
32	(97.0)	1	(3.0)	
1	(0-2)	2	(0-3)	.228
92	(97.9)	11	(91.7)	.207
				.101
80	(87.9)	8	(66.7)	
10	(11.0)	4	(33.3)	
1	(1.1)	0	(0)	
62	(66.0)	7	(58.3)	.602
11	(4-22)	14	(8-22)	.485
79	(84.0)	8	(66.7)	.174
				.225
62	(66.0)	10	(83.3)	
32	(34.0)	2	(16.7)	
				<0.001
73	(77.7)	3	(25.0)	
20	(21.3)	6	(50.0)	
1	(1.1)	3	(25.0)	
				.035
12	(15.6)	4	(44.4)	
65	(84.4)	5	(55.6)	

	EQ-5D-5L index score					Health-related quality of life SF-12 physical	
	Med.	IQR	range	e^2	p=	Med.	IQR
Group total	.81	.74-.92	.08-1.0	-	-	43.1	34.5-52.3
Subgroups				.006	.406		
Male	.82	.70-.96	.08-1.0			44.3	34.6-52.5
Female	.81	.74-.88	.10-1.0			40.5	34.5-50.2
Modified Rankin Scale upon admission*				.133	.001		
0-1	.85	.77-.92	.10-1.0			43.7	36.3-52.8
2-3	.70	.17-.81	.08-.92			32.6	28.5-42.9
4-5	.81	.81-.81	.81-.81			26.1	26.1-26.1
Charlson Comorbidity Index Upon admission				.199	<.001		
0-1	.86	.77-.92	.50-1.0			46.6	36.3-53.3
2-3	.80	.65-.92	.08-.1.0			36.5	31.5-51.5
4 or higher	.14	.65-.89	.08-.22			31.6	32.5-48.7
Cognitive Performance Cat. at discharge				.003	.598		
1-2	.81	.72-.92	.08-1.0			39.7	34.6-52.6
3-4	.81	.62-.89	.08-1.0			43.4	34.3-49.5
Modified Rankin Scale at 12 months				.500	<.001		
0-1	.88	.81-1.0	.65-1.0			49.1	34.6-52.6
2-3	.66	.53-.77	.10-.87			34.1	28.6-38.0
4-5	.14	.08-.18	.08-.22			30.0	28.5-31.0

Table 3. Health-related quality of life index scores at 12 month follow-up for the complete group of responders and for various predefined subgroups. EQ-5D-5L; EuroQoL 5 dimensions/5 layer quality of life questionnaire, SF-12; short form 12 question quality of life questionnaire, med; median score. Range indicates the lowest and highest reported score. Group differences were assessed using the Kruskal-Wallis tests and variance is expressed as e^2(epsilon squared). Med.; median, IQR; interquartile range. At MRS 4-5 there were only few survivors (supplemental figure 1).

scores at 12 month follow-up component scale				SF-12 mental component scale			
range	e^2	p=	Med.	IQR	range	e^2	p=
23.4-58.8	-	-	46.9	38.5-54.5	18.0-62.2	-	-
	.006	.406					.545
23.4-58.8			47.1	38.6-54.6	18.0-62.2		
24.6-57.3			44.2	36.8-53.2	19.0-58.5		
	.114	.003				.009	.623
24.6-57.3			47.1	38.7-54.4	18.0-62.2		
23.4-58.8			41.1	32-8-54.9	21.2-58.8		
26.1-26.1			52.7	52.7-52.7	52.7-52.7		
	.172	<.001				.027	.261
24.6-58.8			48.8	38.9-54.4	18.0-62.2		
23.4-56.9			41.8	33.6-53.6	24.5-57.5		
24.6-39.9			52.1	41.0-55.2	21.2-58.8		
	.009	.341				.001	.799
23.4-55.1			46.9	38.6-54.5	24.5-62.2		
24.6-58.8			56.9	32.9-54.4	18.0-58.8		
	.410	<.001				.136	<.001
26.1-58.8			49.9	41.1-54.7	18.0-58.8		
23.4-43.3			38.7	30.8-44.8	19.0-62.2		
25.7-33.1			28.7	24.5-46.7	21.2-58.8		


EQ5D
Activity
Mobility
Pain
Anxiety
Selfcare
57%
55%
53%
42%
17%
43%
45%
47%
58%
83%
100
50
0
50
100
Percentage
Response
1. No problems
2. Little problems
3. Moderate problems
4. Severe problems
5. Not able

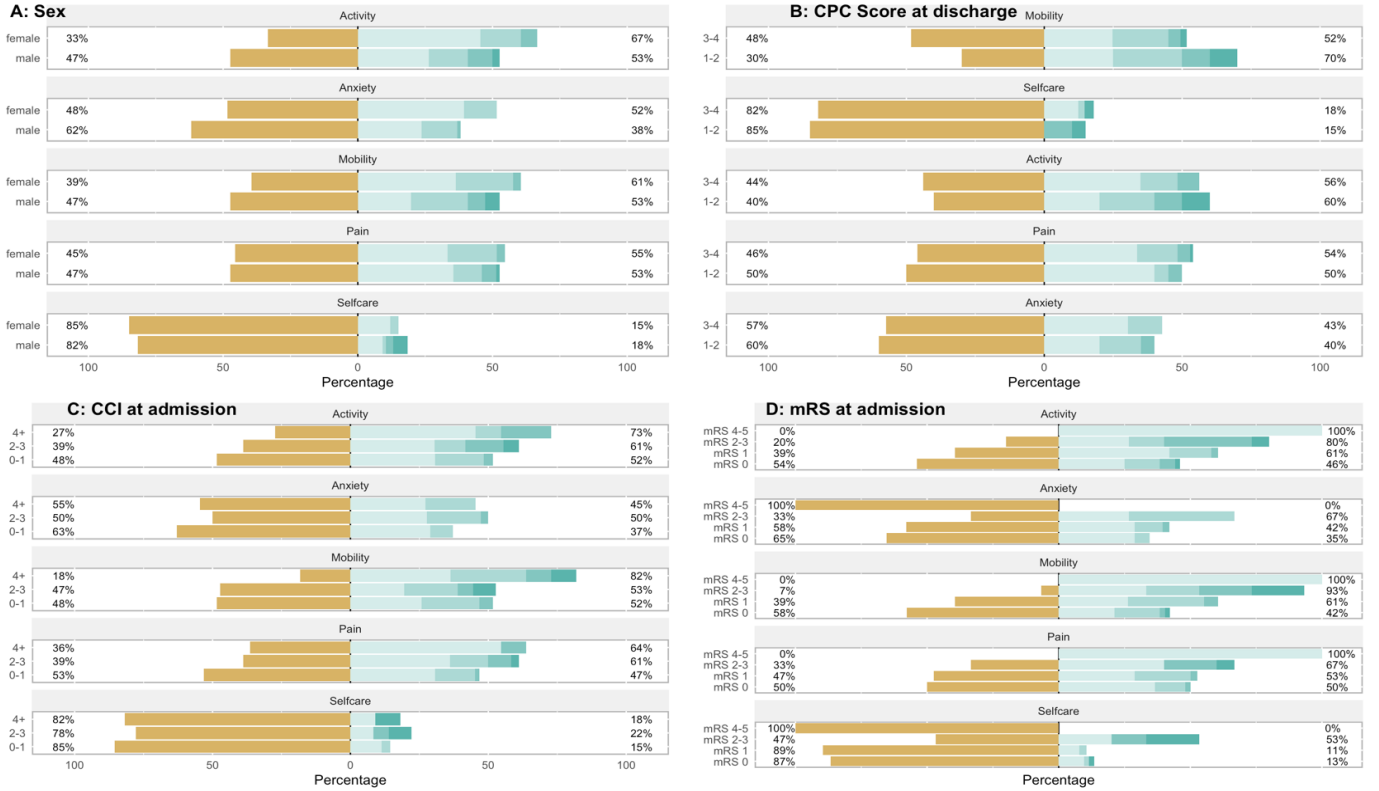


Figure 1. EQ-5D-5L reported problems for pre-specified subgroups. Problems are visualized as no problems (left side bar) or any problems, with the shade of green indicating the severity of the reported problems. CPC: cognitive performance category. MRS: modified Rankin scale.

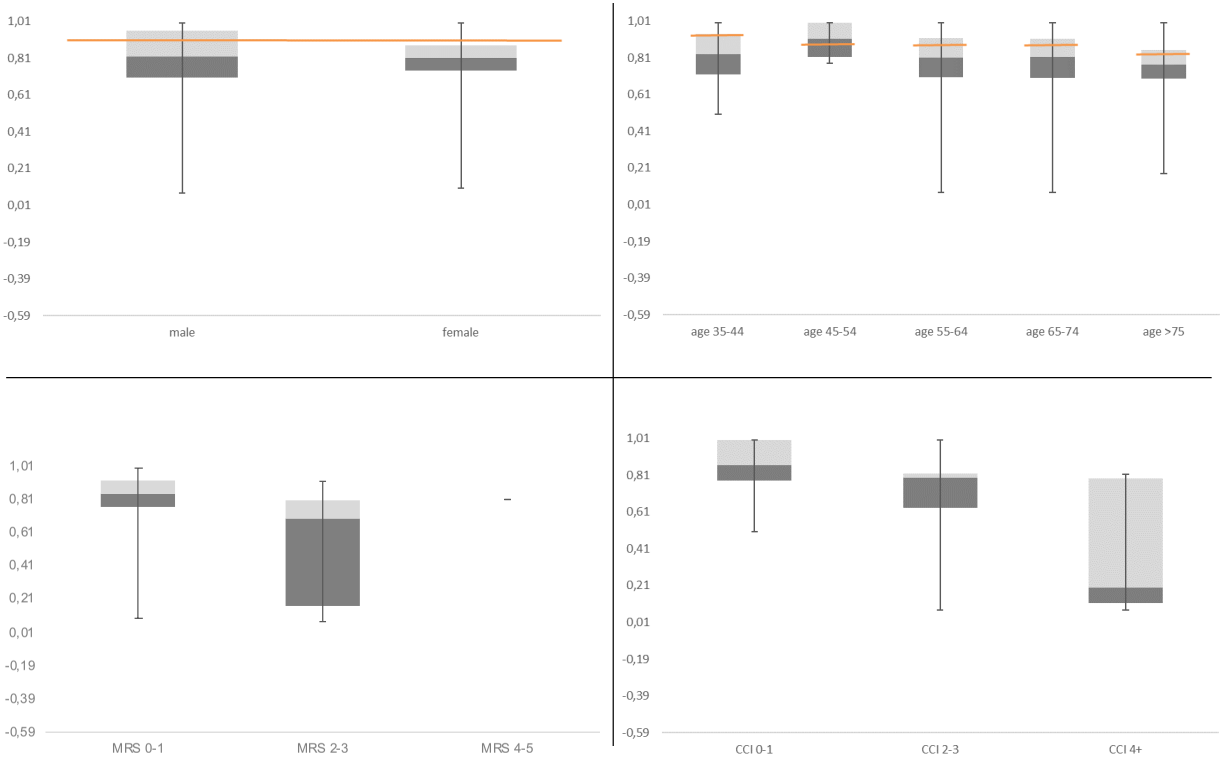


Figure 2. EQ5D-5L utility index scores stratified for sex, age, functional capacity and comorbidity index. All categories were measured upon hospital admission (pre-arrest). Presented are median utility index scores with the boxplot indicating the 25th and 75th (Q1-Q3) percentile and the whiskers indicating the lowest and highest (range) reported index score for each category. The reference median utility index score for the Dutch population is 0.89. Reference scores of the Dutch population per category are indicated by the orange line. For MRS 4-5 the score is 0.81 at n=1, as described in suppl.figure 2 & suppl.table1. MRS: modified Rankin scale for functional capacity. CCI: Charlson Comorbidity Index score.

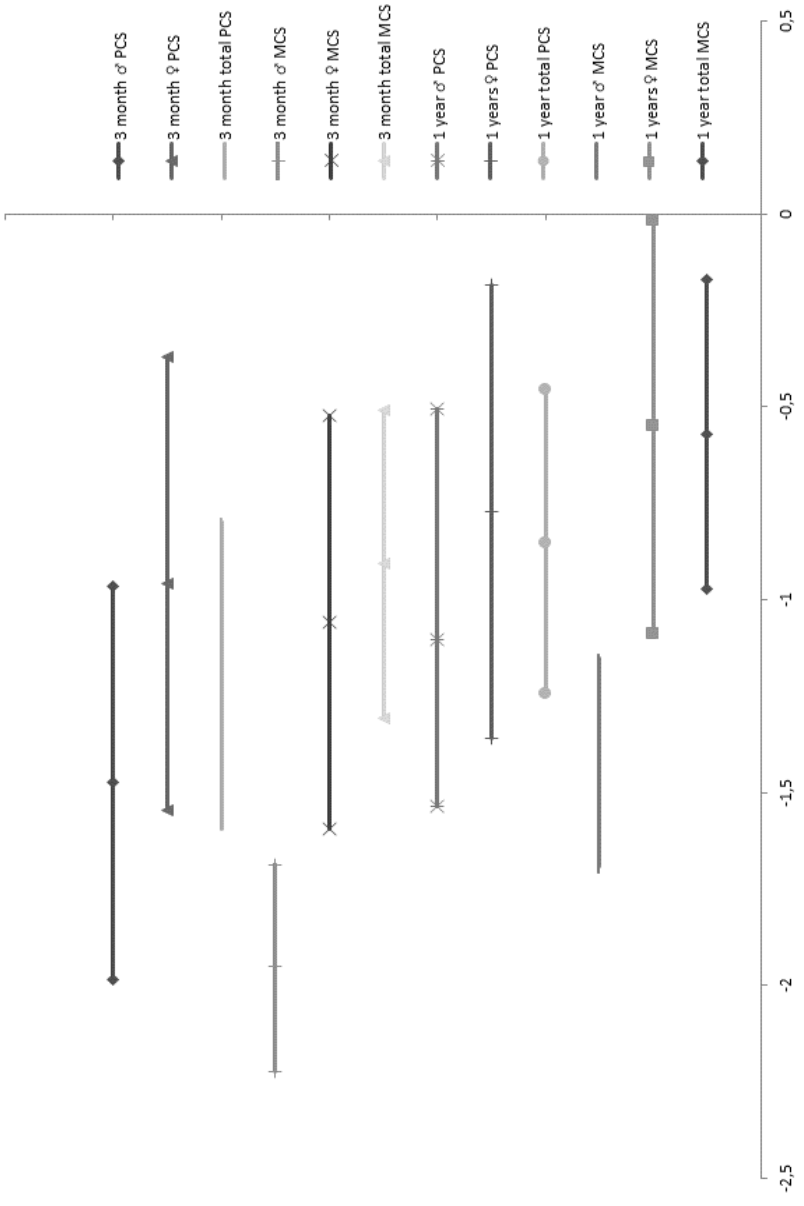


Figure 3. Perception of health state as assessed by SF-12. Standardized mean difference (SMD) of SF-12 scores at 3 months and 12 months for survivors in comparison with Dutch population norms, calculated according to domain (mental/physical) and sex. Patient-only survey. MCS indicates Mental Component Summary; PCS, Physical Component Summary

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Animals are equal, but some animals are more equal than others.

George Orwell, Animal Farm

Chapter 9

Between-centre differences in care for in-hospital cardiac arrest

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Abstract

Background

Survival after in-hospital cardiac arrest is poor, but current literature shows substantial heterogeneity in reported survival rates. This study aims to evaluate care for patients suffering in-hospital cardiac arrest (IHCA) in the Netherlands by assessing between-hospital heterogeneity in outcomes, and to explain this heterogeneity stemming from differences in case-mix or differences in quality of care.

Methods

A prospective multicentre study was conducted comprising 14 centres. All IHCA patients were included. The adjusted variation in structure and process indicators of quality of care and outcomes (in-hospital mortality and cerebral performance category [CPC] scale) was assessed with mixed effects regression with centre as random intercept. Variation was quantified using the median odds ratio (MOR), representing the expected odds ratio for poor outcome between two randomly picked centres.

Results

After excluding centres with less than 10 inclusions (2 centres), 701 patients were included of whom, 218(32%) survived to hospital discharge. The unadjusted and case-mix adjusted MOR for mortality was 1.19 and 1.05, respectively. The unadjusted and adjusted MOR for CPC score was 1.24 and 1.19, respectively. In hospitals where personnel received cardiopulmonary resuscitation (CPR) training twice per year, 183(64.7%) versus 290(71.4%) patients died or were in a vegetative state, and 59(20.8%) versus 68(16.7%) patients showed full recovery ($p<0.001$).

Conclusion

In the Netherlands, survival after IHCA is relatively high and between-centre differences in outcomes are small. The existing differences in survival are mainly attributable to differences in case-mix. Variation in neurological outcome is less attributable to case-mix. CPR training could potentially prove beneficiary to improve neurologic outcome.

Background

In-hospital cardiac arrest (IHCA) is a major adverse event in hospitalized patients. Previous studies have documented the incidence of IHCA between 1-6 events per 1000 hospital admissions [1–3], and both short- and long-term survival after IHCA is poor. A meta-analysis yielded a one-year survival rate of 13.4% but showed substantial heterogeneity between studied cohorts [4]. A US study also showed heterogeneity in incidence and outcomes after IHCA between centres [5]. This observed heterogeneity may be attributed in part to differences in case-mix, or to differences in improvable facets of care (quality of care) at the provider- and hospital-level. In other fields, such as stroke, targeted quality improvement measures have led to improved outcomes [6]. However, it is not known whether outcomes after IHCA can be improved through a similar focus on quality improvement.

Quality of care can be assessed through structures and processes of care, as well as through patient outcomes [7]. Structure of care indicators pertain to hospital-level factors, which apply to all patients. Notable examples of hospital-level structure of care factors relevant to IHCA are availability of advanced-life-support (ALS) trained personnel, cardiopulmonary resuscitation (CPR) training frequency of personnel, assigned roles of specialists in the cardiopulmonary resuscitation team, and the availability of an intensive care physician. These particular structural indicators have been shown to vary substantially between Dutch hospitals [8]. Secondly, there are process of care indicators, which can vary on the patient-level and can easily be acted upon. A potentially relevant process of care indicator for IHCA is the time until ALS is started, at which point the ALS practitioners can provide additional life-sustaining measures: e.g. endotracheal intubation, administration of epinephrine, and potentially initiate extracorporeal life support [9]. A shorter time between IHCA and these interventions could improve short and long-term outcomes. The registration of a rapid response team warning score (RRS) could be an additional relevant process indicator: these scores (the early warning score, EWS; the modified early warning score, the MEWS; the national early warning score, NEWS) may help in identifying patients at-risk for cardiac arrest, in which case extra precautions could be taken [10]. Finally, outcome metrics such as mortality and cerebral performance category (CPC) score at discharge are relevant patient-level quality indicators [11].

This study aims to assess variation in outcomes between hospitals, and to explain heterogeneity in these outcomes by differences in case-mix or by differences in quality of care stemming from structural and procedural metrics.

Methods

Study population

The Resuscitation Outcomes in the Netherlands (ROUTINE) study is a multicentre prospective study aiming to assess care and outcome of IHCA patients [12]. All patients in the 14 participating hospitals who received CPR (i.e. chest compressions) for IHCA between January 2017 and May 2018 were included in the study. This study period was predetermined in the study protocol, as reviewed by the Institutional Review Board at Erasmus MC. Data was collected on patient demographics and clinical characteristics related to cardiac arrest and post-CPR treatment, according to Utstein and COSCA templates [13,14]. For the current hospital-based analysis hospitals that contributed ≤10 patients will be excluded, because a reliable measurement of 'standard' care could not be inferred from such a small sample size.

Hospital characteristics and structural indicators were assessed with a structured questionnaire as part of an earlier project completed in February 2018. Details of this questionnaire can be found in a prior publication [8]. In the current study, we compared hospital characteristics from our sample to the other hospitals that participated in this questionnaire.

Definitions

The patient characteristics that were selected as potential confounders were based on existing literature [2]. These factors consisted of pre-arrest patient characteristics indicative of morbidity and frailty, including: age, the Charlson comorbidity index [15], the pre-arrest modified Rankin scale (MRS), and the pre-arrest cerebral performance category (CPC) (see Supplementary Material 2 for a description of the scales).

The time to advanced life support (ALS) and the reporting of a rapid response team score (RRS) were included as process indicators. The time to advanced life support was defined as the time between ascertaining circulatory arrest (and consequently starting BLS) and the moment the ALS team arrived, in minutes. Reporting of RRS was defined as any RRS reported during the 24 hours prior to cardiac arrest. Since processes of care indicators are likely embedded in a complex clinical framework, we assumed the causal models for the data as illustrated in Figure 1 of Supplementary Material 1. As structure of care indicators, we investigated the 24/7 availability of an ALS-certified physician or the 24/7 availability of an intensivist (also ALS certified), and whether the training frequency of CPR for medical staff was at least twice per year. Finally, as outcome indicators, we considered in-hospital mortality and CPC score at discharge separately. The CPC score was measured and analysed ordinally, ranging from 0 (asymptomatic) to 5 (death).

Statistical analysis

We performed multiple imputation and imputed five datasets under the assumption of missing at random (MAR) for all missing predictor and outcome data, using the MICE package in R [16,17]. The outcomes were included in the imputation model. For the descriptive analysis, patients of the following two groups were compared: patients who died in-hospital and patients who survived after discharge from hospital. Continuous variables were compared using Mann-Whitney U tests, and categorical variables using χ^2 tests or Fisher's exact test where appropriate. A complete case analysis for the main analyses was performed as sensitivity analysis to assess whether the results are sensitive for imputation.

It is not reliable to crudely compare hospitals on these potential process or outcome indicators of quality of care. Due to small sample sizes within hospitals, there is often random variation (noise) between hospitals. Furthermore, a difference in case-mix results in confounding bias. Random variation and confounding bias unjustifiably contribute to the variation between hospitals, and should be adjusted for [18,19]: assessment of quality of care should reflect the complexity of hospital care [20].

We first used fixed-effects logistic regression to model in-hospital mortality and a proportional odds logistic regression to model the CPC score. The fixed-effects logistic regression model was subsequently extended with a random intercept for each individual centre in order to assess between-centre variation in outcomes. Including random intercepts also takes into account random variation between centres due to small sample size [18,19]. The random intercept values of the unadjusted (without the potential confounders) and the adjusted model were compared to assess what part of the variation was attributable to patient characteristics (age, the Charlson comorbidity index, the pre-arrest MRS, pre-arrest CPC). The variation was further quantified using the median odds ratio (MOR): the typical odds ratio between two randomly selected centres, when the centre with higher odds is compared to the centre with the lower odds [21]. Moreover, to assess how much of the variation in outcome could be explained by our predefined case-mix variables, the Nagelkerke R^2 was calculated.

To explore the variation in potential process indicators, mixed effects linear (time to ALS) and logistic regression (registration of RRS) were used. Similar to the variation in outcome, the variation between centres was visually assessed by the comparing the adjusted and non-adjusted random intercept values. The MOR (for registration of RRS only) was also calculated. Moreover, the rankability was calculated. This measure quantifies how reliable it is to rank hospitals by this indicator (supplementary material 3) [18].

Finally, the effect of process and structure of care indicators on outcome was assessed. Only outcomes with variation not attributable to differences in case-mix were selected. For the structure of care processes, the previously mentioned causal model (Figure 1 Supplemental Material 1) was assumed. To specify the variables to correct for in our analysis, we used the back-door-criterion to guide what characteristics to include in our regression model [22]. The back-door criterion is fulfilled when no (causal) paths can be drawn from the exposure of interest to the outcome in the assumed causal model. Using this criterion, we adjusted the effect of time to ALS on functional outcome

for timing (weekend vs weekdays, night or evening versus day), whether the arrest was witnessed, and whether an RRS was reported. The effect of the reporting of an RRS on outcome could not be investigated in this study. The reason is that we assume that reporting RRS affects outcome by preventing cardiac arrest. The ROUTiNE study only included patients who experienced cardiac arrest. Therefore, we did not include the relevant control group (patients without cardiac arrest). Finally, the outcome of patients treated in centres with certain structure of care indicators were compared using Fisher's Exact test (while combining score 4 – vegetative state, and 5 – dead), because no confounders were assumed between structure of care and outcome.

All analyses were performed using R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Used packages include the *lme4* and *ordinal* package for the random effects models, and the *mice* package for the multiple imputation framework. Significance was evaluated an alpha level of 0.05.

Results

Descriptive statistics

The ROUTiNE study included 713 patients from 14 different hospitals. Two hospitals included 10 patients or less, so these patients were excluded (n=12). Therefore, this analysis comprises of 701 patients, included in 12 different hospitals. Of the included patients, 230 (33%) survived to discharge, and 12 (1.7%) patients had missing CPC scores at discharge. The median number of inclusions per hospital was 49 (Figure 1). Our sample mainly comprised teaching hospitals (83.3% versus 55.7% in total), and most hospitals are located in urban or metropolitan areas (91.7% versus 61.4% in total). Compared to other hospitals in the Netherlands, the hospitals included in this study were more often trauma centres (66.7% versus 26.3%), offered thoracic surgery (41.7% versus 17.2%), and were more often able to facilitate extracorporeal membrane oxygenation (ECMO) life support (50.0% versus 14.3%, see Table 1). Note that these data are already partially published elsewhere [8,23].

We compared patients who survived to hospital discharge with patients who died in hospital. Survivors were younger (a median of 67 [56-73], versus 70 [62-77]), more often had normal neurological performance prior to hospital admission (CPC score of 0: 192 [85.3%] versus 334 [74.1%]), and had lower Charlson comorbidity index (median of 1 [0-2], versus 2 [0-3]). Survivors sustained IHCA more often at daytime than non-survivors, and patients at daytime also had better neurological outcomes (Table 2, and Figure 2 Supplementary Material 1). In survivors, cardiac arrest was more often witnessed (212 [92.2%], compared to 339 [72%]), possibly because the location of cardiac arrest was more often at the emergency department (survivors: 26 [11.3%], versus non-survivors: 44 [9.3%]), the intensive care unit (40 [17.4%], 65 [13.8%]), and the operation theatre (19 [8.3%], 13 [2.8%]). Also, the first observed rhythm in survivors was more often shockable (102 [44.3%], versus 82 [17.4%], Table 2 and Table 1 Supplementary Material 1). Only 22 (3.1%) patients received extracorporeal membrane oxygenation (ECMO) during CPR (E-CPR), of which 7 survived to hospital discharge and 1 patient survived, but was in a vegetative state (Table 6 Supplementary Material 1).

Outcomes

All considered pre-arrest patient characteristics were independently associated with in-hospital mortality. Adjusted for CPC score at baseline (OR 1.43 per unit increase, 95% CI: 1.04 – 1.95), pre-arrest MRS had no effect on outcome (OR: 1.10 per unit increase, 95% CI: 0.93 – 1.31). Similar effects were found on the ordinal CPC score (table 3). For in-hospital mortality, the explained variance (Nagelkerke R^2) of the model with these predefined predictors was 9.6%. For CPC score, the Nagelkerke R^2 was 8.4%. A complete case analysis showed similar results (Table 4, Supplementary Material 1).

There was small variation in mortality (median odds ratio [MOR] was 1.19), which decreased by 12% by adjusting for case-mix (adjusted MOR was 1.05). There was moderate variation in CPC score (MOR was 1.24), which decreased 4% by adjusting for case-mix (adjusted MOR was 1.19). This implies that variation in mortality was more dependent on patient characteristics than variation in CPC score (figure 2). The rankability, however, of mortality and CPC score was 1.0% and 12%, indicating that ranking hospitals based on these indicators is not reliable (figure 2, supplementary table 2).

Processes of care

There was little variation in time to ALS across the patient cohort, and this did not change substantially after adjusting for case-mix (Figure 3a). The longest median time to ALS was observed in two centres, in which the ALS team arrived 1.9 and 1.6 minutes later than average. The rankability of this indicator was high: 79% of the variation between centres was not attributable to chance (table 2, supplementary material 1). There was no evidence that higher time to ALS increases the odds of a worse CPC score (OR: 0.99, 95% CI: 0.92 – 1.07).

The variation in the reporting of an RRS was large and did not change substantially after adjusting for case-mix (figure 3b). The adjusted median odds ratio (MOR) was 2.95. The rankability of this indicator was high: 77% of the variation between centres was not attributable to chance (table 2 supplementary material 1).

Structure of care

In hospitals which provided CPR training twice a year, survivors of IHCA had a better functional outcome (Figure 4, Table 5 and 7 Supplementary Material 1): 183 (64.7%) versus 290 (71.4%) patients died or were in a vegetative state, and 59 (20.8%) versus 68 (16.7%) patients showed full recovery ($p < 0.001$). However, patients in hospitals where personnel was trained twice per year were younger (66 [IQR 56-74], versus 71 [IQR 63 – 78]), and had better initial CPC scores (229 [82.4%] had a CPC score of 0, versus 297 [74.6%], Table 8, Supplementary Material 1). When these factors are added in a multivariable ordinal logistic regression model, the effect is rendered insignificant (OR: 0.96 for a higher CPC score, 95% CI: 0.68 - 1.37, table 7 and figure 3 supplementary material 1). The 24/7 availability of an intensivist showed a similar trend towards more favourable CPC scores, but the effect was not significant.

Discussion

In this study we first assessed whether there is substantial variation in outcomes between hospitals in the Netherlands after IHCA. We found small to moderate variation in mortality and functional outcomes. Between-centre differences in mortality rates could largely be explained by case-mix, but between-centre differences in CPC scores at discharge persisted after adjustment for case-mix. To potentially improve functional outcomes, we investigated the reliability and relevance (in terms of association with outcomes) of processes and structure of care indicators. The reliability of the two process indicators was high, but their relevance could not be established with current data. We could not establish this relevance either due to the design of our study, or because our data did not provide evidence against the null hypothesis. In general, quality of care does not often significantly explain variation in outcomes, because treatment effects are generally modest, and not all processes of care apply to all patients [24,25]. However, our data did suggest a positive effect of a structure of care indicator in the analysis where we assume differences between hospitals to be random: offering multiple CPR trainings per year to personnel was associated with better functional outcomes of survivors at discharge.

The group of included centres consisted of teaching hospitals with more extensive facilities than the typical Dutch hospital. Within this group of centres, there was little variation in both mortality as well as CPC score. This finding is in contrast with a U.S. study, which described substantial variation in outcome between centres [5]. One explanation is that this study included a much broader range of hospital levels, while our sample mainly includes teaching hospitals.

Nevertheless, the finding that the observed variation in mortality is explained by differences in case-mix can be seen as a strong indication for a cohesive hospital system with uniform adherence to guidelines carried out by highly-trained personnel. We should consider the possibility that that participating hospitals might have performed better, or reported selectively, simply because they were observed within this study (the Hawthorne effect) [26]. Nevertheless, we hypothesize that the homogeneity in quality of care is an important explanation why survival in our population is higher than described in literature [4,27].

On the contrary, the variation in CPC score could not be entirely explained by differences in case-mix. It can be argued that the explained variance of our models was not high enough. Although the Nagelkerke R^2 is lower than other prognostic studies in cardiac arrest [28,29], it is known that R^2 measures for categorical outcomes are much lower than those of continuous outcomes [30]. Also, because our aim was to explain (and not to predict) outcomes [31], we think this finding has important implications for cardiac arrest care in the Netherlands: improving care might not improve survival rates, but it might improve functional outcomes. We recommend that other hospital systems identify local processes and structures of care indicators and enact appropriate improvements that could lead to better patient outcomes.

Although the reliability for the investigated processes and structure of care indicators was high, only the relevance for structure of care indicators could be confirmed with the current study. We will here discuss the investigated processes and structure of care indicators, and the implication of our evaluation.

First, we found an indication that CPR training frequency of twice per year might improve functional outcomes. However, patients in centres who trained twice per year were younger and had slightly better pre-existing neurological status, coincidentally. Either training twice per year somehow results in a healthier population being resuscitated, or the difference is based on chance. We hypothesize that hospitals that train twice have more awareness of in-hospital cardiac arrest than hospitals that train less. If there is more awareness, we believe cardiac arrests might be noticed earlier, and possible some unnecessary arrests would be prevented. However, we think that the prevented arrests are more likely those in patients with more physiological reserve, since there is more time to prevent cardiac arrest. Therefore, intervening earlier in the process due to higher awareness should result in the remaining patients being older and with worse pre-arrest functional status. Because of this, we think that it is more likely that this difference in case-mix is based on chance, especially because it entails a post-hoc analysis. As only 45% of the Dutch hospitals are described to offer CPR training twice per year [8], increasing adherence to this structure of care indicator could result in improvements in outcome: decreasing intervals between CPR training increases CPR quality in terms of compression depth and rate, and complete chest recoils [32,33].

Second, our results did not suggest that 24/7 availability of intensivists improves outcomes, in spite of evidence to the contrary [34–36]. We believe that the 24/7 availability of intensivists could indeed improve neurological outcomes, but that our study lacks sufficient power to detect an effect due to the small number of included centres with an intensivist 24/7. With 24/7 intensivist coverage, similar mortality between weekdays and weekends have been reported [37,38]. It might be hypothesized that we would have found a significant effect if we would have included more hospitals without 24/7 availability of intensivists.

Third, the absolute variation in time to ALS was limited, but consistent and reliable: the rankability was more than the 70% threshold that is suggested as reasonable for quality indicator to be valid [19]. The effect on outcome, however, could not be established: the assumed mechanism through which a lower time to ALS improves functional outcome is by enabling early treatment of reversible causes [39]. We recommend that future studies register whether a reversible cause was present, and whether this was effectively resolved, to better establish the relevance of this process indicator.

Fourth, the reporting of an RRS varied substantially between hospitals, and was again a reliable process indicator. The presumed effect of RRS on outcomes, however, primarily impacts outcomes through preventing cardiac arrest [10]. Therefore, a study which only includes patients with cardiac arrest cannot evaluate the relevance of this indicator. Nevertheless, as other studies have showed evidence for effective prevention of cardiac arrest [10,40], our results mainly indicate that the implementation of these scores in clinical practice could be more stringent.

This study is limited because we study a selected group of centres due to logistical reasons. The observed variation in outcome could partly be explained by case-mix in these centres, but perhaps this cannot be generalized to all centres. Fortunately, we collected data about characteristics of these centres and were able to compare our sample's characteristics to those of the universe of hospitals in the Netherlands. Because we are transparent about these differences, the data can be interpreted with more context. Another limitation of our study is the presence of missing data. We dealt with missing data by using multiple imputations. Using this method we have assumed that the data was missing at random. Unfortunately, there is no empirical way to check this assumption. The fact that a complete case analysis showed same direction and uncertainty of effects is reassuring. Finally, we only were able to assess the process and structure of care indicators which we collected in this study. Other potential process indicators are the time to defibrillation in patients with IHCA by shockable rhythm, or time to BLS. Both indicators were not (accurately) collected, and therefore could be of interest in future studies. That is, if unexplained differences in outcome are found between centres. This study introduces metrics for the evaluation and improvement of resuscitation care. Notable strengths of our study include the large sample size and the comprehensive adjustment for both random variation and case-mix. Based on our findings, the following two recommendations for clinical management and research for IHCA can be proposed: we should improve care for IHCA mainly to improve neurological outcomes, i.e. through more frequent CPR training of staff; existing outcome measures of IHCA cannot be reliably used to compare hospitals on quality of care, as opposed to processes and structure of care indicators.

Conclusion

In our sample of Dutch hospitals, the variation in both mortality and neurological outcome is not substantial after cardiopulmonary resuscitation for in-hospital cardiac arrest. Survival is relatively high and mainly attributable to differences in case-mix, rather than differences in quality of care. The variation in neurological outcome was less attributable to case-mix, suggesting that improvements in care can lead to better neurological outcomes. Multiple CPR trainings per year could possibly be a way forward to improve care for in-hospital cardiac arrest patients. Finally, this study provides a potential framework for the evaluation of resuscitative care and the identification of improvable facets of resuscitative care.

Characteristic	Total number of centres	centres, not included (N=58)	centres, included (N=12)
GENERAL ASPECTS			
URBAN AREA	70		
metropolitan		22 (37.9)	5 (41.7)
urban		18 (31.0)	6 (50.0)
rural		18 (31.0)	1 (8.3)
HOSPITAL LEVEL	70		
University		6 (10.3)	1 (8.3)
non-teaching		23 (39.7)	1 (8.3)
Teaching		29 (50.0)	10 (83.3)
HOSPITAL SIZE, N BEDS	70		
<300		23 (39.7)	2 (16.7)
300-600		25 (43.1)	6 (50)
>600		10 (17.2)	4 (33.3)
AVAILABILITY OF			
Emergency department	70	57 (98.3)	12 (100.0)
Trauma center	69	15 (26.3)	8 (66.7)
Thoracic surgery	70	10 (17.2)	5 (41.7)
Neurosurgery	70	12 (20.7)	4 (33.3)
Aortic surgery	70	38 (65.5)	12 (100.0)
Cardiac care unit	70	57 (98.3)	12 (100.0)
Rapid Response Team	70	57 (98.3)	12 (100.0)
Rapid response system	70	56 (96.6)	12 (100.0)
Type of rapid resonse system	70		
(M)EWS		54 (93.1)	9 (75.0)
NEWS		1 (1.7)	1 (8.3)
OWN MODIFIED SYSTEM		1 (1.7)	2 (16.7)
ICU	70	57 (98.3)	12 (100.0)
level of ICU*	69		
1		19 (33.3)	1 (8.3)
2		24 (42.1)	4 (33.3)
3		14 (24.6)	7 (58.3)
Intensivist 24/7	69	33 (57.9)	5 (41.7)
ECMO	68	8 (14.3)	6 (50.0)
BOTH VV AND VA	14	8 (100.0)	5 (83.3)
Mechanical CPR device	70	26 (44.8)	7 (58.3)

Characteristic	Total number of centres	centres, not included (N=58)	centres, included (N=12)
PRACTICE/GUIDELINE ADHERENCE			
TARGETED TEMPERATURE	65		
33 ºC		19 (33.3)	1 (8.3)
both 33 and 36 ºC		24 (42.1)	4 (33.3)
36 ºC		14 (24.6)	7 (58.3)
Mandatory DNR-counselling upon admission	70	51 (87.9)	10 (83.3)
ADVANCED LIFE SUPPORT PROTOCOL IS ERC 2015	70	57 (98.3)	11 (91.7)
No. of CPR training sessions per year	70		
Twice a year		26 (44.8)	4 (33.3)
Once a year		29 (50.0)	8 (66.7)
Less than once a year		3 (5.1)	0 (0.0)
ERC ALS-certified physician available	70	55 (94.8)	12 (100.0)
ERC ALS-certified physician 24/7 available	70	32 (55.2)	10 (83.3)

* See table 2 appendix 1 for a detailed description of icu level designation in the netherlands. vv = venous-venous; VA = venous-arterial Table 1, characteristics of the studied hospitals, as part of survey research published earlier (7). Of hospitals with multiple locations, the main locations are shown once: the highest level of care is reported, and if the facilities are present in one location, it is reported as present.

Characteristic	Total number of patients	Survivors (n = 230)	Non-survivors (n = 471)
	PRE-ARREST		
Age (median [IQR])	701	67 [56, 73]	70 [62, 77]
Female (%)	701	83 (36.1)	165 (35.0)
Charlson comorbidity score (median [IQR])*	701	1 [0, 2]	2 [0, 3]
Pre-arrest CPC (%)	676		
0 – asymptomatic		192 (85.3)	334 (74.1)
1 – Good cerebral performance		26 (11.6)	72 (16.0)
2 – Moderate cerebral disability		3 (1.3)	32 (7.1)
3 – Several cerebral disability		4 (1.8)	12 (2.7)
4 – coma or vegetative state		0 (0.0)	1 (0.2)
Pre-arrest MRS (%)	674		
0 – asymptomatic		104 (46.6)	148 (32.8)
1 – No significant disability		73 (32.7)	155 (34.4)
2 – Slight disability		22 (9.9)	67 (14.9)
3 – moderate disability		19 (8.5)	64 (14.2)
4 – Moderately severe disability		3 (1.3)	14 (3.1)
5 – severe disability		2 (0.9)	3 (0.7)
Any RRS score registered 24 before arrest(%)	701	51 (23.4)	179 (38.0)
Type of RRS score	234		
EWS		20 (36.4)	69 (38.5)
MEWS		13 (23.6)	50 (27.9)
NEWS		3 (5.5)	9 (5.0)
Own system		10 (18.2)	29 (16.2)
Not specified		9 (16.4)	22 (12.3)
Trauma (%)	694	6 (2.6)	14 (3.0)
Sepsis (%)	691	19 (8.3)	65 (14.1)
Reversible diagnosis of arrest (%)	689		
Hypoxia		70 (31.0)	173 (37.4)
Hypovolemia		37 (16.4)	83 (17.9)
Hypothermia		0 (0.0)	0 (0.0)
Hypo-/Hyperkalemia/metabolic		8 (3.5)	22 (4.8)
Tamponade		8 (3.5)	25 (5.4)
Thrombo-embolic		86 (38.1)	145 (31.3)
Toxines		15 (6.6)	11 (2.4)
Tension pneumothorax		2 (0.9)	4 (0.9)

Characteristic	Total number of patients	Survivors (n = 230)	Non-survivors (n = 471)
Hypotension before the arrest** (%)	649		
Yes		32 (15.0)	69 (15.8)
Yes, with vasopressors		8 (3.8)	32 (7.3)
No		173 (81.2)	335 (76.8)
Location (%)	701		
Ward		77 (33.5)	240 (51.0)
Emergency department		26 (11.3)	44 (9.3)
Intensive care unit		40 (17.4)	65 (13.8)
Cardac care unit		28 (12.2)	54 (11.5)
Interventional radiology theatre		15 (6.5)	25 (5.3)
Operation theatre		19 (8.3)	13 (2.8)
Other		8 (3.5)	5 (1.1)
	DURING ARREST		
Shockable rhythm (%)	701	102 (44.3)	82 (17.4)
Witnessed arrest (%)	701	212 (92.2)	339 (72.0)
Time of day	678		
Day (08:00-16:00), (%)		68 (30.2)	168 (37.1)
Evening (16:00-22:00), (%)		127 (56.4)	208 (45.9)
Night (22:00-08:00), (%)		30 (13.3)	77 (17.0)
Time to ALS, min (median [IQR])	694	2 [0, 3]	2 [1, 4]
ECMO started during CPR (ECPR)	700	7 (3.1)	15 (3.2)
CPR duration, ROSC	395	5 [2, 10]	10 [5, 20]
CPR Duration, no ROSC	306	-	30 [21, 50]

* See Table 1, supplementary material 1
** Not defined, subjectively reported by each registrar

Table *2*, characteristics of the patients, included in this analysis of the ROUTiNE study.

	In-hospital mortality	Worse neurological outcome (CPC)
Charlson comorbidity index	1.17 (1.08 - 1.27)	1.16 (1.07 - 1.26)
MRS score at baseline	1.10 (0.93 - 1.31)	1.11 (0.94 - 1.31)
CPC score at baseline	1.43 (1.04 - 1.95)	1.55 (1.14 - 2.12)
Age, per decade	1.25 (1.10 - 1.41)	1.22 (1.08 - 1.37)

Table 3, the results of logistic regression models with outcome as an independent variable, and baseline characteristics as dependent variables. The considered outcomes were in-hospital mortality, and CPC score (worse neurological outcome). An odds ration above one indicates a higher chance of mortality, or a higher chance of a worse CPC score.

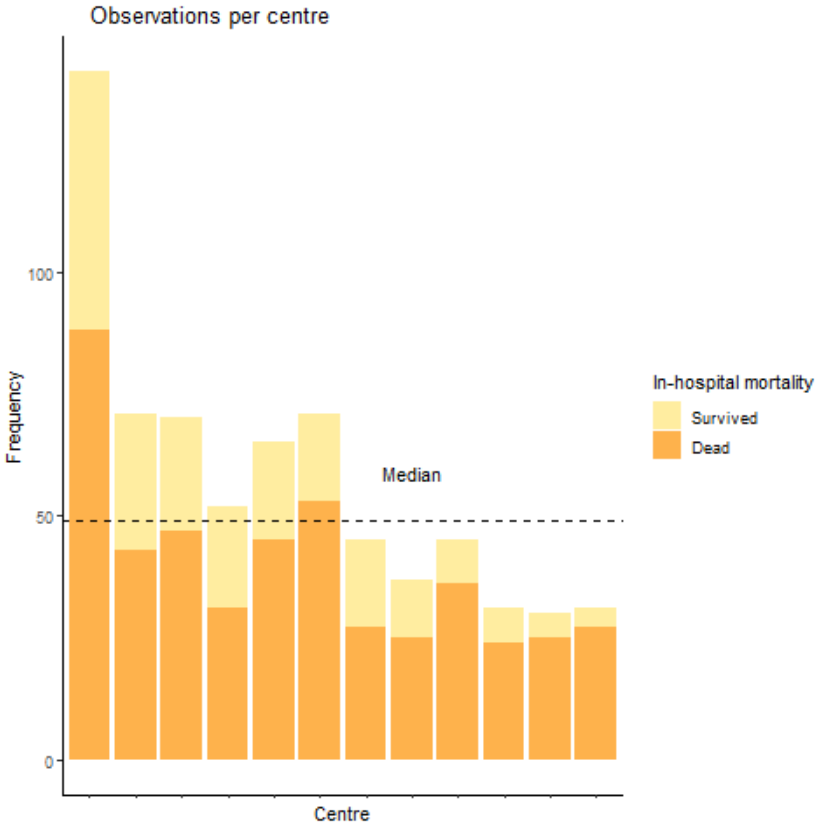

Figure 1. The number of inclusions per participating centre (displayed anonymously) and the primary outcome measure in-hospital mortality per centre.

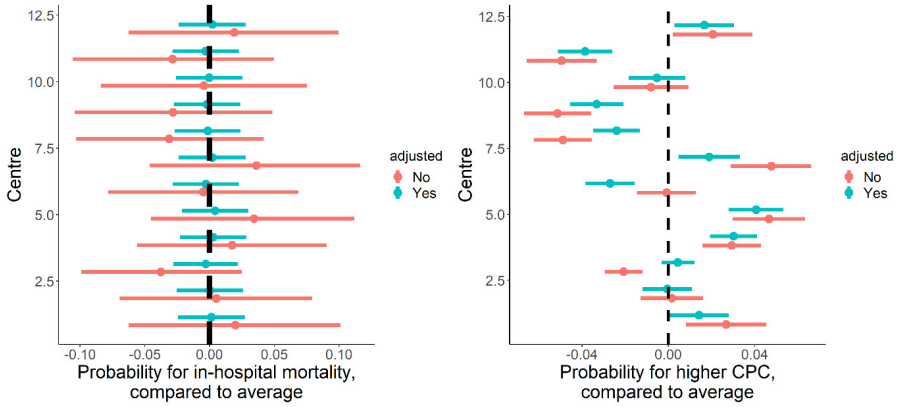

Figure 2. The individual effects of each centre on outcome indicators: mortality on the left, and CPC score on the right. The estimates are the random intercept values of a mixed effects model including the predictors in table 3.

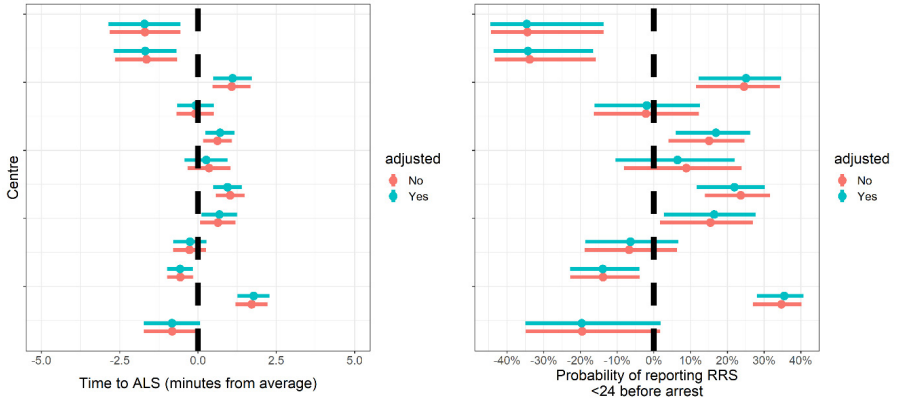

Figure 3. The individual effects of each centre on process indicators: time to ALS on the left, and reporting any RRS score <24 hours before arrest on the right. The estimates are the random intercept values of a mixed effects model including the predictors in table 3.

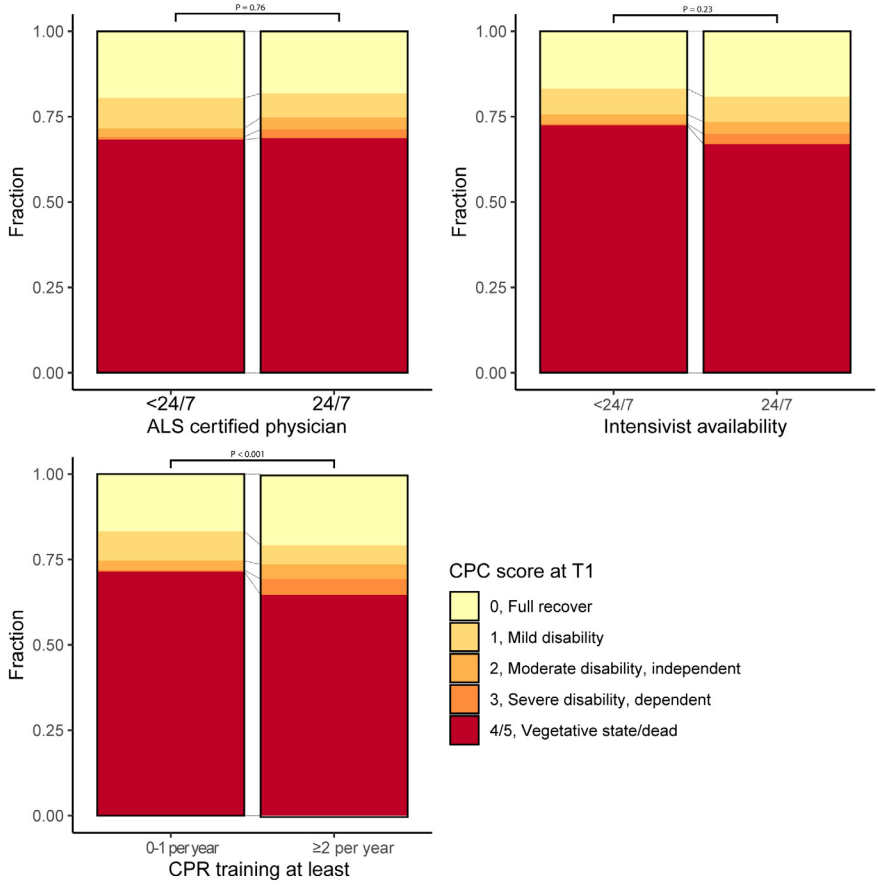

Figure 4, the CPC scores at discharge, stratified per investigated structure of care indicator. The p-value as a result of a Fisher Exact test are displayed above the barcharts. Only patients with known CPC scores are included. For the absolute numbers, see table 5, supplementary material 1.

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Things get broken and sometimes they get repaired, and in most cases, you realize that no matter what gets damaged, life rearranges itself to compensate for your loss, sometimes wonderfully.

Hanya Yanagihara, A little life

Section III

English summary and general discussion

The aim of this thesis was to provide insight in the practices associated with In-Hospital Cardiac Arrest (IHCA) in the Netherlands. In part I, **chapters 1 & 2,** we examined survival after IHCA in the past. In part II, **chapters 3 & 4**, we focussed on current knowledge and standard of care of IHCA and in **chapters 5 & 6**, we assessed the role of extracorporeal life support in current practice. In part III, **chapters 7, 8 & 9**, we focussed on the results of our prospective study assessing the outcomes of IHCA patients, both quantitatively as qualitatively. We looked at factors that could predict outcome, both patient-related, as related to health care quality. In this last chapter we will summarize and discuss the findings. Finally, recommendations for clinical practice and future research are made in this discussion.

In-Hospital Cardiac Arrest has been poorly researched and historical data on survival is limited. In **chapter 1** our systematic review and meta-analyses of 40 studies and more than 1.3 million patients showed the pooled survival rates were 17.6% at hospital discharge and 13.4% at one year after in-hospital cardiac arrest. These data cover the period 1985 – 2018 and show a modest improvement in survival over that period (10-year OR: 1.70, 95% CI: 1.04 – 2.76)**. Chapter 2** contains an explorative study to describe the Dutch situation in terms of survival after IHCA. To examine which factors could be associated with survival, a retrospective single-centre study was performed. This study, done over then period 2003 – 2014, showed a one-year survival rate of 26.0%, with no significant change in survival over the study period of 10 years. We identified several patient factors (e.g. comorbidity) and CPR characteristics (time to ROSC, (non)shockable rhythm) that were associated with one-year outcome, albeit in univariate analysis.

As described in the introduction of this thesis, data ranging from 1960 – 1990 showed an average survival-to-discharge of 15.0%[1]. This would mean that nearly sixty years of medical advances have not created any major survival benefit for IHCA patients. Although survival in the Netherlands appears higher than the global average, the analogous lack of improvement over time is interesting. A supposed explanation lies in the change in case-mix of patients admitted to hospital[2]. The average life expectancy in humans is rising, and predicted to rise even further, mostly because of enhanced longevity after the age of 65 years[3]. This gives rise to an increasing number of people facing multi-morbidity. Simultaneously, advances in medicine allow for patients to receive treatment even for severe or rapidly progressive diseases[4,5]. The same is seen in the intensive care setting; the number of octogenarians and the burden of comorbidity is increasing, but mortality remains stable[6]. The net effect being that the changes in case-mix are balanced out by advances in medicine.

Cardiopulmonary resuscitation and subsequent intensive care treatment of IHCA patients is costly, at €164.442 per quality-adjusted life year. For comparison, out-of-hospital cardiac arrest costs are fifty percent lower[7]. The majority of these costs are made during intensive care treatment. In the retrospective cohort 62.0% of patients admitted to ICU died subsequently, during hospital admission **(chapter 2)**. This large portion of patients received costly and time-consuming treatment without benefiting from it. With a rising number of elderly and multi-morbid patients, the focus of cardiac arrest research needs to be adequate prognostication of good outcome. Age and comorbidity alone do not appear to be sufficient predictors of outcome[8,9]. To increase survival and keep expenses

manageable, patient in whom attempts at resuscitation are futile need to be identified and patients with chance at good outcome need to benefit from the best available health care facilities.

To assess the current status of health care facilities, recent developments in technology and current practice in the identification of patients with low chance at survival after IHCA, four studies were conducted addressing these issues. These comprise **chapters 3 through 6.** In **chapter 3** all Dutch hospitals were asked to complete a questionnaire to establish the differences in practices of cardiopulmonary resuscitation (CPR) for IHCA. Although almost all hospital locations reported following the most current European guidelines for ALS, there are differences between hospitals in CPR training frequencies, the availability of ALS certified intensivists during day and night and constitution of the CPR teams. From this questionnaire, 89% of hospitals reported having mandatory counselling of CPR-directives, i.e. each patient is counselled for the decision to attempt or refrain from CPR if cardiac arrest occurs. In **chapter 4** a cross-sectional interview study was conducted among 1136 patients in 13 hospitals using the flashmob principle[10]. CPR-directives were collected from patients and from the Electronic Medical Record (EMR). Most patients (91.2%) had a documented CPR-directive. Of all patients who participated in the study 55.8% recalled speaking to a health care professional about their CPR-directive. The primary outcome was the number of Do Not Resuscitate (DNR) orders. Of the hospitalized patients included in this study 27.5% had a DNR-order. The prevalence of DNR-status increased with age and with the number of medications used at home. The prevalence of DNR also increased with a higher Age-Combined Charlson comorbidity Index (ACCI). Patients estimated one-year survival after IHCA 2.5 times higher than the actual survival rate found in **chapters 1 & 2**. Another striking discrepancy found was that 7.0% of patients recalled a different CPR-directive than the one in the EMR.

It's positive to see that most hospitals adhere to the most current guidelines. With each new guideline implementation, outcomes of cardiac arrest seem to improve[11]. Furthermore a uniform adherence to life support guidelines and regular training of CPR-teams further improves the success of CPR[12]. The latter was unfortunately not the case in all hospitals, nor was the 24/7 availability of an intensivist certified for Advanced Life Support (ALS) as a part of the CPR-team. Uniform training could prove beneficial, especially if members of the CPR-team come from different backgrounds (e.g. anaesthesia, cardiology, internal medicine). Moreover, training all members of hospital staff (i.e. ward nurses, doctors and CPR-team members) in ALS has been proven to improve survival[12,13].

Reports of mandatory CPR-directive counselling from **chapter 3** are paralleled by findings of documented directives in **chapter 4**, meaning that most patients admitted to a ward have a documented directive. Interestingly enough though, only slightly more than half of the interviewed patients recall speaking about this. This finding may imply that the counselling itself does not occur, but rather just the documentation in the EMR. Moreover, elderly and multimorbid patients tend to have less recollection of the correct CPR-directive. In this chapter we have discussed several possibilities for these discrepancies. The primary solution is providing patients with better information and providing information for a target audience. For example the younger patients, for whom chances of survival are good or reasonable, can receive information via digital media.

The elderly and multimorbid population however would benefit from a more extensive conversation with a specialist. Because a large number of patients will receive digital information, physicians are left with more time for these more extensive and time-consuming counselling sessions[14]. Regardless of the medium though, patients should be well-informed of survival probabilities and of the contents of their own CPR-directive.

An unexpected finding that is worth mentioning, is the gatekeeper-phenomenon we encountered during our interview study[15]. A number of doctors, nurses and managers attempted to stop our interview study, despite permission granted by the ethical committee and the board of directors. They had the best intentions, i.e. protecting their patients. They claimed talking about CPR-directives would be too much of an emotional burden. The research we presented in **chapter 4** however shows that patients are generally not opposed to speaking about the subject. This type of gatekeeping needs to be clarified further in future research.

In **chapters 5 & 6** we examined extracorporeal cardiopulmonary resuscitation (ECPR) by means of a membrane oxygenation circuit as a novel method of CPR-treatment for IHCA. ECPR facilitates return of circulation, albeit artificial. However, it is much more uncertain whether this recovery of circulation translates into survival, or acceptable neurological outcome. Furthermore, its cost-effectiveness has not been evaluated. In **chapter 5** a systematic review was done to examine the potential benefits on outcome. The conclusion is that survival to discharge appears higher than for conventional CPR (30% vs. 17%), with a slightly lower proportion of patients with favourable neurologic outcome (84% vs. 92%). From qualitative analysis of the studies on ECPR it seems this technique is mostly beneficial for selected patient categories. In **chapter 6** our cost-effectiveness analysis describes that the expected costs per IHCA patient of treating each eligible IHCA patient with ECPR are approximately 23,000 euro. Treating all patients with ECPR would yield approximately 3.4 Quality-Adjusted Life Years (QALY) with an incremental cost of 15,000 euro per QALY. Using ECPR for selected patients, for example patients with lower burden of comorbidity, lowers costs. However, using the willingness-to-pay thresholds of Western countries, it appears to be a cost-effective therapy for treating all IHCA patients.

The use of ECPR appears promising and it was included in the 2015 CPR guidelines[16]. It seems that this high-end technique lets certain patients survive who were otherwise likely to have died. It however comes with some important caveats. First of all, neurologic outcome is not the equivalent of quality of life. Evidence pertaining to long-term quality of life after ECPR is still limited and should be taken into account[17]. Second, we should emphasize the role of selection of patients eligible for ECPR. Most studies excluded patients over 75 years old, with a terminal illness or comorbidities that form a contraindication for ICU admission or for intravascular cannulation (e.g. severe cardiac or vascular disease). As can be expected, patients with a with a better a priori chance of survival in general have better chances of surviving IHCA. This does not dismiss a role for ECPR as a mode of treatment, it only stresses the need for evidence-based and uniform indications. This is the case for both extracorporeal as conventional CPR; selecting patients with high chance at survival with good quality of life and determining whether ECPR can increase these odds.

Another question we must keep asking ourselves, is: what defines cost-effectiveness? As mentioned before, cardiac arrest care is costly. Although ECPR falls within the range of the willingness-to-pay threshold, careful evaluations need to be made to determine the use of this technique in the future. The overall problem with studies examining cost-effectiveness of interventions, is its relativistic nature. Is an intervention good and just because it is cost-effective or is it cost-effective because it is in itself good and just. In other words, whether the cost-effectiveness is arbitrary or whether it belongs to the necessary and eternal truths about the nature of things. In this way it parallels Plato's Euthyphro dilemma[18]. Cost-effectiveness is never the nature of an intervention, but a quality which we as people have attributed to it. Therefore, the decision of whether an intervention is or is not desirable based on cost is a societal, and not a clinical one. This reflects in the various Willingness-To-Pay (WTP) thresholds we have incorporated in our model **(chapter 6)**.

In the Resuscitation Outcomes in the Netherlands study, we examined the long-term outcomes of IHCA patients and assessed factors associated with survival and quality of life. A multicentre prospective cohort study was performed in which all patients who suffered IHCA were included during one year, and received follow-up during the next year. Follow-up was done in terms of survival and quality of life. In **chapter 7** we found one-year survival after in-hospital cardiac arrest is 27.8%. Survival to discharge is 32.4%. Of all patients who died within one year after cardiac arrest the majority of deaths occurred in hospital (93.6%). In our study the incidence of IHCA is 1.3 per 1000 admissions. We found several pre-arrest variables to influence one-year survival, most notably pre-arrest functional status (MRS) and the combination of age and comorbidity (ACCI). **Chapter 8** described the health-related quality of life (HRQoL) of survivors. Although a fairly large proportion of survivors have an acceptable quality of life, it is still lower than that of peers. Male survivors more frequently reported psychological distress. Furthermore, HRQoL is lower than in 'regular' ICU survivors. In **chapter 9** we examined variation in outcomes between hospitals in the Netherlands after IHCA. We found small to moderate variation in mortality and functional outcomes. The variation in neurological outcome was less attributable to case-mix, suggesting that improvements in care can lead to better neurological outcomes. Hospitals providing CPR training (at least) twice a year have survivors with better cognitive performance scores at discharge. The 24/7 availability of an intensivist shows a similar trend towards more favourable CPC scores, but the effect was not significant.

Although survival is better for Dutch patients as opposed to their international counterparts described in **chapter 1**, better never means better for everyone. Inevitably a percentage of survivors means an inverse percentage of deaths. Our findings do however suggest that there's room for selection of patients with a good chance at survival in an early stage, for example upon admission to hospital or in the outpatient clinic. The decision could be based on a combination of comorbidity and functional capacity, preferably combined into a validated prognostic score. Known scores and risk factors usually incorporate factors that cannot be known upon admission or at the outpatient clinic[19,20]. For adequate counselling and for informing elderly and multimorbid patients of their chances at survival after IHCA **(chapter 4)**, we propose an update of available prognostic scores. Future research should focus on the integration of such prognostic scores and counselling of patients with an elevated risk of IHCA.

On a positive note, a fairly large proportion of IHCA survivors have acceptable quality of life. The other part of survivors deals with health issues that negatively influence their quality of life. It is peculiar that IHCA survivors should experience lower HRQoL than their OHCA and 'regular ICU' peers; patients who have also suffered grave maladies and invasive treatment. Two possible explanations for the lower HRQoL exist. The first is that the synergy of pre-existing illness and cerebral hypoxia create decline of quality of life in both physical and mental domains, which lead to a sort of generalized suffering. Patients with high depression scores on the HADS questionnaire more often reported functional disability. This is in accordance with prior reports from OHCA populations and warrants for more structured rehabilitation programs aiming at both physical and psychological wellbeing. The second explanation is that there is a lack of recognition. IHCA survivors return to the hospital ward after an ICU session to be treated for their underlying disease rather than receiving physical and neurocognitive rehabilitation aimed at cardiac arrest survivors. With the increasing attention to post-ICU syndrome and psychological impairment after ICU-admission, it feels only logical to include this group in future treatment cohorts[21].

Pertaining to quality of life indices and its usage in prognostication the following question still needs answering: what do patients find important in decision-making? We have now described health-related quality of life and the possible problems IHCA survivors may encounter. We however do not yet have a clear picture of the weight patients attribute to these outcomes and the possible loss in quality of life. In counselling about CPR-directives this should be an important subject. What specific topics patients need to be informed about during a CPR-directive conversation is not yet fully elucidated [14]. In **chapter 4** we report explorative results on what the general opinion is about such conversations and what patients think about timing and location. Furthermore it shows that knowledge about survival rates needs improvement. Future research will need to provide more in-depth knowledge about the quintessential parts of patient-centred CPR-directive counselling.

In **chapter 3** we already described the availability of nationwide CPR-teams, guideline adherence and team training. In **chapter 9** we could link these factors to patient-related outcomes. The benefits of team training also became apparent, as did the availability of ALS-certified staff. We hypothesize that the availability of an intensivist is a proxy for staff that is well-informed of protocols and has the ability to make decisions on treatment strategies (e.g. catherization, ECPR). Our endeavour to examine variation in outcomes between hospitals provided one more notable insight; quality in the Netherlands appears consistent in various hospitals. Besides the effect of team training and staff on cognitive performance at discharge, there were no big effects in terms of survival. Learning from best practice can be useful for future guidelines and the effect of training has once more been underlined. Integration of prognostic scores, counselling, training and treatment should make for an ambitious, but not too farfetched research idea.

Chain of survival

In the introduction the scientific approach to improving survival after In-Hospital Cardiac Arrest is described using the shackles of a chain. Our findings with regard to these shackles are summarized below:

First: preventing cardiac arrest. Although we have not examined prevention, we have established a baseline measurement of incidence and survival. From this measurement the success of future interventions can be measured. Moreover, selection of patients with good chance of favourable outcome will lead to prevention of futile attempts at resuscitation. **(chapters 2 and 7)**

Second: determining the chances of successful CPR in case of cardiac arrest and focusing on health-related quality of life. This thesis provides a comprehensive view of one-year survival in the Dutch IHCA population and its associated factors. **(chapters 1,2, 7 and 9)**

Third: installing advance care directives. As we have learned from our interview study among hospitalized patients, advance care directives about CPR (CPR-directives) are present in most patients. Counselling needs to focus on informing the patients, who are generally open to speaking about the subject. **(chapter 4)**

Fourth: defining the best treatment strategies for CPR. The results from this thesis support CPR-team training of twice or more per year, the availability of ALS-certified hospital staff/physicians. Furthermore, it supports the use of ECPR for IHCA in selected patient populations. **(chapter 3,4,5,6 and 9)**

Fifth: providing post-resuscitation care. Our findings support the need for research into rehabilitation for IHCA patients and early recognition of functional and emotional problems. **(chapter 8)**

Figure 1. The chain of survival for In-Hospital Cardiac Arrest

Conclusion and recommendations

Survival after in-hospital cardiac arrest in the Netherlands is relatively high compared to other countries. This difference is probably attributable to selection of patients with a chance at good outcome and availability of well-trained CPR-teams. Clinical practice should be aimed at training all hospital staff at all facets of CPR: counselling of directives, recognition of IHCA and guideline-based treatment.

Survival of in-hospital cardiac arrest patients can be improved through further selection of patients with a chance at good outcome, based on pre-admission functional status and the combination of age and comorbidities. Clinical practice and future research should focus in the integration of evidence-based risk models and patient counselling.

Quality of life of cardiac arrest survivors is lower than their peers and warrants more attention. Clinical practice and future research should focus on identifying patients who are at risk and may need more intensive rehabilitation.

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Laat me niet in de steek
Neem mijn lucht over als
bloed niet kan stromen
Op tafel of bed

Leid mijn ademtocht
langs grillige patronen
Voel mijn hart slagen
Ben jij mijn bewaker
Welke bergen verzet

En als ik niet zal ontwaken
En jij niet meer kan sturen
Houd het tij dan niet tegen
Zie me met één oog
naar de horizon turen

Komt leven of dood
Breng rust in de nood
Hoef ik me niet alleen
te weten

Section IV

Nederlandse samenvatting
Dutch summary

Het doel van dit proefschrift is om inzicht te verkrijgen in de uitkomsten van reanimaties in het ziekenhuis en de factoren die hierop van invloed zijn.

Een reanimatie omvat het geheel van handelingen voor het herstel van spontane circulatie en ademhaling indien bij een patiënt een circulatiestilstand optreedt (ook vaak hartstilstand genoemd). Hierbij stagneert de bloedsomloop en kan er niet genoeg zuurstof bij de weefsels komen. Met name het brein is gevoelig voor zuurstoftekort en dit kan dan ook tot blijvende neurologische schade leiden. Bij gebrek aan een gangbare Nederlandse term wordt een circulatiestilstand die plaatsvindt binnen de muren van het ziekenhuis aangeduid met de Angelsaksische term *In-Hospital Cardiac Arrest* of de afkorting *IHCA*. Dit begrip omvat dan reanimaties die plaatsvinden op verpleegafdelingen, poliklinieken, operatiekamers, intensive care en ook de eerste hulp, tenzij de reden van bezoek een circulatiestilstand is die buiten het ziekenhuis begon.

In deel I, **hoofdstuk 1 en 2**, hebben we gekeken naar de overleving na IHCA vanuit een historisch perspectief. In deel II, **hoofdstuk 3 en 4**, ligt de nadruk op de kennis die we hebben vergaard over de kenmerken van reanimatiezorg in ziekenhuizen en in **hoofdstuk 5 en 6** belichten we de rol van extracorporele circulatie (een relatief nieuwe behandeling middels hart-longmachine) bij de behandeling van IHCA. In deel III, **hoofdstuk 7, 8 en 9**, worden de resultaten gepresenteerd van een prospectief onderzoek naar de uitkomsten van patiënten die gereanimeerd zijn; de kansen op overleving en de kwaliteit van leven die daarbij hoort. Tevens hebben we gekeken naar factoren die deze uitkomsten mogelijk kunnen voorspellen. In het huidige hoofdstuk vatten we de bevindingen uit eerdere hoofdstukken in dit proefschrift samen en bediscussiëren we de implicaties voor de klinische praktijk.

Er is weinig bekend over de uitkomsten op lange termijn van patiënten die worden gereanimeerd in het ziekenhuis. In **hoofdstuk 1** hebben we een systematische review en meta-analyse verricht van 40 studies met in totaal meer dan 1,3 miljoen patiënten. Hieruit volgde een overlevingspercentage na IHCA van 17,6% bij ontslag uit het ziekenhuis en van 13,4% één jaar na de reanimatie. Deze data beslaan de periode 1985 – 2018 en tonen over die periode een bescheiden verbetering in overlevingskansen (10-jaars OR: 1,70, 95% betrouwbaarheidsinterval: 1,04-2,76)**.** In **hoofdstuk 2** verkennen we de Nederlandse situatie rondom overleving van IHCA. Om dit te onderzoeken hebben we een retrospectieve studie gedaan in het Onze Lieve Vrouwe Gasthuis te Amsterdam, over de periode 2003 – 2014. In deze groep patiënten was een jaar na de reanimatie het overlevingspercentage 26,0%, zonder dat er in deze periode van 10 jaar significante verbetering optrad. We hebben in univariate analyse een relatie met éénjaarsoverleving gevonden van enkele patiëntfactoren, zoals comorbiditeit, en reanimatiekarakteristieken, zoals de duur van de reanimatie.

Zoals in de introductie van dit proefschrift wordt beschreven, is in de periode 1960 – 1980 de gemiddelde overleving na IHCA bij ontslag uit het ziekenhuis 15,0%[1]. Als we dit naast de 17,6% uit onze meta-analyse plaatsen impliceert het dat zestig jaar medische ontwikkeling nauwelijks vooruitgang heeft opgeleverd voor de overleving na IHCA. Ondanks dat de overleving in Nederland hoger lijkt te zijn, is er ook geen verbetering over de tijd zichtbaar. De meest voor de hand liggende verklaring hiervoor is de veranderde samenstelling van patiënten die in een ziekenhuis behandeld worden (ook *casemix*

genoemd)[2]. De gemiddelde levensverwachting van de mens neemt toe en wordt verwacht nog door te stijgen, met name doordat de 65-plussers van nu langer leven[3]. Deze vergrijzing betekent dat steeds meer mensen te maken krijgen met multimorbiditeit. Tegelijkertijd biedt de vooruitgang in behandelopties de mogelijkheid om patiënten met steeds ernstiger en sneller progressief lijden te behandelen[4,5]. Eenzelfde ontwikkeling zien we op de intensive care; het aantal 80-plussers en hun ziektelast neemt toe, terwijl de sterftecijfers hetzelfde blijven[6]. Het netto-effect hiervan is dat de veranderingen in deze *casemix* uitgebalanceerd worden door de voortuitgang in behandelmogelijkheden.

Het behandelen van IHCA, de reanimatie en de daaropvolgende intensive care behandeling, is duur: €164.442 per Quality Adjusted Life Year (QALY; levensjaar in goede gezondheid). Het grootste deel van deze kosten komt door de behandeling op de intensive care. Ter vergelijking, de zorg voor patiënten na een reanimatie buiten het ziekenhuis kost ongeveer de helft. In de retrospectieve studiegroep (**hoofdstuk 2**) overleed 62,0% van de patiënten die na een succesvolle reanimatie op de IC werd opgenomen alsnog. Deze groep patiënten ondergaat een kostbare en tijdrovende behandeling, zonder daar profijt van te hebben. We hebben vrij recent nog geleerd hoe belangrijk intensive care capaciteit kan zijn[7]. Bovendien leek een QALY de Nederlander gemiddeld 50.000 euro waard te zijn[8]. Met de toenemende vergrijzing moet het speerpunt van het reanimatieonderzoek dan ook liggen bij het voorspellen van de kansen op een goede uitkomst. Leeftijd en comorbiditeit alleen lijken niet afdoende te zijn om dit te voorspellen[9,10]. Idealiter zien we af van reanimaties met een geringe kans op kwalitatief goed herstel en optimaliseren we de zorg voor patiënten met goede kansen. Dit kan helpen om de uiteindelijke overlevingscijfers te verbeteren en om de kosten van de reanimatiezorg binnen de perken te houden.

Om een beter beeld te krijgen van de zorg rondom reanimaties in Nederland, hebben we vier studies gedaan in een groot aantal ziekenhuizen in Nederland. Deze staan beschreven in **hoofdstukken 3 tot en met 6.** Ten beginne hebben we in **hoofdstuk 3** een enquête verstuurd naar alle Nederlandse ziekenhuizen om de variatie in de behandeling van reanimaties in kaart te brengen. Bijna alle ziekenhuizen gaven aan dat ze de meest recente Europese reanimatierichtlijn volgden met betrekking tot *Advanced Life Support (ALS)*. Er waren drie verschillen in praktijkvoering: ten eerste in de frequentie van het oefenen van reanimatiescenarios, ten tweede de wisselende beschikbaarheid van een *ALS*-geschoold intensivist tijdens de dag- en nachturen en ten derde de samenstelling van het reanimatieteam. Uit deze enquête kwam verder naar voren dat 89,0% van de ziekenhuizen het maken van een reanimatieafspraak verplicht stelde bij opname in het ziekenhuis, d.w.z. dat iedere patiënt een gesprek heeft gehad en er een beslissing is vastgelegd over het wel of niet starten van een reanimatie in geval van een circulatiestilstand. In **hoofdstuk 4** hebben we een cross-sectioneel multicentrisch onderzoek verricht, waarbij in 13 ziekenhuizen 1136 patiënten zijn bevraagd over gemaakte reanimatieafspraken. De reanimatieafspraken werden op twee manieren geïnventariseerd; bij de patiënt en uit het elektronisch patiëntendossier (EPD). Voor de meeste patiënten (91,2%) was een reanimatieafspraak vastgelegd. Van alle ondervraagde patiënten kon 55,8% zich een gesprek over het reanimatiebeleid herinneren. In beginsel waren we geïnteresseerd in het aantal niet-reanimeerafspraken (NR) en we vonden dat 27,8% van de patiënten een NR in het EPD had staan. Een NR was vaker afgesproken bij oudere patiënten, patiënten met een

hoge comorbiditeitsscore en bij patiënten die thuis meerdere geneesmiddelen gebruikten. Patiënten schatten de overlevingskans na een reanimatie zo'n 2,5 maal hoger dan dat deze beschreven staat in **hoofdstukken 1 en 2**. Een andere discrepantie die het noemen waard is, is dat 7,0% van de patiënten een andere reanimatieafspraak rapporteerde dan in het EPD was vastgelegd.

Het is een positief teken dat de meeste Nederlandse ziekenhuizen reanimeren volgens de vigerende richtlijnen. Recent onderzoek heeft aangetoond dat in de periode na implementatie van nieuwe richtlijnen, de uitkomsten na reanimaties wel enigszins lijken te verbeteren[11]. Regelmatig trainen zou ook voordelig kunnen werken, met name als de leden van het reanimatieteam een verschillende achtergrond hebben (bijv. anesthesie, cardiologie, interne geneeskunde). Daarnaast is bewezen dat het scholen van alle medewerkers die betrokken zijn bij de patiëntenzorg de overleving na reanimaties verbetert[12,13]. Helaas waren er niet in alle ziekenhuizen die we onderzochten vaste trainingen en was er niet overal 24/7 een *ALS*-geschoold intensivist beschikbaar.

Het verplicht vastleggen van een reanimatieafspraak uit **hoofdstuk 3** vinden we terug in de bevindingen van **hoofdstuk 4**. De meeste patiënten die op een verpleegafdeling werden behandeld hadden een gedocumenteerde reanimatieafspraak. Merkwaardig genoeg kon slechts iets meer dan de helft zich herinneren dat ze hierover met een arts gesproken hadden. Dit kan betekenen dat er niet zozeer een gesprek plaatsvindt, maar dat er alleen een beleid in het EPD wordt genoteerd. Daarbij komt nog dat ouderen en multimorbide patiënten zich het afgesproken beleid minder goed herinneren. In dit hoofdstuk noemen we enkele verklaringen voor deze discrepanties. De meest opportune oplossing zou zijn om alle patiënten van betere informatie te voorzien en om de informatie toe te spitsen op specifieke doelgroepen. Als eerste voorbeeld zouden jonge c.q. vitale patiënten, voor wie de kansen op overleving goed of redelijk zijn, hun informatie via digitale media kunnen ontvangen. Vragen kunnen dan achteraf gesteld worden en zullen doorgaans weinig tijd in beslag nemen. De oudere en multimorbide patiënt zal hoogstwaarschijnlijk baat hebben bij een uitvoeriger gesprek met een deskundige. Omdat een groot deel van de patiënten digitaal informatie ontvangt, hebben zorgverleners meer tijd over voor deze wat (tijds)intensievere gesprekken[14]. Ongeacht het medium dat de informatie overbrengt, moeten patiënten goed geïnformeerd worden over de overlevingskansen en over hun eigen reanimatiebeleid.

Een nevenbevinding uit **hoofdstuk 4** is het zogeheten 'gatekeeper'-fenomeen dat we tegenkwamen bij de uitvoering van dit onderzoek[15]. Een aantal artsen, verpleegkundigen en zorgmanagers heeft ons onderzoek tot op het laatste moment geprobeerd af te houden, ondanks toestemming van de Raad van Bestuur. Ze deden dit uit oogpunt van bescherming van de patiënten. Ons onderzoek laat echter zien dat patiënten minder moeite hadden met het onderwerp dan zorgverleners denken.

In **hoofdstuk 5 en 6** hebben we gekeken naar reanimatie met behulp van extracorporele circulatie door een hart-longmachine. Dit heet ook wel *Extraorporeal CardioPulmonary Resuscitation* of *ECPR*. Deze techniek creëert een kunstmatige bloedsomloop, waardoor de weefsels weer van zuurstof worden voorzien. Of het herstellen van de bloedsomloop ook resulteert in betere overleving of minder neurologische schade, is nog niet uitgebreid onderzocht. Bovendien is het een dure behandeling en is de

kosteneffectiviteit ook nauwelijks onderzocht. In **hoofdstuk 5** presenteren we een systematische review en meta-analyse naar de potentiële voordelen van ECPR in vergelijking met conventionele reanimaties op uitkomsten na IHCA. Hieruit komt voort dat de overleving bij ontslag uit het ziekenhuis hoger lijkt dan na conventionele reanimaties (30,0% vs. 17,6%), met een geringer aantal overlevenden met een goede neurologische uitkomst (84,0% vs. 92,0%). Uit kwaliteitsanalyse van de studies blijkt ECPR met name een voordelige techniek in studies waarin patiënten vooraf aan selectiecriteria onderworpen zijn. Dit houdt in dat niet iedereen wordt behandeld met ECPR. In **hoofdstuk 6** beschrijven we dat het behandelen met ECPR van patiënten uit een dergelijke geselecteerde populatie ongeveer 23.000 euro per QALY kost. Dit houdt in dat de patiënt aan bepaalde criteria moet voldoen. Als we alle IHCA-patiënten zouden behandelen met ECPR, levert dit gemiddeld 3,4 QALY per patiënt op en kost één zo'n QALY 15.000 euro. Als ECPR alleen toegepast wordt bij patiënten die bijvoorbeeld weinig comorbiditeit hebben, dan worden de kosten lager. Echter, als we rekening houden met wat een QALY in een gemiddeld Westers land mag kosten (betalingsbereidheid), lijkt het in deze studie kosteneffectief om alle patiënten met ECPR te behandelen.

Het toepassen van ECPR lijkt veelbelovend en in de reanimatierichtlijnen van 2015 is het dan ook opgenomen als mogelijke behandeling[16]. Het heeft er schijn van dat patiënten die anderszins zouden zijn overleden, hiermee wel de reanimatie overleven. Er zijn een paar belangrijke kanttekeningen. Ten eerste staat zuiver het overleven met een goede neurologische uitkomst niet gelijk aan het hebben van een acceptabele kwaliteit van leven. Gegevens over de kwaliteit van leven op lange termijn van patiënten die op deze manier zijn gereanimeerd zijn schaars[17]. Ten tweede moeten we benadrukken dat ECPR in een geselecteerde patiëntengroep werd toegepast. De meeste studies gebruikten deze techniek niet in patiënten ouder dan 75 jaar, met een terminale ziekte of met een andere ziekte die opname op de intensive care verhindert. Zoals te verwachten, hebben mensen met een betere kans op overleving in algemene zin ook een betere kans op overleving na IHCA. Dit maakt niet dat ECPR geen goede behandeloptie is, maar het benadrukt wel de noodzaak van indicatiestelling. Dit geldt overigens voor zowel ECPR, als conventionele reanimaties. Het is belangrijk om patiënten te selecteren met een grote kans op overleving met een goede kwaliteit van leven en om te evalueren of ECPR deze kansen nog groter kan maken.

Een andere belangrijke vraag is: wat maakt iets kosteneffectief? Zoals hierboven beschreven is de zorg rondom IHCA kostbaar. ECPR valt binnen de geaccepteerde grenzen van betalingsbereidheid. Desondanks moeten we goed nadenken over de toepassingen van deze techniek in de toekomst, ook met oog op de vergrijzing. Het probleem met onderzoek naar kosteneffectiviteit van interventies, is de relatieve aard van het begrip. Is de interventie juist omdat het kosteneffectief is, of is het kosteneffectief omdat de aard van de interventie sowieso al juist is. Oftewel, is kosteneffectiviteit arbitrair of behoort het tot de eeuwige waarheid over de aard der dingen. In die zin vertoont het parallellen met het Euthyphro dilemma van Plato[18]. Kosteneffectiviteit is nooit echt de aard van een interventie, maar eerder een kwaliteit die wij als mensen eraan toekennen. Dat maakt dat de beslissing of een interventie kosteneffectief is maatschappelijk is, en niet zozeer vanuit klinische studies kan worden gemaakt. Deze mogelijke invloed op kosteneffectiviteit hebben we weergegeven door in **hoofdstuk 6** verschillende grenzen voor betalingsbereidheid op te nemen in de modellen.

Om een beeld te krijgen van de uitkomsten op lange termijn na IHCA in Nederland, hebben we een prospectief multicentrisch onderzoek verricht. In de *Resuscitation Outcomes in the Netherlands (ROUTINE)* studie zijn alle patiënten geïncludeerd die gedurende een jaar een circulatiestilstand ondervonden in een van de deelnemende ziekenhuizen en zijn deze patiënten een jaar lang gevolgd. In **hoofdstuk 7** beschrijven we de bevindingen van deze studie. We hebben 713 patiënten uit 18 ziekenhuizen geïncludeerd. Het percentage overlevenden één jaar na de reanimatie was 27,8%. Bij ontslag uit het ziekenhuis was de overleving 32,4%. Van de patiënten die na een initieel succesvolle reanimatie alsnog overleden, gebeurde dit in de meerderheid tijdens de ziekenhuisopname (93,6%). We vonden een incidentie van IHCA in Nederlandse ziekenhuizen van 1,3 per 1000 ziekenhuisopnames. De functionele zelfstandigheid van patiënten (MRS; modified Rankin scale) en de combinatie van leeftijd en comorbiditeit (ACCI; age-combined Charlson index) bij opname waren onder andere geassocieerd met de kans op overleven. **Hoofdstuk 8** beschrijft de kwaliteit van leven van patiënten die IHCA hebben overleefd in relatie tot hun gezondheidstoestand. Ondanks dat een redelijk grote groep overlevenden een acceptabele kwaliteit van leven rapporteert, is het lager dan de kwaliteit die gemiddelde Nederlanders uit een referentiegroep ervaren. Overlevenden van het mannelijk geslacht ervoeren vaker psychologische problemen. Los hiervan is de gerapporteerde kwaliteit van leven lager dan die van 'doorsnee' intensive care patiënten. In **hoofdstuk 9** hebben we een analyse gemaakt van de invloed van praktijkvariatie tussen ziekenhuizen op uitkomsten na IHCA. We hebben dit gecorrigeerd voor de variatie in *casemix* van patiënten. We vonden geringe variatie in sterftecijfers en neurologische uitkomsten van patiënten. Omdat het verschil in neurologische uitkomsten minder gerelateerd was aan *casemix*, lijkt het dat verbetering van praktijkvoering kan leiden tot betere resultaten op dit gebied. Ziekenhuizen die twee (of meer) keer per jaar reanimatiescenarios oefenden hadden overlevenden met betere cognitieve scores bij ontslag. De 24/7 beschikbaarheid van een *ALS*-geschoold intensivist toonde een trend naar verbeterde cognitieve scores bij ontslag, maar dit effect was niet statistisch significant.

De overlevingskans na reanimaties in het ziekenhuis is voor Nederlandse patiënten hoger dan voor patiënten uit andere landen, zoals we in de systematische review in **hoofdstuk 1** beschrijven. Onze resultaten suggereren echter dat er mogelijkheden zijn om patiënten met een goede kans op overleving in een vroeg stadium te identificeren. Hiermee bedoelen we bijvoorbeeld bij opname in het ziekenhuis, op de polikliniek of zelfs bij de huisarts. De beslissing zou dan kunnen worden gebaseerd op een combinatie van comorbiditeit en functionele zelfstandigheid, bij voorkeur in een gevalideerd model. De huidige modellen en risicofactoren gebruiken vaak gegevens die niet bekend zijn in een vroeg stadium, maar bijvoorbeeld pas op het moment dat de patiënt gereanimeerd moet worden[19,20]. Om goede gespreksvoering rondom reanimatieafspraken te bevorderen en om de oudere en zwakkere medemens beter te begeleiden in hun keuzes (**hoofdstuk 4**) pleiten we voor een vernieuwing van de huidige modellen.

Positief is dat een redelijk groot deel van de patiënten die een reanimatie overleeft een acceptabele kwaliteit van leven heeft. Het andere deel heeft te kampen met gezondheidsproblemen die een negatieve invloed hebben op hun kwaliteit van leven. Het is noemenswaardig dat patiënten die een IHCA overleven een lagere kwaliteit van leven ondervinden dan hun tegenhangers; de overlevenden van een reanimatie buiten het ziekenhuis en de 'doorsnee' intensive care patiënten. Dit zijn immers

patiënten die evengoed ernstig ziek zijn (geweest) en ingrijpende behandelingen hebben ondergaan. We hebben hiervoor twee verklaringen. De eerste is dat een wederzijdse invloed van reeds bestaande ziekte en zuurstoftekort in het brein leidt tot een verminderd functioneren op zowel het lichamelijke, als geestelijke vlak. Dit creëert de lijdensdruk die de kwaliteit van leven vermindert. Patiënten die op de depressievragenlijst slechter scoorden, ervoeren ook vaker lichamelijke beperkingen. Dit komt overeen met bevindingen bij patiënten die buiten het ziekenhuis werden gereanimeerd en benadrukt de noodzaak van programma's die de fysieke en mentale revalidatie ondersteunen[21]. De tweede verklaring is dat deze patiëntencategorie minder goed herkend wordt. Patiënten die IHCA overleven keren na een intensive care opname terug naar een verpleegafdeling om verder behandeld te worden voor de ziekte waarmee ze oorspronkelijk in het ziekenhuis kwamen. Dit in tegenstelling tot patiënten die in het kader van een reanimatie buiten het ziekenhuis worden opgenomen en de daartoe geëigende revalidatieprogramma's doorlopen. Met een groeiende interesse voor het post-intensive care syndroom (PICS) en de psychologische gevolgen van een opname, lijkt het een logische stap om IHCA patiënten in de toekomst hiervoor te behandelen[22].

Met betrekking tot indices van kwaliteit van leven en hun waarde in de prognose van reanimatiepogingen blijft nog een vraag open: wat vinden patiënten belangrijk tijdens het maken van een reanimatieafspraak? In dit proefschrift worden de kwaliteit van leven en de mogelijke problemen die overlevenden tegenkomen beschreven. Er is echter nog geen duidelijk beeld van de waarde die patiënten zelf hechten aan deze uitkomsten en de mogelijke derving van kwaliteit van leven. Dit zou een belangrijk onderdeel moeten zijn van gesprekken over reanimatiebeleid, alleen welke details voor patiënten belangrijk zijn is nog niet opgehelderd[14]. In **hoofdstuk 4** hebben we globaal beschreven wat de houding van patiënten is ten aanzien van deze gesprekken en wat ze vinden van de timing en de locatie van het gesprek. We hebben ook laten zien dat er meer moet worden voorgelicht over de kans op overleving. Toekomstig onderzoek moet uitwijzen wat voor patiënten essentiële onderdelen zijn van gesprekken over reanimatiebeleid.

In **hoofdstuk 3** hebben we omschreven hoe de praktijk van reanimatiezorg in Nederland er uit ziet. We beschreven de beschikbaarheid van reanimatieteams en het werken en trainen volgens richtlijnen. In **hoofdstuk 9** hebben we deze data gekoppeld aan uitkomsten voor de patiënt. De voordelen van training werden ook hier duidelijk, net als de beschikbaarheid van een *ALS*-geschoold intensivist om het reanimatieteam te bemannen. We denken dat het beschikbaar zijn van een intensivist voor het reanimatieteam een afgeleide is van een medische staf die goed op de hoogte is van de vigerende protocollen en die daardoor snel beslissingen kan maken (bijv. het verrichten van een coronairangiogram of het starten van ECPR). Deze studie om de praktijkvariatie te bestuderen heeft nog één belangrijke andere bevinding opgeleverd: de kwaliteit van reanimatiezorg in Nederland lijkt in Nederland redelijk gelijkmatig verdeeld te zijn. Naast het effect van reanimatietraining en beschikbaarheid van een intensivist op de cognitieve scores bij ontslag, waren er geen noemenswaardige variaties. Leren van de successen van anderen kan helpen bij het verder aanscherpen van Europese richtlijnen. Verder werd het belang van training eens te meer benadrukt. Toekomstig onderzoek naar het effect van prognostische modellen, reanimatietraining en nieuwe behandelmethoden zou een logische stap zijn.

Keten van overleving

In de introductie hebben we de wetenschappelijke manier om de overleving na reanimaties in het ziekenhuis te verbeteren beschreven aan de hand van vijf schakels van een keten.

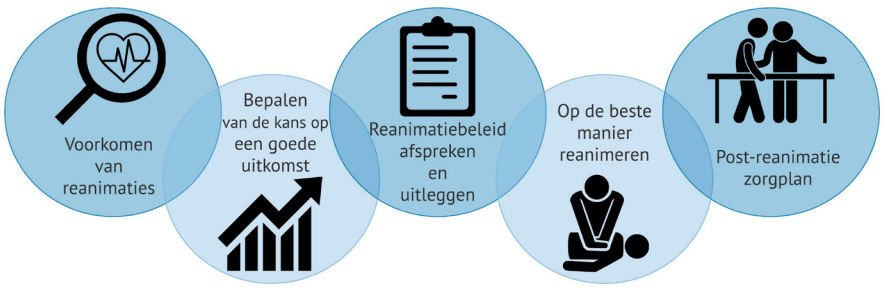
De eerste schakel: het voorkomen van het optreden van reanimaties. In dit proefschrift hebben we geen onderzoek gedaan naar preventie, maar we presenteren wel een beschrijving van de incidentie en de overleving. Aan de hand van deze metingen kan het succes van toekomstige interventies worden gemeten. Daarnaast zal het selecteren van patiënten met een goede kans op overleving en het maken van reanimatieafspraken leiden tot preventie van medisch zinloze reanimatiepogingen. **(hoofdstukken 2 en 7)**

De tweede schakel: bepalen wat de kans op overleving is na IHCA en het beschrijven van kwaliteit van leven. Uit ons prospectief cohortonderzoek hebben we gedetailleerde informatie vergaard over de overleving en de daarmee geassocieerde factoren. **(hoofdstuk 1, 2, 7 en 9)**

De derde schakel: het afspreken van het reanimatiebeleid. Van het vragenlijstonderzoek hebben we geleerd dat de meeste patiënten een gedocumenteerd reanimatiebeleid hebben. De nadruk moet liggen op juiste informatievoorziening voor patiënten, die in het algemeen open staan voor een gesprek over dit onderwerp. **(hoofdstuk 4)**

De vierde schakel: het bepalen van de beste reanimatiemethode. De resultaten die in dit proefschrift gepresenteerd worden moedigen aan om twee keer (of vaker) per jaar reanimatietrainingen te organiseren. Daarnaast lijkt het gebruik van ECPR in bepaalde patiëntengroepen voordelig te kunnen werken. **(hoofdstuk 3, 4, 5, 6 en 9)**

De vijfde schakel: het leveren van post-reanimatiezorg. Onze bevindingen pleiten voor meer onderzoek naar revalidatie van IHCA-patiënten en voor vroege herkenning van functionele en emotionele problemen. **(hoofdstuk 8)**



Figuur 1. De keten van overleving na een reanimatie in het ziekenhuis (IHCA).

Conclusie en aanbevelingen

De overleving van patiënten na een reanimatie in het ziekenhuis in Nederland is relatief hoog in vergelijking met andere landen. Dit verschil wordt hoogstwaarschijnlijk verklaard door selectie van patiënten met kans op een goede uitkomst en de beschikbaarheid van goed getrainde reanimatieteams. In de praktijk zou er gericht moeten worden op het trainen van zorgmedewerkers op alle gebieden van de reanimatiezorg: het maken van de juiste reanimatieafspraken, herkennen van (risico's op) IHCA en de behandeling volgens vigerende richtlijnen.

De overleving van patiënten na een reanimatie in het ziekenhuis kan worden verbeterd door verdere selectie van patiënten met kans op een goede uitkomst, gebaseerd op functionele zelfstandigheid, leeftijd en comorbiditeit. In toekomstig onderzoek moet meer aandacht komen voor de samenhang van gevalideerde risicomodellen en reanimatieafspraken.

De kwaliteit van leven van patiënten die een reanimatie in het ziekenhuis hebben overleefd is lager dan die van de gemiddelde Nederlander, en behoeft derhalve aandacht. In de toekomst moeten onderzoekers en clinici zich richten op het identificeren van patiënten die behoefte hebben aan intensievere revalidatie.

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Never love anyone who treats you like you're ordinary.

Oscar Wilde

Section V

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Familie en schoonfamilie, bedankt voor alle steun! In het bijzonder mijn **tante Marie,** ik denk zo vaak terug aan al die verhalen die je vertelde over je werk in het verpleeghuis en het ziekenhuis. Als jij er niet zo'n feest van had gemaakt, was ik misschien wel helemaal nooit in de gezondheidszorg gaan werken. Dankjewel!

Mama, je hebt me alles gegeven wat ik nodig heb om te zijn wie ik ben. Je houdt onvoorwaardelijk van me, en ik van jou. Het maakte je niet uit wat ik zou worden, maar ik denk dat we allebei wel tevreden kunnen zijn met de uitkomst!

Tim, je bent mijn grote liefde. Ik ben elke dag dankbaar dat ik met jou getrouwd mag zijn. Van student tot specialist ben je bij me geweest en ik wil je bedanken dat je met me mee bent gegroeid. Je bent zo ontzettend slim. Je bent mijn beste vriend.

If at first you don't succeed,
just dust yourself off and try again.

Aaliyah

Section VI

Curriculum Vitae

Curriculum Vitae

Marc Schluep was born on the 31st of July 1989 at the Dijkzigt hospital, or academic hospital of Rotterdam the Netherlands. After graduating from the Emmauscollege in Rotterdam, he started his medical training at Utrecht University in 2007. During his study he had several jobs, as a nursing aid at the pulmonology and emergency department of the Diakonessenhuis and the paediatric ICU of the Wilhelmina's children hospital and as a teaching assistant at the faculty of medicine. After moving to Amsterdam he worked for a homecare organization and the mobile blood testing service, but most notably he started his final internship at the Onze Lieve Vrouwe Gasthuis. This was combined with a research project at the same department. Under supervision of Dr. Rik Endeman he studied the outcomes of in-hospital cardiac arrest survivors, which made the foundation for this thesis.

After starting his training to be an anaesthesiologist in 2014 he was given the opportunity to combine his clinical training with a PhD-trajectory (supervision Prof. Dr. R.J. Stolker, Dr. H. Endeman & Dr. S.E. Hoeks). During this period he got the chance to design his studies in the field of in-hospital cardiac arrest research. In 2017 he won a European Society for Anaesthesiology research grant, which supported the execution of many of his plans. For example his research on communication with patient about advanced directives (with Prof. Dr. M. van Dijk). His clinical training was done in Erasmus MC (Prof. Dr. R.J. Stolker) and Sint Franciscus Gasthuis (Drs. C. van Velzen & Dr. S.J.C. Verbrugge) in Rotterdam.

He finished his training as an anaesthesiologist in 2019, after which he started his intensive care medicine fellowship at OLVG Amsterdam (Prof. Dr. P.H.J. van der Voort & Dr. J. de Metz). After completion of this fellowship he worked to finish his PhD-thesis and at the same time he obtained an Erasmus MC and ZonMW grant with Dr. Eric Geijteman, to continue their research in the field of in-hospital cardiac arrest prognostics, advance care directives and patient communication. During the Corona-pandemic he worked at various institutions as an anaesthesiologist/intensivist.

Marc is married to Tim van Lier and they are currently living in Rotterdam with their cat Broes. After completion of this thesis, they will be traveling the world together for (at least) a year.

If you only read the books everybody else is reading,
you can only think what everyone else is thinking.

Haruki Murakami

Section VII

PhD-portfolio and list of publications

PhD-portfolio Drs. M. (Marc) Schluep

Name PhD student: drs. M. Schluep **PhD period: 2014-2021**
Erasmus MC Department: Anaesthesiology **Promotor: Prof. dr. R.J. Stolker**
Research School: COEUR **Supervisors: dr. S.E. Hoeks, dr. H. Endeman**

1. PhD training	Year	Workload	
		Hours	ECTS
General courses			
Research Integrity	2017		0.3
NIHES – Advanced analysis of prognosis studies	2018		0.9
NIHES – Survival analysis for clinicians	2018		1.9
Discipline Overstijgend Onderwijs (ethiek, gezondheidsrecht, ziekenhuismanagement)	2014-2018		2.5
Basic course Rules and Organisation for Clinical researchers (BROK)	2015/2019		3
Medical courses			
Advanced life support	2014/2019	45	1.6
Advanced trauma life support	2016	28	1
Antibiotics in Dutch practice	2019	42	1.5
Seminars and workshops			
Writing seminar	2017	5	0.2
Journal clubs (anesthesia, intensive care)	2014-2019	60	2
Seminar *'Opleiden op hoog niveau'*	2015	5	0.2
Conference proceedings			
International conferences			
EuroAnesthesia (poster presentation and grant winner)	2017	42	2.5
EuroAnesthesia (poster presentation)	2018	28	2
EuroAnesthesia (poster presentation)	2019	28	2
Resuscitation 2018 (poster presentation)	2018	28	2
Resuscitation 2019 (oral presentation)	2019	28	2
National conferences			
Anesthesiologendagen (NVA)	2015-2019		4.5
Nationaal Reanimatie Congres	2015/2018		1
Dutch intensive care conference with oral presentation (NVIC)	2015		1
COEUR PhD-day with oral presentation (winner of COEUR-cup 2018)	2018		0.5

2. Teaching	**Year**	**Workload**	
		Hours	**ECTS**
Supervising Master's thesis (*G.J.C. van Limpt*)	2017-2018	56	2
Supervising Systematic review and meta-analysis (*B.Y. Gravesteijn)*	2017	56	2
Supervising Cross-sectional point prevalence study (*S. IJmkers and T.M.M. Romijn)*	2018	42	1.5
Teaching various classes *(nurse anaesthetists, sedation nurses, medical students, fellow doctors)*	2014-2019	224	8
TOTAL			**46.10**

List of publications:

Gravesteijn BY, Schluep M, Endeman H, Stolker RJ, Hoeks SE. Between-center differences in outcome after In-Hospital Cardiac Arrest. Critical Care 2021

Schluep M, Hoeks SE, Gravesteijn BY […] Endeman H, Stolker RJ. In-depth assessment of health-related quality of life after in-hospital cardiac arrest. Submitted 2021

Brusse A, Schluep M, […] Smulders Y, Klein Nagelvoort – Schuit CE, Geijteman ECT. Resuscitation decisions in the Emergency Department: a necessary evil? Submitted 2021

Schluep M, Hoeks SE, Endeman H […] Wils EJ, Stolker RJ, van Dijk M. Communicatie rondom reanimatieafspraken in het ziekenhuis. Ned Tijdschr Geneeskd 2021.

Schluep M, Hoeks SE, Endeman H […] Stolker RJ. Long-term survival and health-related quality of life after in-hospital cardiac arrest. Resuscitation 2021

Gravesteijn BY, Schluep M, [...] Endeman H, Hoeks SE. Neurological outcome after extracorporeal cardiopulmonary resuscitation for in-hospital cardiac arrest: a systematic review and meta-analysis. Critical Care 2020

Schluep M, Hoeks SE, Endeman H […] Wils EJ, Stolker RJ, van Dijk M. A cross-sectional investigation of communication in Do-Not-Resuscitate orders in Dutch hospitals. Resuscitation 2020.

Gravesteijn BY, Schluep M, Voormolen D, van der Burgh A, Dos Reis Miranda D, Hoeks SE, Endeman H. Cost-effectiveness of Extracorporeal Cardiopulmonary Resuscitation for in-hospital cardiac arrest: a Markov decision model. Resuscitation 2019.

Schluep M, van Limpt GJC, Stolker RJ, Hoeks SE, Endeman H. Cardiopulmonary resuscitation practices in the Netherlands: results from a nationwide survey. BMC Health Services Research 2019.

Schluep M, Rijkenberg S, Stolker RJ, Hoeks SE, Endeman H. One-year mortality of patients admitted to the intensive care unit after in-hospital cardiac arrest: a retrospective study. Journal of Critical Care 2018

Schluep M, Gravesteijn BY, Stolker RJ, Endeman H, Hoeks SE. One-year survival after in-hospital cardiac arrest: a systematic review and meta-analysis. Resuscitation 2018

Schluep M, Stolker RJ, Hoeks SE, Endeman H, Blans M, Bosch F, et al. Uitkomsten na reanimaties in het ziekenhuis: de ROUTINE-studie. Ned Tijdschr Geneeskd 2017.

And when we're older

And we're ready

To leave earth behind

Here's to hoping

It's exactly

At the same damn time

James Blake, When we're older